Diffuse alveolar hemorrhage associated with ustekinumab treatment

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Purpose. A case of diffuse alveolar hemorrhage (DAH) occurring as a reaction to ustekinumab therapy is reported.

Summary. After starting ustekinumab for treatment of psoriatric arthritis, a 46-year-old female presented with flu-like symptoms and cough with blood-tinged sputum that had begun 1 week previously. Her initial computed tomography scan of the chest demonstrated bilateral ground-glass opacities. On bronchoscopy, the bronchoalveolar lavage (BAL) return became bloodier from sample 1 to samples 2 and 3. Her BAL fluid was more than 90% hemosiderin-laden macrophages, a finding consistent with DAH. We ruled out infectious etiologies and other common vasculitis conditions that can cause DAH. A diagnosis of ustekinumab-induced DAH was made due to a temporal relationship between initiation of the drug and the patient's presentation and the absence of infection and other alternate diagnosis. Prior case reports including ustekinumab-induced pneumonitis, interstitial lung disease with a granulomatous component, and lupus syndrome have been reported, with this being the first case of DAH in a patient undergoing treatment of psoriatic arthritis.

Conclusion. A 46-year-old woman developed DAH during ustekinumab treatment. Symptoms abated after drug discontinuation and supportive treament. Clinicians must remain mindful of this rare complication of ustekinumab use in order to avoid potential delays in appropriate DAH treatment.

Keywords: diffuse alveolar hemorrhage, psoriatic arthritis (drugs and medicine), unwanted effects/adverse reactions, ustekinumab

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Psoriatic arthritis is triggered by multiple genetic, environmental, and immunological factors. The interleukin-17/interleukin-23 axis plays an important role in the pathogenesis of psoriatic arthritis.[1] Ustekinumab is an IL-12/IL-23 inhibitor that blocks the IL-17/IL-23 inflammatory pathway, thereby preventing skin and synovial inflammation.[2] The drug has been proven to be effective in moderate to severe psoriasis, psoriatic arthritis, and induction and maintenance therapy of ulcerative colitis and Crohn's disease.[1,3] Recent reports suggest that ustekinumab has been associated with several pulmonary toxicities.[4-11] Here we report what is, to the best of our knowledge, the first reported case of ustekinumab-induced diffuse alveolar hemorrhage.

Case report

A 46-year-old female with a history of asthma, fibromyalgia, obstructive sleep apnea, and hypertension, as well as psoriatic arthritis during immunosuppressive therapy with ustekinumab, presented with complaints of cough productive of yellowish, blood-tinged sputum for 2 days. She also had experienced chills, shortness of breath, and central pleuritic chest pain for about a week. On questioning, the patient said she had not experienced fever, night

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sweats, weight loss, or wheezing. She said she had no history of pulmonary embolism, recent long-distance travel, or a personal history of cancer. She reported no exposure to tuberculosis, molds, or asbestos. She had never been a smoker. She denied any illicit drug use, including crack cocaine. She denied any freshwater or animal exposure, including exposure to rodents. Her medications included nebulized albuterol as needed, amitriptyline 50 mg daily for fibromyalgia, aspirin 81 mg daily, duloxetine 30 mg daily, fluticasone/salmeterol inhaler 1 puff daily, montelukast 10 mg nightly, oxycodone as needed, pregabalin 200 mg twice daily, omeprazole 20 mg daily, and topiramate 200 mg twice daily. She had been taking all these medications for 3 to 6 years prior to the hospital admission described here. No new medication apart from ustekinumab was added recently (ie, within 1 year). She had been receiving ustekinumab 90 mg by subcutaneous injection every 12 weeks for a little more than a year, with the last dose administered 4 weeks prior to presentation. Physical examination revealed blood pressure of 138/83 mm Hg, pulse of 98 beats/min, axillary temperature of 98°F, respiratory rate of 18 breaths/min, and an oxygen saturation of 94% on room air. Mild bilateral reduction in air entry was notedy, but there was no wheezing, crackles, or use of accessory muscles. Laboratory data demonstrated a white blood cell count of 10,300 cells/μL (neutrophils, 66.3%; lymphocytes, 27.1%; monocytes, 4.9%; eosinophils, 1%; and basophils, 0.3%) and a hemoglobin of 12.3 g/dL with a platelet count of 235 x 10^3/μL. The C-reactive protein level was slightly elevated, at 1.1 mg/dL. Procalcitonin was not elevated. A respiratory viral panel was negative. A chest x-ray demonstrated subtle bilateral parenchymal opacities in the midlung fields. Computed tomography of the lungs demonstrated scattered ground-glass opacities in all lobes. The patient was treated with ceftriaxone and azithromycin for possible community-acquired pneumonia. (Figure 1).

KEY POINTS

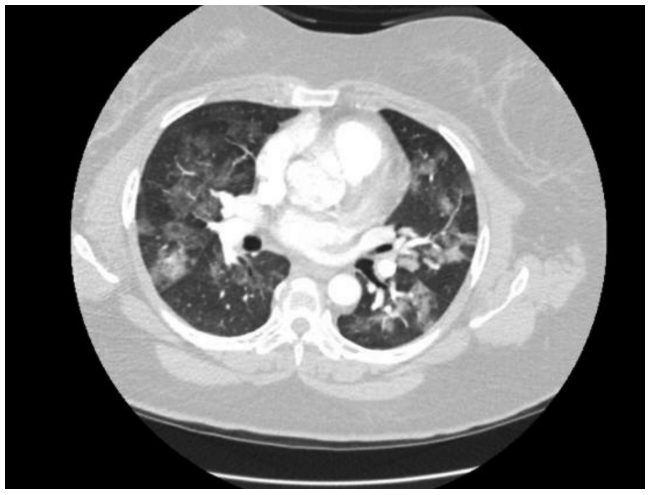
- Diffuse alveolar hemorrhage should be considered in the differential diagnosis in patients with respiratory symptoms after starting treatment with ustekinumab.
- The relationship between drug exposure and the onset of symptoms is helpful for diagnosis; flexible bronchoscopy with sequential bronchoalveolar lavage is the preferred method for definitive diagnosis.
- The main action of treatment is drug discontinuation and supportive therapy. Steroids may be necessary in severe cases involving respiratory failure or life-threatening diffuse alveolar hemorrhage.

Because of her continued hemoptysis, the patient underwent bronchoscopy. Bronchoalveolar lavage (BAL) fluid was red tinged and became bloodier on progressive sampling. BAL fluid cytology demonstrated more than 90% hemosiderin-laden macrophages but was negative for malignant cells. Stains/cultures were negative. These findings suggested diffuse alveolar hemorrhage (DAH). Antineutrophilic cytoplasmic (ANCA) and anti–glomerular basement membrane (GBM) antibodies testing was negative. Antinuclear antibodies (ANA), at a ratio of 1:80, with a speckled pattern; anti–double-stranded DNA (anti–dsDNA) antibodies, at a concentration of 589.7 IU/mL; and anticardiolipin antibodies were detected. Ultimately a diagnosis of ustekinumab-induced DAH was made due to the temporal relationship between initiation of the drug and the patient's symptomatic presentation, in addition to the absence of infection or other alternate diagnoses. Since she did not develop actual or impending respiratory failure or DAH of a life-threatening nature, she was not started on high-dose steroids during the admission. Ustekinumab was stopped and she was later treated with low-dose prednisone (10 mg daily for 2 to 3 days, then tapered to 5 mg daily) and tofacitinib for psoriatic arthritis. At the time of writing she remained free of pulmonary symptoms since the discontinuation of ustekinumab.

Discussion

The safety profile of ustekinumab as a therapy for psoriatic arthritis has been evaluated in clinical trials and by postmarketing analysis. Pulmonary toxicity in the form of interstitial lung

Figure 1. Computed tomography of the chest showing diffuse, bilateral, widespread central and peripheral ground-glass opacities in all lung lobes.



diseases has been reported.[12-14] We report here what we believe to be the first reported case of DAH associated with ustekinumab therapy. Ustekinumab is a fully human monoclonal immunoglobulin G (IgG) antibody approved for use in treatment of psoriasis and psoriatic arthritis after failure of other standard therapies. Its inhibitory action on the IL-23/Th17 axis is postulated to be the mechanism of action (Th17 denotes T helper cells that produce IL-17). It binds to the p40 subunit of IL-12 and IL-23, thereby preventing attachment to receptors. As a result, the Th17 inflammatory pathway is blocked, resulting in suppression of production of IL-17, IL-21, and IL-22, which are major cytokines that mediate auto-inflammation of synovium and skin.[1,2] This inhibitory action shifts the balance towards the Th2 pathway and may provide a mechanism underlying the eosinophilic pneumonia that has been described in patients taking ustekinumab.[4-6] Aska Ali et al[7] reported a case of ustekinumab-associated subacute hypersensitivity pneumonitis in a 61-year-old male that occurred 5 weeks after initiation of the drug. The postulated mechanism was that the drug itself acted as a hapten or might have resulted in cross-reactive antigens. Gad et al[8] reported a disseminated sarcoid-like reaction involving the lungs, liver, spleen, and bones in a patient taking ustekinumab who presented with symptoms of weight loss and dyspnea. Stimulation of cytokines, including IL-12, IL-18, IL-27, and interferon gamma, was proposed to be responsible for the development of sarcoid lesions in the lungs. However, IL-12 and IL-23 are blocked by ustekinumab, so the mechanism of ustekinumab-induced granuloma formation remains unclear. There have been reports of reactivation of latent tuberculosis, nontuberculous mycobacterial infection, and *Legionella* pneumonia in patients treated with ustekinumab for either Crohn's disease or psoriasis.[9-11,15] The incidence of tuberculosis is, however, observed to be much lower than with anti–tumor necrosis factor α (anti–TNF-α) agents.

Table 1. Case Reports of Diffuse Alveolar Hemorrhage Associated with Use of Monoclonal Antibodies[19-26]

Monoclonal Antibody	Primary Diagnosis or Clinical Context	Age/Sex	Onset	Clinical Presentation	Diagnostic Procedure	Treatment Given	Outcome
Alemtuzumab	Multiple sclerosis	29/F	2 days	Chest pain, hemoptysis, dyspnea	BAL	Cessation of drug	Patient recovered
Alemtuzumab	Renal transplantation	18/M	NR	Hemoptysis, dyspnea, fever	BAL	Cessation of drug, steroids, plasma electrophoresis, intubation	Died 31 days post transplant
Alemtuzumab	Renal transplantation	26/M	NR	Hemoptysis, dyspnea	BAL	Cessation of drug, steroids, mechanical ventilation	Patient recovered
Nivolumab	Multiple lung metastases	41/F	3 months	Hemoptysis, respiratory distress	BAL	Cessation of drug, steroids	Died due to lung metastasis
Gemtuzumab	Relapsed AML	51/M	17 days	Cough, dyspnea	BAL	Cessation of drug, steroids	Died of AML
Bevacizumab	Stage IIIB primary adenocarcinoma	71/F	32 days	Hemoptysis	Autopsy	Not reported	NR
Bevacizumab (intravitreal injection)	Not reported	86/M	3 months	Progressive dyspnea	BAL	Cessation of drug, steroids, mechanical ventilation	Patient improved
Infliximab	Crohn's disease	35/F	2 weeks	Fever, dry cough, dyspnea	BAL	Cessation of drug	Patient improved

Abbreviations: AML, acute myeloid leukemia; BAL, bronchoalveolar lavage; NR, not reported;

Our patient presented with a 1-week history of flu-like symptoms and cough productive of blood-tinged sputum. Imaging studies demonstrated bilateral diffuse ground-glass opacities. Initial evaluations for infection were negative. BAL cytology was consistent with DAH and did not identify malignant cells. Negative anti-ANCA and anti-GBM antibody tests militated against vasculitis. The temporal association between exposure to ustekinumab and the patient's clinical presentation, along with the calculated Naranjo scale total score of 7, supports the diagnosis of induced DAH. Compared with previously reported cases of ustekinumab-associated adverse drug reactions, our case was characterized by a late onset (1 year after ustekinumab initiation) and was of mild severity, requiring only supportive care. We speculate that the plausible pathogenesis of DAH in this patient was direct pharmacological effects on alveolar microcapillaries causing pulmonary capillaritis, rather than a immunological mechanism, as treatment with high-dose steroids was not required.

Autoantibody elevations have also been reported with ustekinumab use. Guarneri et al[16] reported an association between ustekinumab therapy and lupus erythematosus skin lesions that presented along with elevated ANA levels. Another case report on drug-induced lupus due to ustekinumab therapy was published by Tierney et al.[17] In addition to having positive ANA test results, their patient tested positive for anti-SSA/Ro and Anti SSB/La antibodies (these antibody types are associated with Sjögren's syndrome and/or lupus), as well as anti–histidyl tRNA synthetase (anti–Jo-1) antibodies, which are often identified in connective tissue diseases, including myositis and interstitial lung disease. Tierney and colleagues postulated that the drug inhibits IL-12 and IL-23 so that T-cell differentiation is shifted towards IL-22 production, culminating in increased production of TNF-α, a potent proinflammatory cytokine involved in the pathogenesis of autoimmune diseases. In our case as well, elevated levels of anti-dsDNA antibodies and anti–cardiolipin IgG levels were thought to be a result of ustekinumab therapy rather than a collagen vascular disease. Drug-induced lupus usually presents with mild symptoms like fever, arthralgia, and myalgia; serositis and cutaneous manifestations have been noted occasionally, although major organ involvement is rare.[18] Drug-induced lupus was ruled out as a possible mechanism for DAH in our case.

There have been numerous reports of DAH associated with the use of monoclonal antibody therapies, which are enumerated in Table 1. These case reports are similar to ours in that aspect. In many of these cases, therapy was discontinued and symptoms of DAH did not recur.

Conclusion

Based on a temporal association with drug administration, BAL findings consistent with DAH, cytology studies that were negative for malignancy, the absence of evident infection, and the relative quiescence of underlying connective tissue disease, we concluded that our patient developed DAH as a result of ustekinumab therapy. In a patient presenting with shortness of breath and hemoptysis after ustekinumab treatment, DAH should be considered.

Disclosures

The authors have declared no potential conflicts of interest.

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