Ticlopidine is a thienopyridine-derived agent that inhibits platelet aggregation induced by adenosine diphosphate (ADP).1 Widely used in the treatment of cerebrovascular and coronary artery disease, ticlopidine has also been shown to be effective in preventing the thrombosis of coronary stents.1 Minor side effects with ticlopidine, such as diarrhea, nausea, vomiting, and rashes are common.2 Blood dyscrasias are the major concern regarding the safety of ticlopidine.3 The most serious adverse reaction, neutropenia, occurs in 2.1% of ticlopidine-treated patients and can be fatal. Lymphocytic colitis, cholestatic jaundice, and hepatitis have also been reported. Serious pulmonary adverse reactions are rare. To our knowledge, ticlopidine-associated diffuse alveolar damage has not been reported.

**Case Report**

A 52-year-old man was admitted due to acute onset of chest pain for 3 hours and 35 minutes. He had a past history of hyperlipidemia and a 45-pack-year history of smoking. There was no chronic cough or exertional dyspnea. On admission, blood pressure was 151/90 mm Hg, pulse rate was 106 beats/min, respiratory rate was 18 breaths/min, and body temperature was 36.4°C. Chest physical examination revealed fine crackles over the basal lung fields and regular heartbeat without murmur. Chest radiograph was normal. Electrocardiography revealed elevation of ST segments over precordial leads V2-5. Elevated levels of serum cardiac enzymes were found. The diagnosis of acute myocardial infarction was made immediately, and he underwent primary percutaneous transluminal coronary angioplasty (PTCA) with coronary stenting for the left anterior descending (LAD) artery 4 hours and 20 minutes after the onset of chest pain. The procedure was successful and the chest pain was completely relieved. The peak serum level of creatinine kinase (CK) was 15,546 U/L (normal, 38 to 160 U/L), CK-MB was 1139.2 U/L (normal, < 16 U/L), and troponin-I was > 100 ng/mL (normal, < 2 ng/mL) at 10 hours after the onset of chest pain. The patient began...
to take ticlopidine after the procedure with a loading dose of 500 mg orally and a maintenance dose of 250 mg twice daily. Concurrent medications included intra-venous infusion of heparin, and oral aspirin, captopril, and magnesium oxide. There was no complication of PTCA or coronary stenting, and his symptoms resolved after the procedure.

On day 3, he became febrile (body temperature, 38.6°C) and developed acute onset of dyspnea. No chest pain, cough, sputum production, hemoptysis or rashes were noted. Blood pressure was 96/64 mm Hg, heart rate was 130 beats/min, respiratory rate was 30 breaths/min, and was body temperature 38.6°C. Physical examination revealed fine inspiratory crackles at basal lungs without wheezes. No cardiac murmur was heard. Chest radiograph showed diffuse haziness in both lungs without pleural effusion. Laboratory tests showed white blood cell count of 14.5 x 10^9/L without eosinophilia. There was no laboratory evidence of impaired hepatic or renal function. Cardiogenic lung edema was suspected, and therefore a Swan-Ganz catheter was inserted which, during infusion of dobutamine at a rate of 1.5 µg/kg/min, showed a pulmonary capillary wedge pressure (PCWP) of 23 mm Hg, a cardiac index of 3.57 L/min/m², a systemic vascular resistance index of 1835 dynes·s·m²/cm⁵, and a pulmonary vascular resistance index of 224 dynes·s·m²/cm⁵. The patient was initially treated for cardiogenic pulmonary edema, but the respiratory distress responded poorly to diuretics, inotropic agents, and even intra-aortic balloon counterpulsation. Empiric intravenous ciprofloxacin, 400 mg every 12 hours, was also administered to treat possible nosocomial infection, but no pathogen was isolated. Urinary Legionella antigen was negative. Dyspnea progressed and the haziness became more prominent in the upper lung fields (Fig. 1). The patient was mechanically ventilated for hypoxemia. The initial PaO₂ was only 34 mm Hg under 60% oxygen supplement and the lung injury score was 3. Drug-induced lung disease was suspected and ticlopidine was replaced by oral clopidogrel 75 mg daily. Methylprednisolone, 40 mg every 8 hours, was administered intravenously. Open lung biopsy was performed on day 7. Pathologic examination of the wedge resected lung tissue showed scattered homogeneous appearing hyaline membrane lining edematous alveolar septa, accompanied by intra-alveolar edema and alveolar lining cell hyperplasia (Fig. 2). The findings were compatible with the

Fig. 1. Chest radiograph taken as respiratory distress progressed, revealing bilateral haziness predominantly over upper lung fields.

Fig. 2. Histologic examination showing diffuse alveolar damage with intra-alveolar edema, scattered hyaline membranes (arrows) lining edematous alveolar septa and alveolar lining cell hyperplasia (arrowhead) [hematoxylin and eosin, x 33].
exudative stage of diffuse alveolar damage (DAD). Cultures of the surgical specimen for viruses, bacteria, fungi, and mycobacteria were all negative. Pathologic study, including intracytoplasmic inclusion body under light microscopy, could find no evidence of viral infection. His pulmonary lesions improved gradually and he was weaned from the ventilator 9 days after administering corticosteroid and discontinuing ticlopidine. Right side pneumothorax complicated the course, but was successfully treated by tube thoracotomy and pleurodesis. The patient was discharged on day 43 with mild exertional dyspnea. A follow-up chest radiography showed resolution of the bilateral haziness, and only some residual fibrotic densities over the right lower lung. Pulmonary function test 3 months after discharge revealed moderate restrictive ventilatory defect [observed forced expiratory volume in 1 second (FEV1) of 1.81 L, 66.1% of predicted value; observed forced vital capacity (FVC) of 2.23 L, 68% of predicted value] and moderate impairment of diffusing capacity for carbon monoxide (observed DLco of 10.6 mL/min/mm Hg, 48% of predicted value). The patient still had mild exertional dyspnea at 10 months’ of follow-up.

Discussion

The management of drug-induced lung disease is challenging. The identification of drug-induced lung diseases may be very difficult in some cases because of considerable variabilities in the manifestations and onset of symptoms and signs. As the number of implicated drugs increases, the diagnosis of a drug-induced lung disease may be even more difficult. Ticlopidine is a relatively safe drug, apart from the potentially life-threatening side effect of blood dyscrasia; fatal pulmonary complication has not been reported. Clinicians may not be aware of the potential for respiratory symptoms resulting from its use.

In the case reported here, there was a plausible temporal sequence between the administration of ticlopidine and the onset of respiratory symptoms as well as radiographic evidence of abnormalities. Clinical improvement followed the withdrawal of ticlopidine and treatment with steroids. Diagnostic criteria of acute respiratory distress syndrome (ARDS) developed by consensus4,5 were fulfilled except that the pulmonary capillary wedge pressure of the patient was 23 mm Hg, higher than the 18 mm Hg of the criteria. However, the pathologic features of the patient’s lung were compatible with ARDS.6 Although the effects of heart failure might also have been a factor causing respiratory distress in this patient, the clinical data and course of the patient indicate that an insult to the lung must have induced DAD. The lack of microbiological evidence and scarcity of symptoms suggesting respiratory tract or systemic infection suggest that the DAD was not caused by infection. Although the patient was not rechallenged with ticlopidine to confirm the link between the drug and adverse reaction, these findings suggest that ticlopidine was responsible for the development of DAD in this patient.

Pulmonary adverse reactions associated with ticlopidine use are very rare, and only 3 cases have been reported previously, including interstitial lung disease,7 bronchiolitis obliterans organizing pneumonia8 and pulmonary nodules.9 Several features of the present case can be noted. First, the lung was the sole organ clinically affected in our patient; the adverse reaction did not affect the function of any other organ system. Second, the 2-day interval between the initiation of ticlopidine and the development of pulmonary side effects in our patient is much shorter compared with the previous reports of ticlopidine-induced pulmonary side effects, which occurred between 1 to 8 months after the drug intake, although the dosage used in our patient did not differ from the other reported cases (250 mg twice daily orally). Third, there was no pathological or laboratory evidence of hypersensitivity pneumonitis in this patient although this suspicion was reasonable based on the relatively rapid onset of respiratory symptoms. It was proposed that chronic hypersensitivity pneumonitis has an insidious onset over a period of months and results from continual low-level exposure to an antigen.10 T-cell-mediated delayed-type hypersensitivity reaction plays an important role in the development of hypersensitivity pneumonitis.10 The characteristic pathological finding of acute and subacute hypersensitivity pneumonitis consists of intense mononuclear inflammatory cells — including lymphocytes, plasma cells, activated macrophages and giant cells — that infiltrate alveoli and interstitial spaces, which is different from the situation in our patient. This suggests that the pathogenesis of DAD in our case is different from the mechanism described above.

DAD is a frequent histologic pattern of drug-induced lung disease. A large number of drugs have been shown to be associated with the development of DAD. In addition to some cytotoxic agents, the administration of various non-cytotoxic agents, including amiodarone, streptokinase, azathioprine, colchicine, gold salts, penicillamine, and sulfasalazine, have been shown to lead to DAD. As with most of these drugs, the mechanism for the development of DAD due to ticlopidine use remains unknown.

In summary, we describe a case of DAD due to ticlopidine use. A delay in resolution of cardiogenic
lung edema despite optimal treatment for heart failure and the development of an unusual chest radiography pattern (alveolar filling pattern at peripheral and upper lung zones) should raise the suspicion of drug-induced lung disease. Prompt discontinuation of the drug and administration of corticosteroid would be an effective treatment for drug-induced DAD. This rare adverse effect, which may be a cause of respiratory distress in patients with heart failure, should be kept in mind in patients treated with ticlopidine.

References