

Bilateral Hemothorax Secondary to Combined Antiplatelet Therapy With Clopidogrel and Acetylsalicylic Acid

Manuel Haro Estarriol,^a Luis Alberto Álvarez Castillo,^a Xavier Baldó Padró,^b Anna Palou Rispuau,^a Matilde Rubio Garay,^b and Manel Rubio Goday^a

^aSección de Neumología, Hospital Universitario de Girona Doctor Josep Trueta, Girona, Spain.

^bServicio de Cirugía Torácica, Hospital Universitario de Girona Doctor Josep Trueta, Girona, Spain.

Clopidogrel is a platelet aggregation inhibitor that increases the risk of bleeding complications when combined with acetylsalicylic acid. We report a rare case of a 79-year-old male treated with clopidogrel and acetylsalicylic acid after coronary angioplasty and stenting to treat unstable angina. 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.

Hemotórax bilateral secundario al tratamiento antiagregante con clopidogrel y ácido acetilsalicílico

El clopidogrel es un inhibidor de la agregación plaquetaria que aumenta el riesgo de complicaciones hemorrágicas cuando se combina con el ácido acetilsalicílico. Presentamos un caso excepcional en un varón de 79 años tratado con clopidogrel y ácido acetilsalicílico después de una angioplastia coronaria y la colocación de un *stent* por una angina inestable. A los 2 meses de tratamiento presentó un derrame pleural bilateral sintomático. El estudio de ambos derrames confirmó el diagnóstico de un hemotórax espontáneo bilateral atribuido a los antiagregantes. El drenaje pleural bilateral y la fisioterapia respiratoria no impidieron la persistencia de importantes secuelas funcionales a los 18 meses del diagnóstico.

Palabras clave: Clopidogrel. Ácido acetilsalicílico. Hemotórax.

Introduction

Clopidogrel bisulfate is a platelet aggregation inhibitor that prevents thrombus formation after the rupture of atherosclerotic plaques from the arterial wall.¹ It is a particularly useful drug for preventing thrombosis in patients with cerebrovascular disease or acute coronary syndrome.^{2,3}

Multiple studies have shown that the combined use of clopidogrel and aspirin enhances the beneficial effects of both drugs in patients with acute coronary syndrome and in patients who have undergone coronary angioplasty and endovascular stenting.^{2,4,5} The combination is reported to only slightly increase the likelihood of complications, yet there is the possibility of increased risk of potentially serious bleeding complications in certain patients. There have been isolated reports of postoperative bleeding and of subarachnoid, intracranial,

and digestive bleeding following invasive diagnostic procedures. Pulmonary hemorrhage is a very rare possibility, and pleural involvement, as in the case we describe, is exceptional.⁶⁻⁸

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 without complications 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

Correspondence: Dr. M. Haro Estarriol.
Sección de Neumología (Planta 4.^a B).
Hospital Universitario de Girona Doctor Josep Trueta.
Avda. de Francia, s/n. 17007 Girona. España.
E-mail: mip.mharo@htrueta.scs.es

Manuscript received August 23, 2005. Accepted for publication September 6, 2005.



Figure 1. Posteroanterior chest radiograph. Bilateral pleural effusion.



Figure 3. Chest radiograph at 18 months. Bilateral inflammation and pleural thickening, mainly on the left.

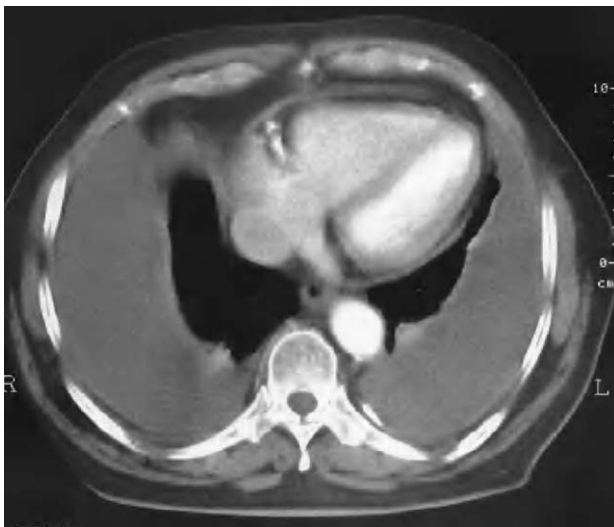


Figure 2. Contrast-enhanced computed tomography scan of thorax. Bilateral pleural effusion with pleural thickening.

TABLE
Biochemical and Cytologic Characteristics
of Pleural Effusions*

	Right	Left
pH	7.26	7.30
Glucose, mg/dL	88	74
LDH, U/L	517	620
Pleural-to-serum LDH ratio	2.1	2.4
Proteins, mg/dL	4.6	5.1
Pleural-to-serum protein ratio	0.8	0.9
Adenosine deaminase, U/L	28.2	25
Cholesterol, mg/dL	98	87
Amylase, U/L	45	46
Red cells/ L	1 680 000 [†]	1 780 000 [†]
White cells/ L	1 500	1 765
Lymphocytes, %	80	70

*LDH indicates lactate dehydrogenase.

[†]Pleural hematocrit greater than 50% of plasma hematocrit.

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/ μ L, 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. Thoroscopic 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

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 hematocrit 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.⁹ Spontaneous, or nontraumatic, hemothorax, in contrast, is much less common but has a wide variety of causes.¹⁰ The main causes of spontaneous hemothorax are neoplasms and anticoagulant use, while less common causes include vascular ruptures (aortic 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.¹¹⁻¹⁴

Leuporelin, oral anticoagulants, and other antiplatelet drugs such as ticlopidine are the main drugs that have been associated with isolated cases of spontaneous hemothorax.^{15,16} 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.¹⁷ 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 clopidogrel 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.^{7,8} 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.¹⁸

REFERENCES

1. Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. *Circulation*. 1999;100:1667-72.
2. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329-39.
3. Antithrombotic Trialists' Collaboration. Collaborative metaanalysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high risk patients. *Lancet*. 2002;324:71-86.
4. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494-502.
5. Hongo RH, Ley J, Dick SE. The effect of clopidogrel in combination with aspirin when given before coronary artery bypass grafting. *J Am Coll Cardiol*. 2002;40:231-7.
6. Ibáñez JJ, Nolla M, León MA, Martín MC. Hemorragia subaracnoidea y clopidogrel. *Med Clin (Barc)*. 2002;119:158-9.
7. Gill DS, Ng K, Ng KS. Massive pulmonary haemorrhage complicating the treatment of acute coronary syndrome. *Heart*. 2004;90:15.
8. Kilaru PK, Schweiger MJ, Kozman HA, Weil TR. Diffuse alveolar hemorrhage after clopidogrel use. *J Invasive Cardiol*. 2001;13:535-7.
9. Jacoby RC, Battistella FD. Hemothorax. *Semin Respir Crit Care Med*. 2001;22:627-30.
10. Villena V, López A, Echave J, Álvarez C, Martín P. Estudio prospectivo de 1.000 pacientes consecutivos con derrame pleural. Etiología del derrame y características de los pacientes. *Arch Bronconeumol*. 2002;38:21-6.
11. Ausín P, Gómez A, Moradiellos FJ. Hemotórax espontáneo por rotura de aneurisma de arteria pulmonar en la enfermedad de Rendu-Osler. *Arch Bronconeumol*. 2004;40:602-3.
12. Barreiro JM, Leiro V, Piñero L. Hemotórax como forma de presentación de angiosarcoma cardíaco. *Arch Bronconeumol*. 2005;41:105.
13. Ausín P, Gómez A, Pérez R, Moradiellos FJ, Díaz V, Martín JL. Hemotórax espontáneo por carcinoma broncogénico. *Arch Bronconeumol*. 2005;41:400-1.
14. Martínez FJ, Villanueva AG, Pickering R, Becker FS, Smith DR. Spontaneous hemothorax. Report of 6 cases and review of the literature. *Medicine (Baltimore)*. 1993;71:354-68.
15. Margolis MT, Thoen LD, Mercer LJ, Keith LG. Hemothorax after Lupron therapy of a patient with pleural endometriosis. A case report and literature review. *Int J Fertil*. 1996;41:53-5.
16. Quinn MW, Dillard TA. Delayed traumatic hemothorax on ticlopidine. *Chest*. 1999;116:257-60.
17. Shennib H, Endo M, Benhameid O. A feasibility study of the safety and efficacy of a combined clopidogrel and aspirin regimen following off-pump coronary artery bypass grafting. *Heart Surg Forum*. 2003;6:288-91.
18. Kalra S, Bell MR, Rihal CS. Alveolar hemorrhage as a complication of treatment with abciximab. *Chest*. 2001;120:126-31.