A Case of Scrofuloderma in a Patient on JAK Inhibitor Treatment for Rheumatoid Arthritis

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A 78-year-old woman with rheumatoid arthritis, who was started on baricitinib five or six months earlier, was referred to our hospital due to a subcutaneous abscess in her right axilla. Contrast-enhanced chest, abdomen, and pelvis computed tomography showed subcutaneous abscesses in her right axilla and lymphadenopathy with calcification. Cultures from the subcutaneous abscess and skin biopsy specimens were positive for *Mycobacterium tuberculosis*. These findings led to the diagnosis of scrofuloderma associated with tuberculous lymphadenitis.
She was started on an antitubercular regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol as the initial phase treatment (first 2 months), followed by isoniazid and rifampicin for 4 months (total 6 months). After 6 months of antitubercular treatment, the abscesses and lymphadenitis disappeared.
Although cases of tuberculosis during JAK inhibitor treatment are rare, they are serious adverse events that require caution.

Key words: scrofuloderma, JAK inhibitor, tuberculous lymphadenitis, baricitinib, cutaneous tuberculosis

INTRODUCTION

JAK inhibitors (JAKis) have been used worldwide for the past 10 years. In Japan, tofacitinib was approved for rheumatoid arthritis in 2013, followed by baricitinib in 2017, peficitinib in 2019, and upadacitinib and filgotinib in 2020. In dermatology, several JAKis are indicated for the treatment of atopic dermatitis, psoriasis, and alopecia areata (baricitinib for atopic dermatitis and alopecia areata, upadacitinib for atopic dermatitis and psoriatic arthritis, abrocitinib for atopic dermatitis, and deucravacitinib for psoriasis vulgaris, pustular psoriasis, and psoriatic erythroderma).

Baricitinib and other JAKis should not be used in patients with active tuberculosis [1], for which they are contraindicated. Baricitinib suppresses cytokines such as interferon (IFN)γ and interleukin (IL)-6 [2], whereas in tuberculosis infection, macrophage activation by IFNγ results in sterilization and decomposition via autophagosome formation. Baricitinib may contribute to the development of tuberculosis because it suppresses these factors. Tuberculosis of the skin is a relatively rare manifestation with a wide spectrum of clinical findings. Scrofuloderma is one of the forms of cutaneous tuberculosis caused by *Mycobacterium tuberdulosis* or *Mycobacterium bovis*, that is the result of contiguous spread to the overlying skin from adjacent structures such as a lymph node, joint, bone, or the epididymis [3].

Herein, we report a case of scrofuloderma on JAKi treatment for rheumatoid arthritis along with a review of relevant literature because the dermatological use of JAKis is expected to increase in the future.

CASE REPORTS

A 78-year-old Japanese woman was referred to our hospital due to a subcutaneous abscess in her right axilla that had developed two months earlier. She had developed polyarthritis four years earlier and was diagnosed with rheumatoid arthritis at another hospital. Her initial treatment with oral salazosulfapyridine was ineffective, so she was started on baricitinib treatment several months ago. Before initial treatment of baricitinib, chest X-ray showed no abnormallity. However, neither Interferon gamma release assay nor tuberculosis skin test was performed by previous doctor. On referral, the initial examination showed a round, elastic soft, subcutaneous mass with a conical nodule and an ulcerated apex in the right axilla (Fig. 1). The laboratory findings were as follows: white blood cell count, 10,000/μl; lymphocyte count, 2,230/μl; C-reactive protein, 4.13 mg/dl; soluble interleukin-2 receptor, 1,410 U/ml; β-D-glucan, 2.9 pg/ml; and tuberculosis IFNγ-release assay, indeterminate. The test for HIV was negative. On contrast-enhanced chest, abdomen, and pelvis computed tomography (CT), right axillary lymphadenopathy, calcification, and subcutaneous ab-

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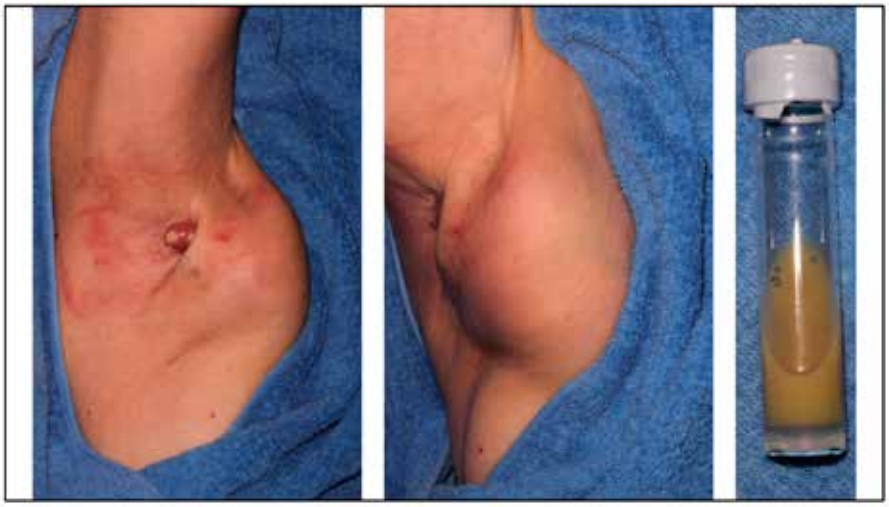

Fig. 1 A round shaped, elastic soft subcutaneous mass with a conical nodule with an ulcerated apex was observed in her right axilla.

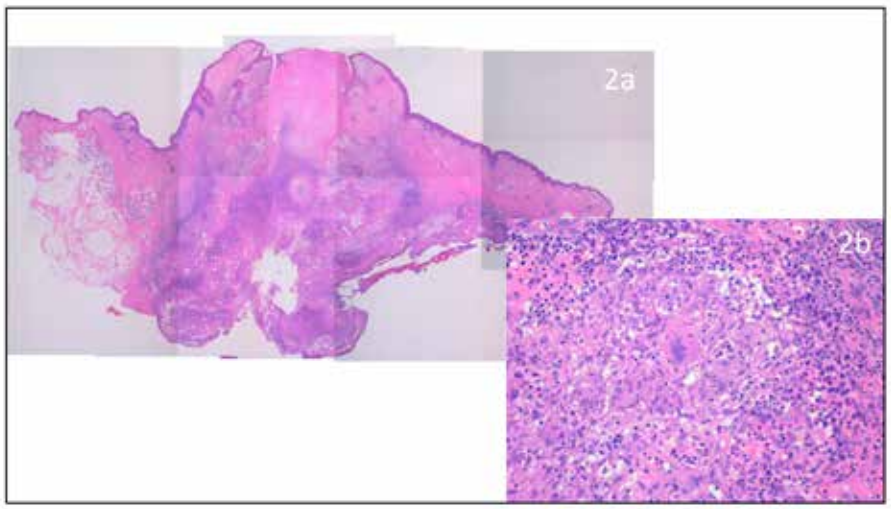

Fig. 2a Hematoxylin-eosin-stained specimen showing the epidermis was ulcerated and caseous necrosis surrounded by inflammatory cells was observed (loupe image).

2b Epithelioid cell granulomas and multinucleated giant cell (original magnification × 100).

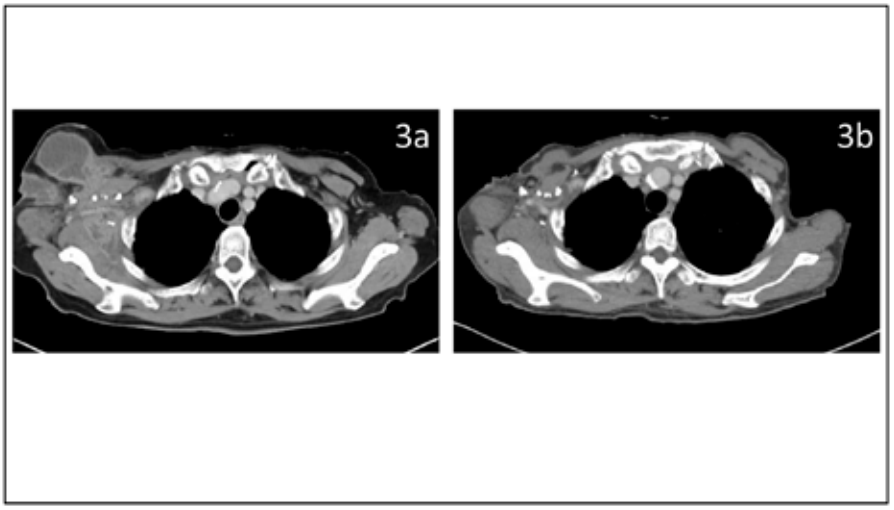

Fig. 3a Initial contrast-enhanced chest CT with some subcutaneous abscesses and lymphadenopathy with calcification in her right axillary.

3b 6 months after her initial treatment. The lymphadenopathy and subcutaneous abscesses disappeared.

scess were seen, with no obvious infection in the lung fields or other organs. On histopathological examination, an ulcer and epithelioid cell granulomas with multinucleated giant cells and caseous necrosis in the dermis to the subcutaneous tissue were seen (Fig. 2a, b). Ziehl-Neelsen staining was negative. Subsequent cultures from the subcutaneous abscess and skin biopsy specimens were positive for *Mycobacterium tuberculosis*. Together, these findings led to the diagnosis of scrofuloderma associated with tuberculous lymphadenitis.

Baricitinib was discontinued after obtaining the agreement of the family rheumatologist, and an incisional drainage procedure was performed in the axilla. The patient was given a standard first-line oral regimen of extrapulmonary tuberculosis treatment (oral administration of 300 mg/day isoniazid, 600 mg/day rifampicin, 1,000 mg/day pyrazinamide, and 1,000 mg/day ethambutol for 2 months, followed by oral administration of 300 mg/day isoniazid and 600 mg/day rifampicin for 4 months). Six months after her initial treatment for tuberculosis, the mass in her right axilla flattened, and the lymphadenopathy and subcutaneous abscesses disappeared (Fig. 3). Her course after her anti-tuberculosis treatment was uneventful.

DISCUSSION

Cutaneous tuberculosis is a rare clinical manifestation of *Mycobacterium tuberculosis* or *Mycobacterium bovis* infection [3]. It occurs in approximately 1 to 2% of all tuberculosis patients [3]. Cutaneous tuberculosis is diagnosed by the detection of *Mycobacterium tuberculosis* on the affected skin lesions. On the other hand, tuberculids represent hypersensitivity reactions to mycobacterial antigens, and no *Mycobacterium tuberculosis* is detected in the skin lesions [3]. Cutaneous tuberculosis includes scrofuloderma, lupus vulgaris, and tuberculosis verrucosa cutis, with scrofuloderma being the most common. Scrofuloderma is one of the forms of cutaneous tuberculosis that is the result of contiguous spread to the overlying skin from adjacent structures such as a lymph node, joint, bone, or the epididymis [3]. The most common sites of involvement are the neck, axillae, or groin. Scrofuloderma initially presents as a firm subcutaneous nodule or nodules that gradually enlarge, become confluent, ulcerate, and form draining sinus tracts of purulent or caseous material [3].

After *Mycobacterium tuberculosis* infection, it is phagocytosed by macrophages and the phagosome undergoes fusion with lysosomes, are sterilized and digested [4]. IFNγ is one of the most important cytokines for the immune response to *Mycobacterium tuberculosis*. It promotes macrophage activity, resulting in sterilization via autophagosome formation. Acquired defects in the IFNγ pathway, such as production of autoantibodies to IFNγ, were found in patients with severe, unexplained nontuberculous mycobacterial infection [2]. As such, IFNγ is a very important cytokine for the immune response to intracellular parasites such as *Mycobacterium tuberculosis*.

Signaling by IFNγ and IL-6 is mediated by JAK1/JAK2 [5], whereas baricitinib inhibits JAK1/JAK2. Cytokines suppressed by baricitinib include IL-2, IL-6, IL-10, IFNγ, and G-CSF [6, 7]. Therefore, it should be noted that tuberculosis infection and latent tuberculosis infection can occur because of IFNγ suppression by baricitinib. One patient was found to be infected with tuberculosis (miliary tuberculosis of the lungs) in the RA-BUILD Phase 3 trial [8]. In some clinical trials of baricitinib in Japan and other countries, five patients with disseminated tuberculosis, four patients with tuberculosis, two patients with bone tuberculosis, one patient with extrapulmonary tuberculosis, and one patient with pulmonary tuberculosis for rheumatoid arthritis were reported [9], whereas no patients infected with tuberculosis were reported in six double-blinded, randomized clinical studies (phase 2: NCT02576938; phase 3: NCT03334396[BREEZE-AD1], NCT03334422[BREEZE-AD2], NCT03428100[BREEZE-AD4], NCT03435081[BREEZE-AD5], NCT03733301[BREEZE-AD7]), one long-term extension study that included both a randomized, double-blinded period (NCT03334435[BREEZE-AD3]) and an open-label period, and one open-label, long-term extension (NCT03559270[BREEZE-AD6]) study of baricitinib for atopic dermatitis [10]. No report has described the scrofuloderma on baricitinib treatment. Our case had no triggers for infection, such as any immunosuppressive agents except for baricitinib. In our case, scrofuloderma developed from tuberculous lymphadenitis because latent tuberculosis was not ruled out before she started treatment with baricitinib, and tuberculosis could occur because of IFNγ suppression by baricitinib. In the clinical trials of baricitinib for rheumatoid arthritis, atopic dermatitis, and alopecia areata, tuberculosis was observed only in patients with rheumatoid arthritis. The average age of patients with rheumatoid arthritis is older than that of those with atopic dermatitis [8, 10], and many of them use immunosuppressive agents. Therefore, it should be noted that excessive immunosuppression may occur when using baricitinib in rheumatoid arthritis, which could lead to tuberculosis infection.

Tuberculosis infection is a serious infectious disease, and, as in the present case, care is needed when treating elderly patients with JAKis. Screening for and treatment of latent tuberculosis infection prior to initiation of biological agents effectively decreases the active tuberculosis rate [11], and, similarly, it is essential to screen for latent tuberculosis infection before JAKis are prescribed.

In conclusion, it is necessary to pay attention to tuberculosis infection and monitor for it before and during the use of JAKis, especially in elderly patients.

CONFLICTS OF INTEREST STATEMENT

None declared.

ETHICS STATEMENT

The patient in this manuscript have given informed consent for publication of their case details.

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