CASE REPORT

Oseltamivir (Tamiflu®)-induced pneumonia

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Received 6 July 2007; accepted 4 March 2008

KEYWORDS
Oseltamivir; Drug-induced pneumonia; Drug lymphocyte stimulation test; Organizing pneumonia; Eosinophilic pneumonia

Summary
We report the first case of oseltamivir-induced pneumonia. A 50-year-old man was diagnosed with influenza and prescribed oseltamivir. He had a persistent high fever, and developed a productive cough with peripheral blood eosinophilia and his chest radiograph showed ground glass opacity. Bronchoalveolar lavage fluid and histological findings obtained from transbronchial lung biopsy suggested eosinophilic pneumonia with component of cryptogenic organizing pneumonia. Drug lymphocyte stimulation test against oseltamivir was positive. In spite of discontinuation of oseltamivir, his condition did not ameliorate. He was treated with prednisolone for oseltamivir-induced lung injury and the symptoms improved immediately. We should recognize oseltamivir-induced pneumonia as a differential diagnosis in the case of developing pneumonia following treatment with oseltamivir.

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Introduction
The numbers of drugs causing lung injury are rapidly increasing. Drug-induced lung injury can be serious and even fatal without quick discontinuation of the causative drugs and the adoption of appropriate measures.1,2 However, the diagnosis of drug-induced lung injury is very difficult, because the clinical, radiographic, and pathological features are nonspecific. Moreover there are no specific tests for diagnosing drug-induced lung injury. Oseltamivir is administered for influenza infection and is stockpiled as a measure against the occurrence of an influenza pandemic. No serious adverse effects induced by oseltamivir have been reported.

Case report
A 50-year-old man consulted a neighboring doctor because of a sudden high fever (38.2 °C), sore throat, and arthralgia.
He had been healthy until then. Although his point-of-care rapid influenza test was negative, he was diagnosed as having influenza because his daughter who lives with him was diagnosed as having influenza A infection almost at the same time by a rapid influenza test (ESPLINE® Influenza A&B-N, FUJIREBIO Inc., Tokyo) and his symptoms were identifiable with acute influenza infection. It was more possible that his negative rapid influenza test was examined too early or not adequately. He was prescribed oseltamivir (150 mg/day) and he took it for 5 days. He took acetaminophen 500 mg only once as antipyretics/analgesics on the first day. A high fever of near 39°C persisted and he developed a productive cough. On Day 6 he consulted the doctor again. Abnormal shadow had not been detected in the chest radiograph when he caught a cold before. A chest radiograph showed ground glass opacity all over the left lung. The white blood cell (WBC) count was 8700/µl, with 68% neutrophilis and 10.0% eosinophilis (870/µl). C-reactive protein (CRP) was 9.1 g/dl. On Day 9 he was referred to our hospital with progressive exertional dyspnea despite the commencement of antibiotics (azithromycin (AZM) 500 mg/day and ceftriaxone sodium (CTRX) 1 g/day) for 3 days under suspicion of secondary bacterial pneumonia. He was a farmer but was not using any pesticides at that time. He also denied any other significant exposure or treatment with medications. He had no past history of allergies and had never smoked. There were no symptoms or examination results suggestive of underlying connective tissue disease. On physical examination, fine inspiratory crackles were noted over the left lung fields. Peripheral blood eosinophilia (723/µl) was prolonged with the elevation of CRP (14.2 mg/dl). Renal and liver function tests were normal. Krebs von den Lungen-6 (KL-6) (377 U/ml) was also normal. Arterial blood gas analysis revealed slight hypoxemia (pH 7.441, PaO₂ 9.99 kPa, PaCO₂ 5.28 kPa in room air). Ground glass opacity shown on the chest radiograph was deteriorated. High-resolution computed tomography (HRCT) demonstrated patchy areas of air space consolidation and ground glass attenuation, dominantly in the peripheral zone of the left lung (Figure 1). The opacity in the right lung was very subtle. Treatment with antibiotics was stopped. On Day 10 (the day after admission), bronchoalveolar lavage (BAL) was performed through left bronchus (B4a) with 60% recovery. BAL fluid disclosed an increased total cell count (134 × 10⁴/µl), with 32.1% lymphocytes, 41.9% neutrophilis, 21.6% eosinophilis, and 3.7% macrophages. The CD4/CD8 ratio of the BAL fluid lymphocytes was 2.51. The culture of BAL fluid was

Figure 1  High-resolution computed tomography scan showing patchy areas of air space consolidation and ground glass attenuation, dominantly in peripheral zone of the left lung and the opacity in the right lung was very subtle.

Figure 2  Histological findings showing fibrinous exudate containing macrophages and eosinophilis, and organization in the alveolar space (used hematoxylin and eosin stain, original 2-1 × 200, 2-2 × 400).
sterile. Histological findings obtained from transbronchial lung biopsy (TBLB) were more likely those of eosionophic pneumonia pattern, showing fibrinous exudate containing macrophages and eosinophils, and organization in the alveolar space (Figure 2). As drug-induced lung injury was highly suspected, drug lymphocyte stimulation test (DLST) was performed. The lymphocyte stimulation index (SI) % was 234% by oseltamivir, 100% by AZM, and 94% by CTRX (control 100%). Only oseltamivir was remarkably positive. Taking the DLST result and his clinical course into account, we concluded that the pneumonia was induced by oseltamivir. Despite the withdrawal of oseltamivir, his condition deteriorated. Hence, he was treated with prednisolone, initially at 45 mg/day. His condition ameliorated immediately. The prednisolone dose was tapered slowly and discontinued over 1 month. He remained well without relapse.

Discussion

Administration of oseltamivir phosphate as its ethyl ester prodrug is efficacious in influenza A and B infection. Oseltamivir is a potent inhibitor of influenza neuraminidase, an enzyme important for influenza replication, in that it facilitates the release of newly formed virus particles from infected cells. Oseltamivir is generally well-tolerated, although nausea and vomiting occur occasionally. No other fatal adverse effects have been described. A case of pneumonia suspected to be induced by oseltamivir was reported in Japan. To our knowledge, no case of definitive oseltamivir-induced pneumonia has been reported.

The diagnosis of drug-induced lung injury begins with suspecting the occurrence. Any drug, herbal medicine, and health food could cause lung injury. We should recognize that drug-induced lung injury could occur not only under administration but also after withdrawal. Drug-induced pneumonia generally improves by discontinuation of the drug. However, we need to be aware of cases that become worse even after withdrawal. Diagnosis requires the temporal association of the manifestation and the administration by detailed history taking, besides the meticulous exclusion of other respiratory illness. Rechallenge test is a conclusive measure with high risk, only if no alternate therapy drug is available for treating the basic disease. In addition, we need to know which pattern of lung injury the drug could cause clinically, radiographically, and histopathologically. Such data are available from the updated Pneumotox website. At the time of admission, we considered the possibility of influenza pneumonia, atypical pneumonia, secondary bacterial pneumonia, and drug-induced lung injury as differential diagnoses. TBLB and BAL are usually useful for diagnosing whether there is infection or not. We found no pathogenesis in these specimens. Without treatment, the fever of people infected with acute influenza commonly resolves within 3 or 4 days and is cured in 1 week. Administration of oseltamivir reduces the duration of illness. Influenza pneumonia was unlikely because he was healthy and took oseltamivir. The appearance of peripheral blood eosinophilia and pneumonia on Day 6 was suggestive of drug-induced lung injury. Acetaminophen was unlikely to be a causative agent because he received this medication only once. At this point we were able to strongly suspect oseltamivir-induced lung injury in the context of his clinical course. There was little likelihood that AZM and CTRX were offensive drugs because of their commencement after the occurrence of the pneumonia.

DLST is the proliferation test to detect a T-cell sensitization to drugs, which measures 3H-thymidine uptake of dividing cells, induced by delay allergy. The test has not been well-established, and its usefulness has been demonstrated in the last year. Nevertheless, a positive DLST is often a valuable contribution of drug allergy. A positive test against only one drug within three candidate drugs is surely helpful to pinpoint the relevant drug, like this case. But, as the sensitivity of DLST is limited, a negative DLST cannot exclude a drug hypersensitivity. DLST may be helpful and adjunctive if drug-induced lung injury is suspected.

Mechanisms of drug-related lung pneumonitis are classified as immunological or toxicological. Allergic types show good response to corticosteroid therapy. The present case shows an eosinophilia in peripheral blood and BAL fluid, a pathological feature of eosinophilic pneumonia and positive result of DLST. All these features suggest that this case was an allergic type. His image was compatible with cryptogenic organizing pneumonia (COP), that is nonsegmental consolidation and ground-glass opacities most commonly involving mainly the peripheral lung region, except for atypical of the extreme asymmetry. However, it is difficult to differentiate between COP and eosinophilic pneumonia. A large number of drug-induced lung injury HRCT are usually of limited value in determining the pathological pattern and prognosis. One drug could induce several patterns simultaneously. This case contains the character of eosinophilic pneumonia and COP. Histological findings were more likely eosinophilic pneumonia pattern, with eosinophilia of BAL and peripheral blood. The findings of BAL were more likely COP rather than eosinophilic pneumonia for reason that the eosinophil count in the BAL was much lower than neutrophil (typically BAL eosinophilia more than 25–30% in eosinophilic pneumonia patients). The BAL pattern in COP is characterized by colorful cell differentials with an increase in all cell types, most markedly in lymphocytes and more moderately in neutrophils and eosinophils. In spite of withdrawal of the causative drug, many cases of drug-induced lung injury worsen and require corticosteroid therapy, and moreover slower tapering of corticosteroid is needed due to the risk of relapse.

It is highlighted the Japanese more frequently develop drug-induced lung injury than Westerners. A large number of drug-induced pulmonary diseases have been reported from Japan. The incidences of fatal drug-induced lung pneumonia by bleomycin, gefitinib, and infliximab are remarkably higher in Japan than those in other countries. This is probably related with ethnic differences.

Conflict of interest statement

None
References


