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Case Report

Successful immunosuppressant-free treatment of a drug-induced sarcoidosis-like reaction caused by dupilumab

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ABSTRACT

We present a case of a drug-induced sarcoidosis-like reaction (DISR) in a 34-year-old female patient who had been receiving dupilumab for eosinophilic rhinosinusitis, for seven months. Computerized tomography scans revealed multiple lymphadenopathies, and biopsies performed on the lung and skin lesions showed the presence of non-caseating granulomas. The patient's serum levels of soluble interleukin-2 receptor and angiotensin-converting enzyme were elevated. There were no findings of *Mycobacterium* spp, or any other bacterial infections. Based on these findings, it was suspected that the sarcoidosis-like reaction observed in this patient was caused by dupilumab. Switching the patient's treatment from dupilumab to mepolizumab improved the DISR.

Abbreviations

DISR	drug-induced sarcoidosis-like reaction
IL:	interleukin
CT	computerized tomography
sIL2-R	soluble interleukin-2 receptor
ACE	angiotensin-converting enzyme
TNF-α:	tumor necrosis factor-α
HAART	highly-active antiretroviral therapy
BALF	broncho-alveolar lavage fluid
EBUS-TBNA	endoscopic bronchial ultrasound transbronchial needle aspiration
TBLB	transbronchial lung biopsy

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1. Introduction

A drug-induced sarcoidosis-like reaction (DISR) is a series of systemic granulomatous reactions which can be triggered by certain drugs. Some drugs that have been reported to cause DISRs include immune checkpoint inhibitors, TNF-α (tumor necrosis factor) inhibitors, interferons, and agents used in highly-active antiretroviral therapy (HAART) [1]. Dupilumab, a monoclonal antibody that targets the interleukin (IL)-4 receptor alpha chain, is commonly used to treat conditions such as asthma, atopic dermatitis, and chronic rhinosinusitis. Its efficacy is due to the blockade of IL-4 and IL-13 pathways, which are critical for type 2 inflammation [2]. Although, dupilumab has been associated with several adverse events such as injection-site reactions, ophthalmic complications, head and neck dermatitis, psoriatic skin lesions, progression of cutaneous T-cell lymphoma, alopecia areata, eosinophilia, and arthritis [3], only two cases of DISRs caused by dupilumab have been reported. In both these cases, the patients were treated with corticosteroids [4,5]. In this report, we present the first case of a DISR, related to the use of dupilumab that improved without immunosuppressive agents.

2. Case presentation

A 34-year-old female patient was referred to our hospital for investigation of multiple pulmonary nodules, which had been discovered during a regular medical check-up. No abnormal findings were noted in the chest X-ray examination, 12 months prior to her referral. She was being treated with dupilumab subcutaneous injections of 200 mg, every two weeks, for eosinophilic rhinosinusitis for seven months. Apart from a subcutaneous nodule, 10 mm in diameter, on the extensor surface of the right upper arm, which the patient had noticed six months prior to her referral, she complained of no other symptoms. Other than the subcutaneous nodule, the physical examination revealed no anomalous findings. Computerized tomography (CT) examination (Fig. 1), revealed random bilateral pulmonary nodules and multiple mediastinal lymphadenopathies. Bronchoscopy revealed no significant intraluminal findings. Analysis of bronchoalveolar lavage fluid (BALF) indicated an elevation in the number of lymphocytes (monocytes 52%, lymphocytes 47%, and neutrophils 1%). CD4/CD8 ratio was 8.0. There were no bacteria or other acid-fast bacilli cultured in the BALF. Transbronchial lung biopsy (TBLB) reports indicated multiple epithelioid granulomas in the interstitium throughout the alveoli (Fig. 2). Ocular lesions included granulomatous keratic precipitates and snowballs, which are signs of aggregation of inflammatory cells in the vitreous humor, posterior to the lens, suggesting the presence of pan-uveitis. Biopsy of the subcutaneous nodule in the right upper arm revealed epithelioid granulomas (Fig. 3). In addition, the level of serum angiotensin-converting enzyme (ACE) was elevated to 39.5 U/mL, and that of soluble interleukin-2 receptor (sIL-2R) was elevated to 1513 U/mL. These abnormal findings were consistent with sarcoidosis. Since chest X-ray taken five months before she commenced dupilumab therapy did not show any abnormalities, the current findings indicated a DISR caused by dupilumab. We discontinued dupilumab, and started treating her with mepolizumab, an

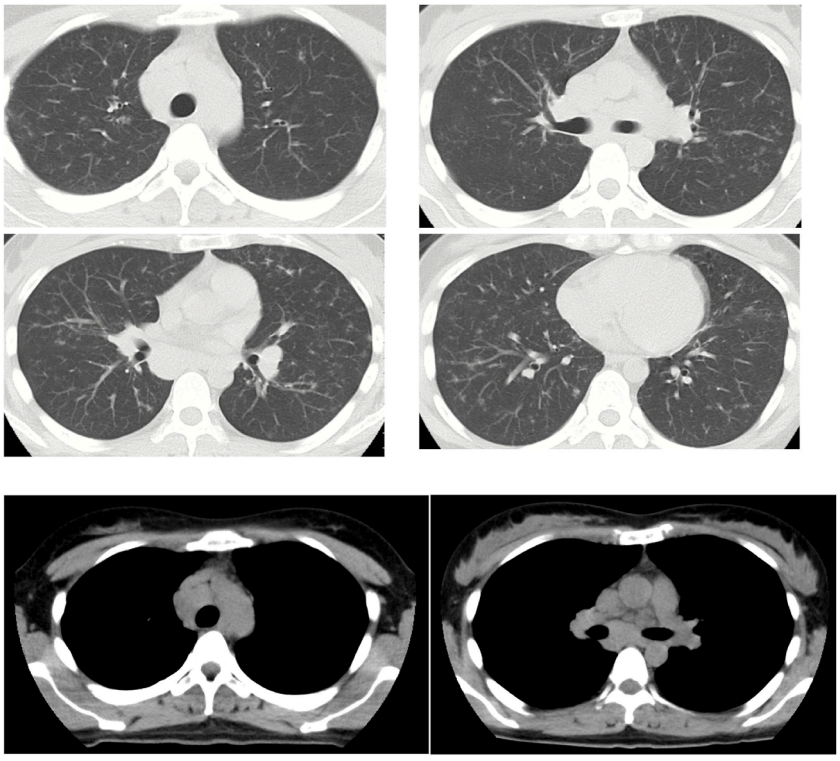

Fig. 1. CT images at the first presentation.
Random-pattern bilateral pulmonary nodules and multiple mediastinal lymphadenopathies are noted.

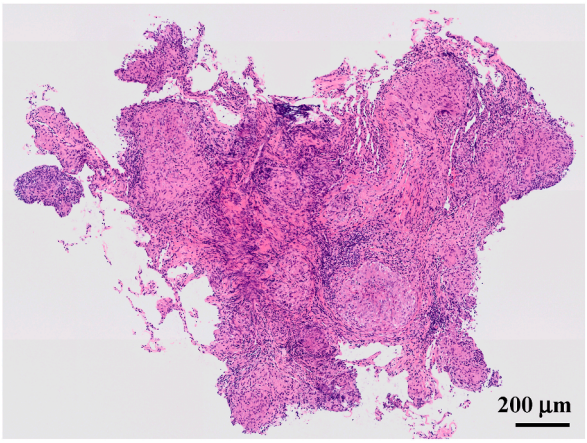

Fig. 2. Hematoxylin-Eosin (HE) -stained microscopic image of the bronchoscopy biopsy specimen collected in TBLB.
Non-necrotizing granulomas and epithelioids are present. Small nodular lesion of aggregation of non-necrotizing epithelioid cell granulomas with lymphocyte rim are present.

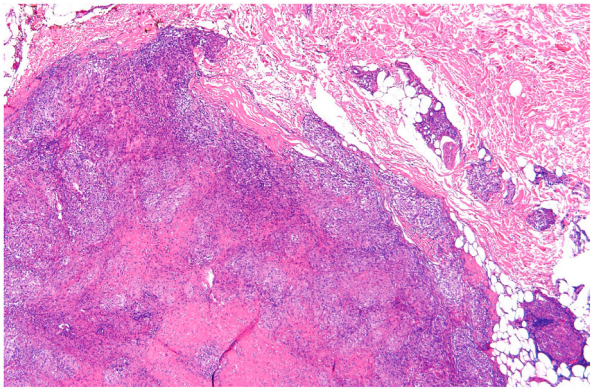

Fig. 3. A HE-stained specimen of the right upper arm lesion.
Epithelioid granulomatous lesions form a 5 mm by 3 mm tubercle in the subcutaneous tissue.

IL-5 inhibitor, for her eosinophilic rhinosinusitis. After cessation of dupilumab, there was a decrease in the levels of serum ACE and sIL-2R. Pulmonary nodules and multiple mediastinal lymphadenopathies also reduced in size (Figs. 4 and 5). She has shown no further signs of the sarcoidosis-like reaction for regularly followed up period.

3. Discussion

DISRs and sarcoidosis share similar features, which include bilateral hilar adenopathy, cutaneous lesions, uveitis, granulomatous infiltration of scars, and non-caseating granulomas. The similarities between the two conditions make it challenging to distinguish between them. In our case, the CT image showed random bilateral pulmonary nodules and multiple mediastinal lymphadenopathies, which suggested the presence of lymphatic lesions. The pathological findings revealed the presence of multiple non-caseating granulomas. These findings were almost indistinguishable from those of sarcoidosis. Considering these findings and the absence of acid-fast bacillus infection, the condition is caused by sarcoidosis-like reactions. In DISRs, the causative drug disturbs the balance of helper T cells (Th), resulting in Th1 dominance, which in turn leads to granuloma formation [1]. Dupilumab thwarts the IL-4/IL-13/IL-4R axis, which is critical for Th2 cell differentiation [6]. IL-4R signal decreases IL-10 production, negatively affecting Th1 cell differentiation [7]. Hence, IL-4R blockade renders the T-cell population Th1-dominant. In Th1-dominant circumstances, proinflammatory and Th1-skewing cytokines, such as IL-1, 6, 8, 12, and 18, interferon (IFN)-γand TNF-α, promote granuloma formation.

Stergios et al. reported a case of a neuro-sarcoidosis-like lesion in a patient being treated with dupilumab [5]. In this report, a 79-year-old male developed neuropsychiatric symptoms. His craniospinal fluid showed an elevated number of lymphocytes, and contrast-enhanced nodular lesions were observed in magnetic resonance imaging. The symptoms and image findings improved after the cessation of dupilumab and treatment with corticosteroids.

In another case reported by N. Belhomme et al. [4], a 28-year-old male, who was on dupilumab therapy for four months, developed meningoencephalitis syndrome and bilateral parotid gland enlargement. The increase in the number of lymphocytes, elevated levels of ACE, perilymphatic micronodular lung infiltration, and non-necrotizing epithelioid granulomas found in bronchial and ac-

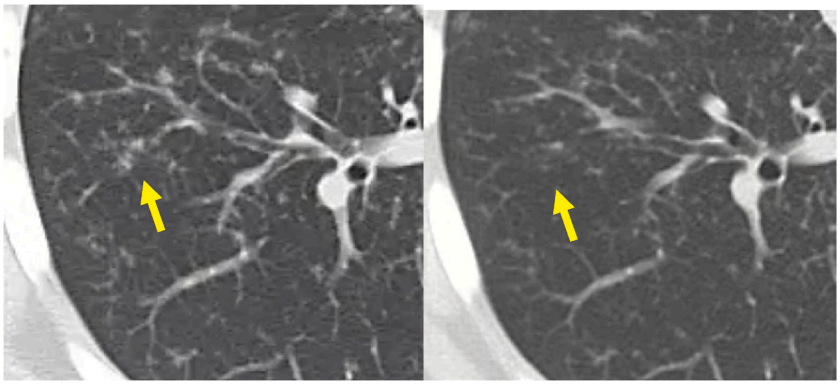

Fig. 4. Lung field lesions before (on the left) and after (on the right) dupilumab cessation.
Arrows indicate one of the improved lesions.

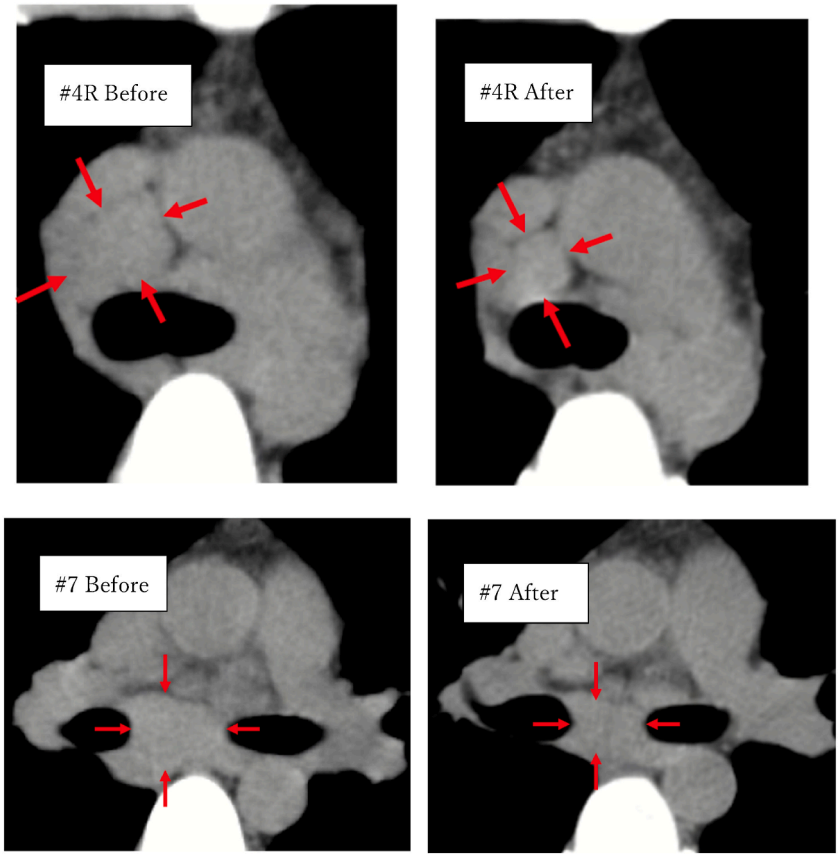

Fig. 5. CT images before and after the cessation of dupilumab. Mediastinal lymphadenopathy (#4R and #7) before (left) and after (right) dupilumab cessation.
Arrows indicate the lesions of lymphadenopathy.

cessory salivary gland samples pointed toward a DISR caused by dupilumab. Discontinuation of dupilumab treatment along with initiation of corticosteroids and methotrexate improved the condition.

In both these cases, corticosteroids were used for the treatment of the DISR caused by dupilumab, while we successfully improved the condition only by switching anti-allergic medication to mepolizumab. To the best of our knowledge, this is the first reported case of a dupilumab-induced sarcoidosis-like reaction, which was resolved without an immunosuppressive agent. IL-5 inhibition with mepolizumab did not promote a sarcoidosis-like reaction in our case. Human IL-5 promotes the proliferation, survival, and activation of precursors and matured eosinophils [8–10]. It also plays a major role in B cell survival, proliferation, and differentiation to antibody-secreting plasma cells [11]. Since human IL-5 mainly affects eosinophils, its blockade with mepolizumab did not interfere with the Th1/Th2 balance, thus it led to normalized Th1/Th2 population and promoted granuloma dissolution. IL-5 inhibitors such as mepolizumab and benralizumab may be administered as substitute medications in case of the development of a DISR by dupilumab.

A limitation of this report is that, there is always the possibility that these sarcoidosis-like reactions were caused by some pathogens. The development of sarcoidosis requires genetic predisposition and exposure to unknown substances [12]. Since it is almost impossible to distinguish DISRs from sarcoidosis, it is possible that these patients could have a genetic predisposition to develop sarcoidosis caused by some pathogen. It is essentially challenging to prove the causal relationship between sarcoidosis and dupilumab. More case reports of DISRs caused by dupilumab are needed for further investigation and validation of this relation between dupilumab and DISRs.

4. Conclusion

In this case report, we have described the occurrence of a DISR caused by dupilumab treatment. The DISR was resolved by switching to alternative anti-allergic medication. We need to consider the possibility that dupilumab may induce a sarcoidosis-like reaction.

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Declaration of competing interest

None.

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