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CASE REPORT

A rare opportunistic infection in a woman with systemic lupus erythematosus and multiple skin lesions

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Cutaneous lesions in patients with systemic lupus erythematosus (SLE) represent diagnostic challenges. Opportunistic infections should be considered when lupus patients are on immunosuppressive therapy and other causes, such as disease activity, are less likely to explain the skin lesions. Within the spectrum of skin opportunistic infections that might occur in SLE patients, *Blastomyces dermatitidis* should be suspected when acid-fast positive material with no bacilliform organisms is seen on Ziehl-Nielsen skin biopsy preparations. In this study, we describe one patient with SLE on immunosuppressive therapy, who developed cutaneous blastomycosis despite living in a non-endemic area. Because of lack of awareness about this association and misinterpretation of the skin biopsy results, the diagnosis of atypical mycobacterial infection was initially considered. Subsequent proper tissue staining and interpretation revealed the correct diagnosis of disseminated cutaneous blastomycosis. This description represents the first report of this rare opportunistic skin infection in SLE, illustrating the importance of performing correct preparation and elucidation of the skin biopsy to avoid misdiagnosis and treatment delay. *Lupus* (2009) **18,** 1100–1103.

Key words: cutaneous blastomycosis; opportunistic infection; SLE

Introduction

Cutaneous manifestations are seen in 70–85% of patients with systemic lupus erythematosus (SLE), and they can occur at any stage of the disease, irrespective of disease activity.[1] Not all skin lesions in SLE patients are associated with the autoimmune process that characterises the disease, and frequently other conditions need to be excluded. Infections can explain the occurrence of cutaneous lesions in SLE patients, especially during immunosuppressive therapy or uraemia. Opportunistic infections of the skin are rarely reported, and they may represent diagnostic challenges leading to delay in prompt diagnosis, mistreatment and increased risk of morbidity and mortality. In this study, we describe a SLE patient who developed multiple cutaneous lesions secondary to *Blastomyces dermatitidis* infection. Due to acid-fastness in the tissue sections, an erroneous diagnosis of atypical mycobacterial infection was initially considered. Alertness on this infectious complication in SLE patients, as well as on the potential diagnosis difficulties, is likely to allow early detection and appropriate treatment, decreasing the risk of more serious outcomes.

Case report

A 35-year-old Hispanic female was referred to the dermatology clinic with approximately 3 weeks of recurrent episodes of fever, chills and the appearance of several papular skin lesions. She had emigrated from Mexico 9 years before; other than Guanajuato, Mexico and Georgia, she had lived in Pasadena, Texas for 8 months in 1991. She denied other travel history, owned no pets and denied agricultural activities. The patient had a diagnosis of SLE in 2003 for which she was treated with low doses of prednisone (7.5–10 mg/day). In December 2007, she presented acute renal failure secondary to rapidly progressive lupus glomerulonephritis and was treated with high

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doses of steroids and haemodialysis. After 2 months on haemodialysis (while she was on 40 mg of prednisone), she was given one pulse of intravenous cyclophosphamide. Three weeks after the first pulse of cyclophosphamide, she noticed the appearance of tender papular, pustular and nodular lesions on her arms and legs. At the dermatology clinic, physical examination was remarkable for several erythematosus, tender lesions (some of them crusted) in her left lateral thigh, left and right upper extremities, and left flank (Figures 1 and 2) ranging from 1 to approximately 3 cm in diameter. The rest of her physical exam was unremarkable, and no lupus activity was evident on other systems. The patient's white blood cell count was 10,000 cells/mm^3 (neutrophils, 82%; bands, 0; lymphocytes, 10%). ANA and anti-DNA$_{ds}$ antibodies were negative, and complement levels were normal. A biopsy of one of the lesions was performed and sent for histological examination, bacterial, mycobacterial and fungal stains and cultures. Clindamycin was prescribed for 10 days while awaiting the pathology results. The biopsy revealed necrotising granulomatous inflammation with acid-fast organisms. Unfortunately, Periodic acid Schiff (PAS) or Gomori methenamine silver (GMS) stains were not done at that time. The bacterial, mycobacterial and fungal cultures were negative. On the basis of the clinical presentation and pathology results, a diagnosis of disseminated cutaneous infection with atypical mycobacteria in an immunocompromised host was established. Treatment with levofloxacin and azithromycin was initiated with no significant improvement after 1 month of treatment. Tissue block was obtained for repeat Ziehl-Nielsen and GMS staining showing multiple yeast-form organisms ranging from 8 to 15 μm in diameter, with a thick wall with double-contour feature and broad-based budding (Figure 3). However, as seen in Figure 4, the Ziehl-Nielsen stain showed abundant acid-fast positive granular material (but with no bacilliform organisms). The histopathology features supported a final diagnosis of cutaneous blastomycosis.

Due to the underlying renal insufficiency and to the lack of other organ involvement (chest X-ray was negative and she had no neurologic signs or symptoms), the patient was started on itraconazole 200 mg orally twice a day. One month after initiating treatment, she was asymptomatic and her skin lesions became smaller and no longer tender. The glomerulonephritis has

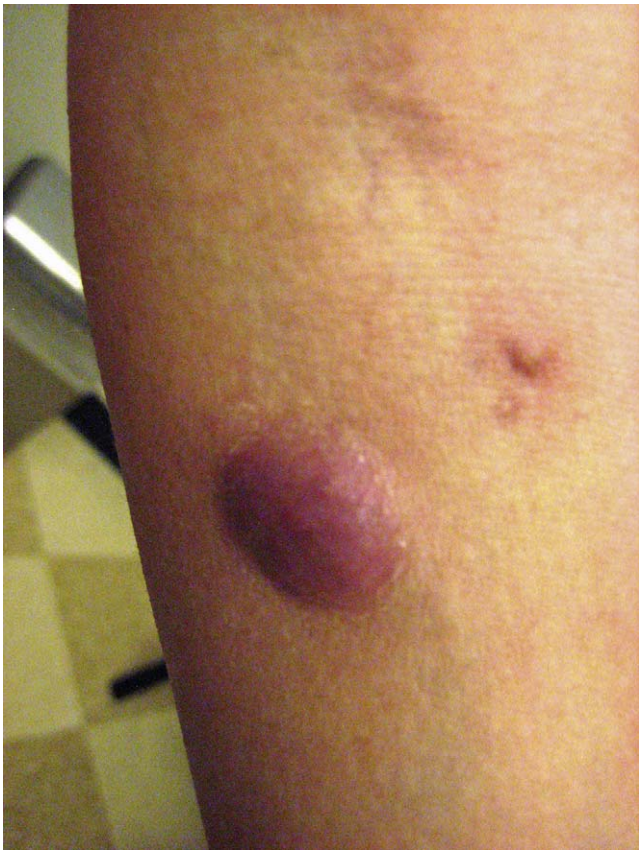

Figure 1 Papular and nodular erythematosus lesions on the anterior aspect of the right forearm.

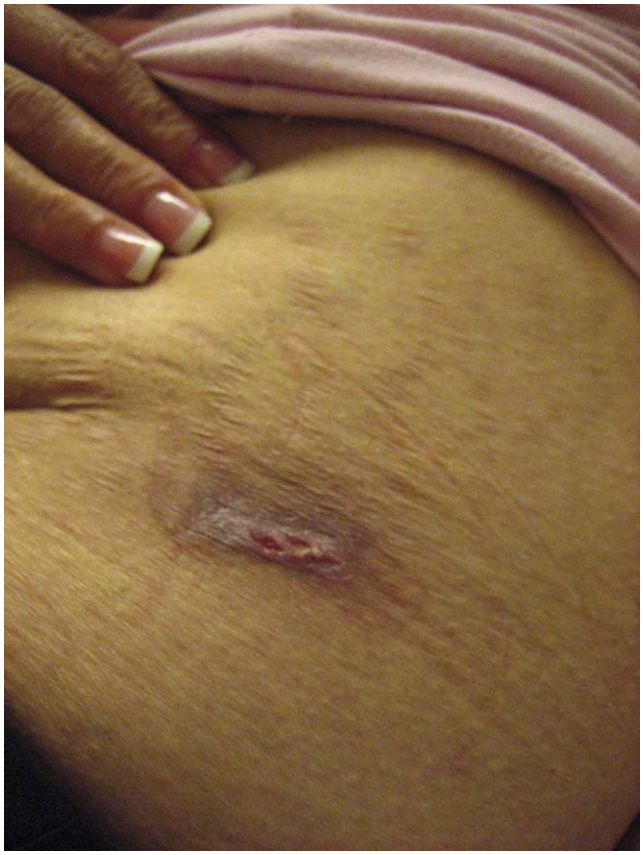

Figure 2 Small pustular lesions on the left flank.

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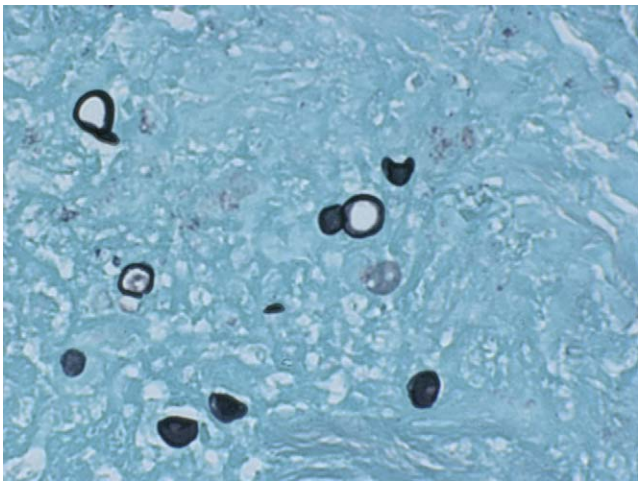

Figure 3 Gomori methenamine silver (GMS) stain of skin lesion showing multiple yeast-form organisms ranging from 8 to 15 μm in diameter, with a thick wall with double-contour feature and broad-based budding (×100).

evolved to end-stage renal failure, and prednisone is being tapered off while she is to remain on chronic haemodialysis. The plan is to continue antibiotic treatment for at least 12 months or until complete resolution of her lesions.

Discussion

Blastomycosis is a systemic endemic fungal disease, caused by inhalation of *B. dermatitidis*. The disease is essentially confined to North America[2] and has a well-defined geographic distribution, overlapping with histoplasmosis endemic areas, but extending further north and east.[3] The most frequent clinical manifestation is pulmonary involvement, seen in 50–90% of patients.[4] Extrapulmonary manifestations are seen in approximately 40% of patients, with or without lung involvement.[4] Of these, cutaneous infection is the most frequent followed by bone, central nervous system and genitourinary involvement in descending order.[4] The disease tends to disproportionately affect males (male-to-female ratio 4:1–15:1) and African Americans, and it is seen infrequently among paediatric patients.[2,4]

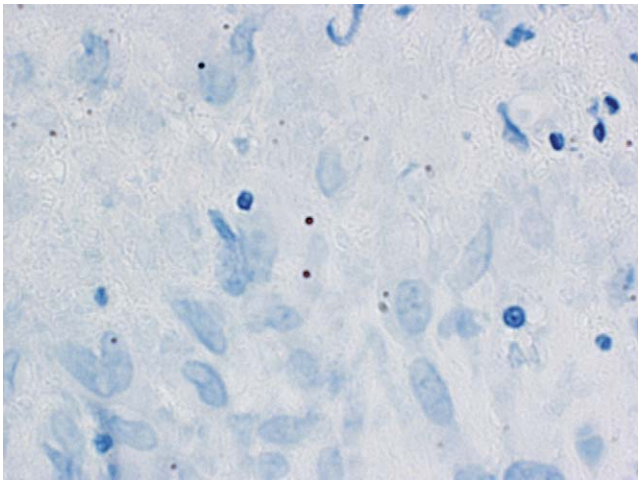

Figure 4 Ziehl-Nielsen stain of skin lesion showing abundant acid-fast positive granular material with no bacilliform organisms.

Unlike other endemic mycoses, blastomycosis has not been recognised as a common opportunistic infection in immunocompromised hosts.[5] In a retrospective review including three hospitals in endemic areas, only 34 cases were identified during a 35-year period.[5] Of these, 12 were patients receiving long-term glucocorticosteroid therapy, and only four of these patients had skin involvement. Eleven patients were on cytotoxic therapy to treat either a haematologic or solid organ malignancy; however, none of these patients had received cyclophosphamide. Among the 34 patients, only three patients had involvement of the skin as the sole manifestation of blastomycosis. Despite similar disease presentations between immunocompetent and immunocompromised hosts, multiple organ and central nervous system involvement are more frequent in the later group. Immunocompromised hosts also have a higher associated mortality.[5,6]

The association between SLE and blastomycosis is not frequent, with only one additional case involving the brain reported in the English literature.[7] Invasive fungal infections overall are not a common occurrence in this patient population and are more frequently due to *Candida* spp., *Cryptococcus neoformans* and *Aspergillus* spp.[8,9] Single cases of nocardiosis, coccidioidomycosis and maduromycosis have also been reported.[8,9] The morphologic characteristics of the skin lesions secondary to *B. dermatitis* are also not specific; therefore, a skin biopsy is required in most of the cases to make a diagnosis. In our patient, the skin biopsy showed a necrotising granulomatous inflammation with acid-fast stained material. The PAS and GMS stains were overlooked leading to an incorrect diagnosis. The GMS staining that confirmed the diagnosis of blastomycosis was realised only after therapeutic failure with antibiotics against atypical mycobacteria was apparent. The granular acid-fast staining organisms corresponded to the yeast observed in the GMS stain. The presence of acid-fastness among up to 60% of infections caused by *B. dermatitidis* and 47% of infections caused by *H. capsulatum* is a fact that deserves considerable attention.[10] It may aid in the differentiation of

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B. dermatitidis and *H. capsulatum* from other fungi.[2] However, if ignored, it might lead clinicians to consider a mycobacterial infection and treat accordingly when cultures are unrevealing. Unlike *M. tuberculosis* and *H. capsulatum*, the acid-fastness of *B. dermatitidis* is not abolished by hydrochloric acid, suggesting that this property is not due to mycolic acid in the later.[10]

Chronic use of steroids and cytotoxic therapy and uraemia resulting from a severe form of lupus glomerulonephritis are the more plausible predisposing factors associated to the infectious complication in our patient. Although the host defence mechanisms seemed to be competent enough to maintain the opportunistic infection temporally localised on the skin, the cutaneous dissemination to different areas of the body suggests that more severe outcomes could have occurred if proper antibiotics had been instituted with longer delay. Our patient had not resided in a classically considered 'blastomycosis endemic area'[3]; however, the patient did admit to gardening occasionally at these locations, which could have possibly explained her exposure to this fungus.[3] To our knowledge, no autochthonous cases have been reported from Mexico.

The recommended treatment for immunosuppressed patients is amphotericin B for 1–2 weeks or until improvement is noted, followed by itraconazole to complete at least 12 months of therapy.[11] Due to the underlying chronic renal disease and no other organ involvement, the patient was treated with itraconazole showing a rapid and significant clinical response.

In summary, to our knowledge, this is the first case of cutaneous blastomycosis in a SLE patient. Awareness about this infectious complication in SLE patients, suitable biopsy methods and correct histopathologic interpretation are important factors that must be considered to avoid misdiagnosis and postponement of appropriate therapeutic management.

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