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 deteriorated general condition. 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 our knowledge, none with such 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.

Key words: Tuberculous panniculitis; sporotrichoid; Mycobacterium bovis; intravesical BCG instillations.
Case report

An 82-year-old man presented to our outpatient dermatology 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 developed in November 2019 in a context of 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 no gardening nor specific outdoor activities. He had recently been diagnosed with a Waldenström disease that could partly explain his general symptoms and 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 1AB). There was no clinical evidence of inguinal lymphadenopathy. The sporotrichoid disposition of these lesions (Figure 1B) suggested the 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 CT-scanner 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. The PCR was positive for tuberculous mycobacteria. The culture later allowed the more specific identification of Mycobacterium bovis. A thoracic CT scanner showed no sign of latent nor active pulmonary tuberculosis.

Treatment combining Isoniazide, Rifampicine, Pyrazinamide and Ethambuthol was initiated. However, Pyrazinamide was rapidly suspended after precise identification of Mycobacterium bovis and Ethambutol was stopped after 4 months due to ophthalmologic toxicity. Isoniazide and Rifampicine were continued for 8 additional months. Under treatment, the skin lesions and the oedema resolved (Figure 1C), the patient’s weight stabilized and his general state greatly improved.
Discussion

Cutaneous involvement of tuberculosis infections is rare, representing only 1 to 2 % of the extrapulmonary cases. The causative microbial agent is mostly *Mycobacterium tuberculosis* but *M. bovis* has also been described as a potential pathogen [1]. Clinical presentation varies greatly according to the dissemination pattern of tuberculous mycobacteria: exogenous direct inoculation, secondary dissemination from an endogenous contiguous source (e.g. scrofuloderma) or haematological dissemination (e.g. miliary tuberculosis) [1]–[3]. Lymphatic dissemination, associated with a sporotrichoid distribution of lesions, is unusual and is more generally observed with non-tuberculous mycobacteria [2] or other microorganisms including sporotrichosis, nocardiosis, leishmania and pyogenic or deep fungal infections [4]. Most reported cases of sporotrichoid tuberculosis are secondary to a primary cutaneous entry point and then spread through the lymphatic system in a linear way, but reverse sporotrichoid spreading forms, emanating from an endogenous source, have also been described [4]. In our case, 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 a 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 *Mycobacterium bovis* to generate a local immune response of the host against neoplastic cells [5]. Despite the frequently reported immediate local sides effects (chemical cystitis, hematuria, pollakiuria, incontinency), it remains a generally well tolerated and effective treatment. Secondary mycobacterial infections are rare but well known complications [5]. 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) [6], [7]. Isolated skin involvement is unusual and has only been reported in a few cases, presenting as unique nodules, abscesses or plaques [6], [8]–[11]. To our knowledge, there are no reports of sporotrichoid distributed panniculitis lesions.

Identified risk factors for secondary BCG infections are immunosuppression, advanced age and traumatic instillation or prior urothelial lesions [5]. At least two of these risk factors were encountered in our 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 [7]. 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 first intravesical BCG instillation) [12]. In a literature review, Cabas et al. later confirmed the observed trend [7] but used the time from last instillation as a reference for categorization, with no clear timing threshold set. However, cutaneous involvements were not considered, probably because of the scarcity of reported cases. In our patient, the lesions appeared more than 3 years after initiation of BCG immunotherapy and 6 months after the last maintenance instillation, suggesting that skin should be considered as a possible organ involved in late infections. This delayed onset could be partly explained by the recent immunosuppression of our 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 [1] and the difficulty in identifying mycobacteria [13]. Special stains, culture or PCR testing often reveal negative results, requiring repeated biopsies and leading to delayed diagnosis [13]. In our case, 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 *Mycobacterium bovis* is known to be intrinsically resistant to Pyrazinamid, the commonly reported treatment for infectious complications following BCG immunotherapy involves 2 months of combined therapy with Isoniazide, Rifampicine and Ethambutol followed by 7 months of Isoniazide and Rifampicine [7]. Prolonged treatment was proposed to our patient because of his immunodepressed status. It allowed a rapid recovery.

**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. It 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.
Declaration of interests

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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Ethical approval

Ethical approval is not applicable.

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References


**Figure 1.** Clinical presentation when patient presented to the dermatology outpatient clinic showing a unilateral oedema of the right lower limb (A) overlaid with multiple inflammatory subcutaneous nodules distributed in a linear way 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).

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