A Fatal Case with Diffuse Alveolar Hemorrhage due to Tirofiban and Clopidogrel therapy

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INTRODUCTION

Drug-induced pulmonary toxicity is increasing and early diagnosis is important because of the associated morbidity and mortality. Diagnosis is often difficult and is usually based on a history of drug therapy and exclusion of infection, radiation pneumonitis, and recurrence of the underlying disease. Diffuse alveolar hemorrhage (DAH) is an uncommon complication of drug therapy, with potentially significant morbidity and mortality. Typical agents that cause diffuse alveolar hemorrhage include anticoagulants, amphotericin B, high-dose cyclophosphamide, mitomycin, cytarabine (ara-C), and penicillamine (1). DAH denotes a diffuse intra-alveolar bleeding from small vessels as a result of severe damage of the alveolocapillary membrane of the lungs. These are comparatively rare, but than often life threatening events. The differential diagnosis is broad and comprises immunologic as well as toxic, infectious, hemodynamic, neoplastic and physical causes. DAH may be a manifestation of systemic diseases such as small vessel vasculitis-microscopic polyangiitis and Wegener's granulomatosis, as well as a result of an injury restricted to the lungs.

The platelet GP IIb/IIIa inhibitors (Tirofiban) and ADP receptor blockers (clopidogrel) are used in the acute coronary syndromes and percutaneous coronary intervention (PCI) as antiplatelet agents (2, 3). In clinical practice, adjunctive therapy with clopidogrel, in addition to aspirin, in survivors after ST-elevation myocardial infarction is associated with a reduction in 1-year mortality in patients treated with early reperfusion therapy (fibrinolysis or primary PCI) (4).

Hereby, we reported a case with DAH due to tirofiban and clopidogrel treatment in a patient underwent primary PCI.

CASE

A 74 year-old male patient underwent primary PCI due to acute inferior myocardial infarction. He was given intravenous morphine, glyceryl trinitrate, heparin, and metoprolol. Oral loading with aspirin 300 mg was given, followed by maintenance doses of 100 mg daily. Coronary angiogram was performed to the patient, and a stent was implanted to the infarct related right coronary artery (RCA), and intravenous tirofiban infusion was started in the cath lab. Also, oral loading with clopidogrel 300 mg was given, followed by maintenance doses of 75 mg/day. 72 hours after the administration of tirofiban, hemoptysis and respiratory distress were observed. Physical examination revealed seldom crackles in basal areas of the lungs, no S3 gallop, no heart murmur, no jugular venous distention and peripheral oedema with 95/65 mmHg of arterial blood pressure and 78 pulse/min of heart rate. His echocardiogram showed normal left ventricular ejection fraction of 60%, and no valvular dysfunction. Chest radiograph (CXR) revealed non-homogenous patchy infiltrations (Figure 1), and arterial blood gases showed hypoxemia in room air (Ph: 7.47,
PaCO$_2$: 25 mmHg, PaO$_2$: 55 mmHg, HCO$_3$: 25 meq/L, Sat O$_2$: 90%.

Figure 1
Figure 1: Chest radiograph revealed non-homogenous patchy infiltrations.

His hemogram was as follows: Htc: 34.2%, Hb: 11.6 gr/dl, Plt: 161,000/dl. Also, tests for bleeding diathesis were within normal limits. Computed tomography (CT) of thorax showed bilateral patchy airspace opacity with air-bronchograms and bilateral pleural effusion (Figure 2).

Figure 2
Figure 2: Computed tomography of thorax showed bilateral patchy airspace opacity with air-bronchograms and bilateral pleural effusion.

Thoracentesis revealed bilateral transudate in the pleural spaces. Although heparin, aspirin, clopidogrel and tirofiban were stopped, hemoptysis insisted as 100 cc daily. Hence, we planned bronchoscopic examination, but respiratory distress worsened progressively with a PaO$_2$/FiO$_2$: 100 mmHg, then he was transferred to the intensive care unit, and mechanical ventilation was started. Unfortunately, he did not show any response to mechanical ventilation, and died within 24 hours.

DISCUSSION
Tirofiban and clopidogrel may lead to serious spontaneous pulmonary bleeding (4, 5, 6). Tirofiban has a half-life of 2–3 h and is highly specific for the GP IIb/IIIa receptor. Platelet aggregation returns to normal in 4–8 h after discontinuation of the drug (7). Recently, it was reported a case with acute coronary syndrome who died with DAH due to tirofiban and clopidogrel administration (6).

Pulmonary hemorrhage is a life-threatening complication of antiplatelet agents. The radiological features of DAH resemble cardiogenic pulmonary edema (8). Clinical suspicion is required in a patient with acute respiratory distress and diagnosis is made by excluding other causes. In patients with acute coronary syndromes, pulmonary infiltrates on CXR may be caused by pneumonia and pulmonary oedema. Our patient had no left ventricular dysfunction, and no other signs of pneumonia. We thought that diffuse pulmonary infiltrates of the patient were related to DAH. Although we planned early diagnostic bronchoscopy to confirm the diagnosis, respiratory distress worsened progressively, and he was intubated. Treatment consists of stopping the drugs and infusing platelets and fresh frozen plasma to correct coagulopathy. Tirofiban can also be removed by haemodialysis. Pulmonary haemorrhage can easily be mistaken for pulmonary oedema, a condition that is common in patients with acute coronary syndromes. Physicians need to be aware of this diagnostic dilemma.

Clinical findings, in addition to sudden fall in haemoglobin with hemoptysis following administration of antiplatelet agents should alert physicians to the likelihood of pulmonary hemorrhage. Therapy remains supportive with discontinuation of all antiplatelet and anticoagulant agents. Blood transfusion or platelet infusion according to monitored hematocrit values may be required. As a conclusion, in patients with pulmonary hemorrhage, also drug therapy including tirofiban and clopidogrel as antiplatelet agents should be questioned as well.
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