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REVIEW

ORIGINAL ARTICLE

CASE REPORT

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REVIEW

Management of Ingrown Nails

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Abstract
Ingrown nails mainly affect the great toes, much less frequently lesser toes and rarely fingers. There are many speculations as to their etiology and pathogenesis; however, at the end, there is almost always a imbalance between too wide the nail plate and too narrow the (distal) nail bed. Ingrown nails occur at all age periods, from newborns to the over-100s though with different frequency, clinical characteristics, and management options. In recent years, conservative treatment options – taping, packing, gutter, braces, and many more - were developed avoiding the often disfiguring results of inadequate surgery. However, they require consistent and long-term therapy. Surgery is either aimed at narrowing the wide nail plate or reducing the hypertrophic lateral nail folds. The number of operation methods is vast; already 150 ago, more 75 different surgical techniques had been known, and there is virtually a new one published every week. Despite ingrown nails being a matter of concern for medical doctors since antique, new aspects continue to be detected, such as retronychia. Further, it was found that orthopedic foot abnormalities are very frequently seen in association with ingrown nails. Their treatment is often necessary to prevent recurrences.

Key words: *Ingrown nails; etiology; pathogenesis; conservative treatment; surgery; recurrence risk*

Introduction
Ingrown nails belong to the frequent and painful conditions affecting predominantly youngsters in their most active physical phase. They may considerably decrease the quality of life and, in extreme cases, even cause suicide ideation. They are typically chronic and the patients' and other lay persons' efforts to get relief usually aggravates the signs and symptoms. There is still an ongoing dispute on the etiology, particularly whether the wide nail plate or the hypertrophic nail folds are primarily to blame; this is also reflected by the terminology of unguis incarnatus *vs*. onychocryptosis.

Types of ingrown nails
Nails may grow into their surrounding soft tissue at any age; newborns may be delivered with ingrown nails and even 100-year-old persons may experience a painful ingrown nail.

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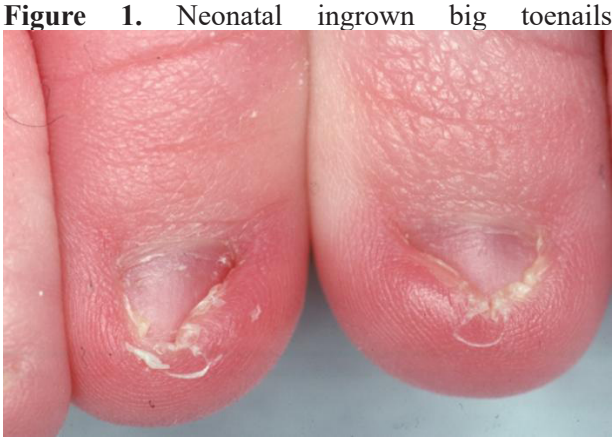
Neonatal ingrown nail

During intrauterine development, the big toenails usually have reached the tip of the toe, which is then overlapped by the nail at birth. However, occasionally, the great toenail has not overgrown the distal bulge and abuts it growing into the distal bulge causing erythematous inflammation and pain. This may be a short self-healing phase or require gentle treatment, usually by the mother. A bit of petrolatum or a similar fatty ointment is applied on the nail and then gently massaged in distal direction to push the distal bulge away while the baby is in a warm bath and held by the mother. The problem is usually solved within a few days. Another variant of neonatal ingrown nail is the bilateral distal ingrown nail (Fig. 1); here again, the nail has not yet overgrown the toe tip but is pinched distally from both sides. The treatment is analogous by gentle massage in a warm bath.

Figure 1. Neonatal ingrown big toenails



Infantile ingrown nail

There are two different types of ingrown nails in infants: the hypertrophic medial lip and congenital malalignment.

The medial nail fold, rarely the lateral one, is hypertrophic and overlaps a part of the nail plate, sometimes more than the half. This creates a deep crypt with accumulation of cellular debris and foreign material that degrade and cause an inflammation, a so-called cryptitis. Although this is rarely painful the mother may be scared and look for medial help. Usually, the overlapping nail fold can be massaged away as described above; however, if this is not effective it may be taken away with an electrical loop, which is an operation taking a few seconds.

Congenital malalignment is seen at birth or in the first months of life; however, it may also develop later if there is a genetic predisposition. Often a preceding trauma is then the precipitating event. Originally, the disease was called congenital dystrophy of the big toenail until Baran recognized that the underlying abnormality was a lateral deviation of the long axis of the nail relative to the axis of the distal phalanx.[3] In the last 25 years, more and different types of congenital toenail dystrophy have been observed, such as upward growing, congenital pincer nails or medial deviation.[4] Very often, congenital lateral malalignment is associated with a hallux valgus or particularly hallux valgus interphalangeus. The nail is thick, dirty yellowish, triangular, medially overcurved, with many transverse furrows and a slightly laterally curved longitudinal axis.

Close inspection reveals a high degree of onycholysis, which is indeed the most important prognostic factor.[5] The detachment of the nail plate from the nail bed leads to loss of counterpressure of the toe pulp during crawling and gait, which therefore becomes distorted dorsally thus forming a distal bulge with shortening and disappearance of the nail bed (Fig. 2). This is clearly seen after cutting away the onycholytic nail, which also reveals an impression of the nail margins into the soft tissue.[6] As the bone is not yet fully developed it tends to become curved upwards aggravating the distal bulge. The condition is apparently genetic as it is seen in monozygous twins, siblings and sometimes unilaterally; this also happens in twins.

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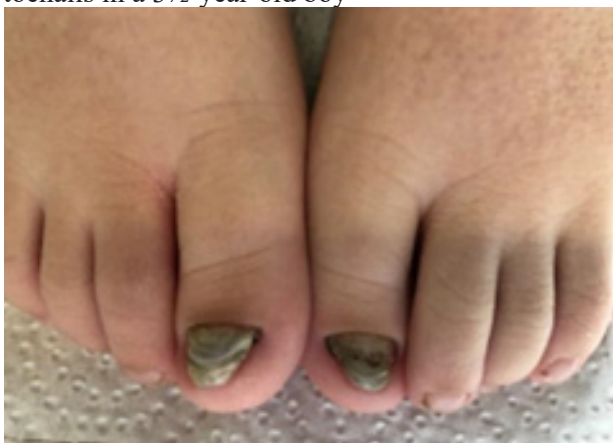
The exact pathomechanism is not known. We believe that the tendency to hallux valgus interphalangeus leads to an asymmetric distal phalanx bone with a higher medial condylus that potentially pushes the matrix in medial-distal direction directly leading to the lateral deviation. However, this hypothesis is not yet proven. A hypertrophy of the dorsal-lateral ligament of the distal interphalangeal joint was forwarded as another explanation;[7] however, surgical elongation of this ligament did not cure the condition.[8]

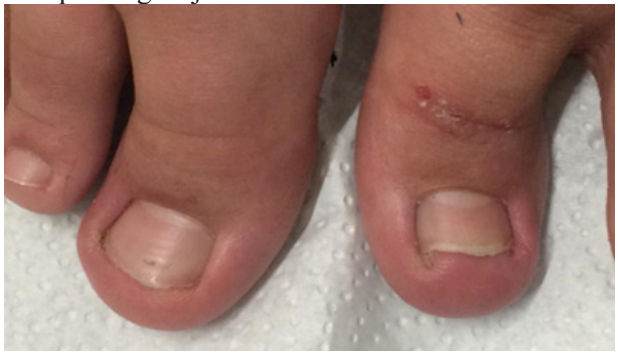
Figure 2. Congenital malalignment of the big toenails in a 3½-year-old boy



Adolescent ingrown nail

This is the most frequent type of ingrown nail. It often starts at school age and may last into young adulthood. One or both nail folds of one or both big toes become red and inflamed, are swollen and painful upon touch and pressure. This is generally called grade one (Fig. 3).

Figure 3. 11-year-old boy with imminent ingrowing nail, grade 1. Note the marked hallux valgus interphalangeus and hyperextension of the interphalangeal joint

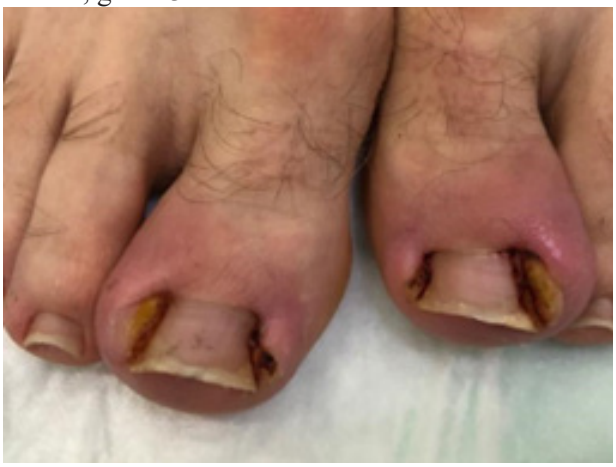


With time, swelling, inflammation and redness increase, oozing and sanguino-purulent discharge develop; this is grade two. Finally, granulation tissue develops, which is sometimes mistaken for pyogenic granuloma (Fig. 4).

Figure 4. Ingrown toenail grade 2 in a 6-year-old girl

In long-standing ingrown nails, swelling and granulation tissue may reach enormous dimensions rendering daily activities difficult to impossible; this is grade three (Fig. 5).[9]

Figure 5. 21-year-old man with chronic ingrown toenail, grade 3

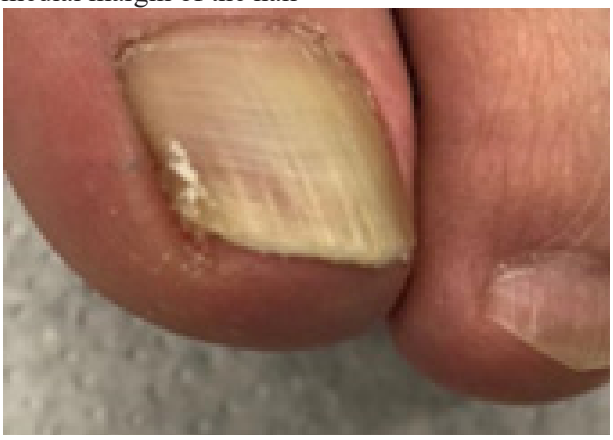


Many youngsters with ingrown big toenails are tall, sub-diabetic, have sweaty feet and the nail is markedly curved.[10] The nail is often cut too short, particularly at its corners, but the corners may also have broken spontaneously.[11] This allows the distal nail bed to be pinched together making it narrower so that the regrowing nail has not enough space and grows into the distal lateral sulcus. Quite often, the lateral nail plate margin has a saw-like appearance as the patient tries to cut the offending margin, which aggravates the condition.

Adult-type ingrown nail

In adults, the ingrown nails are usually thick, strongly curved or asymmetrically kinked, the affected nail fold is thick and fibrotic (Fig. 6). Inflammatory changes may be less marked or like those in adolescents. Pain is usually less intense. Often, a precipitating single trauma is remembered or repeated trauma is found out.

Figure 6. Adult type ingrown big toenail with sharply bent nail, a pointed spicule is seen at the medial margin of the nail



Overcurvature

Nail overcurvature is a frequent condition. It may be entirely painless or cause excruciating pain, which is – curiously – independent from the severity of the curvature; in contrast, nails that show a curvature of 360° or even more are commonly symptomless. The condition is known under several terms, such as pincer nail or *unguis constringens* as the nail bed is pinched together, trumpet nail as it may look like the funnel of a trumpet, omega nail as the frontal view of the nail and pinched nail bed resemble the Greek capital letter omega.[12] The genetic form is apparently an autosomal dominant trait, it is symmetric and virtually always associated with lateral deviation of the nail and distal phalanx of the big toe. Lesser toenails may also be involved and show a medial deviation. Systematic X-ray examinations always showed a lateral deviation and asymmetry of the distal phalanx with marked bony appositions on the condyli of the base of the distal phalanx which were always bigger on the medial side and often had a hook-like appearance with the tip showing distally.[13] This leads to an increase of the width of the base of the distal phalanx with a consecutive widening of the curvature of the matrix. The proximal uncurving causes the distally increasing overcurving of the nail.[14] This phenomenon is bilateral-symmetric in the genetic form of pincer nails (Fig. 7).[15]

Figure 7. Pincer nails in a 40-year-old woman; note the lateral nail deviation of the big toenail and the medially pointing nail axis of the 2nd toe

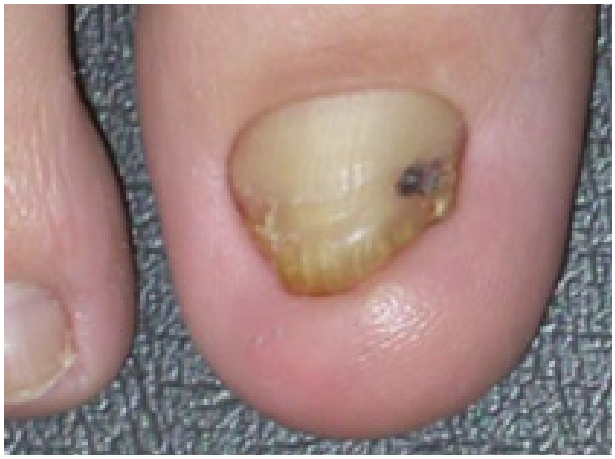
Distal ingrowing

When the big toenail is too short over a longer period or has been avulsed the tip of the toe's soft tissue is slowly dislodged dorsally as the nail plate is lacking and cannot exert counterpressure during gait. With each step, the entire body weight is on the toe tip, but the weight is increased by a factor of 2.5 due to the kinetic energy of the forward thrust during walking; this factor is even higher during running and other similar sports activities.

The distal bulge thus developing is a physical obstacle for the growing nail. In addition, after avulsion, the distal edge of the regrowing nail is usually slightly bent downward digging into the flesh.[16-17] This may lead to the appearance

of granulation tissue or, more frequently, cause an arrest of forward growth of the nail with consecutive thickening of the plate and yellow discoloration (Fig. 8).

Figure 8. Distal nail ingrowing in a 20-year-old soccer player who had lost his big toenail seven times



Retronychia

Retrograde ingrowing of the nail is called retronychia. Although only described in 1999 for the first time it is not a rare condition, particularly considering the frequent non-inflammatory chronic forms that we have termed compression nail in accordance with D. Lubach. The etiology of retronychia is not yet fully understood although the pathomechanism is known: a heavy acute or chronic repeated trauma leads to subtotal onycholysis. As the nail is not firmly attached to the nailbed, which is in fact the stable support for the nail on the dorsal aspect of the distal phalanx, any compression movement of the nail is directly transferred to the matrix, which is a very fragile tissue. This leads to shearing off the nail plate from the matrix with microscopically visible horizontal splits in the nail. The nail is no longer transported forward although the matrix produces new nail substance. Thus, a new layer is formed under the old one raising the proximal margin of the old one.

With each new compression trauma that pushes the nail backward another horizontal rupture is caused leading to a further new nail. The proximal edge of the old nail is hardening and cuts into the overlying proximal nail fold's undersurface that reacts with swelling, inflammation and granulation tissue finally emerging from under the free margin of the nail fold (Fig. 9).[18] This is a painful condition and unfortunately rarely diagnosed correctly but erroneously treated with antibiotics as a primary infectious paronychia. Ultrasound examination of the proximal nail fold may help to make the correct diagnosis.[19] The chronic form of retronychia usually remains without heavy inflammation and has still a certain potential of the nail to grow forward (Fig. 10); however, there are usually many layers of nail similar to onychogryposis that are formed under the old nail, which is eventually seen as an obliquely downward showing nail digging into the distal bulge that had developed because of the long-standing onycholysis. Another chronic form was called the horseshoe crab nail[20] or shrimp nail[21] because of the clinical aspect (Fig. 11).

Retronychia is one of the very rare conditions where nail avulsion is indicated[22] although in light cases topical steroids and in moderate cases steroid injections into the nail fold are often helpful.[23] For chronic retronychia, conservative dermatologic-podologic treatment is highly efficient.[24]

Figure 9. Acute retronychia in a 20-year-old girl. (A) Clinical aspect with swelling and redness of the proximal nail folds. (B) The avulsed nail seen from its proximal shows the V-shaped apical portion with the hard and very sharp superficial margin

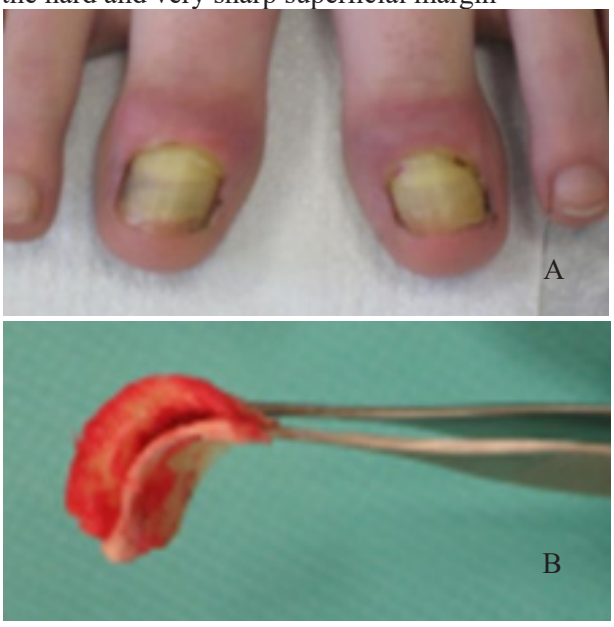


Figure 10. 43-year-old woman with chronic retronychia

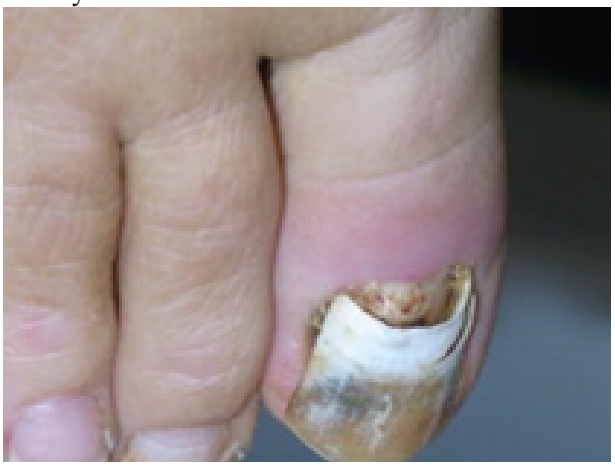
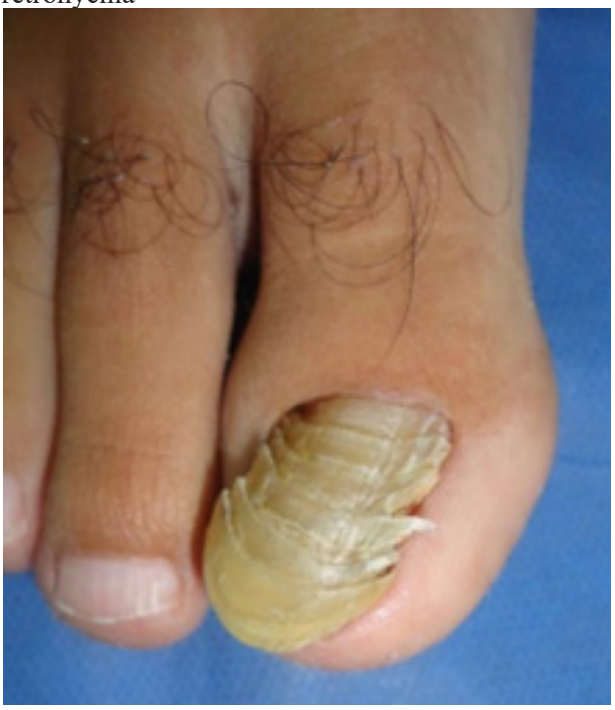


Figure 11. Compression nail also called horseshoe crab or shrimp nail as a chronic repeated form of retronychia



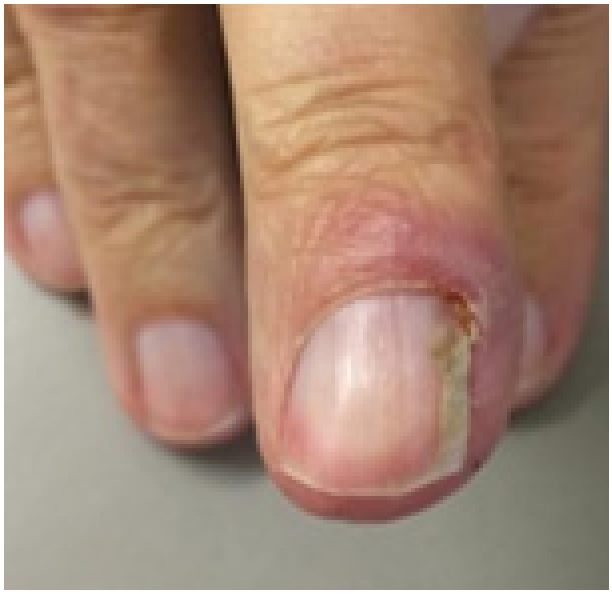
Frequency

Ingrown nails are frequent conditions, particularly between the ages of 6-25 years. Exact numbers of the incidence are, however, lacking. Sports activities, tight shoes, foot maceration, inadequate foot hygiene are all contributing factors. Ingrown toenails are less frequent in populations walking barefoot.[25] About 20% of those presenting to general practitioners with foot problems suffer from ingrown toenails and a survey from the Netherlands gave a prevalence of 54/10,000 in Dutch general practice.[26-27]

Localization

The great toe is by far the most common localization. The lesser toes, particularly 2 and 3, may rarely be involved. Ingrowing fingernails are mainly seen in patients under treatment with epidermal growth factor receptor inhibitors during targeted cancer therapy, retinoids, HAART for acquired immunodeficiency syndrome and some other rare conditions that soften the epidermis in the lateral nail sulcus (Fig. 12).

Figure 12. Ingrown fingernail in a 65-year-old man with colon cancer under targeted cancer treatment with cetuximab



Etiology

The cause of neonatal ingrown nails is the incomplete length of the toenail in relation to the nail bed (Fig. 1).

In congenital malalignment, the medial condylus of the distal phalanx bone is higher pushing the medial matrix horn forward and thus leading to an obliquely oriented matrix. The medial and sometimes also the lateral margin of the triangular nail are bent downward and press on the soft tissue. In addition, there is usually a disappeared nailbed with a receded hyponychium and a large distal bulge (Fig. 2).[28]

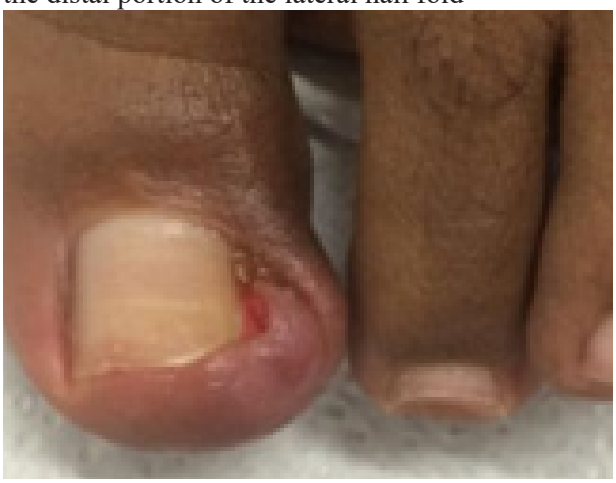
The most frequent type seen in school children, adolescents and young adults has a disbalance of a distally too narrow nail bed and a wide

nail plate. Additionally, the nail is usually markedly curved, and the lateral margins press into the lateral nail sulcus. Particularly when the nail edges are cut too short or broken the continuously growing nail will then dig into the skin and pierce it. This is painful and the patient tries to cut away the offending nail corner aggravating the condition.

Pathogenesis

The nail is a continuously growing keratin plaque. It is embedded on both sides in the nail sulci. When the distal nail corners overlap the toe, they can slide out without complication. However, when they are cut round the nail bed is compressed laterally, and the regrowing nail has not enough space and pierces into the soft tissue. Inflammation, serous and putrid exudation, granulation tissue and finally fibrosis follow (Fig. 13).

Figure 13. Long-standing ingrown big toenail with granulation tissue and massive fibrotic swelling of the distal portion of the lateral nail fold



Clinical Features

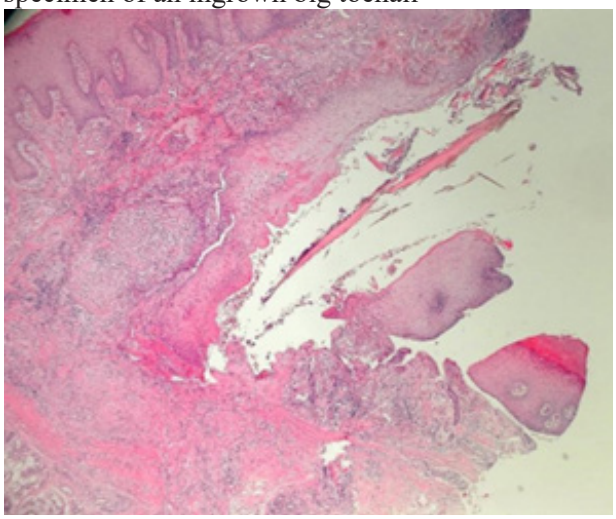
They are already briefly outlined with the description of the various forms and shall only be given in more detail for the most common, the adolescent type.

In grade 1, the distal portion of the nail fold is swollen, red and tender. In grade 2, seropurulent secretion is seen in addition and there is spontaneous pain. In grade 3, the toe is swollen, red on one or both sides, the nail corner is hidden by the nail fold tissue, and granulation tissue has developed (Figs. 3-5). In long-standing severe cases, the inflammation has turned into fibrosis and all the signs mentioned are very pronounced.[9] Extreme cases demonstrate overgrowth of granulation and fibrotic tissue (Fig. 13). The patients usually have stopped their physical activities because of pain.

Histopathology

Histopathologic examinations are rarely performed.[29] They show a very dense inflammatory infiltrate by lymphocytes with an enormously high percentage of plasma cells. The epidermis of the lateral nail fold is often hyperplastic. Specimens of wedge excisions with nail show the direct contact of the nail plate with the dermis and a considerable neutrophilic component attacking the nail keratin. The nail keratin is slowly digested by the neutrophils rendering it soft and fragile (Fig. 14).[30]

Figure 14. Histopathology slide of a wedge excision specimen of an ingrown big toenail



Treatment

The management has to be divided into general, conservative and surgical measures.

General measures

Foot hygiene with daily washing and drying, wearing of adequate shoes and socks, as well as changing socks daily are self-evident. The

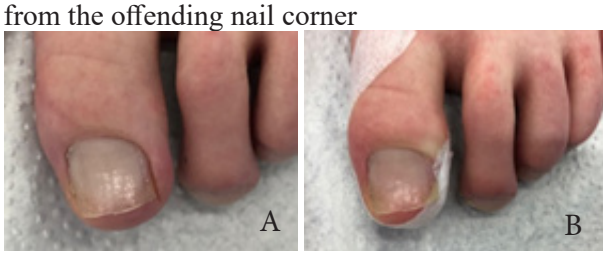
most important is cutting the nail square and leaving the corners of the nail overlapping the toe tip. Routine antibiotics although often given are of no use as it is the nail that causes the inflammation and not a primary infection. It also appears that "prophylactic antibiotics" do not prevent post-operative infections.[31-32]

Conservative treatment

There are many ways to treat an ingrown nail without surgery. However, this usually requires patience and compliance, which many persons do not have. On the other side, skilled caretakers can achieve phantastic results with taping, packing, insertion of a gutter, dental floss, orthonyx braces, or artificial nails.[33]

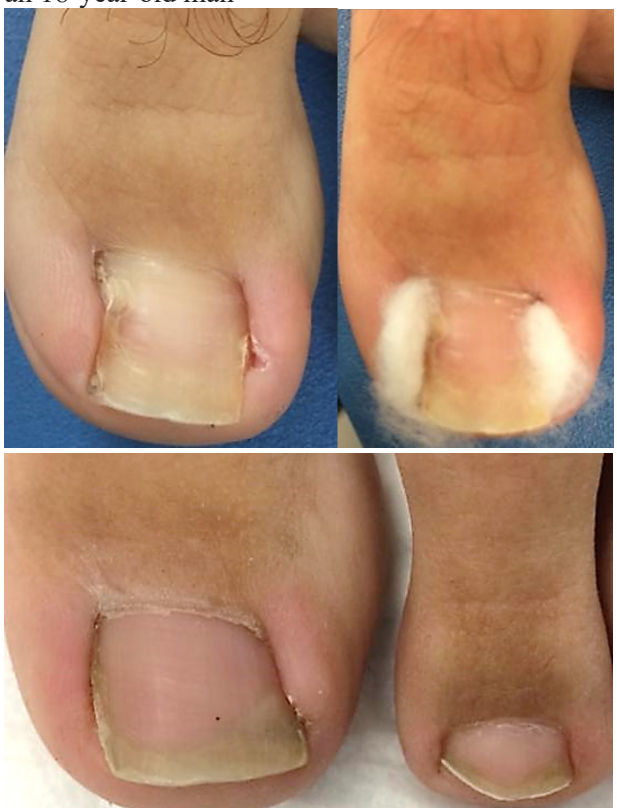
Taping is the simplest way, particularly in the early stage. A tape is firmly applied on the dry skin of the distal portion of the lateral nail fold in order to pull it away from the offending nail margin (Fig. 15). Although this may hurt during tape application the pain disappears almost immediately once the tape is in place. If possible, the tape should be moved under the corner of the nail making the procedure more effective and additionally bringing a buffer between the nail and the soft tissue. The tape is applied daily with increasing pull. Several layers of tape may be applied to anchor the first one.[34]

Figure 15. Early but painful ingrowing. (A) Before; (B) after applying a tape to pull the soft tissue away from the offending nail corner



Packing is the technique of inserting a whisp of cotton under the corner or lateral margin of the nail to keep it away from the soft tissue (Fig. 16). Again, it may hurt when the cotton is inserted but the pain is immediately gone afterwards. This must be repeated until the corner of the nail has overgrown the toe tip. Packing and taping may be combined.

Figure 16. Packing as a treatment for chronic ingrown nail with fibrosis of the lateral nail folds in an 18-year-old man



A "cotton cast" may be inserted on the lateral aspect of the toenail and pressed from the nail to the lateral nail fold thus distancing the fold from the lateral nail margin.[35-36] Gutter treatment comprises the insertion of a gutter over as much of the nail margin length as possible. Usually, a local anesthesia is necessary for this procedure.[37] The gutter may be tailored from the tube of a drip infusion, which is cut lengthwise and moved over the lateral nail margin. It is then fixed by tape, a stitch or acrylic resin.[34]

Artificial nails may be used alone: a thick and long lateral nail margin is modelled so that this overlaps the toe and cannot cut into the sulcus skin anymore.[38] As most ingrown nails have a considerable transverse curvature flattening the curved nail is another approach. There are innumerable different types of nail braces, from plastic bands that are glued on the nail to steel braces that can be readapted. The simplest brace consists of a narrow band of an elastic polymer that is glued onto the lateral margin and then pressed on the medial to lateral third of the opposite side of the nail. Other plastic

bands cover the entire width of the nail. As their force is relatively small, they must be worn for many months to slowly uncurve the nail. More force can be exerted with steel braces. They are hooked under the lateral nail margin and screwed together over the middle of the nail.[39-40] In the course of months the nail will be flatter; however, as the cause of the overcurvature is not tackled the curvature returns within a few weeks to its original shape.

Shape-memory alloy clips are a new approach to uncurve nails.[41] The nail must be cut straight and the clip is pushed over its free margin. In order not to lose the clip it may be fixed with acrylic glue. It slowly unbends the nail. This method has the advantage that the application is not painful.[42]

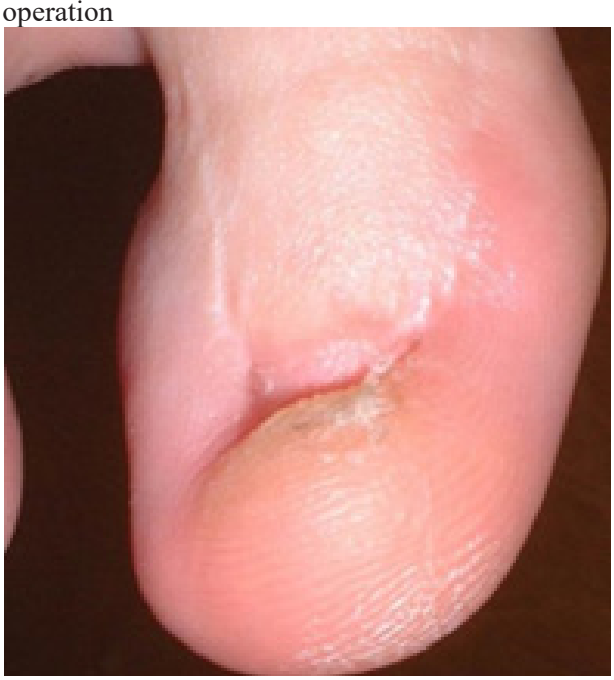
Ideally, conservative therapeutic measures are combined thus enhancing the success rate.[34-43] All these conservative methods require a skilled person to demonstrate the technique and therapy adherence from the side of the patient. Whereas some groups have excellent results[11-34] many others soon gave up and resorted to surgery. Apparently, it is also a question of mentality whether patients are willing to adhere to the noninvasive treatment.[44]

Surgical treatment

Surgery has been the mainstay of ingrown nail therapy since many centuries and innumerable articles deal with a vast variety of different surgical techniques. According to the opinion on etiology and pathogenesis either the nail is made narrower when a wide nail is thought to be responsible for the condition, or the hypertrophic nail fold is reduced or excised if this is thought to be cause. Most of the countless variations of wedge excisions, which excise both a part of the nail bed and the lateral nail fold are wrong in their design and should absolutely be abandoned.

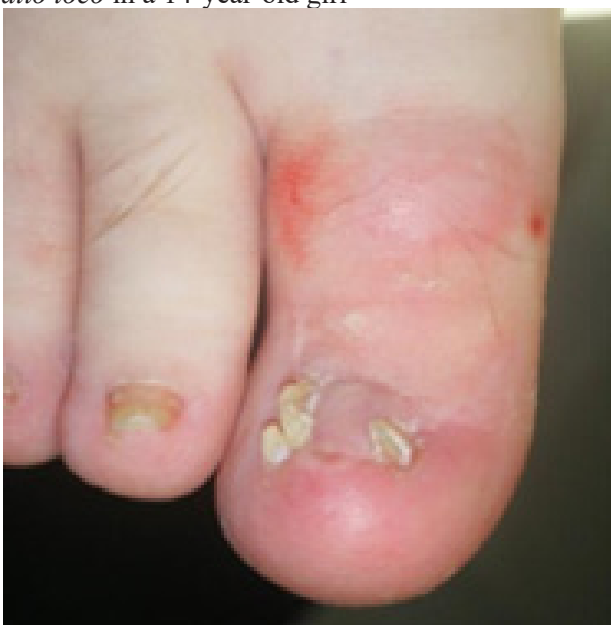
The terminal Syme operation was advocated for chronic ingrown nails. It comprises the amputation of the distal half of the big toe with removal of the matrix and nailbed (Fig. 17).[45] This is a totally inadequate and mutilating method of treating a benign condition for which extremely efficacious, minimally invasive methods exist.[1]

Figure 17. Late result after the terminal Syme operation



Another kind of overtreatment is the Zadik procedure in which the nail matrix is completely excised and the proximal nail fold sutured over the defect as an advancement flap.[46] Both the terminal Syme and the Zadik procedures may leave nail spicules, which is proof of poor surgery (Fig. 18).

Figure 18. Several spicules after Zadik operation *alio loco* in a 14-year-old girl



Nail narrowing methods

As there is a discrepancy between too wide a nail plate and too narrow a nail bed, reducing the nail's width is a logical consequence. Whichever method for the selective lateral/ medial matrix horn removal is used is not critical. It is important to excise, ablate, or cauterize the matrix horn in a manner that no matrix remnants remain, which would give rise to a nail spicule or a recurrence.[1,47] Nail narrowing should not be combined with nail fold excision, thus wedge excisions should not be performed.

Selective nail matrix narrowing

In order to render a wide nail narrower, the lateral or medial matrix horn should be removed. We do not advocate to routinely operate on both sides as this leaves a very narrow and unsightly nail. If one side is narrowed the entire nail has more space and after a short period of conservatively cushioning the lateral nail margin, this will neither be offending nor grow in anymore.

Surgical matrix horn resection is done under sterile conditions and truncal or distal anesthesia. If there is considerable infection an antibiotic prophylaxis may be indicated. The foot is thoroughly disinfected and prepped for the surgery. A tourniquet is applied. Excess granulation tissue is removed with a curette or scissors. The ingrowing lateral nail strip is detached from the nail bed back to the blind end of the matrix, cut longitudinally and avulsed. An oblique or L-shaped incision is made from the junction of the proximal and lateral nail folds in proximal-lateral direction to allow the space of the matrix horn to be opened. An incision is carried out down to the bone at about 5 mm medially from the lateral matrix border and the entire lateral matrix horn is dissected. This is often challenging as it reaches far laterally and proximally.

Care has to be taken to remove the entire matrix horn from the bone. Finally, the incision of the nail fold is closed with either two stitches or suture strips. A bulky padded dressing is applied, and the foot kept up to minimize bleeding and swelling. Postoperative pain is minimal to moderate, but analgesics may be given according to the patient's needs. Healing is fast and the patient can usually return to school or work after 3 days to a week.[49]

The lateral matrix horn may also be destroyed by electrodesiccation. Some radiofrequency device manufacturers offer special insulated spade-shaped electrodes for destruction of the matrix.[50] Conventional electrosurgery is not recommended as it generates too much heat that may damage the underlying periosteum and lead to long-term pain.

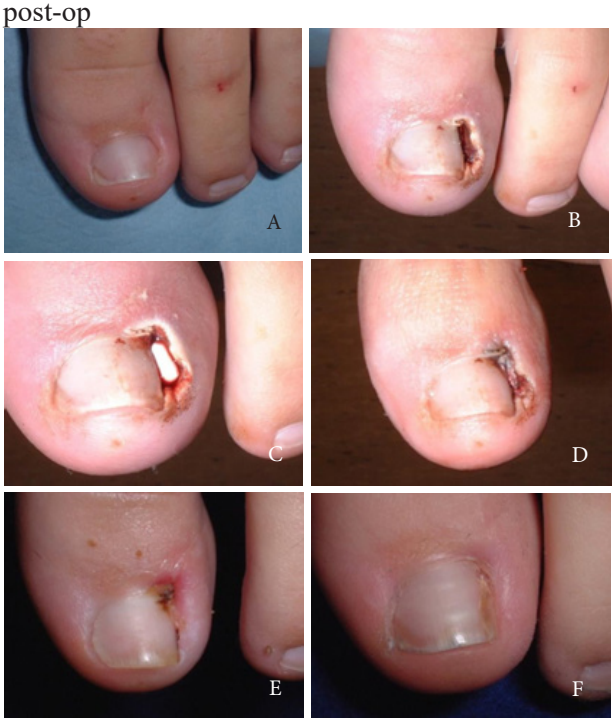
Laser is another option to ablate the matrix. Most commonly, CO2 lasers were used, however, the 1064 nm neodymium-YAG was also used to heat-damage it.[51,52] Chemical matrix horn cautery is now generally used. Which product - phenol, trichloroacetic acid, bichloroacetic acid, sodium hydroxide - is used is not critical provided it is able to necrotize the full thickness of the matrix epithelium. Liquefied phenol is the most widely used nowadays.[53] Phenol has four advantages: It is a strong protein coagulant thus able to necrotize the matrix epithelium; it is a strong disinfectant; it has a neurolytic action; and it is inactivated by blood. This means that we do not need to give antibiotics even in severely inflamed toes, postoperative pain is minimal, and as soon as the tourniquet is opened phenol is "neutralized" rendering "alcohol neutralization" unnecessary.

Phenol matrix horn cauterization, also called phenolization, is a simple, time-honoring method with the lowest recurrence rate of all surgical methods. After complete anesthesia and application of a tourniquet, the lateral nail strip is avulsed. Excess granulation tissue may be curetted. A small cotton ball dipped into liquefied phenol is vigorously rubbed into the bloodless matrix horn under the proximal nail fold for 3 to 4 minutes; we use a fresh cotton with phenol 4 times for a minute each. Excess phenol is wiped away. The tourniquet is opened after the 4-min phenol application. If available small tapered antibiotic tablets containing

framycetin (Leukase®-Kegel) may be inserted into the wound cavity; they keep the wound open and allow the postoperative drainage to escape (Fig. 19). A circular dressing with a petrolatum-based ointment is applied for 24 hours, which is changed after a day.

The patient is asked to elevate the foot for 48 hours as this minimizes postoperative swelling, bleeding, and pain. The postoperative care consists of once – or if in hot climate – twice daily rinsing the wound under a jet of tap water. This considerably shortens the healing time, prevents postoperative infection, and oozing. The patients can resume their daily activities within a few days as there is no risk of wound dehiscence. Rubbing the phenolized matrix with 20% ferric chloride at the end of the procedure shortens the period of drainage.[54]

Figure 19. (A) Right big toenail with broken lateral distal nail corner causing considerable pain though inflammation is barely visible. (B) Immediately after phenolization. (C) End of the phenolization procedure with Leukase® tablets put into the lateral matrix horn and the small wound. (D) 24 hours postoperatively. (E) 3 weeks post-op. (F) 8 weeks post-op



Another option is to use 85 -100% trichloroacetic acid for 1 - 3 minutes.[55] It is said to cause even less postoperative pain and oozing; however, a comparative study did not show a more rapid healing than phenol.[56] Recently, also bichloroacetic acid was used instead of TCA.[57] However, bichloroacetic acid continues to penetrate if its action is not stopped by either rinsing or neutralizing it.

Sodium hydroxide is another chemical to cauterize the matrix horn; in contrast to the aforementioned substances, it is an alkaline chemical. It is used for either 2 min or 1 min after curettage of the matrix. Both regimens were well tolerated and yielded the same good results.[58] A recent literature meta-analysis, however, found that there was no significant difference in the recurrence rate between NaOH and placebo.[59]

Reduction of periungual soft tissue

Some nail surgeons consider a narrow nail plate a cosmetic disadvantage. They propose to reduce or completely excise the lateral nail fold. Depending on the amount of surplus soft tissue this may be done as a limited excision or as a radical removal.[60]

If the nail fold hypertrophy is mild to moderate a fusiform excision from the lateral aspect of the distal phalanx may be performed. Upon suturing the fold is reduced and pulled away from the offending lateral nail margin.[61] Another possibility is to do a large and deep excision to remove a big volume of the soft tissue; the wound may then be sutured.[62]

Quite often, the lateral distal portion of the nail digs into the soft tissue, which forms a bridge from the lateral fold to the hyponychium. This is usually the result of a nail corner cut too short. A small banana-like excision may pull this false extension of the lateral nail fold down. The small defect may be stitched with 2-0 sutures that are knotted up to ten times. This maxi-knot is placed under the nail corner elevating it and allowing the nail to grow over this obstacle.[63]

The Vandenbos technique removes both nail folds starting about 5 mm in the lateral aspect of the proximal nail fold and excising the lateral

fold as a large soft tissue wedge down to the middle of the lateral distal phalanx and distally to the hyponychium including one third of it. This is done on both sides thus about one third of the toe's circumference is removed and only the central third of the hyponychium is left. The large wound heals by secondary intention, which may take 4 – 6 weeks. The aesthetic result is usually good. The recurrence rate is lower than that of Winograd's wedge resection.[64]

Similar though even more radical is the super U technique. The lateral nail folds and the hyponychium are generously cut away freeing three sides of the nail. The wound is left for second intention healing, which takes several weeks. There is a risk of a parrot beak nail deformity because of shrinking of the hyponychial scar.[65]

It is beyond the scope of this short review to mention all reported variations of the methods described in the literature. The understanding of the pathomechanism is the basis for all treatments. Radical surgeries like the terminal Syme operation, Zadik procedure or most wedge excisions are obsolete and demonstrate that the surgeon does not understand the condition.

Complications

Complications of ingrown nails are infection, pain, disability to walk and serious impairment of all physical activities.

Postoperative complications may be wound infection, particularly after scalpel surgery. This is the reason why many general surgeons routinely administer antibiotics. It is usually not necessary for phenol matrix horn cautery. This method is also blessed by minimal postoperative pain.

Potential long-term and permanent complications of ingrown nail surgery are nail dystrophy, deviation of the nail toward the operated side, and toe mutilation (Figs. 20 & 21).

Figure 20. Result of bilateral wedge excisions with nail avulsions for ingrown nails in a 39-year-old woman

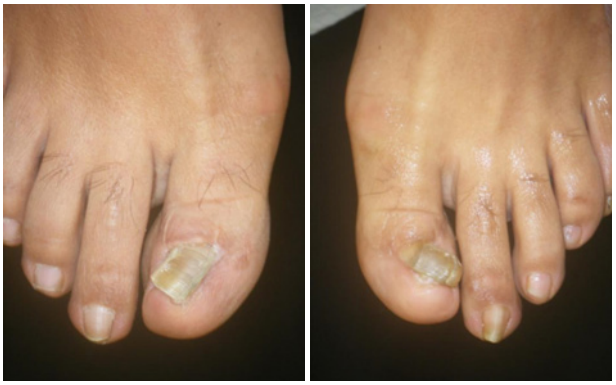
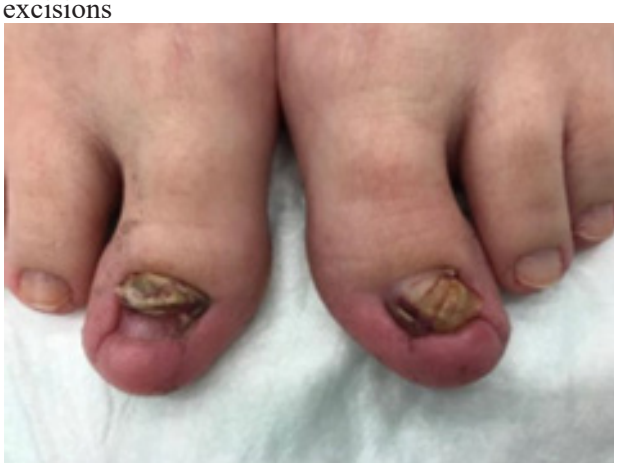


Figure 21. Nail dystrophy after bilateral wedge excisions



Recurrence

Recurrences after treatment of ingrown nails are common. Unfortunately, ingrown nail surgery is delegated in many surgery departments to young and unexperienced staff.[66] They do their surgical operations often without surveillance of experienced specialists and thus believe it is correct what they do. This poor surgery is then taken as routine with both poor to catastrophic results and very high recurrence rates. Even textbooks of "minor surgery" display wrong incision lines for wedge excisions that virtually invite recurrences as the authors of such books apparently do not know the anatomy of the matrix of the big toe.

With properly executed phenolization the recurrence rate is between 1 – 3% whereas publications on wedge excisions mention recurrences in 25 – 50% or even more.[67]

Ingrown nail patients should not be left alone after surgery. A follow-up after 3 – 6 months and another one after a year is important to recognize any imminent recurrence or complications and demonstration of what to do in such a case are crucial.

Conclusion

Ingrown toenails are frequent conditions, particularly in youngsters. They may considerably impair the quality of life due to pain and restrictions of physical activities. Their treatment should be initiated as soon as possible as early stages are usually amenable to conservative therapy. Prevention is often easy with correct nail trimming, avoidance of inadequate footwear and prevention of soggy feet. Conservative modalities are varied with taping, packing, gutter placement, orthonyxia braces, shape-memory alloy clips, and many more methods. They require some dexterity and above all compliance.

If conservative methods are not successful surgery is indicated. Of the many approaches, selective matrix horn removal, either surgically or by chemocautery, is the treatment of choice. Soft tissue resection takes weeks to heal but usually gives good results.

Conflict of Interest Declaration

The author have no conflict of interest to declare.

Acknowledgement

Nil

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ORIGINAL ARTICLE

A Prospective Cohort Study of Laboratory Abnormalities During Isotretinoin Treatment For Acne Vulgaris

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Abstract

Background

Acne vulgaris is a chronic inflammatory condition of the pilosebaceous unit. Isotretinoin is used to treat moderate to severe acne that is resistant to antibiotics and topical agents. However, it may cause alterations in lipids and liver enzymes.

Methods

A total of 129 patients with acne vulgaris (moderate to severe facial acne) treated with isotretinoin were recruited between May 2020 and July 2021 from the dermatology clinics at Hospital Serdang and Hospital Kuala Lumpur. Of these, 120 patients with complete data of lipid panel (total cholesterol, low density lipoprotein cholesterol [LDL], triglycerides [TG], and high density lipoprotein cholesterol [HDL]) and hepatic panel (alanine transaminase [ALT] and aspartate transaminase [AST]) levels at baseline, and in three subsequent follow-up visits (i.e., one, three, and six months) were included in the analyses. Abnormalities were graded according to standard laboratory values and their severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE)grading system.

Results

Of the 120 study participants, 83% were female and 37% were male between the ages of 15 and 36 years. We observed a significant increase in median values at baseline and at the six-month follow-up for total cholesterol ($p<0.0001$), triglycerides ($p<0.0001$), LDL ($p<0.0001$), ALT ($p<0.0001$), and AST ($p<0.0001$). We observed a significant correlation between body mass index and the HDL ($r^2=-0.26$, $p=0.01$) and ALT ($r^2=0.383$, $p=7.9x10\text{-}06$) levels. Based on the CTCAE grading system, almost all study participants with abnormal results had grade 1 abnormalities. Only one patient had a grade 2 abnormality in ALT, which required treatment discontinuation.

Conclusion

Low dose isotretinoin therapy for acne vulgaris may cause mild and non-progressive elevation of LDL, total cholesterol, and liver transaminases which do not require treatment withdrawal in most cases.

Key words: *Acne vulgaris; Isotretinoin; Lipid profile; liver transaminases*

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Introduction

Acne vulgaris is the formation of comedones, papules, pustules, nodules, and/or cysts as a result of obstruction and inflammation of pilosebaceous units (hair follicles and their accompanying sebaceous glands).[1] Acne vulgaris can be classified as non-inflammatory (characterized by comedones) and inflammatory (characterized by papules, pustules, nodules, and cysts).[2]

An estimated 9.4% of the global population is affected by acne, making it the eighth-most prevalent disease worldwide.[3-5] Approximately 80% of people are affected by acne between the onset of puberty and 30 years of age.[4] In the local scenario, a study conducted among medical students aged 19-25 years at Hospital University Kebangsaan Malaysia between 2011 and 2012 showed that the prevalence of acne was 68.1%, with a comparable ratio of males to females (1:1.1).[6]

Isotretinoin or 13-cis-retinoic acid (i.e., a synthetic analogue of vitamin A) is recommended for the treatment of severe inflammatory acne of the nodulocystic or conglobate types and for cases of acne vulgaris with evidence of resistance to previous treatments with antibiotics or topical medication. Isotretinoin acts on the sebaceous glands by binding to specific retinoid receptors, modifying gene transcription.[7] It reduces the activity and size of the gland, decreasing the quantity of sebum it produces and reducing the number of Cutibacterium acnes.[7] It produces a significant reduction in comedogenesis by decreasing hyperkeratinization.[8]

Isotretinoin also may cause clinical side effects and laboratory changes, the most important being teratogenicity.[9] Mucocutaneous side effects include cracked lips, dryness of the skin and nasal mucosa, skin redness, eye dryness, and eye irritation.[3,10]

Isotretinoin treatment may increase liver transaminases (alanine aminotransferase, ALT and aspartate aminotransferase, AST), serum triglycerides (TGs), and low-density lipoproteins (LDL) cholesterol and reduce the level of high-density lipoprotein (HDL) cholesterol.[10,13] Abnormalities in serum lipid levels were common during isotretinoin therapy, while abnormalities in transaminase levels were less common and generally mild.[13] High levels of TGs and low levels of HDL cholesterol are risk factors for coronary heart disease and ischaemic stroke.[13] Isotretinoin causing drug-induced pancreatitis through hypertriglyceridemia has been reported but is rare.[14]

There are very limited data on changes in the liver enzymes and lipid levels among isotretinoin users in Malaysia. Laboratory monitoring of serum lipids and liver function tests are also at the discretion of the physician, and there is wide variation in the type and frequency of monitoring that is performed. The aim of this study was to evaluate alterations in lipid parameters (i.e., total cholesterol, TG, LDL, HDL) and liver transaminases (i.e., AST and ALT) in acne vulgaris patients treated with low dose isotretinoin.

Materials and Methods

This was a prospective cohort study conducted between May 2020 and July 2021 in the dermatology clinics of Hospital Kuala Lumpur and Hospital Serdang.

Using the two population means formulae, paired t-test (published mean of ALT at three months=18.2 (±4.59), published mean of ALT at six months=23.3 (±20.23), α-value=0.05, power of statistical test=80%, confidence level=95%, four follow-up visits, and consideration of 20% dropout rate), the calculated sample size was 117 study participants. A total of 129 eligible study participants diagnosed with acne vulgaris (moderate to severe) who did not respond to combined therapy (i.e., topical, and systemic treatment) were screened and recruited. Of these, 120 participants completed the study.

Participants were briefed about the study and their written consent was obtained by the clinicians. Acne vulgaris patients with the

following conditions were excluded from the study: i) pregnant or planning for pregnancy, ii) history of hypersensitivity reactions to isotretinoin, iii) pre-existing liver disease, iv) hematological disorders, or v) receiving isotretinoin therapy for conditions other than acne.

The severity of acne in the study participants was assessed and determined using the Comprehensive Acne Severity Scale criteria.[2] A standardized data collection form was used to collect sociodemographic data as well as the laboratory biochemical tests of lipid profile (i.e., total cholesterol, TG, LDL, and HDL) and liver transaminases (i.e., ALT and AST) at recruitment (baseline). Patients were followed up at three different visits, i.e., at one month, three months, and six months. At each follow-up visit, the patients were assessed by their treating clinicians, and the isotretinoin dose was adjusted, whenever necessary, according to the standard clinical practice at both study sites.

Blood was also drawn from patients to quantify lipid profile and liver transaminases. Outcomes were recorded based on standard laboratory values and their severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grading system.[16]

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Malaysian Good Clinical Practice Guidelines. Ethical approval was obtained from the Medical Research and Ethics Committee of the Malaysian Ministry of Health [KKM/NIHSEC/P20-925(12)].

Descriptive statistics were performed to describe the characteristics of the study population and data set. Numerical values were presented as mean and standard deviation (SD) or median and interquartile range (IQR), while categorical variables were presented as absolute number and percentage. The Friedman test, a nonparametric alternative to the one-way ANOVA with repeated measures, was used to test for median differences in lipid profiles and liver transaminases between different clinical visits. The Spearman correlation test was performed to investigate the correlation between lipid profile and liver transaminases and ody mass index (BMI). Results with $p<0.05$ were considered statistically significant. All data analyses were performed using IBM SPSS Statistics for Windows version 21.0.

Results

Nine study participants defaulted follow-up, hence excluded from the data analyses. Of the 120 remaining participants, 83 (69.2%) were female and 37 (30.8%) were male, with ages ranging between 15 and 36 years. Of the 120 participants, 36 (30%) were overweight and obese, while only three individuals (2.5%) had comorbidities. Eighty-six patients (71.7%) were diagnosed with moderate acne and 34 (28.3%) with severe acne, with the mean duration of acne being 6±4.20 years.

All the study subjects were treated with low doses of isotretinoin ranging from 0.2 to 0.4 mg/kg, with daily doses of between 10 to 30 mg daily, which is the standard clinical practice at the study sites (see Table 1). Our data showed that 89.2%, 65%, and 80.8% of participants were treated with the lowest isotretinoin dose of 10 mg daily at baseline, which was continued at first and third months of follow-up, respectively till 6th month of treatment (Table 1).

A total of 107 patients received 10 mg daily during the first month. At the second follow-up, the dose was increased to 20 mg daily in 28 (26%) of the patients for the subsequent 2 months. At the third follow-up, the treatment dose was reduced back to 10 mg daily in 14 (50%) of the 28 patients for the final 3 months. These adjustments were based on the clinical responses and the biochemical test results (i.e., lipid profile and liver transaminase).

Table 1. Patient characteristics and isotretinoin doses on repeated follow-up

Variables (n=120)		Mean±SD	n (%)
Age 15-25 26-29 30-36		23±5.0	 96 (80) 13 (11) 11 (9)
Sex Male Female			 37 (30.8) 83 (69.2)
Ethnicity Malay Chinese Indian Others			 110 (91.7) 6 (5.0) 2 (1.7) 2 (1.7)
Body Mass Index (kg/m^2) Healthy (18.5-24.9) Overweight (25.0-29.9) Obese (≥30.0)		22.9±3.96	 84 (70.0) 29 (24.2) 7 (5.8)
Comorbidities Absent Present			 117 (97.5) 3 (2.5)
Severity of acne Moderate Severe			 86 (71.7) 34 (28.3)
1st treatment with isotretinoin 2nd treatment with isotretinoin			118 (98.3) 2 (1.7)
Duration of acne (years)			6 ± 4.20
Isotretinoin dose (mg) at 1st month (1st visit)	10		107 (89.2)
	20		12 (10.0)
	30		1 (0.8)
Isotretinoin dose (mg) at 2nd and 3rd month (2nd visit)	10		78 (65.0)
	20		41 (34.2)
	30		1 (0.8)
Isotretinoin dose (mg) at 4th-6th month (3rd visit)	10		97 (80.8)
	20		22 (18.3)
	30		1 (0.8)

Lipid profile and liver transaminase

Our data demonstrated significantly higher levels of the total cholesterol, TG, and LDL, but not the HDL, at the six-month follow-up when compared with the baseline. Likewise, a significant increasing trend was observed in the liver transaminases, i.e., ALT and AST as shown in Table 2.

We further compared the incidence of abnormal laboratory parameters (i.e., lipid profiles and liver transaminase) at baseline and in each follow-up visit. Since the majority of our patients (n=107) were prescribed the lowest dosage (10mg) of isotretinoin at baseline, our analysis of the incidence of abnormal laboratory parameters included only these study participants. In addition, we investigated whether dose adjustment at different clinical visits affects the incidence of abnormal laboratory parameters. Interestingly, we observed a significant increase in the incidence of abnormal LDL from 65.4% to 81.3% ($p<0.05$) (see Table 3).

Table 2. Effects of oral isotretinoin on repeated measures of lipid profiles and liver transaminases

Laboratory variable	Baseline Median (IQR)	1st month Median (IQR)	3rd month Median (IQR)	6th month Median (IQR)	*p-value*
Total cholesterol	4.8 (1)	4.9 (1)	5.1 (1)	4.9 (1)	<0.001
Triglycerides	0.8 (0.5)	0.8 (0.5)	0.9 (0.5)	0.9 (0.5)	<0.001
LDL	2.98 (0.9)	3.1 (0.8)	3.1 (0.7)	3.1 (0.7)	<0.001
HDL	1.4 (0.4)	1.4 (0.3)	1.4 (0.4)	1.4 (0.4)	0.656
ALT	12 (10)	12 (9)	14 (11)	15 (12)	<0.001
AST	18 (5)	19 (6)	20 (7)	20 (6)	<0.001

Although increasing trends of abnormal incidence were observed for total cholesterol, TGs, HDL, ALT and AST, these were however nonsignificant. We further observed that, of the 28 participants prescribed with an increment of isotretinoin dosage at the 1st-month follow-up visit (from 10 mg daily to 20 mg daily), half of these participants (n=14, 50%) were adjusted to the initial starting dosage of 10 mg at the 3rd month by the treating clinicians based on the clinical observations and laboratory findings (see Table 3).

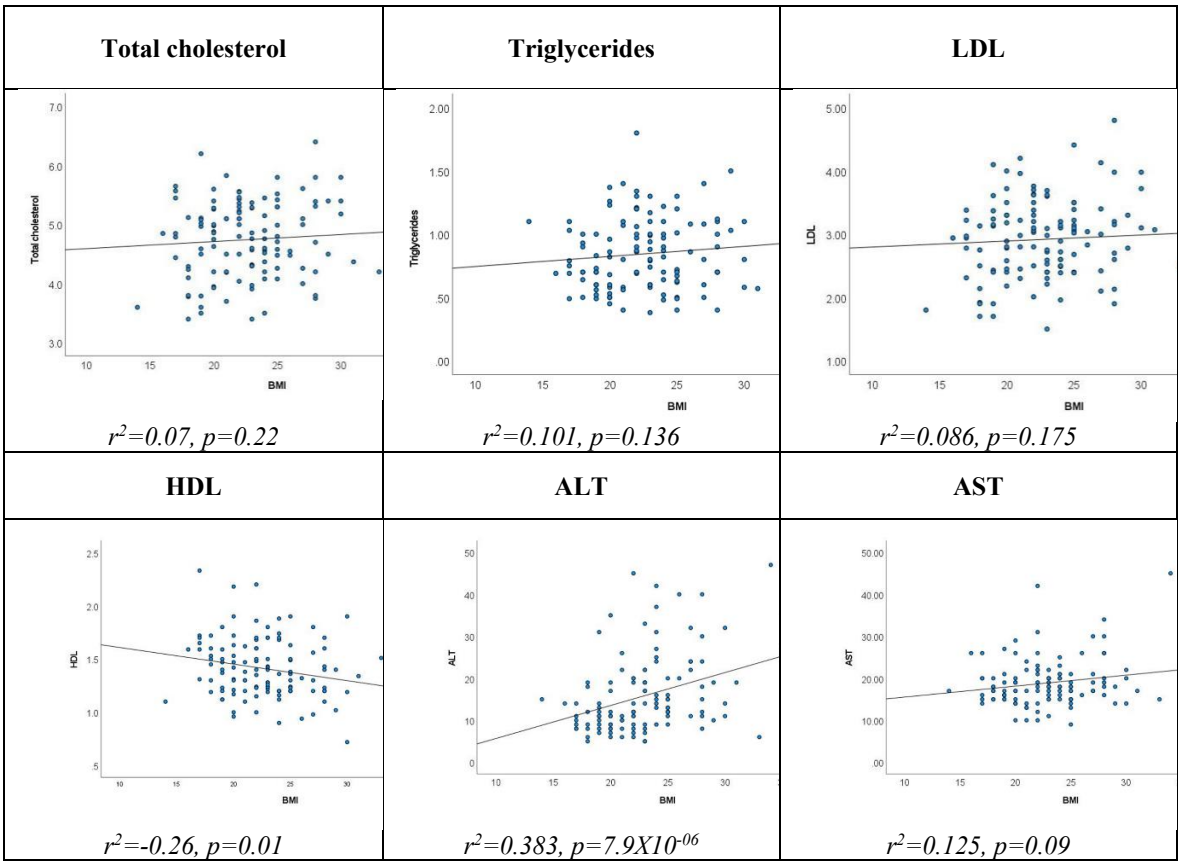
We then investigated the relationship between body mass index (BMI) and the baseline laboratory parameters, i.e., lipid profile and liver transaminases, which were quantified. Our data showed a significant negative correlation between BMI and HDL level ($r^2=-0.26$, $p=0.01$), indicating the higher the BMI of the participants in this study cohort, the lower the HDL level. On the other hand, we observed a positive correlation between BMI and ALT ($r^2=0.383$, $p=7.9X10^{-06}$).

Table 3. Incidence of acne vulgaris patients with abnormal levels of lipids and liver transaminase parameters

Biochemistry Test	Baseline		1st month		3rd month			6th month		
	Normal (n, %)	Abnormal (n, %)	Normal (n, %)	Abnormal (n, %)	Dose adjustment	Normal (n, %)	Abnormal (n, %)	Dose adjustment	Normal (n, %)	Abnormal (n, %)
Total Cholesterol	79 (73.8)	28 (26.2)	72 (67.3)	35 (32.7)	Overall	65 (60.7)	42 (39.3)	Overall	65 (60.7)	42 (39.3)
					10 mg daily	48 (73.8)	30 (71.4)	10 mg daily	54(83.1)	34 (81)
					20 mg daily	17 (26.2)	11 (26.2)	20 mg daily	11(16.9)	8(19)
					30 mg daily	0 (0)	1 (2.4)	30 mg daily	0	0
TG	107 (100%)	NA	105 (98.1)	2 (1.9)	Overall	105 (98.1)	2 (1.9)	Overall	105 (98.1)	2 (1.9)
					10 mg daily	77 (73.3)	1 (50)	10 mg daily	87(82.9)	1(50)
					20 mg daily	27 (25.7)	1 (50)	20 mg daily	18(17.1)	1(50)
					30 mg daily	1 (1)	0	30 mg daily	0	0
LDL	37 (34.6%)	70 (65.4) *	25 (23.4)	82 (76.6) *	Overall	20 (18.7)	87 (81.3) *	Overall	20 (18.7)	87 (81.3) *
					10 mg daily	16 (80)	62 (71.3)	10 mg daily	17(85)	71(82)
					20 mg daily	4 (20)	24 (27.6)	20 mg daily	3(15)	16(18.4)
					30 mg daily	0	1 (1.1)	30 mg daily	0	0
HDL	28 (26.2%)	79 (73.8)	24 (22.4)	83 (77.6)	Overall	26 (24.3)	81 (85.7)	Overall	26 (24.3)	81 (75.7)
					10 mg daily	20 (76.9)	58 (71.6)	10 mg daily	22 (84.6)	66 (81.5)
					20 mg daily	6 (23.1)	22 (27.2)	20 mg daily	4 (15.4)	15 (1.2)
					30 mg daily	0 (0)	1 (1.2)	30 mg daily	0 (0)	0 (0)
ALT	105 (98.1)	2 (1.9)	112 (95.3)	5 (4.7)	Overall	100 (93.5)	7 (6.5)	Overall	100 (93.5)	7 (6.5)
					10 mg daily	73 (73)	5 (71.4)	10 mg daily	82 (82)	6 (85.7)
					20 mg daily	26 (26)	2 (28.6)	20 mg daily	18 (18)	1 (14.3)
					30 mg daily	1 (1)	0 (0)	30 mg daily	0 (0)	0 (0)
AST	106 (99.1)	1 (0.9)	116 (99.1)	1 (0.9)	Overall	106 (99.1)	1 (0.9)	Overall	106 (99.1)	1 (0.9)
					10 mg daily	77 (72.6)	1 (100)	10 mg daily	87 (82.1)	1 (100)
					20 mg daily	28 (26.4)	0 (0)	20 mg daily	19 (17.9)	0 (0)
					30 mg daily	1 (1)	0 (0)	30 mg daily	0 (0)	0 (0)

*Statistically significant increase in the incidence of abnormal level of LDL at 6th month compared with baseline

Figure 1. Correlation between baseline lipid profile and liver transaminase with BMI



Discussion

Our study explored the changes in liver enzymes (AST and ALT) and lipid profile (total cholesterol, TG, LDL, and HDL) during typical treatment with oral isotretinoin over a six-month period. This study showed a statistically significant increase in total cholesterol, LDL, TG, and liver transaminases (ALT and AST). Liver enzymes were less affected by isotretinoin therapy than lipid profiles. No significant changes were observed in HDL. Several studies evaluating the effects of isotretinoin on liver enzymes and lipids suggest that oral isotretinoin may cause changes to varying degrees, alterations in liver transaminases (AST and ALT), and lipid profiles (particularly TG, LDL, and total cholesterol).[1,4] Many studies suggest that isotretinoin use is associated with increases in TG and LDL and decreases in HDL levels.[8,10,14]

Zane et al. studied 13,772 patients with acne who received oral isotretinoin therapy between 1995 and 2002. They reported a cumulative incidence of new abnormalities in patients with normal baseline values with a frequency of 44% for TG, 31% for total cholesterol levels, and 11% for transaminase levels. Moreover, these abnormalities were generally transient and reversible.[11] Most studies show a moderate increase in serum lipids (but a decrease in HDL) in a minority of patients, usually occurring at baseline and plateauing or declining in subsequent weeks.[15]

Our study supports these findings. However, this study is limited to observation of treatment over a 6-month period, so the subsequent consequences of abnormalities in test results at the end of treatment could not be evaluated. Interestingly, most abnormalities were observed in the first 3 months of treatment, with no further changes toward the end of treatment. Of the study participants with abnormal results, almost all had grade 1 abnormalities in both lipids and liver transaminases (based on CTCAE grading). Only one patient developed a grade 2 abnormality at ALT, which required treatment discontinuation. The abnormalities

in this cohort were generally mild and did not require treatment interruption.

Although many studies have reported significant changes in total cholesterol and TG and liver transaminases, other studies have reported that these adverse effects are minimal and do not affect the course of treatment.[17] Alcalay et al studied 907 patients who had completed five to nine months of treatment. They reported that only 1.5% of patients had serum TG levels above 400 mg/dL. Serum levels of liver enzymes were not sufficiently elevated to a degree necessitating discontinuation of treatment.[18] In addition, Brito et al conducted a prospective clinical and laboratory evaluation of 150 patients treated with oral isotretinoin before initiation of therapy, one month after initiation, and every three months thereafter until completion of treatment. They found no statistically significant changes in liver transaminases, TG, or cholesterol levels.[1] In another study of 30 participants, Baxter et al also reported no significant changes in TG or cholesterol levels measured at baseline or during.[19]

All our patients received an isotretinoin dose of 0.2-0.4 mg/kg, with 89.2% (n=107) of the patients receiving an isotretinoin dose of 10 mg at baseline. In approximately 42% of the study participants, the dose was increased during the first 3 months of treatment. A statistically significant increase in abnormal LDL levels ($p<0.05$) from baseline to follow-up at month 6 was observed in most participants who received a 10 mg dose at baseline. Increasing trends in the occurrence of abnormalities were also observed for total cholesterol, TGs, HDL, ALT, and AST, but these were not significant. The low isotretinoin dose used for clinical treatment in this cohort may be a contributing factor to the mild biochemical changes and better tolerability in patients. A study by Bettoli et al. showed that a low initial dose of 0.1-0.2 mg/kg/day, or about 10 mg daily, and a gradual increase to the highest dose tolerated by the patient, is a successful way to achieve good clinical results while minimizing side effects compared with a standard dose of 0.5 mg/kg/day.[20]

Approximately 27.5%, 79%, and 74% of study participants had abnormal baseline total cholesterol, LDL, and HDL, respectively. Our data showed that 30% of the study participants fell into the overweight and obese category (BMI). This study was conducted during the Covid pandemic, in which most people had a sedentary lifestyle compared with the pre-pandemic period. This may have contributed to the unhealthy BMI and lipid abnormalities at baseline. However, changes in BMI and its correlation with blood levels were not studied during the six-month follow-up period. These participants also had a negative correlation between BMI and HDL (the higher the BMI, the lower the HDL). Significantly low HDL levels accompanied by high LDL levels and an unhealthy BMI at baseline suggest a potential risk for metabolic syndrome and cardiovascular disease. A positive correlation between BMI and ALT in this study may indicate the risk of fatty liver in participants. Close monitoring of lipid profile and liver enzyme parameters is particularly important in patients at high risk of developing metabolic syndrome.

Although our study demonstrated statistically significant increases in total cholesterol, LDL, TG, ALT, and AST, they are clinically insignificant as low-dose isotretinoin was well tolerated by the study participants. Nevertheless, lipid profiling and liver function tests should be routinely performed in all patients starting treatment with isotretinoin. This should be followed by repeat blood testing after two months. If repeat test results are normal after two months, further laboratory monitoring may not be necessary. If abnormalities are present, or a higher dose adjustment is required, more frequent monitoring is recommended.

Limitations

Low-dose isotretinoin was used in this study with most patients receiving 0.2-0.3 mg/kg. This may explain the mild changes observed in liver transaminases and lipid panels. This study was conducted in the Klang Valley area only, hence the results may not represent the whole

population of Malaysia.

Conclusion

Low-dose isotretinoin therapy for acne may cause mild and non-progressive elevation of LDL, total cholesterol, and liver transaminases which do not require the withdrawal of treatment in most cases.

Conflict of Interest Declaration

The author have no conflict of interest to declare.

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ORIGINAL ARTICLE

Impact of Psoriasis on Quality of Life of Family Members and Its Association with Anxiety and Depression

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Abstract

Background

Psoriasis is a chronic immune-mediated, multisystem inflammatory skin disease that can profoundly impact the quality of life (QoL) of both patients and their families. This study aimed to analyse the impact of psoriasis on the QoL of patients' family members and its association with anxiety and depression.

Methods

This was a cross-sectional study which had a total of 240 subjects (80 patients, 80 family members, and 80 healthy controls). The Dermatology Life Quality Index (DLQI) questionnaire was used to evaluate the QoL of patients, and the Family Dermatology Life Quality Index (FDLQI) questionnaire was used to assess the QoL of family members. In addition, the Hospital Anxiety and Depression Scale (HADS) was used to evaluate the state of anxiety or depression of all subjects, including the healthy controls.

Results

Up to 82.5% of family members of psoriasis patients had impaired QoL (FDLQI ≥2). The mean DLQI was 8.89±7.58, whereas the mean FDLQI scores was 7.58±6.09, showing the considerable impact of psoriasis on both patients and family members' quality of life. There was a positive correlation between family members' QoL with patients' anxiety (r_s=0.348; p=0.002) and depression (r_s=0.276; p=0.013) level. However, no association was found between family members' QoL with patients' psoriasis severity (r_s=0.173; p=0.126) and the DLQI scores (r_s=0.137; p=0.224). Based on the HADS, the mean anxiety scores was 5.29±4.07 and the mean depression scores was 4.54±4.20 for family members. An anxiety disorder was suggested in 32.5%, while depression was suggested in 23.8% of family members.

Conclusion

Psoriasis has a significant impact on both patients and their family members, who experienced impairment of their QoL and higher levels of anxiety and depression.

Key words: *DLQI; FDLQI; HADS; psoriasis; quality of life*

Introduction

Psoriasis is a chronic, immune-mediated, multisystem inflammatory disease with variable prevalence among populations, affecting between 0.5 to 11.4 percent among adults.[1-3] It is characterised by well-demarcated erythematous and scaly papules and plaques that are usually accompanied by burning sensation, pain and itching. Patients with disfiguring psoriasis plaques over visible or

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sensitive areas of the body, may encounter a high level of stigmatisation, social isolation and psychological distress.[4-6] This substantially compromise their social functioning, personal relationship, work, daily activities, and health-related quality of life (QoL), especially in those with moderate-to-severe disease.[7]

Furthermore, the negative impact of psoriasis has been shown to extend beyond the patients into their families. Family members often experience physical and mental exhaustion, social disruption, marital problems and financial implications in their lives due to the chronic nature of psoriasis.[8] Numerous studies have examined the influence of psoriasis on the quality of life and psychosocial health of patients.[9-12] However, the studies that have analysed the secondary impact on individuals living with psoriatic patients are limited.[13-18]

There was a higher level of anxiety and depression among individuals living with psoriatic patients. Research studies had shown that the severity of psoriasis disease was not the main factor that contributed to the mental impairment among family members.[19] Instead, the extent of their psychological distress was mainly related to the level of psychological distress of the patients.[13-14] Family quality of life and psychosocial health is considered an essential factor in patient management and should be analysed additionally to the quality of life of the patients.[13] Nevertheless, clinicians usually overlook this for various reasons, including time limitation and difficulty in assessing it. Data on the impact of psoriasis on the quality of life of their family members in Malaysia was also not well-established, and it has not received much attention yet.

Therefore, this study aimed to analyse the impact of psoriasis on the quality of life of family members of psoriatic patients, to assess the potentially related factors and to explore the impact of psoriasis on family members' mental health.

Materials and Methods

Study Design and Subject Selection

This was a cross-sectional, questionnaire-based study conducted at the dermatology clinic in Selayang Hospital, Malaysia, from June 2020 to January 2021. We analysed three groups: patients with psoriasis, patients' family members, and healthy controls.

Patients

Male and female patients were eligible for this study if they met the following criteria: aged 18 years old and above, could give informed consent and had a clinical diagnosis of plaque psoriasis for at least 6 months. Patients were excluded if they had another dermatological disease, severe medical or psychiatric disorders that might influence their judgment or QoL.

Family members

Family members enrolled in this study were usually first degree relatives aged 18 years old or older, who were the main caregivers and stayed with patients for the past year. Most patients had a single caregiver. However, in the event of multiple caregivers, one of them was randomly selected for the study. Family members with dermatological diseases, severe medical or psychiatric disorders that might influence their judgment or QoL were excluded.

Healthy controls

Controls were healthy subjects with no personal or family history of psoriasis (in a first-degree relative) or other dermatological diseases. Also, they were age-and-sex matched to family members. They were mainly healthcare staffs or their family members. They were excluded if they had other medical illnesses and psychological problems, that might influence their overall psychological health.

Study Procedures

Patients who were clinically diagnosed with plaque psoriasis were approached along with a family member. The detailed information regarding the study was given by the clinical investigators. Eligible patients' medical records were reviewed by investigators to verify the

diagnosis of psoriasis and duration of disease. After consent, each subject's demographics, including age, sex, occupation, marital status, and level of education were gathered and recorded. This step was followed by an assessment of disease severity by using the psoriasis area and severity index (PASI). The impact of psoriasis on the QoL of the patients was determined by using the 10-item Dermatology Life Quality Index (DLQI). The impact of psoriasis on the QoL of family members was measured with the Family Dermatology Life Quality Index (FDLQI). The Hospital Anxiety Depression Scale (HADS) was used to evaluate the state of anxiety or depression of all subjects, including the healthy controls.

Disease Severity Assessment

Psoriasis area and severity index(PASI)

The PASI was used to measure of the physical severity of psoriasis. Skin lesions are graded based on the extent and character of psoriasis (i.e. erythema, induration, and scaling) and provides a severity score ranging from 0 to 72.[20-21] A score of less than 10 suggest mild psoriasis, while 10-20 and >20 indicating moderate psoriasis and severe psoriasis, respectively.

Quality of Life Instruments

Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item questionnaire validated to evaluate the health-related quality of life of adult patients suffering from skin diseases.[22-24] Published in 1994, the DLQI was the first dermatology-specific quality of life questionnaire. This questionnaire asks about the impact of skin disease on symptoms, self-perception, shopping, clothing choice, social activity, physical activity, working/studying, personal relationships, sexual functioning, and treatment. With this questionnaire, patients define how much their skin disease has affected their life, with the scoring for each item ranging from "not at all" to "very much". Each response is scored on a scale from 0 to 3. Then, the numbers are summed to obtain the total score out of 30 points. A greater DLQI score indicates a greater quality of life impairment. Therefore, the DLQI punctuation is interpreted as 0–1=no effect at all; 2–5=small effect; 6–10=moderate effect; 11–20=very large effect; and 21–30=extremely large effect.

Family Dermatology Life Quality Index (FDLQI)

The FDLQI is a dermatology-specific questionnaire designed for the family members of patients with any skin disease.[25] It measures the adverse impact on the health-related QoL of family members. The FDLQI consists of 10 items with possible answers on a 4-point scale: not at all/not applicable, a little, quite a lot, and very much. The items concern the impact of a patient's skin disease on different aspects of the family caregivers' QoL (i.e. emotional and physical wellbeing, relationships, social life, leisure activities, burden of care, impact on job/study, housework, and expenditure). The scores of individual items (0–3) are added to give a total score that ranges from 0 to 30. Higher total FDLQI scores indicate greater impairment of the family member's quality of life and vice versa. FDLQI could be interpreted similarly to DLQI: 0–1=no effect at all; 2–5=small effect; 6–10=moderate effect; 11–20 =very large effect; and 21–30=extremely large effect.

Hospital Anxiety Depression Scale (HADS)

The HADS is a validated instrument for screening of depression and anxiety.[26-27] This questionnaire consists of seven questions in each sub-scale of anxiety and depression. The items are scored on a four-point scale from zero (not present) to three (severe). The item scores are then summed, giving sub-scale scores on the HADS-A and the HADS-D from 0 to 21. A lower score indicates less severity and vice versa. Scores consistent with anxiety or depression are each defined by subscale scores of 8 or greater, and categorised as normal (score of 0-7), mild (score of 8-10), moderate (score of 11-14), and severe (score of 15-21). Several researchers have explored HADS data to establish the cut-off points for caseness of anxiety or depression. For example, Bjelland et al. (2002)[28], through a literature review of a large number of studies, identified a cut-off point of 8/21 for anxiety or depression.

For anxiety (HADS-A), this gave a specificity of 0.78 and a sensitivity of 0.9. For depression (HADS-D), this gave a specificity of 0.79 and a sensitivity of 0.83. Importantly, HADS has been validated for use in a range of different languages and conditions.[28-29] This study utilised both English and translated Malay versions of the original tool. The translated Malay version of HADS showed good sensitivity and specificity (sensitivity 90.0% and specificity 86.2% for anxiety; sensitivity 93.2% and specificity 90.8% for depression) and, therefore, is a valid instrument for use in the Malaysian population.[29]

Study Analysis

Statistical analyses were performed using Statistical Package for Social Sciences version 26 (SPSS, IBM Corporation, Chicago, IL, USA). Descriptive statistics for continuous variables were expressed as mean±standard deviation while categorical variables as frequencies and percentages. Comparisons involving categorical data were performed using the chi-square test. The significance of differences was assessed using independent-samples t-test for continuous data in the univariate analysis when normality and equal variance assumptions were satisfied. One-way analysis of variance (ANOVA) with a post hoc analysis was used to determine significance between three or more groups. Associations between continuous variables were analysed using the Spearman coefficient of rank correlation (r_s). Particularly, the correlation coefficient between 0.1 and 0.25 was considered low, while the value between 0.26 and 0.5 was considered moderate, and those over 0.5 were considered high. A multivariate analysis was carried out using multiple linear regression to determine the independent associated factors of FDLQI. Statistical significance was set at $p<.05$.

Ethical Approval

This study was registered with the National Medical Research Registry (NMRR-19-4047-51235). Ethical approval for the study was obtained from the Medical Research and Ethics Committee, Ministry of Health, Malaysia.

Results

Demographic Characteristics

A total of 240 subjects were enrolled in this study (i.e. 80 patients with psoriasis, 80 family members and 80 healthy controls). The demographic characteristics of study subjects are shown in Table 1. The mean age of patients was 44.09±14.2 years, and 48 patients (60%) were men. Forty-nine patients (61.3%) had mild disease, 23 patients (28.7%) with moderate disease and 8 patients (10%) had severe disease based on PASI scores. Their mean PASI score was 8.18±8.79.

Clinical characteristics of patients with psoriasis are presented in Table 2. More than half of patients had scalp (82.5%) and nails (78.8%) involvement. Thirty-eight (47.5%) patients had joints involvement, and only 6 (7.5%) patients had genital involvement. The mean age of family members was 42.66±12.5, ranging from 20 to 73 years. Twenty-eight (35%) family members were men, and 52 (65%) were women. Most of the family members were married (81.2%), employed (66.3%) and with secondary educational level (61.3%). There were 80 healthy controls, where there were with 27 males and 52 females with a mean age of 43.00±12.69. There were no significant differences among the groups with regard to age (p=0.774) and ethnicity (p=0.109).

DLQI

The mean DLQI score was 8.89±7.58, with a range of 0 to 29 in patients. As shown in Figure 1, a total of 29 (36.3%) patients had a DLQI score of more than 10, indicating psoriasis had a very large to extremely large effect on their QoL. There were 14 (17.5%) psoriatic patients who reported psoriasis had a moderate effect on their QoL, while 25 (31.3%) patients reported psoriasis had a small effect on their quality of life. There was no statistically significant relationship between DLQI and patients' age, sex, ethnicity, marital status, education level, occupation, and disease severity (Table 3). Although the DLQI score was higher in patients with severe disease and those with joints involvement, the difference was not statistically significant (p>0.05).

Table 1. Demographic characteristics of 240 study subjects

Demographic	Patients, n=80	Family members, n=80	Healthy controls, n=80	*p*-value
	Mean±SD or n (%)	Mean±SD or n (%)	Mean±SD or n (%)	
Age (years) Age range	44.09±14.2 (18-78)	42.66±12.5 (20-73)	43.00±12.7 (22-72)	0.774[a]
Sex				
Male	48 (60)	28 (35)	27 (33.8)	**0.001**[b]
Female	32 (40)	52 (65)	53 (66.3)	
Ethnicity				
Malay	45 (56.2)	45 (56.3)	44 (55.0)	0.109[b]
Chinese	23 (28.7)	23 (28.7)	28 (35.0)	
Indian	9 (11.3)	9 (11.3)	7 (8.8)	
Other ethnics minorities	3 (3.75)	3 (3.75)	1 (1.3)	
Marital status				
Single	23 (28.7)	15 (18.8)	36 (45.0)	**0.004**[b]
Married	57 (71.3)	65 (81.2)	43 (53.8)	
Divorced	0 (0)	0 (0)	1 (1.3)	
Education				
Primary	4 (5)	5 (6.3)	2 (2.5)	**<0.001**[b]
Secondary	52 (65)	49 (61.3)	8 (10.0)	
Tertiary	24 (30)	25 (31.3)	70 (87.5)	
Illiterate	0 (0)	1 (1.3)	0 (0)	
Occupation				
Employed	58 (72.5)	53 (66.3)	79 (98.8)	**<0.001**[b]
Unemployed	22 (27.5)	27 (33.8)	1 (1.2)	

[a]ANOVA; [b]*Chi-Square test;* SD: Standard deviation

Table 2. Clinical characteristics of psoriatic patients (*n*=80)

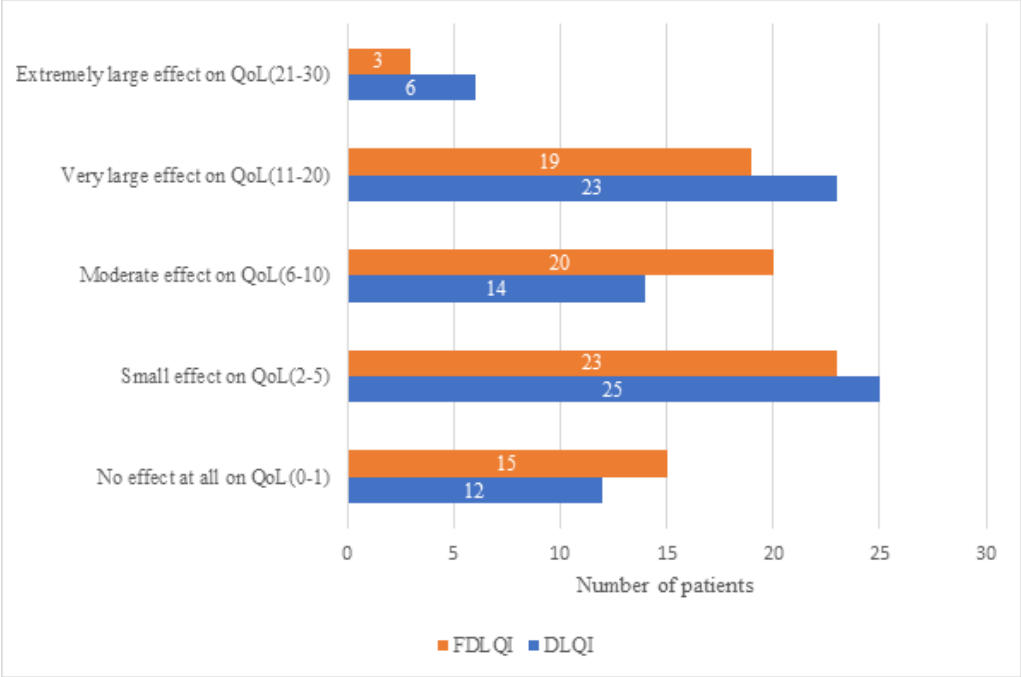
Variables	**Patients, n (%)**
PASI	
Mild (<10)	49 (61.3)
Moderate (10-20)	23 (28.7)
Severe (>20)	8 (10.0)
Scalp involvement	
Yes	66 (82.5)
No	14 (17.5)
Nails involvement	
Yes	63 (78.8)
No	17 (21.2)
Joints involvement	
Yes	38 (47.5)
No	42 (52.5)
Genital involvement	
Yes	6 (7.5)
No	74 (92.5)
Medical comorbidities	
Yes	29 (36.2)
No	51(63.8)

Table 3. DLQI and FDLQI scores related to demographics and clinical parameters

	DLQI	*p-value*	FDLQI	*p-value*
	Mean±SD		Mean±SD	
Means	8.89±7.58		7.58±6.09	
Age(years)				
r_s	0.104	0.359	0.035	0.760
Sex				
Male	9.71±7.37	0.238a	6.82±5.66	0.420a
Female	7.65±7.85		7.98±6.33	
Ethnicity				
Malay	9.31±7.96	0.256b	7.40±6.24	0.978b
Chinese	8.22±7.20		7.96±6.79	
Indian	10.44±7.58		7.22±4.55	
Others	3.00±2.00		8.33±4.04	
Marital status				
Single	10.83±9.02	0.064a	4.07±2.94	<0.001a
Married	8.11±6.85		8.38±6.36	
Education				
Primary	6.75±4.65	0.399b	3.20±2.59	0.051b
Secondary	8.85±7.37		9.00±6.69	
Tertiary	9.33±8.54		5.72±4.44	
Illiterate	-		6.00±0.00	
Occupation				
Employed	8.60±7.14	0.590a	6.92±5.71	0.183a
Non-employed	9.64±8.79		8.85±6.72	
Disease severity				
Mild	8.51±7.52	0.369b	6.86±6.46	0.301b
Moderate	8.43±6.94		8.14±4.71	
Severe	12.50±9.62		10.11±6.85	
Scalp involvement				
Yes	8.89±7.61	1.000a	7.85±6.04	0.268a
No	8.89±7.79		5.44±6.44	
Nail involvement				
Yes	8.40±7.40	0.268a	8.17±6.03	0.090a
No	10.71±8.23		5.35±5.98	
Joint involvement				
Yes	7.92±6.41	0.281a	7.38±5.48	0.771a
No	9.76±8.48		7.78±6.72	
Genital involvement				
Yes	10.50±6.47	0.591a	9.17±6.11	0.509a
No	8.76±7.69		7.45±6.11	

[a]Independent T-test; [b]ANOVA; r_s: Spearman coefficient of rank correlation; SD: standard deviation

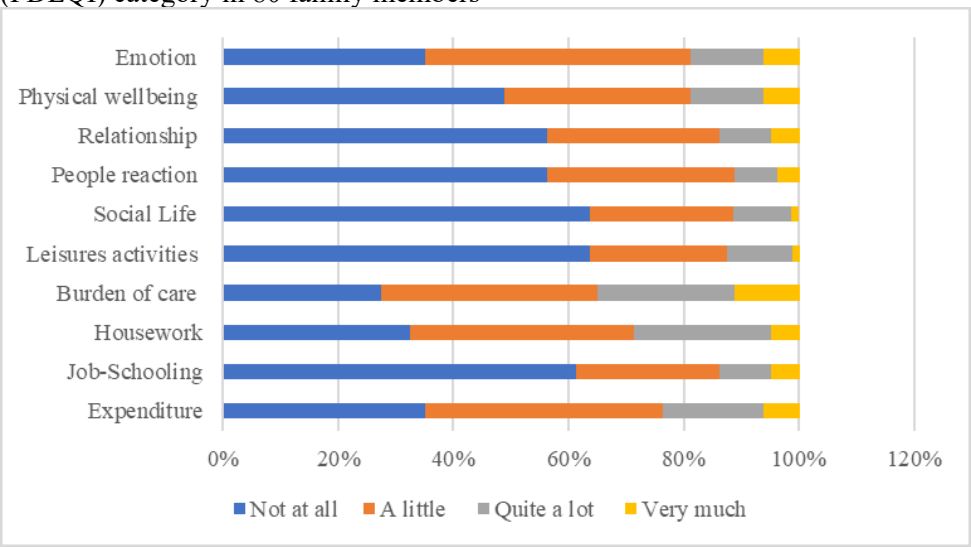
Figure 1. Quality of life impairment among patients and family members based on DLQI and FDLQI scores



FDLQI

Up to 82.5% of family members of psoriasis patients had impaired QoL(FDLQI ≥2). A total of 42 (52.5%) family members reported an FDLQI score of>6, indicating moderate to severe QoL impairment as a result of psoriasis (Figure 1). The mean FDLQI score of the family members was 7.58±6.09, and it ranged from minimal score 0 to a maximum score of 27. We compared FDLQI scores with demographics and clinical parameters (Table 3). Married family members were more affected than those who were single (8.38±6.36 vs. 4.07±2.94; *p< 0.001*). There was no statistically significant correlation between FDLQI scores with family members' age, sex, ethnicity, education level, and occupation. The presence of nails, scalp or genital psoriasis in patients did not significantly affect the mean FDLQI scores of family members (*p>0.05)*. As shown in Figure 2, family members' QoL was most highly affected in the aspect of emotion, the burden of care, housework and extra household expenditure. Social life and leisure activities were the aspect of life that was least affected by psoriasis.

Figure 2. Degree of impairment by psoriasis to quality of life based on Family Dermatology Life Quality Index (FDLQI) category in 80 family members



The FDLQI scores of family members did not show statistical correlation with DLQI scores (r_s=0.137; p=0.224) and psoriasis disease severity (r_s=0.173; p=0.126), as shown in Table 4. However, there was a positive correlation between FDLQI scores with patients' anxiety (r_s=0.348; p=0.002) and depression (r_s=0.276; p=0.013) level. Family members' QoL was strongly correlated with their anxiety and depression level (r_s=0.505; p<0.001 and r_s=0.420; p<0.001, respectively) as shown in Table 4 and Figure 3. The mean FDLQI scores was higher among family members with moderate to severe anxiety and depressive symptoms.

Table 4. Correlation between clinical features and Family Dermatology Life Quality Index (FDLQI) scores in family members

	FDLQI scores	
DLQI	r_s=0.137	p=0.224
Disease severity(PASI)	r_s=0.173	p=0.126
Patients' anxiety	r_s=0.348	**p=0.002**
Patients' depression	r_s=0.276	**p=0.013**
Family members' anxiety	r_s=0.505	**p<0.001**
Family members' depression	r_s=0.420	**p<0.001**

Multivariate linear regression revealed an association between family members' anxiety and FDLQI scores, regardless of their age, sex, educational level, occupation, and depression level and the PASI and DLQI scores of the patients (standardised ß=0.453; p=0.001).

Table 5. Multiple linear regression analysis of independent predictors associated with Family Dermatology Life Quality Index*

Predictors	Unstandardised B	Standardised Coefficients Beta	t	p-value
Patient's variables				
DLQI	0.051	0.063	0.641	0.523
PASI	1.041	0.118	1.214	0.229
Family member's variables				
Age	-0.029	-0.061	-0.593	0.555
Sex	0.283	0.022	0.213	0.832
Educational level	0.408	0.040	0.372	0.711
Occupation	1.101	0.087	0.775	0.441
Anxiety level	0.674	0.453	3.334	**0.001**
Depression level	0.207	0.143	1.013	0.315
Constant			-0.102	0.919

*Dependent variable: Family Dermatology Life Quality Index, Adjusted R square=0.279 (p=0.001)

Figure 3. Mean FDLQI scores with different anxiety and depression levels in family members (n=80)

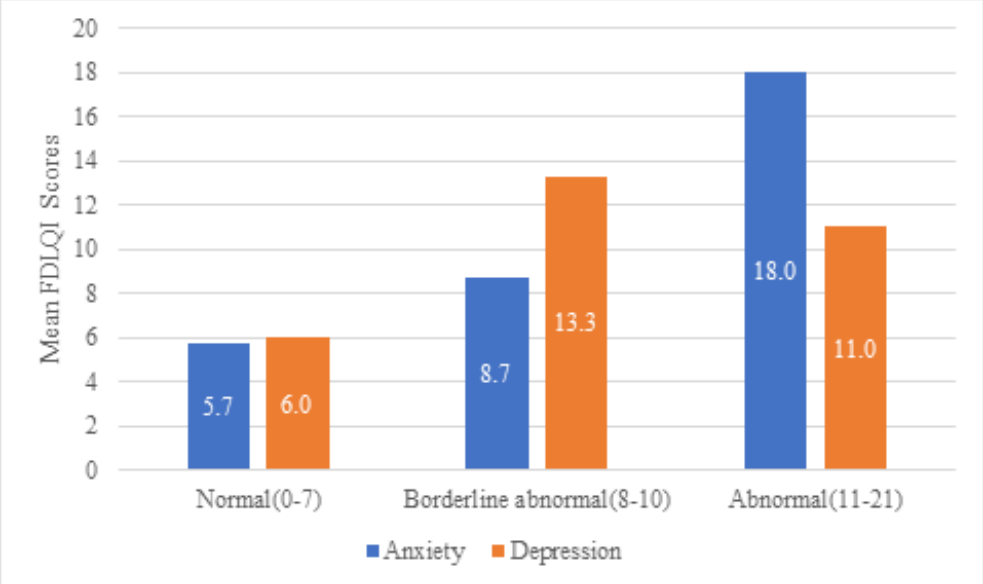
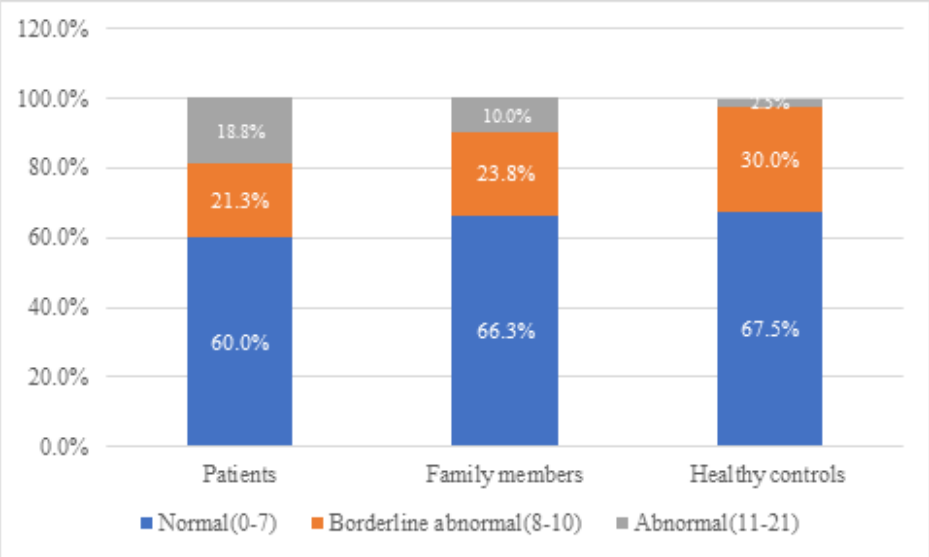


Table 6. Comparison of anxiety and depression among psoriasis patients, their family members and healthy controls (n =240)

Variables	Subjects	Significant case *n (%)*[a]	Mean±SD	*p*-value	Mean difference (95% CI)
HADS-A	Patients	32 (40.1)	6.25±4.18	**0.041**	1.46 (0.02, 2.90)*
	Family members	27 (33.8)	5.29±4.07		0.50 (-0.94,1.94)*
	Controls	26 (32.5)	4.79±2.95		
HADS-D	Patients	29 (36.3)	5.45±3.94	**0.025**	1.50 (0.09, 2.91) †
	Family members	19 (23.8)	4.54±4.20		0.59 (-0.83,2.00)†
	Controls	12 (15.0)	3.93±2.87		

[a]Significant case means a score of 8–21 for each subscale of HADS
p-value generated using the ANOVA test
*Post-hoc analysis: Bonferroni test was applied. A significant difference ($p< 0.05$) was found between patients vs controls ($p= 0.045$), no significant difference was found between patients vs family members ($p= 0.324$) and family members vs controls ($p= 1.000$)
†Post-hoc analysis: Bonferroni test was applied. A significant difference was found between patients vs controls ($p= 0.034$); no significant difference was found between patients vs family members ($p=0.363$) and family members vs controls ($p= 0.953$)
SD: Standard deviation

Figure 4. Bifurcation of subjects as normal, borderline abnormal or abnormal cases of anxiety in patients, family members and healthy controls (n=240)



Anxiety

The mean HADS anxiety scores (HADS-A) was 6.25±4.18 for patients, 5.29±4.07 for family members, and 4.79±2.95 for healthy controls, with significant differences (p=0.041) being detected among the groups (Table 5). Patients and family members had similar anxiety levels (p=0.324) and patients' anxiety level was significantly higher than the healthy controls (6.25 vs 4.79; p=0.045). However, no significant difference was found between the anxiety level of family members and healthy controls based on post-hoc analysis (p=1.000).

Thirty-two (40.1%) of the psoriatic patients had a HADS-A score ≥ 8, whereas 27 (33.8%) of the family members had a HADS-A score ≥8, which is suggestive of anxiety disorder, as shown in Figure 4. Even though 26 (32.5%) healthy controls reported anxiety symptoms, but most of them only had mild symptoms (n=24).

Figure 5. Bifurcation of subjects as normal, borderline abnormal or abnormal cases, for depression in patients, family members and healthy controls (n=240)

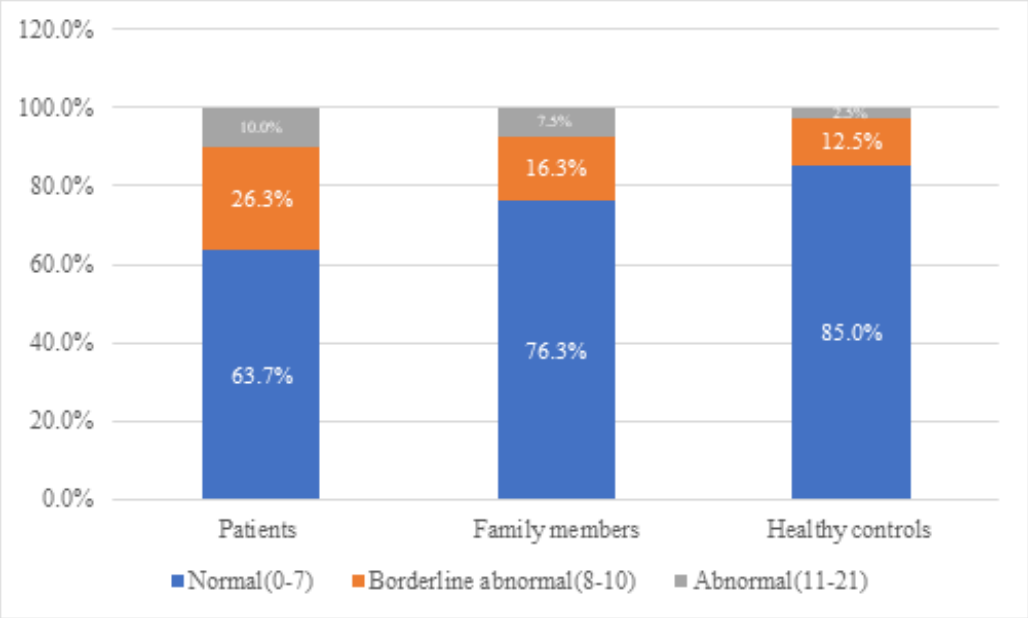


Table 7. Correlation study (r_s coefficient and *p*-value) between family members' anxiety scores and other study variables: Psoriasis Area Severity Index (PASI) and patients' anxiety and depression, and family members' depression scores

	Family members' anxiety scores	
Disease severity(PASI)	r_s=0.128	p=0.256
Patients' anxiety	r_s=0.414	p<0.001
Patients' depression	r_s=0.359	p<0.001
Family members' depression	r_s=0.674	p<0.001

The anxiety level of family members was correlated to the patient's anxiety and depression level (r_s=0.414; p<0.001 and r_s=0.359; p<0.001, respectively), as shown in Table 7. The anxiety level of family members was also strongly correlated with their own depression level (r_s=0.674; p<0.001). However, no significant correlation was found between family members' anxiety level and the patient's psoriasis severity (r_s=0.128; p=0.256).

Depression

The mean depression scores (HADS-D) was 5.45±3.94 for patients, 4.54±4.20 for family members, and 3.93±2.87 for healthy controls, with significant differences (p<0.001; Table 6) detected among the groups. Depression levels were similar between patients and family members (p=0.363). Patients' depression level was significantly higher than the control group (5.45 vs 3.93; p=0.034), but there was no significant difference between the depression level of family members and the control group based on post-hoc analysis (p=0.953).

Twenty-nine (36.3%) psoriatic patients had a depression score≥8, and 19 (23.8%) family members had a depression score≥8, which is suggestive of depression disorder. Twelve (15.0%) healthy controls reported depression scores ≥8, as shown in Figure 5.

The depression level of the family members had a positive correlation with the patients' anxiety and depression level (r_s=0.430; p<0.001 and r_s= 0.416, p<0.001, respectively; Table 8). As expected, the depression level of family members was strongly correlated with their own anxiety level ((r_s=0.674 ; p<0.001). However, no association found between family members' depression level and psoriasis disease severity (r_s=-0.004; p=970).

Table 8. Correlation of the family members' depression score with patient's psoriasis area severity index (PASI) score and patient's psychological state

	Family members' depression scores	
Disease severity(PASI)	r_s=-0.004	p=0.970
Patients' anxiety	r_s=0.430	p <0.001
Patients' depression	r_s=0.416	p <0.001

The study subjects with a HADS-A or HADS-D score≥8 were informed, and with their permission, they were referred to a psychiatrist for further assessment.

Discussion

Psoriasis is associated with significant psychosocial morbidity and profoundly impacts patients' quality of life. The burden of disease is not limited to the patients but may extend to the rest of the family. Therefore, family impact data are potentially essential measurements of the overall burden of skin disease. The impact of psoriasis on patients' quality of life in Malaysia has been reported previously,[30-32] but only limited data is available on the secondary impact of psoriasis on close family members.

The most important finding of this study is the considerable burden of psoriasis on the QoL of patients and their families. In this study, the mean DLQI of patients was 8.89±7.58, with one-third (36.3%) of the patients having a DLQI score of more than 10, showing the considerable impact of the disease on patients' life. This finding was similar to the 10-year review of the Malaysian Psoriasis Registry,[31] in which the mean DLQI was reported as 8.5±6.6, with 33.1% of the patients scoring more than 10. Another local study on 223 patients,[32] evaluating the health-related QoL of psoriatic patients using DLQI, also showed a similar finding with 30% of the psoriatic patients experienced severe impairment of QoL with a median DLQI of 7.

The present study results revealed that psoriasis had significantly impaired the quality of life of close family members. A total of 42 (52.5%) family members reported a moderate-to-severe impairment in their QoL**.** The mean FDLQI score of family members was 7.58±6.09, with 27.5% (*n*=22) of family members sustained severe QoL impairment with a score of more than 10. The most highly affected areas were the emotional distress, the burden of care, housework and extra household expenditure. Emotional impairment had been reported as the most affected item in previous studies that based on the FDLQI questionnaire.[15,33] As expected, families of patients with moderate to severe psoriasis based on PASI reported significantly higher scores on the FDLQI compared to those with mild psoriasis. A greater impact was also found in married family members, implying a potential negative effect of psoriasis on the couple relationships. Patient sexual dysfunction greatly impairs partners' quality of life.[34] According to previous studies, after getting psoriasis, a reduction in the frequency of sexual intercourse occurred in more than 90% of the relationship and 40% of psoriasis partners suffer from sexual dysfunction.[35-36]

In our study, no significant correlation could be found between PASI and FDLQI scores of family members. There was also no association found between PASI and the psychological state of both patients and family members. This observation suggests that psychosocial distress and quality of life are not always proportional to the disease severity. Instead, the degree of deterioration in the quality of life of family members was more strongly influenced by patients' psychological distress. These findings were consistent with previous studies that examine the impact of psoriasis on patients and families' lives.[36-38] This may be due to the pitfalls of the disease severity assessment tool i.e. PASI, which does not attach additional importance to small, yet visible or sensitive body parts such as the face, hands and genitals. Furthermore, psoriasis affects patients' perception of themselves and patients may still have a significant psychosocial disability even with limited skin disease.[40] Psoriatic patients usually have an unfavourable self-perceptions with lowered self-esteem and negative body image.

The presence of anxiety and depression has been established in patients with psoriasis. In addition, it has been reported that the point prevalence of mental disorders was higher in patients with psoriasis than in patients with other dermatological conditions.[41-43] We discovered a significantly higher prevalence of moderate to severe anxiety (18.8% vs. 2.5%) and depression (10.0% vs. 2.5%) among psoriatic patients than controls. These findings were comparable with a similar study using HADS for psoriatic patients in Singapore. In their research, 17% of their cohort of psoriatic patients had anxiety, and 15% had a depressive disorder with a score of more than 11.[44] In comparison with another similar study by Bakar RS et al. in Malaysia[45], our study had a higher prevalence of anxiety (40.1% vs 16.9%)) and depression (36.3% vs 8.5%) among psoriatic patients based on the cut-off point of 8 on HADS. These could be possibly due to differences in the socio-economic background of the study population, as our study was done in an urban population and the ongoing COVID-19 pandemic could also be a contributing factor as well.

In this study, the prevalence of family members with anxiety symptoms was 32.5% with a HADS-A mean score of 5.29±4.07, whereas for depression, there were 23.75% of family members who had experienced depressive symptoms with a HADS-D mean score of 4.54±4.20. It was comparable to the control group, in which the prevalence of anxiety and depression was 25% and 21.25%, respectively. However, most of the controls only experienced mild anxiety and depressive symptoms compared to the family members who had higher percentages of moderate to severe anxiety and depressive symptoms. The prevalence of anxiety and depression of healthy controls was significantly higher compared to the overall national prevalence of depression and anxiety, which ranges between 8 and 12%.[46-49] This is probably due to the ongoing COVID-19 pandemic. The emergence of the COVID-19 pandemic has negatively affected mental health either due to its direct psychological effects or long-term economic and social consequences.[50-52] A substantial increase in the prevalence and burden of major depressive disorder and anxiety disorders as a result of the COVID-19 pandemic has been reported.[53]

It is crucial to identify psychiatric comorbidity among psoriasis patients and their family members as it would negatively affect the response to psoriasis treatment.[53] Future studies are needed to determine the mechanism by which psoriasis is associated with depression, anxiety, and approaches to prevent such adverse outcomes in patients with psoriasis and families. Our study results support the adoption of an integrated approach that recognises that psoriasis does not affect the patients alone. We should treat the patient holistically, considering not only the QoL and psychological health of patients, but it is also essential to ensure the overall well-being of their family members. Moreover, healthcare policy should consider not only patients' needs but also their cohabitants.

Limitations

This study was limited by its cross-sectional design, which allowed for correlation but no causation. Furthermore, the number of participants in our study was relatively small, and it was a single centre study that may not reflect the actual characteristic of the local population. Further studies with larger numbers of patients and cohabitants are needed before any comparisons can be made among groups of different psoriasis severity. In addition, many patients included in this study had mild to moderate psoriasis, which could have depreciated the results. Moreover, controls in the present study were mainly healthcare staffs, whose psychological stress might be higher than that of the general population during the COVID-19 pandemic.[54] Assessing the quality of life in healthcare settings is challenging, since psychometric instruments can often not accurately translate the magnitude of the impact imposed by any disease on an individual's life.

Conclusion

In summary, this study showed that psoriasis has a profound impact on the QoL and psychological health of the patients and their family members. Therefore, healthcare professionals should adopt a comprehensive approach while treating psoriasis patients, taking into account the physical aspect and the quality of life and psychosocial health of both patients and their family members.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

Evaluation of Knowledge, Disease Severity and Quality of Life of Patients with Psoriasis

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Abstract

Background

Psoriasis vulgaris is a chronic immune-mediated inflammatory multi-system disease characterised by keratinocyte hyperproliferation. Data regarding patients' disease severity, knowledge and quality of life (QOL) is important to optimize treatment strategies for psoriasis. This study aims to evaluate and investigate the relationship between disease severity, knowledge and QOL of patients with psoriasis.

Methods

A cross-sectional multicentre study utilizing a socio-demographic data collection form, Psoriasis Knowledge Assessment Questionnaire (PKAQ), Dermatology Life Quality Index (DLQI) and Psoriasis Area and Severity Index (PASI was conducted. Correlations between PKAQ, DLQI and PASI were analysed using Spearman's test.

Results

A total of 114 subjects participated in this study. Majority of them had mild psoriasis (n=73, 64%) based on PASI. The mean score of PKAQ was fourteen out of a total possible score of twenty-five, whereas the DLQI had a non-parametric distribution with a median (interquartile range) of 7 (10). Most subjects (32.5%) stated that psoriasis had a 'moderate effect' on their QOL, while only 3.5% said that it had an 'extremely large effect' on their QOL. There was a statistically significant correlation between PASI and DLQI (r_s = 0.264, p = 0.004), with higher PASI scores corresponding to higher DLQI scores. No statistically significant correlation was found between DLQI and PKAQ (r_s= -0.048, p= 0.612), and between PASI and PKAQ (r_s= 0.058, p= 0.542).

Conclusion

Impairment of QOL was positively associated with severity of psoriasis. However, there was no significant relationship between knowledge and quality of life, as well as between knowledge and psoriasis severity.

Key words: *Psoriasis, DLQI, PASI, quality of life, patient knowledge, Malaysia*

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Introduction

Psoriasis vulgaris is a chronic immune-mediated inflammatory multi-system disease characterised by keratinocyte hyperproliferation and uncontrolled epidermal differentiation. Psoriasis is characterised by bilateral,

symmetrical beefy-red plaques with thick, adherent silvery scales, often affecting nails and joints.[1] The global prevalence of psoriasis is about 2 to 3%,[2] and men have a slightly higher incidence compared to women, with a ratio of 1.3 to 1.[3]

The symptoms of psoriasis are highly variable within the population, with skin pain and redness being the primary reported symptoms.[4] Other symptoms include desquamation (68%), pruritus (41%), dry skin (40%) and erythema (30%). Although psoriasis is neither contagious nor curable, the symptoms can be well-controlled with a range of treatment modalities such as topical and systemic medication, as well as phototherapy.[5]

In addition to the unpleasant pain and itchy sensation, psoriasis can also negatively affect one's physical, physiological, psychological and social wellbeing. With regards to the physical and physiological wellbeing, psoriasis is associated with an increased prevalence of other chronic conditions such as obesity, hypertension, dyslipidemia and diabetes mellitus.[3,6] In addition to that, the psychological and social wellbeing of patients with psoriasis are often compromised, with cases of depression and anxiety frequently reported among them.[7] To mitigate these issues, more information is required regarding disease severity, disease knowledge and quality of life (QOL). With better information, suitable interventions can be planned to minimise the negative impacts of psoriasis on patients.

Previous studies identified a few predictors of poor QOL including young age, single status, active employment, sport activity, extensive psoriatic lesions, psoriatic arthropathy and nail dystrophy.[8,9] Despite many of the determinants being unavoidable, educational intervention was found to be effective in improving QOL. Azmi et al.[10] demonstrated a significant improvement in QOL based on the Dermatology Life Quality Index (DLQI) scores [8.64(5.66) vs 5.60(5.35), 95% CI 2.23-3.86] after 2 months of a flipchart education counselling intervention, suggesting that knowledge of psoriasis may be associated with QOL and/or disease severity.

While QOL among psoriasis patients and the factors associated with it has been widely investigated, few studies described the knowledge level of patients regarding the disease, as well as evaluated the association between knowledge level with patient's QOL and disease severity, especially among the Malaysian population. Hence, the objective of this research is to evaluate and investigate the relationship between disease severity, disease knowledge and QOL of patients with psoriasis, and assess their knowledge regarding psoriasis and QOL.

Materials and Methods

Study Population

This was a cross-sectional multicenter study conducted in the dermatology clinics of Hospital Sultan Haji Ahmad Shah (HoSHAS) and Hospital Tengku Ampuan Afzan (HTAA), two tertiary-care hospitals located in Pahang, Malaysia between January 2019 and January 2020. Patients were eligible to participate in the study if they were diagnosed with psoriasis at least six months prior to recruitment. Patients who were less than eighteen years old, pregnant, and cognitively impaired were excluded from this study.

Sample Size Calculation

The study was designed to include at least 50 patients to have a 95% confidence interval and power of 80%. This calculation was based on an estimated psoriasis population of 3%[2] and a drop-out rate of 10%.

Study Design

Data collection was carried out during patients' routine clinic appointments. Written informed consent was obtained from the subjects before recruitment, after which they were given a set of questionnaires to be answered. These included a socio-demographic data collection form, Psoriasis Knowledge Assessment Questionnaire (PKAQ) and Dermatology Life Quality Index

(DLQI) questionnaire. The attending doctor then evaluated and completed the Psoriasis Area and Severity Index (PASI) score for each subject. All forms and questionnaires were then verified by one of the investigators to ensure data completeness and all data were then entered into a database for analysis. A second investigator cross-checked all entries to ensure accuracy during data transfer.

Measurement of Outcomes

Psoriasis Area and Severity Index (PASI)

PASI is a commonly used validated tool to assess the severity of psoriasis.[11]In PASI, the body surface area is divided into four sections: head and neck, trunk, upper extremities and lower extremities. The assessment of severity of the symptoms, namely erythema (redness), induration (thickness) and desquamation (scaling), is performed separately for each region, resulting in a total score ranging from zero to seventy-two. The severity of psoriasis is then categorised based on the total score, giving a three-tier severity of mild (<7), moderate (7-12) and severe (>12).[12]A different disease severity classification compared to the Malaysian Clinical Practice Guidelines for the management of psoriasis vulgaris was used.[13]

Psoriasis Knowledge Assessment Questionnaire (PKAQ)

PKAQ is a validated questionnaire to assess the knowledge of study subjects in psoriasis.[14] The questionnaire consisted of twenty-five statements related to psoriasis, including the basic facts (nine items), the triggering factors (five items), the disease process (seven items) and the treatment aspects (four items). Subjects were requested to mark each statement as 'true', 'false' or 'do not know'. A correct response was scored as one, while incorrect and 'do not know' responses were scored as zero. The final possible score ranged from zero to twenty-five. The questionnaire which is available in the English language, was translated to the Malay version for ease of comprehension. Face and content validation were performed by a dermatology pharmacist and a dermatologist with native language background. Cronbach's alpha tested on ten random samples had a score of 0.595.

Dermatology Life Quality Index (DLQI)

The DLQI questionnaire[15]is a self-explanatory, validated questionnaire used to measure patients' QOL affected by skin disease over the past seven days. The questionnaire consisted of ten questions which were categorised into six domains of QOL: symptoms and feelings (question 1 and 2), daily activities (question 3 and 4), leisure (question 5 and 6), work and school (question 7), personal relationships (question 8 and 9), and treatment (question 10). Each question had four possible responses: 'not at all', 'a little', 'a lot' or 'very much', with their corresponding scores of zero, one, two and three, respectively. Patients were only allowed to choose one response for each question. The DLQI was then calculated by summing the scores of all questions, resulting in a final index score ranging from zero to thirty. The higher the index score, the greater the impairment of QOL. The scores were categorised into several bands of ascending impact levels: no effect (DLQI 0-1), small effect (DLQI 2-5), moderate effect (DLQI 6-10), very large effect (DLQI 11-20) and extremely large effect (DLQI 21-30).[16]The questionnaire is available in multiple languages. The Malay and English bilingual version were used in this study. Cronbach's alpha tested on ten samples had a score of 0.784.

Statistical Analysis

Descriptive statistics were presented using mean, median, standard deviation (SD), interquartile range (IQR) and percentage, as appropriate. Correlations between PKAQ, DLQI and PASI scores were analysed using Spearman's test. A value of $p<0.05$ was considered significant. All analysis was conducted using IBM SPSS Statistics for Macintosh, Version 26.0. Armonk, NY: IBM Corp

Ethics Approval

Ethical approval was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia prior to data collection (KKM/NIHSEC/P19-1040(6)).

Results

Demographic

A total of 114 subjects participated in this study. The mean age of the study population was 48.8 ± 15.15 (Table 1). The study population was equally distributed among women (50.9%) and men (49.1%). Most of the subjects were Malay (76.3%), followed by Chinese (13.2%), Indian (9.6%) and Indonesian (0.9%). Only five (4.4%) subjects did not have any formal schooling, while thirty-seven (32.5%) subjects attained the highest qualification in education at university level. At the time of the study, a high proportion of the subjects were married (78.1%) and were presently employed (55.3%). The median duration of suffering from psoriasis was 8 years (range 1-59). The most common type of psoriasis encountered was plaque psoriasis (88.6%), followed by pustular psoriasis (4.4%), guttate psoriasis (3.5%), and erythrodermic psoriasis (2.6%). Approximately 1% of subjects had concomitant psoriatic arthropathy.

Psoriasis Area Severity Index (PASI)

The median PASI score was 4.4 (IQR = 7.7). Majority of the subjects (64%) had mild psoriasis, defined by a PASI score of less than 7, while 20.2% of subjects had severe psoriasis (PASI >12), and 15.8% moderate psoriasis (PASI 7-12) (Table 1).

Psoriasis Knowledge Assessment Questionnaire (PKAQ)

The mean score for PKAQ was 14.2±4.4. The lowest score reported was one, whereas the highest was 23. Half of the subjects (50.9%) had the misconception that psoriasis is contagious. In addition to that, 78.1 % of subjects also believed that psoriasis is curable. A majority of the subjects were aware that psoriasis can affect both men and women (93%), can affect the entire skin (88.6%) and joints (55.3%), and can happen at any age (91.2%). More than half of the subjects were able to correctly identify stress (72.8%), certain medications (63.2%) and infection (64%) as triggering factors for psoriasis (Table 2). However, 55.3% of them did not know that injury to the skin may also trigger the disease. More than half of the subjects were able to correctly identify that psoriasis can affect the nails (63.2%), palms and soles (55.3%), but not the brain (51.8%). Furthermore, most of the subjects (70.2%) were aware that psoriasis was not transmitted through sex and sharing of food. Nevertheless, 57.9% subjects had the misconception that diet restrictions may cure psoriasis. More than two-thirds (70.2%) of the subjects were aware of the possibility of side effects from certain medications used in the treatment of psoriasis. A large proportion of subjects were also aware that moisturizers (87.7%) and oral medications (63.9%) helped treat psoriasis. Conversely, only 39.5% subjects recognised phototherapy as an effective treatment modality (Table 2).

Dermatology Life Quality Index (DLQI)

The median DLQI score was 7 (IQR = 10), with the minimum score being zero and the maximum was 26. Figure 1 depicts the DLQI score and their respective frequencies within each category, while Figure 2 details the degree of impairment within each domain. Most subjects experienced a moderate impairment to their QOL (Figure 1). In comparison to other domains, the highest number of subjects (43.9%) reported psoriasis as having 'a lot of' to 'very much' effect on their symptoms, feelings, work or school. The least affected domain was 'personal relationships', where 54.4% of subjects were not affected by their disease, while only 1.8% of subjects were extremely affected.

Correlation between PASI, PKAQ and DLQI

There was a significant association between PASI and DLQI (r_s = 0.264, p = 0.004) (Figure 3). A higher PASI score correlated with a higher DLQI score. However, there was no statistical significance between the PASI and PKAQ scores (r_s = 0.058, p = 0.542), as well as between DLQI and PKAQ scores (r_s = -0.048, p = 0.612).

Table 1. Baseline demographics and clinical characteristics of subjects (n=114)

Age	
Mean (±SD)	48.8 (±15.15)
Range	18-83
Gender	
Male	56 (49.1%)
Female	58 (50.9%)
Race	
Malay	87 (76.3%)
Chinese	15 (13.2%)
Indian	11 (9.6%)
Indonesian	1 (0.9%)
Marital Status	
Married	89 (78.1%)
Single	16 (14%)
Divorced or Widowed	9 (7.9%)
Education Level	
No formal education	5 (4.4%)
Primary education	14 (12.3%)
Secondary education	58 (50.9%)
Tertiary education	37 (32.5%)
Occupational Status	
Employed	63 (55.3%)
Unemployed	51 (44.7%)
Type of Psoriasis	
Plaque	101 (88.6%)
Pustular	5 (4.4%)
Guttate	4 (3.5%)
Erythrodermic	3 (2.6%)
Psoriatic Arthropathy	1 (0.9%)
PASI Category	
Median (range)	4.4 (0-36)
Mild	73 (64%)
Moderate	18 (15.8%)
Severe	23 (20.2%)
Duration of Disease (years)	
Median (range)	8 (1-59)
DLQI	
Median (range)	7 (0-26)
PKAQ	
Median (range)	15 (1-23)

SD: standard deviation; PASI: Psoriasis Area and Severity Index; DLQI: Dermatology Life Quality Index; PKAQ: Psoriasis Knowledge Assessment Questionnaire

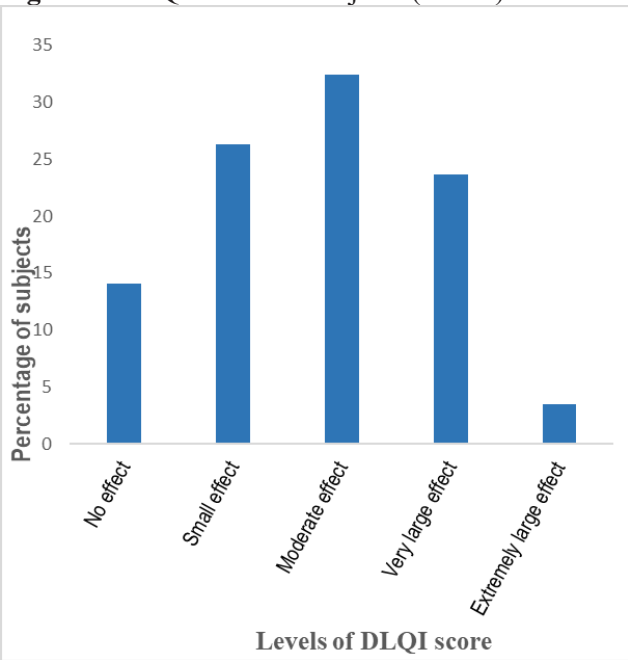
Table 2. Distribution of responses to each of the items of PKAQ (n=114). The shaded boxes represent the correct response

No	Statements	True	%	False	%	Don't Know	%
1	Psoriasis is contagious.	58	50.9	41	36	15	13.2
2	Psoriasis may begin at any age.	104	91.2	3	2.6	7	6.1
3	Psoriasis can affect the entire skin.	101	88.6	7	6.1	6	5.3
4	Psoriasis affects both men and women.	106	93	3	2.6	5	4.4
5	Psoriasis is a curable disease.	89	78.1	15	13.2	10	8.8
6	The exact cause of psoriasis is known.	33	28.9	21	18.4	60	52.6
7	Psoriasis can be associated with joint pain.	63	55.3	23	20.2	28	24.6
8	Specific food intake or restrictions may cure psoriasis.	66	57.9	24	21.1	24	21.1
9	In psoriasis, skin cells are multiplying too slowly.	40	35.1	38	33.3	36	31.6
10	Injury to the skin may cause psoriasis to appear at that site in persons already having psoriasis.	51	44.7	33	28.9	30	26.3
11	Psoriasis never occurs in the nails.	21	18.4	72	63.2	21	18.4
12	Certain drugs may increase the severity of psoriasis in persons already having psoriasis.	72	63.2	19	16.7	23	20.2
13	Certain infections may increase the severity of psoriasis in persons already having psoriasis.	73	64	8	7	33	28.9
14	Stress plays no role in psoriasis.	17	14.9	83	72.8	14	12.3
15	Psoriasis increases in winter.	16	14	41	36	57	50
16	Having close blood relatives affected with psoriasis determines to great extent whether a person will have psoriasis or not.	55	48.2	30	26.3	29	25.4
17	Psoriasis never occurs in the palms and soles.	29	25.4	63	55.3	22	19.3
18	Psoriasis damage brain.	6	5.3	59	51.8	49	43
19	Psoriasis is transmitted through sharing food.	12	10.5	80	70.2	22	19.3
20	Psoriasis is transmitted among sexual partners.	8	7	80	70.2	26	22.8
21	Photo / light therapy is useful in treating psoriasis.	45	39.5	17	14.9	52	45.6
22	Oral medications are useful in psoriasis.	74	64.9	16	14	24	21.1
23	Certain drugs which are used to treat psoriasis may have side effects.	80	70.2	10	8.8	24	21.1
24	Psoriasis is seen all over the world.	100	87.7	3	2.6	11	9.6
25	Treatment of psoriasis can include moisturizers.	100	87.7	2	1.8	12	10.5

Discussion

This study demonstrated that the severity of psoriasis significantly affected QOL, with poorer QOL seen among patients with more severe disease. This was in consensus with several local[8,9] and international studies.[17-18]A Taiwanese study of 305 patients found that for every 1-point increment in the PASI score, there was an estimated increase in DLQI by 0.24 points *(p-value 0.0086)*. Similar findings were noted when Psoriasis Disability Index (PDI) was used as a parameter of QOL, with higher PDI scores having a greater impact on QOL, especially among those with higher PASI scores *($p<0.001$ and $p=0.005$)*.[19-20] Hence, to minimize the impact of psoriasis on patients' QOL, PASI scores need to be reduced by optimally treating psoriasis.

Figure 1. DLQI scores of subjects (n=114)



**DLQI 0-1= No effect. 2-5= Small effect. 6-10= Moderate effect. 11-20= Very large effect. 21-30= Extremely large effect*

This study also revealed that patients did not have adequate knowledge about psoriasis. In the future, a leaflet about psoriasis should be provided to the newly diagnosed patients. Patients should also be allowed time to ask questions at every clinic visit. A study by Jankowiak et al.[21] found that patients with a higher education level had greater knowledge concerning psoriasis. This may explain the moderately low mean score of PKAQ (14.2) in this study, where a majority of the subjects (67.6%) had secondary education and below. A lack of knowledge regarding psoriasis among patients had also been highlighted in several studies. In a previous study using the same PKAQ by Nagarajan et al[14], 52% of 200 subjects had inadequate knowledge. The same study discovered that a large number of subjects (49%) did not know that psoriasis was incurable, similar to our study where 78.1% thought psoriasis was curable. An alarming 50.9% of

Figure 2. Quality of life impairment in psoriasis patients based on categories of Dermatology Life Quality Index

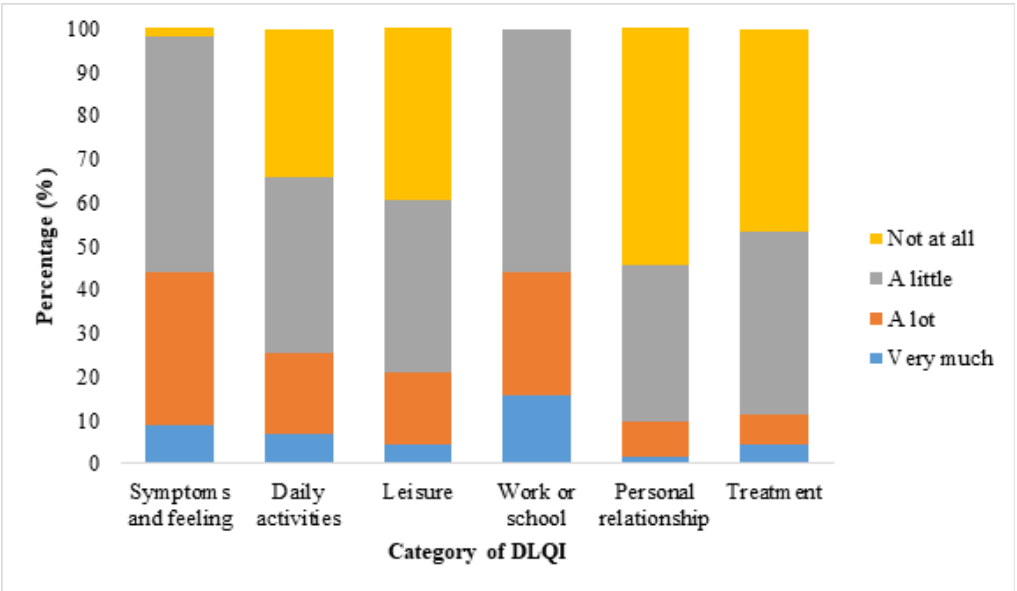
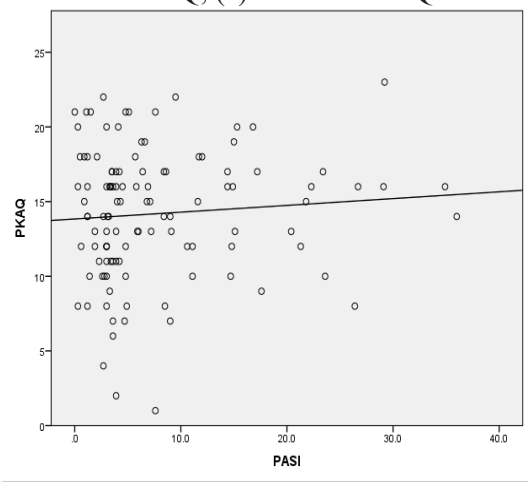
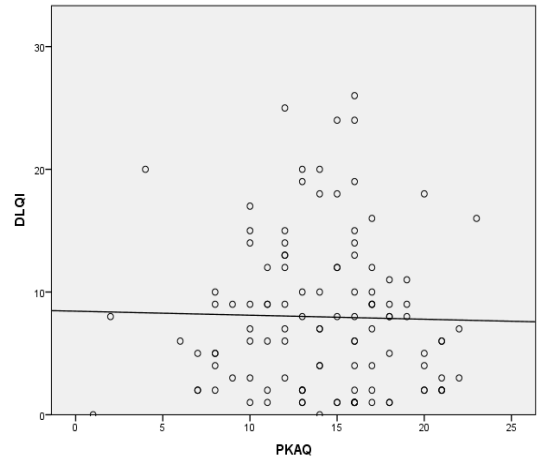


Figure 3. Correlation between (a) DLQI and PKAQ; (b) PASI and PKAQ; (c) PASI and DLQI



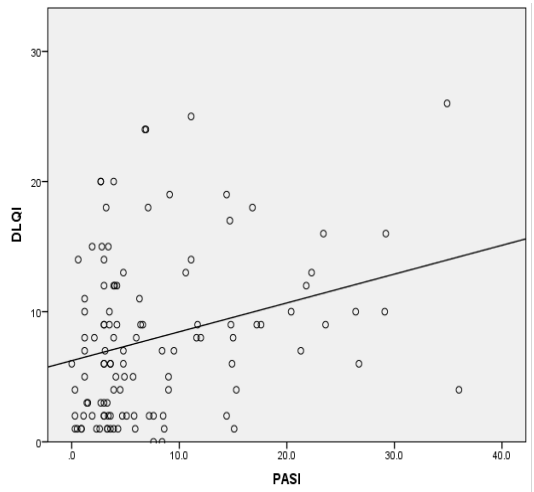
Spearman's correlation = -0.048 (p= 0.612)

(a)



Spearman's correlation = 0.058 (p= 0.542)

(b)



Spearman's correlation = 0.264 (p= 0.004)

(c)

subjects had the misconception that psoriasis was contagious. These findings highlight the need for proper patient education by healthcare providers to clarify patients' doubts and reduce misconceptions about the disease. Most subjects (72.8%) were able to identify stress as a trigger, similar to a study by Wahl et al[22] who used a 49-item Psoriasis Knowledge Questionnaire (PKQ). They also found that more than half of the study subjects did not know that sunburn and infections could trigger psoriasis. Meanwhile in our study, 55.3% of subjects could not identify injury as a triggering factor. Equally alarming was that 57.9% of our study subjects wrongly believed that diet restrictions could cure psoriasis, which poses a risk of malnutrition among them. This prevalence is much higher compared to another study which documented a misconception of only 28.5%.[14] With regards to treatment, a majority (60.5%) of subjects were unable to identify phototherapy as one of the treatment modalities of psoriasis. Nagarajan et al[14] also found that 85% of their subjects did not know about phototherapy being used to treat psoriasis. One possible reason for our finding could be that the majority of our subjects had mild disease (64%), which did not necessitate phototherapy as a treatment option.

Most of our subjects' QOL was moderately affected by psoriasis, as evidenced by their DLQI scores. This is similar to another local study by Nyunt et al,[8] involving 223 patients, with a median DLQI score of 7 (IQR = 7). In comparison, another study from Taiwan involving 480 patients had a mean DLQI score of 9.16 ± 6.3.[23] A closer examination into individual components revealed that the most affected domains were 'symptoms and feelings', and "work or school', while the least affected domain was 'personal relationships'. This was also consistent with findings from Nyunt et al,[8] Tang et al[9] and Lin et al[23] On the other hand, a study of 72 Mexicans showed that the most impacted domain was 'symptoms and feelings' (157 points), but the least impacted domain was 'school or work' (25 points).[18] Patients' negative feelings may be due to the affected skin areas that were difficult to conceal, thus stigmatization

can ensue.[24] Therefore, patients' self-esteem and perception towards self-body image should also be taken into consideration when managing a patient with psoriasis. Troubling symptoms such as itchiness and pain need to be identified and treated appropriately. The least affected "personal relationships" domain could be due to good psychosocial support and acceptance from the patients' families, partners and community.
Our results found no statistically significant relationship between disease severity and knowledge score of psoriasis patients. This is in agreement with a study by Fortune et al.[25] who also did not find any significant association between severity of psoriasis and beliefs held by patients about their condition, measured using the Illness Perception Questionnaire (IPQ). However, two studies by Wahl et al[22, 26] at different periods confirmed that patients with greater disease severity had stronger beliefs about the chronicity, negative consequences and emotional impact of psoriasis, in addition to better baseline knowledge. In comparison to the milder cases, patients with severe disease may be more interested to learn about the disease to have better control over the symptoms. However in our study, patients' knowledge score could be diminished due to factors such as their level of education and treatment modality. This is especially so when only 32.5 % of our patients attended universities and 64% of the cases were mild. Thus, they were unable to identify phototherapy as one of the treatment options.

We also found no significant relationship between knowledge scores and QOL. A study found that patients with more knowledge about psoriasis had a better QOL, since they were less worried about the disease and perceived less severe consequences.[21] Despite the lack of objective evidence in the literature to support the association between knowledge and QOL, there are several studies which have demonstrated an improvement in QOL following an active educational intervention.[10,27-28] Balato et al[27]used mobile phone text messages to send educational information and reminders to patients for a period of 12 weeks, which resulted in an increase in patients' QOL after the intervention compared to the control group *($p<0.05$)*. Bostoen et al[28]created a 12-week educational programme of 2-hour sessions twice a week and showed a significant reduction in the mean DLQI score from 8.4 to 4.4 after the programme. In another study, the researchers used the PDI score to measure QOL before and after a 12-week video-teaching programme, and found a decrease in disability scores from 15.6±6.9 to 9.9 ±5.1 after 3 months of intervention.[29] These observations highlight that the clinicians' efforts to educate patients translate into positive QOL. However, there might be the potential of observer bias (Hawthorne Effect) in intervention studies. Since educational intervention was not carried out in our study, the effect of knowledge increment on reducing the impact on QOL could not be observed.

This study had a few limitations. The major limitation was that most of the subjects had mild psoriasis. As a consequence, the result may not adequately represent patients with moderate and severe psoriasis. In addition, there was misclassification bias among patients with special sites such as the genitalia, face and palms. They may be wrongly classified as having mild psoriasis since disease severity was based on PASI, and special sites are not considered in PASI calculation. Future research should study the effect of educational intervention towards improving QOL among patients suffering from psoriasis.

Conclusion

In summary, severe psoriasis was associated with higher impairment in QOL. However, there was no correlation between knowledge and severity of psoriasis, as well as between knowledge and QOL. Future research should quantify the effect of patient education intervention, to investigate if knowledge increment will improve their disease severity and QOL.

Conflict of Interest Declaration

The author have no conflict of interest to declare.

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ORIGINAL ARTICLE

The Socio-demographic and Quality of Life of People Living with HIV (PLHIV) Presenting with Cutaneous Manifestation: A Cross-Sectional Study in the Department of Dermatology, Sarawak General Hospital

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Abstract

Background

People living with Human Immunodeficiency Virus (PLHIV) are living longer with the advent of highly active antiviral therapy (HAART). Aside from extending the life span, quality of life is vital in PLHIV management. However, there is a paucity of data on the cutaneous manifestations in PLHIV on HAART. The objective of this study is to ascertain the prevalence of cutaneous manifestations, effect on daily lives, and relation to CD4 levels.

Methods

This is a prospective cross-sectional study comparing 2 groups of PLHIV patients on HAART and not on HAART therapy done from March 2020 to November 2020.

Results

A total of 259 patients were recruited in this study with a mean age of 40 years. There were 216 (83.4%) male and 43 (16.6 %) female. Men having sex with men accounts for 49%. The most common cutaneous disorder was post-inflammatory pigmentation (20.4%). Infective dermatoses were 43 (6.7%), and cutaneous malignancy 3 (0.6%). Mean DLQI in PLHIV on HAART were 2, as compared to PLHIV not on HAART which scored 3. Bidayuh ethnicity accounts for 30% of adverse drug reactions with Bactrim being the most common drug.

Conclusion

There is a high prevalence of dermatoses in PLHIV. HAART increases the CD4 count of patients thereby reducing the risk of opportunistic infection and related disorders. However, it did not reduce the cutaneous manifestations in PLHIV, as HAART itself may increase the risk of adverse cutaneous drug reactions. DLQI is not the best tool to assess quality of life.

Key words: *Human Immunodeficiency Virus, quality of life, cutaneous manifestation*

Introduction

Human Immunodeficiency Virus (HIV) is a multifaceted burden of modern society. The march on awareness and control of HIV infections resulted in a successful reduction in the number of new infections and deaths. However, there is a continuous increase in the number of people living with HIV (PLHIV) globally. In 2019, Malaysia recorded a total of 87 000 HIV cases, of which 5 600 are newly

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diagnosed with 2 600 deaths from HIV.[1]

HIV was first described in 1981 in light of 5 cases of Pneumocystis carinii pneumonia (PCP) among previously healthy young men. There is no cure but a lifelong manageable therapy. Highly Active Antiviral Therapy (HAART) inhibits HIV proliferation hence suppresses the viral load and leads to improvement of CD4 function. Due to the nature of persistent viral reservoir, complete eradication is not possible with current therapy.[2] HAART extends the life span of people living with HIV (PLHIV) and sustains the nation's powerhouse as this infection predominates in young to middle-aged adults.[3] The focus on the quality of life in PLHIV is emerging in the literature across the world as researches for cure are underway.

The prevalence of cutaneous manifestations in acute HIV-infected patients is greater than 90%.[4] They range from subtle to severe impairment in the quality of life. On the contrary, data on mucocutaneous disorder in chronic HIV infection is lacking. These data are crucial to aid in understanding and improving the quality of life in PLHIV.

This study aims to determine the prevalence of dermatoses with its impact on the quality of life and to determine the correlation between various factors (demographic, HAART, severity of immunosuppression) in PLHIV.

Materials and Methods

This is a prospective, cross-sectional study conducted on adult HIV-infected patients from March to November 2020 (8 months). Patients were recruited from the HAART Clinic of Sarawak General Hospital, a tertiary referral center in East Malaysia.

Approval from the Medical Research and Ethics Committee was obtained before the commencement of this study (NMRR approval code: NMRR-19-3446-52216). Consented subjects were examined, notes reviewed and then subjected to Dermatology Life Quality Index (DLQI) questionnaire.

DLQI is a user-friendly validated tool used to assess impact of skin diseases on the quality of life. In this study, validated DLQI both in Bahasa Melayu and English language were used. It consists of 10 questions concerning patients' perception on different aspect of daily living in the past weeks. The DLQI is calculated by adding the score of each question, resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. Impact on the quality of life is as follow;

- 0 – 1 no effect at all on patient's life
- 2 – 5 small effects on patient's life
- 6 – 10 moderate effects on patient's life
- 11 – 20 very large effect on patient's life
- 21 – 30 extremely large effect on patient's life.

Cases that required further management will be referred to the Dermatology Department of Sarawak General Hospital. Stable HAART is defined as the duration of HAART treatment for more than 1 year.[5]

Data on demographic, dermatological diagnosis, and characteristics were recorded and analyzed using SPSS Version 21. Descriptive statistics were presented as counts and percentages for categorical variables. Fisher's exact test was used for analysis of dermatoses comparing HAART treated and HAART not treated group as the data collected were of small sample size and non-parametric distribution. Statistical significance was set at $p<0.05$. As for the correlation analysis, Spearmann's rho method analysis was used data.

Results

A total of 261 patients were seen in HAART Clinic. Out of these, 1 patient declined to participate while another patient had false-positive result of HIV. This resulted in a final sample size of 259. Among the study population, 13.1% required dermatology referral, 35.9% were given a prescription, and 1.1% had skin biopsy done. Demographic characteristics are shown in Table 1.

Table 1. Characteristics of the study population

Characteristics	n	%
Age	40.7±12.68 (18-87)	
18-29	61	23.6
30-39	76	29.3
40-49	61	23.6
>50	61	23.6
Gender		
Male	216	83.4
Female	43	16.6
Ethnicity		
Malay	82	31.7
Bidayuh	62	23.9
Chinese	58	22.4
Iban	47	18.1
Others	3	1.2
Indian	2	0.8
Kayan	2	0.8
Melanau	1	0.4
Kelabit	1	0.4
Kenyah	1	0.4
Education		
None	1	0.4
Primary	40	15.4
Secondary	132	51
Tertiary	86	33.2
Marital status		
Single	172	66.4
Married	77	29.7
Divorced	9	3.5
Widowed	1	0.4
Occupation		
White collar	39	15.1
Blue collar	131	50.6
Housewife	11	4.2
Unemployed	78	30.1
Mode of Transmission		
Homosexual	105	40.5
Heterosexual	96	37.1
Bisexual	23	8.9
Unknown	20	7.7
IVDU usage	12	4.6
Vertical	3	1.2
CD4		
>500	68	26.3
200-499	115	44.4
<200	74	28.6
Not available	2	0.8
Viral load		
<200 copies/ml	197	76.1
>200 copies/ml	35	13.5
Not available	27	10.4
On HAART treatment		
No	38	14.7
Yes	221	85.3
Duration on HAART		
<1 years	57	25.8
>1 years	164	74.2

Table 2. Comorbidities in PLHIV

Comorbidities		n	%
Before HIV diagnosis		68	26.3
After HIV diagnosis		45	17.4
Non-infective			**83.2**
	Dyslipidaemia	26	15
	Hypertension	25	14.5
	Atopic Diseases	24	13.9
	Diabetes mellitus	18	10.4
	Chronic Kidney Disease	6	3.5
	Psychiatry disorders	5	2.9
	Gastritis	5	2.9
	Adrenal insufficiency	4	2.3
	G6PD	3	1.7
	Malignancy	3	1.7
	Ischemic heart disease	3	1.7
	Seizure	3	1.7
	Stroke	2	1.2
	Gout	2	1.2
	Pregnant	1	0.6
	Liver cirrhosis	1	0.6
	Anaemia	1	0.6
	Others	16	9.2
Infective			**16.8**
	Syphilis	31	17.9
	Tuberculosis	20	11.6
	Hepatitis C	5	2.9
	Hepatitis C and Syphilis	4	2.3
	Hepatitis B and Tuberculosis	4	2.3
	Hepatitis B	3	1.7
	Hepatitis C and Tuberculosis	3	1.7
	Tuberculosis and Syphilis	3	1.7
	Hepatitis B and Hepatitis C	2	1.2
	Hepatitis B and Syphilis	1	0.6

The mean age in this study population was 40.1 years (ranging from 18 to 87 years). The

mean age of HIV diagnosis was 35.7 years. There were 216 (83.4%) males and 43 (16.6 %) females, with a ratio of male to female being 5 to 1. Eighty-two subjects are Malay (31.7%), followed by Bidayuh (23.9%), Chinese (22.4%), Iban (18.1%) and foreigners (1.2 %).

The literacy rate was high (99.6%), of which 51% PLHIV had secondary school education, and 33.2% had tertiary education, meanwhile only one subject did not have any formal education. Hence the corresponding DLQI was obtained via assistance. There is a great role for designing interactive questionnaires for low-literate persons. Majority of the participants were single (66.4 %), whereas only 29.7% of the subjects were married. Blue-collar workers recorded the highest distribution which accounts for 50.6%, whereas unemployment was 30 %. Sexual transmission was the most common mode of infection. Homosexuality accounted for 40.5 percent, followed by heterosexuality (37.1%), IVDU (4.6%), and vertical transmission (1.2%).

The mean CD4 count was 362 cells/m³ with 74 participants (28.6%) who had CD4 level below 200 cells/mm³. There were 85.3% of participants who were on HAART treatment with the mean duration of 2.9 years (ranges up to 18 years from the initiation of treatment). In addition, prior HIV diagnosis, 26.3% had pre-existing comorbidity, where else 17.4 % developed new comorbidity after HIV diagnosis. Non-infective comorbidities in this study population were dyslipidemia 15%, hypertension 14.5%, diabetes mellitus 10.4%, atopic diseases 13.9%, psychiatry disorders 2.9% and others (Table 2). Infective comorbidities account for 16.8% of the participants which include syphilis 17.9%, tuberculosis 11.6 %, hepatitis C 2.9%, and hepatitis B 1.7%, while the remainder is attributed to mixed infection.

The overall prevalence of cutaneous manifestations in PLHIV was 90.7%, whereas for PLHIV on HAART was 78.9%. In this study, 64.9% of PLHIV had more than 1 type of cutaneous diagnosis. Two types of dermatoses were the highest, accounting for 92 participants (41.6%). The highest number of dermatoses were 6 (0.9 %) (Table 3). In this study, stable PLHIV on HAART with CD4 more than 200 cells/mm³ accounts for 64.7%, where as, CD4 less than 200 cells/mm³ were 9.5%. A total of 481 dermatoses were found in 259 patients. Table 4. As high as 48.6% participants in this study complained of pruritus, whereas aesthetic concerns were 29.5 %, scaly skin 18.6%, and pain 3.2%.

The types of dermatoses were divided into infective 8.1%, non-infective 87.9%, malignant 0.6%, and drug-induced adverse events 1%. In comparison between HAART-treated and untreated ones, drug-induced maculopapular eruption was statistically significant ($p = 0.01$). Table 4.

The negative correlation coefficient between the severity of immunosuppression with DLQI was not statistically significant (Spearman's rho correlation coefficient, $p = -0.23$). There was an extremely large effect on the quality of life in PLHIV with severe immunosuppression (Table 5). Untreated HIV participants had a mean DLQI of 3, meanwhile treated HIV participants had a mean DLQI of 2. However, there was no statistically significant difference in DLQI between the treated and untreated group.

Table 3. Number of dermatoses in the study population in correlation with CD4 and duration of HAART

Duration HAART	CD4, cells/mm³	Number of dermatoses, n						
		0	1	2	3	4	5	6
< 1 years	>500	2	1	2	1	0	0	0
	201-499	3	7	7	6	1	0	0
	<200	1	4	15	5	1	1	0
> 1 years	>500	7	14	23	11	4	1	0
	201-499	9	25	36	9	2	1	1
	<200	0	5	9	3	3	0	1

Table 4. Distribution of dermatosis in PLHIV on HAART and without HAART

Dermatosis	Not on HAART, n (%)	On HAART, n (%)	*p-value*
	N=68	N=413	
Infective dermatosis			
Fungal			
Tinea coporis	1(1.5)	9(2.1)	*0.98*
Tinea pedis	0	9(2.1)	*0.36*
Tinea Cruris	2(2.9)	3(0.7)	*0.16*
Tinea capitis	1(1.5)	1(0.2)	*0.27*
Onychomychosis	0	2(1.5)	*0.10*
Bacterial			
Impetigo	1(1.5)	1(0.2)	*0.27*
Ecthyma	0	1(0.2)	*0.98*
Syphilis	0	1(0.2)	*0.98*
Viral			
Genital warts	3(4.4)	6(1.5)	*0.13*
Non genital warts	2(2.9)	2(4.9)	*0.10*
Herpes zoster	1(1.5)	2(4.9)	*0.31*
Molluscum contagiosum	0	2(4.9)	*0.97*
Parasites			
	0	0	*NA*
Non infective Dermatosis			
Inflammatory disorder			
Post inflammatory pigmentation	15(22.1)	83(20.1)	*0.86*
Xerosis	9(13.2)	70(16.9)	*0.45*
Folliculitis	5(7.4)	25(6.1)	*0.78*
Eczema	2(2.9)	22(5.3)	*0.55*
Contact dermatitis	0	19(4.6)	*0.09*
Seborrheic Dermatitis	4(5.9)	12(2.9)	*0.23*
Acne vulgaris	2(2.9)	7(1.7)	*0.62*
Psoriasis	2(2.9)	5(1.2)	*0.27*
Nail pitting	1(1.5)	4(1)	*0.55*
Chronic spontaneous urticaria	0	4(1)	*0.92*
Livedo reticularis	1(1.5)	2(0.5)	*0.14*
Stasis eczema	0	2(0.5)	*0.93*
Cheilitis	0	1(0.2)	*0.97*
Prurigo nodularis	0	1(0.2)	*0.97*
Ulcer	0	1(0.2)	*0.97*
Post Infective desquamation	1(1.5)	0	*0.15*
Thrombophlebitis	1(1.5)	0	*0.15*
Pruritic papular eruption	0	0	*NA*
Oral lesions	0	0	*NA*
Non-inflammatory disorder			

Scars	2(2.9)	24(5.8)	*0.39*
Tattoo	3(4.4)	16(3.9)	*0.75*
Melanonychia	3(4.4)	15(3.6)	*0.73*
Chronic paronychia	1(1.5)	14(3.4)	*0.71*
Scabs	0	9(2.2)	*0.36*
Subungual hematoma	1(1.5)	1(0.2)	*0.27*
Sebaceous cyst	0	1(0.2)	*0.98*
Scrotal angioma	0	1(0.2)	*0.98*
Acanthosis nigrican	0	1(0.2)	*0.98*
Striae	0	1(0.2)	*0.98*
Lipoid atrophy	0	1(0.2)	*0.98*
Lipoma	0	1(0.2)	*0.98*
Tophi	0	1(0.2)	*0.98*
Delusional parasitosis	0	1(0.2)	*0.98*
Ganglion cyst	0	1(0.2)	*0.98*
Degenerative disorder			
Deformed nail	0	8(1.9)	*0.61*
Seborrheic keratosis	0	4(1)	*0.90*
Cherry angioma	0	3(0.7)	*0.95*
Alopecia	0	3(0.7)	*0.95*
Skin tag	0	3(0.7)	*0.95*
Callus	0	2(0.5)	*0.97*
Guttate hypomelanosis	0	1(0.2)	*0.99*
Malignant			
Kaposi Sarcoma	1(1.5)	2(0.5)	*0.38*
Squamous cell carcinoma	0	0	*NA*
Basal cell Carcinoma	0	0	*NA*
Melanoma	0	0	*NA*
Drugs adverse event			
Maculopapular lesion	3(4.4)	1(0.2)	*0.011*
Acne	0	1(0.2)	*0.98*

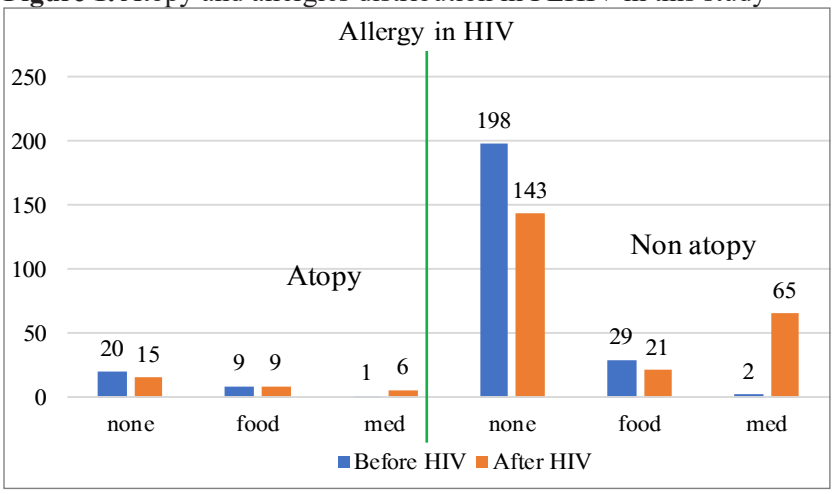
NA: not available as the statistic analysis is unable to perform for the comparison to obtain p-value
p-value is obtain from Fisher exact test
**One patient may have multiple mucocutaneous manifestations; the percentage reported is based on total patients in each group*

Table 5. Correlations of severity of immunosuppression with DLQI in PLHIV

CD4, cells/mm³	DLQI, n (%)				
	No effect	**Small effect**	**Moderate effect**	**Very Large effect**	**Extremely Large effect**
>500	57(22.2)	9(3.5)	2(0.8)	0	0
200-499	79(30.8)	25(9.8)	9(23.5)	1(0.4)	1(0.4)
<200	41(16)	20(7.8)	10(3.9)	1(0.4)	2(0.8)

Spearmann's rho corelation shows negative corelation with insignificant p =0.224

Figure 1. Atopy and allergies distribution in PLHIV in this study



None: no allergy; Food: allergy to food; Med: allergy to medication

A quarter of the allergies (25.1%) in PLHIV were attributed to medication. In non-atopy arm, 143 participants (55%) remain allergy-free after initiation of HAART (Figure 1). Allergy incidents before and after HIV diagnosis were 41(16%) and 101(39.3%) respectively. However, these differences were not statistically significant. (Table 6).

Table 6. Overview of DLQI scores in this study

DLQI Severity	DLQI score	n	%
No effect	0	125	48.3
	1	53	20.5
Small effect	2	29	11.2
	3	11	4.2
	4	8	3.1
	5	7	2.7
Moderate effect	6	5	1.9
	7	7	2.7
	8	3	1.2
	9	3	1.2
	10	3	1.2
Very large effect	11	1	0.4
	15	1	0.4
Very large effect	22	1	0.4
	24	1	0.4
	25	1	0.4

A total of 91 participants had adverse drug event. Despite the Malay race having the highest prevalence of PLHIV in this study, Bidayuh ethnicity had the most frequent adverse drug reactions (30.8%). Bactrim accounts for the highest incidence 64.8%, followed by HAART 12.1%, dapsone 8.8%, antibiotics 7.7 %, and others 6.7%. (Table 7).

Table 7. Distribution of adverse drug event based on ethnicity in PLHIV in Sarawak

Ethnic\ Drugs	Bactrim	Dapsone	HAART	Antibiotics	Others
Bidayuh	19	4	2	2	1
Chinese	11	1	2	1	1
Iban	13	1	4	3	2
Malay	13	2	3	1	2
Indian	1	0	0	0	0
Other	1	0	0	0	0
Kelabit	1	0	0	0	0
Melanau	0	0	0	0	0
Kayan	0	0	0	0	0
Kenyah	0	0	0	0	0

Discussion

HIV infection is complex and multifactorial. The male gender, compounded by homosexual practice, raises the risks of HIV infection. This is consistent with our local[6] and international studies.[7-8] Anal intercourse is associated with a higher rate of infection due to biological factors as compared to vaginal intercourse. However, in other parts of the world, females are the predominant gender.[9-10] This is supported by literatures on the differences in HIV acquisition by gender[11] and pathophysiology of sex and hormone levels with inflammation induced by the microbiome.[12-13]

Adults, young to middle-aged are the most often infected group. This study majority of PLHIV is in between 18 to 39 years old. This is supplemented by our national HIV data in 2018 which shows that 67 % prevalence of HIV infection occurs in those who are 20 to 39 years old. Data from CDC US in 2019 states that, the rate of HIV infection was highest for persons aged 25–34. Curiosity and the drive to be unique are probably the key factors to the rate of infection in this region. Additionally, social media, population density, adaptive change in urbanisation and information accessibility could be the other contributing factors.

Comorbidities observed in stable HIV were mainly non-infective, where as in acute HIV infection, infective disorders predominate.[14] Significant metabolic disorders in this population are attributed to HAART itself and the other conventional risk factors such as diet, lifestyles, and genetic predispositions. Once PLHIV is stable, clinicians are left with another hurdle to manage the arising comorbidity and focus on the quality of life.

This study recorded 74.2% of stable PLHIV on HAART. In this group, the number of diseases is expected to reduce because of improved immune systems. On the contrary, the number of dermatoses observed have increased. Non-HIV related cutaneous malignancy was not observed in this study despite the older HIV-infected population. Kaposi sarcoma with an incident of 1.2% was the only cutaneous malignancy observed. It is associated with men who have sex with men (MSM) practice. Usage of saliva as a lubricant was postulated to be the main principle of transmission as the viral load of Kaposi sarcoma in the semen is substantially low.[15] Also called human herpesvirus-8, has since been shown to be the etiologic agent for several other tumors and diseases, including primary effusion lymphoma (PEL Half of the Kaposi sarcoma in this study failed to achieve complete resolution despite being stable HAART, which is consistent with the previous research.[16] These findings can be explained by immune deviation instead of normalising immune function due to HAART via persistent HIV replication in memory T lymphocytes despite optimal HIV virus control.[17] There were no statistically significant differences between cutaneous manifestations in a treated and untreated patient in this study ($p = 0.357$). As PLHIV are surviving longer, degenerative cutaneous disorders are more apparent in our study. However, more comparison data is required to conclude this finding.

The occurrence of genital warts was higher in PLHIV not on HAART, as compared to those on HAART. High-risk Human Papillomavirus (HPV) types commonly affect the anogenital and the oral cavity.[18] Prolonged life span in stable HAART group predisposes to oncogenic transformation.[19] HAART had not been shown to reduce incidents of HPV-related cervical diseases in women living with HIV.[20] The impact of HAART on cervical cancer, however, remains uncertain. The objective of this review is to summarize the last ten years of registry-based and clinical research into the impact of HAART on human papillomavirus Census from Human Papillomavirus and Related Diseases Report Malaysia recorded significant HPV-related cervical cancer in the high-risk type of HPV in the non-HIV population. Data on HPV related cancer in the treated HIV population in this region is lacking. HPV vaccination have since been included in the national vaccination scheme for 13-year-old girls in schools since 2012. Data on the effective regime of HPV vaccination in PLHIV is lacking,[21] hence more trials are needed before implementation in the national health scheme.

Impact on living due to cutaneous manifestation was highest in the stable HIV with higher CD4 levels. This is due to a higher number of dermatosis and demand on quality of life as a struggle to blend into stigmatised society towards HIV. However, a lower mean DLQI score compare to a recent study, could be explained by different expectations of the quality of life in different urban populations; Johor (East Malaysia)[22] and Kuching, Sarawak (West Malaysia). Furthermore, population

with lower socioeconomic status are more ignorant of the non-life-threatening nature of the cutaneous manifestation, resulting in an underrepresentation of the actual situation. Despite 85.3% of PLHIV are on HAART in Kuching which is higher than the national statistics record of 48%, the unemployment rate is significant at 30% in contrast to local unemployment rates of 15% (2018, Sarawak statistics). This result is also observed in France where the unemployment rate in PLHIV is 15.9% as compare to 6.1% in the population in 2011.[23] unemploymet has increased among people living with HIV. Employment is one of the important defining factors on the quality of life. The high unemployment rate in the background of high literacy rate is the result of social stigma, discriminatory policies prohibitive laws and ultimately, the lack of societal support. Another factor with great impact on the quality of living is the side effect of HAART which is statistically significant in this study. Due to the nature of this study, no severe cutaneous adverse reactions syndrome (SCARS) was reported as most SCARS would necessitate inpatient treatment.

The limitation of this study is the small sample size and the absence of data from suburban areas. Covid-19 pandemic has a significant implication on both the quality and quantity of the data collected in this study.

Conclusion

There is a shift in the mode of transmission from intravenous to sexual route and from infective to non-infective disorders in PLHIV. Ultimately, our findings revealed that, despite the introduction of HAART, the number of cutaneous manifestations in HIV patients have not significantly reduced. Quality of living in PLHIV is best defined by unemployment rate and ADR rather than DLQI scoring due to the socioeconomic factors. As we embark on our quest to cure HIV and raise the standard of living of those living with HIV, we will constantly face new challenges. A comprehensive registry and awareness are needed to provide a clearer picture to redefine management guidelines.

Conflict of Interest Declaration

The authors have no conflict of interest to declare. There is no affiliation or significant financial involvement in any organisation or entity with direct financial interest in the subject matter or materials discussed in the manuscript.

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ORIGINAL ARTICLE

Dermatoses in Human Immunodeficiency Virus Infected Patients with A Focus on Infections: A 12-month Cross-sectional Study in Hospital Sungai Buloh

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Abstract

Background

Cutaneous disorders are common clinical manifestations of the Human Immunodeficiency Virus (HIV). In the era of antiretroviral therapy (ART), the spectrum of cutaneous disorders in HIV-infected patients has changed. We assessed the types of dermatoses, including cutaneous infections in HIV-positive patients and the association between the peripheral CD4 cell count and the severity of skin infection.

Methods

All HIV-positive patients referred to the Dermatology Department of Hospital Sungai Buloh from January 2021 – December 2021 were enrolled in a prospective cross-sectional study. Patients were subjected to a complete medical and physical examination and appropriate investigation to confirm the diagnosis.

Results

A total of 112 (92.6%) male and 9 (7.4%) female patients with a mean age of 38.76 ± SD years participated. The majority of patients were Malay (56.2%), with MSM (54.5%) being the commonest mode of transmission. 65.2% of patients had CD4≥350 cells/ mm^3 and 86.7% of patients were on ART. Infections (56.1%) were the most common group of mucocutaneous manifestations, with 45.6% of these due to viral infections. There was no statistically significant correlation between the CD4 count and the severity of skin involvement in bacterial (*p=0.302*), viral (*p=0.145*) and fungal (*p=0.533*) infections.

Conclusion

Viral infection were the commonest cutaneous manifestations in HIV- positive patients. The frequency and severity of the cutaneous infections were much more common in patients with more advanced immunosuppression.

Keywords: *HIV, mucocutaneous manifestations, CD4 count*

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Introduction

Cutaneous disorders are common clinical manifestations of the Human Immunodeficiency Virus (HIV). These skin manifestations are not only associated with terminal immunodeficiency but also occur throughout the course of HIV

infection.[1] More than 90% of patients will develop skin lesions at some time during their illness.[2-3]

Skin diseases have been proven to be a sensitive and useful measure by which HIV progression can be monitored. With diminished and dysregulated cell-mediated immunity, HIV-infected individuals are susceptible to myriad skin conditions[4], which can be broadly classified into infectious and noninfectious dermatoses. Although these skin manifestations are also encountered in immunocompetent individuals, their occurrence in HIV-infected patients tend to present earlier, are often atypical, more severe, explosive, extensive or resistant to therapy.[5]

The clinical spectrum and prevalence of skin disorders in HIV- infected patients are well documented in western populations. However, there are fewer data available from Asia. Bender et al. found significant racial differences in the prevalence and risk of dermatological conditions in patients with HIV.[6] Studies in Singapore and Thailand reported notable differences in the prevalence and types of skin conditions in their local population of HIV- infected patients compared to the Western cohorts.[7]

This study aimed to determine the type of dermatoses affecting HIV-infected patients, describe the types of cutaneous infections and determine the relationship between HIV-related immunodeficiency with type and severity of cutaneous infection in a Malaysian HIV-infected population.

Materials and Methods

A prospective cross-sectional study was performed. The study population was all HIV-positive patients referred to the Dermatology Department in Hospital Sungai Buloh for assessment who fulfilled the inclusion and exclusion criteria during the study period from January 2021 – December 2021. Hospital Sungai Buloh is the main referral center for Infectious diseases and HIV in Malaysia and serves a large number of Klang Valleys HIV-positive population. Accessibility to a large cohort of HIV-positive individuals provides an opportunity to fully explore the prevalence of skin infections of HIV-infected patients in our local population. The inclusion criterion was Malaysian, HIV- positive patients aged 18 and above. HIV-infected patients with adverse drug reactions were excluded from the study.

All patients were subjected to a detailed face-to-face interview and physical examination. Information was collected on demography details, mode of transmission of HIV infection, Anti-retroviral therapy (ART) treatment, most recent CD4 count and viral load. When required to confirm a diagnosis, appropriate investigations were performed as per standard clinical management. This included, when necessary, skin biopsies, tissue cultures, tzank smears, skin scrapings and PCR analysis. The mucocutaneous manifestations were classified as skin infections (bacterial, fungal, viral and parasitic infections) or inflammatory dermatoses (eczematous, psoriasis, seborrheic dermatitis and Pruritic Papular Eruption in HIV). Cutaneous infections were subsequently subclassified into superficial or subcutaneous skin infections.

The sample size of this study was calculated based on a cross-sectional study by Uthayakumar et.al[8] Sample size estimation was calculated using the population proportion formula. The prevalence of cutaneous manifestations in HIV-infected patients was 0.914. The population size of 1000 was based on Hospital Sungai Buloh's internal database. The Type I error probability in rejecting the null hypothesis was 0.05. With the additional 5% dropout rate, the sample size required was 114 patients.

Analysis of the data was done using the IBM-Statistical Package for the Social Sciences (IBM-SPSS®) version 25.0 for Windows. Descriptive statistics described the sample characteristics. Continuous variables were expressed as mean and standard deviation. For non-normally distributed data, median and interquartile ranges were used. For categorical

variables, frequency and percentage were used to present the data. Fischer exact test tested the hypothesis of whether there was an association between type of infection and CD4 count categories. The level of significance was set at 0.05 with two-tailed probabilities. A p value less than 0.05 concludes significant associations between two categorical variables.

This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guidelines. Data collection was commenced after obtaining Medical Research and Ethics Committee approval. (Approval reference: KKM/NIHSEC/P20-2250(11)).

Results

A total of 121 HIV-positive patients were enrolled. Of these, 112 (92.6%) were male and 9 (7.4%) were female. The majority of the patients were Malay (56.2%), followed by Chinese (33.9%) and Indians (9.9%). Their average age was 38.7 years. The commonest mode of HIV transmission was men who have sex with men (MSM) (54.5%). Heterosexual and intravenous drug use (IVDU) accounted for 29.8% and 10.7% of transmission respectively. A total of 79 patients (65.2%) had CD4 $\geq$ 350 cells/mm^3 and 34.7% had CD4 < 200-349 cells/mm^3. The majority of the patients were on antiretroviral therapy (ART) (86.7%). Characteristics of the study population are summarized in Table 1.

When screening for cutaneous infections, 43.8% of the patients had non-infective skin dermatoses commonly associated with HIV, including seborrheic dermatitis (11.5%), psoriasis (3.3%), eosinophilic folliculitis (6.6%), pruritic papular eruption in HIV (14.8%) and papular eczema (7.4%). This is summarized in Table 2.

The most common cutaneous manifestations seen were infectious in origin. Of the 121 patients enrolled in the study, 68 (56.1%) patients had infectious lesions. Table 3 summarizes the type of cutaneous infections in the study population. Sixteen out of the 68 patients (23.5%) in this subgroup had cutaneous bacterial infections. This included botryomycosis (1.4%), folliculitis (11.8%), cutaneous tuberculosis (4.4%) and cutaneous manifestations of syphilis (5.9%).

The diagnosis of botryomycosis was suspected clinically. The patient presented with a fleshy, subcutaneous nodule which developed into a non-healing ulcer over the dorsum of the hand. Tissue culture grew *Staphylococcus aureus*. The patient was treated with amoxycillin/clavulanic acid and responded well with resolution of the lesion after 2 weeks of treatment.

Viral Infections accounted for the majority of infective cutaneous lesions (45.6%). Ten patients (14.7%) had cutaneous lesions due to *human papillomavirus* (condyloma acuminata), 7.4% of patients had lesions due to *poxvirus* (molluscum contagiosum), *herpes simplex virus* (oral and anogenital ulcers) and *human herpes virus* (Kaposi sarcoma). 8.8% of patients had lesions due to *Varicella zoster virus* infection (Varicella Zoster).

Cutaneous fungal infections accounted for 26.5% of infectious lesions. Talaromycosis (14.7%), histoplasmosis (1.4%), sporotrichosis (2.9%) and dermatophyte infection (7.4%) were the second most common infectious causes seen in the study population after viral infections. Three (4.4%) cases of parasitic infections (scabies) were encountered.

Sub analysis was done to determine the association between cutaneous infections with the CD4 count. The cutaneous infections encountered were grouped based on their invasiveness or severity. Superficial cutaneous infections were defined as infections of the epidermis, hair and nails. These included molluscum contagiosum, folliculitis, varicella zoster infection, scabies, tinea corporis, tinea cruris, genital warts and herpes simplex infection.

Infections that penetrated the epidermis and the dermis to infect the deeper tissues were classed as subcutaneous or systemic infections.

Table 1: Characteristics of the study population

Characteristics	Mean±SD or n (%)
Age, in years	38.76±10.96
Minimum	18
Maximum	74
Gender	
Male	112 (92.6)
Female	9 (7.4)
Ethnicity	
Malay	68 (56.2)
Chinese	41 (33.9)
Indian	12 (9.9)
Duration of HIV diagnosis (months)	58.41±42.59
Minimum	12
Maximum	240
Mode of transmission	
MSM	66 (54.5)
Heterosexual	36 (29.8)
IVDU	13 (10.7)
Undisclosed	6 (5.0)
CD4 count	
CD4 ≥ 350 cells/mm^3	79 (65.2)
CD4 < 200 -349 cells/mm^3	42 (34.7)
Viral load	
Suppressed (< 200 copies/ ml)	67 (55.3)
Not suppressed (> 200 copies/ ml)	54 (46.6)
Not Available	5 (4.1)
ART	
No	16 (13.2)
Yes	105 (86.7)
Systemic co-morbidities	
Diabetes	7 (5.7)
Hypertension	7 (5.7)
Hepatitis/ Liver Cirrhosis	11 (9.1)
Syphilis	12 (9.9)
Tuberculosis	10 (8.2)

Table 2: Types of non-infective dermatoses affecting HIV-infected patients in Sungai Buloh Hospital

Type of Dermatoses	n (%)
Seborrheic Dermatitis	14 (11.5)
Psoriasis	4 (3.3)
Eosinophilic Folliculitis	8 (6.6)
Eczematous Dermatoses	
Pruritic Papular Eruption in HIV	18 (14.8)
Papular Eczema	9 (7.4)

These included kaposi sarcoma, cutaneous tuberculosis, sporotrichosis, secondary syphilis, histoplasmosis, botryomycosis and penicilliosis. Table 4 summarizes these findings.

Amongst patients with subcutaneous or systemic bacterial infections, 77.8 % had a CD4 < 200-349 cells/mm^3 and 22.2% had a CD4 ≥ 350 cells/mm^3. Majority of cutaneous viral infections were in patients with CD4 < 200-349 cells/mm3, for both superficial and subcutaneous infections. In patients with subcutaneous/ systemic fungal infections,11 patients had a CD4 < 200-349, compared to 2 patients with CD4 > 350 cells/mm^3. Subcutaneous or systemic viral infections were found in all patients with CD4 <200-349 cells/mm^3. There was no significant association between CD4 count with severity of infection

Overall, when comparing all types of superficial infections (bacterial, viral and fungal), 22 patients had a CD4 < 200-349 cells/mm^3 and 17 patients had a CD4 ≥ 350 cells/mm^3. The difference was more obvious when comparing subcutaneous/ systemic infections with 24 patients having CD4 < 200-349 cells/mm^3 and only 6 patients with CD 4 ≥ 350 cells/mm^3

Table 3: Types of cutaneous infection in the study population

Type of Infection	n (%)
Bacteria	**16 (23.5)**
Botryomycosis	1 (1.4)
Folliculitis	8 (11.8)
Cutaneous Tuberculosis	3 (4.4)
Syphilis	4 (5.9)
Viral	**31 (45.6)**
Herpes simplex Virus	5 (7.4)
Varicella Zoster Virus	6 (8.8)
Human Papillomavirus (condyloma acuminata)	10 (14.7)
Poxvirus (molluscum contagiosum)	5 (7.4)
Human Herpes Virus (Kaposi Sarcoma)	5 (7.4)
Fungal	**18(26.5)**
Talaromycosis	10 (14.7)
Histoplasmosis	1 (1.4)
Sporotrichosis	2 (2.9)
Dermatophytes	5 (7.4)
Parasitic	**3 (4.4%)**
Scabies	3 (4.4)

Table 4: Relationship between HIV-related immunodeficiency based on CD4 count with the type of cutaneous infection

Type of infection, n (%)	CD4 count		*p*-value
	< 200 -349 cells/mm^3 n (%)	≥350 cells/ mm^3 n (%)	
Bacteria (n=16)			0.302
Superficial	3 (42.9)	4 (57.1)	
ubcutaneous	7 (77.8)	2 (22.2)	
Virus (n=31)			0.145
Superficial	16 (64.0)	9 (36.0)	
ubcutaneous	6 (100)	0 (0)	
Fungus (n=18)			0.533
Superficial	3 (60.0)	2 (40.0)	
ubcutaneous	11 (84.6)	2 (15.4)	

Discussion

It is estimated that 87,041 people live with HIV (PLHIV) in Malaysia at the end 2018.[9] Skin disorders are extremely common in PLHIV and in many patients, they may be the earliest sign of HIV disease.[10]

The epidemiologic profile of dermatologic illnesses in relation to HIV varies between countries.[10] Tan et al and Jing et al found that this is mainly affected by economic and political factors pertaining to the availability of HAART, as well as the risk-taking behavior of patients.[10-11] This study prompted us to revisit these conditions and examine the changing incidence and prevalence of these conditions in the local population of Malaysia.

Demographic and Clinical Characteristics

In this study, the majority of the patients were Malay males with a mean age of 38. This is consistent with our national data [9] stating that > 70% of HIV- infected patients were males between the age of 20 and 39 years. Similar data were reported in 2 other studies in the region, reported by Huang et al in China and Goh et.al in Singapore.[1,7] The trend of HIV epidemic in Malaysia has now shifted to sexual transmission since 2011. Men who have sex with men (MSM) were expected to become the main driver for the epidemic [9] and this is reflected in the results of this study with the commonest mode of transmission being MSM (54.5%). The main aim of the Global AIDS Monitoring indicators was to have at least 90% of people who know their HIV-positive status accessing ART by 2020.[12] In this study, 86.7% of the study population were on ART, with 55.3% having suppressed viral loads.

Types of dermatoses affecting HIV-infected patients

Skin disease may be uniquely associated with HIV infection or AIDS, but is more often due to common disorders that are more severe and recalcitrant to treatment in HIV patients.[13] Seborrheic dermatitis, psoriasis and varicella zoster virus infection are examples of common clinical skin conditions that are both more frequent and more severe with advanced immunosuppression. Kaposi sarcoma and pruritic papular eruption (PPE) in HIV are examples of skin disorders that serve as a marker of disease progression.[14] These cutaneous conditions can also present as new dermatological manifestations related to Immune reconstitution inflammatory syndrome (IRIS) or as worsened forms of previous disease.[15]

In this study, 43% and 56.1% of patients had non-infective and infective lesions respectively. Of the non-infective lesions, purpuric papular eruption (PPE) in HIV was the most common diagnosis (14.8%). These results were comparable with Goh et al and Chan et al who reported PPE as the most common non-infectious manifestations in their study cohort at 14.9% and 31% respectively.[7,16] It is well recognized that PPE is a cutaneous marker of advanced HIV infection[7] and this was confirmed in this study with all patients diagnosed with PPE having a CD4 < 200-349 cells/mm^3.

Seborrheic dermatitis (SD) is an early skin manifestation that is mostly seen in patients who have CD4 > 200.[17] In this study, SD was found to be the second most common noninfectious manifestation (11.5%), which was also reported by Edith et al.[17] Four (3.3%) of patients in this study were diagnosed with psoriasis. These results are comparable to an audit done by

Davarpanah et al and Supanaranond et al which reported 2.9% and 4.7% of their study population who were diagnosed with psoriasis.[18-19]

Eosinophilic folliculitis (EF) is a common skin disorder in individuals with HIV who have CD4 count < 250cells/mm^3 and is uncommon in persons without HIV.[13] Eight (6.6%) patients in this study were diagnosed with EF. Similar results were reported by Goh et al reporting 4% of their cohort being diagnosed with EF.[7]

Cutaneous infections in HIV-infected patients
In HIV-infected individuals, typical skin lesions, with more inflamed, widespread, disfiguring and destructive presentations may be the result of diminished CD4-positive T cell- mediated immune response.[4] In the era of ART, the spectrum of cutaneous infections has changed. However, common cutaneous infections from methicillin-resistant *Staphylococcus aureus* (MRSA) and human papillomavirus (HPV) are growing causes of morbidity and mortality despite overall seemingly improved immune function with antiretroviral therapy.[15]

We found that the most common dermatoses in our cohort of patients were infectious in origin (56.1%). Similar results were reported with slightly higher prevalence by, S. Uthayakumar et al. in the UK, Chan et al in Malaysia and Basida et al in India.[8,16,20]

Cutaneous viral infections have been reported as the most common dermatological disorder among HIV patients in various studies in the past decade. Similar results were observed in this study and in China, Taiwan and India.[1,2,3] In this study, condyloma acuminata contributed the majority of the total viral- related dermatoses (14%). Uthayakumar et al similarly observed condyloma acuminata (14%) to contribute to the majority of cutaneous viral infections.[8] Human papillomavirus (HPV) infection is more common in the HIV/AIDS population, as HPV has been found to facilitate HIV gene expression.[13] Diagnosis and treatment of these lesions are important because of the risk of HPV-associated anal and cervical carcinomas.

It is well recognized that Kaposi sarcoma (KS) develops almost exclusively in HIV positive homosexual men and that homosexual contact is a risk factor for *human herpes virus-8* (HHV-8) acquisition.[7] In this study, Kaposi Sarcoma was diagnosed as frequently as the common cutaneous lesions due to *herpes simplex virus* and *pox virus* (7.4%), suggesting that KS still represents one of the more common HIV associated cutaneous conditions in this population. Interestingly, other studies in this region, i.e., Singapore and Thailand reported no cases of KS in their cohorts.[7,21] The apparent absence of KS in their study to be due to the significantly lower proportion of homosexual individuals in their study population. This is another contrast to the demography this study, where the majority (54.5%) of the study population were homosexual individuals.

Fungal infections were the second most common cutaneous infection observed in this study (26.5%). Talaromycosis accounted for the majority (14%) of fungal dermatoses, a result which was similarly reported by Chan et al and Wiwanitkit.[16,21] The high prevalence of Talaromycosis in this region relative to western studies is likely due to *Penicillium marneffei* being endemic to tropical Asia and is now considered an AIDS-defining illness in endemic areas.[4]

Dermatophyte infections only accounted for 7.4% of total cutaneous fungal infections in our study cohort, which differs from findings in previous studies. Vasudevan et al reported dermatophytosis as the most common cutaneous fungal infection.[22] The reason for this difference seen in this study may be referral bias. Patients with milder skin disorders, that are treatable by HIV physicians may have not been referred to us and therefore, may not represent the true prevalence in the HIV population.

Staphylococcus aureus is the most common cutaneous and systemic bacterial pathogen in HIV- infected individuals. Approximately 54% of AIDS patients experience symptoms due to *S. aureus.*[13] The high frequency of *S. aureus* skin

infections in HIV-infected patients is attributed to high rates of recurrent or chronic nasal carriage in this population, including carriage of methicillin-resistant organisms.[4] This is reflected in the results of this study with 9 out of 16 patients with cutaneous bacterial infections diagnosed with S. aureus skin manifestations; i.e., folliculitis and botryomycosis.

Relationship between immunodeficiency and severity of infection

HIV attacks the helper/Inducer T cells (CD4+ cells), resulting in syncytial formation and lysis with slow but progressive destruction of this cell population. In general, the CD4+ cells (%CD4+ or absolute count) progressively decreases as HIV disease advances.[20]

Traditionally lower CD4 counts are reported to be associated with infective dermatoses.[23] Cutaneous infections encountered among those with CD4 <200-349 cells/mm^3 in our cohort were 2 times more than those with CD4 >500 cells/mm^3. These results are comparable to Chan et al who reported 2.7X more cutaneous infections in patients with a CD4< 500 cells/mm.[3,16]

Overall, when comparing the severity and invasiveness of these cutaneous infections, we observed that those with advanced HIV (CD4 <200-349 cells/mm^3) had relatively higher percentages rates for both, superficial and subcutaneous manifestation for all types of cutaneous infections. S Uthayakumar et al similarly reported an increasing severity index in the skin lesions associated with a CD4 count of less than 200cells/mm^3.[8] Fleischer et al and Kaplan et al. demonstrated a significant association between the number and severity of cutaneous abnormalities and low CD4 count.[24,25]

The difference was not statistically significant in this study. Supanaranond et al and Coopman et al reported no statistically significant association between the incidence of skin infections and the level of CD4 counts.[19,26] The reason for these results may be the small sample size in this sub-group analysis.

Similar studies previously done in Malaysia were retrospective in nature. However, the data from this prospective study is limited by the relatively modest sample size. Further larger-scale prospective studies are needed to better describe the mucocutaneous manifestations of HIV-infected individuals, its changing spectrum in the era of ART and its evolution through the different stages of HIV.

Conclusion

The spectrum of cutaneous disorders in our study differs slightly from data around South East Asia, namely Singapore and Thailand with the preponderance of infective lesions observed in our study. MRSA infections, malignant transformations of HPV disease and Kaposi sarcoma due to HHV-8 infection are likely to continue to increase as HIV populations have longer life expectancies in the era of ART. Awareness of the varied types and patterns of these manifestations would help in the early diagnosis and management of HIV infection and ultimately decrease the morbidity and improve the quality of life of HIV-infected patients.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

Clinical Characteristics of Anogenital Warts Among Patients Attending Genitourinary Medicine Clinic Hospital Kuala Lumpur Between 2015 and 2020

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Abstract

Background

Anogenital human papillomavirus (HPV) is the most frequent reported sexually transmitted infection in the world. We aim to describe the local demographic data and the clinical characteristics of anogenital warts (AGWs).

Methods

This is a retrospective study on all patients with AGWs who attended the GUM clinic between 2015 and 2020. Data was obtained from case notes and further analysed.

Results

A total of 935 patients with AGWs attended the GUM clinic between 2015 and 2020. The mean age was 30.4 years (range 12-84). The male to female ratio was 2.35:1. Majority were Malaysian (97%). Majority of the Malaysian were Malays (61.5%) followed by Chinese (27.7%) and Indian (8.9%). About 5.6% had a history of substance abuse. While the majority (57.9%) were heterosexual, 34.8% were homosexual and 6.4% were bisexual. About 59.8% had more than one sexual partner. A quarter (25.6%) was infected with the human immunodeficiency virus. The most frequent site of AGWs in males was the perianal area (52.6%), followed by the penis (45.7%), and with a fifth of them having lesions at multiple sites. For female patients, the most frequent site of AGWs was the posterior fourchette (45.2%) followed by the labia minora (33%) with 46.6% had involvement at multiple sites. Approximately 17.6% had other concomitant sexually transmitted infections. Local treatment application used included cryotherapy (86.4%), podophyllin (35.3%), tri-chloroacetic acid (26.8%) and imiquimod (2.6%). About 41.5% required combination of these modalities. Nearly 6.2% experienced recurrence. About 2% required surgical intervention.

Conclusions

AGWs was more commonly observed in male. The most frequent site of involvement was perianal for male (52.6%) and posterior fourchette in female (45.2%).

Key words: *Sexually transmitted infections, anogenital warts, Human Papilloma Virus, Human Immunodeficiency Virus*

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Introduction

Anogenital human papillomavirus (HPV) is the most frequently reported sexually transmitted viral infection in the world.[1] HPV 6 and 11 account for the majority of anogenital wart

(AGWs) cases and are highly infectious; approximately 65% of individuals with an infected partner develop AGWs within 3 weeks and 8 months.[2] Recent prospective studies reported that the median time between infection with HPV types 6 or 11 and the development of AGWSs was 11 to 12 months among males and 5 to 6 months among young females.[2] The transmission are predominantly through oral, anal and genital sexual contact, and, in rare instances, through vertical transmission and autoinoculation.[2] AGWs were strongly believed to be associated with high sexual partner numbers and unprotected sexual intercourse. This diagnosis was more common in men who have sex with men (MSM) and in women reporting sex with women.[1,2]

Four distinct sub-types of AGWs have been described which include condylomata acuminata (pointed warts), flat/macular lesions, papular, and keratotic lesions.[3] The first two sub-types are mainly found on moist, non-keratinized epithelia, while the latter two are usually present on keratinized epidermis.[3] They manifest as visible lesions, namely as single or multiple papules on the vulva, perineum, perianal area, vagina, cervix, penis, anus, scrotum and urethra.[3] Clinical symptoms may include pruritus, burning, vaginal discharge and bleeding. In rare cases, AGWs can be associated with malignant lesions, namely Buschke Lowenstein tumours.[3] Although AGWs do not usually result in major immediate morbidity or mortality, the psychological morbidity and very substantial healthcare costs is significant.[4]

This study aims to describe the local demographic data and the clinical characteristics of AGWs at Genitourinary Medicine Clinic, Department of Dermatology, Hospital Kuala Lumpur (HKL).

Materials and Methods

This is a retrospective study on all patients with AGWs attended GUM clinic, HKL between 1st July 2015 and 30th June 2020. Information including demographics, clinical features, human immunosuppressive virus (HIV) status, co-morbidities, co-infections, treatment durations, treatment modalities and recurrent rate was recorded into data collection form. Data collected was further analysed using SPSS version 21.

Results

A total of 935 patients with AGWs attended the GUM clinic, HKL between 2015 and 2020. A quarter (25.6%) of them was infected with the human immunodeficiency virus (HIV). The demographic data is shown in Table 1. The mean age of all the patients at presentation was 30.4 years (range 12-84), with a significant younger mean age among those infected with HIV. Majority of the patients (55.8%) were in the age group between 20-29 years. The male to female ratio was 2.35:1. More than 98% of those infected with HIV were male. Majority were Malaysians (97%) whereby 61.5% were Malays, followed by Chinese, (27.7%) and Indian (8.9%).

While majority (57.9%) were heterosexual, 34.8% were homosexual and 6.4% were bisexual. Interestingly, 80.3% of those infected with HIV were homosexual (vs non-HIV 19.1%, $p<0.0001$). A significant higher number of patients infected with HIV engaged casual sex partner (71.1% vs 28.3%, $p<0.0001$). About 59.8% had more than one sexual partner 6 months prior to presentation and it was significantly higher among HIV infected patients (83.3% vs 51.7%, $p<0.0001$). Fifty-two patient (5.6%) were documented to have substance abuse. About 17.6% had other concomitant sexually transmitted infections. Except chlamydial infection, the rate of syphilis, gonorrhea and herpes genitalis were significantly higher among those infected with HIV. Seventy females (25% of all female patients), all non-HIV infected, were pregnant at presentation. Furthermore, three patients (0.3%) had active malignancy and were undergoing anti-cancer treatment at presentation.

Table 1: Demographic characteristics of 935 patients attending GUM clinic Hospital Kuala Lumpur with anogenital warts

Characteristics		**Total**	**HIV status**		
		n = 935 (%)	**Positive** *n= 239 (%)*	**Negative** *n=696 (%)*	***p***
Gender	Male	656 (70.2)	235 (98.3)	421 (60.5)	**<0.0001**
	Female	279 (29.8)	4 (1.7)	275 (39.5)	
Mean age in years (range)		30.4 (12-84)	28.3 (15-68)	31.2 (12-84)	**<0.001**
Age group in years, n (%)	<20	32 (3.4)	9 (3.8)	23 (3.3)	**<0.001**§
	20-29§	**522 (55.8)**	**158 (66.1)**	**364 (52.3)**	
	30-39	258 (27.6)	52 (21.8)	206 (29.6)	
	40-49	61 (6.5)	10 (4.2)	51 (7.3)	
	50-59	37 (3.95)	8 (3.3)	29 (4.2)	
	60-69	17 (1.8)	2 (0.8)	15 (2.2)	
	>70	8 (0.85)	0 (0)	8 (1.1)	
Ethnicity, n (%)	Malay	558 (59.7)	141 (59.0)	417 (59.9)	**0.02**
	Chineseφ	**251 (26.8)**	**78 (32.6)**	**173 (24.9)**	
	Indian	81 (8.7)	10 (4.2)	71 (10.2)	
	Others (Bumiputera Sabah, Sikh)	17 (1.8)	7 (2.9)	10 (1.4)	
	Foreigner	28 (3.0)	3 (1.3)	25 (3.6)	
Sexual orientation, n (%)	Heterosexual	541 (57.9)	15 (6.3)	526 (75.6)	**<0.0001**¶
	Homosexual¶	**325 (34.8)**	**192 (80.3)**	**133 (19.1)**	
	Bisexual	60 (6.4)	28 (11.7)	32 (4.6)	
	Missing data	9 (1)	4 (1.7)	5 (0.7)	
Type of sexual partners, n (%)	**Casual**φ	**367 (39.3)**	**170 (71.1)**	**197 (28.3)**	**<0.0001**φ
	Regular	239 (25.6)	52 (21.8)	187 (26.9)	
	Spouse	233 (24.9)	3 (1.3)	230 (33.0)	
	Sex worker	24 (2.56)	1 (0.4)	23 (3.3)	
	More than 1 type	48 (5.13)	4 (1.6)	44 (6.3)	
	No partner	24 (2.56)	9 (3.8)	15 (2.2)	
Number of patients with 2 or more partners in the past 6 months, n (%)		559 (59.8)	199 (83.3)	360 (51.7)	**<0.0001**
Number with documented substance abuse, n (%)		52 (5.6)	13 (5.4)	39 (5.6)	0.94
Concomitant sexually transmitted infections (STI), n (%)	Syphilis	83 (8.9)	59 (24.7)	24 (3.4)	**<0.0001**
	Gonorrhoea	44 (4.7)	18 (7.5)	26 (3.7)	**0.02**
	Herpes genitalis	25 (2.7)	12 (5.0)	13 (1.9)	**0.02**
	Chlamydial infection	24 (2.6)	3 (1.3)	19 (2.7)	0.29
	Multiple other STI*	18 (1.9)	16 (6.7)	2 (0.3)	**<0.0001**
Comorbidities, n (%)	Pregnancy	65 (7.0)	0 (0)	65 (9.3)	-
	Diabetes mellitus	50 (5.3)	4 (1.7)	46 (6.6)	<0.001
	Pregnant with diabetes mellitus	5 (0.5)	0 (0)	5 (0.7)	-
	Malignancy	3 (0.3)	0 (0)	3 (0.4)	-
	Others	33 (3.5)	4 (1.7)	29 (4.2)	-

HIV – human immunodeficiency virus; * including hepatitis B and hepatitis C viruses

Table 2: Clinical Characteristics and treatments of anogenital warts (AGWs) in 935 patients attending GUM clinic, Hospital Kuala Lumpur

Characteristics		**Total** *n = 935 (%)*	**HIV status**		
			Positive *n= 239 (%)*	**Negative** *n=696 (%)*	***p***
Distribution of AGWs in men,	***Total***	***656***	***235***	***421***	
	Perianal	345 (52.6)	206 (87.7)	139 (33.0)	**<0.0001**
	Penis	300 (45.7)	38 (16.2)	262 (62.2)	<0.0001
	Scrotum	67 (10.2)	10 (4.3)	57 (13.5)	<0.0001
	Intra-anal	14 (2.1)	47 (20.0)	20 (4.8)	**<0.0001**
	Intra-urethral	11 (1.7)	2 (0.9)	16 (3.8)	0.02
	Mon pubis	1 (0.2)	0 (0)	1 (0.2)	-
	Multiple sites	135 (20.6)	66 (28.1)	69 (9.9)	**0.0002**
Distribution of AGWs in women,	***Total***	***279***	***4***	***275***	
	Posterior fourchette	125 (44.8)	0 (0)	125 (45.4)	-
	Labia minora	92 (33,0)	3 (75)	89 (32.4)	0.11
	Labia majora	80 (28.7)	3 (75)	73 (26.5)	0.07
	Clitoris	88 (31.5)	0 (0)	88 (32.0)	-
	Perineum	7 (2.5)	0 (0)	7 (2.5)	-
	Mons pubis	1 (0.4)	0 (0)	1 (0.4)	-
	Urethra	1 (0.4)	0 (0)	1 (0.4)	-
	Vagina	29 (10.4)	0 (0)	29 (10.5)	-
	Cervix	1 (0.4)	0 (0)	1 (0.4)	-
	Anus	6 (2.2)	0 (0)	6 (57.1)	-
	Multiple sites	130 (46.6)	3 (75)	127 (46.2)	0.30
Treatment provided	Cryotherapy	808 (86.4)	214 (89.5)	594 (85.8)	0.09
	Podophyllin	330 (35.3)	107 (44.8)	223 (32.0)	**0.0004**
	Tri-chloroacetic acid	251 (26.8)	90 (37.7)	161 (23.1)	**<0.0001**
	Imiquimod	24 (2.6)	5 (2.1)	19 (2.7)	0.62
	Combined modalities	388 (41.5)	131 (54.8)	257 (36.9)	**<0.0001**
Number who improved with treatment provided, n (%)		717 (76.7)	176 (73.6)	541 (77.7)	0.20
Number who required surgical intervention, n (%)		17 (1.8)	6 (2.5)	11 (1.6)	0.37
Mean number of treatments (range)		3.84 (0-62)	5.21 (1-62)	3.38 (0-28)	**<0.001**
Mean duration of treatment received in months (range)		2.16 (0-26)	3.09 (0-26)	1.84 (0-19)	**<0.001**
Recurrence within 6 months, n (%)		58 (6.2)	14 (5.8)	44 (6.3)	0.82
Lost to follow up		417 (44.6)	121 (50.6)	296 (42.5)	**0.03**

HIV – human immunodeficiency virus

The characteristics of AGWs and type of treatments provided are shown in Table 2. The most common site of AGWs in males was perianal (52.6%) followed by warts at penis (45.7%) and 20.6% had lesions at multiple sites. Interestingly, HIV infected male patients had a significant higher rate of AGWs at perianal and intra-anal region, with nearly 30% of them had involvement at multiple sites. For female patients, the most frequent site of AGWs was posterior fourchette (44.8%) followed by labia minora (33%) and about 46.6% had involvement of multiple sites. Biopsy was performed in 5 patients (0.5%) and they showed condylomata acuminata, with no dysplasia or carcinoma.

Local ablative treatment provided included cryotherapy (86.4%), podophyllin (35.3%), tri-chloroacetic acid (26.8%) and imiquimod (2.6%). About 41.5% required combination of these modalities and the rate was significantly higher rate among those infected with HIV (54.8% vs 36.9%, *p<0.0001*). Majority of our patients (76.7%) improved with these treatment modalities. The mean number of treatments was 3.84 with a range of 0-62. Patients who had very large lesions (2%) that were not suitable for local ablative treatment were referred for surgical intervention. The mean duration of treatment was 2.16 months with a range of 0-26 months. The duration and number of treatments for AGWs with concurrent HIV infected patients were significantly higher (both *p<0.001*). The overall rate of lost to follow up was high at 44.6%, higher among those infected with HIV. There were 126 patients (13.5%) lost to follow up after the first visit itself. Nearly 6.2% experienced recurrence with the rates were similar between those infected with HIV and without HIV.

Discussion

Previous audits done in Hospital Kuala Lumpur showed that AGWs are one of the most common sexually transmitted infections (STIs) encountered in GUM clinic as shown in Table 3.[5,6,7] A 10-year retrospective study on changing pattern of sexually transmitted infections in Hospital Kuala Lumpur showed that there was an overall decrease in bacterial STIs but an increase in viral STIs (genital warts, genital herpes and HIV).[5] In the United Kingdom, the number of genital warts in 2004 showed a 32% increase compared to 1995.[3] AGWs are a common manifestation of an HPV infection, particularly among young men and women. The prevalence of AGWs was estimated to range between 0.13% and 0.20% typically in most studies.[2]

Most of our local studies showed a male predominance in STI acquisition and sexual experience.[5,6,8] Multiple partner behaviour was found to be significantly associated with male gender.[8] Our data is similar to other countries (Table 4) whereby there was a male predominance for anogenital warts.[2,9,10,11] One of the reasons stated in some studies is that males who initially present with symptoms usually seek consultations with urologists or dermatologists whereas females routinely visit gynaecologists. The specialty of the physicians most frequently performing the initial diagnosis of AGWs varies depending on the healthcare system of individual countries, which could contribute to the differences in reported AGWs among genders.[2]

The most common age group presenting with warts was from 20 to 29 years and this was also observed in other reports worldwide (Table 4).[2,9-12,13-22] This age group is more sexually active and has a higher risk of behavioural vulnerability to acquiring STIs given the number of sexual partners. There are also more frequent partner changes compared to the older group. Another study found that anogenital wart incidence peaked among younger males due to high-risk sexual behaviour; this peak corresponded to new partner acquisition as well.[2] In the United States the median age of those with genital warts was 31.3 years among men who reported having sex only with women and 33.2 years among men who have sex with men (MSM)[10] and the mean age group in our cohort is 30.4.

AGWs was also reported to be higher among men who have sex with men (MSM) and in women reporting sex with women.[12,23] In Thailand the rate of human immunodeficiency virus (HIV) infection among those with anogenital warts was 15%.[13] Our data, however, showed a much higher rate of HIV in those with AGWs at 25.6%. The Genitourinary clinic, Hospital Kuala Lumpur is the one of the main referral centres for treatment of anogenital warts in HIV infected patients from health clinics around the vicinity of Kuala Lumpur and Selangor. This is because we provide ablative treatments.

AGWs are strongly associated with multiple partners and unprotected sex. Additional risk factors include the use of oral contraceptives,

Table 3: Comparison of clinic-epidemiological trend on anogenital warts (AGWs) in Genitourinary Medicine Clinic, Hospital Kuala Lumpur from 1995-2017

Study	Study year	n	% of AGWs among of all sexually transmitted diseases	Age group with highest frequency of AGWs or Mean age in years
Lim et al.[5],2007	1995-1999	171	5.43	30-49
	2001-2005	301	10.35	20-39
Hariyadurai et al.[6], 2019	2015-2016	389	30.2	32.09 ± 12.080
Krishnasamy et al.[7], 2019	2013-2017	273	43.2	31.2

Table 4: Comparison of clinic-epidemiological studies on anogenital warts in other countries

Author, year, country	**n**	**Male to female ratio of anogenital wart**		**Mean Age in years or most frequently affected age group**	**HIV (%)**	**Most frequent affected site**	**Treatment modalities used**
		Male	**Female**				
Tan et al, 2022, Malaysia (present study)	935	2.35:1		30.4	25.6	Male – perianal; Female - Posterior fourchette	Cryotherapy, podophyllin, tri-chloroacetic acid, imiquimod
		656	279				
Nyári et al.[14], 2004, Hungary	397	0	397	35.5	N/A	N/A	N/A
Dinh et al.[15], 2007, USA	11 454	1:1.12		35- 44	N/A	N/A	N/A
Kjaer SK et al.[16], 2007, Nordic countries	7351	0	7351	31.8	N/A	N/A	Suggest prophylactic HPV vaccine
Nyitray et al.[17], 2008, USA	222	222	0	18 –29	0	N/A	N/A
Suligoi et al.[18], 2008, Italy	63	0	63	25–34	0	N/A	Advice vaccination
Castellsague et al.[19], 2009, Spain	56 446	1.29:1		31	N/A	N/A	Imiquimod or podophyllotoxin
Marra et al.[20], 2009, Canada	39 493	N/A	N/A	20-29	N/A	N/A	N/A
Lin et al.[21], 2010, Hong Kong	721	4.55:1		18-30	N/A	N/A	N/A
Lee et al.[22], 2010, South Korea	167 767	1:2.33		30–34	N/A	N/A	N/A
Jiamton et al[13], 2014, Thailand	181	181	0	31.1	15	Penile shaft	Suggest quadrivalent HPV vaccine
Sonnenberg P et al[12], 2018, UK	9 902	1:1.45		20-25	N/A	N/A	Advice vaccination

N/A – Not available; HIV - human immunodeficiency virus; HPV – human papilloma virus; N/A – data not available

history of ever having used cocaine or street drugs, history of sexually transmitted infections, smoking, or immunosuppression.[15,24] This was similarly reflected in our observation as more than half of our cohort had more than one sexual partner while 17.6% had other concomitant sexually transmitted infections.

Limited data is available on the prevalence of AGWs in pregnant women. Our cohort showed that a quarter of the female patients with AGWs were pregnant. AGWs in pregnancy has an implication on the mode of treatment and delivery. Caesarean delivery is indicated for women with genital warts if the pelvic outlet is obstructed or if vaginal delivery would result in excessive bleeding.[1] Rarely, HPV types 6 and 11 can cause respiratory papillomatosis in infants and children.[24,25] Whether caesarean section prevents respiratory papillomatosis in

infants and children is however, unclear.[25]

Treatment options for AGWs include patient-applied (podofilox, imiquimod), physician applied (podophyllin, trichloroacetic acid, interferon) and ablative treatments (cryotherapy, surgical removal, laser treatment).[24] We provide all modalities of treatment for AGWs at our centre except podofilox, interferon and laser treatment. If we exclude those who were referred for surgical excision of the lesions, an average duration of 2.16 months is required to remove the visible lesions in nearly 80% of our patients the treatment modalities provided. A study done in Canada also reported an average episode of care for genital warts of about 2 to 3 months.[20]

HPV type 16, 18 31 33 and 35 are occasionally found in anogenital warts (usually as coinfection with HPV 6 or 11). It is associated with foci of high grade squamous intraepithelial lesions particularly in persons who have HIV infections.[1] Squamous cell carcinomas arising in or resembling genital warts might occur more frequently among immunosuppressed persons. While AGWs are diagnosed based on clinical appearance, a biopsy to assess lesions suspicious of malignant transformation may be indicated. Screening for anal intraepithelial neoplasia by cytology can be considered in view of the increased incidence of anal cancer in HIV infected MSM.[27] A study demonstrated that biopsies of genital lesions consistent with condylomata acuminata from immunosuppressed patients contained significantly more HPV types than lesions from the control group.[28] HPV types associated with an increased risk of dysplasia (high-risk types) were in 100% specimens from immunosuppressed patients in which 24 patients were immunosuppressed, with a third were organ transplant recipients and the remaining were infected with HIV.[28]

Genital warts in HIV infected patients are more difficult to treat with frequent recurrences.[29] Our HIV infected patients required higher number and longer treatment duration in order to achieve about 70% clinical improvement. Interestingly the recurrence rate among our HIV cohort did not differ from those without HIV infection. The high recurrence rate described in the literature may be due to defects in cell-mediated immunity and untreated asymptomatic subclinical infections that may act as an unnoticed source of infection.[13]

AGWs can be prevented by the administration of the human papilloma virus vaccine. Three prophylactic vaccines, Cervarix®, Gardasil® (quadrivalent HPV) and Gardasil®9 (nano valent HPV), have been approved by the Food and Drug Administration (FDA) in the United States to protect against HPV infections.[30] Gardasil® vaccine protects against HPV 6 and 11, which are associated with 90% of genital warts and 95% of recurrent respiratory papillomatosis.[31] In clinical trials conducted with 92 to 319 HIV patients, seroconversion to HPV was observed in 75-100% of vaccinated HIV patients.[32-34] Gardasil®9 is also expected to protect against ~80-85% cases of HPV-associated vaginal cancers, 90-95% of HPV-associated anal cancers, 85-90% of HPV-associated vulvar cancers.[35]

Gardasil® has been the vaccine of choice worldwide. It has been chosen by health authorities in the United States, Australia, New Zealand, Canada, Switzerland, Italy, Spain, and Sweden for regional or national vaccination programmes against cervical cancer.[36] The United Kingdom substituted the bivalent vaccine with the quadrivalent one in 2012, since the government clarified that the aim is to protect girls against the types of HPV that cause cervical cancer and those that cause genital warts.[37] In Spain, there was a decline in genital warts when female subjects were vaccinated with quadrivalent HPV vaccine.[38] In Australia & New-Zealand, cases of genital warts reduced after the introduction of HPV vaccine.[26,39]

In Malaysia, the routine vaccination was started in 2010 for all teenage girls. The only vaccine proposed by the ministry to be used in hospitals and clinics of ministry of health is bivalent type (Cervarix®) from GlaxoSmithKline (GSK)

Biological manufacturer to prevent a cervical cancer caused by HPV type 16 and type 18.[40] However, evidence has shown that bivalent vaccine does not confer cross-protection against genital warts caused by HPV 6 and 11, therefore teenage girls who have been vaccinated with Cervarix® can still contract genital warts.[12] Based on this knowledge, it would be best that quadrivalent vaccine (Gardasil) or Gardasil 9 be administered instead. Gardasil® should also be offered to MSM (up to and including 45 years of age) as studies have shown that MSM have a higher incidence of HPV infection and related diseases.[37, 41] This knowledge, along with the expectation that MSM will benefit less from herd protection from the vaccination of women, quadrivalent vaccination should be offered to MSM attending sexual health and HIV clinics, as a cost-effective intervention.[12,42]

The biggest challenge we face in our setting is to ensure patients stay in contact with our tertiary medical services and adhere to the treatment plan. If the AGWs are inadequately managed, these patients will be a risk to others. There are several factors contributing to the high rate of lost to follow up in our cohort. Patients tend to miss their appointments once they experience resolution of symptoms. Other reasons included the inability to adhere to frequent follow-up as patients are normally seen every two weeks in the GUM clinic until complete resolution of visible warts. Effective lost to follow up strategies need to be endorsed and enforced to overcome this issue as described by Rayment et al.[43] Primary care physicians and other health care provider such as home visit health care team may need to be involved in this initiative. Further studies are needed to determine the causes of the high lost to follow up rate. Strategies that can be implemented to reduce this high rate include structured patient education on first consultation and a more flexible appointment system etc.

Conclusion

AGWs was more commonly observed in male. The most frequent site of involvement was perianal for male (52.6%) and posterior fourchette in female (45.2%). The most frequent treatment modality used was cryotherapy (86.4%) and about 41.5% required combination of treatments. About 6.2% experienced recurrence. The human papilloma virus vaccination in our national immunization should be promoted to male students to reduce the prevalence of genital warts.

Conflict of Interest Declaration

All authors have no financial/conflict of interest to disclose.

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CASE REPORT

Case Report of A Rare Case of Adult-Onset Multi-site Lichen Striatus in an Adult

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Summary

Lichen striatus (LS) is a rare self-limiting inflammatory dermatosis characterized by Blaschkoid distribution. We report a 34-year-old woman with a 1-year history of asymptomatic unilateral rashes on her left trunk and limbs. Physical examination revealed light to dark brown papules, macules, patches and plaques with some erythematous areas in a Blaschkoid pattern with proven skin biopsy as well. Patient received potent topical corticosteroid therapy which resulted in the resolution of the lesion. This case report highlights two rare aspect of lichen striatus; involvement of multiple sites and late adult-onset. It is also a reminder that lichen striatus should be included in the differentials of acquired linear dermatoses.

Key words: *Lichen striatus, adult onset, linear dermatoses*

Introduction

Lichen striatus is a self-limiting, localised blaschkolinear inflammatory condition. There are three clinical patterns; typical LS, LS albus and nail LS.[1] Typical LS is as in present case discussion whereas LS albus, is characterized by hypopigmented lesions at the onset of the eruption and nail LS with longitudinal ridging, splitting.

The pathophysiology of LS remains to be elucidated, interaction of environmental stimuli in a genetically predisposed individual has been postulated.[2] The Blaschkoid distribution suggests a form of cutaneous mosaicism. Somatic mutation during early embryogenesis results in abnormal epithelial cell clones, leading to LS formation upon exposure to environmental stimuli.[2] Environmental factors that may trigger LS include viral infection, vaccination, drugs and cutaneous injury.[3-4] Familial occurrences support the theory that genetic factor contributes to LS development.[3,5]

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Multiple adult-onset LS is uncommon. LS typically presents as a single lesion in children between the age of 3 to 15 years old.[1] In adults, the mean age of onset is 30.3 years. Females are approximately four times more commonly affected than males.[6] We present a case of multi-site lichen striatus in an adult female, successfully treated with potent topical corticosteroid.

Figure 1. Linear hyperpigmented and erythematous papules, macules and plaques with minimal fine scales on the left side of her trunk (a) and posterior left leg (b)

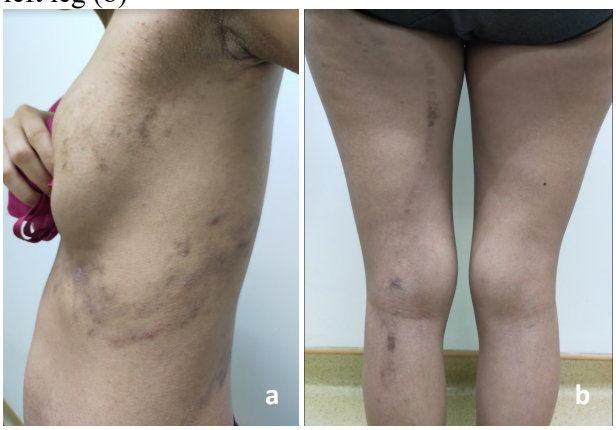
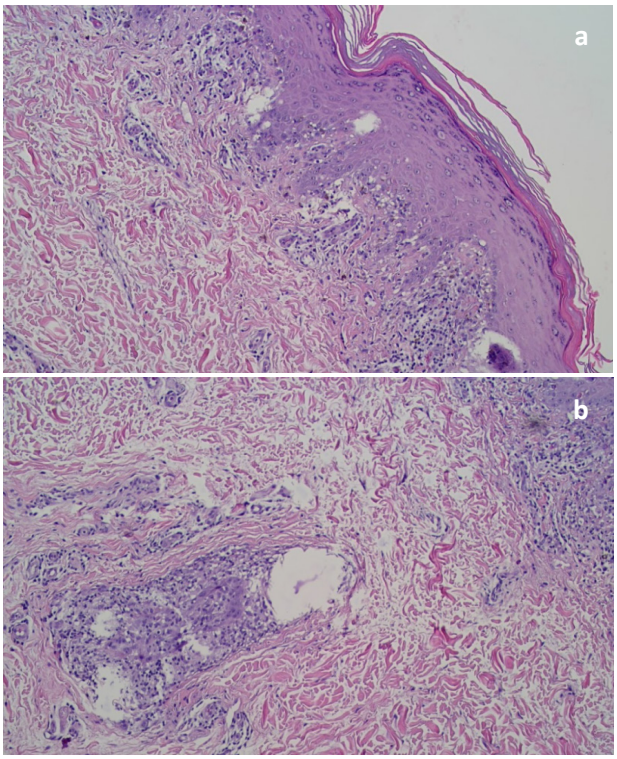


Figure 2. a) Band like infiltration of lymphohistiocytes at superficial dermis with basal layer vacuolar degeneration; b) Lymphohistiocyte infiltrates at superficial perifollicular and peri-eccrine areas



Case Report

A 34-year-old woman with bronchial asthma presented with relapsing and remitting asymptomatic rashes affecting her left side for one year. Physical examination revealed hyperpigmented papules, macules and plaques interspersed with a few erythematous papules and plaques with minimal fine scales arranged in a linear pattern on the left side of her trunk and posterior left leg (Figure 1). There were no nail, hair or mucosal abnormalities. There was no any aggravating relieving factors for the rashes.

The differential diagnoses include lichen striatus, linear lichen planus, inflammatory linear verrucous epidermal nevus, incontinentia pigmenti and linear porokeratosis. A skin biopsy was performed and histopathology features include dense bandlike infiltration of lymphohistiocytes at superficial dermis with vacuolar alteration of the basal layer (Figure 2a). Similar infiltrates were observed at superficial perivascular, perifollicular and around the eccrine glands (Figure 2b). A diagnosis of lichen striatus was made. The patient was treated with a potent topical corticosteroid (TCS) which resulted in complete resolution of the rash.

Discussion

LS most commonly present as asymptomatic erythematous or skin-coloured, flat-topped papules that coalesce to form a continuous or interrupted linear plaque. About 11% of cases complained of pruritis, almost all of these patients had atopy.[3] And that's when patient usually comes for consultation. Typical LS occurs on the lower limbs. Other less common sites include the trunk, upper limbs and face.[3-4]

LS is diagnosed clinically. However, a skin biopsy is helpful to differentiate it from other Blashkoid dermatoses. The histopathological finding of LS is often confused with linear lichen planus.[8] A characteristic feature of LS is lymphohistiocytic infiltrate seen around eccrine glands and hair follicles.[6-7] Other non-specific findings include exocytosis, hyperkeratosis,

spongiosis, necrotic keratinocytes, parakeratosis and perineural infiltrate.[7]

The options for treatment usually includes topical corticosteroids or intralesional cortiocosteroid, salicylic acid or coal tar. However, many studies on Vitamin D analgoues and cryotherapy are also emerging now. Lichen striatus has been successfully treated with other topical (pimecrolimus) or oral (acitretin, cyclosporin, or corticosteroids) agents

As for topical steroid, there are conflicting reports about whether topical steroids shorten the duration of the lesions. In a retrospective study of 115 children with LS, Patrizi et al[3] did not conclude in any shortening of the duration of either the inflammatory stage of LS or the duration of the post-inflammatory hypopigmentation in patients treated with topical steroids as compared to those who were not treated.

On the other hand, combination topical corticosteroid with vitamin D analogue or retinoid has been used with success.[8] Complete resolution of lesions with 2 sessions of cryotherapy 2 weeks apart was reported in a patient.[9]

As the cause of LS is uncertain, and recent studies has hypothesised that LS is a T-cell mediated inflammatory skin disease associated with autoimmune response to mutated keratinocyte cloning.[10-11] Accordingly there is a role of topical tacrolimus[13] and pimecrolimus[14] as the new choice treatment for LS. Korean literature has reported the effects of this treatment whereby 1% pimecrolimus cream is found to be beneficial and efficacious treatment option for lichen striatus in children because it carries no risk for skin atrophy compared with topical corticosteroid application.[12]

This case report highlights the need to consider LS in the differential diagnosis of Blashkoid and linear rash despite its rarity in adult population and its distribution. Although in some circumstances, very few potent TCS alone or in combination with topical retinoids, TCI monotherapy and cryotherapy are one of the many treatments options that may be considered.

Conclusion

This case report has demonstrated the efficacy and tolerability of corticosteroid treatment of LS in the adult population for the first time. Our patient's clinical presentation was not uniformly pathognomonic for either blaschkitis or lichen striatus. The involvement of the chest and her adult age matched the classic clinical presentation of blaschkitis; however, the involvement of the right upper extremity was more characteristic of lichen striatus. The pathology features of her skin biopsies - an inflammatory band-like infiltrate of lymphocytes and histiocytes along with the presence of necrotic keratinocytes which was consistent with lichen striatus. Lichen striatus typically resolves spontaneously within six to 12 months and does not recur as it did for our patient. Topical corticosteroids may be used for the treatment of lichen striatus especially if it's associated pruritus. However, they usually do not reduce the duration of the disease or the occurrence of post-inflammatory dyspigmentation. Lichen striatus has been successfully treated with other topical (pimecrolimus) or oral (acitretin, cyclosporin, or corticosteroids) agents. Ideally, a placebo-controlled, randomized study would be helpful to confirm the superior efficacy of the combination treatment as delineated in this study.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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CASE REPORT

Disseminated Cutaneous Sporotrichosis with Fungal Sinusitis As An Initial Presentation of Underlying Myeloproliferative Neoplasm

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Summary
Sporotrichosis is a rare and chronic granulomatous subcutaneous mycotic infection caused by a dimorphic fungus, *Sporothrix schenckii*. We describe a patient with disseminated cutaneous sporotrichosis who was later diagnosed with myeloproliferative neoplasm and discuss the challenges and importance in diagnosing this rare condition.

Key words: *Disseminated sporotrichosis, fungal sinusitis, myeloproliferative neoplasm*

Introduction
Sporotrichosis is a chronic granulomatous subcutaneous mycotic infection caused by *Sporothrix schenckii,* a dimorphic fungus found in soil, sphagnum moss and contaminated organic matter.[1,2] It presents as nodules, plaques, and subcutaneous swellings which often make clinical diagnosis a challenge, particularly in nonendemic areas.[1] Here, we report a case of recalcitrant disseminated cutaneous sporotrichosis with fungal rhinosinusitis in an apparent immunocompetent individual, who was later diagnosed with myeloproliferative neoplasm.

Case Report
A 49-year-old man presented with painful ulcerated nodules on his face, trunk and extremities for the past 1 month associated with low-grade fever, malaise, appetite loss and weight loss. His past medical history includes hypertension, coronary artery disease and gout. He works in a plant nursery and has a wild cat at home. On examination, there were multiple ulcerated nodules and hyperkeratotic plaques on the face, trunk, and extremities (Figure 1a&b). Lung examination was normal. Abdominal examination revealed a non-tender

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splenomegaly. No enlarged lymph nodes were detected. Blood investigations revealed leukocytosis of 11.88 x 10^9/L, normocytic normochromic anaemia with a Hb of 11.5 g/dL, and mild thrombocytosis of 542 x 10^9/L. Liver function, renal function, blood glucose, serum cortisol, human immunodeficiency virus (HIV) test, viral hepatitis test, and chest radiograph results were normal. Histopathological examination (HPE) of the skin biopsy showed a chronic granulomatous inflammation in the dermis (Figure 2a). *Myobacterium leprae* and *Mycobacterium tuberculosis* were not detected. Fungal culture from the skin lesions grew *S. schenckii*, confirming the diagnosis of disseminated cutaneous sporotrichosis. His clinical response to 6 months of oral itraconazole and 3 months of combined oral itraconazole and terbinafine was poor. A repeated skin biopsy showed similar HPE and fungal culture findings. Abdominal ultrasonography revealed hepatomegaly and massive splenomegaly.

Bone marrow aspirate and trephine biopsy demonstrated features of myeloproliferative neoplasm (MPN). He was positive for JAK V617F, which is pathognomonic for MPN. He experienced intermittent epistaxis for the past few months. Functional Endoscopic Sinus Surgery revealed ulcerated and perforated nasal septum with crusted necrotic tissues over the middle and inferior turbinate. HPE of the nasal septum was consistent with a chronic granulomatous inflammation with fungal yeasts morphologically consistent with *S. schenckii* (Figure 2a&b). Fungal culture from nasal septum isolated *S. schenckii.* Computed tomography scan showed mucosal thickening of maxillary sinuses and hyperdense soft tissue over the right frontal sinus. He was admitted for treatment with intravenous (IV) amphotericin B, and for further workup of the newly diagnosed MPN. Regular nasal irrigation was performed by the otorhinolaryngologist. After two weeks of IV amphotericin B, he was discharged from the hospital against medical advice and opted for conservative management for his myeloproliferative disease. Unfortunately, he succumbed to severe sepsis secondary to infected cutaneous ulcers three months later.

Figure 1. (a) Disseminated sporotrichosis on left upper limb and (b) anterior trunk, demonstrating numerous erythematous nodules with occasional ulceration

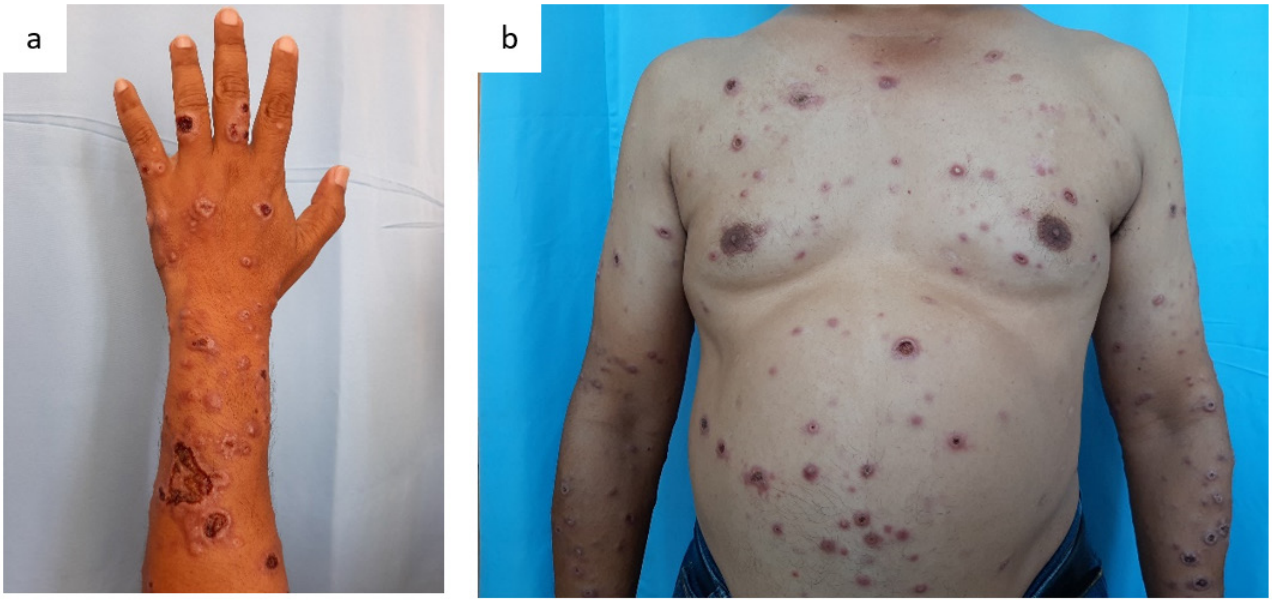
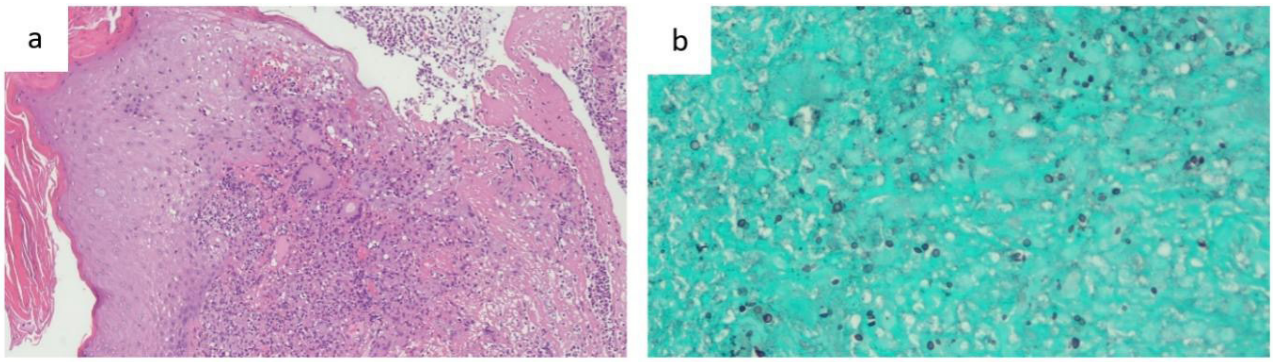


Figure 2. (a) Left arm skin biopsy, haematoxylin and eosin stain (20X) showing chronic granulomatous inflammation in the dermis; (b) Nasal septum biopsy, Gomori methenamine stain (40X) demonstrating ovoid and elongated fungal spores



Discussion

Sporotrichosis is a cutaneous fungal infection reported worldwide.[2,3] Its clinical manifestations depend on the route of infection, burden of inoculum and immune status of the host.[4,5] Dissemination may occur in immunocompromised individuals.[4] Infection with HIV, iatrogenic immune suppression, and haematological malignancies are some of the reported predisposing conditions.[4] Myeloproliferative conditions like myelofibrosis are also associated with extracutaneous sporotrichosis.[1] The newly diagnosed MPN in this case may have contributed to the progression of disseminated disease.

Cutaneous infection is commonly associated with trauma during outdoor activities.[3] *S. schenckii* may enter the body directly through a thorn prick, abrasion or blunt injury, or indirectly through animal bites or scratches.[6] Our case does significant outdoor work and is thought to have contracted the infection through skin inoculation, from traumatic implantation of thorns and splinters, or inhalation. The activation and proliferation of macrophages and T lymphocytes are involved in controlling fungal infection.[7] The immune response against *S. schenckii* infections is most likely a combination of humoral, cellular and innate immune responses.[2]

Treatment with amphotericin B was initiated according to the current guideline recommendations in Malaysia.[8] Several studies have reported the *in vitro* efficacy of other agents such as amphotericin B and posaconazole against disseminated sporotrichosis.[4,9] In a similar case report, Bunce *et al*. (2012) reported a significant improvement using a combined antifungal treatment of amphotericin B and posaconazole in a patient with disseminated sporotrichosis who had underlying hairy cell leukemia that was refractory to initial therapy with liposomal amphotericin B and oral itraconazole.[4] The patient, who worked as an outdoor contractor, achieved resolution of symptoms after 8 months of treatment with amphotericin B, and remains stable on posaconazole after 5 months.[4] Thus, this supported the use of amphotericin B in our patient.

Conclusion

In summary, we have reported a case of disseminated *S. schenckii* infection in a patient with newly diagnosed MPN initially refractory to oral itraconazole and terbinafine, and eventually required IV amphotericin B. A high index of clinical suspicion is important for early diagnosis to prevent further complications of this disease.

Conflict of Interest Declaration

The authors declare that there is no conflict of interest in this work.

Acknowledgement

The authors would like to thank the Director General of Health, Malaysia for his permission to publish this case report.

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CASE REPORT

A Unique Drug Rash: Bleomycin-induced Flagellate Erythema in a Patient with Hodgkin Lymphoma

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Summary

Flagellate erythema is characterized by "whiplike" linear streaks, usually following bleomycin chemotherapy or is associated with consumption of shiitake mushrooms, dermatomyositis, adult onset still disease as well as human immunodeficiency disease. Here, we describe a case of bleomycin-induced flagellate erythema in a patient with Hodgkin lymphoma.

Key words: *Bleomycin-induced flagellate rash, flagellate erythema, Hodgkin lymphoma*

Introduction

Flagellate erythema is a unique patterned eruption, which is described as "whiplike" linear streaks, usually following bleomycin chemotherapy or is associated with consumption of shiitake mushrooms, dermatomyositis, adult onset still disease as well as human immunodeficiency disease.[1,2] In severe cases, it may cause intolerable pruritus. The onset of the eruption is between 1 day to 9 weeks after the administration of bleomycin in a dose dependent manner.[3] During the recovery phase, the lesions may have a brown appearance, commonly known as flagellate pigmentation.

Case Report

We herein report a case of a 44-year-old man with refractory Hodgkin lymphoma stage IV, having completed 4 cycles of ABVD chemotherapy (adriamycin, bleomycin, vinblastine, dacarbazine) and post autologous stem cell transplant. He presented with multiple hyperpigmented, haphazard, linear streaks over his back (Fig 1a and 1b).

The lesions appeared 2 weeks after the first cycle of chemotherapy. He denied any pruritus or pain. His presentation was compatible with the diagnosis of bleomycin-induced flagellate

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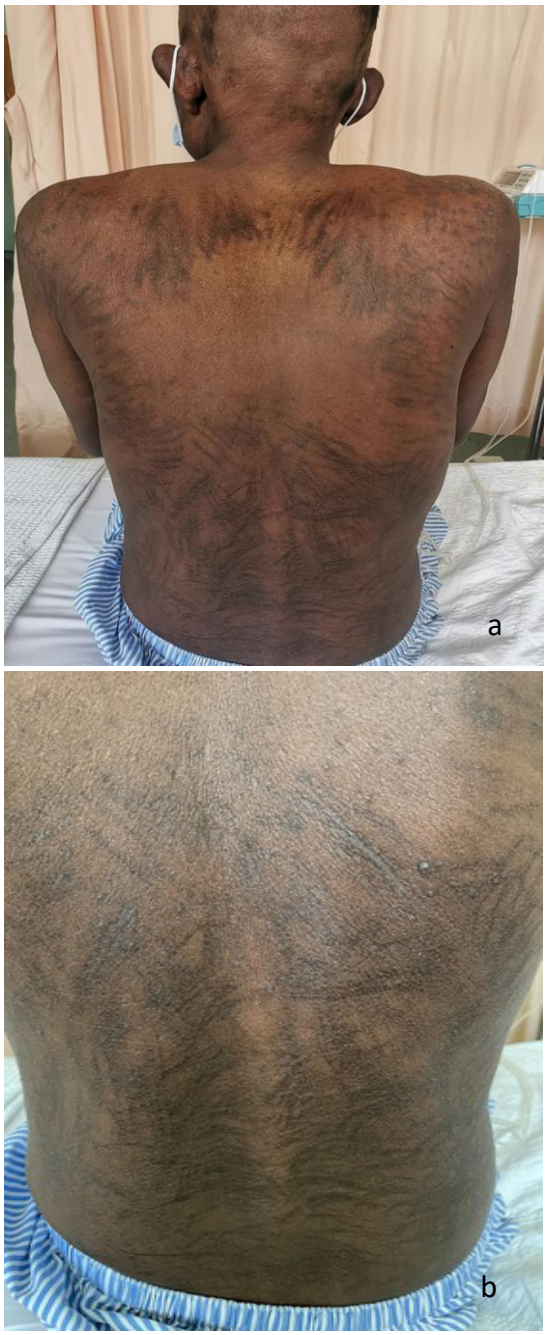
erythema. No treatment was given as the patient was asymptomatic.

Figure 1. (a&b) Multiple hyperpigmented, haphazard, linear streaks over his back



Discussion

Bleomycin is an antitumor drug, commonly used in the treatment of Hodgkin lymphoma and squamous cell carcinoma.[4] Adverse effects of bleomycin predominantly occur in the lungs and skin due to bleomycin hydrolase, which is a cytosolic cysteine proteinase enzyme for inactivation of bleomycin.[5] Bleomycin-induced flagellate erythema was first reported by Moulin et al in 1970 with the reported incidence rate of 8-22%.[6] However, it is infrequently reported in clinical practice.

The appearance of bleomycin-induced flagellate erythema can occur irrespective of any routes of administration: intravenously, intramuscularly, subcutaneously or even intrapleurally.[7] The exact pathogenesis of bleomycin-induced flagellate erythema remains uncertain. A number of theories have been postulated with regards to the etiology of bleomycin-induced flagellate erythema. Heat-recall and reduced epidermal turnover allowing prolonged melanocytes and keratinocytes contact may contribute to the appearance of the rash.[7] One of the theories is that scratching causes vasodilatation with local bleomycin accumulation in the skin leading to subsequent fixed drug eruption.[8]

The rashes are self-limiting and normally improve 3-4 months following discontinuation of bleomycin.[9] However, permanent post-inflammatory hyperpigmentation is a common complication.[10] Antihistamines and topical corticosteroid can be used for symptomatic relief.[11]

Conclusion

Bleomycin-induced flagellate erythema is a rare and unique adverse effect. This report emphasizes the significance of awareness and early recognition of this classical rash by the clinician in order to make an appropriate judgment on modifying or discontinuing the chemotherapy regime.

Conflict of Interest Declaration

The author have no conflict of interest to declare.

Acknowledgement

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CASE REPORT

No Epidermis: Is it the drug, COVID-19 or Something Else?

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Summary

Staphylococcal toxic shock syndrome (TSS) is a clinical disease with acute onset of fever, rash, hypotension and multi-organ system involvement. *Staphylococcal* scalded skin syndrome (SSSS), mostly described in neonate and children, is a superficial blistering disease caused by the exfoliative toxin of specific strains of *Staphylococcus aureus*. TSS and SSSS rarely occur concurrently in adults. We here describe a 35-year-old woman who was initially referred to dermatology team as toxic epidermal necrolysis. She presented with a rapid epidermal detachment without mucosal involvement, fever and shock, associated with acute kidney injury and transaminitis, severe metabolic acidosis, complicated by COVID-19 infection, and finally succumbed within 36 hours of hospitalization. Early recognition and prompt treatment are the key factors in the management as TSS itself can lead to mortality. *Staphylococcal* TSS and SSSS are important differential diagnosis to consider in acute epidermal detachment, as not all cases are drug-induced.

Key words: E*pidermal detachment, toxic shock syndrome, Staphylococcus aureus, Staphylococcal scalded skin syndrome*

Introduction

Staphylococcal toxic shock syndrome (TSS) is a life-threatening clinical condition characterized by the rapid onset of fever, hypotension, skin rashes (diffuse macular erythroderma, followed by desquamation 1-2 weeks later), with multisystem involvement.[1] At least three or more of the following systems are affected in TSS which include gastrointestinal symptoms (vomiting and watery diarrhoea), muscle (severe myalgia with raised muscle enzyme), central nervous system involvement (headache and confusion which may lead to delayed presentation, seizure, loss of consciousness, agitation), mucous membrane hyperemia (vaginal, oropharyngeal, or conjunctival), kidney and liver impairment, and thrombocytopenia.[1]

It was first described in paediatric patients in 1978 by Todd.[2] Subsequently there was a peak of cases when highly absorbable tampons were introduced in the 1980s.[3] However, the overall incidence of TSS remains low. The incidence of TSS is around 0.8 to 3.4 per 100,000 in the United States.[4] TSS has also been described in

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non-menstruating individuals, including in the paediatric population and male patients.[5] Non-menstrual cases are associated with higher mortality, earlier onset of fever and rash, with more pronounced renal and central nervous system complications, but less musculoskeletal involvement.[6]

Staphylococcal scalded skin syndrome (SSSS), also known as Ritter disease, is a cutaneous emergency mostly described in neonate and children.[7] It is caused by exfoliative toxin produced by specific strains of *Staphylococcus aureus*, resulting in rapid blister formation on a widespread tender erythroderma with tissue paper-like wrinkling of the skin at the periorificial or flexural area.[7] It typically spares the mucous membrane.[7] The initial source of *Staphylococcal aureus* infection is usually localized at upper respiratory tract, inner ear, conjunctiva, umbilical stump and others.[7]

Here we describe a young female who succumbed to *Staphylococcal* toxic shock syndrome with possible coexistent SSSS, who was initially referred to dermatology team as toxic epidermal necrolysis.

Case Report

A 35-year-old Myanmarese waitress, with no known medical illness or allergy, presented to the emergency department with a GCS of E3V5M6. Based on the history given by her housemate, she had severe painful skin peeling over bilateral lower limbs and suprapubic area for a week. She had history of swimming in seawater 2 days before she developed itchiness over the bilateral lower limbs. She denied any trauma, burn or bite. There was no known drug, supplement, or traditional medication exposure prior to the incident. She did not seek treatment for her symptoms. Instead, she used topical medications bought over the counter to the affected pruritic area. The painful rash followed by skin peeling developed rapidly and was associated with difficulty in ambulation.

There was no documented fever at home. She had no history of abdominal pain, vomiting or diarrhoea, limb weakness, numbness or muscle ache. There was no facial, eye, oral or genital involvement as well. She completed 2 doses of CoronaVac (Sinovac, China) vaccination and was unaware of any COVID contact. She did not smoke, consume alcohol or use recreational drugs. She had been living in Malaysia for more than 10 years. She was single with no significant sexual history. However, there was no information regarding her menstrual history and tampon practice. She had no pets.

On arrival, she was hypotensive with blood pressure of 53/28mmHg, tachycardic with a heart rate of 121/minute, and febrile with a temperature of 39.5°C. Oxygen saturation was 98% under room air. Her estimated body mass index was 25 kg/m^2. There was epidermal detachment over anterior and posterior aspects of bilateral lower thighs, extending to the knees and legs sparing the soles as shown in Figure 1(a) involving nearly 35% of body surface area. There was a small erosion over right labia majora. Confluent erythema associated with oedema was noted over lower abdomen and suprapubic region. No other skin lesions were seen. There was no enanthem and no mucosal erosions.

She had treatment-resistant hypoglycaemia, with glucometer readings ranging from 2.3 to 3.2mmol/l, and was oliguric. The patient was given aggressive fluid resuscitation followed by maximum inotropic support, boluses and maintenance dextrose solution. A dose of intravenous Cefuroxime 1.5g was given at 1 hour after presentation and sodium bicarbonate infusion was initiated. She was then intubated for respiratory support in view of severe metabolic acidosis (pH=7.23, bicarbonate 9.2mEq/L, lactate 4.9mmol/L).

Blood investigations showed microcytic hypochromic anaemia (haemoglobin 10.2 g/dL), leucocytosis (total white cell count 14.6 x10^9/L) with neutrophil predominant, thrombocytopenia (platelet 106 x10^9/L). She had acute kidney injury (urea 31.6 mmol/L, creatinine 416µmol/L), hyponatraemia (127mmol/L), elevated creatinine kinase (360

U/L), hypoalbuminaemia (15g/L), mildly raised total bilirubin (27μmol/L), transaminitis (ALT 175 U/L), and coagulopathy (PT 17.6sec, INR 1.6). C-reactive protein was markedly elevated at 263.5 mg/L. Her troponin T was raised as well 176 ng/L (normal <15). Her electrocardiograph showed sinus tachycardia, with no features of ischaemia. There were ground glass opacities seen over bilateral lungs on her chest X-ray as shown in Figure 1b. Her tracheal aspirate for 2019-NCoV PCR was detected, with CT value of 24.5.

Our provisional diagnosis was *Staphylococcal* Toxic Shock Syndrome (TSS) with COVID-19 co infection. Differential diagnosis such as *Staphylococcal* Scalded Skin Syndrome (SSSS), generalized bullous fixed drug eruption (GBFDE), toxic epidermal necrolysis, and COVID-19 multisystem inflammatory syndrome were also considered.

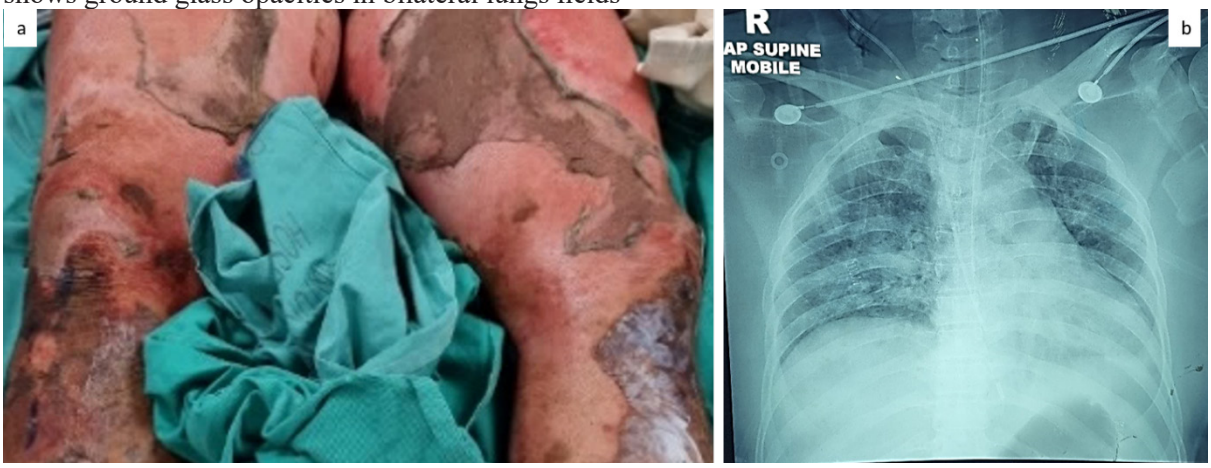
Intravenous piperacillin-tazobactam was later initiated with five doses given over the course of less than 2 days. Despite aggressive intravenous antibiotic administration, fluids resuscitation and inotropic support, the patient continued to deteriorate. She progressed to disseminated intravenous coagulopathy and succumbed 36 hours after admission. Her blood culture was later reported to grow *Methicillin-Sensitive Staphylococcus aureus* (MSSA).

Discussion

According to the United States Centre for Disease Control and Prevention (CDC), the clinical criteria for a confirmed case of *Staphylococcal* TSS includes fever with temperature ≥38.9ºC, hypotension with systolic blood pressure ≤90mmHg, diffuse macular erythroderma followed by desquamation one or two weeks later, involvement of ≥3 organ systems, positive cultures for *Staphylococcus aureus* and negative for alternative pathogens with serologic tests negative for other conditions.[8] Our patient's presentation fulfilled the clinical criteria for *Staphylococcal* TSS.

SSSS is characterized by oedematous erythema of the eyelids and nostril, generalized cutaneous pain, erythema, superficial blistering, and desquamation, associated with fever, with no mucous membrane involvement.[7,9] Although SSSS is more common in the paediatric population, adult SSSS has been reported at an annual incidence of 0.98 cases/million.[10] The three criteria that are required to make a diagnosis of SSSS include (1) a clinical pattern of erythroderma, desquamation or bullae formation; (2) histopathological evidence of intraepidermal cleavage through the stratum granulosum and (3) isolation of an exotoxin A (ETA) and/or exotoxin B (ETB) producing *Staphylococcus aureus* from the skin lesions.[11]

Figure 1. (a) confluent epidermal detachment over anterior and posterior aspect of bilateral lower limbs and lower abdomen leaving raw erosion involving 35% body surface area; (b) chest X-ray (supine, rotated film) shows ground glass opacities in bilateral lungs fields



There are only 5% of *Staphylococcus aureus* isolates produce exfoliative toxin ETA and ETB. These exfoliative toxins are serine proteases that target and cleave desmoglein 1 (Dsg1), which is a desmosomal cadherin maintaining keratinocytes adhesion. *Staphylococc*al exfoliative toxin results in hydrolysis of the amino-terminal extracellular domain of Dsg1. Hence, skin biopsy on a SSSS lesion typically shows splitting within the stratum granulosum without inflammatory cells or bacterial cocci.

Adult SSSS was associated with a higher mortality and complications.[12] Interestingly, about 60% of adults SSSS grow *Staphylococcus aureus* in the blood culture.[9] Co-existence of TSS and SSSS has been described rarely in adults and was associated with underlying renal impairment and immunosuppression.[13,14] Similar to children, adults with SSSS demonstrate a fever and lesions over the face.[7,12] Our patient, although presented with scalded like erosions over the lower abdomen and both thighs, she had no lesions over the face which is the primary affected site in SSSS.

Epidermal detachment could be a manifestation of generalized bullous fixed drug eruption (GBFDE) or drug-induced epidermal necrolysis which includes Steven Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or SJS/TEN overlap syndrome. In GBFDE, a history of similar eruptions at the same site with each exposure to a similar drug, with widespread blisters and erosions involving more than 10% BSA in at least three out of six sites (head and neck, anterior trunk, back, upper limbs, lower limbs and genitalia) should be elicited.[15] However; GBFDE has limited mucous membrane involvement. Drug induced epidermal necrolysis should be considered if it is accompanied with severe erosions at two or more mucous membranes.[16] There was, however, no prior history of drug exposure in this patient. In addition, she had minimal mucosal erosions (at the right labia majora only).

COVID-19 multisystem inflammatory syndrome might be considered as well, as this patient was diagnosed with COVID-19 infection via tracheal aspirate PCR, with multi-organ involvement. However, the most commonly reported cutaneous manifestations of COVID-19 were morbiliform rash, pernio-like acral lesions, urticaria, macular erythema, vesicular and/or papulosquamous eruption, and retiform purpura.[17] Epidermal detachment as the only manifestation of COVID-19 infection has not been described in the literature.

Interestingly, Yilin et al. reported a case of non-fatal TSS post-COVID-19. In that case, the patient presented with high grade fever, hypotension, erythematous and dusky-coloured plaques with bullae and superficial flaking, as well as yellow crusting, scaling, and widespread erosions which involved 40% of total body surface area. Although cultures were negative, skin biopsy was reported to favour TSS.[18] There was an interval between the COVID-19 infection and the rash onset in the case reported. However, our patient presented with skin lesions and was diagnosed to have COVID-19 concurrently. There were no respiratory symptoms reported prior to her presentation.

TSS can be caused by *Staphylococcus aureus* or *Streptococcus pyogenes.* Both are normal flora of skin and mucous membrane in humans. *Staphylococcus aureus* contributes to almost all menstrual TSS and half of non-menstrual TSS. *Streptococcus pyogenes* causes only non-menstrual TSS.[19] In addition to menstruating females, *Staphylococcal* TSS can occur in postpartum and postsurgical states especially when packings are used, in cases where barrier contraceptives are used, in *staphylococcal* pneumonia, sinusitis, and superinfected skin lesions.[20] *Streptococcal* TSS is preceded by trauma to the skin.

Staphylococcal TSS can be caused by both methicillin-susceptible or methicillin-resistant *Staphylococcus aureus* (MRSA), and is associated with mortality.[21,22] *Staphylococcus aureus* produces TSS toxin-1 (TSST-1), a type of exotoxin, which acts as a superantigen that can activate T cells, causing massive cytokine

production.[23] Insufficient antibody response to TSST-1 is found to be the cause of toxic shock syndrome.[24] Apart from exotoxin, enterotoxins produced by *Staphylococcus aureus* may play an important role in the disease manifestations. Inflammatory mediators including interleukin (IL)-1, IL-2, tumour necrosis factor (TNF)-alpha, TNF-beta, and interferon (IFN)-gamma are produced in large amounts.[25] Due to the presence of IL-1, high fever is noted. IL-1 is also involved in proteolysis of skeletal muscle; resulting in myalgia and high creatinine kinase.[25] This explains the raised creatinine kinase and Troponin T level in our patient. TNF inhibits polymorphonuclear leukocyte functions, hence purulence is not observed.[25]

To assist with the diagnosis, cultures from the blood, wound sites and mucosal sites including vaginal canal and nares, should be obtained. Any foreign material such as tampons, contraceptive sponges or intrauterine devices in vaginal canal should be promptly removed.[26] TSST-1 assays are useful in diagnosis, however the test is not available in our setting. It would have been important to perform a vaginal examination in this case to remove any foreign material and to take a vaginal swab for culture. Apart from that, to assess the possibility of concurrent SSSS, isolation of ETA and/or ETB producing *Staphylococcus aureus* from denuded skin as well as a skin biopsy would be helpful. Regrettably, our patient was intubated very soon on arrival before verbal consent could be obtained to examine the genitalia as well as skin biopsy. In addition, there was no next of kin who could give the consent on behalf of her.

The management of *Staphylococcal* TSS and SSSS involves aggressive treatment of shock, antibiotic therapy, intravenous fluids regimens, and surgical debridement of the primary source if indicated. Anti-*Staphylococcal* antibiotics are the mainstay of treatment and it is recommended to be administered within 1 hour upon recognition of septic shock.[27,28] Beta-lactam antibiotics, such as penicillin or cephalosporins should be combined with clindamycin for TSS due to MSSA, while vancomycin can be combined with clindamycin for TSS secondary to MRSA.[28] Vancomycin, clindamycin and piperacillin-tazobactam/cefepime/carbapenem can be started empirically if staphylococcal TSS is highly suspected. The rationale of adding clindamycin (bacteriostatic) to beta-lactams (bactericidal) is due to the lower effectiveness of beta-lactams on bacteria in stationary phase of growth, especially in large inoculations, where there are loss of several penicillin-binding proteins.[29] In addition, Clindamycin has the additional benefit of inhibiting bacterial toxins from *Staphylococcus aureus*. The duration of antibiotic treatment ranges from 10 to 14 days in cases without bacteraemia or other focus of infection.

The effectiveness of intravenous immunoglobulin (IVIG) in the treatment of TSS is debatable.[27] There are studies which are unable to draw a conclusion regarding the efficacy of IVIG in TSS.[27] However, there are observational studies that reported lower mortality rates with the use of IVIG in addition to antibiotic, compared with the use of antibiotics alone.[30] Since IVIG neutralizes the superantigens and halts the cytokine production, it can be accepted as an adjuvant treatment option in the management of TSS, after considering the side effects, which include transfusion reactions, thromboembolic events, kidney failure and aseptic meningitis.[31]

The use of systemic corticosteroids has been reported in TSS. A comparative retrospective analysis done by James et al in 1984 concluded that corticosteroids result in significantly reduced illness severity when given in the first 2 to 3 days of TSS.[2,32] Latest evidence suggested that hydrocortisone 200mg per day should be given intravenously to adults with septic shock, especially those who require norepinephrine or epinephrine dose of ≥0.25mcg/kg/min.[27] Our patient succumbed despite intensive management, likely due to advanced sepsis and concurrent COVID-19 infection.

Conclusion

We describe a COVID-19 infected female who succumbed to *Staphylococcal* TSS with possible concomitant SSSS that was initially referred to dermatology team as toxic epidermal necrolysis. *Staphylococcal* TSS and SSSS should be considered in patients who present with acute painful erythema followed by epidermal detachment, associated with high grade fever, and hypotension with multisystem involvement. Early recognition and prompt treatment are the keys points in the management especially in TSS, as it can lead to rapid fulminant deterioration resulting in mortality.

Conflict of Interest Declaration

The author have no conflict of interest to declare.

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