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CASE REPORT

Tacrolimus-induced lung injury in a rheumatoid arthritis patient with interstitial pneumonitis

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Abstract A 74-year-old woman was experiencing rheumatoid arthritis complicated with interstitial pneumonitis (IP), and tacrolimus treatment was started. She presented with dyspnea. Chest X-ray and computed tomography (CT) showed ground-glass opacity and IP. Although tacrolimus was stopped, she died of respiratory failure. At autopsy, both the upper and lower lung fields showed usual IP and the organizing stage of diffuse alveolar damage. The former is common, but the latter is uncommon, suggesting tacrolimus may cause severe alveolar damage.

Keywords Rheumatoid arthritis · Tacrolimus · Interstitial pneumonitis

Introduction

Tacrolimus is an immunosuppressant often administered following organ transplantation [1, 2]. Moreover, in Japan, it has been administered to about 9,000 patients as a disease-modifying antirheumatic drug (DMARD) for treating rheumatoid arthritis (RA) [3]. Hyperglycemia and renal dysfunction are known to be adverse events associated with tacrolimus, but lung injury occurs more rarely with tacrolimus than with methotrexate. Until now, in fact, there have been no reports of tacrolimus-induced lung injury among RA patients, whether or not their condition was complicated by interstitial pneumonitis (IP). In this report, we describe a case in which tacrolimus induced severe lung injury in an RA patient with IP, resulting in her death from respiratory failure.

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Case report

The patient was a 74-year-old woman diagnosed in 2000 at another hospital as having RA complicated by IP. Initially, auranofin, salazosulfapyridine, and bucillamine were used to treat the RA, but they proved ineffective. In March 2002, the patient visited our hospital for further treatment, and salazosulfapyridine, D-penicillamine, and etanercept were prescribed, which also proved ineffective. In January 2006, therefore, tacrolimus was started at 1 mg/day. At this time, serum Krebs von der Lungen (KL)-6 levels were 1,710 U/ml (normal range <500 U/ml); surfactant protein (SP)-D was 245 ng/ml (normal range <110 ng/ml). Chest X-rays (Fig. 1) and chest computed tomography (CT) (Fig. 2) showed an interstitial shadow on the lower parts of the lungs. When that therapy, too, proved ineffective, the dose was increased to 2 mg/day, but the RA remained refractory. On 15 July 2006, the patient presented complaining of dyspnea at rest, which worsened over the next 2 weeks. On 29 July 2006, she visited our hospital emergency room.

On physical examination, it was apparent the patient was having a very difficult time breathing. Her vital signs

were as follows: temperature 36.5°C, pulse 110 beats/min, respiratory rate 20 breaths/min, blood pressure 120/78 mmHg, and arterial oxygen saturation by pulse oximetry 82% on room air. A chest examination was notable for bilateral inspiratory fine crackles at the bases. Cardiac examination revealed tachycardia without murmurs, rubs, or gallops. Her abdomen was soft with no distension and normal bowel sounds and no hepatosplenomegaly. Her extremities showed the stigmata of RA, with swelling of the left wrist joint and bilateral knee joints.

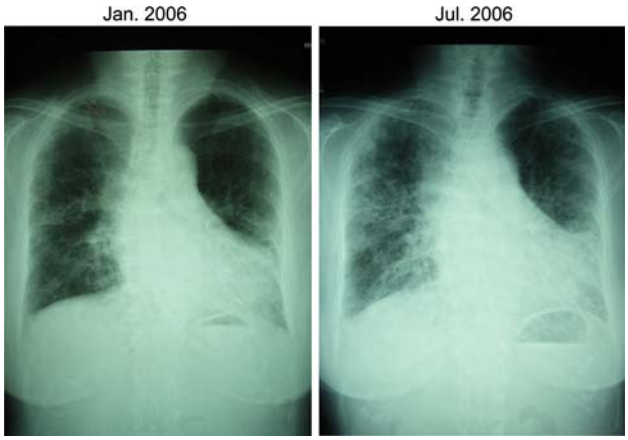

Fig. 1 Left-sided chest radiograph showing an interstitial shadow on the lower lungs (Jan. 2006). Right-sided chest radiograph showing ground-glass opacity on the upper parts of both lungs and an interstitial shadow on the lower lungs (July 2006)

Laboratory findings at the time of admission showed a white blood cell count of 12,900/mm^3 and a hemoglobin level of 12.5 g/dl. Results of liver and renal function tests were normal, as were levels of serum protein, electrolytes, glucose, and calcium. Erythrocyte sedimentation rate was 93 mm/h, C-reactive protein level was 6.3 mg/dl, and lactate dehydrogenase was 505 IU/L (normal range 130–220 IU/L). Serum KL-6 level was 2,520 U/ml and SP-D was 1,190 ng/ml, both of which were elevated compared with before tacrolimus treatment for RA. Serum tacrolimus level was 4.6 ng/ml. Tests for *Candida*, *Aspergillus*, and cytomegalovirus antigenemia were all negative. Sputum cultures for bacteria, tuberculosis, and *Pneumocystis* pneumonia also were all negative. Chest X-rays (Fig. 1) and CT (Fig. 2) showed ground-glass opacity on the upper parts of both lungs and an interstitial shadow on the lower parts of the lungs.

The patient was then admitted to our hospital, tacrolimus administration was stopped, and administration of pulsed methylprednisolone, various antibiotic and antifungal drugs, and a sulfamethoxazole–trimethoprim combination was begun in an effort to treat the lung disease. The patient's oxygenation level continued to decline, however, and her chest X-ray findings worsened. She was then placed on a ventilator and administered pulsed cyclophosphamide as well as cyclosporine A and prednisolone. Despite our efforts, the patient died of respiratory failure (Fig. 3). At autopsy, both the upper and lower lung

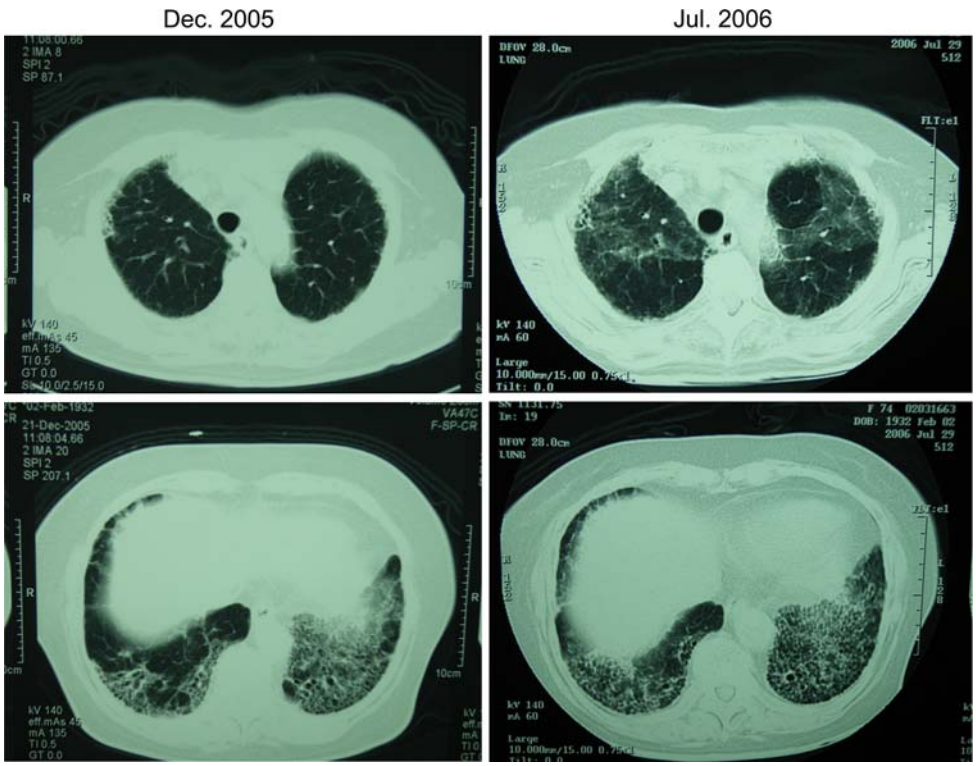

Fig. 2 Left-sided chest computed tomography (CT) showing an interstitial shadow on the lower lungs (Dec. 2005). Right-sided chest CT showing ground-glass opacity on the upper parts of both lungs and an interstitial shadow on the lower lungs (July 2006)

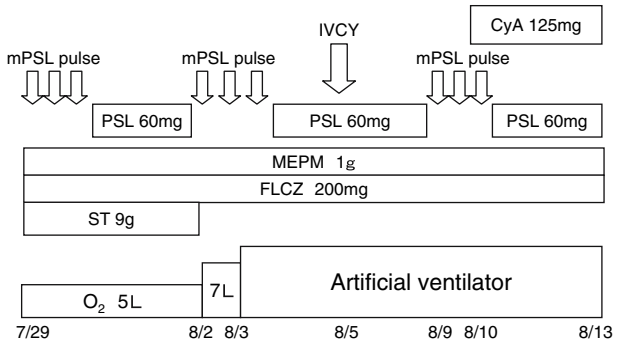

Fig. 3 Clinical course after admission

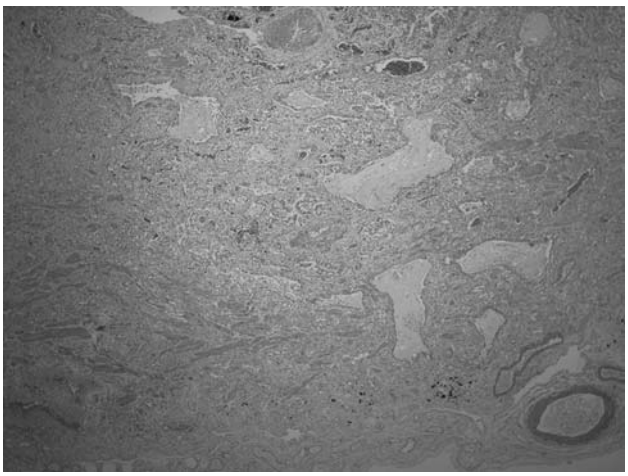

Fig. 4 Section of lung tissue collected at autopsy (hematoxylin and eosin). The left lower lung shows subpleural collapse of alveoli with marked elastosis and tractive dilatation of small bronchi (×10)

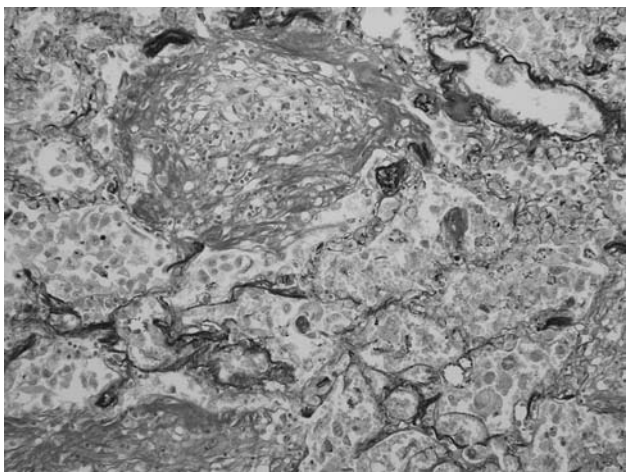

Fig. 5 Section of lung tissue collected at autopsy (Elastica van Gieson stain). The left lower lung shows hyaline membrane, fibrotic polyps, and collagen globules (×40)

fields showed usual IP and an organizing stage of diffuse alveolar damage (Figs. 4, 5). The former is common in RA, but the latter is uncommon.

Discussion

Tacrolimus is used as an immunosuppressant following organ transplantation [1, 2] and in the treatment of immunological diseases such as RA, [3, 4] Wegener granulomatosis [5], and myasthenia gravis (MG). In addition, polymyositis/dermatomyositis with IP and both polymyositis/dermatomyositis and IP are attenuated by tacrolimus administration [6, 7]. In Japan, about 9,000 RA patients have been treated with tacrolimus, which appears to inhibit calcineurin and suppress signal transduction in activated T cells [8, 9], thereby producing a good response in patients with refractory RA. Adverse events known to be associated with tacrolimus include renal dysfunction and hyperglycemia, but lung injury occurs more rarely with tacrolimus than with methotrexate. Indeed, at present, there are only two reported cases of tacrolimus-induced lung injury: one occurred in a patient with hemolytic–ureamic syndrome [10] and the other in a patient following bone marrow transplantation [11].

RA is complicated by IP in about 31% of cases based on chest X-ray findings [12] and in about 50% of cases based on high-resolution chest CT findings [13]. Notably, under some circumstances, IP can develop into a catastrophic lung disease that responds poorly to corticosteroids and immunosuppressants. Three types of lung injury occur in RA patients: damage due to infectious disease, drug-induced lung injury, and aggravation of the lung disease already present. In our case, sputum cultures for bacteria, tuberculosis, and *Pneumocystis* pneumonia were all negative. With respect to drug-induced lung injury, the serum tacrolimus level was 4.6 ng/ml and the drug's half-time was about 35 h. If the lung injury was caused by the tacrolimus, one might expect improvement once the drug was stopped. In our case, however, the patient's condition continued to deteriorate after tacrolimus was stopped. We suggest tacrolimus worsened the patient's existing IP, as new interstitial opacity appeared on upper parts of both lungs during tacrolimus monotherapy, which is consistent with acute exacerbation of IP. At autopsy, moreover, both the upper and lower lung fields showed an organizing stage of diffuse alveolar damage [14], which is uncommon in RA patients. It was speculated to result from the use of tacrolimus. Tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-8 developed a network of inflammatory cytokines and activated neutrophil-produced injury to endothelial cells. For the last time, it progressed to acute respiratory distress syndrome (ARDS).

In choosing DMARDs to the treat of RA complicated by IP, we avoid using methotrexate, bucillamine, and leflunomide, all of which can cause lung injury. There were no reports of tacrolimus-induced lung injury in RA patients whether or not it was complicated by IP.

Conclusion

When administering tacrolimus to patients with RA complicated by IP, great care should be taken because there is the possibility of inducing a catastrophic complication resulting in death due to respiratory failure.

Conflict of interest statement This article does not contribute to any conflict of interest.

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