Clarithromycin-induced Eosinophilic Pneumonia

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Abstract

Clarithromycin (CAM) has been widely used for the treatment of respiratory infection. Macrolides are generally well tolerated and their adverse reactions are rare. An 80-year-old woman with nontuberculous mycobacterium infection was treated with combined chemotherapy, including isoniazid, rifampicin, and ethambutol. She developed a fever and peripheral blood eosinophilia, and new subpleural consolidations were observed on chest radiography three days after add-on therapy with CAM. The symptoms and clinical findings improved with the withdrawal of CAM. Histopathologic examinations confirmed the diagnosis of eosinophilic pneumonia. This is the first report of CAM-induced eosinophilic pneumonia. (Internal Medicine 43: 231–235, 2004)

Key words: drug-induced pneumonitis, eosinophilia, macrolides, eosinophilic cationic protein, interleukin-5, nontuberculous mycobacterium infection

Introduction

Clarithromycin (CAM), a macrolide antimicrobial, has been well tolerated in the treatment of community-acquired pneumonia and peptic ulcers caused by Helicobacter pylori and in the treatment and prevention of Mycobacterium avium complex (MAC) infection (1, 2). There have been few reports of adverse reactions to CAM, even in cases of long-term prophylaxis (3, 4). Moreover, there have been no reports of pulmonary side effects. We present herein a case of CAM-induced eosinophilic pneumonia with increased levels of eosinophilic cationic protein (ECP), but not of interleukin-5 (IL-5), in the bronchoalveolar lavage fluid (BALF) and serum.
Figure 1. (A) A chest radiograph on admission showed a large cavity, 4.5×6.0 cm in size, with fluid collection and infiltrates in the right middle lung field. (B) A chest radiograph four days after administration of CAM revealed new subpleural consolidations (arrowheads) in bilateral middle lung fields.

Figure 2. Clinical course of the patient. Symptoms including fever, cough, and wheezes. CAM: clarithromycin, INH: isoniazid, RFP: rifampicin, EB: ethambutol, Eosin.: peripheral blood eosinophils (closed circles), CRP: C-reactive protein (open circles), BFS: bronchofiberscopy.
lobe showed accumulation of eosinophils in the alveolar spaces and interstitial tissue, without granulomas or organizing pneumonia. Evidence of eosinophil activation was demonstrated by increased levels of ECP in the BALF (21.7 μg/l, normal <2 μg/l) and serum (40.6 μg/l, normal <14.7 μg/l). However, the levels of IL-5 in the BALF (<7.8 pg/ml) and serum (<7.8 pg/ml, normal <7.8 pg/ml) were normal. Serum level of total IgE (85 IU/ml, normal <170 IU/ml) was within normal limits, and the IgE antibody for specific allergens such as food, pollen, and fungal allergens (IgE radioallergosorbent test) were negative. Repetitive fecal test failed to reveal parasite ova. Serological tests for the evidence of parasite infection were negative by a commercial multipledot enzyme-linked immunosorbent assay kit (MBC, Tokyo).

Cessation of CAM led to remission of the symptoms and consolidations without steroid treatment or cessation of antituberculous agents, and the number of peripheral eosinophils (236/μl, 5.8%) was normalized. The patient was successfully treated with INH, RFP, and EB for 6 months without any recurrence of the abnormal chest shadows or eosinophilia.

Lymphocyte stimulation tests (LST) for CAM, INH, RFP, and EB were negative. A detailed history revealed that the patient had also taken CAM alone for three days before admission and she developed the same symptoms as with the second administration of CAM. The second administration of CAM was therefore an incidental provocation challenge, and we finally diagnosed the patient with CAM-induced EP.

Discussion

CAM is the most frequently used macrolide antibiotic and is available in more than ninety countries in the world. The efficacy of CAM to treat and prevent MAC infections is better than that of other anti-tuberculous agents, because MAC has intrinsic resistance to the majority of anti-tuberculous agents (3, 4). However, because drug resistance develops in some patients after CAM monotherapy, a combination chemotherapy with other drugs is recommended (3, 4). We treated our patient with combination chemotherapy, including INH, RFP, EB, and CAM. The patient developed eosinophilic pneumonia after administration of CAM. Many drugs, including anticonvulsants, antidepressants, anxiolytics, neuroleptics, muscle relaxants, cytotoxics, nonsteroidal anti-inflammatory drugs, antihypertensives, and antimicrobials, are well-known causes of eosinophilic pneumonia (5). To our knowledge, however, this is the first report of CAM-induced eosinophilic pneumonia in the researched literature (MEDLINE 1966-June 2003 and Japan Centra Revuo Medicina 1983-June 2003).

The diagnosis of drug-induced eosinophilic pneumonia is mainly based on a very detailed history of drug exposure, pathologic evidence of eosinophil accumulation in the lung, and exclusion of other causes. Differential diagnoses include a diverse group of eosinophilic lung diseases such as parasitic infections, idiopathic hypereosinophilic syndrome, asthma, allergic bronchopulmonary aspergillosis, Churg-Strauss syndrome, eosinophilic granuloma, collagen vascular diseases, idiopathic eosinophilic pneumonia, sarcoidosis, Pneumocystis carinii pneumonia, idiopathic pulmonary fibrosis, and Hodgkin’s disease (5). Important laboratory tests for differential diagnoses include a peripheral blood cell count, sputum bacteriology, serum IgE, fecal and serologic
examinations for parasite infections, skin allergy tests, LST, pulmonary function tests, bronchoalveolar lavage, and lung biopsy (5). Provocation drug challenge is considered by many as the gold standard for diagnosis of adverse drug reactions (6). Indeed, the relapse of drug-induced pneumonitis after accidental rechallenge is sometimes the only clue to identify the causative drug, as observed in this patient. However, voluntary challenge is unethical and may cause life-threatening adverse reactions, e.g. acute respiratory distress syndrome, toxic epidermal necrosis, Steven-Johnson syndrome, or anaphylaxis (6). It should be strictly limited to rare situations, such as when no alternative treatment is available. In the present case, a detailed medical history revealed that the patient had also taken CAM for three days before admission and she developed the same symptoms as with the second administration of CAM. The symptoms, eosinophilia, and chest infiltrative shadows gradually improved during combination chemotherapy without CAM. This first improvement is retrospectively thought to reflect natural remission of CAM-induced eosinophilic pneumonia, but not MAC infection, since MAC infection generally takes a long time to improve. The patient developed eosinophilic pneumonia after the second administration of CAM. Eosinophilic pneumonia improved after withdrawal of CAM alone without steroid treatment or cessation of antituberculous agents. The second administration was therefore an incidental provocation challenge for drug-induced pneumonitis. The diagnosis of the present case was clearly CAM-induced eosinophilic pneumonia because the temporal disease sequence was associated with the administration of CAM and other causes were excluded from the results of laboratory examinations.

The LST for CAM was negative in the present case. A recent study of drug allergy found the sensitivity and specificity of the LST was 78% and 85%, respectively (7). This is a useful diagnostic test in drug allergy; however, it should be noted that the positive result of the LST could only signal a previous contact with the drug, immune memory, or proliferation of regulatory T cells (6). Moreover, the sensitivity of the LST will be varied with the type of drugs, the form of disease manifestation, and/or the metabolic modification of drugs in vivo (6, 7). Indeed, the LST has been reported to be less diagnostic for minocycline-induced pneumonitis, which is generally manifested as eosinophilic pneumonia (8). The LST was positive in only 4 out of 26 (15.4%) previously reported cases with minocycline-induced eosinophilic pneumonia (8). A positive result of the LST may support the diagnosis of drug allergy, but a negative LST could not exclude the possibility of drug-induced pneumonia.

Eosinophils are main effector cells mediating lung damage in eosinophilic lung diseases because of the release of cytotoxic mediators such as ECP (9). Cytokines of the Th2-subtype (IL-3, IL-4, IL-5, and granulocyte macrophage colony stimulating factor) regulate both recruitment and activation of eosinophils (9). Increased levels of ECP and IL-5 in the BALF and serum have been reported in patients with eosinophilic lung diseases, especially in idiopathic chronic eosinophilic pneumonia (9–17). Moreover, these levels correlate with the degree of eosinophil activation in involved lung tissues and reflect the disease activity in patients with eosinophilic lung diseases (9–17). ECP seems to play an important role in the pathogenesis of lung damage in this patient, because eosinophil activation especially in the lung was also confirmed by an increased level of ECP in the BALF. However, the mechanism of eosinophil recruitment and activation within lung tissues is unknown, because the BALF level of IL-5 was not increased. Other eosinophil growth factors such as IL-3, IL-4, and/or granulocyte macrophage colony stimulating factor may have contributed to recruitment and activation of eosinophils.

The most common adverse reactions of macrolides involve the gastrointestinal tract. Other rare side effects include prolongation of the QTc interval on electrocardiogram, interstitial nephritis, cholestatic hepatitis, deafness, myasthenia gravis, and anaphylaxis (1, 2). There is also the potential for interaction with other drugs metabolized by cytochrome P450 because macrolides are also metabolized in this pathway (1, 2). There are a few case reports of macrolide-induced pulmonary side effects, including pulmonary infiltration with eosinophilia syndrome associated with midecamycin, and roxithromycin-induced eosinophilic pneumonia (18, 19). Recently, sirolimus (rapamycin), one of the 31-membered ring macrolides and a new immunosuppressive drug for organ transplantation, has been reported to be a possible cause of pulmonary adverse reactions, including interstitial pneumonitis, bronchiolitis obliterans organizing pneumonia, and pulmonary hemorrhage, but not eosinophilic pneumonia (20). The macrolides have recently been shown to affect several inflammatory responses, such as migration of neutrophils, the oxidative burst in phagocytes, and production of pro-inflammatory cytokines (21). Moreover, they may also suppress eosinophilic inflammation in patients with asthma (21). This could be the reason why eosinophilic pneumonia is a rare side effect of macrolide treatment.

Although the macrolides may rarely cause drug-induced lung disease, physicians need to be aware of their potential to induce lung diseases, such as eosinophilic pneumonia.

References


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