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Drug-induced Lung Disease Associated With Ustekinumab in a Pediatric Patient With Crohn Disease

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Our patient was diagnosed with Crohn disease (CD) at 8 years of age when he presented with abdominal pain and diarrhea with esophagitis, gastritis, duodenitis, and colitis with granulomas. He was initially treated with prednisone, methotrexate, and mesalamine. After weaning off corticosteroids, however, he had recurrence of symptoms and persistence of inflammation on repeat endoscopy. Partial enteral nutrition was also trialed. He was started on infliximab at 12 years of age. The patient did well on infliximab, with normalization of his laboratories and fecal calprotectin. However, he developed severe psoriasis after 1 year.

He was started on ustekinumab at 13 years of age. Two days after receiving the induction infusion of ustekinumab, he developed fever, severe pleuritic chest pain, and dyspnea. He was admitted to the hospital in which chest x-ray revealed bilateral interstitial opacities (Fig. 1). Initial laboratory tests showed leukocytosis (16.6 K/μL), thrombocytosis (394 K/μL), and elevated sedimentation rate (98 mm/h) and C-reactive protein (4.3 mg/dL). Fecal calprotectin was normal. He was treated with azithromycin for atypical pneumonia with minimal improvement. Chest computed tomography (CT) revealed numerous subpleural and parenchymal pulmonary nodules in the bilateral lung fields (Fig. 2). Pulmonary function testing revealed mild restrictive pattern, although normal lung volumes and diffusion capacity.

He underwent infectious testing, flexible bronchoscopy with bronchoalveolar lavage, and CT-guided lung biopsy.

Overall, testing was unrevealing, including negative quantiferon gold, histoplasmosis and cryptococcus tests, respiratory viral panel, and bacterial and fungal cultures. Bronchoscopy revealed normal airways, and bronchoalveolar lavage cell count was remarkable for a slightly elevated lymphocyte count (36%) with normal cytology. Biopsy of the nodules was unrevealing. Based on these findings and time course, drug-induced pneumonia or pneumonitis from ustekinumab was felt to be most likely. The differential also included infection, Crohn-related lung disease, cryptogenic organizing pneumonia, and sarcoidosis.

Ustekinumab is a human interleukin-12 (IL-12) and IL-23 antagonist used in patients with moderate to severe CD, plaque psoriasis, and psoriatic arthritis. Ustekinumab has been favored for its excellent safety profile. However, in postmarketing surveillance through the Food and Drug Administration, a few cases of noninfectious pneumonia with ustekinumab have been reported. All of the cases of pulmonary complications with ustekinumab have been in adults, the majority in patients with psoriasis. This is the first case reported in a pediatric patient.

The diagnosis of noninfectious pneumonia is defined by pneumonia or pneumonitis from a noninfectious source; drug-induced lung disease (DILD) is one type (1,2). DILD can be difficult to identify as it requires exclusion of alternative diagnoses and there are no hallmark imaging or histologic findings. Moreover, the clinical phenotype, imaging, and histopathologic patterns vary significantly between drugs and between patients on the same drug. Typically DILD is suspected when onset of symptoms is in conjunction with certain medication exposures such as chemotherapeutic, antimicrobial, and cardiovascular agents (3). Biologic therapies, such as anti-TNF therapy, and methotrexate have also been implicated (2,4).

In a retrospective analysis of cases of DILD from ustekinumab, 12 cases were identified based on reports through the FDA's Adverse Event Reporting System database and PubMed publications. Of these 12 cases, 7 were diagnosed as interstitial pneumonia, 3 eosinophilic pneumonia, 1 organizing pneumonia, and 1 hypersensitivity pneumonitis. The median age was 63 years. Eleven (92%) patients were prescribed ustekinumab for psoriasis and 1 for pyoderma grangrenosum. The most common symptoms were cough, dyspnea, and fatigue. All of the cases resulted in hospitalization, however, only 1 patient required mechanical ventilation. A temporal association with use of ustekinumab was found in all cases; pulmonary symptoms appeared after 1 to 3 doses. Ustekinumab was stopped in all patients and 7 (58%) patients had documented improvement after discontinuation. One of these 7 patients had recurrence of interstitial pneumonia after reintroduction of ustekinumab (1).

The youngest patient to develop presumed DILD in the literature was 27 years old. This patient developed shortness of breath and chest pain after 2 doses of ustekinumab for plaque psoriasis. Imaging revealed multiple nodular opacities. Tests for other etiologies were negative, similar to our patient. Symptoms and radiographic findings resolved after discontinuation of ustekinumab (5). A few adults with CD have had pulmonary complications on ustekinumab. A 61-year-old patient with Crohn colitis developed shortness of breath, cough, and hypoxemia 6 weeks after receiving ustekinumab. CT demonstrated multifocal nodular consolidations with additional negative testing. He improved after ustekinumab was stopped (6). Another patient with CD developed *Legionella pneumophila* after his first dose of ustekinumab. He was treated with antibiotics and corticosteroids with improvement in his symptoms. Ustekinumab was later reintroduced without further issues (7).

The mechanism of DILD is not fully understood. It is primarily thought to be a hypersensitivity reaction. The specific drug serves as an antigen, activating the immune system by drug-specific antibodies or drug-specific T cells, leading to lung injury. Deposition of antigen-antibody complexes can also trigger an inflammatory response (2). Yashiro et al (8) described a case of eosinophilic pneumonia after starting ustekinumab, a type of DILD, and suggested that ustekinumab's inhibitory effects on IL-12 and IL-23 may lead to a dominant Th2 response and trigger eosinophilic pneumonia (2).

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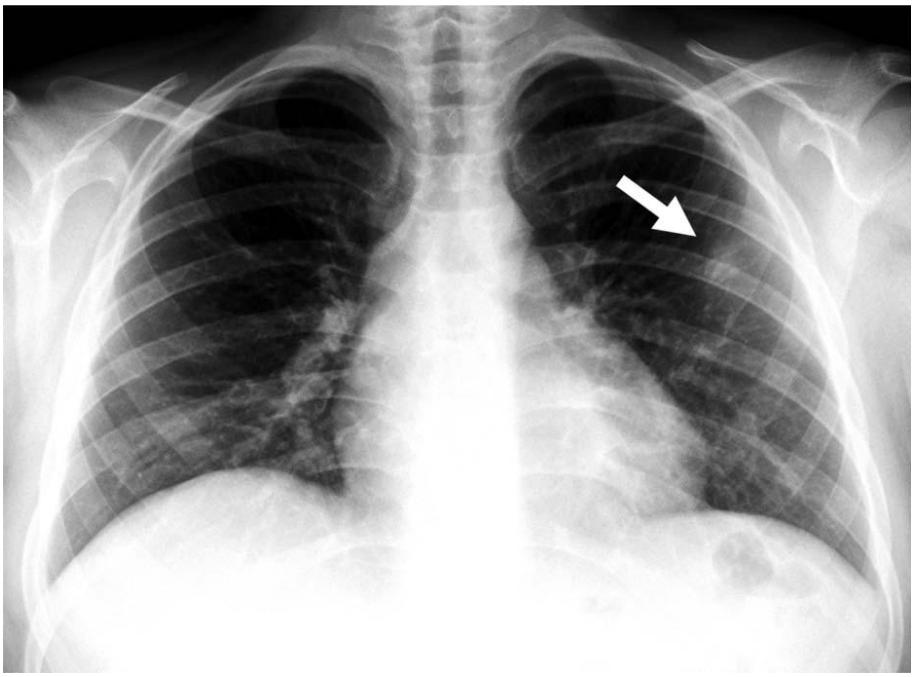

FIGURE 1. Posteroanterior projection chest radiograph demonstrates interstitial pattern with pulmonary opacities and subtle left upper lung pulmonary nodule (arrow).

Our case demonstrates that when a patient receiving ustekinumab presents with respiratory symptoms such as shortness of breath with minimal exertion, chest pain, and cough, noninfectious pneumonia or pneumonitis secondary to use of ustekinumab should be considered. This is the first reported pediatric case of DILD associated with ustekinumab. Early recognition and appropriate management in DILD is necessary to prevent progression to serious outcomes such as hospitalization and respiratory failure. In our patient, ustekinumab was discontinued, and he was started on vedolizumab. Although early in his course of vedolizumab, his IBD has remained in remission, respiratory symptoms have resolved, and imaging has improved 1 month after discontinuation of ustekinumab (Fig. 3).

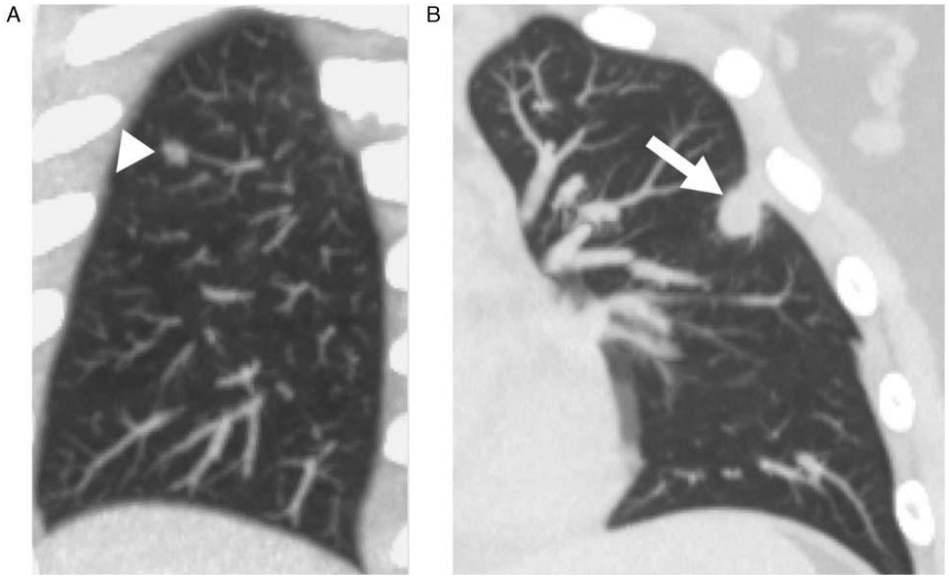

FIGURE 2. Coronal maximum-intensity-projection (MIP) chest computed tomography (CT) at presentation demonstrates (A) a 0.5 cm right lower lobe (superior segment) nodular opacity and (B) a 1.3 cm left-upper lobe solid subpleural pulmonary nodular consolidation (arrow).

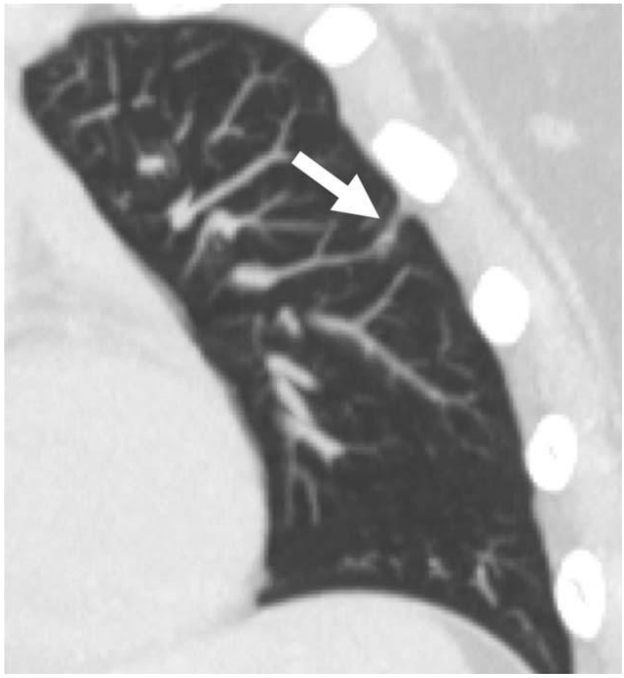

FIGURE 3. Coronal maximum-intensity-projection (MIP) chest computed tomography (CT) performed 5 months after cessation of ustekinumab demonstrates near-complete resolution of the left upper lobe lesion in Figure 2B with only minimal, residual linear opacity (arrowhead).

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