Long-lasting cutaneous tuberculosis owing to *Mycobacterium bovis* masquerading as sarcoidosis

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Key words: cutaneous tuberculosis; lupus vulgaris; *Mycobacterium bovis*; sarcoidosis.

INTRODUCTION

Cutaneous mycobacterial infections are difficult to diagnose in paucibacillary forms such as lupus vulgaris. The main causal agent is *Mycobacterium tuberculosis* but *Mycobacterium bovis* may be involved. We present a case of cutaneous tuberculosis caused by *M bovis*, considered to be sarcoidosis for14 years until discovered by immunosuppressive therapy.

CASE REPORT

A woman with no medical history was seen in our department for the first time in 2001 at the age of 62 with erythematous slightly squamous plaques on the right arm and back (Fig 1, *A*). Skin biopsy was suggestive for sarcoidosis with well-formed noncaseating granulomas. Neither Ziehl Neelsen staining, tissue culture, nor DNA analysis was performed. No systemic involvement was found. From 2001 to 2009, she received successive treatments including hydroxychloroquine, thalidomide, doxycycline, methotrexate, colchicine, and systemic steroids. The lesions failed to respond and were slowly extending centrifugally with atrophic zones, without any systemic involvement (Fig 1, *B* and *C*). This treatment failure led to the introduction of adalimumab in 2009. Chest radiograph at this time was normal and QuantiFERON-TB was negative. Adalimumab induced painful ulcerations limited to the plaques that regressed within a few days after stopping the treatment. From 2009 to 2015, she received short courses of oral steroids, dapsone, and doxycycline, without any efficacy. Skin lesions were stable, and there were no symptoms suggestive of internal organ involvement. A new extracutaneous staging was performed in September 2015, including thoraco-abdomino-pelvic computed tomography scan, which was normal, and there was only a slightly high level of serum angiotensin-converting enzyme. Mycophenolate mofetil (MM) was started in November 2015 to treat what was considered to be recalcitrant sarcoidosis. Six months later, the plaques suddenly worsened and became erosive and extensive (Fig 2, *A*). New extracutaneous staging, including chest radiograph, was normal, and QuantiFERON-TB was negative. A new skin biopsy of ulcerative lesions showed an inflammatory infiltrate in the dermis with an ill-defined noncaseating granuloma (Fig 2, *B*). Stains for mycobacteria, bacteria, and fungi were negative. The first 24-hour polymerase chain reaction (PCR) (GenoQuick® MTB, Hain Lifescience) was negative. After 5 weeks, tissue culture was positive for a mycobacterium from the tuberculosis complex. DNA analysis by PCR (Genotype MTBC, Hain Lifescience) identified an *M bovis* that was sensitive to rifampicin, ethambutol, and isoniazid, but resistant to pyrazinamide. MM was discontinued, and a triple therapy comprising isoniazid, rifampicin, and ethambutol was administered for 2 months, followed by isoniazid and rifampicin for 4 months. The ulceration rapidly healed and the lesions gradually resolved and cleared, with only hypertrophic

Abbreviations used:

MM: mycophenolate mofetil
PCR: polymerase chain reaction

From the Dermatology Department, University Hospital of Bordeaux.
Funding sources: None.
Conflicts of interest: None disclosed.
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JAAD Case Reports 2019;5:1-4.
2352-5126

https://doi.org/10.1016/j.jdcr.2018.07.020

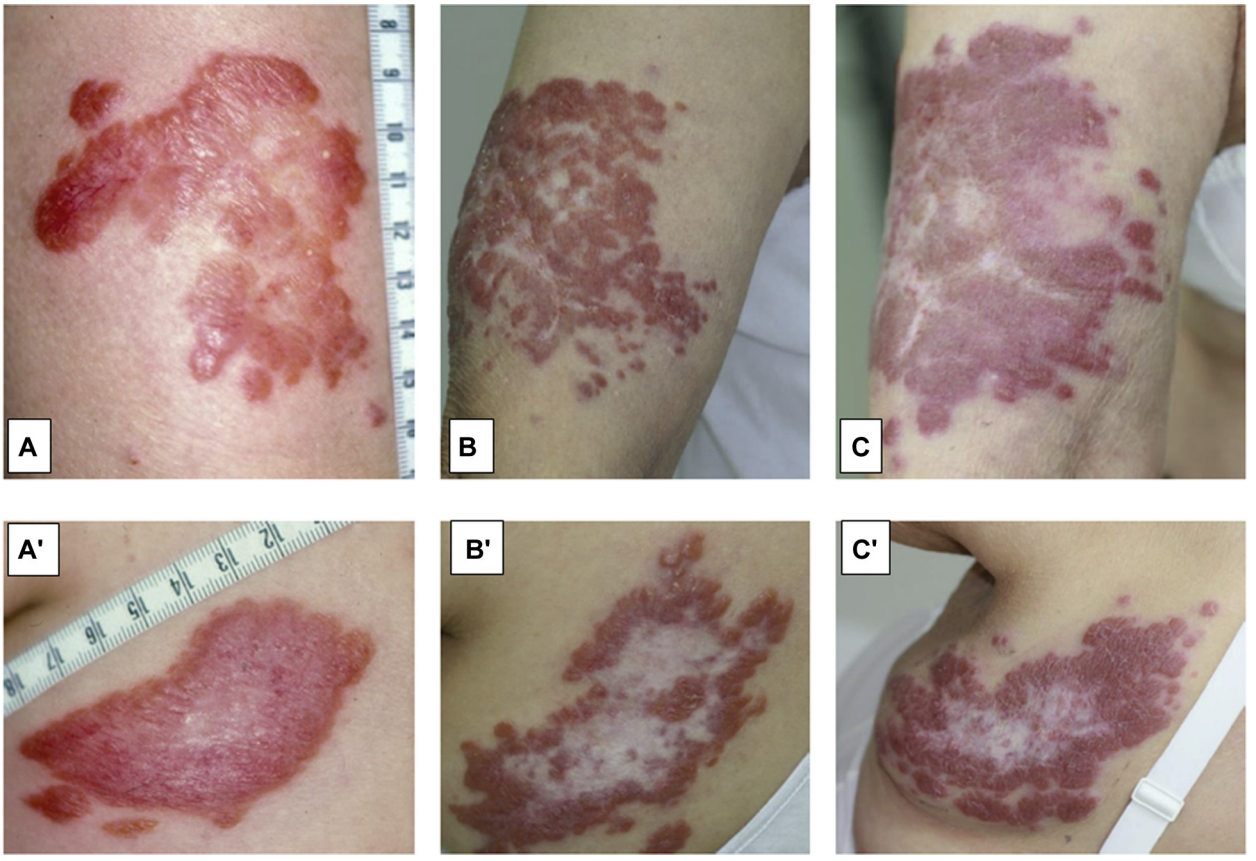

Fig 1. Clinical presentation over 14 years of follow-up for presumed sarcoidosis. Erythematous slightly squamous plaques on right arm and back in 2001 (**A** and **A'**). Centrifugal extension with central atrophic areas in 2011 (**B** and **B'**) and 2015 (**C** and **C'**) despite successive treatments.

scars remaining at the end of treatment (Fig 2, *C*) without recurrence after 18 months of follow-up.

DISCUSSION

M bovis is a member of the *M tuberculosis* complex. In recent years, *M bovis* infection has become very rare in developed countries thanks to the screening of farm animals and milk pasteurization.[1,2] It is transmitted to humans through unpasteurized milk or by direct contact with animals, notably in cattle workers and veterinarians.[1-6] Isolated cases of cutaneous tuberculosis caused by *M bovis* have been reported. In most of them, the lesions presented as lupus vulgaris and were long lasting from 10 to 60 years, with possible contamination during childhood.[3,4,6,7] Atrophic scarring of lesions and apple jelly color on diascopy are characteristic of lupus vulgaris. Histologically, it presents as nonnecrotizing granulomas in which acid-fast bacilli are usually not found.[8] Our delayed diagnosis was possibly owing to low clinical suspicion with a presentation at unusual sites.[1,2,8] By re-interviewing our patient, we established that the first lesions began during her adolescence spent on a farm in Southwest France where she was in contact with cows. The skin lesions had slowly enlarged for years, and she sought medical advice only at the age of 62, when we saw her for the first time with the sarcoidosis suspicion.No extracutaneous involvement was observed, and, as in the other cases of cutaneous *M bovis* reported, regression was rapidly obtained with specific treatment.[3,4,6,7] Pyrazinamide should not be used to treat *M bovis* owing to its intrinsic resistance.[2,5,8] Diseases caused by either *M bovis* or *M tuberculosis* are considered clinically and radiologically indistinguishable from each other. Tissue culture and PCR were the keys to the diagnosis, allowing identification of the *Mycobacterium* species involved and its suitable treatment, as species have different sensibility and resistance to antituberculosis antibiotics.[2,5]

We emphasize the importance of challenging the diagnosis of sarcoidosis in the event of refractory lesions with noncaseating granuloma and considering the possibility of mycobacterial infection. Quantiferon TB was negative in our patient probably owing to MM. It was also previously negative before adalimumab. Our hypothesis is that the immunosuppressive treatments (methotrexate and systemic steroids) she has

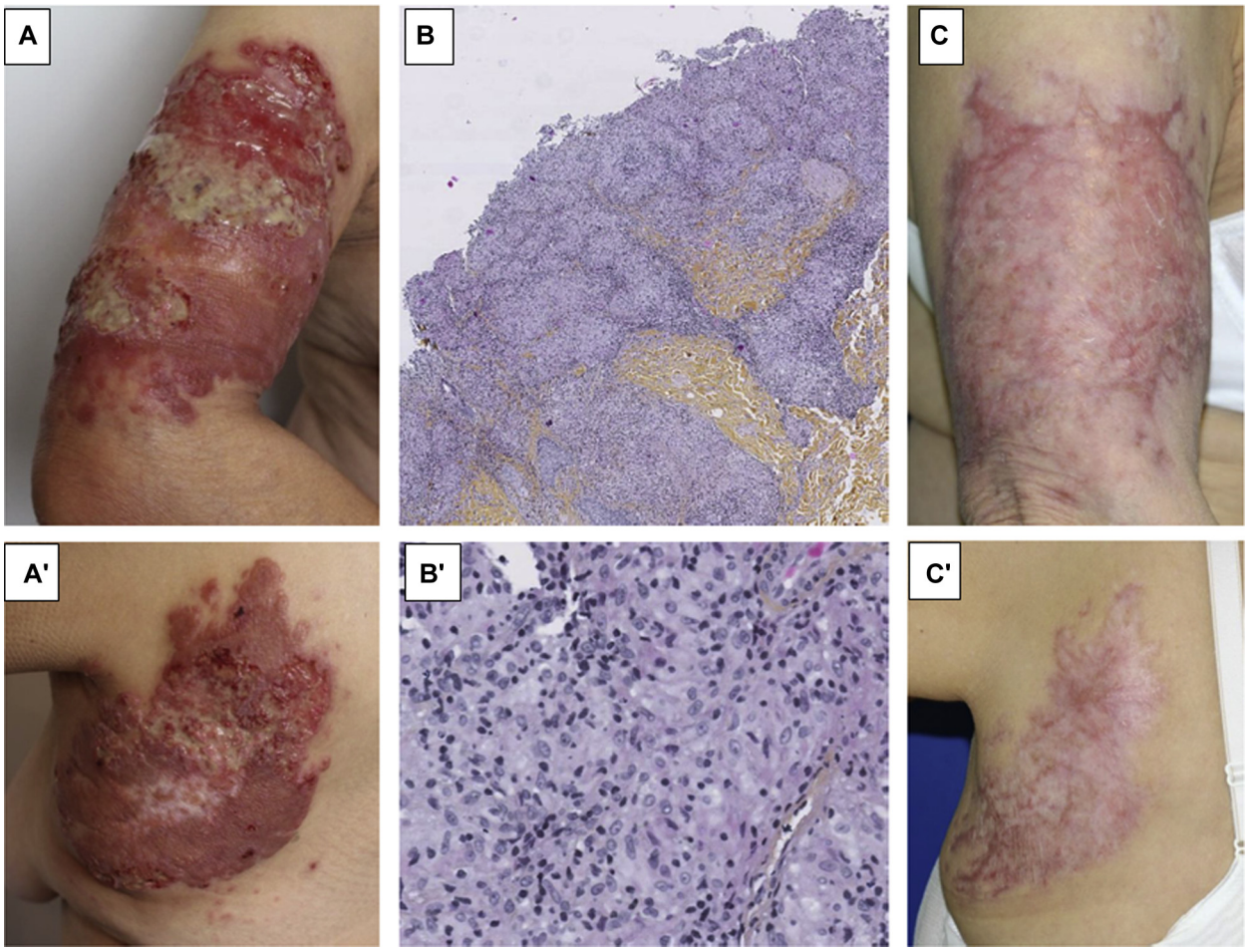

Fig 2. Clinical presentation at time of diagnosis of *M bovis* infection. Clinical exacerbation after 6 months of MM treatment (**A** and **A'**). Skin biopsy: inflammatory dermis infiltrate with no caseating granulomas. (**B**, Hematoxylin-eosin stain; original magnifications: **B**, ×25; **B'**, ×100.). Complete regression after 8 months of antibiotherapy (**C** and **C'**).

received may lead to false negativity. Cutaneous sarcoidosis was the diagnosis in our patient for 14 years and was refractory to several treatments. The lesion exacerbation was first observed during treatment with adalimumab, probably owing to its inhibitory effect on the immune response to granulomatous infection. The severe worsening 6 months after beginning MM led to the final diagnosis. A similar sequence of events was reported by Fraser et al.[9] Cutaneous tuberculosis caused by *M tuberculosis* was discovered by infliximab prescribed for a presumed cutaneous sarcoidosis.[9] In our report the differential diagnosis between sarcoidosis and cutaneous tuberculosis was difficult. In fact, cutaneous granulomatosis is a heterogeneous group of skin diseases and the elementary lesion corresponds to an infiltrated papule, painless, rounded, well limited, reddish-pink, with a yellowish color on diascopy. The common histologic denominator is the presence of a granulomatous inflammatory infiltrate in the dermis or hypodermis. Causes are diverse and not restricted to infectious diseases. Therefore, clinicians have to keep in mind that the diagnostic confirmation is always based on 4 points: clinical examination, histologic analysis, infectious analysis (bacterium culture or mycobacterium culture), and preservation of a fresh biopsy for PCR.[10]

The authors thank Ray Cooke for copyediting the manuscript.

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