Int J Hematol (2012) 95:223–224
DOI 10.1007/s12185-011-0997-2

LETTER TO THE EDITOR

Interstitial pneumonitis associated with the immunomodulatory drugs thalidomide and lenalidomide

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Received: 23 August 2011 / Revised: 12 December 2011 / Accepted: 12 December 2011 / Published online: 27 December 2011

The immunomodulatory drugs (IMiDs), thalidomide and lenalidomide, and the proteasome inhibitor bortezomib have recently been indicated for multiple myeloma treatment. Although pulmonary complications associated with bortezomib are widely known [1], those of IMiDs are thought to be rare. We present a multiple myeloma patient treated with bortezomib, who subsequently developed interstitial pneumonitis (IP) after treatments with both thalidomide and lenalidomide.

A 51-year-old Japanese man was diagnosed with multiple myeloma (IgG-lambda type), Durie–Salmon stage II and International Staging System stage II in 2005. After induction therapy with vincristine, doxorubicin, and dexamethasone (VAD, 3 courses), he underwent tandem autologous peripheral blood stem-cell transplantation and achieved complete remission. However, in April 2008, he relapsed with complaints of rib pain and hypercalcemia. The recurrent multiple myeloma was a more immature non-secretory type. We immediately administered bortezomib and dexamethasone (two courses), but without effect. We, therefore, started thalidomide (100 mg, daily) in August 2009. This therapy achieved immediate symptom relief and a 5-month remission. In February 2010, he experienced dyspnea and dry cough, and visited our clinic. On admission, his temperature was 36.6°C, oxygen saturation (pulse-oximetry, room air) 86%. Laboratory work-up showed a white blood cell (WBC) count of $3.2 \times 10^3/\mu l$, hemoglobin level of 10.2 g/dl, platelet count of $11.8 \times 10^4/\mu l$, lactose dehydrogenase (LDH) of 376 IU/l, C-reactive protein (CRP) of 2.2 mg/dl, sialylated carbohydrate antigen KL-6 of 245 U/ml, surfactant protein (SP)-D of 55.6 ng/ml, negative β-D-glucan and negative leukocyte cytomegalovirus antigen. Chest X-ray and computed tomography (CT) scan revealed patchy interstitial infiltrates, ground-glass opacities and pleural plasmacytoma in both lungs (Fig. 1a), suggesting cryptogenic organizing pneumonitis pattern. Bronchoscopic biopsy showed lymphocytic interstitial infiltration and polypoid granulomatous masses in respiratory bronchiolar lumens. No malignant cells were detected in pulmonary tissues. Broncho-alveolar lavage (BAL) demonstrated 1.45×10^6 cells/ml with 64% lymphocytes (CD 4/8 ratio, 0.88), 31% macrophages, 4% neutrophils, and 1% eosinophils. Microbial culture of BAL fluid revealed neither bacterial nor fungal pathogens. Polymerase chain reaction examinations showed BAL fluid to be negative for *Pneumocystis jirovecii*, tuberculosis, and *mycobacterium avium* complex. As was suspected thalidomide to have caused these pulmonary changes, it was immediately discontinued, and prednisolone (60 mg, daily) was started. Symptoms resolved within a few days, and infiltrative lung shadows diminished within a week. In March 2010, VAD regimen re-administered for plasmacytoma progression. Six courses of VAD were partially effective, but the effect duration was limited. Therefore, lenalidomide (25 mg, day 1–21) and dexamethasone (LD: 10 mg, day 1, 8, 15) were started in September 2010. On day 24 of the first LD course, the patient developed a cough. Oxygen saturation was 96% at room air. Chest CT revealed ground-glass opacities of the lung (Fig. 1b), suggesting non-specific IP. Laboratory data including WBC counts, CRP, LDH, KL-6 and SP-D were within normal ranges. Lenalidomide was immediately discontinued. As symptoms were mild, we did not administer prednisolone, instead only observed the clinical course. Two weeks later, interstitial change had diminished and we

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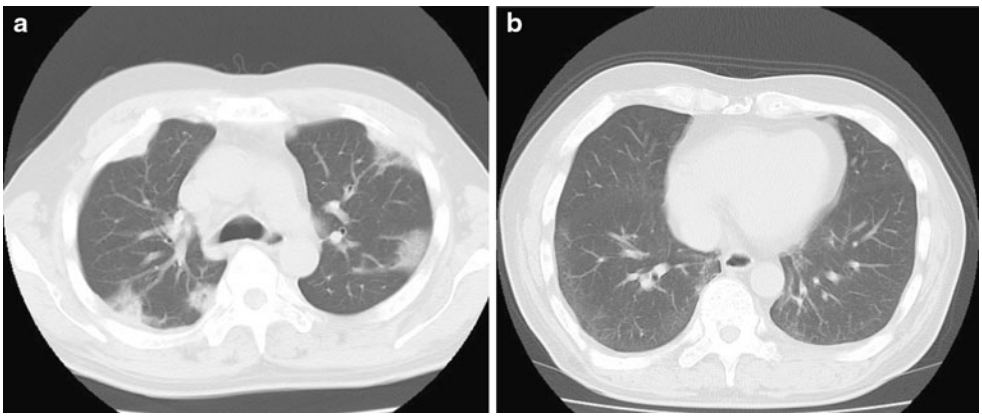

Fig. 1 Chest CT scans obtained **a** on the day of hospital admission in February 2010, exhibiting bilateral patchy lung infiltrates, ground-glass opacities and pleural plasmacytoma, and **b** on day 24 of lenalidomide administration in September 2010, exhibiting bilateral lung ground-glass changes predominantly in the subpleural area

re-administered lenalidomide, but at a low dose (5 mg, day 1–21), with dexamethasone (20 mg, day 1, 8, 15). In January 2011 (after two courses of low-dose LD), he again complained of cough. Chest CT findings resembled the first IP episode after lenalidomide. LD was again discontinued, and he was observed until the cough resolved. Thromboembolism was excluded by normal plasma D-dimer levels during treatments with both IMiDs. Since February 2011, he has received melphalan, prednisolone, and bortezomib, and obtained a partial response. We chose this bortezomib-containing regimen as there were no pulmonary toxicities with previous bortezomib treatment. He has had no respiratory symptoms since discontinuation of IMiDs.

In our present case, although neither bronchoscopy nor laboratory data revealed the cause of IP, infection and malignancy were unlikely to account for his symptoms judging from the clinical course. Radiological findings and rapid improvement after IMiD cessation and corticosteroid administration strongly suggest pulmonary toxicity of IMiDs.

Several myeloma patients treated with thalidomide have reportedly developed IP [2–4], and the pulmonary toxicity of lenalidomide has also recently been described [5–7]. One patient developed thalidomide-induced pneumonitis, but showed good tolerance to subsequent lenalidomide treatment [8]. Furthermore, there were patients with good tolerance to thalidomide, who subsequently developed lenalidomide-induced pulmonary complications [6, 9]. Therefore, a specific drug-induced hypersensitive mechanism has been suggested to account for this adverse event. However, our case suggests that drug-class specific pulmonary toxicities of IMiDs must also be considered. To our knowledge, this is the first case report of pulmonary toxicities to both thalidomide and lenalidomide. Although the mechanisms underlying IMiD-induced pulmonary toxicities remain unknown, different immunomodulatory profiles such as tumor necrosis factor-α down-regulation properties of thalidomide and lenalidomide [10] may contribute to the development of different IP patterns. Physicians should be aware of pulmonary complications in patients who develop respiratory symptoms while being treated these medications.

Conflict of interest The author declares that he has no conflicts of interest.

References

1. Miyakoshi S, Kami M, Yuji K, Matsumura T, Takatoku M, Sasaki M, et al. Severe pulmonary complications in Japanese patients after bortezomib treatment for refractory multiple myeloma. Blood. 2006;107:3492–4.
2. Iguchi T, Sakoda M, Chen CK, Yokoyama K, Hattori Y, Ikeda Y, et al. Interstitial pneumonia during treatment with thalidomide in a patient with multiple myeloma. Rinsyo Ketsueki. 2004;45:1064–6.
3. Onozawa M, Hashino S, Sogabe S, Haneda M, Horimoto H, Izumiyama K, et al. Side effects and good effects from new chemotherapeutic agents. Case 2. Thalidomide-induced interstitial pneumonitis. J Clin Oncol. 2005;23:2425–6.
4. Sasaki M, Isobe Y, Tsukune Y, Kawahara S, Hamano Y, Ando J, et al. Thalidomide may induce interstitial pneumonia preferentially in Japanese patients. Eur J Haematol. 2009;82:73–4.
5. Thornburg A, Abonour R, Smith P, Knox K, Twigg HL. Hypersensitivity pneumonitis-like syndrome associated with the use of lenalidomide. Chest. 2007;131:1572–4.
6. Lerch E, Gyorik S, Feilichenfeldt J, Mazzucchelli L, Quadri F. A case of lenalidomide-induced hypersensitivity pneumonitis. Onkologie. 2010;33:249–52.
7. Chen Y, Kiatsimkul P, Nugent K, Raj R. Lenalidomide-induced interstitial lung disease. Pharmacotherapy. 2010;30:325.
8. Pretz J, Medeiros BC. Thalidomide-induced pneumonitis in a patient with plasma cell leukemia: no recurrence with subsequent lenalidomide therapy. Am J Hematol. 2009;84:698–9.
9. Sakai M, Kubota T, Kuwayama Y, Ikezoe T, Yokoyama A. Diffuse alveolar hemorrhage associated with lenalidomide. Int J Hematol. 2011;93:830–1.
10. Muller GW, Chen R, Huang SY, Corral LG, Wong LM, Ocampo CJ, et al. Amino-substituted thalidomide analogues; potent inhibitors of TNF-alfa production. Bioorg Med Chem Lett. 1999;9:1625–30.