

GENERAL DERMATOLOGY - Case Report

Churg Strauss Syndrome in a 40 year old womanTan SS, Chan LC, *MMed*, Tan WC, *MRCP***Keywords** *Churg-Strauss syndrome, vasculitis***Introduction**

Cutaneous vasculitis is a common manifestation of many systemic diseases. In the setting of asthma, eosinophilia and multiple disparate signs and symptoms, more serious cause of vasculitis like Churg-Strauss syndrome (CSS) should always be considered.

Case report

A 40 year-old Malay housewife presented with a two months history of purpuric rash and non-healing leg ulcers followed by one month history of bilateral hand numbness. She was diagnosed to have bronchial asthma about a year ago and was started on inhalers. She did not have history of fever, oral ulcer, photosensitivity rash or alopecia.

Physical examination showed varying sizes of ulcers on both ankles and anterior abdominal wall with multiple non-blanching purpuric lesions over

the both hands and both feet (Figure 1, 2, 5 & 6). Neurological examination revealed peripheral mixed sensory and motor neuropathy with the right side more affected than the left side. Other systemic examinations were normal.

Investigations showed white blood cell count of $19,200/\text{mm}^3$ with eosinophilia of 22.3%, ESR of 45 mm/hour and positive pANCA. Other investigations like ANA, serum cryoglobulin, hepatitis B, C and HIV were negative. Her chest x-ray and complements C3/C4 levels were normal. Lung function test showed obstructive lung disease picture. Histopathology of the skin biopsy from her left leg was consistent with leukocytoclastic vasculitis with infiltration of eosinophils and neutrophils within and around vessels (Figure 3). The direct immunofluorescence showed deposition of C3, C4, IgM and fibrin within the dermal vessel walls (Figure 4).

Figure 1 & 2 Vasculitic lesions and ulcers over both palms & forearms**Correspondence**

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Nerve conduction study was suggestive of mononeuritis multiplex. Churg-Strauss syndrome was subsequently diagnosed. She responded to treatment with prednisolone at 1mg/kg/day (Figure 5 & 6).

Figure 3 & 4 Histopathology showing endothelial cells swelling, degeneration of the vessel wall, fibrinoid depositions, extravasation of erythrocytes with perivascular eosinophils and neutrophils infiltration. DIF showed C3 deposits within the dermal vessel walls.

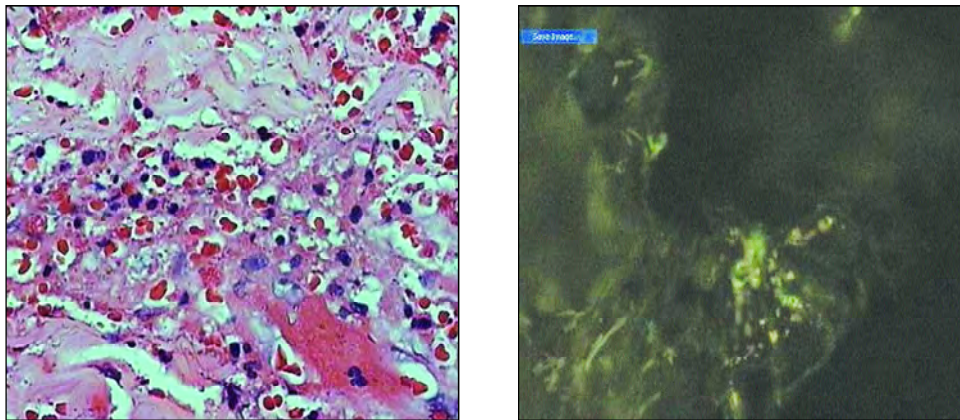


Figure 5 & 6 Pre and post-treatment photos of legs ulcers



Unfortunately, she developed worsening of vasculitic lesion, cyanosis of right middle and ring fingers and bilateral wrist drop after missing her medication for a week. She was then treated with intravenous (IV) methylprednisolone, followed by oral prednisolone and monthly pulses of IV cyclophosphamide. After four pulses of cyclophosphamide, all her skin lesions had resolved. However, she still had residual peripheral mixed sensory and motor neuropathy.

Discussions

CSS is a rare syndrome that affects small- to medium-sized arteries and veins. It was first described in 1951 by Churg and Strauss¹. The American College of Rheumatology (ACR) has proposed 6 criteria for the diagnosis of Churg-

Strauss syndrome². The presence of 4 or more criteria yields a sensitivity of 85% and a specificity of 99.7%. The 6 criteria are as follow:

- (1) Asthma (wheezing, expiratory rhonchi)
- (2) Eosinophilia of more than 10% in peripheral blood
- (3) Paranasal sinusitis
- (4) Pulmonary infiltrates (may be transient)
- (5) Histological proof of vasculitis with extravascular eosinophils
- (6) Mononeuritis multiplex or polyneuropathy

This patient fulfilled four of the six ACR criteria for the diagnosis of CSS. These include vasculitis, adult onset asthma, peripheral neuropathy with mononeuritis multiplex and eosinophilia.

The incidence of CSS is approximately 2.4 to 3.3 per 1 million population³. Symptoms usually appear between 20 and 40 years of age, with a slight predominance in men⁴.

The cause of CSS is unknown⁵. It is possibly an allergic or autoimmune reaction to an environmental agent or drug.

The most prominent signs and symptoms of CSS are those related to pulmonary, cardiac, dermatologic, renal, and peripheral nerve. Pulmonary involvement may be seen in 96 to 100% of patients in the form of asthma, pleural effusions, or nonfixed patchy infiltrates on chest films. The neurologic findings may be either mononeuritis multiplex or polyneuropathy in 66 to 75% of patients³.

Laboratory findings include anemia, eosinophilia, elevated ESR, CRP & serum IgE level, hypergammaglobulinemia, positive rheumatoid factor and abnormal renal function test with proteinuria and hematuria if there is renal involvement. ANCA is present in approximately 40% of patients with Churg-Strauss syndrome (CSS). Most of these patients are perinuclear-ANCA (p-ANCA)-positive (antimyeloperoxidase antibodies)⁶.

Levels of eosinophil cationic protein (ECP) and soluble interleukin-2 receptor (sIL-2R) in CSS are elevated which indicate an immunoregulatory defect associated with vasculitis and eosinophilia. Besides, soluble thrombomodulin (sTM), which is a marker of endothelial cell damage, are also elevated.

Other investigations that are done only when clinically indicated include bronchioalveolar lavage, chest x-ray, computed tomography scan, ECG, echocardiogram, endoscopy, biopsy, electromyogram & others. Pulmonary opacities can be found in 26% to 77% of cases of Churg-Strauss syndrome, and films demonstrate no abnormalities in approximately 25% of patients⁷.

CSS is associated with high mortality especially when major organs like cardiac, pulmonary or renal are involved. The principal causes of morbidity and mortality in Churg-Strauss syndrome are myocarditis and myocardial infarction secondary to coronary arteritis⁸. A 5-year survival rate is about

25% without treatment. However, if it is treated, the 1-year survival rate is 90% and the 5-year survival rate is 62%^{9,10}.

Glucocorticoids alone are usually adequate for the treatment of Churg-Strauss syndrome^{11,12}. High dose corticosteroids and other cytotoxic agents like cyclophosphamide, oral mycophenolate or azathioprine are required if it involved major life-threatening organ^{11,12}. High doses of interferon can maintain remission in patients who have responded incompletely to cyclophosphamide¹³.

Conclusion

Many systemic diseases can present with vasculitis. Early recognition and prompt treatment of those vasculitides associated with major complications like CSS is essential.

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References

1. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. *Am J Pathol.* Mar-Apr 1951;27(2):277-301
2. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum.* Aug 1990; 33(8):1094-100
3. Cakir B, Cykert S et al. Asthma associated with worsening leg ulcer: a case of vasculitis in primary care. *South Med J.* 2003 Jul;96(7):677-80
4. Wechsler ME, Finn D, Gunawardena D, et al. Churg-Strauss syndrome in patients receiving as treatment for asthma. *Chest* 2000;117:708-713
5. Hellmich B, Ehlers S, Csernok E, Gross WL. Update on the pathogenesis of Churg-Strauss syndrome. *Clin Exp Rheumatol.* Nov-Dec 2003;21(6 Suppl 32):S69-77
6. Sablé-Fourtassou R, Cohen P, Mahr A, et al. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med.* Nov 1 2005;143(9):632-8
7. Kim Y, Lee KS, Choi DC, et al. The spectrum of eosinophilic lung disease: radiologic findings. *J Comput Assist Tomogr.* Nov-Dec 1997;21(6):920-30
8. Hasley PB, Follansbee WP, Coulehan JL. Cardiac manifestations of Churg-Strauss syndrome: report of a case and review of the literature. *Am Heart J.* Oct 1990;120(4):996-9
9. Guillevin L, Cohen P, Gayraud M, et al. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore).* Jan 1999; 78(1):26-37

10. Grau RG. Churg-Strauss syndrome: 2005-2008 update. *Curr Rheumatol Rep.* Dec 2008; 10(6):453-8
11. Keogh KA, Specks U. Churg-Strauss syndrome: update on clinical, laboratory and therapeutic aspects. *Sarcoidosis Vasc Diffuse Lung Dis.* Mar 2006;23(1):3-12.
12. Mukhtyar C, Flossmann O, Hellmich B, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. *Ann Rheum Dis.* Jul 2008;67(7):1004-10
13. Solans R, Bosch JA, Perez-Bocanegra C, et al. Churg-Strauss syndrome: Outcome and long -term follow-up of 32 patients. *Rheumatology (Oxford)* 2001; 40: 763-771

GENERAL DERMATOLOGY - Case Report

Childhood disabling Pansclerotic Morphoea complicated by leg ulcers, contractures and gangrene

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Keywords *morphea, ulcers, contracture, gangrene*

Introduction

Disabling pansclerotic morphoea of childhood is a subset of localized scleroderma. It is a rare disease in both the adult and paediatric population. Etiological factors are unknown although autoimmune, infectious, genetic and environmental factors have been postulated. Sclerotic plaques predominantly affect the scalp, face, trunk and extensor surfaces of limbs, leaving fingertips and toes uninvolved. The absence of Raynaud's phenomenon, dysphagia, visceral involvement and certain laboratory derangements differentiate systemic sclerosis and disabling pansclerotic morphoea of childhood. Diagnosis can be supported by histology. There are several management options including topical, systemic and phototherapy.

Case report

An 11-year-old Chinese boy presented with Raynaud's phenomenon, progressive skin hardening and joint contractures at the age of four (Figure 1 a & b). There were no dysphagia or sicca symptoms. A skin biopsy showed morphoea (Figure 2). Anti-nuclear antibody, anti-double stranded DNA and extractable nuclear antigen (ENA) antibodies were negative. As the cutaneous symptoms were severe and progressive and there were no systemic manifestations of scleroderma, he was diagnosed to have pansclerotic morphoea of childhood. Differential diagnoses of this clinical presentation include scleromyxedema and nephrogenic fibrosing dermopathy / nephrogenic systemic fibrosis (although not common in this age group).

He was started on prednisolone, followed by azathioprine, methotrexate and cyclosporine. However, he did not show any response and his parents opted to discontinue oral therapy after three years of failed treatment. He also developed persistent transaminitis even after the discontinuation of methotrexate. Hepatitis markers and hepatic imaging were unremarkable, and the transaminitis resolved with empiric treatment with prednisolone. He was diagnosed to have probable autoimmune hepatitis.

Over the years, the sclerosis of the skin and tendon and joint contractures became progressively more severe. He had difficulty ambulating and had to use a wheelchair for long distances. His quality of life was severely impaired. In spite of his medical condition, he was able to cope well with his studies.

The patient developed bilateral lower leg ulcers three years after the diagnosis of disabling pansclerotic morphoea. The ulcers were more severe over the left medial malleolus and there was also cellulitis at his right ankle. The family was not keen for a biopsy of the skin. He developed the complications of *Staphylococcus aureus* bacteraemia and septic arthritis of the left knee and was treated with intravenous cloxacillin. There were resultant contractures and flexion deformities of his knees due to disuse, and the patient became wheelchair-bound.

Thereafter, he developed progressive painful dark discolouration of his left big toe for a week's duration after his mother accidentally stepped on it. Other toes were not involved. On examination, he was afebrile with normal vital signs. Dry gangrene was seen involving the left big toe, extending proximally to the first metatarso-phalangeal joint. (Figure 3 a & b) There was generalized sclerosis involving the face, trunk and limbs with fixed flexion deformities of both legs. Foul smelling exudates with crusted areas were seen on dorsum of the left foot. Multiple excoriated scaly plaques and macerated ulcers were present on the extremities.

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The full blood count showed a normal total white cell count ($9.98 \times 10^9/L$) and mild anemia (hemoglobin 11.3 g/dL). Erythrocyte sedimentation rate and C-reactive protein were elevated at 65mm/min and 15.5 mg/L respectively. Blood bacterial cultures were negative. Bacterial wound culture from the left big toe grew *Staphylococcus aureus* and Gram-negative bacilli. A radiograph of

the left foot did not suggest an abscess or osteomyelitis.

Intravenous ampicillin and cloxacillin were commenced, which were oralised after four days of therapy. His parents were not keen for surgical intervention. A decision was made for conservative treatment and auto-amputation of the affected toe.

Figure 1 a & b Progressive skin hardening with joint contractures



Figure 2 A skin biopsy showing features of morphea: thickening of collagen, and a decrease in the number of fibroblasts and adnexal structures (H&E, 10x)

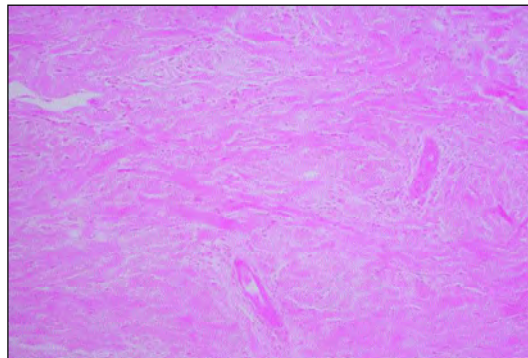


Figure 3 a & b Ulceration of the lower limbs progressing to gangrene of the left big toe



Discussion

Scleroderma is characterized by skin induration and thickening with tissue fibrosis. It is differentiated into systemic sclerosis and localized scleroderma. Peterson et al¹ further classified localized scleroderma into five major categories: plaque, generalized, bullous, linear, and deep morphea. Involvement of deep dermis, subcutaneous tissue, fascia and muscle characterizes deep morphea. Disabling pansclerotic morphea of children (DPMC) is a subtype of deep morphea that can extend to the fascia, muscle, tendons and bones².

Localised scleroderma (LS) is a rare disease with an incidence of 27 cases per million in the adult population in an epidemiological review done by Peterson et al³, out of which about 11% are cases with deep morphea. In the paediatric population, localized scleroderma is far commoner than systemic sclerosis but the actual prevalence has not been well evaluated. A retrospective analysis by Uziel et al⁴ in 30 paediatric patients with LS showed female predominance of 1.5:1; 7.9 years being the average age of onset with a range of 1 to 14 years old. Kornreich et al⁵ reported a series of 35 paediatric patients, with age of 6 years being the average age of onset. Our patient presented with sclerotic plaques and joint contractures at 3 years old.

It is unknown what causes LS. Several etiologies like autoimmune, infectious, genetic and environmental factors have been postulated but never proven. Circulating autoantibodies can be found in cases of LS and may point to an autoimmune cause. LS may also be genetically linked as reported by Kuhl et al⁶ where development of morphea is related to HLA-A3B7 and DR2. *Borrelia burgdorferi* infection has been associated with morphea. There has been conflicting reports of borrelial antibodies being detected in patients with morphea, with up to 45% of patients with morphea testing positive in a Scandinavian study and none in a Canadian study^{4,7}. Infection by Epstein-Barr virus has also been thought to cause LS⁸. Other factors like trauma, surgery, vaccination, varicella infection, post radiotherapy in oncology patients and ischaemic injury have been associated with LS. In our patient with DPMC, no possible causative factors have been identified.

The pathogenesis of morphea can be divided into 3 pathways, namely vascular alteration, disrupted collagen metabolism and immunoregulatory defects. Endothelial cell damage and perivascular infiltration of macrophages and mast cells feature prominently in biopsies. Autologous complement also contributes to vascular damage as levels of complement regulatory proteins are decreased in morphea⁹. Disruption to collagen metabolism occurs in morphea due to increased expression of pivotal cytokines like transforming growth factor (TGF- β) and interleukin-4. They stimulate dermal fibroblasts, causing the build-up of extracellular matrix components, in particular types 1 and 3 fibrillary collagen. Immunoregulatory defects involving cellular and humoral abnormalities have been implicated in the pathogenesis of LS. There is abnormal activation of B and T cells.

In DPMC, sclerotic plaques predominantly affect the scalp, face, trunk and extensor surfaces of limbs, leaving fingertips and toes uninvolved. Multiple joint contractures result from skin sclerosis over the joints^{10,11}. The absence of Raynaud's phenomenon, dysphagia and visceral involvement differentiate systemic sclerosis and disabling pansclerotic morphea of childhood. Sclerotic plaques occurred in the typical distribution in our patient, together with fixed flexion deformities in both his knees and multiple contractures in other joints. He had Raynaud's phenomenon but no evidence of visceral involvement, dysphagia or sicca symptoms.

Certain laboratory abnormalities are present in children with localized scleroderma. A positive anti-nuclear antibody (ANA), rheumatoid factor (RF), hypergammaglobulinaemia, eosinophilia and high erythrocyte sedimentation rate (ESR) are the more commonly detected abnormalities^{12,13}. In localized scleroderma, ANA can be positive in between 23% to 73% of patients¹² and in a study by Falanga et al¹⁴ ANA positivity was more prevalent in patients with severe and extensive linear scleroderma. 39% of patients with localized scleroderma show RF positivity¹¹ and similar to ANA, it was associated with more severe disease in those with linear scleroderma. Anti-histone antibodies and anti-single stranded DNA antibodies can also be present¹⁴. Hypergammaglobulinaemia with raised IgG and IgM levels occur in between 13% to 50% of patients^{15,16} and those with joint contractures have higher IgG levels¹⁷.

Raised ESR and blood and tissue eosinophilia characterize deep morphoea¹³. An association has been shown between blood eosinophilia and clinical disease activity¹³ with eosinophilia preceding exacerbations and declining levels indicating disease remission¹⁷.

Patients with localized scleroderma do not have antibodies to extractable nuclear antigens (ENA) like anti-Scl 70, which differentiates them from those with systemic sclerosis. Our patient with DPMC had raised ESR (65mm/50 minutes) and negative ANA, RF and ENA antibodies.

Histopathological findings are characterized by fibrosis and thickened homogenized collagen bands. The depth of inflammation and sclerosis is used to differentiate between the different subtypes. In the subcutis, there are lymphocytes and plasma cells with thickened collagen and hyalinization. Thickened septa and obliteration of fat lobules are present. Deep dermis hyalinization is common. Sclerosis of the entire dermis and panniculus characterize disabling pansclerotic morphoea¹⁰. The fascia is fibrotic and sclerotic, with vacuolated muscle fibres separated by edematous stroma and inflammatory infiltrates^{18,19}. The histology of our patient corresponded to that of deep morphoea.

The majority of children with localized scleroderma do not have systemic manifestations but it has been reported by Uziel et al⁴ that up to 40% have arthritis or arthralgia. Diaz et al¹⁰ reported 43% of children with DPMC had pulmonary or esophageal abnormalities. Although there have been reports of morphoea progressing to systemic sclerosis, it is extremely rare. Our patient did not have any systemic manifestations.

As a result of pansclerotic involvement, painful ulcers and severe joint contractures can develop. These ulcers often have super-imposed bacterial infections, of which *Pseudomonas aeruginosa*, *Enterobacteriaceae spp*, *Streptococci*, *Enterococci*, *Stenotrophomonas maltophilia* and *Serratia Marcenscens* have been reported²⁰. Systemic antibiotics are often necessary and in some patients, repeated wound debridements may be needed. Our patient developed disabling joint contractures, chronic non-healing lower limb ulcers and dry gangrene of his left big toe after minimal trauma. The bacterial culture from his ulcers grew Staphylococci and Enteric bacilli. There was no evidence of underlying osteomyelitis.

Other complications include soft tissue calcification. There have been reports of squamous cell carcinomas arising from long-standing ulcers in patients with DPMC. The annual incidence of patients with DPMC developing squamous cell carcinoma is 6.7%, far higher than patients who were cancer survivors and those with hereditary cancer prone syndromes²⁰. Visceral complications like abnormal pulmonary function tests, esophageal motility disorders and myopathic electromyographic disorders in sclerotic areas can occur¹⁰.

The management of a paediatric patient with morphoea requires a holistic approach. Both medical and psychosocial needs of the patient and the family have to be addressed. Medical therapy include topical and systemic treatments, phototherapy, physical and surgical options. All treatments have to be individualized.

Topical therapies include topical or intralesional corticosteroids and calcipotriene ointment. These treatment options are the initial choices for mild, localized plaque morphoea but in our patient with generalized morphoea, the therapeutic effects would be minimal.

Systemic therapy is indicated for severe extensive disease, linear scleroderma across joints where contractures result and facial involvement like en coup de sabre. Multiple treatment regimes and options like D-penicillamine, systemic corticosteroids and antibiotics, phenytoin, retinoids, cyclosporin and plasma exchange have been reported but there has been none with universal good results.

Use of systemic corticosteroids in the therapy of LS is questionable. Joly et al²¹ reported an improvement in 76% of patients after 6 weeks of 0.5 to 1mg/kg of oral corticosteroid but relapse rate was high (35%) after discontinuation. In contrast, Rosenwasser et al²² reported ineffectiveness of oral corticosteroids. Methotrexate has been reported to be useful in the treatment of adults with widespread morphoea and anecdotal reports in children have shown encouraging results as well. The need for regular blood monitoring, systemic toxicity issues and drug interactions have to be considered. Our patient was initially started on oral prednisolone at 1mg/kg/day and methotrexate 7.5mg/week. The dose of methotrexate was gradually increased for a steroid-sparing effect but the patient developed transaminitis and methotrexate had to be eventually stopped.

Oral calcitriol is also an option in the treatment of LS. Humbert et al²³ reported the use of oral calcitriol (1,25-dihydroxyvitamin D3) in an adult with severe LS and improvement was noted. In a study by Elst et al²⁴ in paediatric patients with linear scleroderma, 5 of 7 patients showed good improvement, 1 had a relapse that responded to a second course of calcitriol and 1 with severe disease showed no benefit.

Ultraviolet (UV) A irradiation alone, or together with psoralens, a photosensitizing agent, has been utilized in the treatment of LS. Encouraging results have been noted with UVA (320-400nm), UVA-1 (340-400nm) and psoralens with UVA (PUVA). There has been positive results of PUVA and UVA-1 in treatment of DPMC^{25,26}, especially for UVA-1, which has been thought to retard disease progression, including joint contractures²⁷. Although phototherapy is useful in the therapeutic armamentarium of LS, concerns regarding possible long-term carcinogenic risks, especially in children, may restrict its use. However, the benefits to quality of life of this patient may outweigh the risks of skin cancer, which is by no means certain to occur. Extracorporeal photophoresis has also been shown to be useful in some patients²⁸.

Physiotherapy involving heat, splinting, casting, muscle strengthening exercises and joint mobilization are useful in patients with flexion contractures. Surgical procedures are rarely considered as impaired tissue perfusion leads to difficulties in wound healing.

Roldan et al²⁹ reported the use of bosentan, a dual oral endothelin receptor antagonist, for 4 weeks in a paediatric patient with DPMC and chronic ulcers. An improvement was noted in the ulcers, degree of skin sclerosis and joint mobility. This could be utilized in our patient as he had chronic non-healing ulcers that did not respond well to dressings alone.

For non-healing chronic ulcers that are not infected, topical agents like chlorhexidine and betadine can be used as they have a broad antimicrobial spectrum with low tissue toxicity. Antimicrobial products containing silver, polyhexamethylene biguanide, Cadoxemer Iodine or polyacrylates can be used to treat superficial infections³⁰. Necrotic tissue impairs wound healing and encourages bacterial growth thus surgical debridement may be considered at

times. However, in patients with DPMC, impaired tissue perfusion could also lead to difficulties in wound healing post-operatively. Dressings that facilitate autolytic debridement can be used. These include hydrogels, films and hydrocolloids. Moisture balance is essential to wound healing, and the nature of exudates in chronic ulcers in DPMC may impair this³¹. Thus, the removal of exudates in chronic ulcers is necessary to promote wound healing. Dressings that serve this function include calcium alginate, foam, fibre and composite dressings. Synthetic skin grafts could also be considered to aid in tissue healing. Our patient had been on various dressings including silver dressings (mepilex silver), iodisorb, hydrogels and duoderm.

Systemic antibiotics are required to treat infected ulcers and these should be tailored according to the sensitivities of the organisms. Our patient was treated empirically with intravenous ampicillin and cloxacillin and converted to oral cloxacillin and amoxicillin when culture results of his ulcers showed Staphylococci and Enteric bacilli sensitive to the above antibiotics.

Wollina et al²⁰ reported efficacy on use of sildenafil together with porcine small intestinal submucosal acellular matrix in the treatment of chronic ulcers associated with DPMC. A porcine acellular matrix skin substitute was applied on the ulcers and together with oral sildenafil for 2 weeks, significant improvement in granulation of the ulcers was noted. This combination therapy had a synergistic effect that was far more efficacious than either therapy alone. In addition, sildenafil has also been reported to improve digital flexibility and dexterity³². The combination therapy could be considered in our patient as his ulcers are long-standing and has been showing poor response to conventional therapies of antibiotics and wound care.

Daily transcutaneous application of dry carbon dioxide gas can also be utilized to reduce colonization of the ulcers and aid in the granulation process³³. A 5-day course of intravenous immunoglobulin, followed by another dose a month later, has been used by Wollina et al³⁴ with good effect. The improvement noted in the ulcers lasted for nearly a year. Intravenous pentoxifyllin had been tried with poor results by the same authors³⁴.

In conclusion, treatment of patients with disabling pansclerotic morphea of childhood is difficult and quality of life is often severely impaired. Judicious skin care and prompt treatment of complications such as joint contractures and chronic ulcers is essential.

References

- Peterson LS, Nelson AM, Su WPD: Classification of morphea (localized scleroderma). *Mayo Clin Proc* 70:1068-1076, 1995
- Bielsa I, Ariza A: Deep morphea. *Semin Cutan Med Surg.* 2007 Jun;26(2):90-5
- Peterson LS, Nelson AM, Su WE et al: The epidemiology of morphea (localized scleroderma) in olmsted county 1960-1993. *J Rheumatol* 24:73-80, 1997
- Uziel Y, Krafchik BR, Silverman ED, et al Localized scleroderma in childhood: A report of 30 cases. *Semin Arthritis Rheum* 23:328-340, 1994
- Kornreich HK, King KK, Bernstein BH, et al: Scleroderma in childhood. *Arthritis Rheum* 20:343-350, 1977 (suppl 2)
- Kuhnl P, Sibrowsky W, Broehm BO, et al: Association of HLA antigens with progressive systemic sclerosis and morphea. *Tissue Antigens* 34:207-209, 1989
- Buechner SA, Winkelmann RK, Lautenschlager S, et al: Localized scleroderma associated with *Borrelia burgdorferi* infection: Clinical, histologic, and immunohistochemical observations. *J Am Acad Dermatol* 29:190-196, 1993
- Longo E Saletta S, Lepore L, et al: Localized scleroderma after infection with Epstein-Barr virus. *Clin Exp Rheumatol* 11:681-683, 1993
- Venneker GT, Das PK, Naafs B, et al: Morphea lesions are associated with aberrant expression of membrane cofactor protein and decay, accelerating factor in vascular endothelium. *BJr Dermatol* 131:237-242, 1994
- Díaz-Perez JL, Connolly SM, Winkelmann RK : Disabling pansclerotic morphea of children. *Arch Dermatol* 116:169-173, 1980
- Falanga V, Medsger TA, Reichfin M, et al Linear scleroderma. *Ann Intern Med* 104:849-857, 1986
- Rosenberg AM, Uziel Y, Krafchik BR, et al: Antinuclear antibodies in children with localized scleroderma. *J Rheumatol* 22:2337-2343, 1995
- Falanga V, Medsger TA Jr: Frequency, levels, and significance of blood eosinophilia in systemic sclerosis, localized scleroderma, and eosinophilic fasciitis. *J Am Acad Dermatol* 17: 648-656, 1987
- Falanga V, Medsger TA Jr, Reichlin M: Antinuclear and anti-singlestranded DNA antibodies in morphea and generalized morphea. *Arch Dermatol* 123:350-353, 1987
- Tuffanelli DL: Localized scleroderma. *Semin Cutan Med Surg* 17:27-33, 1998
- Schacter RK: Localized scleroderma. *Curt Opin Rheumat* 2:947-955, 1990
- Falanga V: Localized scleroderma. *Med Clin North Am* 73:1143-1156, 1989
- Jablonska S: Localized scleroderma, in Jablonska S (ed): *Scleroderma and Pseudoscleroderma* (ed 2). Warsaw, Poland, Polish Medical Publishers, 1975, p277
- Fleischmajer R, Nedwich A: Generalized morphea: I. Histology of the dermis and subcutaneous tissue. *Arch Dermatol* 1106:509-514, 1972
- Wollina U, Buslau M, Heinig B et al: Disabling pansclerotic morphea of childhood poses a high risk of chronic ulceration of the skin and squamous cell carcinoma. *Int J Low Extrem Wounds.* 2007 Dec;6(4):291-8
- Joly P, Bamberger N, Crickx B, et al: Treatment of severe forms of localized scleroderma with oral corticosteroids: Follow-up study on 17 patients. *Arch Dermatol* 130:663-664, 1994
- Rosenwasser TA, Eisen AZ: Scleroderma, in Fitzpatrick TB, Eisen AZ, Wolff K, (eds): *Dermatology in General Medicine* (ed 5). New York, NY, McGraw-Hill, 1993, pp 2156-2167
- Humbert PG, Dupond JL, Rochefort A, et al: Localized scleroderma-response to 1,25-dihydroxyvitamin D3. *Clin Exp Dermatol* 15:396-398, 1990
- Elst EF, Van Suijlekom-Smit LW, Oranje AP: Treatment of linear scleroderma with oral 1,25-dihydroxyvitamin D3 (calcitriol) in seven children. *Pediatr Dermatol.* 1999 Jan-Feb; 16(1):53-8
- Gruss C, Stücker M, Kobyletzki G et al: Low dose UVA1 phototherapy in disabling pansclerotic morphea of childhood. *Br J Dermatol.* 1997 Feb; 136(2):293-4
- Scharffetter-Kochanek K, Goldermann R, Lehmann P et al: PUVA therapy in disabling pansclerotic morphea of children. *Br J Dermatol* 1995; 132:830 1.
- Kroft EB, Berkhof NJ, van de Kerkhof PC et al: Ultraviolet A phototherapy for sclerotic skin diseases: a systematic review. *J Am Acad Dermatol.* 2008 Dec;59(6):1017-39.
- Neustadter JH, Samarin F, Carlson KR, Girardi M. Extracorporeal photochemotherapy for generalized deep morphea. *Arch Dermatol.* Feb 2009;145(2):127-30
- Sibbald RG, et al. Preparing the wound bed-debridement, bacterial balance, and moisture balance. *Ostomy Wound Manage.* 2000;46:14-22
- Okan D, et al. The role of moisture balance in wound healing. *Adv Skin Wound Care.* 2007;20:39-53.
- Yung A, Reay N, Goodfield MD: Improvement in digital flexibility and dexterity following ingestion of sildenafil citrate (Viagra) in limited systemic sclerosis. *Arch Dermatol* 2005;141:8;31-3
- Wollina U, Heinig B, Uhlemann C. Transdermal CO2 application in chronic wounds. *Int J Lower Extremity Wounds* 2004; 3:103-6
- Wollina U, Looks A, Uhlemann C et al: Pansclerotic morphea of childhood-follow-up over 6 years. *Pediatr Dermatol.* 1999 May-Jun;16(3):245-7

GENERAL DERMATOLOGY - Case Report

Wegener's Granulomatosis: A case report and literature review

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Keywords *Wegener's granulomatosis, systemic vasculitis, anti-neutrophil cytoplasmic antibody*

Introduction

Wegener's granulomatosis is a rare multisystem necrotizing granulomatous vasculitis affecting small - and medium-sized vessels. Its clinical manifestations can be nonspecific during the initial stages and indistinguishable from a variety of neoplastic, infectious, and inflammatory diseases. The disease may run a course from indolence to one of rapid progression leading to life-threatening multiorgan failure. We report a rare case of rapidly progressing Wegener's granulomatosis.

Case report

A 39 year old Malay housewife with no comorbidity, presented to us with a 2-month history of

multiple painful non healing ulcerated nodules and plaques involving the left face, right thigh and both shins. The lesions were initially papular and progressively enlarged to form nodules which ruptured with pus discharge and eventually formed ulcers. Apart from that, she also had non productive cough, symptoms of rhinitis, anorexia and loss of weight for the past 1 month. This was associated with bilateral reduced hearing but without ear discharge or pain. There was no fever, epistaxis, haemoptysis, dyspnoea or urinary symptoms.

Clinically, she was afebrile and normotensive. She had an ulcerated plaque on left cheek (Figure 1), 3 ulcerated plaques on both shins (Figure 2 and 3) and an ulcerated plaque on right thigh. All these ulcers were extremely tender with deep punched-out margins and covered with a haemorrhagic crust. The diameter of these ulcers ranged from 1 to 2cm.

Figure 1

Single ulcerative plaque with haemorrhagic crust on left cheek



Figure 2

Multiple ulcerative plaque on both shins



Figure 3

Close view of a ulcerative plaque with haemorrhagic crust on right shin



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There was also a tender nodule with normal overlying skin on the right cheek measuring 1x1cm. Examination of the respiratory, cardiovascular and neurologic systems were essentially normal. There was no organomegaly on abdominal examination. An ear, nose and throat assessment revealed the nasal septum to be ulcerated and crusted with bilateral moderate to profound mixed hearing loss, otitis media and chronic sinusitis. At this point of time, our differential diagnosis included Wegener's granulomatosis, polyarteritis nodosa, pyoderma gangrenosum, a deep fungal infection, cutaneous tuberculosis or non-tuberculous mycobacterium infection.

Investigations revealed that she had normochromic normocytic anaemia (Hb 10.8). Her erythrocyte sedimentation rate and c-reactive protein were both raised at 108 mm/hour and 35.75 mg/dl respectively. Tumour markers for CA125, CA19-9, alfa-fetoprotein and carcinoembryonic Antigen were all normal. There was no haematuria or proteinuria. Her chest x-ray, renal profile and liver function tests were normal. Serology for human immunodeficiency virus, hepatitis B and hepatitis C were negative. A swab from the ulcer grew *Staphylococcus aureus*. However, a swab from the ears did not grow any organism. CT scan of brain and neck showed pansinusitis, bilateral mastoiditis with otitis media and small subcutaneous abscess collection at the angle of the mandible.

Figure 4

Biopsy of the ulcerated skin showed granulation tissue with marked neutrophils infiltration. Evidences of vasculitis were absent. However, a few vague granulomas were present. (Haematoxylin and Eosin x400)

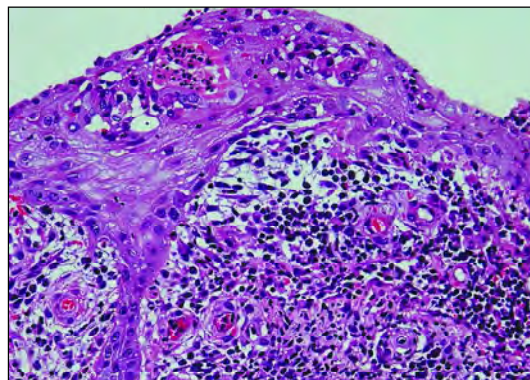


Figure 5

Biopsy from the nasal mucosa showed granulomas as well as multinucleated giant cells admixed lymphoplasmacytic cells surrounding the blood vessel. (Haematoxylin & Eosin x 400)

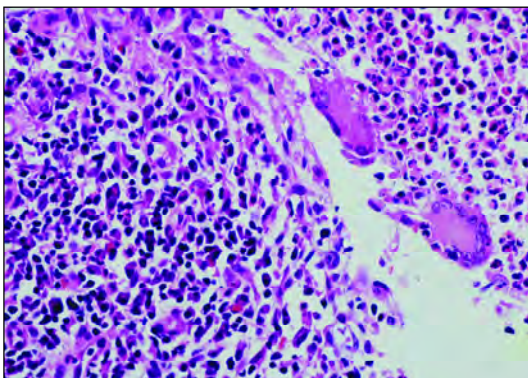
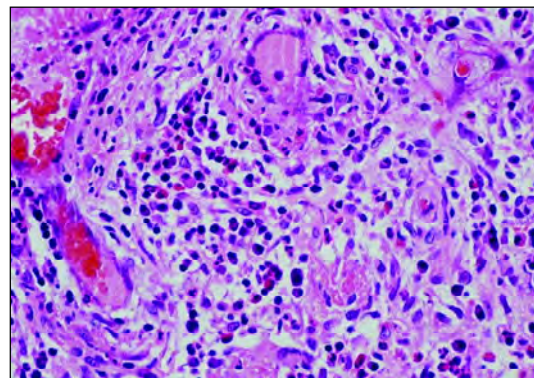


Figure 6

Biopsy from nasal mucosa: Fibrinoid necrosis of the small arterioles and neutrophilic infiltration of the blood vessels were clearly seen at tissue distance from the ulcerated mucosa. (Haematoxylin and Eosin x 400)



A skin biopsy of the ulcer on her left shin showed a cluster of granuloma with multinucleated giant cells and abundant surrounding neutrophils and plasma cells (Figure 4). There were no features to suggest vasculitis from the skin biopsy. Special stains for PAS, GMS and Ziehl Neelsen were all negative. Tissue culture for mycobacterium, fungus and bacteria were negative. However, her nasal biopsy showed a chronic necrotizing granulomatous inflammation with small vessel vasculitis (Figure 5, 6). Serology using indirect immunofluorescence for anti-neutrophil cytoplasmic antibody (ANCA) was positive for cytoplasmic pattern antineutrophil cytoplasmic antibodies (c-ANCA) but negative for perinuclear pattern antineutrophil cytoplasmic antibodies (p-ANCA). These features confirmed the diagnosis of Wegener's granulomatosis. The patient however, insisted on being discharged against medical advice to seek for traditional treatment before any treatment specific treatment could be initiated. She did not improve with alternative therapy and presented to another hospital 1 month later with acute renal failure. Unfortunately, she succumbed to severe pulmonary haemorrhage eventually.

Discussion

Wegener's granulomatosis (WG) is a multisystem disease characterized by necrotizing granulomatous inflammation of the upper, lower respiratory tracts and kidneys with necrotizing vasculitis affecting small- and medium-sized vessels¹. It is an autoimmune inflammatory process with antineutrophil cytoplasmic antibodies (c-ANCA) directed at neutrophil proteinase 3 (PR3). It is uncommon with a prevalence of approximately 3 per 100,000 in USA³. It affects males and females equally². The age group as reported in the literature, is between 40 to 55 years⁴ as in our patient. There is increasing evidence that *Staphylococcus aureus* plays a role in the pathogenesis of WG but the mechanism is still unclear⁵.

The clinical course of WG is characterized by an initial localized or limited phase followed by a generalized or systemic phase. In the initial limited phase, symptoms arise from granulomatous inflammation of the upper and/or lower respiratory tract whereas generalized WG is characterized by clinical signs of systemic vasculitis¹. Limited WG accounts for 25% of cases and it usually spares the kidney³. In generalized WG, patients present with life threatening pulmonary-renal syndrome as a

result of necrotizing alveolar vasculitis and rapidly progressive necrotizing glomerulonephritis¹.

In general, over 90% of patient with WG initially seek medical attention for upper and/or lower airway symptoms². The most frequently affected sites of granulomatous inflammation are the nose and paranasal sinuses (60-80%)². Patients may complain of nasal congestion, epistaxis, pain of the sinus cavities, persistent rhinorrhea, perforation of the nasal septum, hyposmia and saddle nose deformity. Ear disease occurs in 25 to 40% of WG and most commonly manifest as otitis media with effusion due to eustachian tube obstruction as a result of luminal granuloma or nasopharyngeal inflammation². Hearing loss is also common and it may be sensorineural, conductive or mixed². Oral cavity and oropharynx involvement are uncommon. The most common oral lesion is strawberry gingivitis which presents as an exophytic gingival growth with petechiae⁶. This may be the first sign and is nearly pathognomonic of WG⁶. Lung involvement is almost universal in patients with WG and it can affect pulmonary parenchyma, bronchi and pleura². Typically the patient presents with cough, haemoptysis, dyspnea and pleuritic pain. Chest radiograph may show pulmonary nodules, cavitating lesions, or diffuse alveolar haemorrhage^{1,2}. Our patient had evidence to suggest upper airway involvement of WG which included persistent rhinitis, chronic sinusitis and otitis media with hearing loss. However, there was no radiological evidence to suggest lung involvement on her initial presentation even though she succumbed to pulmonary haemorrhage eventually.

Cutaneous manifestations of WG encompass a diverse spectrum and occur in 40-50% of cases². The most common skin lesion is palpable purpura due to leucocytoclastic vasculitis⁷. Other presentations include nodules, papules, vesicular lesions, ulcerative pyoderma gangrenosum-like lesions and deep erythema nodosum-like subcutaneous nodules^{2,7}. These lesions commonly occur on the distal arms and legs⁷. Our patient presented with multiple ulcerative plaques mimicking pyoderma gangrenosum or cutaneous infections. In fact, skin lesions were the main problem that brought her to our hospital. However, it can be very challenging to determine the underlying cause at the initial stage as histopathology of skin biopsy can be non specific as shown in our patient.

Renal involvement is the most serious manifestation of WG and presents in about 20% of patients at diagnosis but develops in 80% of patients during the course of their disease². The patient can develop rapidly progressive renal failure as a result of necrotizing glomerulonephritis^{1,2}. Renal biopsy is not a routine as findings are usually nonspecific and it most often shows a focal and segmenting necrotizing proliferative glomerulonephritis^{8,9}. Our patient did not have any renal involvement initially. Unfortunately her disease progressed rapidly within a month after she was discharged on her own accord. She subsequently presented with acute renal failure in another hospital. WG can also involve other organs such as the eye (causing proptosis, necrotizing keratoscleritis conjunctivitis, retinal vasculitis), cardiac (causing pericarditis, myocarditis, conduction abnormalities) and neurologic system (causing mononeuritis multiplex, cerebral vasculitis)⁴. Our patient did not have any of these rare presentations.

Diagnosis of WG is generally based on a combination evidence of clinical findings, biopsy of involved tissue showing necrotizing granulomas/vasculitis and laboratory evidence of cANCA⁸. The American College of Rheumatology has proposed that the diagnosis of WG can be made if two of the following criteria are included: 1) ulcerative lesions in oral mucosa or nasal bleeding or inflammation, 2) nodules, fixed infiltrates or cavities in chest radiograph, 3) abnormal urinary sediment (red cell cast or 5 red blood cell per high power field), and 4) granulomatous inflammation on biopsy¹⁰. Our patient had evidence to suggest WG based on clinical presentation, histopathology from nasal biopsy and a positive cytoplasmic pattern antineutrophil cytoplasmic antibodies (cANCA).

Three major histopathologic findings of Wegener's granulomatosis include parenchymal necrosis, vasculitis, and granulomatous inflammation². The site of biopsy affects the diagnostic yield with paranasal sinus biopsy offering the highest yield². Cytoplasmic pattern ANCA (cANCA) positivity is found in more than 90% of generalized WG but only 50% in limited WG². Levels of cANCA also correlates with disease activity in WG¹¹. The titers of these antibodies decline during treatment but may rise again before relapse¹¹. As was the case in this patient, an increase in erythrocyte

sedimentation rate and C-reactive protein is common in WG.

WG is highly fatal if not treated early with more than 90% mortality in the first two years and renal failure is the most common cause of death¹. Delay in the diagnosis of WG is mainly due to the nonspecific symptoms or signs that are experienced by the patient during the initial phase of the disease¹¹. Hence, early diagnosis and treatment is important as the presence of advanced disease at diagnosis limits the potential benefit of therapy. Treatment of WG requires induction of remission followed by maintenance. Current remission induction treatment protocols in systemic WG consist of cyclophosphamide and corticosteroids supported by plasma exchange in case of severe renal vasculitis or pulmonary hemorrhage^{1,2,12}. Cyclophosphamide may be given as continuous low dose oral treatment or by intravenous pulses initially at 2-3 week interval¹². This treatment is continued for 3 to 6 months until patient has achieved remission¹². During maintenance therapy, cyclophosphamide should be withdrawn and substituted with either azathioprine or methotrexate to avoid the side-effects of cyclophosphamide¹². Patients should continue maintenance therapy for at least 24 months following successful disease remission¹². Optimization of treatment protocols has led to remission rates of 70-90% in the first year and 5-year survival rate is now reported to be over 75%^{1,2}. However, relapse rate is high ranging from 10% in the first year to 66% during long-term follow-up¹. Long term treatment with low dose of trimethoprim/sulfamethoxazole has shown satisfactory response to control bacterial infection¹. This treatment is based on the hypothesis that infection exposes neutrophil proteases to autoantibodies and justifies the attempt to control the infection². In this patient, we were not able to initiate appropriate treatment as she insisted on discharge against medical advice upon confirmation of her diagnosis.

Conclusion

This report has described one case of rapidly progressing Wegener's granulomatosis based on clinical, histopathology, and laboratory evidence of cANCA. Our patient presented initially with an upper airway and skin manifestation but her disease progressed rapidly with subsequent renal and pulmonary involvement 1 month after she was discharged. Diagnosis of this condition may be very

at the initial stage and requires a high index of suspicion due to non-specific presentation. Treatment need to be initiated as early as possible to improve the outcome of this condition as it carries a high mortality rate.

References

1. Anna M. Schilder. Wegener's Granulomatosis vasculitis and granuloma. *Autoimmunity Reviews* 2010;9:483-487
2. A. M. Khan, F. Elahi, S.R. Hashmi et al. Wegener's granulomatosis: A rare, chronic and multisystem disease. *Surgeon* 2006;1:45-52
3. Lynn E. Harman, Curtis E. Margo. Wegener's Granulomatosis. *Survey of Ophthalmology* 1998;42:458-480
4. Cotch MF, et al. The epidemiology of Wegener's granulomatosis. *Arthritis Rheum* 1996;39:87-92
5. Kallenberg CG, Tadema H. Vasculitis and infections: contribution to the issue of autoimmunity reviews devoted to "autoimmunity and infection". *Autoimmunity Reviews* 2008;8:29-32
6. Hellevi R, Tapani H, Johanna A et al. Strawberry-like gingivitis being the first sign of Wegener's granulomatosis. *European J of Int Med* 2009;20:651-653
7. Angelo Valerio Marzano Daniele Fanoni. Oral and cutaneous findings are valuable diagnostic aids in Wegener's granulomatosis. *European Journal of Internal Medicine* 2010;21:49
8. Bajema IM, Hagen EC, Vander Woude FJ, Brujin JA. Wegener's granulomatosis: a meta-analysis of 349 case reports. *Journal of Laboratory and Clinical Medicine* 1997; 129:17-22
9. Dana M. Hartl, Patrick Ai'dan, Olivier BrugiGre, Olivier Sterkers. Wegener's Granulomatosis Presenting as a Recurrence of Chronic Otitis Media. *American Journal of Otolaryngology* 1998;19:54-60
10. Leavitt RY, Fauci AS, Bloch DA, et al: The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum* 1990;33:1101-1107
11. I. Ponniah, Ahmed Shaheen, K. A. Shankar, M. G. Kumaran. Wegener's granulomatosis: The current understanding. *India Oral Surgery Oral Medicine, Oral Pathology, Oral Radiology and Endodontology* 2005;100:265-70
12. CC. Lapraik, R. Watts, P. Bacon et al. BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis. *Rheumatology* 2007;46:1615-1616

GENERAL DERMATOLOGY - Self Assessment

Clinical diagnostic skill test

Tick at the provided space [✓] against answers that correlate to the slide.
Check your answer on **page 45**. Refer to the given criteria in **page 46** to discover your clinical diagnostic skill status.

Slide A



A

- bacterial Infection
- fungal infection
- allergy
- viral exanthem
- drug exanthem
- skin scalding syndrome
- atopic dermatitis
- candidiasis
- impetigo
- seborrhoeic dermatitis

Slide B



B

- allergy
- ADR
- dermatitis
- bacterial infection
- viral infection
- angioedema
- photodermatitis
- hypereosinophilic sensitivity syndrome (HESS/DRESS)
- psoriasis
- contact dermatitis

Slide C



C

- allergy
- skin infection
- dermatitis
- impetigo
- acne
- deep fungal infection
- chickenpox
- viral wart
- molluscum contagiosum
- eczema herpeticum

Slide D



D

- deep fungal infection
- cutaneous tuberculosis
- atypical mycobacterium infection
- tumour
- lymphadenitis
- abscess
- squamous cell carcinoma
- sporothricosis
- fish tank granuloma

Slide E



E

- allergy
- non infective inflammation
- dermatitis
- insect bite reaction
- autoimmune disease
- contact dermatitis
- bullous impetigo
- pemphigoid
- pemphigus
- eczema herpeticum

Slide F



F

- ADR
- hormonal disorders
- fungal infection
- viral infection
- appendageal disorders
- candidiasis
- varicella zoster
- milia crystalina
- herpes viral infection
- molluscum contagiosum

A study of the cause and prognosis of chronic Urticaria in Malaysian children

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Abstract

The aetiologies of chronic urticaria (CU) in childhood remains incompletely understood because of limited data in children. The objective of this study was to determine the clinical features, aetiological factors, and response to treatment of chronic urticaria (CU) in children by focusing on the autoimmune and IgE, urticarial vasculitis, parasitic infestation and food allergy. Children 2–16 yr of age with CU were investigated for complete blood count, erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), complement factors, ASST, Radioallergosorbent test (RAST), urine cultures and stool examination for parasites. Twenty five children who met the criteria for CU were recruited. None of these patients had clinical features of urticarial vasculitis. None had raised ESR or CRP and all had normal infective screening. Positive ASST was found in 60%. There were no differences in medication requirement and CU remission between patients with positive and negative ASST. None had parasites infestation. RAST to foods was positive in 25%. Food avoidance was beneficial to the subgroup of patients with positive history of food allergy. The prognosis for spontaneous remission is good in children with chronic urticaria.

Keywords *Chronic urticaria, prognosis, causes*

Introduction

Urticaria is a distressing skin eruption and may be acute, chronic or intermittent, with or without angioedema. Around 25% of the population suffer from urticaria at some time in their lives, causing considerable discomfort¹. Various aetiological factors have been identified, however, the prevalence of the subtypes in children is essentially unknown, and the aetiological factors in paediatric urticaria have not been fully investigated. Recently, a specific autoimmune mechanism has been identified as causative by Greaves MW^{2,3} and has been repeatedly confirmed independently elsewhere. Autoimmune urticaria has been demonstrated in childhood⁴, but its prevalence, significance and prognosis in this age group has yet to be determined.

The aim of this study is to determine the clinical features, aetiological factors, and response to treatment of chronic urticaria (CU) in children.

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Methodology

A total of 25 children were studied from the age of 2 to 16 years. The study was undertaken at the Institute of Paediatrics, Hospital Kuala Lumpur (HKL) over a 2 year period from July 2002 to July 2004. The diagnosis was made on clinical grounds. Chronic and intermittent urticaria were identified conventionally⁵.

Initial evaluation

The history was taken using a questionnaire, which includes demography, relevant history on foods, drugs, infections, infestations, aggravating physical factors, family history, general medical history, history of immunization, possible insect stings, and other supposedly allergic events.

A full physical examination was carried out and the duration and specific features of individual wheals were assessed.

Laboratory investigations included a full blood picture, ESR, LFT, CPK, CRP, serum antibodies to EBV, CMV, Hep B & C, Toxoplasma, Enteroviruses and Herpes simplex, total IgE, specific IgE to penicillin, milk proteins and other foods, ANF, complement profile and serum protein

electrophoresis. The specific IgE was analysed using Pharmacia CAP-RAST system. The normal value for total IgE is less than 100 ku/L and less than 0.35 ku/L for specific IgE.

Microbiological studies included urine microscopy and culture and stool examination for ova and cysts.

Autologous serum skin test (ASST) to support the diagnosis of autoimmune urticaria was performed using the technique as described by Greaves MW et al². The ASST has a sensitivity of approximately 70% and a specificity of 80%.

Skin biopsy was carried out in children suspected to have urticarial vasculitis clinically. These children were followed up every 3 months for a year to determine the treatment response and outcome of CU.

Patients with acute urticaria and with severe systemic illness were excluded. The study was approved by the local ethics committee.

Definition

Urticaria is defined as pruritic wheals which last for less than 24 hours. CU is defined as the presence of daily or almost daily wheals for at least 6 weeks. Intermittent urticaria is recurrent bouts of urticaria which lasts up to 6 weeks or more for each episode.

Analysis of data

Statistical analysis was carried out using SPSS programme.

Results

Demographic data

There were fourteen (56%) Malays, 7 (28%) Chinese and 4 (16%) Indian children. Thirteen (52%) were males and 12 (48%) females. The male to female ratio was 1.1:1. The children were between 2 to 16 years old with a mean age of 7.5 years.

Clinical presentation

Thirty two percent of the children were 3 years old at the onset of symptoms. Twenty percent were more than 10 years and the mean age at onset was 5.6 years. The duration of symptoms ranged between 2.5 months and 100 months with a mean of 13 months.

All had pruritus and wheals on the limbs, palms and soles. Eighty four percent had wheals on the face and perioral region. Only two children had angioedema. Most of the children had wheals intermittently (72%) rather than on a continuous (28%) basis. Ninety six percent of the wheals were annular in shape.

Twenty five percent had a positive family history of atopy such as asthma, eczema and rhinitis. One out of 25 children had wheals lasting more than 24 hours, but the skin biopsy did not show any features of urticarial vasculitis.

Investigations

All the total white blood cell counts were normal (range: 4 to 10 x 10⁹ cells/L) and the mean WBC was 6.7 x 10⁹ cells/L. The mean eosinophil and basophil counts were 3.0% and 0.9% respectively. However, none of the children had a positive stool for ova and cysts. Urine culture and sensitivity were normal in all children. All the children had a negative blood test for Hepatitis A, B and C. None had a positive antinuclear factor.

The mean total IgE was 770ku/L (range: 60 to 3351ku/L). Twenty two children had their total IgE analysed and 72% were positive. The IgE level to peanut was positive in two children (8%) but only one was symptomatic with pruritus and wheals. Six children were positive to fish (4%) but only two were symptomatic with pruritus and wheals. Three children were positive to milk (12%) but only two were symptomatic with pruritus and wheals. One child was symptomatic and positive to wheat. Twenty four percent were positive for egg and 8% for wheat and soy (Figure 1).

ASST was tested in all children, and 60% were positive. The basophil counts were low in 13 children but the eosinophil counts were all normal. There is a statistically significant association between the basophil count and the ASST with a p value of 0.001. The ASST correlates inversely to the basophil count ($r = -0.752$).

Sixteen percent of children had a history of taking antibiotics prior to the development of urticaria and none took non steroidal anti-inflammatory drugs. None of the children had any associated infection or complaints of passing out worms.

Suspected physical factors which aggravated the symptoms were cold water in one child, thirteen to sweating and seven to exercise. The other four did not have any aggravating factors. No children had insect bites, previous history of immunization or other allergic events.

Treatment and outcome

Almost all the children received an H1 antagonist (either loratidine or ceterizine) for symptomatic relief and none required prednisolone or an H2 antagonist. Sixty percent went into remission and 40% were still on treatment. Fourty seven percent of children with autoimmune urticaria, went into remission by one year. Only ten percent of children with cholinergic urticaria went into remission.

Discussion

Although urticaria is common in children, the aetiological factors causing CU among them are limited and only a few reports have been published on this subject.

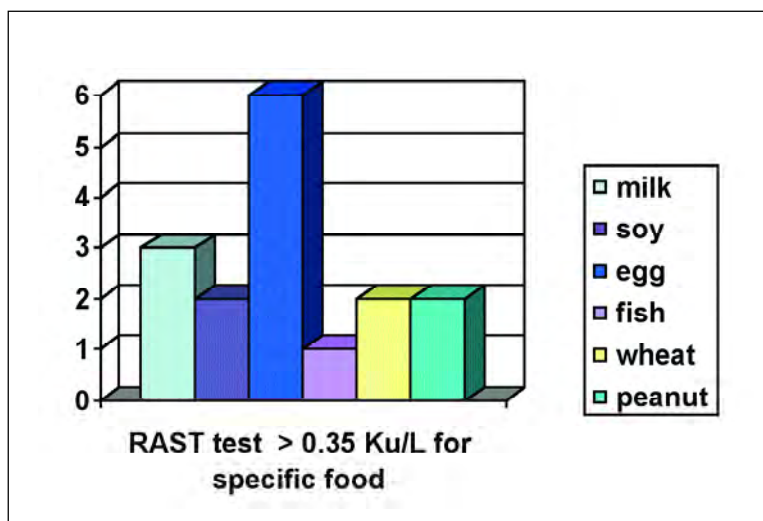
In our study, associated angioedema was not as commonly reported as in other studies⁵. Only two children had angioedema, one to wheat and the other child to seafood.

Although the mechanisms responsible for CU are not fully understood, it has recently been documented of a strong association with the presence of circulating functional autoantibodies directed against either the high affinity IgE receptor (Fc_RI_) and/or against IgE^{2,6,7}. Evidence for an association between circulating autoantibodies and CU in children is largely restricted to thyroid autoantibodies.⁸ Other aetiologies for both children and adults with CU include viral infection, parasitic infestation, food allergy, food additive reactions and aeroallergen allergy^{9,10,11}. None of these satisfactorily account for all patients with CU.

Low basophil count (55%) is demonstrated in this study. Basophil paucity was also demonstrated in other studies¹². The finding that peripheral blood basophils are reduced or absent in patients with CU with histamine-releasing autoantibodies may prove to be a helpful clinical marker of autoimmune urticaria once rapid and reliable methods for measuring small numbers of circulating basophils are available¹³.

Sixty percent of our children were positive to ASST. The ASST is currently the best in vivo clinical test for detection of in vitro basophil histamine-releasing activity¹⁴. ASST is correlated inversely to the basophil count¹⁵.

Figure 1 RAST test for specific food



The normal eosinophil counts and the absence of parasites in stool do not support the role of helminthic infestation as the cause of CU in this study.

Food allergy was implicated in 25% of children with positive specific IgE to wheat, milk, egg and peanuts.

Twenty percent of children had suspected physical urticaria especially, cholinergic urticaria.

Oral antihistamines are the mainstay of treatment for CU. They reduce the itch and wheal. In this series, nearly all children were symptomatically relieved with oral antihistamine except for one child requiring systemic steroid¹⁶.

Sixty percent went into complete remission by one year. In other studies, 35% went into remission and 29% had reduced symptoms^{17,18}.

Conclusion

This study demonstrated that nearly 25% of CU patients had no laboratory abnormality. An autoimmune mechanism may underlie the pathogenesis of chronic urticaria in a subset of children and CAU was identified in more than one-third these children. However, a long-term follow-up would be important to identify any association of CAU and other autoimmune diseases. Urticarial vasculitis was not identified in the absence of typical clinical features. Food allergy was encountered in a small number of patients and clinical significance was found in the subgroup of patients with positive history of allergy to related foods. Avoidance of specific foods could be of benefit in a subgroup of patients. Parasitic infestation was not found in our children with CU. Overall, our investigation supports the concept that detailed history taking and thorough examination will help to avoid unnecessary investigations. And in general, the prognosis for spontaneous remission is good in children with chronic urticaria.

References

- O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on quality of life. *Br J Dermatol* 1997;136: 197-201
- Hide M, Francis DM, Grattan CE, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Eng J Med* 1993;328(22):1599-1604
- Greaves MW. Chronic Urticaria. *N Eng J Med* 1995;332:1767
- Greaves MW. Chronic Urticaria in childhood. *Allergy* 2000;55(4):309-320
- Champion RH, Roberts SOB, Carpenter RG, Roger JH. Urticaria and angioedema - a review of 554 patients. *Br J Dermatol* 1969;81:588-9
- Sabroe RA, Francis DM, Greaves MW. Chronic idiopathic urticaria: comparison of the clinical features of patients with and without FcRI or anti-IgE autoantibodies. *J Am Acad Dermatol*. 1999;44:446-452
- Tong LJ, Balakrishnan G, Kochan JP, Kinet J-P, Kaplan AP. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol* 1997;99:461-465
- Levy YSN, Weintrob N, Danon YL. Chronic Urticaria: association with thyroid autoimmunity. *Arch Dis Child* 2003; 88:517-519
- Dalal I, Levine A, Somekh E, Mizrahi A, Hanukoglu. A chronic urticaria in children: expanding the autoimmune kaleidoscope. *Pediatrics* 2000;106:1074-1077
- Volonakis M, Stratigos J. Etiological factors in childhood chronic urticaria. *Ann Allergy* 1992;69:61-65
- Harris A, Geha RS. Chronic urticaria in childhood; natural course and aetiology *Ann Allergy* 1983;51:161-165
- Rorsman H. Basopenia in urticaria. *Acta Allergol* 1962;17:168-184
- Grattan CEH, Walpole D, Francis DM, Niimi N, Dootson G, Edler S, et al. Flow cytometric analysis of basophils numbers in chronic urticaria: basopenia is related to serum histamine releasing in chronic urticaria *Clin Exp Allergy* 1997;27:1417-1424
- Grattan CEH, Sabroe RA, Greaves MW. Chronic urticaria. *J Am Acad Dermatol* 2002;46:645-657
- Sabroe RA, Grattan CEH, Francis DM, Barr BM, Kobza Black A, Greaves MW. The Autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999;140(3):446-453
- Greaves MW. Chronic Urticaria. *J Allergy Clin Immunol* 2000;105(4):664-672
- Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. Natural history of physical and chronic urticaria and angioedema in 220 patients. *J Am Acad Dermatol* 2001;45:387-391
- Van Der Valk PGM, Moret G, Kiemeny LALM. The natural history of CU and angioedema in patients visiting a tertiary centre. *Br J Dermatol* 2002;146:110-113

PAEDIATRIC DERMATOLOGY - Short Communication

Netherton Syndrome presenting as Erythroderma in newborn

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Dear Editor,

We would like to report a newborn with erythroderma. He was born borderline premature via emergency C-section. He did not have any family history of atopy or skin disease. He was born with a paper thin erythematous dry scaly skin with erythema seen prominently on the scalp, face, neck, ears, perigenital and gluteal regions. The nails and mucous membranes were spared. Staphylococcus coagulase negative bacteria was isolated from blood culture during this time and he was treated with the appropriate intravenous antibiotics. However, the whole skin gradually became more erythrodermic with extensive scaling. He later developed severe hypernatremic dehydration which required aggressive fluid resuscitation. This was attributed to extreme insensible fluid loss.

Due to the worsening skin condition, a skin biopsy was performed which revealed features suggestive of Congenital Ichthyosis. Histopathology of the skin revealed mild hyperkeratosis, parakeratosis

with acanthosis and mild spongiosis. The upper dermis showed mild lymphocytic infiltrate in the superficial perivascular region. He was reviewed by a visiting Paediatric Dermatologist and a diagnosis of Netherton Syndrome (NS) was entertained when his scalp hair showed trichorrhexis invaginata. Immunodeficiency work up was also carried out revealing generalized hypogammaglobulinemia. The patient was treated with emollients and mild topical steroids. He was discharged well after achieving his birth weight at Day 10 of life.

He was closely monitored for infections and weight gain during his clinic follow up. His skin condition showed tremendous improvement with topical applications alone. After the first few months of life, the erythroderma slowly resolved and plaques typical of ichthyosis became evident. Despite being able to tolerate well orally, he had chronic diarrhoea with severe failure to thrive and had to be admitted at 6 months of age for observation of feeding pattern and optimization of his calorie intake. He developed multiple complications during this

Figure 1 Generalised scaly and paper thin skin at birth



Figure 2 Erythroderma at 6 weeks of life



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admission including difficulty in setting the intravenous line, hypoglycaemia and severe osmotic diarrhoea. He was discharged against medical advice and was brought in very ill a few days later to Casualty where he succumbed despite active resuscitation.

The early diagnosis of the NS is usually difficult due to erythroderma in the first few months of life, which later slowly disappears, and lesions typical of ichthyosis linearis circumflexa become evident as in this patient. During the first months of life erythroderma predominates with hypernatremic dehydration and failure to thrive. Erythroderma can be caused by multiple factors: immunodeficiency, metabolic disease like acrodermatitis enteropathica, ichthyosis, atopic dermatitis, psoriasis and seborrhoeic dermatitis. Sometimes the origin remains unknown. The specificity of clinical and histopathological features is low in neonates and therefore there is usually a delay before the final diagnosis is established.

Ultrastructural analyses of skin in patients with NS, congenital ichthyosiform erythroderma, and erythrodermic psoriasis can be of great value in establishing a correct diagnosis¹. Ultrastructural analyses of skin in patients with NS show replacement of stratum corneum with parakeratotic cells. Distinctive features include premature secretion of lamellar bodies and foci of electron dense material in the intercellular spaces of stratum corneum, which are not observed in other erythrodermic disorders, appear to be frequent and relatively specific markers for NS. Ultrastructural analyses of the skin of patients with NS may facilitate the early diagnosis of NS².

Erythrodermic neonates are at risk of sepsis, hypernatremic dehydration, malnutrition, failure to thrive, and other life threatening conditions. In some patients with NS an intermittent aminoaciduria has been observed³. It has been proposed that increased caloric demands consequent to increased epidermal metabolism and hyper proliferation are the basis for failure to thrive in this condition. However, it is unclear whether the caloric and nutrient drain of a hypermetabolic epidermis alone can account for the extra caloric requirements for adequate weight gain in children with this condition.

Specific nutritional deficiencies arising from skin exfoliation or gastrointestinal malabsorption may also be a problem. Nutritional deficiencies could exacerbate the barrier defect in these patients. For example, essential fatty acids may be lost through excessive desquamation, and gastrointestinal malabsorption, if present, could further amplify this deficiency. Linoleic acid is a critical constituent of the stratum corneum lamellar membranes. Essential fatty acid deficiency results in an epidermal phenotype characterized by erythroderma, hyperplasia, and transepidermal water loss (TEWL), a phenotype similar to that seen in patients with erythrodermic ichthyosis. Thus, a potentially vicious cycle could arise in patients with ichthyosis who also have essential fatty acid deficiency.

Gastrointestinal malabsorption from a primary or secondary enteropathy may also contribute to growth failure in these patients. Two studies have demonstrated jejunal villous atrophy in some infants and children with Netherton syndrome. Our patient suffered from gastrointestinal involvement⁴ which could be the reason for the dystrophy and a poor weight gain during his infancy period.

In the second year of life, the erythroderma slowly disappears and migratory gyrate lesions with double-edged scaling become evident. Hair shaft abnormalities on the scalp manifest as trichorrhexis invaginata, pili torti and/or trichorrhexis nodosa⁵. In our patient, ultra structural analysis of the hair disclosed trichorrhexis invaginata. Some patients can remain severely affected with erythrodermic flares or have erythroderma with pustules⁶. In patients with NS, atopy is usually manifested as angioedema, allergic rhinitis, asthma, urticaria and elevated IgE^{7,8}. Our patient was not tested for IgE. Patients with NS usually have normal values of serum immunoglobulin levels but selective antibody deficiency to bacterial polysaccharide antigens can be found, so it is important to evaluate the functional antibody response to both protein and bacterial polysaccharide⁴. In our patient the IgG, IgA and IgM were low.

Therapy with topical steroids, tars, emollients, PUVA, and oral vitamin A derivatives is not satisfactory, and offers temporary effects^{5,9}. Long-term treatment with topical tacalcitol was tried in a few cases with good results and without severe side effects, but its effect should be additionally proven

on a larger group of patients. Children with ichthyosis and growth failure may have uncompensated caloric needs because of an impaired skin barrier (unpublished data). Gastrointestinal dysfunction and nutritional deficiencies are uncommon and do not appear to be primary causes of the growth failure in these children. Because growth failure is of early onset in these children, we suggest that nutritional evaluation and caloric supplementation should be instituted early to maximize growth potential. Close monitoring of patient's nutritional status as well as prompt recognition and treatment of infections are fundamental in ensuring patient's survival to adulthood. In our patient, even the strict hypoallergenic diet did not improve the skin condition and dystrophy, characterized by a poor weight gain.

Netherton Syndrome should be excluded in newborns presenting with erythroderma. Close monitoring, continuous intensive therapy, repeated family education and support on how to cope with a child with a chronic disease is necessary for better outcome.

References

1. Williams ML. Ichthyosis and Disorders of Cornification. In: Schachner LA, Hansen RC eds. *Paediatric Dermatology*. New York: Churchill Livingstone, 1988: 412
2. Fartasch M, Williams ML, Elias PM. Altered lamellar body secretion and stratum corneum membrane structure in Netherton syndrome: differentiation from other infantile erythrodermas and pathogenic implication. *Arch Dermatol* 1999; 135: 823-32
3. Caputo R, Vanutti P, Bertani E. Intermittent aminoaciduria have been observed in some patients. *Arch Dermatol* 1984; 120: 220-2
4. Schwayder T, Bernarjee S. Netherton syndrome presenting as congenital psoriasis. *Pediatr Dermatol* 1997; 14: 473-6
5. Blaschke S, Möller R, Hauser I, Lamprecht IA, Paul E. Comel-Netherton-Syndrom. *Hautarzt* 1998; 49: 499-504
6. Judge MR, Morgan G, Harper JI. A clinical and immunological study of Netherton syndrome. *Br J Dermatol* 1994; 131: 615-21
7. Judge MR, Green SL, Müller SA. Netherton syndrome. Report of a case and review of the literature. *J Am Acad Dermatol* 1985; 13: 329-37
8. Plautin P, Delaire P, Guillet MH, Labouche F, Guillet G. Netherton syndrome, current aspects. A propose of 9 cases. *Ann Dermat et Venereol* 1991; 118: 525-30
9. Kansky A, Podrumac B, Prelog I. Hereditary ichthyosis. Pathogenesis and possibilities of treatment. *ACTA Dermatoven APA* 1997; 6: 47-54

Answers to Clinical Diagnostic Skill Test

- Slide A**
- 1 bacterial Infection
 - 2 fungal infection
 - 0 allergy
 - 0 viral exanthem
 - 0 drug exanthem
 - 2 skin scalding syndrome
 - 2 atopic dermatitis
 - 1 candidiasis
 - 1 impetigo
 - 1 seborrhoeic dermatitis
- This patient has skin scalding syndrome as evidence by the golden crust radiating from the corners of the mouth & eyes. It is important to recognise this condition because of the risk of toxemia. Misdiagnosis can result in fatality if therapy is delayed.
- Slide B**
- 1 allergy
 - 1 ADR
 - 2 dermatitis
 - 2 bacterial infection
 - 2 viral infection
 - 2 angioedema
 - 2 photodermatitis
 - 2 hypereosinophilic sensitivity syndrome (HESS/DRESS)
 - 2 psoriasis
 - 2 contact dermatitis
- When patient presents with angioedema with dermatitis or vasculitis, think of hypereosinophilic sensitivity syndrome especially if patient has been on medication before development of skin lesions. This condition may be associated with fever, eosinophilia and raised liver enzymes. If the drug is not stopped, it can result in prolonged morbidity.
- Slide C**
- 3 allergy
 - 1 skin infection
 - 3 dermatitis
 - 3 impetigo
 - 2 acne
 - 2 deep fungal infection
 - 1 chickenpox
 - 2 viral wart
 - 1 molluscum contagiosum
 - 1 eczema herpeticum
- Suspect cutaneous deep fungal infection when patient with human immunodeficiency virus presents with persistent crops of papular lesions with central umbilication or scab on the face. Fungal spores can be detected by bedside Tzanck test within one day if the facility is available. Thus urgent antifungal therapy can be instituted as this sign is an AIDS defining disease.
- Slide D**
- 1 granuloma
 - 1 deep fungal infection
 - 1 cutaneous tuberculosis
 - 1 atypical mycobacterium infection
 - 0 tumour
 - 1 lymphadenitis
 - 1 abscess
 - 0 Squamous cell carcinoma
 - 1 sporothricosis
 - 1 fish tank granuloma
- Suspect cutaneous deep fungal infection or atypical mycobacterial infection if there is a persistent ulcer with multiple nodules arranging in a linear fashion (lesion with sporothricoid or lymphatic spread).

Slide E	<input type="checkbox"/> 0	allergy	Suspect autoimmune bullous disease if an adult present with flaccid blisters that ends in crust. It can be induced by certain drug ingestion. Misdiagnosis may result in delayed commencement of immunosuppressant resulting in prolonged morbidity and can be fatal if untreated.
	<input type="checkbox"/> 1	non infective inflammation	
	<input type="checkbox"/> -3	dermatitis	
	<input type="checkbox"/> -2	insect bite reaction	
	<input type="checkbox"/> 1	autoimmune disease	
	<input type="checkbox"/> -3	contact dermatitis	
	<input type="checkbox"/> -3	bullous impetigo	
	<input type="checkbox"/> 1	pemphigoid	
	<input type="checkbox"/> 2	pemphigus	
	<input type="checkbox"/> -3	eczema herpeticum	

Slide F	<input type="checkbox"/> -1	ADR	Firm pearly papules with central umbilication in children prompt the diagnosis of molluscum contagiosum.
	<input type="checkbox"/> -2	hormonal disorders	
	<input type="checkbox"/> -2	fungal infection	
	<input type="checkbox"/> 1	viral infection	
	<input type="checkbox"/> -2	appendageal disorders	
	<input type="checkbox"/> -2	candidiasis	
	<input type="checkbox"/> 0	varicella zoster	
	<input type="checkbox"/> -2	milia crystalina	
	<input type="checkbox"/> 0	herpes viral infection	
	<input type="checkbox"/> 2	molluscum contagiosum	

Sum up the number of score 2, 1, 0, -1, -2 and -3 that you have collected.

SCORE	TOTAL NUMBER COLLECTED	IMPLICATION
-3		Delayed diagnosis may result in irreversible outcome / deformity
-2		Delayed diagnosis may result in prolonged morbidity
-1		Therapy for wrong diagnosis may worsen the primary skin lesion
0		No effect on outcome of primary skin lesion but cost wastage of medication, investigation kit and money
1		Therapy for this diagnosis can have good outcome
2		Correct diagnosis enables appropriate investigations, therapy and even long term follow-up

How did you performed? You should aim for correct diagnosis and minimize delayed diagnosis.