Grand Rounds in Rheumatology

When typical is atypical: mycobacterial infection mimicking cutaneous vasculitis

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Abstract

Patients with systemic lupus erythematosus (SLE) who present with skin disease pose the clinician with diagnostic challenges. The skin disease can reflect an increase in systemic disease activity suggested by other features of active lupus and, as such, usually responds well to more aggressive immunosuppressive therapy. Other possibilities of skin disease include drug eruptions, skin disease unrelated to SLE and, more rarely, opportunistic skin infection. In patients who show a poor response to more aggressive immunosuppressive therapy, consideration must be given to the possibility of opportunistic infection. A high index of suspicion will allow prompt treatment. We describe two patients with SLE who developed cutaneous atypical mycobacterial infection during immunosuppressive therapy. The diagnosis of cutaneous vasculitis was considered in both cases, but subsequent skin biopsy revealed the correct diagnosis. This report illustrates the importance of skin biopsy in patients with suspected cutaneous lupus who are not responding to immunosuppressive therapy.

KEY WORDS: Systemic lupus erythematosus, Skin manifestations, Tuberculosis, Atypical tuberculosis.

Case 1

A 68-yr-old widow with a 15-yr history of systemic lupus erythematosus (SLE) manifest as discoid lupus erythematosus, photosensitive skin rash, mouth ulcers, arthritis and sensorimotor peripheral neuropathy was admitted for management of a painless leg ulcer, which had appeared suddenly 2 weeks beforehand, in the absence of trauma. She was positive for anti-nuclear antibody (ANA; 1/2560) and antibodies against Ro, had a reduced serum C4 level (<0.06 g/l; normal range 0.19–0.45 g/l), but had never had antibodies detected against DNA. Positivity for lupus anticoagulant was detected in 1995 following a deep vein thrombosis, at which point warfarin was commenced. Tissue typing showed her to be homozygous for HLA DR3, DRw52, DQ2. Initially her disease was treated with up to 10 mg prednisolone per day.

Several weeks before admission, she developed increasing symptoms of inflammatory arthritis, myalgia and mouth ulcers and had a reduction in complement levels. She was treated by increasing the prednisolone dose and addition of azathioprine. On admission, culture from the well-demarcated, superficial ulcer showed no significant bacterial growth. Conservative therapy was continued following review by the plastic surgeons. Four days later she developed increasing myalgia, general malaise and pyrexia of 37.5°C and a firm, painless, erythematosus nodule developed on the forearm (Fig. 1). The white cell count was normal (5.4 x 10⁹/l) but the erythrocyte sedimentation rate (ESR) was elevated (30 mm/h). The C-reactive protein (CRP) concentration was 60 mg/l (normal values <10 mg/l). The level of complement C3 was normal but C4 was again low (0.45 g/l) and C3d was elevated at 15–19.5 U/ml (normal values <12.5 U/ml), implying complement consumption. A clinical diagnosis of SLE exacerbation with cutaneous vasculitis was made and the prednisolone dose was increased.

Biopsy of the skin lesion demonstrated collections of neutrophil polymorphs surrounded by bands of granulomatous inflammation within the reticular dermis, which extended into underlying fat (Fig. 2a). Acid-fast bacilli were identified using Ziehl–Neelsen stain (Fig. 2b). The large number of neutrophils raised the possibility of atypical mycobacterial infection. Subsequent biopsies taken for culture purposes showed a similar pattern, but no evidence of vasculitis was present.

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Chest X-ray and bone marrow showed no evidence of systemic infection. Azathioprine was discontinued and ethambutol and rifampicin therapy commenced. Subculture resulted in rapid growth (3 days) on Löwenstein–Jensen, pyruvate and paranitrobenzoic slopes between 25 and 30°C but only scanty growth at 37°C. Tests based on restriction fragment length polymorphism analysis, confirmed by oligonucleotide-specific capture plate hybridization, identified the organism as *Mycobacterium chelonae*. Treatment was changed to ciprofloxacin and clarithromycin after sensitivity testing confirmed that these were the only appropriate antimycobacterial agents in this case. Following 7 months of therapy, the nodules had resolved, with no further new lesions, and the leg ulcer had almost completely healed.

Case 2

The second patient was a 37-yr-old female with a 16-yr history of SLE, manifest clinically as photosensitivity, Jaccoud’s arthritis, alopecia, nephritis and serositis. Laboratory findings included lymphopenia, positivity for anti-nuclear antibody (1/2560), and anti-double-stranded (ds) DNA (dsDNA) antibodies 600 U/ml (normal values <100 U/ml). She was also hypocomplementaemic with reduced C3 (0.74 g/l) and C4 (0.19 g/l) and elevated C3d, suggesting complement activation. She was positive for immunoglobulin (Ig) G and IgM anti-cardiolipin antibody in the absence of lupus anticoagulant. Class II tissue typing showed HLA DR7/17 and DQ 2/3.

She responded to prednisolone at doses ranging between 15 and 25 mg/day. Previous immunosuppressive therapies had included azathioprine, cyclosporin and hydroxychloroquine. Azathioprine was discontinued following the development of a pruritic erythematous rash, which on biopsy was characteristic of a drug eruption. She had presented with several other cutaneous disorders during the course of her disease, including a benzoate allergy and a herpes zoster infection of the T7 dermatome.

Two years prior to this presentation, she had developed proteinuria of 4 g/day with a rise in dsDNA antibody titre and a reduction in C3 and C4 levels to 0.41 and 0.11 g/l respectively. Lupus nephritis (WHO grade IV) was confirmed on renal biopsy (activity index 17/24, chronicity index 3/12). She received three pulses of intravenous methylprednisolone followed by oral prednisolone at 60 mg/day. In addition, she received six pulses of intravenous cyclophosphamide at monthly intervals. After 6 months, azathioprine was reintroduced, initially at 25 mg daily, with no initial adverse cutaneous effects, and steroids were slowly reduced.

She presented with a 4-week history of a painful nodule on her left leg while taking 14 mg prednisolone and 75 mg azathioprine/day. Blood parameters were suggestive of active SLE (low C3 and C4 with elevated C3d), and a diagnosis of cutaneous vasculitis was considered. The ESR and CRP were elevated (36 mm/h and 32 mg/l respectively), with lymphopenia (0.63 × 10⁹/l) in the presence of a normal total white blood cell count. Biopsy of the affected area was arranged. Histological analysis showed dermal inflammation with granulomas and micro-abscesses. Fat necrosis was observed in the subcutaneous tissues and mycobacteria were identified by Ziehl–Neelsen staining (not shown). Initial treatment with rifampicin 600 mg per day, ethambutol 15 mg/kg and ciprofloxacin 750 mg twice daily was changed to clarithromycin and ciprofloxacin after typing (as above) had revealed the organism to be *M. chelonae* and its sensitivities confirmed.

Discussion

Symptoms and signs in both these cases suggested an exacerbation of SLE with cutaneous vasculitis, but biopsy confirmed features consistent with mycobacterial infection, the organism responsible subsequently being identified as the atypical mycobacterium *M. chelonae*. Infections are common in SLE [1] and are reported to be responsible for up to 50% of all deaths in SLE patients [2]. The confusion arises when symptoms and signs of infection mimic those of active lupus, as in these cases,
because immunosuppressants are contraindicated in active infection.

One cutaneous manifestation of *M. tuberculosis* infection is ‘lupus vulgaris’, the nomenclature suggesting that the two diseases have historically shared similarities in their dermatological manifestations. Classical *M. tuberculosis* has been long recognized in SLE [3], particularly in areas where it is endemic [4–6]. In contrast, atypical mycobacterial infections are much less common, with only rare case reports in SLE [7–9], but the present cases are the first reported instances of *M. chelonae* infection in SLE. However, one case of skin infection with *M. chelonae*, also mimicking cutaneous vasculitis, was reported in a middle-aged female with idiopathic multifocal uveitis being treated with steroids and immunosuppressants [10].

**Mycobacterial skin infection**

Cutaneous infection with *M. tuberculosis* is rare, accounting for <1% of extrapulmonary cases; 95% of all cases occur endogenously, either from a contiguous focus or via haematogenous spread [11]. Cutaneous infection is similarly rare in SLE patients; in one study of 16 cases of *M. tuberculosis* infection in 311 American patients (5%), 15 had lung involvement, one had an infected hip joint [3] and none skin involvement. In a more recent study of 54 cases of *M. tuberculosis* in SLE patients from the Philippines, only four (7%) developed skin abscesses, all of whom had concomitant or recent pulmonary involvement [5]. Similarly, in only 11% of an Indian cohort of infected SLE patients was the infection subcutaneous [6]. This implies that, in most cases, the cutaneous manifestations of *M. tuberculosis* in SLE are rare and are likely to arise secondarily to an infection elsewhere.

Clinical appearances are dependent on the site of primary infection [11, 12]. If the focus is deep to the cutaneous site, scrofuloderma can evolve with a red/blue induration, usually over the affected lymph nodes, epididymis or underlying bone. While ulceration can develop and sinus formation has been reported, the development of fibrosis and scarring that can resemble keloid scars between the areas of infection is not infrequent. If the primary site is in the visceral organs, then single or multiple yellow/brown nodules can develop, particularly commonly over the anogenital...
areas. They are usually painful, ulcerate without scarring and have a poor prognosis because they are usually a late manifestation of disease [11].

If spreading is via a haematogenous route, the result can be lupus vulgaris or gumma formation. Lupus vulgaris occurs in areas where *M. tuberculosis* is endemic; it starts with groups of red/brown nodules on the lower limbs—though the face is the commonest site—perhaps explaining the shared nomenclature with SLE. Classically, the nodules coalesce into gelatinous plaques which, when flattened and observed by diascopy, have the classical apple jelly appearance, and when they ulcerate they can cause deformity. Gummata form from non-tender nodules that occur anywhere on the body and can become fluctuant and break down to form local sinuses; they have a poor prognosis in malnourished individuals [12].

**Atypical mycobacterial skin infection**

The commonest atypical mycobacterial skin infection is *M. marinum*, which follows inoculation into superficial sites of injury after swimming in infected pools or immersion in aquaria. The fish-tank granuloma classically forms painless nodules on the extremities 4–6 weeks after superficial skin damage [12], but tenosynovitis can occur in the presence of penetrating injuries [13]. Cutaneous infection is increasingly seen in immunocompromised individuals, with 88% of atypical cases found in immunocompromised patients, whereas only 30% of cases of cutaneous *M. tuberculosis* infection were seen in such patients [14]. The HIV pandemic in particular has led to an increase in cases of atypical infections, and the number of cutaneous infections has consequently risen [15]. Other atypical mycobacteria reported to produce skin involvement include *M. ulcerans, M. avium intracellulare* and *M. haemophilum*, and two ‘rapid growers’, *M. fortuitum* and *M. chelonae*, which can cause extensive infection in immunodeficient patients.

Two studies examined a total of 24 patients with confirmed atypical mycobacterial infection [16, 17]. The clinical manifestations consisted of draining sinuses and abscesses and, as in our cases, ulcers and nodules that can evolve into scaly plaques [12] or, in one case, mimic cellulitis [18]. Although a painless ulcer was present in our first case, we were not able to establish that this was related to underlying *M. chelonae* infection, but it is of interest that it healed concomitantly with chemotherapy. There have been previous reports of cutaneous atypical mycobacterial infection in patients with systemic rheumatic disease [19], including SLE [7–9, 20], most of whom were taking immunosuppressive therapy, usually with steroids. The initial manifestations mimic the features seen in patients in the absence of underlying connective tissue disease, being characterized by the formation of papules that later become nodular with crusting, and can ulcerate [12]. Cutaneous lesions can be the first and only sign of atypical mycobacterial disease; biopsy for culture remains the definitive diagnostic procedure and should be performed in suspected cases, even if stains for acid-fast bacilli are negative.

*Mycobacterium chelonae* itself is ubiquitous in soil, dust and water and belongs to a group of rapidly growing mycobacteria with optimal growth at 28°C. It is Gram-positive but may be weakly acid-fast. Polymerase chain reaction and mycolic acid analysis may be required for exact identification. It is easily transmissible by inoculation: the largest outbreak involved 232 patients, in whom infection followed contaminated injections given as part of an alternative medical therapy [21]. This established the incubation period for *M. chelonae* as 15–59 days and confirmed that elderly males were most at risk. There was no evidence of person-to-person spread.

Human infections with *M. chelonae* are uncommon and typically follow trauma, surgery or injection, occurring mainly in immunocompromised patients, as described here. Although a variety of clinical syndromes, including dissemination, have been reported, infection generally involves the skin and soft tissues, characteristically resulting in multiple subcutaneous nodules on the extremities [22–24]. It can also cause keratitis and corneal ulceration if affecting the eye.

**Histology of atypical mycobacterial skin infection**

Histological appearances of atypical mycobacterial infection are not specific but can include large numbers of neutrophils in the biopsy, as in our case 1. Our second case showed abscess formation [25, 26], also reported to be a predominant feature in proven cutaneous *M. chelonae* infection. Granulomatous inflammation is also common [27–29] and was seen in both cases, but a diffuse inflammatory infiltrate with only focal granuloma formation has also been observed [30, 31]. The inflammation may involve the dermis and underlying fat, and necrosis may be present [25, 26, 29], as in case 2. The organisms are usually identifiable on histological sections but occasionally may not be detected even with a variety of stains [30].

Immunosuppression may affect the type of inflammatory response. Bartralot et al. [32] showed that a deep inflammatory infiltrate was present in 100% of immunosuppressed patients but only 39% of patients in an immunocompetent group. Other features more common in immunocompromised hosts included suppurrative granulomas (50% compared with 28%), acanthosis in the epidermis (83% compared with 30%) and a lack of epidermal response. Granulomas are commonly apparent when the history is less than 3 months. A rare response in immunocompromised patients is the formation of spindle cell pseudotumours, a type of reactive inflammatory lesion that can resemble a sarcoma, a poorly differentiated carcinoma or a benign mesenchymal tumour [33, 34]. These usually contain acid-fast bacilli and have been reported in patients with HIV [35], following organ transplantation [36] and steroid therapy [37], and in Hodgkin’s disease [38].
**Treatment of mycobacterial infection**

Chemotherapy of cutaneous M. tuberculosis infection is based on multidrug regimes for pulmonary tuberculosis, as recommended by the British Thoracic Society [39], the Infectious Diseases Society of America and The American Thoracic Society [40]. It should be remembered that non-compliance is the major cause of treatment failure and the emergence of drug-resistant strains, so establishment of directly observed therapy may be necessary. Occasionally surgery may be necessary [41].

Specific treatment of M. chelonae infection usually involves a combination of chemotherapy and surgical debridement of infected tissues, although the latter was not required in either of our cases. The lack of consensus on treatment is a reflection of the paucity of data derived from clinical trials. The Joint Tuberculosis Committee of the British Thoracic Society [42] has prepared guidelines entailing multidrug therapy for most opportunistic mycobacterial infections, with debridement if necessary [43], but recommends that expert advice be sought. Therapy should be tailored according to sensitivity results, but most isolates are sensitive to clarithromycin [44] and monotherapy with this agent has resulted in good response rates. Of the oral antibiotics, sensitivity to ciprofloxacin and doxycycline is variable while tobramycin and imipenem are the parenteral agents of choice. Anecdotal evidence suggests that treatment should be with a minimum of two agents, including clarithromycin, for at least 6 months, and that this should reduce relapse rates and prevent emergence of resistance. In immunocompromised patients, treatment may have to be continued for longer.

**Conclusion**

Patients with SLE, particularly those with active disease, are susceptible to infection and those on immunosuppressant therapy are at particular risk. The incidence of reported cases of opportunistic infections that were once considered rare is now increasing and these should be borne in mind in SLE patients, especially those that fail to respond. As in the case of patients with lung infiltrates on chest X-ray, in whom atypical infection is high on the list of differential diagnoses, cases of unusual or treatment-resistant skin lesions should raise the possibility of atypical mycobacterial infection. A high index of suspicion, supported by histopathological and bacteriological investigations, can assist early identification of atypical mycobacterial infection, thereby ensuring appropriate treatment and avoiding the use of unnecessary or potentially harmful immunosuppressants.

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