CASE REPORT

Tuberculous granuloma: a rare cause of a non-healing ulcer

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SUMMARY

A 78-year-old woman on ciclosporin for aplastic anaemia presented to her general practitioner with a 2 cm cystic swelling on the right side of her forehead. After a period of 8 months the lesion ruptured and, despite good wound care, failed to heal over a period of seven further months. Imaging demonstrated an invasive process and a biopsy was taken, which showed granulomatous inflammation that stained positively for mycobacteria. Further investigation with cross-sectional imaging revealed no other sites of disease. The only history of exposure to tuberculosis was 64 years prior to presentation. Differential diagnoses of mycetoma, autoimmune disease and non-tuberculous mycobacterial infection were considered, but culture confirmed tuberculosis. This case demonstrates an unusual presentation of isolated cutaneous tuberculosis in a patient with suppressed immune function.

BACKGROUND

Chronic ulcerating lesions have a broad differential diagnosis and typically present first to primary care. Diagnosis can be challenging, particularly in patients with impaired immune function.

Incidence of tuberculosis (TB) remains stable in the UK, although rates remain among the highest in Western Europe.¹ Cutaneous TB is an uncommon manifestation of the disease. Reports of non-tuberculous mycobacterial (NTM) infection are rising in the UK, with the rate increasing fastest in those over 65.² NTM cutaneous infection has tripled in some centres, with the increase largest in those aged over 60.³

Diagnosis of mycobacterial infection is challenging, particularly in the elderly and those with non-pulmonary disease, and delays from presentation to diagnosis are common.

CASE PRESENTATION

A 78-year-old woman presented to her general practitioner (GP) with a 2-week history of a painful swelling on the right side of her forehead. There was no history of injury or foreign travel and she had no pets (figures 1 and 2).

She had been diagnosed with aplastic anaemia 2 years previously and had undergone bone marrow transplant. At presentation she was taking ciclosporin 75 mg twice daily (level 85 µg/L).

On examination she had a 2 cm cystic swelling on the right side of her forehead that was tender to palpation. There were no regional lymph nodes. She was diagnosed with an infected epidermoid cyst and treated with antibiotics. The lesion became

Figure 1 Appearance at presentation.

more comfortable and she was referred to the general surgeons.

While waiting to be listed for an excision under local anaesthetic, the lesion discharged its contents and the patient returned to her GP with a 2×3 cm ulcer (figure 3). The ulcer was dressed for 7 months, during which time the ciclosporin was stopped and the patient was treated with prednisolone with doses ranging from 5 to 40 mg. With limited evidence of healing, she was referred to the plastic surgeons, who arranged an X-ray and MRI of the skull, which demonstrated a lytic lesion in the frontal bone consistent with osteomyelitis or malignancy (figures 4–6).

The patient then underwent a biopsy of the lesion. Histology demonstrated chronic granulomatous inflammation with central necrosis involving blood vessels. Ziehl-Neelsen stain for mycobacteria was positive (figures 7–9). Stains for fungi and actinomyces were negative.

Eighteen months from her initial presentation, she was referred to the chest clinic where a history of exposure to TB as a teenager was elicited and a diagnostic culture was performed.

INVESTIGATIONS

Blood tests: QuantiFERON test was positive. Serum antineutrophil cytoplasmic antigen (ANCA) was negative.

Chest X-ray: Normal.

Figure 2 Appearance at presentation.

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Figure 3 Appearance after discharging contents.

Skull X-ray: 2.5 cm lytic lesion in frontal bone anteriorly consistent with osteomyelitis was seen.

MRI: There was a right parasagittal defect in the dermis and subdermal fat, which breached the outer table of the skull. There was no intracranial extension. There was no evidence of oedema on short τ inversion recovery sequences, but avid enhancement of the margins of the defect on postcontrast imaging was seen.

Biopsy: (1) Fragments of tissue showed marked chronic granulomatous inflammation with central necrosis. The process also involved blood vessels. Occasional fragments of bone were present. Elastic stain confirmed the involvement of blood vessels. Stain (Ziehl-Neelsen) for mycobacterial organism was positive. Stains for fungi and actinomyces were negative.

The features were those of a chronic necrotising granulomatous process with secondary vasculitis. The presence of mycobacterial organisms confirmed a mycobacterial infection and vasculitis was considered to be a bystander process. However, serology was recommended to exclude systemic vasculitis.

(2) The specimen showed chronic inflammation with some neutrophil polymorphs and granulomas. There was no caseous necrosis. Stains for fungi and actinomyces were negative.

Mycobacterial culture: culture from the first biopsy was not requested, a repeat biopsy grew *Mycobacterium tuberculosis*.

Figure 4 Anteroposterior skull X-ray showing defect.

Figure 5 Sagittal MRI showing defect.

DIFFERENTIAL DIAGNOSIS

Lesions with similar clinical appearances can be seen with both local and systemic infections. Subcutaneous mycoses can cause chronic draining sinuses and ulcers, as can localised infection with actinomyces, bartonella, nocardia, TB or NTM. Disseminated infection with NTM, TB and treponema pallidum can also produce chronic ulcers. Granulomata may be seen in vasculitides, such as Wegener's. Potential malignant causes with similar appearances include cutaneous lymphoma and squamous cell carcinoma.

Although histological examination showed involvement of blood vessels (vasculitis), it was thought to be a bystander process, as may be seen in mycobacterial infection, rather than a primary vasculitis. This assumption was supported by a negative

Figure 6 Transverse MRI showing defect.

Figure 7 Biopsy sample showing granulomatous infiltration, with thanks to Dr R Hadden.

ANCA. Weakly positive Ziehl-Neelsen staining has been reported with nocardia and actinomyces infection, but fungal and silver stains specifically considering these pathogens were negative. Although this woman had a history of prior exposure to TB and a positive QuantiFERON blood test, mycobacterial culture was necessary to differentiate between NTM and TB.

TREATMENT

Culture of a biopsy sample from the lesion grew TB sensitive to standard treatment. The patient had never been able to swallow tablets. Consequently, she could not manage pyrazinamide tablets so was treated with liquid rifampicin and liquid isoniazid for 9 rather than the standard 6 months. Ethambutol is also only available in tablet form, but was not needed as the patient's childhood exposure to TB predated the clinical use of antituberculous antibiotics and hence the development of resistant strains of TB.

OUTCOME AND FOLLOW-UP

At 3 months the patient had suffered no significant side effects from treatment, her ulcer had epithelialised and she was systemically well. Antimycobacterial treatment continued for a further 6 months, at which point the wound had healed ([figure 10](#)).

DISCUSSION

The differential diagnosis of isolated ulcerated lesions is broad. In patients with chronic ulcerated lesions, consideration should

Figure 8 Biopsy sample showing bystander vasculitis, with thanks to Dr R Hadden.

Figure 9 Biopsy sample showing Ziehl-Neelsen-positive bacilli, with thanks to Dr R Hadden.

be given to comorbidity, local factors affecting wound healing and specific possible causes of the ulcer. In this patient, the unusual site, chronicity and absence of healing after 7 months raised suspicions of an infective or malignant process; and the degree of compromised immunity and childhood exposure led to the diagnosis.

Incidence of TB in the UK has stabilised since 2005, but rates remain among the highest in Western Europe. In 2013 patients over 65 made up 14% of all those diagnosed and around half of all patients had extra-pulmonary disease. The disease remains a diagnostic challenge with 43% having a delay of 90 days before diagnosis.¹

Cutaneous TB is an uncommon manifestation of the disease. It assumes a variety of different appearances that are due to either direct infection or hypersensitivity, and is most frequently classified by the system proposed by Tappeiner and Wolff—based on route of infection.⁴ Similar clinical appearances to this case, of nodular lesions that progress to form chronic ulcers, are seen with primary inoculation TB, scrofuloderma and metastatic tuberculous abscesses. Histological examination and microbial culture are necessary for diagnosis.

Cutaneous mycobacterial infections are more commonly caused by NTM than TB and are increasing in incidence, particularly among those over 60 and the immunosuppressed. NTM are ubiquitous opportunistic pathogens that usually cause cutaneous infection by direct inoculation. *M. marinum*, *M. ulcerans*, *M. fortuitum* and *M. bovis* can all present as

Figure 10 Appearance after 9 months of treatment.

isolated discoloured nodules that progress into ulcers.⁵ Human-to-human transmission is not known to occur, but transmission between humans and animals is seen and cases in UK domesticated animals have risen in the past decade.⁶ Although there are no previous reported cases of this route of transmission, we considered whether the patient might have had direct inoculation of TB from an infected cat licking her face. However, she has no pets.

Histopathological features have been identified that can differentiate cutaneous TB and NTM, but these features vary and culture remains critical to identify the causative organism and in determining bacterial sensitivities to guide treatment.⁷

Learning points

- ▶ The differential diagnosis of chronic granulomatous skin lesions is broad and includes autoimmune disease, fungal and bacterial infection. Clinicians should have a low threshold for thoroughly investigating atypical lesions.
- ▶ Cutaneous tuberculosis (TB) is a rare manifestation of the disease in the developed world, forming only 1–2% of all cases, and is usually seen with infection at multiple sites. Manifestations vary with mechanism of infection and host immunity.
- ▶ Cases of cutaneous non-tuberculous mycobacterial infection are more common than cutaneous TB and are increasingly reported. Animal vectors must be considered and culture is vital to guide appropriate treatment.

Reactivation of historic foci of TB is a recognised risk of immunosuppression that has been reported previously for systemic as well as cutaneous disease. Typical cutaneous manifestations in these circumstances are multiple metastatic abscesses with evidence of disease at other sites.^{8–9} Isolated cutaneous lesions without disseminated disease are unusual.

Contributors GEAG wrote the article, which was supervised by RJ (who saw the patient in primary care) and DD (who saw the patient in chest clinic).

Competing interests None.

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