Case reports

Laryngeal and cutaneous sarcoidosis treated with methotrexate

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Sarcoidosis is a multisystem disorder of unknown cause characterized by non-caseating granulomas. Laryngeal involvement is uncommon. We present a case which illustrates the clinical features and complications and discuss the response to methotrexate.

Case report

This 50-year-old man presented the first sign of sarcoidosis with a cutaneous facial lesion aged 26. The Kveim test was positive and he was treated with topical steroids. Seven years later he developed rapidly progressive dysphonia and noisy breathing. He was reviewed and admitted immediately for tracheostomy as he had inspiratory stridor. At laryngoscopy he had a distorted pharynx and larynx with extensive submucosal swelling and scarring. Biopsies confirmed the presence of active sarcoidosis and treatment with intralesional steroids was started. He was maintained for some years on intermittent dilatation of the post-nasal space, laser therapy and intralesional steroid injections. By 1980, stenosis of the palatal isthmus had developed. He was then commenced on weekly adrenocorticotrophic hormone (ACTH) injections (40 IU), and the frequency slowly reduced. Investigations revealed a normal chest X-ray, blood calcium, angiotensin converting enzyme and β-2-microglobulin level.

Recently, the cutaneous lesions became more widespread and a lesion adjacent to the nasal rim developed (Figure 1). He commenced on methotrexate 10 mg/week in March 1993 and the nasolaryngeal and cutaneous lesions have since improved. The ACTH injections and intralesional steroids have been discontinued.

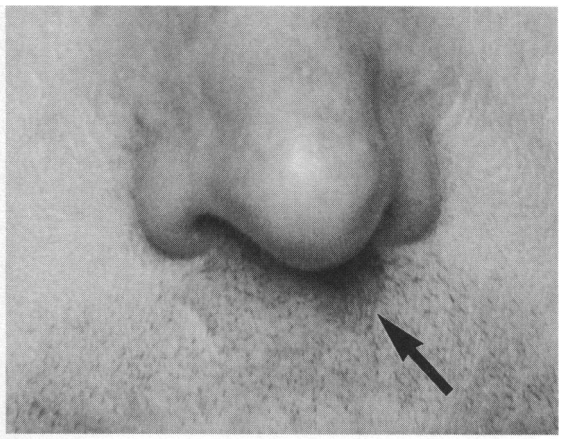

Figure 1. Nasal rim lesion of sarcoidosis (arrowed)

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Discussion

Sarcoidal involvement of the upper airway occurs in 6% of those with multisystem disease[1,2]. Laryngeal sarcoidosis is rarer and in a review of 1250 cases affected only 1.3%[3]. It usually occurs with nasal mucosal disease[1,2], although it occasionally develops in isolation[4].

The disfiguring reddish-blue violaceous plaques and nodules, affecting cooler areas of the skin that are seen in sarcoidosis are called lupus pernio. In upper respiratory tract sarcoidosis a third to a half have nasal lupus pernio[1,2]. Conversely, 20% of those with nasal lupus pernio have upper airway involvement.

More recently, the association between upper airway sarcoidosis and nasal rim lesions of sarcoidosis, as seen in this patient, has been recognized[5]. One author reported mucosal involvement in three of four patients with cutaneous nasal rim sarcoidosis[6]. Thus, the association between upper respiratory tract sarcoidosis and lupus pernio seems the strongest, there being a weaker association with nasal rim sarcoidosis.

Laryngeal sarcoidosis can be difficult to diagnose. Common symptoms of hoarseness, stridor and dysphagia are helpful but cough and breathlessness may be wrongly attributed to pulmonary disease[4]. Some patients are asymptomatic. In those with dyspnoea and cough a normal chest X-ray may be falsely reassuring. Delay in diagnosis is common[4,7,8] and in one case proved fatal[4]. Indeed, the patient reported here had a severely compromised airway before the laryngeal disease was recognized.

Pulmonary function tests may show a reduced maximum voluntary ventilation. The flow volume loop can be particularly helpful with slowing of the peak flow rates indicating upper respiratory tract obstruction.

Many different treatments are used in sarcoidosis including steroids, the 4-aminoquinolines, methotrexate, chlorambucil and cyclosporin A. Methotrexate and oral prednisolone, both induce an increase in vital capacity and decrease in broncho-alveolar lymphocyte numbers. Treatment reduces macrophage release of hydrogen peroxide and tumour necrosis factor[9].

The patient described here was commenced on weekly methotrexate as the long-term side-effects were likely to be less than with prednisolone. An improvement in symptoms of nasal stuffiness and discharge occurred within weeks although skin lesions have been slower to respond. Previous reports suggest that cutaneous lesions may take anything from 4 to 26 months to clear[10].

Case presented to Section of Dermatology, 17 June 1993

References

1 James GD, Barter S, Jash D, MacKinnon DM, Carstairs LS. Sarcoidosis of the upper respiratory tract. *J Laryngol Otol* 1982;**96**:711-8
2 Neville E, Mills RGS, Jash DK, MacKinnon DM, Carstairs LS, Geraint James D. Sarcoidosis of the upper respiratory tract and its association with lupus pernio. *Thorax* 1976;**31**:660-4
3 Maycock RL, Bertrand P, Morrison CE. Manifestations of sarcoidosis. *Am J Med* 1963;**35**:67-89
4 Bower JS, Belen JE, Weg JG, Dantzker DR. Manifestations and treatment of laryngeal sarcoidosis. *Am Rev Respir Dis* 1980; **122**:325-32
5 Paller AS, Surek C, Silva-Walsh I, Krespi Y, Freinkel RK. Cutaneous sarcoidosis associated with sarcoidosis of the upper airway. *Arch Dermatol* 1983;**119**:592-6
6 Jorizzo JL, Koufman JA, Thompson JN, *et al.* Sarcoidosis of the upper respiratory tract in patients with nasal rim lesions: A pilot study. *J Am Acad Dermatol* 1990;**22**:439-43
7 Becker GL, Tenholder MF, Hunt KK. Obligate mouth breathing during exercise. Nasal and laryngeal sarcoidosis. *Chest* 1990; **98**:756-7

8 Murray ME, Stokes TC. Endobronchial sarcoidosis presenting as severe upper airways narrowing with normal chest radiograph. *Respir Med* 1991;85:425-6
9 Baughman RP, Lower EE. The effect of corticosteroid or methotrexate therapy on lung lymphocytes and macrophages in sarcoidosis. *Am Rev Respir Dis* 1991;127:1034-40
10 Veien NK, Brodthagen H. Cutaneous sarcoidosis treated with methotrexate. *Br J Dermatol* 1977;97:213-16

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Venous thrombosis of the bladder associated with antiphospholipid syndrome

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Keywords: bladder; venous thrombosis; gangrene; antiphospholipid syndrome; anticardiolipin antibodies

Bladder gangrene is an uncommon condition. A case is described of acute bladder necrosis secondary to venous thrombosis, in a patient with anticardiolipin antibodies. Although venous occlusion has been described in the literature as an aetiological factor in vesical necrosis, there are no previous reports of an association with antiphospholipid syndrome.

Case report

A 41-year-old Thai male, was admitted with a 1 day history of bloody diarrhoea, frank haematuria, and severe abdominal pain. He had a past history of ulcerative colitis and intracerebral venous thrombosis. On examination he was hypotensive, tachycardic and pyrexial with lower abdominal tenderness. Proctoscopy and sigmoidoscopy revealed oedematous haemorrhagic mucosa overlying the prostate, but normal mucosa elsewhere. The white blood count was 16.2 ($\times 10^3$/l), urine culture sterile, renal ultrasound normal and plain abdominal X-ray unremarkable. He was resuscitated with intravenous fluids and antibiotics.

Cystoscopy revealed bizarre large fronds of velvet urothelium with necrotic tissue lying in a small capacity bladder. Biopsies showed necrotic, haemorrhagic bladder wall containing dilated thrombosed veins, but patent arterioles (Figure 1). At laparotomy there was oedema and haemorrhage beneath the pelvic peritoneum. A transverse colostomy was fashioned.

Subsequent normal investigations included autoantibodies, prothrombin time, activated partial thromboplastin time and thrombin time, protein C, S and antithrombin III, and lupus anticoagulant. Fibrinogen was elevated at 6.8 g/l (normal 2-4) and anticardiolipin antibodies were present at 21.9 units/ml (normal <9).

Three months later he was experiencing intense frequency and recurrent bouts of haematuria. A tiny fibrosed bladder was found at laparotomy and an ileal substitution cystoplasty performed. Five months later he was continent with tolerable frequency. A long tight rectal stricture prevented closure of his transverse colostomy which he was happy to keep. He remains well on long-term anticoagulation with warfarin.

Discussion

Sterling and Hopkins[1] reviewed 207 cases of bladder gangrene of which 67 were obstetric complications, 24 secondary to outflow obstruction and 34 associated with sepsis. The mortality was high (120 died).

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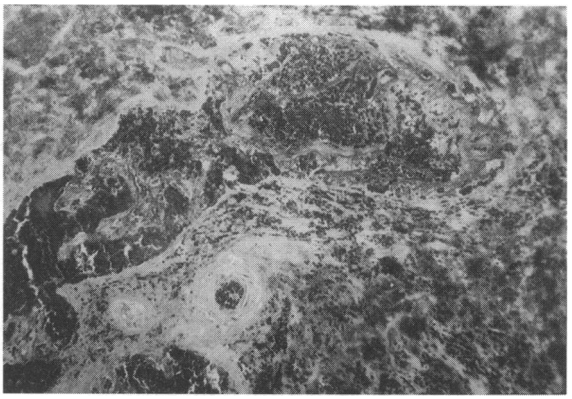

Figure 1. Bladder biopsy showing haemorrhage into the bladder wall and thrombosis in a large vein lying above a small patent arteriole (H & E, ×400)

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A review by Cristol and Greene[2] introduced a classification based on aetiological factors, distinguishing between 'direct' causes, i.e. chemical or physical irritation and infections, and 'indirect' causes, i.e. mechanical injury, disease of the blood vessels, and neural deficit.

A more recent review by Love and Notley[3] suggested that the condition was becoming increasingly rare with changes in medical practice. They emphasized the distinction between true bladder gangrene, i.e. primary necrosis of the bladder wall which may or may not be complicated by sepsis, and pseudomembranous cystitis associated with severe infections which seem to affect only the superficial layers of the wall. They described 18 cases including three[4-6], where the aetiology was thought to be pelvic thrombophlebitis.

Antiphospholipid antibodies (lupus anticoagulant, and anticardiolipin antibody), were originally described in the sera of patients with systemic lupus erythematosus (SLE), associated with a high incidence of thromboses. Subsequently these antibodies have also been found in patients without SLE (primary 'antiphospholipid syndrome' APS).

In a review of 70 patients with primary APS, Asherson *et al.*[7] found most patients had multiple thrombotic events, the commonest being deep vein thrombosis (54%), and pulmonary embolism (26%).

Arterial occlusions occurred in 44% with resulting strokes, transient ischaemic attacks or coronary occlusions. Recurrent fetal loss was present in 34%. Many other vascular occlusions have been reported including renal artery[8] and vein[9], hepatic vein[10], and mesenteric vessels[11].

Diagnosis and treatment of bladder gangrene present a number of problems. Many report confusion with cystoscopic findings and the first impression may be of tumour. Initial treatment should be aimed at resuscitation and achieving adequate bladder drainage. The natural history of this condition suggests that bladder regeneration can occur[4,5], and the necrotic cast of the bladder wall may pass *per urethram*[2,12]. Immediate complications include spontaneous rupture of the bladder[13], while long-term problems relate to intense fibrosis with ureteric stricture and diminished bladder capacity.

The best long-term therapy to prevent recurrent thrombosis with APS has yet to be determined but low and full dose