


## Lenalidomide-induced eosinophilic pneumonia

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### Keywords

Eosinophilia, lenalidomide, lung injury.

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### Abstract

Multiple myeloma is a plasma cell dyscrasia accounting for 10% of haematologic malignancies. Lenalidomide is an immunomodulatory drug analogous to thalidomide that is approved for use in patients with myelodysplastic syndrome, and in combination with dexamethasone for refractory or relapsed multiple myeloma. Lenalidomide is preferred to thalidomide because of reduced toxicity, and pulmonary side effects are considered rare. We present, to our knowledge, an unusual and first reported case of a patient with relapsed multiple myeloma who received lenalidomide after autologous stem cell transplant, then developed eosinophilic pneumonia presenting as dyspnoea, peripheral eosinophilia, and bilateral pulmonary opacities. Bronchoscopy with bronchoalveolar lavage was negative for infection, and transbronchial lung biopsies showed eosinophilic pneumonia. After discontinuation of lenalidomide and initiation of prednisone therapy, his dyspnoea improved and eosinophilia resolved; however, symptoms recurred when the drug was restarted at a lower dose, confirming its causative role. In the absence of infection, clinicians should always bear in mind drug toxicity in the differential diagnosis of patients receiving lenalidomide and related agents.

### Introduction

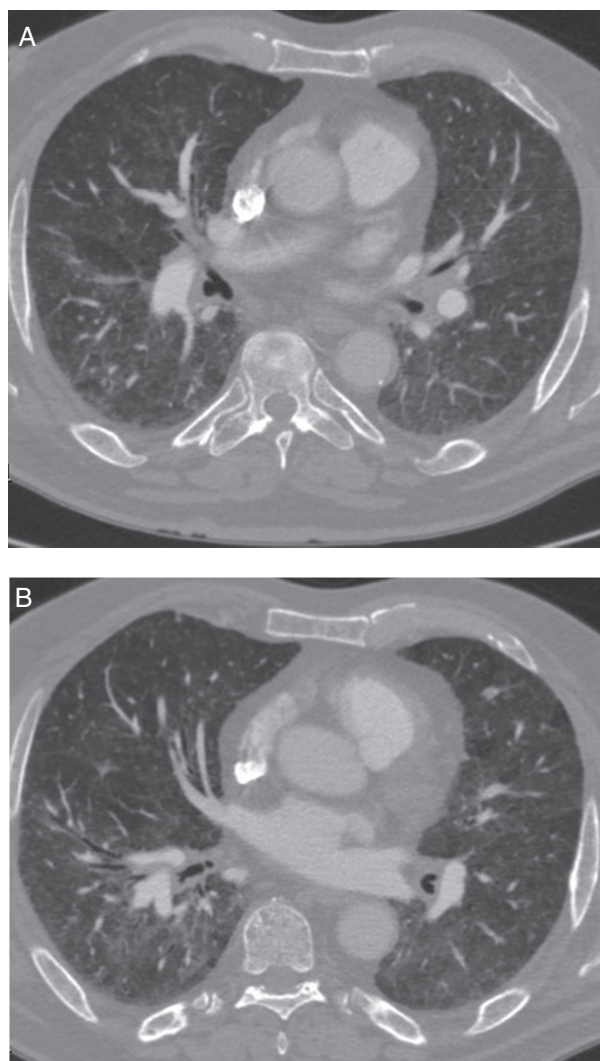
Multiple myeloma (MM) is a haematologic malignancy clinically characterized by lytic bone lesions, anaemia, and renal dysfunction. Although the introduction of targeted therapies has improved outcomes, cures remain infrequent and it is recommended that eligible patients undergo autologous stem cell transplantation (ASCT). Lenalidomide was initially approved by the Food and Drug Administration (FDA) in 2005 for treatment of myelodysplastic syndrome (MDS), and in 2006 for MM in conjunction with dexamethasone [1]. Recent data indicate that lenalidomide maintenance may improve disease-free survival in MM patients who have received ASCT [2,3]. Lenalidomide is also included in the suggested treatment algorithm of patients who are ineligible for transplantation or who have recurrent or relapsed disease [4]. Lenalidomide has a favourable side effect profile in comparison to thalidomide secondary to reduced incidence of peripheral neuropathy

[5]. There are few published case reports of pulmonary toxicity due to lenalidomide and it is possible that the incidence is under-reported [6–10]. We have reviewed the literature and are adding to it by presenting a detailed clinico-radiologic-pathologic case of eosinophilic pneumonia while on lenalidomide for maintenance after ASCT.

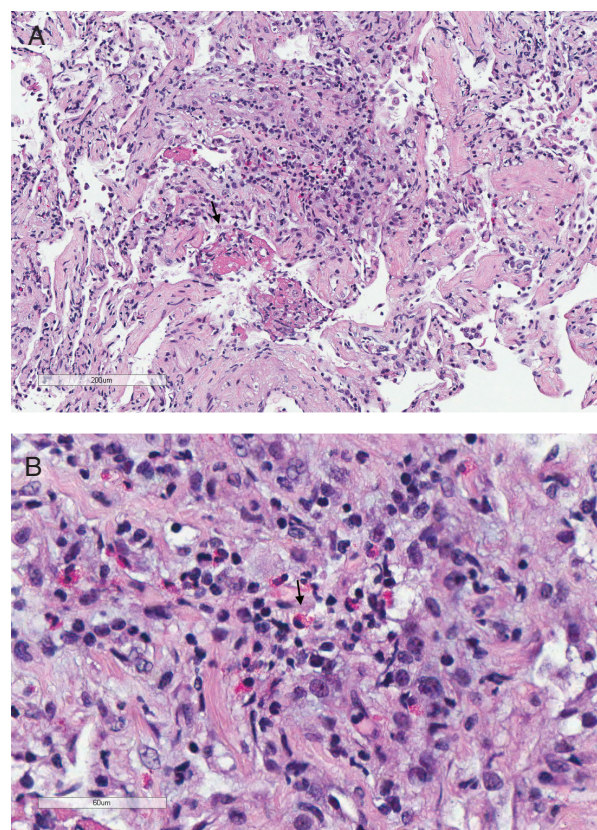
### Case Report

Our patient is a 68-year-old man, former smoker, who received a second ASCT for relapsed and refractory MM. A week and a half after his second transplantation, he had fever, skin rash, and diarrhoea. Skin biopsy was performed and he was diagnosed with a graft-versus-host-disease-like engraftment syndrome that responded well to oral and topical corticosteroids. At 100 days post-ASCT lenalidomide was initiated at 10 mg daily dose as per the institutional protocol. About two and a half months after

initiation of lenalidomide therapy, he presented with dyspnoea and dry cough but no fever. A work-up at this time revealed a white blood cell count of  $3000/\mu\text{L}$  of which 24% were eosinophils. Review of records at this time indicated that the eosinophilia had increased from less than 5% at baseline to 24% after receipt of lenalidomide. Further work-up and chest X-ray revealed non-specific lung opacities that were concerning for pneumonia. He was started on cephalexin but showed no improvement in symptoms. He then underwent computed tomography (CT) of the chest which revealed bilateral ground glass opacities and mosaic attenuation with diffuse airway wall thickening and mild upper lobe emphysema (Fig. 1A and B). CT angiography did not reveal pulmonary embolism or mediastinal lymphadenopathy. A bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial lung biopsies were then



**Figure 1.** (A and B) CT of the chest showing ground glass opacities and mosaic attenuation.



**Figure 2.** (A and B) Transbronchial biopsies showing interstitial inflammation and scattered eosinophils. (A) Low powered view showing inflammation and fibrin deposition (arrow). (B) High powered view showing eosinophils (arrow).

performed. The BAL was negative for infection, including bacterial, fungal, viral, and mycobacterial pathogens. Transbronchial biopsies obtained from all three lobes on the right lung demonstrated focal eosinophilic pneumonia, characterized by acute alveolar injury including intra-alveolar fibrin, interstitial inflammation, eosinophils, and rare poorly formed granulomas (Fig. 2A and B). Based on lung pathology findings and exclusion of infection, we established a diagnosis of drug-induced pulmonary toxicity presenting as eosinophilic pneumonia secondary to lenalidomide. The patient initially responded well to drug withdrawal and therapy with prednisone. However, due to the lack of effective alternative therapies for MM, the patient was re-challenged with a lower dose of lenalidomide at 5 mg per day. Unfortunately, the symptoms returned leading to subsequent permanent discontinuation of the drug. The patient improved clinically from a pulmonary standpoint, but had an aggressive relapse of MM. He underwent trial of cyclophosphamide, carfilzomib, dexamethasone, and thalidomide; he continued to have disease progression and eventually died while on hospice care.

**Table 1. Summary of published reports on lenalidomide-induced lung injury and clinical patterns.**

Study	Diagnosis	Bronchoscopy	Fever	Imaging	Peripheral eosinophilia	Location of care	Time on lenalidomide
Thornburg 2007 Chest [8]	HP-like syndrome	BAL Neg for infxn. 65% lymphs CD4: CD8 0.61 TBBx: non-specific inflammation	Yes	Bilateral GGO	3%	IP	2 months
Chen 2010 Pharmaco- therapy[13]	Drug-induced interstitial pneumonitis	BAL Neg for infxn. TBBx: with OP	No	Bilateral patchy GGO	No	IP	9 weeks
Lerch 2010 Onkologie [16]	Drug-induced hypersensitivity pneumonitis	BAL Neg for infxn, CD4:CD8 1.6. Cell count 41% PMNs, 15% lymphs, 6% eos TBBx: Lymphohistiocytic inflammation and granulomas	Yes	Bilateral GGO	20%	OP	2 weeks
Sakai 2011. Japanese Soc of Heme [14]	Diffuse alveolar haemorrhage	BAL Neg for infxn TBBx: haemosiderin laden macrophages	No	Bilateral GGO and partial consolidation L > R	No	ICU	7 days
Zagouri 2011. Am J Hematol [12]	Drug-induced interstitial pneumonitis NSIP pattern	No	Yes (3/8)	Bilateral GGO, NSIP	No	IP (7/8)	3–5 months
Coates 2012 J Oncol Pharm Prac [7]	Drug-induced interstitial pneumonitis NSIP pattern	No	No	Bilateral peripheral reticulation and GGO	4–6%	OP	2 months
Kunimasa 2012 Intern Med [10]	Drug-induced interstitial pneumonitis	BAL: Neg for infxn. CD4:CD8 1.8 TBBx: lymphocytic infiltrate alveoli and interstitium	Yes	Pleural effusion, 13% reticular markings, GGO	13%	IP	12 days
Amraoui 2013 Eur Resp Rev [6] (two patients)	Drug-induced interstitial pneumonitis in both	1. BAL 72% lymphs, 6% eos CD4:CD8 2.4 2. BAL 54% lymphs, 6% eos CD4:CD8 0.66	Yes (both)	1. Bilateral patchy interstitial infiltrate. 2. Bilateral GGO, LUL consolidation	No (both)	1. ICU 2. IP	1. 24 months 2. 17 months
Mankikian 2014 Heart and Lung [9]	OP and ARDS	BAL: Neg for infxn. 67% lymphs, 0% eos	Yes	Bilateral GGO and peripheral consolidation	No	ICU	8 months

HP, hypersensitivity pneumonitis; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; TBBx, transbronchial biopsies; Neg, negative; Infxn, infection; ICU, intensive care unit; IP, inpatient; OP, out-patient; GGO, ground glass opacities.

## Discussion

Drug-induced interstitial lung disease is a diagnosis of exclusion and is often not considered during initial evaluation of pulmonary infiltrates. However, drug-induced pulmonary toxicity is increasingly being recognized as a cause of both acute and chronic lung disease especially with targeted chemotherapeutic agents. Moreover, manifestations may be life-threatening and delays in diagnosis are hazardous. Although the most common manifestation is diffuse alveolar damage, toxicity spans a wide spectrum of bronchospasm, pulmonary haemorrhage, pleural effusions, pneumothorax, pulmonary embolism, and interstitial pneumonitis including eosinophilic pneumonia.

The Naranjo scale is a questionnaire designed to determine the likelihood of an adverse reaction being related to the drug in question. Scores range from 0 to 13, with a score greater than 9 indicating a definite adverse drug reaction. Our patient received a score of 9 which corresponds to the “definite” category of likelihood of drug toxicity [11]. The importance of making this diagnosis should not be understated. While drug toxicity comprises less than 5% of interstitial lung disease, this proportion also represents a group of patients that can be cured by simple withdrawal of the offending agent. A temporal relation of symptoms to drug, improvement of these symptoms after withdrawal of the drug, and characteristic imaging or pathologic features are some of the determining factors of drug-induced pulmonary toxicity.

In general, there is no particular histological or imaging feature that is specific for pulmonary drug reaction. Histological patterns of drug-induced lung injury that manifest as interstitial lung disease include acute interstitial pneumonia, hypersensitivity pneumonitis, pulmonary haemorrhage, organizing pneumonia, eosinophilic pneumonia, and non-specific interstitial pneumonia. Similar to other agents, lenalidomide use is associated with a wide spectrum of pulmonary toxicities with different acuities of presentation, radiological manifestations, and histological findings. In one study evaluating 237 consecutive unselected patients with MM or AL amyloidosis, the incidence was around 3.4% based on clinical and radiographic presentation [12]. Pulmonary toxicity from lenalidomide includes non-specific interstitial pneumonitis, hypersensitivity pneumonitis, organizing pneumonia, diffuse alveolar haemorrhage, and acute respiratory distress syndrome [13,14]. In Table 1, we review the published history of drug toxicity from lenalidomide. Although reported with thalidomide, to our knowledge, this is the first report of eosinophilic pneumonia induced by lenalidomide that was confirmed by transbronchial lung biopsy. Interestingly, there has been a single case report of eosinophilic myocarditis presumed secondary to lenalidomide toxicity [15].

Bronchoscopy remains a cornerstone for the work-up and diagnosis of drug-related pulmonary toxicity. In addition to microbiologic studies to rule out infection, the BAL may be sent for cell count and differential, as well as flow cytometry [6,9,16]. Transbronchial biopsies often reveal a non-specific histological pattern of inflammation but should be considered, if can be done safely, in immunocompromised hosts to maximize diagnostic yield in ruling out infection [17].

There is close structural homology between thalidomide and lenalidomide [1]. Our patient did receive thalidomide prior to ACST and therefore it is conceivable that prior thalidomide exposure could have primed the patient's immune system for a hypersensitivity to lenalidomide. It is unknown whether this reaction would occur with other immunomodulatory agents (IMiDs) related to lenalidomide and would thus be considered a “class effect.” But with the advent of multiple other forms of therapy for MM including proteasome inhibitors and monoclonal antibodies, it is probably best to avoid other members of the IMiD class, if possible.

In conclusion, eosinophilic pneumonia may be an adverse drug reaction related to lenalidomide use. A high index of suspicion is necessary with appropriate diagnostic tests including bronchoscopy to make the diagnosis. As additional chemotherapeutic agents become available in clinical use, the incidence of drug-induced lung injury is likely to increase. Practitioners evaluating patients with new respiratory symptoms should take a thorough medication history with close attention to temporal relationships and have high index of clinical suspicion. Infection should be ruled out, especially as this population of patients is profoundly immunosuppressed. Withdrawal of the offending agent is always the first line of therapy for a drug reaction, but corticosteroids may additionally be employed to help speed up recovery. If diagnosed early most patients should fully recuperate pulmonary function.

## Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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