CASE REPORT
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# Thalidomide Induced Nonspecific Interstitial Pneumonia in Patient with Relapsed Multiple Myeloma

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A 63-year-old female diagnosed with relapsed multiple myeloma visited our hospital complaining of a persistent cough. Since July 2006, she had been taking 100 mg thalidomide daily and gradually developed shortness of breath and a persistent dry cough. A chest X-ray and computed tomography showed ground glass opacities in both lungs. An open lung biopsy of the right middle lobe under general anesthesia revealed chronic peribronchial inflammation, mild interstitial fibrosis, and intra-alveolar macrophage infiltration, with some hemosiderin features, compatible with non-specific interstitial pneumonia (NSIP). After discontinuing the thalidomide, the patient's symptoms did not deteriorate, although the radiographs did not improve. The patient is alive and well with regular outpatient follow-up without progression of the NSIP. **(Korean J Intern Med 2010;25:447-449)**

**Keywords:** Lung diseases, interstitial; Thalidomide; Multiple myeloma

## INTRODUCTION

Thalidomide has anti-angiogenic and immunomodulatory effects. Recently, it has been used increasingly worldwide as a first-line and salvage therapy for multiple myeloma. Pulmonary adverse effects of thalidomide are rare, although the use of thalidomide alone or combination with steroids was recently reported to cause pulmonary embolism and "bronchiolitis obliterans with organizing pneumonia." Because cases of drug-induced non-specific interstitial pneumonia (NSIP) are rare, we report this case of NSIP that occurred in a patient with multiple myeloma.

## CASE REPORT

A 63-year-old female visited our hospital complaining of shortness of breath and a persistent dry cough. She had been diagnosed with multiple myeloma in September 1998 and achieved complete remission with first-line cyclophosphamide and prednisolone treatment. In March 2004, elevated M-protein was detected on serum electrophoresis, and vincristine, adriamycin, and dexamethasone chemotherapy was administered, which partially relieved her symptoms. In January 2005, disease progression was observed and combined bortezomib and dexamethasone chemotherapy was given, resulting in complete remission. In June 2006, elevated M-protein was again detected on serum electrophoresis, so she was given 100 mg thalidomide daily beginning in July 2006. Beginning in December 2006, the patient reported a persistent dry cough and dyspnea on exertion.

Coarse breath sounds were heard in both lungs. Pulmonary function tests revealed a restrictive ventilatory defect (FVC, 1.13 L, 50.4% of normal predicted value; $FEV_1$, 1.06 L, 56.8% of normal predicted value; normal $FEV_1$/FVC, 88.3%). Her arterial blood gas analysis showed hypoxia on room air (pH, 7.37; $PO_2$, 59 mmHg; $PCO_2$, 49

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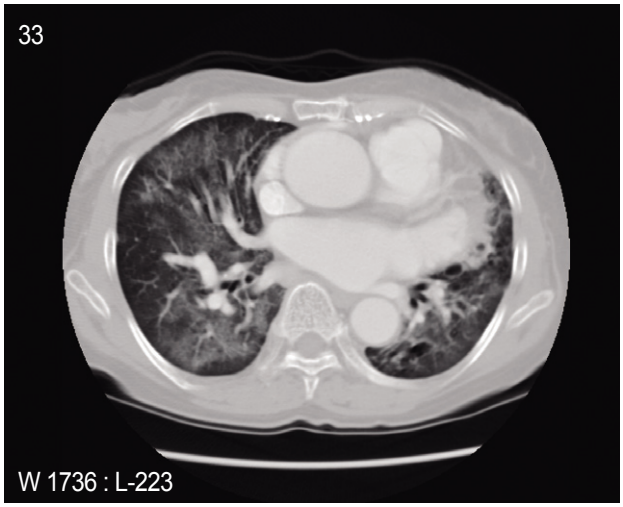


**Figure 1.** Computed tomography of the lung showed new bilateral patchy ground-glass opacities and underlying bronchiectasis.

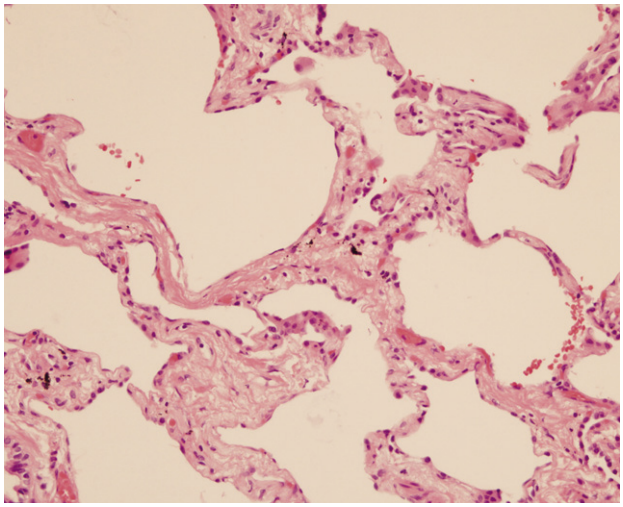

**Figure 2.** The open lung biopsy revealed chronic peribronchial inflammation, mild interstitial fibrosis, and intra-alveolar infiltration with some hemosiderin features, consistent with non-specific interstitial pneumonia (H&E, × 200).

mmHg; $O_2$ saturation, 90%).

Gram staining and special stains of sputum for acid-fast bacilli, *Pneumocystis carinii*, and fungi were negative. Routine cultures for bacteria, fungi, and mycobacteria showed no growth. The chest X-ray showed progressive infiltration of both lung fields. Computed tomography (CT) of the lungs revealed new bilateral patchy ground-glass opacities, suggestive of interstitial pneumonitis and underlying bronchiectasis (Fig. 1).

Extrathoracic echocardiography showed normal left ventricular contractility with an unaltered ejection fraction and the cardiac enzymes were normal. Chest CT angiography showed no evidence of pulmonary artery embolism. Fiberoptic bronchoscopy revealed no evidence of an endobronchial lesion. No malignant cells were found in the bronchoalveolar lavage fluid (BALF).

Gram stains, special analysis, and cell cultures of BALF and sputum following fiberoptic bronchoscopy were negative for bacteria, acid-fast bacilli, fungi, and *P carinii*. The results of a polymerase chain reaction study and viral culture of BALF were negative for cytomegalovirus. A bronchoscopyguided transbronchial lung biopsy was performed and showed non-specific chronic inflammation.

The use of thalidomide was suspended for 1 month, and no further deterioration of her symptoms was detected. In February 2007, the use of thalidomide was resumed. Two months later, the chest X-ray and CT showed progression of the diffuse ground-glass appearance in both lungs, and her dyspnea on exertion had worsened. In April 2006, to assess causality, an open lung biopsy of the right middle lobe was performed under general anesthesia. This showed chronic peribronchial inflammation, mild interstitial fibrosis, and intra-alveolar infiltration, with some hemosiderin features, compatible with NSIP (Fig. 2). Subsequently, the thalidomide was stopped completely, and the chest X-ray and CT 1 month later showed slight improvement in the bilateral pulmonary lesions, along with some symptom improvement. She is alive and doing well on regular outpatient follow-up with no progression of the NSIP after discontinuing thalidomide.

## DISCUSSION

Thalidomide was developed as an antiemetic drug in the 1950s and found to induce congenital anomalies, so its use was banned. Since 1998, based on the fact that this drug exerts anti-angiogenic and immunomodulatory effects, its use as a standard therapeutic agent for multiple myeloma has increased [1]. Common reported side effects of thalidomide include constipation, vertigo, edema, fatigue, emotional change, and peripheral neuropathy [2].

Drug-induced interstitial pneumonia has been reported with approximately 20 types of drug, including various antibiotic, chemotherapeutic, and anti-inflammatory agents [3]. In most cases, the symptoms of drug-induced interstitial pneumonia develop within a few weeks to a few months after drug administration, and there is rapid symptom improvement after discontinuing the drug. To diagnose drug-induced interstitial pneumonia, it is important to rule out other infections and malignant tumors and to suspect that the symptoms are induced by specific drugs.

Pulmonary embolism is the most frequent respiratory side effect of thalidomide, while interstitial pneumonia is very rare [4-6]. A case report described a pattern of right-side heart failure and concomitant dyspnea, with features of interstitial pneumonia on a chest X-ray [7]. On discontinuing the thalidomide, this patient's symptoms improved; however, because no chest CT or bronchoscopic findings were described in this case, it could not be concluded that the pulmonary side effects were definitely caused by thalidomide. Another case report describes pulmonary toxicity that occurred during treatment with docetaxel and thalidomide in three patients with hormone-refractory prostate cancer [8]. One of the patients shows interstitial pneumonia, although it was determined that the main cause of the pulmonary toxicity in this patient was more likely docetaxel than thalidomide.

In 2005, a case of typical interstitial pneumonia induced by thalidomide was reported [9]. Chest CT showed diffuse interstitial infiltration and cultures of BALF and sputum obtained by bronchoscopy were negative. After discontinuing the thalidomide, the patient's symptoms and chest radiographs improved, although the results were not validated histologically by a biopsy.

Thalidomide-induced interstitial pneumonia should be suspected in patients who develop dyspnea, cough, and fever after taking thalidomide, without a definite cause, when the chest X-ray shows a diffuse pulmonary infiltration [4-6,9].

Our patient had an ongoing cough and dyspnea on exertion after taking thalidomide, and pulmonary infection, malignant tumor, and lung involvement of multiple myeloma were excluded through various tests. We diagnosed this case as NSIP, based on an open lung biopsy, and thalidomide was suspected to be cause. The drug was discontinued, and subsequently her symptoms improved.

When patients taking thalidomide have persistent respiratory symptoms without a definite cause, drug-induced interstitial pneumonia should be considered, although rare, and appropriate examinations and management of this disease should be considered.

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

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