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Medical Imagery

Sporotrichoid distributed tuberculous panniculitis as a late complication of intravesical bacillus Calmette–Guérin (BCG) immunotherapy

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ABSTRACT

An 82-year-old man presented with unilateral oedema of the right lower limb overlaid with multiple sporotrichoid distributed panniculitis lesions. These symptoms appeared in a context of immunodepression and were associated with significant weight loss and a deterioration in general condition. The patient's medical history, the histological findings, PCR testing, and bacterial culture led to a diagnosis of cutaneous tuberculosis due to *Mycobacterium bovis*. This infection occurred as a late complication of intravesical bacillus Calmette–Guérin (BCG) instillations that the patient had received as an adjunctive immunotherapy for bladder cancer. This is an unusual clinical presentation and aetiology of cutaneous tuberculosis. Indeed, the observed sporotrichoid pattern is uncommon for tuberculous mycobacteria. Moreover, the occurrence of tuberculous skin lesions after intravesical BCG instillations is extremely rare, with only a few cases described, and, to the authors' knowledge, none with such a clinical presentation. This case report suggests that a medical history of BCG immunotherapy should always be considered when assessing any infectious-type cutaneous lesions and that skin should be regarded as a possible late localization of infectious complications of this treatment.

Case report

An 82-year-old man presented to the dermatology outpatient department with a 3-week history of unilateral oedema of the right lower limb associated with multiple painful skin lesions that had appeared secondarily. The oedema and skin lesions had developed in November 2019 in a context of a deteriorated general condition and recent significant weight loss. The patient did not report any prior trauma or wound on the involved leg. He had not travelled recently and had not participated in any gardening or specific outdoor activities. He had recently been diagnosed with Waldenström disease, which could partly explain his general symptoms. This was being closely monitored in the haematology department, with no current need for treatment. Furthermore, his medical history also included prostatic adenocarcinoma treated by radical prostatectomy in 2006 and high-grade transitional papillary carcinoma of the bladder treated with transurethral resection in 2016 and adjuvant intravesical bacillus Calmette–Guérin (BCG) immunotherapy.

Physical examination revealed unilateral oedema of the right lower limb overlaid with multiple infiltrated, nodular, inflammatory and painful subcutaneous lesions (Figure 1A, B). There was no clinical evidence of inguinal lymphadenopathy. The sporotrichoid appearance of these lesions (Figure 1B) suggested a differential diagnosis of infectious (atypical mycobacteria or fungal) panniculitis. Given the patient's neoplastic medical history and the associated limb oedema, carcinomatous lymphangitis was also considered.

A computed tomography (CT) scan of the pelvis did not reveal any compressive process, and a Doppler ultrasound excluded deep venous thrombosis of the involved limb. Three large skin biopsy specimens were sampled for histological examination, mycobacterial and fungal PCR testing, and culture. The histological findings reported lobular panniculitis with epithelioid granulomas (Figure 2A) and no associated vasculitis. Some of these granulomas were centred on caseous necrosis (Figure 2B). BK Ziehl and Wade–Fite (Figure 2C) stains revealed the presence of several mycobacteria. PCR was positive for tuberculous mycobacteria. Culture later allowed more specific identification of *Mycobacterium bovis*. A thoracic CT scan showed no sign of latent or active pulmonary tuberculosis.

Treatment combining isoniazid, rifampicin, pyrazinamide, and ethambutol was initiated. However, pyrazinamide was rapidly suspended after precise identification of *M. bovis*, and ethambutol was stopped after 4 months due to ophthalmological toxicity. Isoniazid and rifampicin were continued for an additional 8 months. Under treatment, the skin lesions and the oedema resolved (Figure 1C), the patient's weight stabilized, and his general state improved greatly.

Discussion

Cutaneous involvement of tuberculosis infections is rare, representing only 1–2% of extrapulmonary cases. The causative

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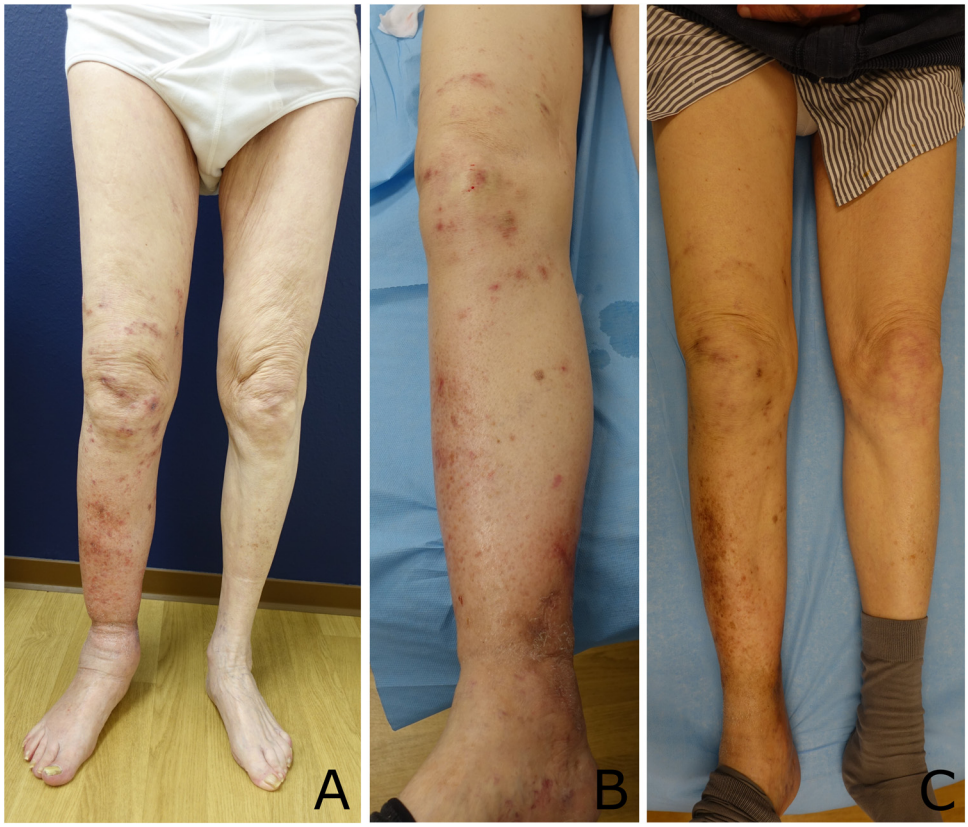

Figure 1. Clinical photographs obtained at the time the patient presented to the dermatology outpatient clinic, showing unilateral oedema of the right lower limb (A) overlaid with multiple inflammatory subcutaneous nodules distributed in a linear pattern on the inner side of the leg (B). Note the associated stasis dermatitis at the anterior surface of the leg secondary to the oedema (A and B). Clinical evaluation 2 months after treatment initiation showed visible regression of the oedema and cicatricial aspect of the skin lesions (C).

microbial agent is mostly *Mycobacterium tuberculosis*, but *M. bovis* has also been described as a potential pathogen (Chen et al., 2019). The clinical presentation varies greatly according to the pattern of dissemination of tuberculous mycobacteria: exogenous direct inoculation, secondary dissemination from an endogenous contiguous source (e.g., scrofuloderma), or haematological dissemination (e.g., miliary tuberculosis) (Chen et al., 2019; Franco-paredes et al., 2019; Hill and Sanders, 2017). Lymphatic dissemination associated with a sporotrichoid distribution of lesions is unusual and is more generally observed with non-tuberculous mycobacteria (Franco-paredes et al., 2019) or diseases caused by other microorganisms including sporotrichosis, nocardiosis, leishmaniasis, and pyogenic or deep fungal infections (Hadj et al., 2014). Most reported cases of sporotrichoid tuberculosis are secondary to a primary cutaneous entry point, with subsequent spread through the lymphatic system in a linear way; however, reverse sporotrichoid spreading forms, emanating from an endogenous source, have also been described (Hadj et al., 2014). In the case presented here, the linear distribution of skin lesions and the associated oedema strongly suggested a lymphatic dissemination. However, the endogenous source of infection (intravesical BCG instillations) would imply reverse lymphatic spreading. Another possible explanation for this unusual clinical presentation could involve distal haematogenous mycobacterial implantation in the right lower limb with secondary lymphatic dissemination.

Intravesical BCG immunotherapy is currently the standard adjunctive therapy (after transurethral resection) for the management of high-risk non-muscle invasive transitional carcinoma of the bladder. It uses a live-attenuated strain of *M. bovis* to generate a local immune response of the host against neoplastic cells (Waked et al., 2020). Despite the frequently reported immediate local sides effects (chemical cystitis, haematuria, pollakiuria, incontinence), it remains a generally well tolerated and effective treatment. Secondary mycobacterial infections are rare but well known complications (Waked et al., 2020). The majority of reported cases are systemic infections (such as miliary tuberculosis), followed by loco-regional infections affecting the genito-urinary tract and osteoarticular complications (mono-, oligo- or polyarthritis) (Pérez-Jacoiste Asín et al., 2014; Cabas et al., 2021). Isolated skin involvement is unusual and has only been reported in a few cases, presenting as unique nodules, abscesses, or plaques (Pérez-Jacoiste Asín et al., 2014; Ng et al., 2006; Mangiarotti et al., 2002; Markovic et al., 2017; Kanamori et al., 2012). It appears that there are no previous reports of sporotrichoid distributed panniculitis lesions.

Identified risk factors for secondary BCG infections are immunosuppression, advanced age, and traumatic instillation or prior urothelial lesions (Waked et al., 2020). At least two of these risk factors were encountered in the case patient: advanced age (82 years) and immunodepression due to the patient's Waldenström disease.

The delay between intravesical BCG instillations and the occurrence of these infectious complications can vary greatly, from several days up to many years (Cabas et al., 2021). Gonzalez et al. were the first to identify a timing pattern, distinguishing organs involved in early, intermediate, and late infections (<3 months, 3–12 months, >1 year after the first intravesical BCG instillation) (Gonzalez et al., 2003). In a review of the literature, Cabas et al. later confirmed the observed trend (Cabas et al., 2021), but used the time from last instillation as a reference for categorization, with no clear timing threshold set. However, cutaneous involvement was not considered, probably because of the scarcity of reported cases. In the patient presented here, the

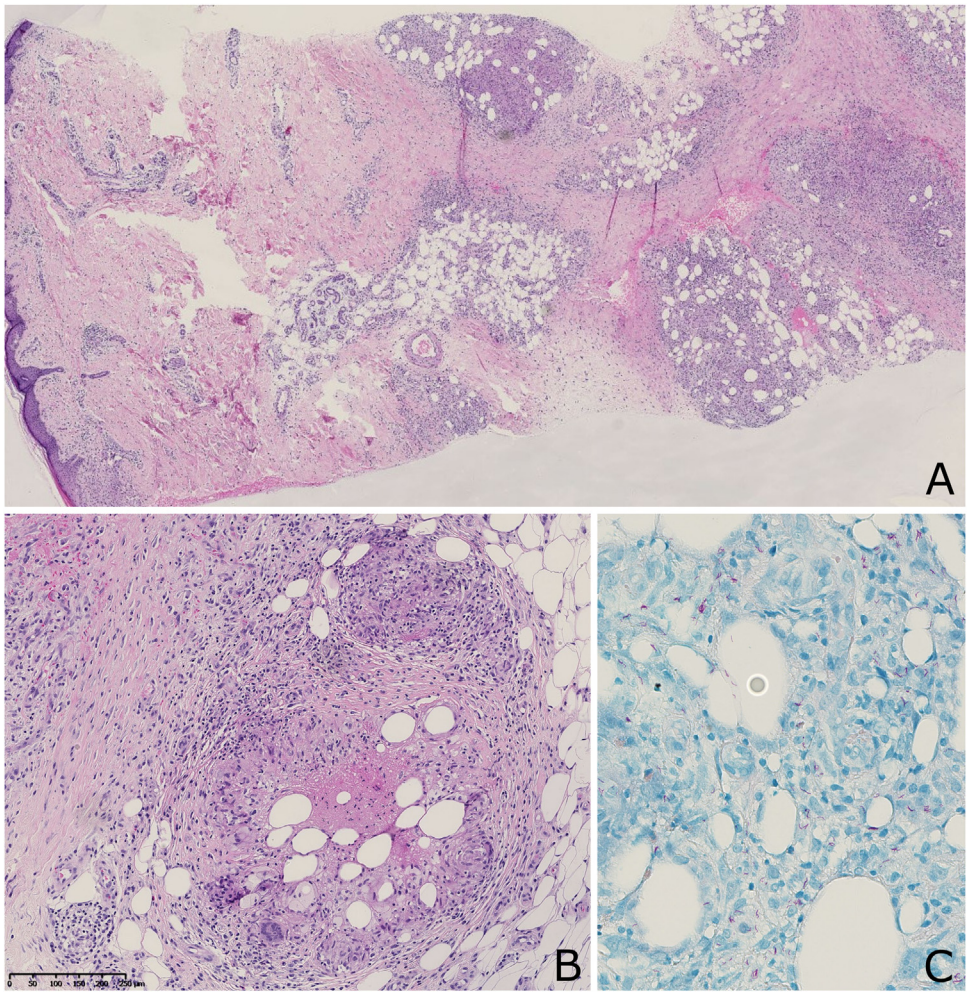

Figure 2. Histological findings after haematoxylin and eosin (HE ×1,56) staining (A and B), showing lobular panniculitis without associated vasculitis (A). Epithelioid granulomas centred on caseous necrosis can be seen at higher magnification (HE ×10) (B). The presence of several mycobacteria is highlighted with the Wade–Fite (WF ×40) staining technique (C).

lesions appeared more than 3 years after the initiation of BCG immunotherapy and 6 months after the last maintenance instillation, suggesting that the skin should be considered as a possible organ involved in late infections. This delayed onset could be explained in part by the recent immunosuppression of the patient that was absent at the initiation of intravesical BCG instillations.

The diagnosis of cutaneous tuberculosis is challenging because of the diversity of clinical presentations (Chen et al., 2019) and the difficulty in identifying mycobacteria (Larsen et al., 2020). Special stains, culture, and PCR testing often reveal negative results, requiring repeated biopsies and leading to delayed diagnosis (Larsen et al., 2020). In the case presented here, because of the uncommon sporotrichoid presentation suggestive of atypical mycobacterial or fungal panniculitis, enlarged skin biopsies were sampled at the first dermatological consultation and sent for histological examination, PCR testing, and culture. This enabled rapid diagnosis and treatment initiation.

As *M. bovis* is known to be intrinsically resistant to pyrazinamide, the commonly reported treatment for infectious complications following BCG immunotherapy involves 2 months of combined therapy with isoniazid, rifampicin, and ethambutol followed by 7 months of isoniazid and rifampicin (Cabas et al., 2021). Prolonged treatment was proposed for the case patient because of his immunodepressed status. This allowed a rapid recovery.

In conclusion, this case demonstrates an unusual clinical presentation and aetiology of cutaneous tuberculosis. Indeed, the observed sporotrichoid pattern is uncommon for tuberculous mycobacteria, and the occurrence of tuberculous skin lesions after intravesical BCG instillations is extremely rare. This highlights the great variety of appearances that tuberculosis can display and illustrates the wide range of clinical presentations that can be expected as a late consequence of intravesical BCG instillations. A medical history of BCG immunotherapy should always be considered when assessing any infectious-type cutaneous lesions, and skin should be regarded as a possible late localization of secondary infections after such treatment.

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Ethical approval

Ethical approval is not applicable.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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