Unusual presentation of more common disease/injury

A severe case of multisystem sarcoidosis complicated by aspergillosis and aspergillomas

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Summary

The authors present an atypical case of multisystem sarcoidosis presenting at a late stage with severe lupus pernio sarcoidosis skin lesions and stage IV pulmonary sarcoidosis complicated by semi-invasive chronic necrotising aspergillosis and aspergillomas. Lepromatous leprosy, tuberculosis and active atypical mycobacterial infection had to be ruled out en route to reaching the final diagnoses. His case presented us with a management dilemma, specifically concerning treatment of his sarcoidosis with corticosteroid and other immunosuppressive agents, as these risked aggravating his active invasive fungal disease. The patient's semi-invasive aspergillosis was treated first with antifungal agents for 6 months before treatment with corticosteroids and hydroxychloroquine was started. The patient has tolerated his treatments well, and over a 3-year follow-up period, has had a significant improvement in his respiratory and systemic symptoms, with some improvement in his lupus pernio sarcoidosis skin lesions.

BACKGROUND

With the advancement in healthcare provision in developed societies in recent decades, it has become a rarity to encounter conditions such as sarcoidosis in their raw and severest forms. Our case is an example of a relatively common condition presenting with severe manifestations, including the rare presence of multiple oral sarcoidosis lesions. We have found the illustrations of the skin lesions particularly interesting. A careful consideration of the risks and benefits of treatment was required as treatment conferred an increased risk of exacerbating a co-existing invasive fungal infection.

CASE PRESENTATION

A 40-year-old UK born male of Afro-Caribbean origin presented to our district general hospital in March 2007. He was originally from London but had spent the previous 4 years in Nevada and Southern California coaching football. He had previously been a professional footballer and denied any smoking history. Previous travel history included holidays in Jamaica, Ethiopia and Sweden. He gave a 2-year history of gradually progressive exertional shortness of breath, a 1-year history of a cough productive of grey sputum (~50 ml per day), a 6-month history of night sweats and 7 kg weight loss over a 6-month period. Other medical history included a 'skin condition' comprising of a variety of lesions ranging from soft fluctuant nodular lesions, more indurated lesions and scaly plaques. These skin lesions first started to appear 5 years previously, and distribution was widespread affecting the face, nose, lips, tongue, buccal mucosa, fingers, elbows, soles and toes with relative sparing of the trunk (figure 1A–C). The patient also described intermittent joint swelling affecting the wrists and interphalangeal joints (figure 1D).

On presentation, the patient was non-feverish and normotensive with a sinus tachycardia of 110 beats per minute. Auscultation of the chest revealed bronchial breathing and crackles over both upper zones. Cardiovascular, abdominal and neurological examinations were unremarkable. Enlarged lymph nodes were palpable in the axillary, inguinal and cervical regions.

INVESTIGATIONS

- ▶ Full blood count, serum urea and electrolytes, serum calcium and C reactive protein levels were within the normal ranges. Erythrocyte sedimentation rate was elevated at 87 mm/h, alkaline phosphatase levels were elevated at 152 U/l (50–120) with all other liver function tests within normal ranges.
- ▶ Chest radiograph and CT images of the thorax are shown in figure 2A–D. The CT of the thorax was reported by a thoracic radiologist as showing widespread fibrobullous destruction of the upper lobes, widespread emphysematous change in the lower zones, and widespread mediastinal and axillary lymphadenopathy. There were two mycetomas, one in each upper lobe, with surrounding appearances suggestive of an invasive fungal process. There were no radiographic changes to suggest of active mycobacterial infection.
- ▶ One of six sputum samples sent for acid-fast bacilli (AFB) culture grew *Mycobacterium avium* Complex (MAC) after 15 days.
- ▶ Bronchoalveolar lavage samples from the right upper lobe cultured *Aspergillus fumigatus* and normal respiratory tract bacterial flora. AFB culture was negative after 8 weeks and it is suspected that the single MAC isolate from the sputum was a contaminant.
- ▶ A skin biopsy was performed and was reported as showing pandermal non-infiltrative tuberculoid granulomata,

Figure 1 March 2007. (A,B) Facial lesions, (C) fluctuant tongue lesion and (D) left hand joint lesions.

with some evidence of nerve destruction. Lepromatous leprosy was excluded as there was very little lymphocytic infiltrate, the nerves in the deep dermis were not affected, and the granulomas were widely distributed.

- Skin scrapings and biopsy culture did not culture any *Mycobacterium leprae*.
- An inguinal lymph node biopsy revealed numerous epithelioid cell granulomas, compact and sharply demarcated from intervening small lymphocytes.
- Serum angiotensin converting enzyme level was elevated at 115 U/l (normal range 0–81). Serum total Immunoglobulin E (IgE) level was 581 g/l, specific IgE to aspergillus was weakly positive, and aspergillus precipitans (Immunoglobulin G) was strongly positive. Eosinophil count was $0.2 \times 10^9/l$. Serological tests for

coccidiomycosis and histoplasmosis were negative. Antibodies to HIV were negative and no other abnormalities to suggest a compromised immune system were detected.

- Tuberculin skin test was negative.

DIFFERENTIAL DIAGNOSIS

- Skin lesions – the dermatologists' differentials list after initial review was as follows: lepromatous leprosy, lupus pernio sarcoidosis lesions, systemic fungal infection (histoplasmosis, coccidiomycosis) and other granulomatous diseases. The presence of skin lesions on the lips and tongue is rare in sarcoidosis and more common in coccidiomycosis and histoplasmosis.

Figure 2 March 2007. (A) Chest radiograph on presentation March 2007 and (B–D) selected CT scan images.

- Respiratory disease – differential list after the initial investigations included: pulmonary tuberculosis, active non-tuberculous mycobacterial infection on a background of established lung destruction (possibly due to previous pulmonary tuberculosis), stage IV pulmonary sarcoidosis, aspergilloma with or without invasive aspergillosis and other invasive fungal lung disease (eg, coccidiomycosis).
- Lymphadenopathy: lepromatous leprosy, sarcoidosis, lymphoma and tuberculosis.

Final diagnoses of stage IV pulmonary sarcoidosis with advanced lupus pernio sarcoidosis skin disease, semi-invasive chronic necrotising aspergillosis and aspergillomas were reached after the results of the complete set of investigations detailed above were available.

TREATMENT

During his inpatient hospital stay, the patient developed sepsis syndrome associated with persistent fevers and a worsening cough productive of grey-green sputum. This did not settle after treatment with two different courses of high-dose broad spectrum antibiotics (piperacillin/tazobactam 4.5 g three times daily with gentamicin 7 mg/kg once daily for 7 days, followed by meropenem 1 g three times daily for 7 days). Invasive aspergillosis infection was suspected of being the cause of his sepsis and he was therefore treated with 2 weeks of intravenous amphotericin-B. He made good clinical progress with resolution of his fevers and reduction in his sputum volumes. There was significant concern surrounding whether to treat,

and when to start treatment of, this patient's sarcoidosis as this would involve high-dose corticosteroids and other immunosuppressive agents. Such treatment may aggravate his underlying invasive fungal infection and is unlikely to lead to any significant improvement in his underlying lung destruction, though it may lead to partial or complete resolution of some of the skin lesions¹ and joint disease. He was therefore maintained on oral posaconazole for 6 months before a treatment course of pulsed intravenous methylprednisolone (750 mg daily for 3 days) was administered, followed by oral prednisone starting at 1 mg/kg weaning down to a maintenance dose of 10 mg daily, in addition to hydroxychloroquine 200 mg twice daily. Hydroxychloroquine was chosen, rather than methotrexate, to minimise the degree of immunosuppression and associated risk of worsening fungal infection, as well as its efficacy in treating sarcoid skin disease.

OUTCOME AND FOLLOW-UP

Over the 4 years following his initial presentation the patient's night sweats resolved, his productive cough improved significantly, his weight had increased by 12 kg, and most of the soft fluctuant skin, joint and oral lesions had resolved. Many granulomatous lesions also improved; however, the established endurated lesions, including the facial ones, did not improve or left significant residual scarring (see figure 3A–D). The patient also had some improvements in his lung function parameters: between July 2007 and September 2009, forced expiratory volume in 1 second improved from 1.84 l (48% predicted) to 2.54 l (54%

Figure 3 January 2011. (A,B) Facial lesions, (C) tongue lesion and (D) left hand lesions.

predicted), forced vital capacity improved from 2.66 l (49% predicted) to 3.42 l (63% predicted), and diffusion in the lung of carbon monoxide improved from 2.41 (22% predicted) to 3.37 (29% predicted). Cross sectional imaging of his thorax in April 2010 showed no progression of his underlying lung disease compared to his earlier CT scans.

DISCUSSION

This case demonstrates an atypical and severe presentation of a multisystem granulomatous disease encountered frequently by respiratory physicians. This was complicated by invasive fungal infection and the initial presentation may have been clinically consistent with pulmonary tuberculosis or atypical mycobacterial infection. Treating his sarcoidosis may yet precipitate a deterioration in his

fungal infection, and a judgement in corroboration with the patient's wishes had to be made balancing the risks and benefits of embarking on such therapy once his fungal infection was under control. At present, the plan is to continue on long-term posaconazole, low-dose prednisolone and hydroxychloroquine.

The other interesting aspect of his presentation is the extent of his lupus pernio sarcoidosis skin disease. Oral lesions are infrequent in sarcoidosis and a recent review of the English-language literature turned up only 47 well-documented cases of oral sarcoidosis lesions affecting the soft tissue of the oral cavity.² This review found that in the majority of the published cases, sarcoidosis lesions of the oral mucous membrane tend to be unique and not associated with multisystem sarcoidosis. In very few cases do

the lesions affect more than one part of the oral cavity. Another review had found 71 cases of oral sarcoidosis with the tongue involved in 7% (n=5) of patients, and multiple oral lesions in 4.2% of the patients (n=3).³ Our patient had lesions involving the lips, tongue and buccal mucosa and this prompted consideration of other differentials such as lepromatous leprosy, coccidiomycosis and histoplasmosis.

Learning points

- ▶ Sarcoidosis can present with both severe and rare multisystem manifestations, and should always be considered in the differential diagnoses any multisystem disease.
- ▶ Sarcoidosis skin lesions rarely involve the oral mucosa and tongue, but sarcoidosis should be considered as a differential even in the context of multisystem sarcoidosis.
- ▶ Treatment of sarcoidosis with immunosuppressive agents can lead to significant symptomatic improvements in chronic advanced and seemingly non-reversible lupus pernio sarcoidosis skin lesions.
- ▶ Co-existing infection should be fully investigated and adequately controlled prior to commencement of therapy for sarcoidosis.
- ▶ The optimal length of treatment with oral antifungals is unknown, and we feel that in this case they are probably warranted on a long-term basis in the context of immunosuppressive therapy.

Competing interests None.

Patient consent Obtained.

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