Case 2: Behcet's Syndrome

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CASE SUMMARY

History

A 31-year old Chinese lady first presented in 1994 with bloody diarrhoea, rectal bleeding and abdominal pain in Paris. Colonoscopy was performed and histology of colonic biopsy showed features of ulcerative colitis. The symptoms responded rapidly to prednisolone enema. In September 1996, there was relapse of bloody diarrhoea which was controlled again with prednisolone enema only. In November 1996, she noticed for the first time ulceration of her skin which resolved spontaneously.

She was well since then until April 1997 in Beijing when her bowel symptoms recurred. She was treated with prednisolone enema but this time there was only partial response. She also received treatment from traditional Chinese herbalist at that time. In November 1997, she presented to Cannosa Hospital in Hong Kong with multiple skin ulcers, mucosal ulceration, joint pain and bloody diarrhoea. She was subsequently transferred to Queen Mary Hospital for further work-up and management. Her past health was good and her family history was unremarkable.

Physical examination

On presentation she had high swinging fever and multiple arthritis, mainly involving peripheral joints. Multiple ulcers were found on lower limbs, perineum, back and shoulders (Figure 1). Each ulcer had a necrotic base and a violaceous border. Multiple aphthous ulcers were noted on the palate and lower lip (Figure 2). Pathergy test was positive (Figure 3).

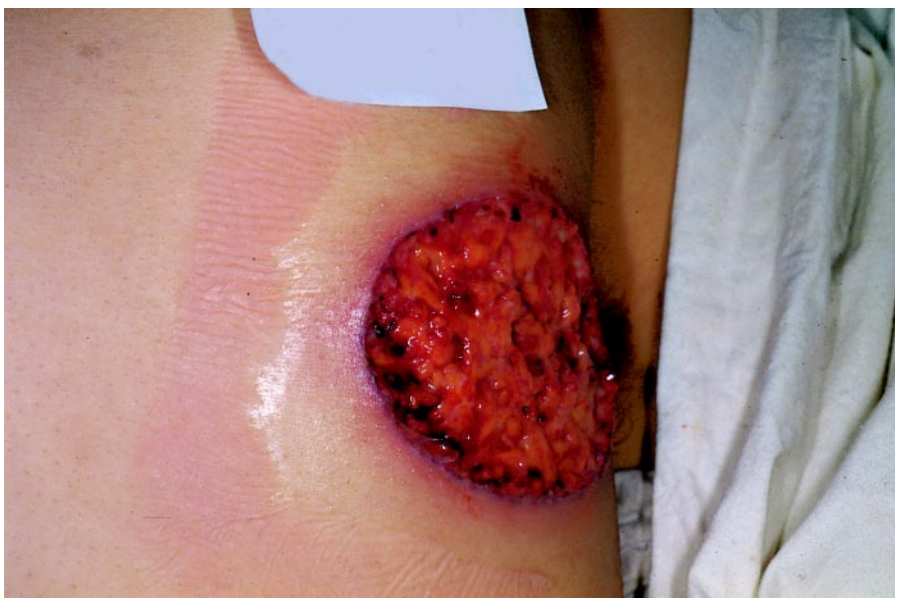

Figure 1: Pyoderma gangrenosum lesion on the buttock

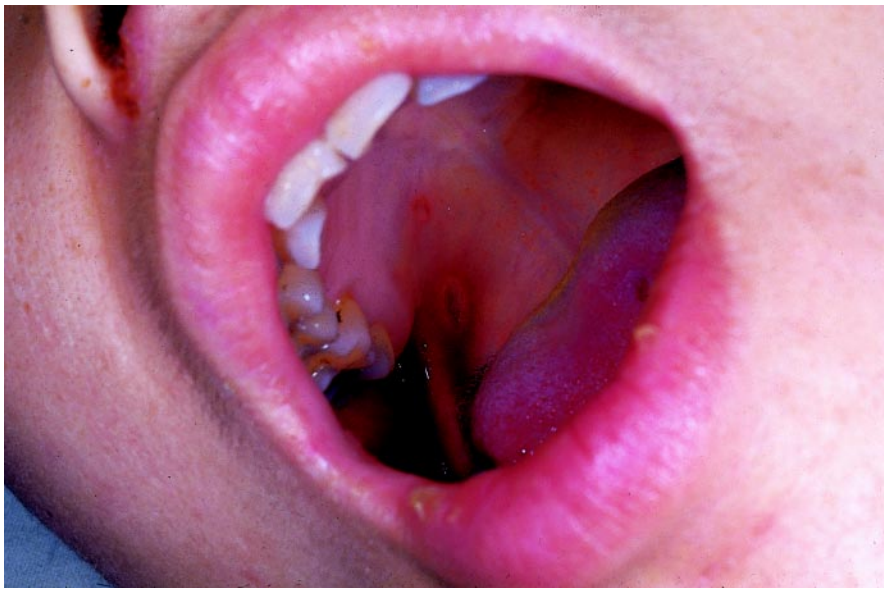

Figure 2: Aphthous ulcers on the palate

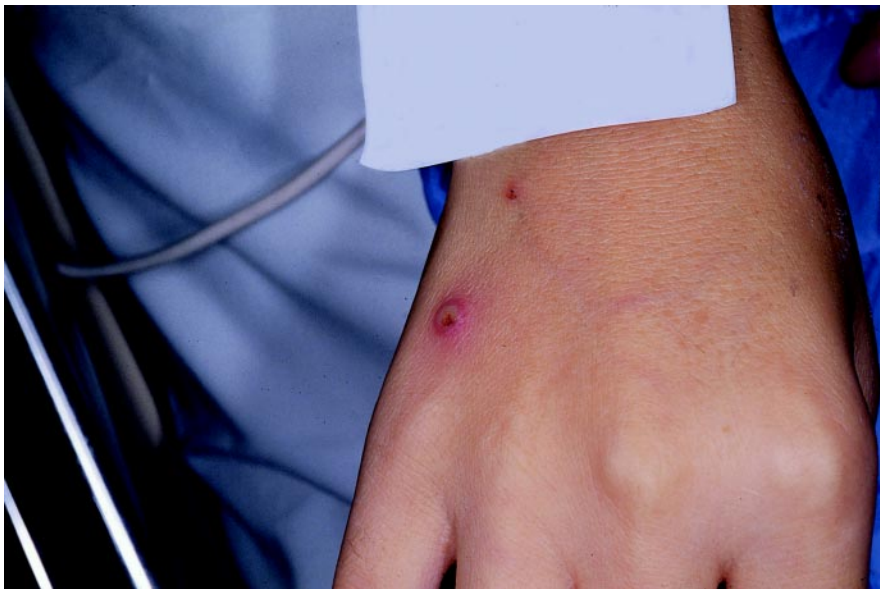

Figure 3: Sterile erythematous papulopustule at venepucture site. Positive Pathergy test

Investigations

Haemoglobin dropped from 11.6 g/dL to 8 g/dL after admission. Erythrocyte sedimentation rate was 70. Reticulocyte count was raised to 4.4%. The liver and renal function tests showed hypoalbuminaemia of 29g/l. Immune markers screening revealed a raised anti-nuclear factor titre of 1/360; anti-double-strand DNA was not increased; C3 C4 level and immunoglobulin pattern were normal; anti-ENA and ANCA were both negative. Septic screen was negative. Ulcer swabs were taken for culture and were all negative.

Sigmoidoscopy was performed by gastroenterologists in November 1997. There was only mild inflammation in the rectum. In the sigmoid colon, multiple deep aphthous ulcers and denuded areas with mucosal islands but no pseudopolyposis were seen. The clinical features were suggestive of Behcet's syndrome

or Crohn's disease. ***Biopsy*** was taken which showed acute on chronic colitis with evidence of ulceration. There were uniform heavy transmural mixed inflammatory infiltrate with focal cryptitis and crypt abscesses. Evidence of chronic injury in the form of glandular atrophy, architectural disturbance and Paneth cell metaplasia were noted. There was no granuloma formation. The picture was compatible with active chronic inflammatory bowel disease; suggestive of ***ulcerative colitis.***

Skin biopsy was performed on edge of the ulcer on left shoulder. (November 97). Patchy erosion and necrosis of the epidermis with polymorphs and mononuclear cell infiltrate were seen. There was marked necrosis of the dermis with similar infiltrates. No bacteria, acid-fast bacilli or fungus was seen. The finding was compatible with ***pyoderma gangrenosum***.

Colonoscopy was performed in December 1997. The terminal ileum, caecum, ascending and transverse colon were all normal. From splenic flexure downwards, there were marked inflammation, ulceration and pseudopolyposis. Previous deep aphthous ulcers were partially healed. Rectum was normal. **Biopsy** from terminal ileum, caecum and the ascending colon did not show any significant pathology. The descending colon, sigmoid colon and rectum specimen were heavily inflamed with ulceration. There were mixed inflammatory infiltrate; mild neutrophilic cryptitis and focal crypt abscess formation. A small focus of foreign body giant cells was noted but no well-formed granuloma was seen. The features were those of active chronic procto-colitis with severe disease activity and ulceration. This was compatible with ***Behcet's syndrome.***

Management and progress

In 1997, she was treated with intravenous methylprednisolone 40 mg daily for three days and then switched to oral prednisolone 50 mg daily. Prednisolone enema was given daily for her rectal bleeding. Hexetidine gargle, benzdamine hydrochloride gargle and triamcinolone in orabase were used for the oral aphthous ulcers. Mupirocin ointment was applied to the skin ulcers. She was also started on oral sulphasalazine and the dose was gradually stepped up to 2.5 gm per day.

Once the disease activity was under control, the oral prednisolone was tapered to 30 mg daily. Other treatment included ferrous sulphate 200 mg thrice daily, sulphasalazine 2.5 gm daily, voltaren SR 75 mg twice daily, prednisolone enema and mesalt dressing. The mucocutaneous ulceration, joint and bowel symptoms gradually improved.

Diagnosis

The overall clinical picture was Behcet's syndrome with gastrointestinal tract involvement and associated with pyoderma gangrenosum.

REVIEW ON BEHCET'S SYNDROME

Behcet's syndrome is due to systemic vasculitis of unknown aetiology.[1] It was first reported by Professor Hulusi Behcet based on two patients with triple symptom complex: hypopyon, recurrent oral and genital ulcerations. Pathergy phenomenon was first observed by Blobner in 1937.

Aetiology [1, 2]

The aetiology is still obscure. Herpes simplex virus or streptococcus sanguis infections leading to defect in immuno-regulation were postulated. Immune abnormalities detected include increased cytokine formation; increased interleukin-2 receptor; raised polymorphonuclear leucocyte activity; and decreased CD4/CD8 ratio. Auto-immune mechanism is unlikely since auto-antibody screening is negative.

The **HLA B51** is associated with more severe disease.[1] There is positive association with genital ulcer and negative association with thrombophlebitis.[3]

Pathogenesis of mucocutaneous lesions

Inoue C et al performed a histological and immunohistochemical study on mucocutaneous lesions of Behcet's syndrome and concluded that the pathogenesis is different from that of collagen disease. The C_3 deposits on vessels play an important role in the development of mucocutaneous lesions where polymorphonuclear cells are the main infiltrates.[4]

Clinical feature[1]

The age of onset is usually from the thirties to forties. There is increased prevalence in China, Japan and Iran. Therefore, it is nicknamed 'The Silk Route Disease'.

Genital ulceration

About 80-90% of Behcet's syndrome develops genital ulcer. It appears after the oral ulcer. The ulcer has a greyish yellow base covered by an eschar or exudative slough with a prominent margin. In male, it occurs on scrotum, prepuce, glans penis and the penile shaft. In female, vulva, vagina, cervix and the clitoris are affected. The occurrence is often accompanied by rigor, fever, and tender lymphadenopathy. It usually heals within 2 to 4 weeks.

Oral ulceration

Oral aphthous ulcers occur in 97% of cases. There are three forms summarised in the following table.

	Minor	Major	Herpetiform
no. of lesions	<5	>5 - 10	100 shallow
size (cm diameter)	<1	3	0.2
site	non-keratinized oral mucosa	+ fauces, pharynx, soft palate	any part of oral mucosa
scar	-	+	-

Skin lesions

About 80% of patients develop skin lesions. There are three types of characteristic lesions: erythema nodosum-like lesion; papulopustular lesion and acneiform lesion. The histology is characterised by polymorphs infiltrating the walls of small blood vessels with fibrinoid necrosis. Behcet's syndrome can be associated with pyoderma gangrenosum,[5-9] but the frequency of association is unknown.

Eye

About 50% has ocular involvement. It is commoner in younger male (>70%). It usually develops two years after the presentation of oral and genital ulceration. The commonest manifestation is recurrent anterior uveitis. hypopyon, posterior uveitis, retinal vasculitis. Vitreous opacities can occur. ***Fundal fluroescein angiography*** is a very sensitive method to pick up any subtle diseases.

Arthritis

About 45% patients complain of joint pain. It is usually mono- or oligo-articular affecting knee, ankle, wrist and elbow.

Central nervous system

About 10-12% may have neurological complications. The highest prevalence is in Japan and Turkey. It can present as headache, aseptic meningitis and focal cerebral infarct. The CSF finding is non-specific: there may be lymphocytic pleocytosis, decreased CSF glucose: blood glucose ratio, elevated protein, and raised CSF pressure.

Lung

Pulmonary disease affects 10% of patient. Haemoptysis can occur as a result of pulmonary thrombosis and infarct and pulmonary arterio-bronchial fistula. Ventilation and perfusion scan will show perfusion defect.

Cardiovascular system

Aneurysms can occur.

Gastrointestinal (GI) tract

Ulceration can affect the entire GI tract. It is more common in Japan. The histology is similar to ulcerative colitis with extensive mucosal ulceration.

Diagnosis[1]

International diagnostic criteria[1]

Recurrent oral ulceration (at least 3 times in 12 months) +
Two of the following four:
Eye lesions
Recurrent genital ulceration
Skin lesion
Positive Pathergy test

Pathergy test

It is a cutaneous hypersensitivity reaction following skin puncture with a sterile instrument. The recommended method is to insert a sterile 21 G needle obliquely to a 5 mm depth of the skin of forearm and

read 48 hours later. The development of erythematous papules or pustules (>2 mm) at 48 hours is interpreted as positive. It is positive in only 60% of patients with Turkish decent and occurs in less than 20% in English patients. The sensitivity increases if two or more simultaneous skin tests are done.

There is no diagnostic laboratory test.

Management[1]

The management should be tailored according to individual clinical manifestation.

Local treatment

Topical local anaesthetic is used for symptomatic treatment of oral and genital ulceration. Topical steroid is prescribed for oral ulcers. Intra-articular steroid injection can be given in monoarthritis.

Systemic treatment

Systemic ***prednisolone*** of 0.5-1 mg/kg/day is prescribed in severe oro-genital ulceration and systemic vasculitis. Intravenous pulse methylprednisolone 1 gm on alternate day for 3 doses is useful in life-threatening oropharyngeal scarring and CNS involvement.

Azathioprine (2.5 mg/kg/day) can be given to cases with severe oro-genital ulcers, arthritis and ocular involvement. It should be started early in those at risk of severe eye disease.

Cyclophosphamide can be administered intravenously at a dose of 500 mg as a bolus weekly or 1-1.5 gm monthly or orally 1.5-2 mg/kg/day in patients with systemic vasculitis and eye disease.

Colchicine [1, 9] is widely used in treating Behcet's syndrome. It is proven to be beneficial by controlled trial for erythema nodosum-like lesions and arthralgia.

Thalidomide (100-400 mg/day) is useful in erythema nodosum-like lesions, oro-genital ulcer and CNS involvement. Its action is via inhibitory modulation of circulating immune complex-mediated vasculitis. It is reported to be effective in Behcet's syndrome associated pyoderma gangrenosum.[6, 8]

Cyclosporin A (5-10 mg/kg/day) can be used in oral, ocular and cutaneous diseases. Interferon **a**2a 3 MU 3 times/week SC is reported to be useful.[10] ***Sulphasalazine*** (2-4 gm/day) is an effective treatment in GI tract involvement.

Learning points:

Interpretation of Pathergy test could be very difficult and nowadays rheumatologists seldom do this test. The diagnosis of Behcet's syndrome is therefore mainly based on the clinical ground.

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