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SHORT COMMUNICATION

Pseudo-Behçet's disease associated with tuberculosis: a case report and review of the literature

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Abstract Orogenital ulcer is one of the clinical manifestations of Behçet's disease (BD). However, orogenital ulcer may be observed in various conditions, such as complex aphthous dermatitis and herpes simplex virus infections. Therefore, orogenital ulcer along with skin lesions, including acne or erythema nodosum, may be misdiagnosed as BD, but is actually pseudo-BD instead. We report here a case of pseudo-BD due to *Mycobacterium tuberculosis* infection in which anti-tuberculous treatment resulted in complete resolution. Furthermore, we review the literature regarding the association of BD and *M. tuberculosis* infection.

Keywords Behçet's disease · Pseudo-Behçet's disease · Orogenital ulcer · *Mycobacterium tuberculosis*

Introduction

Extrapulmonary manifestations of tuberculosis (TB) may occasionally be difficult because aseptic clinical symptoms occur in different organs distant from infected organs. Aseptic inflammatory arthritis and aseptic skin lesions are called Poncet's disease [1] and tuberculids [2], respectively. These are considered to be hypersensitivity reactions to *Mycobacterium tuberculosis*. We report a case of tuberculous lymphadenitis with recurrent orogenital ulcerations, erythema nodosum-like skin lesions, and migratory arthralgia, which was initially diagnosed as Behçet's disease (BD). However, all of the patient's clinical symptoms disappeared after anti-TB treatment.

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Case report

A 45-year-old woman presented with recurrent oral ulcers for 3 years, recurrent genital ulcers, and erythema nodosum-like skin lesions for 1 year. She had fever and migratory arthralgia, and visited a general hospital. Minor multiple ulcerations were observed on the oral mucosa and multiple erythema nodosum-like skin lesions on her lower legs. She was referred to a gynecologist for recurrent and painful genital ulcers. A physical examination revealed minor multiple ulcerations on the labia minora and vaginal vestibule. No eye problems were detected. She was diagnosed with BD and treated with non-steroidal anti-inflammatory drugs and topical corticosteroid with no effect. She was referred to our hospital for further examination. On physical examination, her left cervical and supraclavicular lymph nodes were swollen, and erythema nodosum-like skin lesions on her lower legs and nodules with crust on the extensor surface of her knees were observed (Fig. 1). Arthritis in the fifth proximal interphalangeal joint on the left hand and in the fourth metatarsophalangeal joint in her left foot was also observed. She previously had a Bacillus Calmette–Guérin vaccination, and there was no medical history of TB. Laboratory tests were unremarkable except for a slightly elevated C-reactive protein level (0.6 mg/dl) and erythrocyte sedimentation rate of 40 mm/h.

Rheumatoid factor, anti-cyclic citrullinated peptide antibodies, and anti-nuclear antibodies were negative. The histocompatibility leukocyte antigen (HLA) type was B13 and B65, and a pathergy test showed negative results. However, the Mantoux test and interferon-γ releasing assay by means of QuantiFERON TB Gold (Cellestis Ltd, Carnegie, Australia, via BCG Supply Ltd, Tokyo, Japan) showed positive results. Contrast-enhanced computed tomography indicated left cervical, supraclavicular, and axillary lymph node swelling (Fig. 2). A biopsy from the left cervical lymph node showed granulomatous inflammation with caseous necrosis and multinucleated giant cells, indicating tuberculous lymphadenitis (Fig. 3). A skin biopsy from a nodule on the knee showed multiple epithelioid granulomas, indicating papulonecrotic tuberculid. Although polymerase chain reaction analysis of *M. tuberculosis* using tissue samples from the lymph node and skin did not indicate positive results, treatment with rifampicin, isoniazid, ethambutol, and pyrazinamide completely improved her symptoms and she has been asymptomatic for 40 months after treatment.

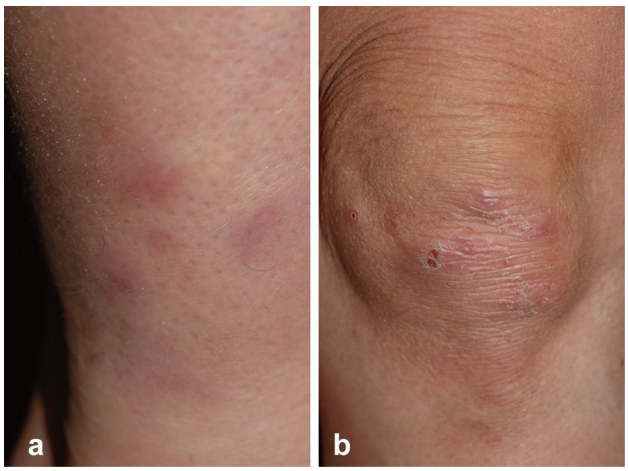

Fig. 1 Erythema nodosum-like skin lesions on the patient's lower legs (**a**) and nodules with crust on the extensor surface of her knees (**b**) were observed

Discussion

The clinical manifestations of the present case satisfy the diagnostic criteria of the International Study Group for BD [3]. However, all of her symptoms completely resolved after anti-TB therapy. Therefore, we concluded that she suffered from pseudo-BD. Pseudo-BD is a condition resembling BD in various diseases presenting with oro-genital syndrome. A previous review regarding pseudo-BD mentioned that some diseases, such as complex aphthous dermatitis, herpes simplex virus infections, inflammatory bowel disease, and Reiter's syndrome, could also be diagnosed as BD [4]. The characteristic features of orogenital ulcerations of BD are difficult to distinguish from these diseases. Ulcers can be small (minor ulcers, <1 cm), large

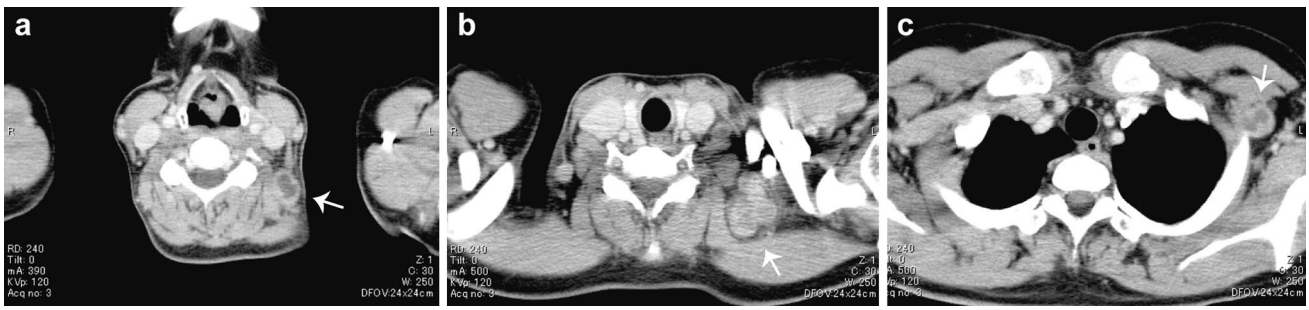

Fig. 2 Contrast-enhanced computed tomography shows left cervical (**a**), supraclavicular (**b**), and axillary lymph node (**c**) swelling

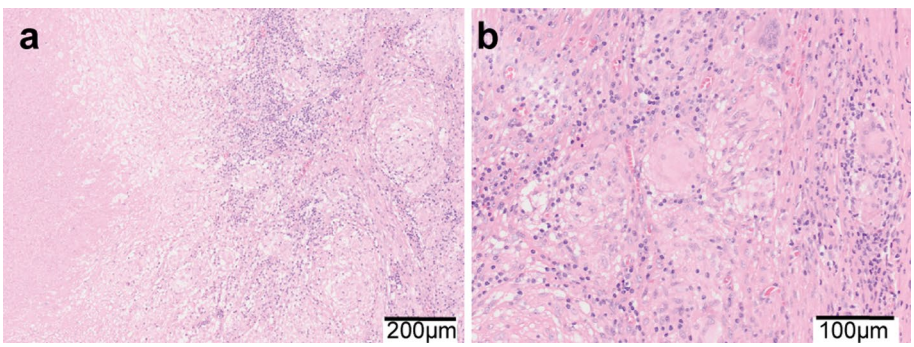

Fig. 3 Hematoxylin–eosin-stained histopathological images. Lymph node biopsy from the left cervical lymph node shows chronic granulomatous inflammation with caseous necrosis and multinucleated giant cells. **a** Low-power (original magnification, ×40) and **b** high-power (original magnification, ×100) magnification

Table 1 Characteristics of nine cases of TB associated with pseudo-Behçet's or BD

Age (y)/sex (references)	Diagnosis	Orogenital ulcer	Eye lesions	Skin lesions	Arthritis	Resolution of Behçet's symptoms with TB drugs	Diagnosis
45/F our case	Lymphadenitis	+	−	EN, nodules	+	Complete resolution of all symptoms after anti-TB therapy	Pseudo-BD
45/M [6]	Papulonecrotic tuberculid	+	Conjunctivitis	EN	+	Complete resolution of all symptoms after anti-TB therapy	Pseudo-BD
25/F [7]	Pulmonary TB	+	nd	Acneiform nodules	nd	TB occurred after thalidomide therapy for probable Pseudo-BD. Anti-Tb therapy resulted in complete resolution of all symptoms	Pseudo-BD (probable)
21/F [7]	Miliary TB lymphadenitis	+	Episcleritis with uveitis	EN	+	TB occurred after thalidomide and steroid therapy for probable Pseudo-BD. Anti-TB therapy resulted in complete resolution of all symptoms	Pseudo-BD (probable)
37/F [8]	Pulmonary TB	+	Uveitis	EN	nd	3 years after anti-TB therapy, BD was diagnosed. TB and BD recurred after 6 months' cessation of steroid therapy for BD. Anti-TB therapy resulted in a good prognosis†	BD + TB
28/F [8]	TB pleuritis	+	Uveitis	EN	+	TB occurred 2 years after steroid therapy for BD. Anti-TB therapy resulted in a good prognosis†	BD + TB
31/F [8]	Pulmonary TB	+	Uveitis	Pustules, thrombophlebitis	+	TB occurred 2 months after cessation of steroid therapy for BD. Anti-TB therapy resulted in a good prognosis†	BD + TB
35/F [9]	Pulmonary TB	+	nd	EN	+	TB was diagnosed soon after colchicine treatment. Anti-TB therapy resulted in a good prognosis, except for orogenital ulcer	BD + TB
38/F [10]	Lymphadenitis	+	−	EN	+	TB was diagnosed after colchicine, steroids, and azathioprine treatment for intractable BD. Anti-TB therapy resulted in a good prognosis except for oral ulcers and arthritis	BD + TB

TB tuberculosis, *BD* Behçet's disease, *EN* erythema nodosum, *nd* not described

† The prognosis of BD was not described in detail

(major ulcers, >1 cm), or occasionally herpetiform. Oral ulcers normally occur on the gingival and buccal mucosa, tongue, and lips, although ulcers can also appear in the soft and hard palate, pharynx, and tonsils. Genital ulcers resemble oral ulcers in appearance, are usually painful, and, when deep, may heal with scarring. Genital ulcers in females affect the vulva and vagina, and occasionally, the cervix. However, making a diagnosis based on the appearance of genital ulcers on examination is difficult [5].

TB patients with BD-like symptoms can be classified into two types of pathological conditions (Table 1). One condition can be diagnosed as pseudo-BD, similar to our case, because BD-like symptoms achieved complete remission by anti-TB therapy [6, 7]. The other condition leads to incomplete recovery, although some clinical symptoms are improved by anti-TB therapy [8–10]. In these cases, TB might act as an aggravating factor for BD. Two cases reported by Hamill et al. [7] were first treated by thalidomide based on the diagnosis of BD. However, the development of TB and disappearance of all BD symptoms after anti-TB therapy suggested the possibility of pseudo-BD.

Reactive arthritis associated with TB has been reported, which is known as Poncet's disease [11]. Erythema nodosum is observed in 6 % of patients as an extra-articular lesion of Poncet's disease. Although recurrent orogenital ulcers have not been described in Poncet's disease, Poncet's disease presenting as pseudo-BD was reported recently [6].

The pathogenesis of BD (pseudo-BD) and TB is still unknown. Three cases reported by Efthimiou et al. [8] were HLA-B5 positive. They discussed that BD and TB may have a common genetic background, and BD itself may produce a defect in cell-mediated immunity, which increases the individual susceptibility to TB. Two cases reported by Hamill et al. [7] were HLA-B51 negative. They discussed that orogenital ulcer is mediated by cross-reactivity between microorganism antigens and mucosal protein, possibly acting via the 65-kD heat shock protein (HSP65) of *Mycobacterium*.

HSP65 antigens obtained from *Mycobacterium* have been reported to have a high homology with human protein 60-kD HSP (HSP60) [3, 12]. HSP60 is mainly expressed in mitochondria. However, during stress, there is intracellular redistribution of HSP60 and cell surface expression. Local HSP60 overexpression is present in recurrent oral ulcerations of BD and in the epidermal regions of erythema nodosum and papulopustules in BD [12].

Conclusion

We describe a case of pseudo-BD during a course of tuberculous lymphadenitis. A precise diagnosis for BD is difficult because of an absence of specific diagnostic markers for BD and the unspecific combinations of clinical symptoms. TB should always be considered in the clinical setting in case of conditions mimicking BD, such as arthritis, orogenital ulcers, and erythema nodosum-like skin lesions.

Conflict of interest There is no financial support or other benefits from commercial sources for the work reported on in the manuscript, or no other financial interests that any of the authors may have, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

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