In conclusion, primary pulmonary lymphatic disorders or neoplasms are rare and are often difficult to diagnose and classify [2]. Lymphatic abnormalities frequently mimic other pathologic processes, particularly neoplastic processes. These lesions are benign (as malignant change has not been documented) but tend to infiltrate surrounding tissues [8]. Provided that the tumour is completely resected, recurrences are rare. We believe this case adds a significant contribution to the literature due to its rarity and unusual location.

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Pulmonary toxicity after long-term treatment with lenalidomide in two myeloma patients

To the Editor:

A white male was diagnosed with immunoglobulin G κ-chain multiple myeloma at age 63 yrs. He initially received a combination of thalidomide, doxorubicin and dexamethasone with concomitant radiotherapy (30 Gy) to the dorsal vertebrae. The first course of this combination was complicated by profound pancytopenia and lobar pneumonia with severe sepsis in the setting of neutropenia, leading to the discontinuation of thalidomide because of concerns regarding haematological toxicity. The pneumonia was not microbiologically documented but considered as being probably of bacterial origin given the clinicoradiological presentation and a satisfying
evolution under broad-spectrum antibiotics. A diagnosis of pulmonary toxicity of thalidomide could, nevertheless, not be formally ruled out. The patient continued treatment with doxorubicin and dexamethasone, and then received consolidative high-dose melphalan with an autologous stem-cell transplant (ASCT) resulting in a partial response.

Disease progression occurred 19 months after ASCT, and bortezomib and dexamethasone were started, again resulting in a partial response. Bortezomib had to be interrupted because of peripheral neuropathy after four cycles. The disease progressed again 23 months after cessation of bortezomib and the patient was started on lenalidomide (15 mg·day⁻¹ on days 1–21, every 28 days, adapted to renal function). Dexamethasone was added during the first 2 months of treatment but then withheld because of concerns expressed by the patient regarding potential toxicity. A rapid partial response was obtained and it was decided to continue the same treatment until disease progression. The dose was eventually reduced to 10 mg·day⁻¹ on days 1–21, every 28 days, after 16 cycles because of haematological toxicity (neutropenia).

During the course of his 21st cycle of lenalidomide, the patient developed cough and fever. He was first treated with amoxicillin–clavulanate. Because of worsening symptoms and the apparition of dyspnoea, he was admitted to our hospital. Physical examination revealed polypnoea (32 cycles per minute). Oxygen saturation was 88% while breathing room air. Auscultation revealed bilateral pulmonary crackles. The white cell count showed 2,800 leukocytes per mm³ with 86% neutrophils, 8% lymphocytes and no eosinophils. Blood gas analysis revealed severe hypoxaemia. Repeated blood cultures were sterile; pneumococcus and Legionella urinary antigens were negative. The ECG was without significant changes. Brain-type natriuretic peptide concentration was 515 ng·L⁻¹ (normal range <100 ng·L⁻¹). A chest computed tomography with bolus intravenous contrast agent revealed diffuse patchy opacities (fig. 1).

The patient received empirical broad-spectrum antibiotic treatment with high-dose trimethoprim–sulfamethoxazole (the patient was taking this medication at a lower dose as a prophylaxis against *Pneumocystis jirovecii* pneumonia), spiramycin and cefotaxime, and lenalidomide was discontinued. The bronchoalveolar lavage fluid contained 500,000 cells·mL⁻¹ with 72% lymphocytes, 2% neutrophils, 6% eosinophils and 20% macrophages. Flow cytometric analysis showed that the vast majority of lymphocytes were T-cells (96%) with a CD4/CD8 ratio of 2.4. No infectious agent was found.

Despite receiving empirical diuretic therapy and supplemental oxygen, the patient’s condition worsened and the patient required mechanical ventilation. Without any other therapeutic intervention, the patient’s condition then progressively improved, permitting weaning from mechanical ventilation.

The possibility of pulmonary lenalidomide toxicity having arisen, this medication was temporarily stopped for a period of 5 months, during which the patient received no other therapy for his myeloma. The disease showed signs of progression after 5 months, thus we decided to start him again on lenalidomide 10 mg·day⁻¹ under close medical observation in the hospital. The patient was informed of the potential risks and benefits, and gave his consent. After having received only two doses of 10 mg lenalidomide, he again developed fever, cough and hypoxaemia with bilateral pulmonary infiltrates on the chest radiograph. Lenalidomide was definitively stopped and the patient’s condition quickly improved.

The myeloma was treated with three cycles of bendamustine and prednisone without efficacy, then with a combination of melphalan, cyclophosphamide and dexamethasone, which did not control the disease. The patient ultimately died from uncontrolled multiple myeloma, 7 yrs after the initial diagnosis.

A white female was diagnosed with light chain multiple myeloma at age 82 yrs. The patient was initially treated with high-dose steroids, and then received melphalan, prednisone and thalidomide. Thalidomide had to be interrupted after only 2 months because of neurological toxicity (tremor). The patient received a total of 12 courses of melphalan and prednisone, and went into partial remission. After 4 months without any specific therapy, the disease relapsed and the patient was treated with lenalidomide (10 mg·day⁻¹ on days 1–21, then every 28 days) and dexamethasone (20 mg·week⁻¹). She again went into partial remission and received a total of 17 cycles of treatment.

During the course of her 17th cycle, 3 weeks before hospital admission, she began to present a progressively worsening dyspnoea associated with cough, expectoration and fever. She received broad-spectrum oral antibiotics (amoxicillin–clavulanate and levofloxacin) without significant improvement. She finally had to be admitted to the emergency department of our hospital. On physical examination, the patient was conscious, had polypnoea (30 cycles per minute) and had an oxygen saturation of 91% while breathing room air. Auscultation revealed symmetric bilateral sibilant rales. The white cell count
showed 8,100 leukocytes per mm$^3$: 84% neutrophils, 6% lymphocytes and no eosinophils. Blood gas analysis revealed mild hypoxaemia with hyperventilation. Repeated blood cultures were sterile; pneumococcus and Legionella urinary antigens were negative. The ECG was without significant changes except tachycardia. A chest computed tomography without intravenous contrast agent revealed diffuse ground-glass opacities and consolidation of the left apex.

Lenalidomide was discontinued and a bronchoalveolar lavage was performed before the addition of any antibiotics. The bronchoalveolar lavage fluid contained 360,000 cells·mL$^{-1}$, with 54% lymphocytes, 17% neutrophils, 6% eosinophils and 25% macrophages. Flow cytometric analysis showed that the vast majority of lymphocytes were T-cells (97.8%), with a CD4/CD8 ratio of 0.66. Again, no infectious agent was found. Following bronchial endoscopy, the patient’s condition worsened and she had to be admitted to the intensive care unit. She required noninvasive ventilatory support and spiramycin was started under the hypothesis of atypical pneumonia. Serology for chlamydiae, Legionella and Mycoplasma were later obtained, and were negative. Lenalidomide was definitively discontinued. The patient’s condition progressively improved without mechanical ventilation. She is currently under treatment with bortezomib and dexamethasone for her myeloma.

Iatrogenic drug-induced pneumonias are an increasingly frequent cause of morbidity and mortality. More than 350 medications have already been implicated [1]. Pulmonary toxicity of lenalidomide seems fairly reasonable in our cases based on the exclusion of alternative causes, imaging and bronchoalveolar lavage findings, and clinical course (regression after cessation of lenalidomide in both patients and, in one case, relapse upon taking lenalidomide again).

To the best of our knowledge, five other cases of lenalidomide-associated pulmonary toxicity have been reported, all in patients with multiple myeloma [2–6]. In all these cases, the first symptoms of pulmonary toxicity appeared after a limited treatment duration (2–9 weeks), contrasting with our two patients, who developed the first symptoms after 24 and 17 months, respectively. Pulmonary toxicity has been reported in patients treated with thalidomide [1,7] and more recently with lenalidomide plus dexamethasone respectively. Pulmonary toxicity has been reported in patients treated with thalidomide [1,7] and more recently with lenalidomide plus dexamethasone versus 7.4% in the dexamethasone-treated group [8].

Physicians should be informed of this possible complication of lenalidomide therapy and evoke the diagnosis whenever a lenalidomide-treated patient presenting with pulmonary infiltrates, fever and hypoxaemia fails to improve after treatment with broad-spectrum antibiotics.

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