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Case Report / Olgu Sunumu

Stop Being So Sensitive: An Exceptionally Rare Report of Ustekinumab-Induced Sub-acute Hypersensitivity Pneumonitis

Bu Kadar Duyarlı Olmaktan Vazgeçin: Son Derece Nadir Görülen Ustekinumab Kaynaklı Subakut Hipersensitivite Pnömonisi Vakası

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Abstract / Öz

Hypersensitivity pneumonitis (HSP) is a rare syndrome characterised by granulomatous inflammatory lung disease due to repeated sensitisation from a specific antigen. We present the case of a 61-year old male veteran with a history of nodular eczema who presented with 2 weeks of progressive dyspnoea on exertion and pleuritic chest pain. The patient was started on ustekinumab 5 weeks prior to presentation. Initial workup revealed ground-glass opacities on computed tomography (CT) scan of the chest. Cardiac workup was unrevealing with a normal myocardial perfusion stress test. The patient was started on inhaled corticosteroids and albuterol for reactive airway disease. Due to the persistence of symptoms despite treatment, the patient underwent bronchoscopy with bronchoalveolar lavage (BAL), transbronchial biopsy and endobronchial ultrasound-guided biopsy (EBUS). Bronchoscopy showed normal appearing airways of both right and left lungs. The BAL was remarkable for chronic inflammation and pulmonary macrophages. The BAL cell count differential was 1% granulocytes, 50% lymphocytes, 17% eosinophils and 32 mononuclear cells. The pathology from the mediastinal lymph nodes showed reactive inflammatory cells and no malignancy. The pathology from the transbronchial biopsy of the anterior basilar segment of the right lower lobe showed organising pneumonia with occasional ill-defined granulomas that stained negative for Acid Fast Bacilli (AFB) and Grocott's methenamine (GMS) appeared to be consistent with hypersensitivity pneumonitis. Based on the pathological diagnosis of HSP, the patient was managed with discontinuation of ustekinumab, with subsequent improvement of his symptoms. To our knowledge, this is the first report suggesting ustekinumab, like other biological therapies, has the potential to cause HSP.

Keywords: Hypersensitivity pneumonitis, ustekinumab, eosinophilia

Hipersensitivite pnömonisi (HSP) belirli bir antijene karşı tekrarlayan duyarlılaşmadan kaynaklanan granulamatöz enflamatuar akciğer hastalığı ile karakterize nadir bir sendromdur. Bu çalışmada 2 haftadır eforla görülen progresif dispne ve plöritik göğüs ağrısı ile birlikte nodüler egzama öyküsü olan 61 yaşında bir erkek hasta sunulmaktadır. Hastaya bu şikayetlerle olan başvurusundan 5 hafta önce ustekinumab başlanmıştı. İlk değerlendirmede bilgisayarlı tomografisinde (BT) buzlu cam görünümlü opasiteler görüldü. Miyokaridyal perfüzyon stres testi ile yapılan kardiyak değerlendirme normaldi. Hastaya reaktif havayolu hastalığı için inhale kortikosteroid ve albuterol tedavisi başlanıldı. Tedaviye rağmen semptomların devam etmesi nedeniyle hastaya bronkoskopi ile bronkoalveolar lavaj (BAL) yapıldı. Ayrıca hastadan transbronşiyal biyopsi ve ultrason eşliğinde endobronşiyal biyopsi (EBUS) alındı. Bronkoskopide sağ ve sol akciğerlerde normal görünümlü havayolları gözlendi. BAL'da kronik inflamasyon ile birlikte pulmoner makrofajlar görüldü. Diferansiyel BAL hücre sayımında, %1 granülosit, %50 lenfosit, %17 eozinofil ve %32 mononükleer hücre vardı. Mediastinal lenf nodlarından alınan patolojide reaktif enflamatuvar hücreler görülürken, malignite izlenmedi. Sağ alt lob anterior baziler segmentten alınan transbronşiyal biyopsinin patolojik değerlendirmesinde; aside dirençli bakteri (afb) ve grocott metenamini açısından negatif olan, seyrek görülen ve tam tanımlanamayan granülomlarla birlikte organize pnomoni izlendi. Bu bulgular hipersensitivite pnomonisi ile uyumluydu. Bu patolojik bulgulara dayanarak HSP tanısı konan hastanın ustekinumab tedavisi kesildi ve ardından hastanın semptomlarında iyileşme görüldü. Bilgimize göre bu makale ustekinumabın, diğer biyolojik tedaviler gibi, HSP'ye yol açma potansiyeli olduğunu ortaya koyan ilk vaka sunumudur.

Anahtar Sözcükler: Hipersensitivite pnömonisi, ustekinumab, eozinofili

Introduction

Hypersensitivity pneumonitis (HSP), also known as extrinsic allergic alveolitis, is a syndrome characterised by granulomatous inflammatory lung disease due to repeated sensitisation from a specific antigen in predisposed individuals (1, 2). Although the pathogenesis of HSP is not fully understood, it is believed to include cellular and humoral immune responses to certain antigens, leading to mononuclear cell alveolitis, intra-alveolar beds, granulomas and fibrosis (3). Despite being mostly obtained from animal models, both pathways appear to begin after inhaled antigens are phagocytosed by macrophages (4). Interleukin-12 (IL-12) is thought to play a role in the development of a granulomatous inflammatory response (2). Patients often present with non-specific symptoms, such as cough and dyspnoea, with histological findings of

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bronchiolitis, interstitial inflammation and scattered granulomas on lung biopsy (5-7). While interstitial markings may be seen on chest radiographs, 20% of them may be normal (6), with high resolution chest tomography (HRCT) scan being more sensitive for HSP, particularly in detecting early interstitial disease (8).

Ustekinumab is a human monoclonal antibody directed against IL-12 and IL-23 that causes rapid and prolonged responses, with an excellent safety profile, in the treatment of moderate to severe psoriasis (9). In fact, this biological therapy has demonstrated no cumulative toxicity over a 4-year follow-up (10).To date, only rare cases have been reported that attribute ustekinumab to eosinophilic pneumonia or organising pneumonia; however, no cases have been linked ustekinumab to HSP (11, 12).

Case Presentation

We present the case of a 61-year-old Caucasian male veteran who presented to the emergency room with a one-month history of shortness of breath, dyspnoea on exertion, pleuritic chest pain, cough and pruritic right knee rash. The patient reported that his dermatologist had prescribed ustekinumab for worsening psoriasis 5 weeks prior to presentation. His past medical history was significant for non-alcoholic steatohepatitis, osteoarthritis, allergic rhinitis and nummular eczema (spongiotic, psoriasiform dermatitis). He was a non-smoker and had no history of illicit drug use. His physical exam was significant for mild rales in the left lung base; circular, scaly, plaque-like rash on the right lower extremity inferior to the patella; and a 0.5 cm furuncle with surrounding erythema on the right medial mid-shin. Laboratory evaluation was most notable for white blood count of 4.61 k cmm^{-1} with 3.9% eosinophils and 13.4% monocytes (66.1% granulocytes and 14.5% lymphocytes). Diagnostic testing included chest radiograph and computed tomography (CT) scan of the chest with contrast, which showed mild airspace disease (Figures 1a and b) and no pulmonary emboli with progressive bilateral patchy airway disease (Figures 2a-c), and mediastinal lymphadenopathy (Figure 2d), respectively. Electrocardiogram showed sinus tachycardia at rate of 104 and old, stable left axis deviation. He underwent a myocardial perfusion stress test, which was normal. He was treated with budesonide/formoterol and albuterol for presumed reactive airway disease given the extensive history of eczema and allergic rhinitis. Despite this initial treatment, his respiratory symptoms did not improve and repeat CT showed worsening of ground-glass opacities (Figure 2d).

Due to the persistence of symptoms despite treatment, the unremarkable cardiac workup, and the abnormalities seen on chest imaging, the patient underwent bronchoscopy with bronchoalveolar lavage (BAL), transbronchial biopsy and endobronchial ultrasound-guided biopsy (EBUS). Grossly, the bronchoscopy showed normal appearing airways of both right and left lungs. The BAL was remarkable for chronic inflammation and pulmonary macrophages. The BAL cell count differential was 1% granulocytes, 50% lymphocytes, 17% eosinophils and 32% mononuclear cells. The pathology from the mediastinal lymph nodes was largely unremarkable and showed reactive inflammatory cells. The pathology from the transbronchial biopsy of the anterior basilar segment of the right lower lobe showed pneumocytic infiltration and organising pneumonia with ill-defined granulomas seen in low power 10X (Figures 3a-c), medium power 20X (Figures 4a-c) and high power 40X (Figure 5a). Further staining showed that the sample was negative for Acid Fast Bacilli and Grocott's methenamine (GMS; Figures 5b, c). Due to the transbronchial biopsy findings, combined with the recent initiation of ustekinumab, the patient was diagnosed with ustekinumab-induced hypersensitivity pneumonitis. He was treated with cessation of the biological therapy, topical emollients and topical steroids for eczema. Systemic steroids were not prescribed given the patient's active psoriasis.

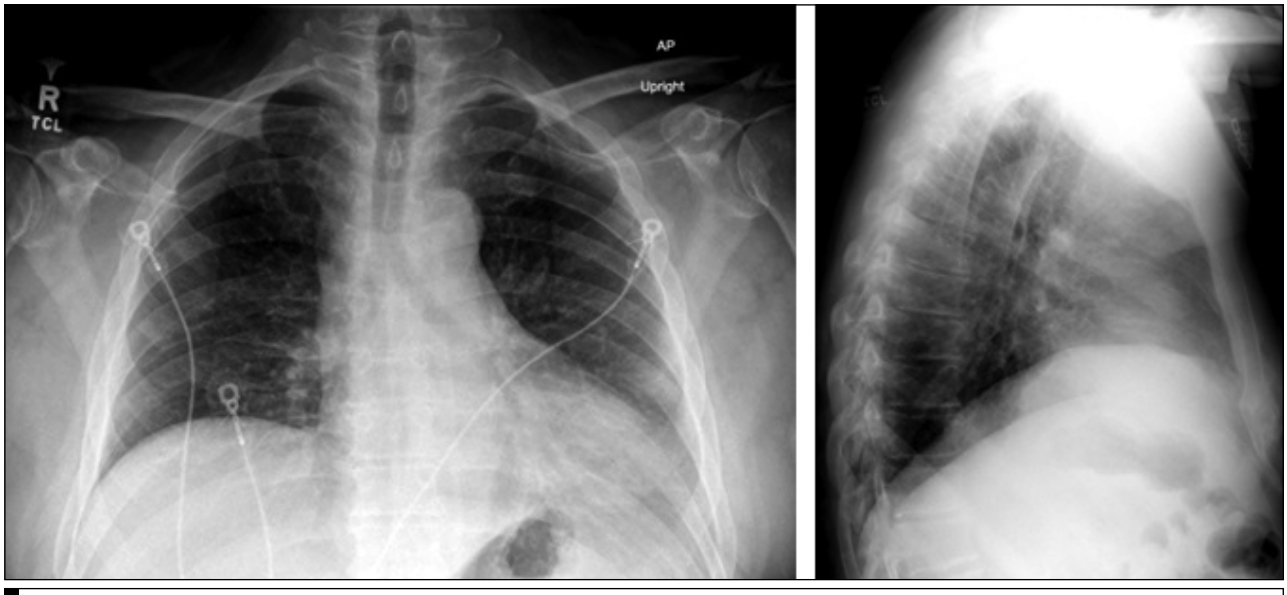


Figure 1. a, b. CXR AP view shows mild airspace disease (a). CXR lateral view shows mild airspace disease (b)

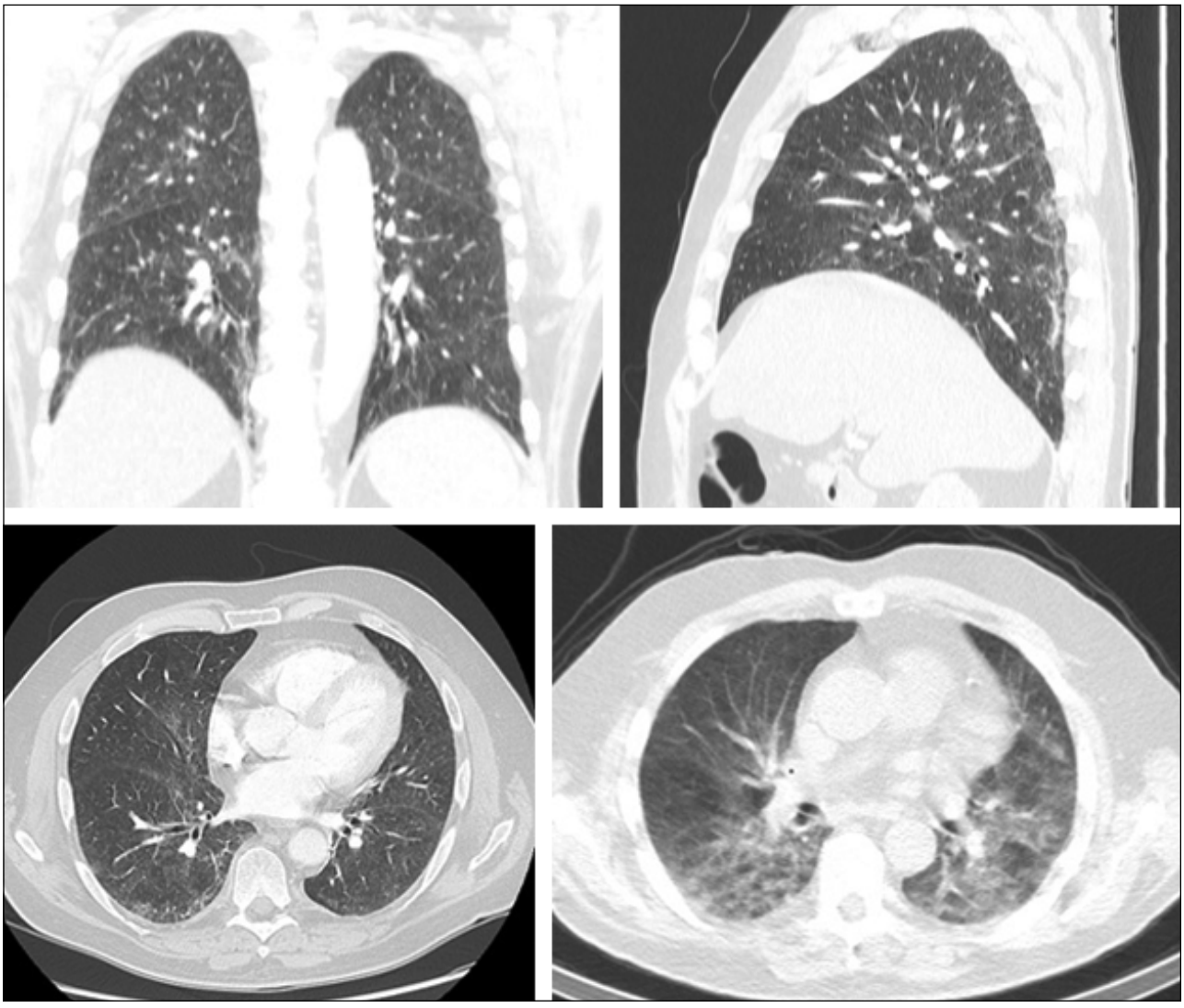
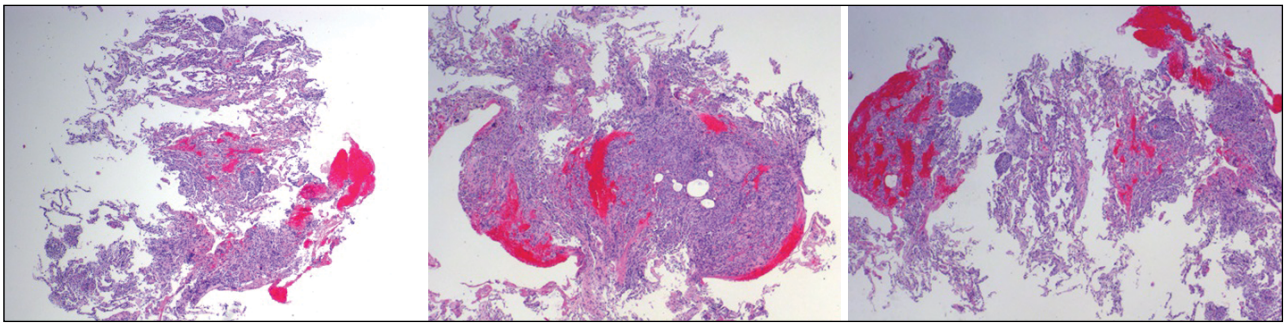


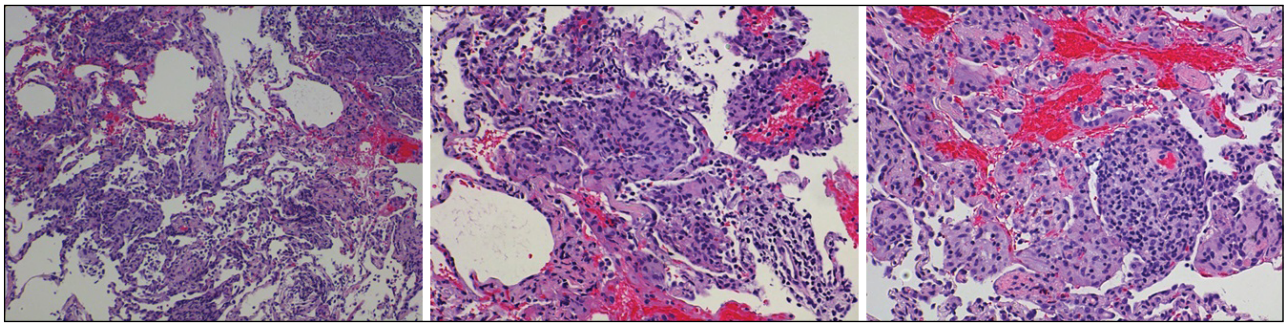
Figure 2. a-d. Coronal CT shows diffuse airspace disease (a). Sagittal CT shows diffuse airspace disease (b). Axial CT shows diffuse ground-glass opacities (c). Coronal CT shows worsening ground-glass opacities and diffuse airspace disease (d)



Figures 3. a-c. 10X haematoxylin and eosin stain showing pneumocyte reaction to the inflammation and focal granulomas

Discussion

Numerous cases of non-infectious pulmonary complications have been reported with use of tumour necrosis factor-α (TNF-α) inhibitors, such as tocilizumab and rituximab (13). These adverse effects include granulomatous disease, pulmonary nodules and variable forms of interstitial lung disease (ILD) (14). ILD is a particularly well-documented complication of TNF-α inhibitors, accounting for 97% of biological agent-induced ILD (15-17). Ustekinumab is favoured for moderate to severe psoriasis for its excellent safety profile. Rates of serious infections were stable over time; cases of tuberculosis, atypical mycobacterial infections, or increase in malignancy rate were not reported in patients treated with



Figures 4. a-c. 20X haematoxylin and eosin stain showing focal lymphocyte infiltrates and small granulomas

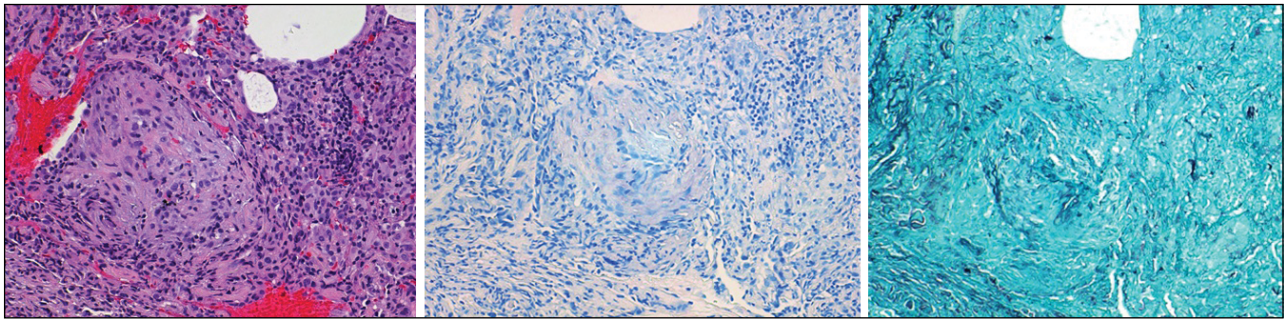


Figure 5. a-c. 40X haematoxylin and eosin stain showing granuloma in high power (red arrow) (a). 40X showing high power granuloma negative for Acid Fast Bacilli (b). 40X showing high power granuloma negative for Grocott's methamine silver stain (c)

ustekinumab (10). Recent case reports have associated ILD with the use of ustekinumab. Yashiro et al. (12) described a patient on ustekinumab with eosinophilic pneumonia that resolved with the discontinuation of therapy and pulse steroids. Teferra et al. (11) reported a patient on ustekinumab who developed organising pneumonia on biopsy that resolved with the discontinuation of therapy. Kikuchi et al described two cases where ILD was diagnosed based on elevated KL-6 (a marker of ILD) levels with the presence of new ground-glass infiltrates on chest CT after starting ustekinumab. No tissue histology was obtained but KL-6 levels normalised and infiltrates resolved after the discontinuation of therapy (18). Given these prior reported cases and the timing of symptoms with beginning ustekinumab, there was a strong suspicion for drug-induced ILD in our patient. Transbronchial biopsy confirmed the diagnosis of HSP. While HSP is more commonly seen in occupational and environmental exposures (19), it has also been documented with the use of biologic agents (20).

Conclusion

To our knowledge, this is the first report suggesting ustekinumab, like other biological therapies, has the potential to cause HSP. We suggest that physicians should consider HSP in the differential diagnosis when patients present with symptoms of dyspnoea after starting ustekinumab.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

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