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Single Case

Certolizumab Pegol-Induced Folliculitis-Like Lichenoid Sarcoidosis in a Patient with Rheumatoid Arthritis

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Keywords

Anti-TNF-α · Lichenoid sarcoidosis · Paradoxical reaction · Certolizumab pegol · Rheumatoid arthritis

Abstract

Anti-tumor necrosis factor α (TNF-α) biologic agents are used for treating refractory sarcoidosis. However, sarcoidosis-like epithelioid cell granulomas may develop during anti-TNF-α treatment. A 63-year-old man suffering from rheumatoid arthritis was treated with oral methotrexate and methylprednisolone for 4 years. He subsequently started biweekly subcutaneous injections of certolizumab pegol. Three months later, light red follicular papules developed on his chest and they spread over the trunk and bilateral upper arms. Histopathology of a lesion showed a sharply demarcated noncaseating epithelioid cell granuloma with multi-nucleated giant cells in the upper perifollicular area. The follicular papules subsided following discontinuation of certolizumab pegol. Folliculitis-like lichenoid sarcoidosis should be included among the adverse cutaneous reactions of anti-TNF-α treatment.

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Introduction

Anti-tumor necrosis factor α (TNF-α) therapy is effective for several immune-mediated inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel diseases, psoriasis, and sarcoidosis. However, anti-TNF-α agents may also paradoxically induce or exacerbate these inflammatory diseases. Herein, we present a case of paradoxical lichenoid sarcoidosis in a patient with rheumatoid arthritis who was treated with certolizumab pegol (CZP).

Case Report

A 63-year-old man had been suffering from rheumatoid arthritis for 4 years. He received oral methotrexate and methylprednisolone without satisfactory therapeutic response. Bi-weekly subcutaneous injection of CZP was added in September 2013. Three months later, he visited our clinic due to pruritic reddish eruptions on his chest. A physical examination revealed light red follicular papules that were approximately 2 mm in size on his chest. Topical and oral antibiotic therapies were not effective, and the skin lesions gradually spread over the trunk and bilateral upper arms (Fig. 1a, b). A skin biopsy of a papule disclosed a sharply demarcated non-caseating epithelioid cell granuloma with multi-nucleated giant cells in the upper perifollicular area. Considerable mononuclear lymphoid cells had infiltrated around the granuloma (Fig. 2). Neither Ziehl-Neelsen staining nor auramine staining identified any acid-fast bacilli. A blood test, chest roentgenographic examination, and computed tomography did not reveal any remarkable change. An ophthalmological examination did not reveal any signs of ocular sarcoidosis or tuberculosis (TB). The patient's serum angiotensin-converting enzyme level was normal. The tuberculin skin test and interferon-gamma release test (QuantiFERON® TB-Gold) results were marginally positive (10 × 10 mm and 0.10 IU/mL, respectively). These findings suggested the diagnosis of lichen scrofulosorum. We discontinued CZP and started anti-TB therapy. The follicular papules began to subside. However, at 8 weeks following the initiation of anti-TB therapy, exudative erythema developed with histopathological findings of epidermal spongiosis and massive dermal eosinophilic infiltration. A drug-induced lymphocyte stimulation test for rifampicin was positive and the anti-TB therapy was discontinued. During the course of these events, the patient's rheumatoid arthritis worsened with marked arthralgia, which urged us to re-initiate the CZP therapy. Several follicular papules reappeared again, but they improved with topical glucocorticoid therapy. Eight weeks after starting the second CZP treatment, the patient developed arrhythmia and CZP was discontinued. The follicular papules gradually subsided and did not develop again. We finally diagnosed the skin lesions as lichenoid sarcoidosis.

Discussion

The patient's follicular papules were initially suspected to be superficial bacterial folliculitis. However, histopathology of the lesion disclosed a non-caseating epithelioid cell granuloma in the upper dermal perifollicular area, suggesting the diagnosis of lichen scrofulosorum. This was excluded because: (1) the patient did not develop TB during the oral

methotrexate and methylprednisolone therapy, suggesting that he did not have latent TB; (2) TB bacilli were never detected in the skin lesions; (3) no obvious systemic TB developed after the re-initiation of CZP therapy; (4) after cessation of the CZP therapy, the follicular papules subsided without anti-TB drugs; and (5) the follicular papules responded to topical glucocorticoid treatment. These findings together with the histopathology led to the diagnosis of CZP-induced lichenoid sarcoidosis.

Sarcoidosis is a multi-organ chronic inflammatory disease characterized by non-caseating epithelioid cell granulomas. TNF-α is among the key cytokines of granuloma formation, and anti-TNF-α treatment has been shown to be effective for refractory sarcoidosis [1, 2]. More than 50 cases of anti-TNF-α therapy-associated sarcoidosis have been reported [1]. In approximately 75% of the cases, the clinical presentation was systemic, mainly respiratory symptoms, such as dyspnea, chest pain, and cough. So far, 17 cases, including ours, of cutaneous non-caseating "sarcoidosis-like" granulomas with or without visceral involvement have been described (Table 1). The cutaneous manifestations include papules, nodules, plaques, subcutaneous masses, scar infiltration, and follicular papules (the current case). The time lapse between the initiation of anti-TNF-α treatment and the onset of sarcoidosis varies from 1 month to 4 years. However, in approximately half of the cases (9/17), granulomas developed within the first year of treatment.

In conclusion, we present the first case of rheumatoid arthritis with lichenoid sarcoidosis induced by the anti-TNF-α agent CPZ. The patient's skin lesions mimicked superficial folliculitis, which is relatively common in cases under immunosuppressive treatments. Folliculitis-like lichenoid sarcoidosis should also be considered in patients receiving anti-TNF-α treatment as adverse cutaneous reactions, especially when follicular papules do not respond to conventional anti-microbial treatment.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare no conflicts of interest.

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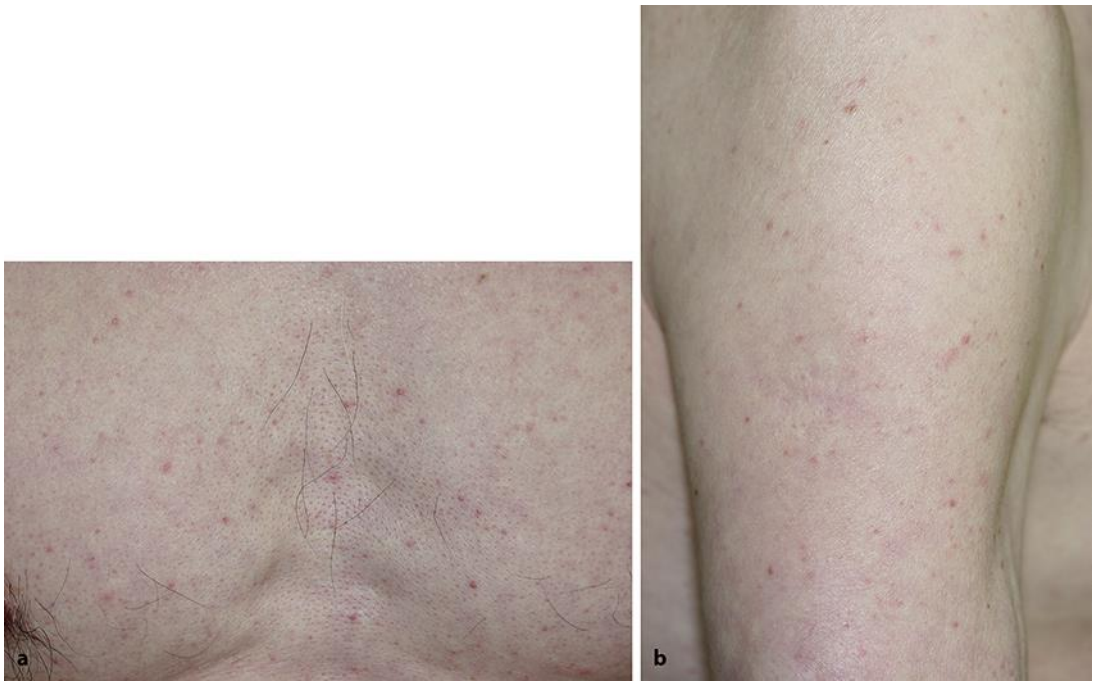

Fig. 1. Light red follicular papules of approximately 2 mm in size are distributed on the chest (**a**) and right upper arm (**b**).

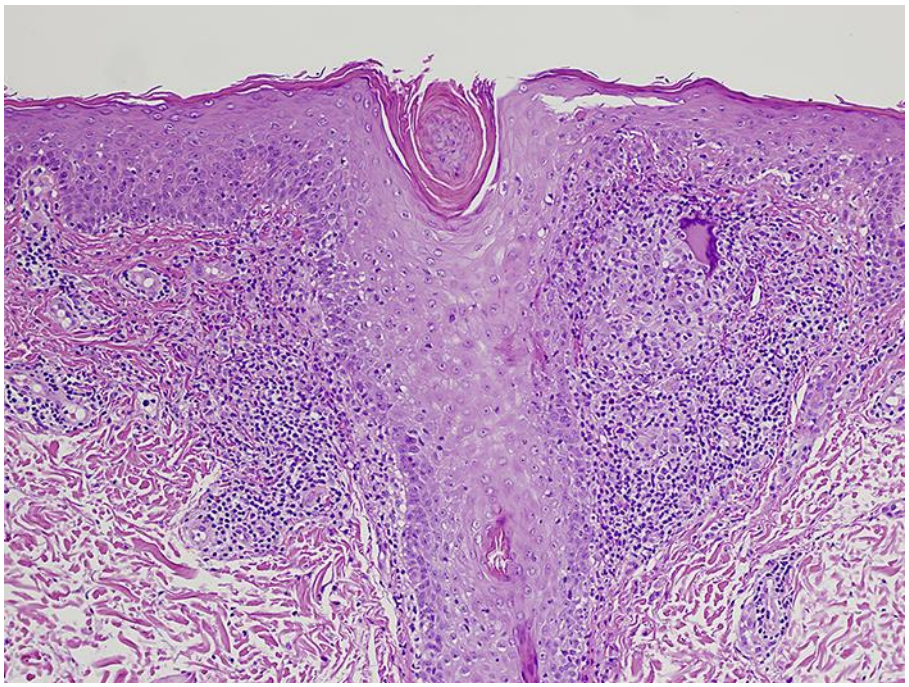

Fig. 2. A skin biopsy specimen taken from the patient's abdomen shows a sharply demarcated non-caseating epithelioid cell granuloma with multi-nucleated giant cells in the upper perifollicular area.

Table 1. Cases of cutaneous sarcoidosis during anti-TNF-αtreatment

First author [Ref.]	Anti-TNF-α agent	Age, years/ sex	Underlying disease	Time interval between treatment and onset	Clinical manifestations of the cutaneous granulomatous lesions	Other organ involvement
Peno-Green [3]	ETA	50/F	RA	2 months	Scattered nonpruritic skin lesions on the plantar surfaces of both feet and at the site of superficial scars on the extremities	Diffuse reticulonodular infiltrates in the mid- and lower lung zones
González-López [4]	ETA	70/M	AS	19 months	Firm, nontender, red-brown nodular lesions on the face	Bilateral hilar and paratracheal lymphadenopathy
Bachmeyer [5]	ETA	39/M	AS	1 month	Asymptomatic erythematous papules on a tattoo	No
Verschueren [6]	ETA	46/F	RA	12 months	A plaque lesion on the right forearm	Bilateral hilar and paratracheal lymphadenopathy
Daïen [7]	ETA	46/M	PsA	2 months	Three cutaneous nodules on the face	No
	ETA	72/F	RA	18 months	Inflammatory and painful scars	No
	IFX	54/F	AS	14 months	Brownish nodules on arms and legs	Basal infiltration and mediastinal lymph node
	ADA	53/F	RA	21 months	Nodules on lower limbs	Mediastinal lymph nodes and infiltrates
Dhaille [8]	IFX	47/M	PsA	4 months	Painful subcutaneous firm nodules on the right temple, palms, soles, knees, sternal area, and scars	No
	ADA	56/F	PJR	1 months	Red nodular lesions on the right forearm, ankles, and legs with increased redness of pre-existing scars	No
Takahashi [9]	IFX	35/M	CD	7 months	An infiltrated erythematous plaque on the right knee	Bilateral nodular infiltrates and miliary reticulonodular densities of the lung
Clementine [10]	IFX	49/F	RA	60 months	Multiple shiny violaceous erythematous papules on the left lower leg	Anterior uveitis, hilar and mediastinal lymphadenopathy, fibrotic lung disease
Burns [11]	ETA	59/F	RA	48 months	A subcutaneous mass measuring 4×7 cm on the left forearm and multiple smaller nodules on the distal upper extremities, knees, and buttocks	Pretracheal, subcranial, hilar and peribronchial adenopathy
Fok [12]	IFX	66/F	UC	23 months	Increased prominence of previous scars and several painful dermal nodules over the extensor surfaces of the upper and lower limbs	No
Lamrock [13]	ETA	56/F	PsA	9 months	Erythematous nodules on the knees and right elbow	No
Au [14]	ADA	49/F	Sarcoidosis	8 months	Multiple subcutaneous nodules on the arms and legs	Pulmonary sarcoidosis, costochondritis secondary to sarcoidosis
Present case	CZP	63/M	RA	3 months	Disseminated follicular papules on the trunk and arms	No

AS, ankylosing spondylitis; CD, Crohn disease; PJR, polyarticular juvenile rheumatoid arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis; ADA, adalimumab; CZP, certolizumab pegol; ETA, etanercept; IFX, infliximab.