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Uveitis developing in tuberculous lymphadenitis-associated Behçet's disease during anti-tuberculosis therapy

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Keywords
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Abstract

Behçet's disease (BD) is thought to be elicited by triggers such as tuberculosis (TB) infection in individuals with genetically aberrant immune activity, although the exact pathogenesis remains unknown. Seven cases of BD thought to be triggered by TB have been reported to date. In all cases, Behçet's symptoms improved smoothly after starting TB treatment. We present the first report of uveitis developing two months after starting TB treatment in a 46-year-old woman with tuberculous lymphadenitis presenting with oral and genital ulcers and erythema nodosum-like lesions on diagnosis of TB. The appearance of uveitis was attributed to a paradoxical reaction in TB because of simultaneous relapse of lymphadenopathy and retinal findings on fluorescein angiography. Although rare, physicians should be aware that ocular involvement can occur during anti-TB therapy, most likely with extrapulmonary TB, because ocular involvement may decrease patient quality of life if visual symptoms become irreversible with delayed diagnosis and treatment.

Introduction

Behçet's disease (BD) is a syndrome characterized by four major symptoms: recurrent oral aphthae, genital ulcers, skin lesions, and eye lesions. The exact pathogenesis of BD is unknown, but immunological abnormalities due to genetic predispositions such as human leukocyte antigen (HLA)-B51 are considered to be involved, and abnormal activation of innate and acquired immunity is triggered by environmental factors such as tuberculous infection [1]. Cross-immunoreactivity is reportedly induced against host heat shock protein (HSP) 60, which is highly homologous with the mycobacterial 65-kDa HSP in patients presenting with tuberculosis (TB)-associated BD [2]. TB infection is known to cause reactive lesions (an arthritis known as Poncet's disease, erythema induratum of Bazin, or uveitis) and paradoxical reactions. Seven cases of TB-associated BD have been reported to date [3–9]. All Behçet's symptoms in these seven cases showed smooth improvement after starting anti-TB drugs with or without treatment for BD. We present the first report of uveitis developing in tuberculous lymphadenitis-associated BD accompanied by paradoxical reaction in TB.

Case Report

A 46-year-old woman presented with a smoking history of 40 pack-years, left cervical adenopathy of unknown cause at 12 years, and oral abscess at 15 years. She had a one-month history of low-grade fever, recurrent oral aphthae, pain in the peripheral extremities, and erythema nodosum-like lesions on the extremities. Genital ulcers and flare swelling of both ankle joints appeared one week prior to presentation. She had lost 3 kg in the preceding month and visited our hospital for further examination and treatment. Body temperature was 37.7°C and blood testing showed: white blood cell count, 4800/μL; C-reactive protein (CRP), 5.8 mg/dL; soluble interleukin-2 receptor, 770 U/mL; and angiotensin-converting enzyme, 9.5 U/L. Positive results were identified for quantiferon. Results for *Treponema pallidum* antibody, rapid plasma reagin, HIV

antigen–antibody combination assays, herpes simplex virus immunoglobulin (Ig) M, and varicella zoster virus IgM were all negative. Imaging with ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) showed increased FDG uptake in enlarged lymph nodes of the right supraclavicular, mediastinal, and hilar regions (Fig. 1A). Endobronchial ultrasound-guided transbronchial needle aspiration was performed the next day (day 1). Mycobacteria and caseating granuloma were detected in biopsied lung tissue, and polymerase chain reaction (PCR) of the tissue yielded positive results for TB. Tuberculous lymphadenitis was therefore diagnosed. Four anti-TB drugs (isoniazid, 300 mg/day; rifampin, 600 mg/day; ethambutol, 750 mg/day; and pyrazinamide, 1500 mg/day) were started on day 3. Ophthalmological evaluation revealed no ocular lesions. BD was diagnosed and colchicine was started at 0.5 mg/day on day 4, increasing to 1 mg/day after one week. Celecoxib was also used at 400 mg/day. The patient showed an HLA type of A24, 33; B44, 62. After colchicine was started, the patient reported that her ankles still hurt, although fever and skin eruptions were alleviated. Prednisolone was therefore started at 20 mg/day. However, she reported pain in the limbs and trunk after starting prednisolone, and prednisolone was therefore discontinued. On day 21, *Mycobacterium tuberculosis* was identified from lung tissue cultures and confirmed as a drug-sensitive strain. Blurred vision developed on day 42, and an ophthalmologist diagnosed bilateral retinal phlebitis from fluorescein angiography on day 49. On day 56, blood testing again showed rising CRP, and CT showed mediastinal and hilar lymph nodes larger than at the start of treatment (Fig. 1B, C). A paradoxical reaction was suspected, and TB treatment was continued. Intravenous infliximab was started at 300 mg (5 mg/kg body weight) to treat ocular symptoms, as she did not wish to resume prednisolone. TB was treated for a total of nine months, and CT at the end of TB treatment showed marked reductions in sizes of the mediastinal and hilar lymph nodes (Fig. 1D). Colchicine, infliximab, and celecoxib have been continued for BD. Behçet's symptoms have been recurring, but remain alleviated.

Discussion

This is the first report of uveitis developing in tuberculous lymphadenitis-associated BD after starting anti-TB drugs. Development of uveitis was attributed to a paradoxical reaction by the TB, because of the simultaneous relapse of mediastinal and hilar lymphadenopathy, and retinal phlebitis rather than capillaritis on fluorescein angiography. Meanwhile, we concluded the patient had BD, as Behçet's symptoms have been recurring despite completing anti-TB therapy and infliximab was effective in alleviating these symptoms.

Paradoxical reactions reportedly occur in 3–14% of TB patients and appear more likely to arise in patients with extrapulmonary TB or in HIV-positive patients. Such reactions often appear as an exacerbation of the primary lesion, but 25% of cases show development of new lesions [10]. Two previous reports have described the development of new ocular lesions due to paradoxical reactions. One case involved tuberculous lymphadenitis without any Behçet's symptoms at diagnosis [11], while another case involved pulmonary TB with neuro-Sweet disease diagnosed simultaneously [12]. TB infection has been reported as a trigger for the development of BD, and seven cases of TB-associated BD have been reported. Previous reports (Table 1) suggest that Behçet's symptoms associated with TB infection are more likely to occur with extrapulmonary TB, and the

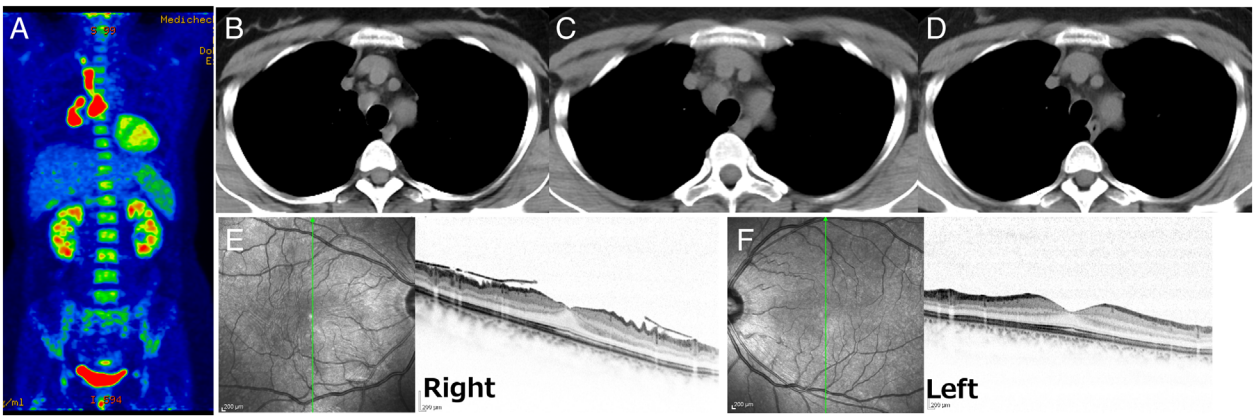

Figure 1. (A) Image from positron emission tomography/computed tomography (PET/CT) at the time of diagnosis. ^{18}F-fluorodeoxyglucose (FDG) has accumulated in the right supraclavicular, mediastinal, and hilar lymph nodes. (B) Mediastinal lymph nodes two days before starting tuberculosis (TB) treatment. (C) Mediastinal lymph nodes on day 56. Note the nodes are larger than before starting TB treatment. (D) Mediastinal lymph nodes at the end of TB treatment. (E) Optical coherence tomography of the right eye on day 49 shows the surface of the retina is distorted and an epiretinal membrane is present. (F) Optical coherence tomography of the left eye on day 49 shows the surface of the retina is slightly distorted.

Table 1. Previous reports of TB-associated BD.

References	Age	Sex	Oral ulcers	Skin lesions	Genital ulcers	Eye lesions	Type of HLA	Manifestation of TB	Behçet's symptoms after initiating TB treatment	Treatment of BD	History of diagnosis
[3]	45	F	+	+	+	Uveitis	B27	Lymphadenitis	Disappeared	None	The diagnosis was cutaneous TB with BD-like symptom
[4]	45	M	+	+	+	Conjunctivitis	Not described	Cutaneous	Disappeared	None	The diagnosis was cutaneous TB with BD-like symptom
[5]	38	F	+	+	+	−	B51	Lymphadenitis	Improved	Colchicine	BD was diagnosed and treatment was started. But, her symptoms did not improve, and then TB was diagnosed by further examination
[6]	45	F	+	+	+	−	B13, B65	Lymphadenitis	Disappeared	NSAIDs, topical steroid	BD was diagnosed and treatment was started. But, her symptoms did not improve, and then TB was diagnosed by further examination
[7]	70	F	+	−	−	−	B51	Cutaneous	Improved	Prednisolone	TB and BD were diagnosed simultaneously
[8]	35	F	+	+	+	−	A11, A29, B12, B14	Pulmonary	Improved	Colchicine	TB and BD were diagnosed simultaneously
[9]	48	M	+	+	+	−	A24, B7, B52	Lymphadenitis	Improved	NSAIDs, topical steroid	TB and BD were diagnosed simultaneously
Our case (2020)	46	F	+	+	+	− → + Uveitis	A23, A24, B44, B62	Lymphadenitis	Uveitis developed two months after starting TB treatment. Symptoms have been alleviated but recurring	Colchicine, NSAIDs → added infliximab for uveitis	TB and BD were diagnosed simultaneously

BD, Behçet's disease; NSAID, non-steroidal anti-inflammatory drugs; TB, tuberculosis.

occurrence of these symptoms does not appear to depend on the HLA subtype. In two cases, Behçet's symptoms disappeared after anti-TB therapy alone. In the remaining five patients, Behçet's symptoms improved smoothly after treatment for TB and BD. Uveitis developing in TB-associated BD after starting anti-TB drugs has not previously been reported, making this report the first.

TB can cause BD or reactive lesions (e.g. erythema induratum and uveitis), probably depending on the immune response of patients. Reactive lesions that meet the diagnostic criteria for BD and improve with treatment for TB alone are called "pseudo-BD". Paradoxical reaction in TB can also cause pseudo-BD. Causes of the differences between BD and pseudo-BD have yet to be clearly elucidated.

Regarding uveitis in our patient, although uveitis due to rifabutin is well known, uveitis due to the first-line anti-TB drugs administered to this patient has not been reported. Judging from the fact that uveitis persisted after discontinuation of anti-TB drugs, the uveitis in this patient was considered unlikely to be drug-induced.

Although rare, physicians should be aware that ocular involvement can occur during anti-TB therapy, most likely in extrapulmonary TB, because ocular involvement may decrease quality of life for patients if symptoms become irreversible following delays in diagnosis and treatment.

Disclosure Statements

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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