Introduction
Clopidogrel bisulfate is a platelet aggregation inhibitor that prevents thrombus formation after the rupture of atherosclerotic plaques from the arterial wall. It is a particularly useful drug for preventing thrombosis in patients with cerebrovascular disease or acute coronary syndrome.1 Two months after initiation of therapy, the patient presented with symptomatic bilateral pleural effusion. Examination of both effusions confirmed the diagnosis of spontaneous bilateral hemothorax due to combined antiplatelet therapy. Serious functional sequelae were still present 18 months after diagnosis despite bilateral pleural drainage and respiratory therapy.

Key words: Clopidogrel. Acetylsalicylic acid. Hemothorax.

Case Description
The patient, a 79-year-old male and ex-smoker of 20 pack-years, was receiving calcium channel blockers to treat essential arterial hypertension and had a history of recurrent unstable angina despite medical treatment. He had undergone cardiac catheterization with coronary angioplasty and endovascular stenting 3 months earlier. The chest radiograph was normal and an oral regimen of clopidogrel (75 mg/d) and acetylsalicylic acid (300 mg/d) was prescribed.

At the 2-month follow-up visit, the patient presented with dyspnea on moderate exertion of recent onset and a radiograph that showed bilateral pleural effusion. Diuretics were administered to treat suspected heart failure but no evident clinical or radiological improvement followed (Figure 1). The dyspnea persisted without fever, chest pain, or hemoptysis, and it was decided to perform diagnostic thoracentesis on both effusions. Clopidogrel was withdrawn on observation of clearly bloody pleural fluid.

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fluids (Table), and treatment with acetylsalicylic acid was continued to prevent stent occlusion. Physical examination ruled out signs of right heart failure, deep vein thrombosis, and palpable peripheral lymph nodes. Heart sounds were normal and lung auscultation revealed sounds that were consistent with bilateral pleural effusion. Laboratory results, including platelet count, coagulation values, D-dimer levels, thyroid hormone levels, carcinoembryonic antigen levels, and collagen marker levels, were all normal. The plasma red cell count was 3.370.000 cells/µL, hemoglobin concentration was 10.5 g/dL, and the hematocrit was 30%. A rectal examination and urine sediment were unremarkable, and the tuberculosis test was negative. Doppler ultrasound of the lower limbs and ventilation-perfusion scintigraphy ruled out venous thromboembolic disease. Intravenous contrast-enhanced computed tomography scans of the chest and abdomen confirmed the existence of bilateral pleural effusion, with a uniform thickening of both pleurae but no parenchymal, mediastinal, or diaphragmatic lesions, or images that were suggestive of pulmonary embolism (Figure 2).

Bronchoscopic findings revealed no significant endobronchial lesions. Bronchial aspirate cytology, culture, and sputum smear results were all negative. Thoracentesis was repeated on both effusions, and a left percutaneous pleural biopsy performed with an Abrams needle ruled out the existence of granulomas or atypical cells. Thorascopic biopsies of the right effusion confirmed nonspecific inflammation of the pleura, and the pleural fluid was drained. Respiratory physiotherapy was initiated and a left pleural drainage tube was inserted until the effusion resolved. The patient was discharged with outpatient follow-up.

Eighteen months after diagnosis, the patient’s functional class had improved very slightly and there had been no new episodes of coronary ischemia. The chest radiograph showed that both pleurae were still

| Biochemical and Cytologic Characteristics of Pleural Effusions* |
|-----------------|-----------------|
| pH              | 7.26            |
| Glucose, mg/dL  | 88              |
| LDH, U/L        | 517             |
| Pleural-to-serum LDH ratio | 2.1 |
| Protein, mg/dL  | 4.6             |
| Pleural-to-serum protein ratio | 0.8 |
| Adenosine deaminase, U/L | 28.2 |
| Cholesterol, mg/dL | 98  |
| Amylase, U/L    | 45              |
| Red cells/µL    | 1.680.000       |
| White cells/µL  | 1.500.000       |
| Lymphocytes, %  | 80              |

LDH indicates lactate dehydrogenase.

Pleural hematocrit greater than 50% of plasma hematocrit.
thickened and inflamed with a predominant involvement of the left pleura (Figure 3). Lung function tests showed a forced vital capacity (FVC) of 1.87 L (41%), a forced expiratory volume in 1 second (FEV1) of 1.28 L (40%), a ratio of FEV1 to FVC of 69%, a residual volume of 70%, and a total lung capacity of 56%. Arterial blood gas analysis at rest showed values of pH 7.43, PaO2 73.5 mm Hg, and PaCO2 31 mm Hg.

Discussion

The extraction of a clearly bloody pleural fluid in the absence of chest trauma necessitates consideration of hemothorax, although this can only be definitively ruled out by a pleural fluid hemocrit equal to or greater than 50% of peripheral hematocrit. Most cases of hemothorax are caused by open or closed chest trauma, or by certain procedures such as the insertion of a central venous line, catheterization, thoracentesis, percutaneous pleural biopsy, and fine-needle aspiration biopsy.2,3 Spontaneous, or nontraumatic, hemothorax, in contrast, is much less common but has a wide variety of causes.4 The main causes of spontaneous hemothorax are neoplasms and anticoagulant use, while less common causes include vascular ruptures (saccular dissection, arteriovenous fistulas, etc.), pulmonary infarction, rupture of pleural adhesions due to pneumothorax, pleural endometriosis, idiopathic forms, and other conditions that may alter coagulation, such as hemophilia, thrombocytopenia, and antiplatelet therapy.4,5

Leuprolin, oral anticoagulants, and other antiplatelet drugs such as ticlopidine are the main drugs that have been associated with isolated cases of spontaneous hemothorax.6,7 In a review of the literature (MEDLINE, 1966-2005), we found no reports of spontaneous hemothorax attributed exclusively to the use of acetylsalicylic acid or clopidogrel. We did, however, find a case in which spontaneous hemothorax was attributed to the combined use of these drugs, although the patient in question, unlike ours, had previously undergone coronary revascularization surgery.8 The diagnosis of spontaneous bilateral hemothorax secondary to the combined use of clopidogrel and acetylsalicylic acid—the first such case to be reported—we believe—is supported by tests performed to exclude other causes and by consideration of the risk of bleeding that accompanies the combined use of these drugs, the bilateral involvement of the pleura, the timing of the events in the absence of trauma and risk-related invasive procedures, the absence of recurrence, and the clinical course once 1 of the antiplatelet drugs had been withdrawn.

This diagnosis is of particular consequence for patients with serious or unstable heart disease if we consider that bilateral pleural effusion can be easily attributed to heart failure and can worsen a patient’s respiratory or hemodynamic status, which, in most cases, are already compromised. Taking into consideration the possibility of bleeding complications and the characteristics of pleural fluid extracted by thoracentesis should suffice to assure this diagnosis is not overlooked and prevent the performance of unnecessary procedures. Two episodes of acute coronary syndrome with spontaneous massive alveolar hemorrhage in patients treated with aspirin alone and in combination with other antiplatelet drugs following catheterization have been reported; both episodes were spontaneous and could have easily been mistaken for heart failure or pneumonia.9,10 Despite the low incidence of these 2 potentially lethal complications, the possibility of either occurring as the result of the combined use of antiplatelet agents necessitates correct diagnosis to enable early discontinuation of the therapy. It is also a reminder of the importance of establishing appropriate treatment and selecting alternatives on detection of either acute coronary syndrome or spontaneous massive alveolar hemorrhage.11

REFERENCES