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Case Report

Bronchiolitis Obliterans Organizing Pneumonia Induced by Minocycline

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We report a case of bronchiolitis obliterans organizing pneumonia (BOOP) caused by minocycline (MINO). A 59-year-old man visited to our hospital because of flu-like symptoms. He had been treated with MINO for a few weeks for the skin eruption. The chest radiograph showed consolidations in both lung fields. He was admitted to our hospital for further examination. An elevation of lymphocyte percentage was seen in his bronchoalveolar lavage and a diagnosis of BOOP was confirmed by video-assisted thoracoscopic lung biopsy. The symptoms, laboratory and radiological findings gradually improved without steroid therapy. Although the lymphocyte stimulation test (LST) of peripheral blood for MINO was negative, a positive oral provocation test confirmed the role of MINO in the induction of BOOP.

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Introduction

Bronchiolitis obliterans organizing pneumonia (BOOP) is mainly diagnosed pathologically as an interstitial pneumonia characterized by the presence of granulation tissue and infiltration of inflammatory cells in the terminal and respiratory bronchioles. It is important to distinguish BOOP from other pulmonary diseases, especially idiopathic pulmonary fibrosis, because BOOP can respond well to steroid therapy and its prognosis is usually benign[1].

Minocycline (MINO) is a frequently used antibiotic for various infections such as inflammatory skin diseases, purulent injuries, upper respiratory infections, and atypical pneumonia. Several adverse effects have been reported for MINO. These include vestibular disturbances, candida infection, gastrointestinal disturbance, cutaneous symptoms (pigmentation, pruritus, photosensitive rash and urticaria), discoloration of the bone and dentition, benign intracranial hypertension, lupus syndrome, hypersensitivity reaction, autoimmune hepatitis, and pneumonitis[2-7]. In one study, side effects were recorded in 13.6% of patients with acne vulgaris who were treated with 100-200 mg/day MINO[2].

However, it is rare that MINO causes BOOP as a pulmonary involvement, although more than twenty cases of "MINO-induced pneumonitis" have been reported in Japan as "drug-induced pneumonitis" or "eosinophilic pneumonia"[8-10]. We encountered a rare case that was diagnosed as MINO-induced BOOP pathologically by video-assisted thoracoscopic lung biopsy (VATS-LB). The diagnosis was confirmed by a positive oral provocation test.

Case Report

A 59-year-old man, a non-smoker, had a skin eruption on the left hand for more than 10 years, which was noticed to grow slowly during this period. He visited the dermatology clinic at the local hospital on March 30th, 1998. Infection was highly suspected, which was treated with MINO at 200 mg/day orally from March 31st to April 19th. However, he became unwell on April 13th and complained of general malaise on April 17th. Fever (38.7℃) and dry cough appeared on April 19th. He visited a clinic on April 24th because of exertional dyspnea with Hugh-Jones II°.

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Chest X-ray showed abnormal shadows in the both lung fields and C-reactive protein (CRP) was 21.0 mg/dl. The patient was transferred to our hospital for further examination of the abnormal shadows of the chest X-ray on April 30th.

On admission, he was 160 cm tall and weighed 53 kg. Body temperature was 36.7℃, pulse rate 78 bpm, and blood pressure 134/80 mmHg. Examination of the cardiovascular system was normal and normal vesicular breath sound was heard over the lungs. There were no abnormal findings on examination of the abdomen, lower extremities or nervous system. A red eruption, measuring 5×5 cm, was noted on the dorsum of the left hand. Laboratory tests on admission showed the followings. Hemoglobin (Hb) 13.7 g/dl, red blood cells (RBC) $475\times10^4/\mu$l, white blood cells (WBC) 10,800/μl, neutrophils 75%, lymphocytes 12%, monocytes 10%, basophils 2%, and eosinophils 1%, platelet count $42.8\times10^4/\mu$l, total protein 6.5 g/dl, albumin 51.0%, α1-globulin (gl) 5.1%, α2-gl 12.3%, β-gl 11.2%, γ-gl 20.4%, CRP 2.45 mg/dl, RA test was negative, and anti-nucleus antibody (ANA) test was negative. Anti-viral antibodies were negative except anti-parainfluenza 3 virus (HI): ×512, and anti-RS virus (CF): ×8. Respiratory function tests showed restrictive ventilatory impairment; with vital capacity (VC) 1.95 l, %VC 57.9%, forced expiratory volume in 1 second (FEV_1) 1.66 l, FEV_1%; FEV_1/forced vital capacity (FVC) 85.1%, residual volume (RV)/total lung capacity

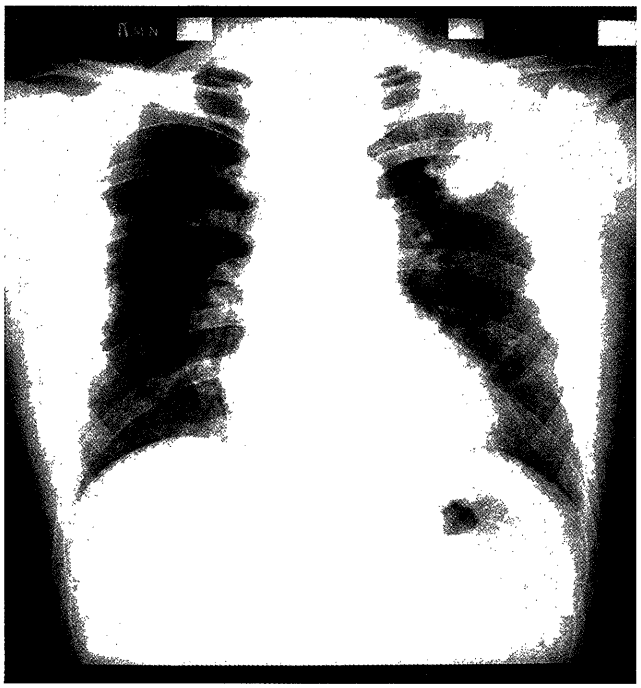

Figure 1. Chest X-ray film on admission shows consolidations in both left and right middle lung fields and the left upper lung field, mainly in the peripheral lung zones.

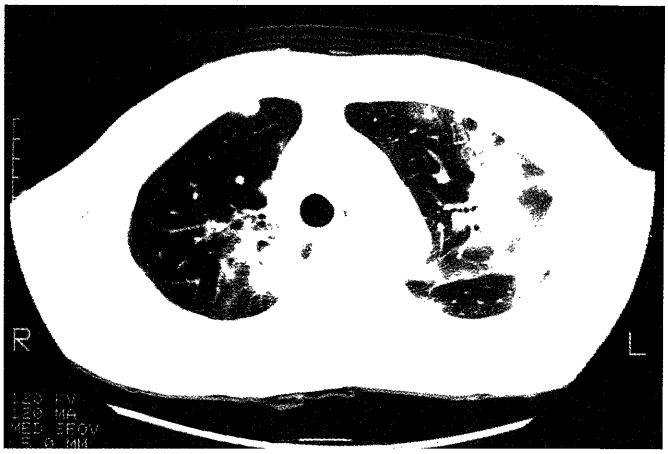

Figure 2. Chest CT scan on admission shows consolidations in both upper lobes and lS^6, mainly located in subpleural region.

(TLC) ratio 35.5%. Arterial blood gas analysis under room air revealed; PaO_2 78.8 torr, $PaCO_2$ 42.4 torr, pH 7.451. A chest X-ray film showed consolidations in both right and left middle lung fields and the left upper lung field, mainly in peripheral lung zones (Fig 1). Chest computed tomography (CT) scan revealed consolidations in bilateral upper lobes and left S^6, mainly located in the subpleural region (Fig 2). Cytological examination of inducible sputum was negative. Bronchoscopic examination was performed on day 7 after admission. A fiberscope was wedged into left B^3 and bronchoalveolar lavage (BAL) was performed. Only 50 ml of sterile physiological saline was instilled once because of severe cough. Sixteen ml of BAL fluid (F) was retrieved, and analysis of BALF showed increased percentage of lymphocytes; total cell count of 2.9×10^5/ml, macrophages 22.0%, neutrophils 13.0%, lymphocytes 60.0%, eosinophils 4.0%, CD4/CD8 ratio 0.62. Subsequently, VATS-LB was performed on day 19. Pathological findings of the specimens from left S^6 were as follows; there were no necrosis, hyaline membrane, large space of fibrosis, or malignant cells. There were centrilobular granulation tissues. Accumulations of foamy cells, macrophages containing rich lipid, and infiltration of lymphocytes were seen in the small airways including respiratory bronchioles and alveolar ducts. Diffuse but mild thickening of alveolar wall was evident with proliferation of type II alveolar cells and mild fibrosis. Normal alveolar wall was noted in only about 5% of all alveoli (Fig 3A, B). Based on the above features, BOOP was established as the final diagnosis. Spontaneous recovery was noted on conservative treatment; dyspnea gradually disappeared, the inflammatory signs became negative, and the shadows on chest X-ray gradually improved as we

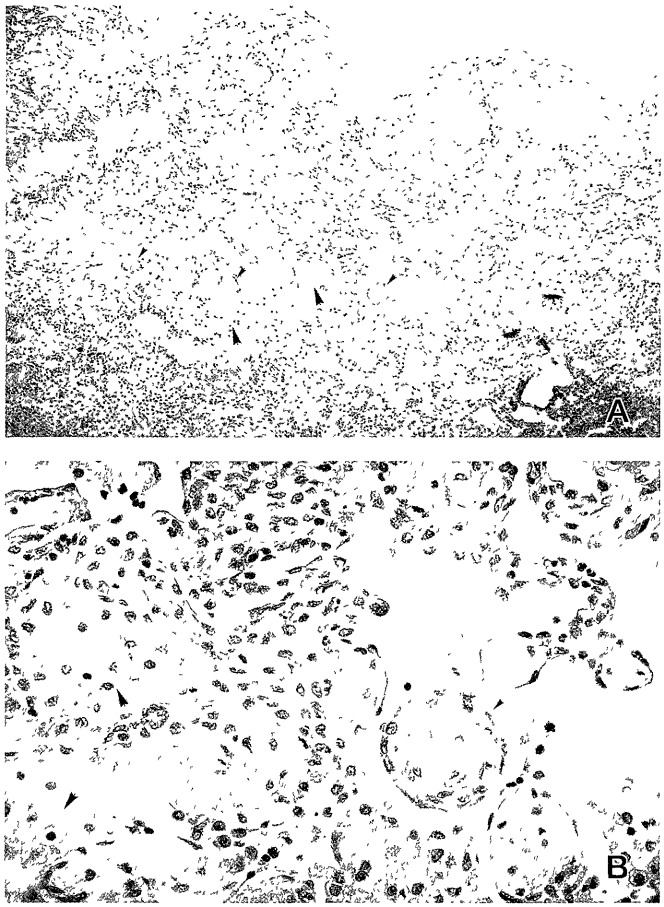

Figure 3. Histopathological findings of VATS-LB specimens from left S^6. (A) Note the presence of centrilobular granulation tissues (small arrowhead) and accumulation of macrophages (big arrowhead) (HE stain, × 16). (B) Granulations (small arrowhead) and foamy cells (big arrowhead) are seen in the small airways (HE stain, ×80).

could not detect them.

The patient was seen at follow-up visit the dermatology clinic on June 9th in order to receive therapy for the skin eruption on the left hand. The lesion was diagnosed as the granuloma by common bacterial infection, because the results of the skin cultures of the eruption in the local hospital were negative for atypical mycobacterium and sporotrichum. MINO was administered at 200 mg twice daily for two days. Fever of 39.3℃, cough and yellow sputum appeared on June 10th. Laboratory data were as follows; WBC 19,400/μl , neutrophils 83%, lymphocytes 1%, monocytes 10%, basophils 0%, eosinophils 6%, platelet count 17.3×10^4/μl, CRP 19.74 mg/dl. The lymphocyte stimulation test (LST) of peripheral blood for MINO was negative. A chest X-ray film and chest CT scans showed recurrent shadows at the same regions seen on admission. Symptoms and abnormal shadows improved gradually without steroid therapy after discontinuation of MINO. The above clinical presentation confirmed MINO-induced BOOP, i.e., incidental positive oral provocation test.

Discussion

The differential diagnosis in our patient included hypersensitivity pneumonitis, drug-induced pneumonitis, non-specific interstitial pneumonia (NSIP), or BOOP based on analysis of BALF, which showed increased percentage of lymphocytes and low CD4/CD8 ratio[11]. Pathological findings of the specimens by VATS-LB were consistent with the findings of BOOP. We had excepted BOOP induced by MINO out of differential diagnosis by misleading, because BOOP induced by MINO was too rare. There was only one case report of BOOP induced by MINO at that time. We introduced our patient to the dermatology clinic as a patient of idiopathic BOOP and we did not give the patient's history of MINO in details. The eruption was diagnosed as common bacterial infection and MINO was administered again. As a result, the oral provocation test for MINO was positive and secondary BOOP as an adverse reaction to MINO was diagnosed.

More than 20 cases of MINO-induced pneumonitis have been reported in the Japanese literature as drug-induced pneumonitis or eosinophilic pneumonia[8-10]. The final diagnosis in these cases was based on examination of bronchoalveolar lavage (BAL), transbronchial lung biopsy (TBLB), and/or clinical course. Histopathologically, most cases showed infiltration of eosinophils[8-10] . However, our case exhibited histopathological features consistent with BOOP by VATS-LB, which was induced by MINO, although most reported cases were negative to LST, similar to our case.

To our knowledge, only two cases of MINO-induced BOOP were reported[12 13]. Piperno et al.[12] reported a 20-year-old female patient with MINO-induced BOOP, diagnosed by open lung biopsy. The patient had no symptoms and signs. Chest radiologic findings included alveolar opacities, and lung function tests showed a mild restrictive ventilatory defect. The second case of MINO-induced BOOP was reported by Kondo[13]. The patient was 39-year-old woman who had been treated for acne with MINO as well as the first case. She had dry cough, and chest CT scans showed multiple ring-shaped opacities in both lungs. She was diagnoted by TBLB and her clinical course, although she was negative to LST, similar to most cases of MINO-induced pneumonitis. No provocation tests were performed in those two cases.

Several groups have reported cases of drug-induced BOOP including sulfasalazine[14], penicillamine[15], bleomycin[16], nitrofurantoin[17], phenytoin[18] and amiodarone[19, 20]. The clinical features of these patients, chest X-ray findings, clinical course, and prognosis resemble those of other types of BOOP[13-19]. Therefore, physicians should be aware of BOOP as a possible adverse effect of MINO, although the underlying mechanisms involved in the induction of BOOP by the above drugs remain to be identified.

In conclusion, a case history of treatment with MINO, fever, dyspnea, cough, inflammatory signs on laboratory data, restrictive respiratory dysfunction and alveolar opacities on radiological examination, may suggest MINO-induced BOOP. However, pathological diagnosis is necessary to rule out other types of drug-induced pulmonary diseases such as eosinophilic pneumonia, hypersensitivity pneumonitis, diffuse interstitial pneumonia, or fibrosis.

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