

Drug-Related Pneumonitis in Patients Receiving Vedolizumab Therapy for Inflammatory Bowel Disease

Noninfective drug-related pneumonitis (DRP) is a well-known adverse effect of several drugs: clinical manifestations have mostly an acute/subacute onset and vary from mild to life-threatening. Several DRP cases have been described in patients receiving anti-tumor necrosis factor α , rituximab, and tocilizumab.^{1,2} To date, only 4 reports of vedolizumab-related pneumonitis have been presented.³⁻⁵

Data were extracted retrospectively from the medical records of 3 Italian referral inflammatory bowel disease (IBD) centers. Inclusion criteria were the development of respiratory symptoms after vedolizumab initiation and ruling out alternative causes. Baseline characteristics, IBD clinical activity, laboratory findings, respiratory symptoms and therapies, and, whenever available, radiologic and pathologic findings were reported.

Ten patients affected by IBD developed DRP while on vedolizumab therapy (patient characteristics are summarized in Supplementary Table 1). None had a history of lung disease or remarkable abnormalities at screening chest radiography. Four patients were ex-smokers, and the remaining were nonsmokers. Eight patients had been exposed previously to anti-tumor necrosis factor α . All received anti-integrin therapy because of moderate to severely active IBD.

At DRP onset, patients received a median of 4 vedolizumab infusions, for a median time of 12 weeks; IBD was quiescent or mild in all of them, but an increase in C-reactive protein levels was observed (mean C-reactive protein, 15.7 mg/L $\pm$ 22.6 SD).

The most common presenting symptoms were cough (10 of 10 patients), fever (7 of 10 patients), and dyspnea (3 of 10 patients). Three patients were admitted to the hospital because of symptoms worsening. One patient, affected by chronic heart failure and atrial fibrillation, required tracheal intubation and mechanical ventilation. All patients had a chest radiograph, with the most common findings of bilateral interstitial opacities (5 of 10 patients), peribronchial thickening (5 of 10 patients), lobar consolidation (3 of 10 patients), and multiple pulmonary nodules (1 of 10 patients); 5 chest computed tomography scans showed focal consolidation with interlobar septal thickening and centrilobular nodules in

1 patient, scattered ground-glass opacities in 2 patients, and bilateral pulmonary nodules with prevalent centrilobular distribution in the remaining 2 patients (Figure 1). Respiratory virus serology and routine sputum cultures were negative in all patients. In 2 patients, bronchoalveolar lavage was performed and the stains and cultures of the alveolar milieu were negative for mycobacterial (also polymerase chain reaction), bacterial, and fungal infections. Cytologic analysis showed a dominant lymphocyte proportion in both patients. One patient underwent a pulmonary biopsy showing chronic mononuclear interstitial infiltrates and macrophage desquamation with obliterative and evident eosinophilic aspects. Two patients underwent pulmonary function tests showing mild and moderate restrictive ventilatory patterns with consensual reduction of carbon monoxide-diffusing capacity.

Antibiotic therapy (oral fluoroquinolones or macrolides and/or parenteral penicillins) was used as first-line monotherapy in all patients, but no significant clinical improvement was recorded in any patients. All patients received corticosteroids (prednisolone equivalent dose, 50 mg/d, tapered within 6 weeks) with prompt resolution of symptoms and of pulmonary infiltrates on follow-up chest radiograph (median, 7 weeks after onset; range, 3–12 wk).

In 1 patient, vedolizumab was restarted after pneumonitis resolution. However, symptom relapse occurred 2 weeks after rechallenge, requiring vedolizumab definitive cessation and a new course of oral corticosteroids, with improvement.

Here, we report a large series of noninfective vedolizumab-related pneumonitis. All patients developed respiratory symptoms and radiologic findings of pneumonitis after vedolizumab initiation, with full recovery after its withdrawal and steroidal therapy. Radiologic findings showed a mainly interstitial pattern, predominantly with a centrilobular distribution. Three significant features from our cohort need to be highlighted: (1) the main alternative etiologies were ruled out; (2) we reported the first case of pneumonitis relapse after vedolizumab rechallenge, supporting a causative association with drug exposure; and (3) 2 patients were bio-

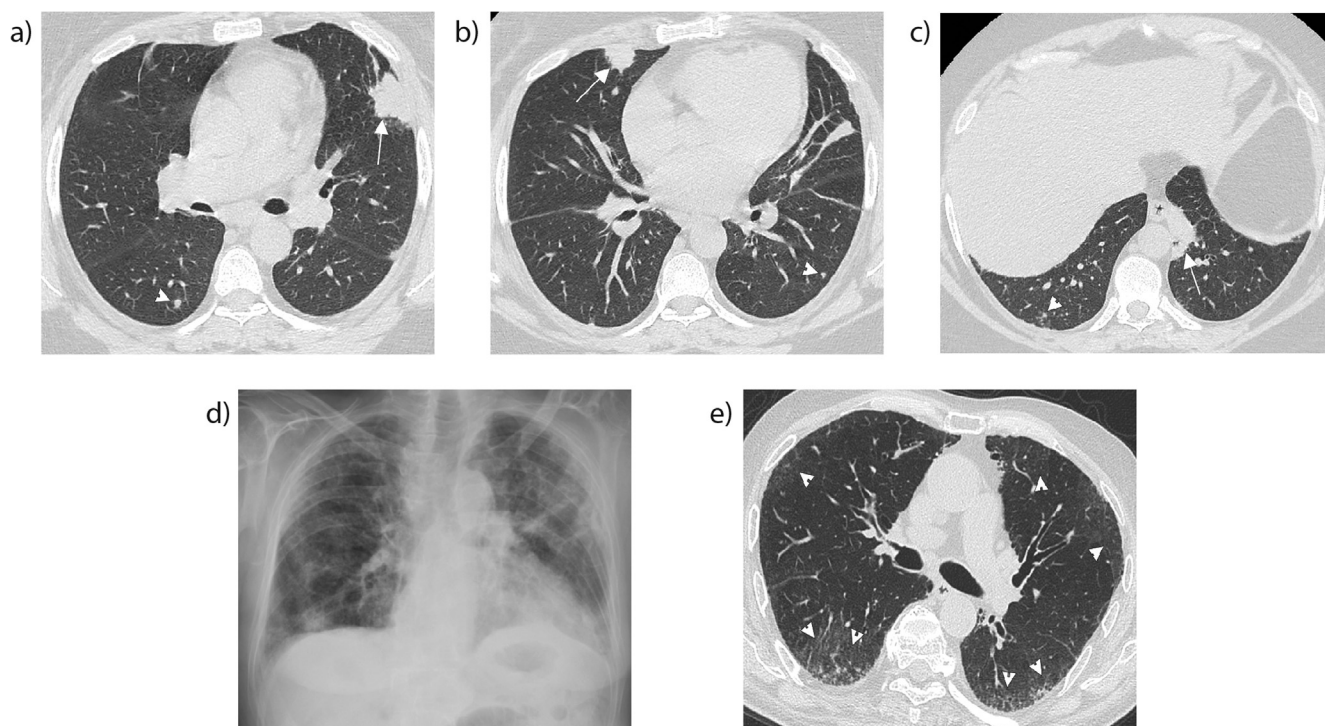


Figure 1. (A–C) Chest computed tomography (CT) scan of a patient who developed lung consolidations secondary to vedolizumab. Axial CT scans show bilateral areas of consolidation (white arrows), with subpleural patchy distribution. Some centrilobular micronodules also are evident (arrowheads), especially in the inferior lobes. (D and E) Patient who developed interstitial lung involvement secondary to vedolizumab. (D) Chest radiograph shows bilateral ill-defined hazy opacities with a reticular pattern; some alveolar opacities with peripheral distribution also are evident in midzones and in the lung bases. (E) Axial CT scan shows bilateral ground-glass areas (arrowheads) with a predominantly peripheral distribution, located primarily in the lower lobes; a superimposed septal thickening also is present in some ground-glass opacities.

naïve, excluding that DPI could represent an uncommon extraintestinal manifestation, emerged after switching from a systemic to a putatively gut-selective drug. The exact underlying mechanism has not been elucidated. The bound of vedolizumab to $\alpha 4\beta 7$ causes its internalization, making other integrins more prevalent on leukocyte surfaces⁶; under these circumstances, proinflammatory leukocytes homing might be skewed toward nonintestinal sites, where they cause immune-mediated damage. Lung endothelial cells, in response to antigen presentation, can increase the expression of E- and P-selectin, which bind $\alpha 4\beta 1$ integrin,⁷ whose expression on intestinal leukocytes is increased in vedolizumab-treated Crohn's disease patients.⁸ Limitations of our study include the limited availability of a computed tomography scan for more careful radiographic evaluation and limited availability of bronchoalveolar lavage, which could exclude mycobacterial and viral infections and allow differential cell counts to characterize the lesions.

Comprehensively, our report suggests that noninfective DRP might represent a significant and, potentially underdetected, adverse effect of vedolizumab, which can range in severity from mild to life-threatening and might require therapy suspension and out-of-class switch.

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Table 1. Patient Baseline Characteristics, Diagnostic Work-Out, and Therapeutic Outcomes

Patient	Age, y	Sex	Disease	Smoking history	Comorbidities	Previous exposure to anti TNF- α	Duration of VDZ therapy, wk	Symptoms	Laboratory findings	Radiograph CT scan	BAL	Spirometry test	Outcome
1	35	F	UC	Former	Endometriosis	Yes	12	Cough and fever	Normal	Consolidation area in the right basal area	NA	NA	Pneumonitis resolution after VDZ discontinuation and steroid therapy
2	46	F	UC	No	None	Yes	40	Cough, dyspnea, and fever	Neutrophilic and eosinophilic leukocytosis	Subpleuric consolidation areas in the bilateral basal area	Negative for bacteria, yeast, and malignant cells	Mild restrictive ventilatory pattern with mild reduction of DLCO	Admission to hospital Pneumonitis resolution after VDZ discontinuation and steroid therapy
3	71	M	UC	Former	Psoriasis	Yes	2	Cough and fever	Neutrophilic leukocytosis Slight increase in CRP level	Bronchovascular accentuation in the bilateral midbasal area	NA	NA	Pneumonitis resolution after VDZ discontinuation and steroid therapy Pneumonitis recurrence after VDZ rechallenge Resolution after VDZ discontinuation and steroid therapy
4	50	F	UC	Former	Sacroiliitis	Yes	16	Cough and fever	Neutrophilic and eosinophilic leukocytosis	Consolidation area in the right midbasal area	NA	NA	Pneumonitis resolution after VDZ discontinuation and steroid therapy
5	74	M	CD	No	Chronic heart failure and atrial fibrillation	No	4	Cough, fever, and dyspnea	Neutrophilic leukocytosis	Interstitial pneumonia in bilateral basal area	NA	Moderate restrictive ventilatory pattern with moderate reduction of DLCO	Pneumonitis resolution after VDZ discontinuation and steroid therapy

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Table 1. Continued

Patient	Age, y	Sex	Disease	Smoking history	Comorbidities	Previous exposure to anti TNF- α	Duration of VDZ therapy, wk	Symptoms	Laboratory findings	Radiograph CT scan	BAL	Spirometry test	Outcome
6	74	M	CD	No	Type 2 diabetes	No	1	Cough and fever	Neutrophilic leukocytosis and increase in CRP level	Multiple bilateral consolidation areas	NA	NA	Pneumonitis resolution after VDZ discontinuation and steroid therapy
7	38	M	UC	Former	none	Yes		Cough	Normal	Bronchovascular accentuation in the bilateral midbasal area	NA	NA	Pneumonitis resolution after VDZ discontinuation and steroid therapy
8	73	M	UC	No	Atrial fibrillation	Yes	12	Cough and dyspnea	NA	Bilateral interstitial pneumonia	Negative for bacteria, yeast, and malignant cells	NA	Admission to hospital, tracheal intubation and oxygen therapy Pneumonitis resolution after VDZ discontinuation and steroid therapy
9	52	F	CD	No	None	Yes	24	Cough and fever	NA	Right-sided lobar pneumonia	NA	NA	Pneumonitis resolution after VDZ discontinuation and steroid therapy
10	32	F	CD	No	None	Yes	32	Cough	NA	Left-sided basal pneumonia	NA	NA	Pneumonitis resolution after VDZ discontinuation and steroid therapy VDZ rechallenge without pneumonitis recurrence

BAL, bronchoalveolar lavage; CD, Crohn's disease; CRP, C-reactive protein; CT, computed tomography; DLCO, carbon monoxide diffusing capacity; F, female; M, male; NA, not applicable; TNF- α , tumor necrosis factor α ; UC, ulcerative colitis; VDZ, vedolizumab.

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Conflicts of interest

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