Diffuse Alveolar Haemorrhage Due to Clopidogrel Use in a Patient Who Had Undergone Primary Percutaneous Intervention

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ABSTRACT

Anti-thrombotic drugs are inevitable and represent the most suitable drug therapy for patients presenting with stable angina pectoris and acute coronary syndromes [unstable angina pectoris, non-ST segment elevation myocardial infarction (NSTEMI) and STEMI]. Anti-platelet and anti-coagulant drugs have reduced the incidence of death and transmural myocardial infarction in patients with acute coronary syndromes (ACSs). Besides their favourable effect in terms of inhibiting thrombus formation, they increase the risk of bleeding by inhibiting platelets in ACS by the same mechanism. Here we present a case of a patient who was admitted to our institution with chest pain and who was diagnosed with anterior myocardial infarction. After initiating anti-platelet therapy with 300 mg acetylsalicylic acid orally and 600 mg clopidogrel orally, the patient underwent primary percutaneous coronary intervention, which ended with predilatation and stent implantation of the left anterior descending artery (LAD). After 2 hours of clopidogrel ingestion, the patient presented with bloody sputum and dyspnoea in the coronary care unit just after the intervention. Thoracic high-resonance computed tomography (HRCT) revealed diffuse alveolar haemorrhage, and clopidogrel was stopped. Diffuse alveolar haemorrhage due to clopidogrel is a very rare major complication, and considering how commonly clopidogrel is used, diagnosis and management of this complication are crucial.

Key Words: Acute anterior myocardial infarction; clopidogrel use; diffuse alveolar haemorrhage; complication

Primer Perkütan Koroner İşlem Sonrasında Klopidogrel Kullanımına Bağlı Difüz Alveoler Hemoraji

ÖZET

Antitrombotik ilaçlar stabil anjina pektoris ve akut koroner sendrom (kararsız angina pektoris, ST segment yükselmesiz miyokart infarktüsü, ST segment yükselmeli miyokart infarktüsü) ile başvuran hastalar için olmazsa olmaz ve en uygun ilaç tedavisidir. Antiplatelet ve antikoagülan ilaçlar, akut koroner sendromda ölüm ve transmural miyokart infarktüsü insidansını azalttı. Bu ilaçların trombüs oluşumunu engelleme ve trombositleri inhibe etme mekanizması ile benzer şekilde kanama riskini artırırlar. Burada göğüs ağrısı ile kliniğimize başvuran ve anterior miyokart infarktüsü tanısı konulan bir olgu sunulmuştur. Hastaya rutin klopidogrel 600 mg ve asetilsalisilik asit 300 mg oral başlandıktan sonra sol ön inen arter (LAD)'e predilatasyon ve stent implantasyonu uygulandı. Klopidogrel alınmasından iki saat sonra koroner yoğun bakım ünitesindeki takibinde kanlı balgam ve nefes darlığı gelişti. Toraks yüksek rezonans bilgisayarlı tomografide difüz alveoler hemoraji saptandı ve klopidogrel kesildi. Klopidogrele bağlı difüz alveoler hemoraji çok nadir görülen bir komplikasyon olmakla birlikte bu ilacın ne kadar sıklıkta kullanıldığı düşünülürse tanı ve tedavinin önemi ortaya çıkar.

Anahtar Kelimeler: Akut anteriyor miyokart infarktüsü; klopidogrel kullanımı; difüz alveoler hemoraji

INTRODUCTION

Combined treatment with clopidogrel and aspirin reduces systemic ischaemic events after percutaneous coronary intervention (PCI) in high risk-patients[1,2]. Additional anti-thrombotic drugs such as GPIIb/IIIa inhibitors increase the risk of minor and major bleeding as a side effect. Gastrointestinal bleeding is particularly observed as a major bleeding complication in case of the use of GPIIb/IIIa inhibitors. Here we discuss the case of a patient who presented with a diffuse alveolar haemorrhage (DAH) after primary percutaneous intervention, which was attributed to clopidogrel use.

CASE REPORT

A 56-year-old male was referred to our tertiary cardiovascular and thoracic surgery centre from an emergency department of a general hospital. On his arrival, he had strong retrosternal

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chest pain, which was radiating to the left shoulder and both the arms. His medical history revealed that he had hypertension (HT) treated with angiotensin receptor blockers and diabetes mellitus (DM) treated with subcutaneous insulin injections. In 2005, because of diabetic foot, his right foot was amputated under the knee. Since then, 100 mg acetylsalicylic acid was started orally once a day because of risk factors of coronary artery disease and peripheral artery disease. In his physical examination, the blood pressure was 137/89 mmHg, heart rate was 76 bpm, body temperature was 37.1°C and respiratory rate was 14/min. His haemoglobin level was 14.8 g/dL, white blood cell count was 15.300/mm^3 and platelet count was 290.000/mm^3. Creatinine kinase myocardial band (CK-MB) and troponin were positive. Electrocardiography revealed acute anterior myocardial infarction (MI) with ST segment elevation from V1 to V4 in precordial leads. As soon as the patient was administered 600 mg clopidogrel and 300 mg chewable aspirin, diagnostic coronary angiography was performed. Coronary angiography revealed total occlusion of proximal LAD with no antegrade and retrograde blood flow, a critical stenosis of the distal right coronary artery (RCA) and proximal and mid significant stenosis of the circumflex artery. PCI was planned for total occlusion of the proximal LAD. After administration of 5.000 units of heparin, a wire was passed through the lesion and predilatation was performed with a 2 × 20 mm balloon (Invader, Alvimedica). A bare metal stent sized 3 × 24 mm (Ephesos, Alvimedica) was implanted. LAD distal blood flow was TIMI-3, and the intervention ended. The patient was admitted to the intensive coronary care unit after PCI, which took 1 hour, and his haemodynamic parameters were good (130/70 mmHg blood pressure and 73 bpm heart rate). One hour later, we were alerted by the nurses that the oxygen saturation of the patient had dropped to 72%, as observed by pulse oximetry, and the patient started to cough. Rales in both lower segments of the lungs were present, as observed during physical examination. Bloody sputum was observed, and arterial blood gas analysis confirmed a decrease in oxygen saturation to 70%. The patient's activated clotting time (ACT) was 227 s in the intervention room and was 201 s after bloody cough. Immediate chest X-Ray at the bedside showed pulmonary oedema-like infiltration of both mid and basal segment of the lungs. The patient took the orthopneic position in bed despite the right femoral sheath. Further, 2D echocardiography at the bedside showed a decrease in ventricular performance (EF) to 30%, with anterior and anteroseptal hypokinaesia. Ruling out acute mitral regurgitation and papillary muscular rupture, continuous positive air pressure (CPAP) was started, and chest disease specialist evaluated the patient. In total, 40 mg furosemide was intravenously administered. After 45 min of CPAP therapy, oxygen saturation of the patient increased to 86%, which was sufficient to transfer the patient to perform thoracic computed tomography (CT), which was ordered by the chest disease consultant. Thoracic high-resonance computed tomography (HRCT) demonstrated ARDS-like

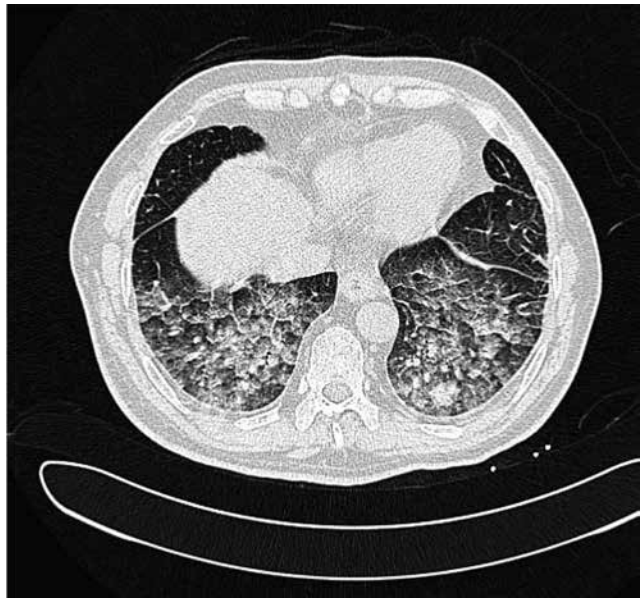

Figure 1. Coronal view of thoracic contrast-enhanced computed tomography showing diffuse ground glass opacities of both lungs.

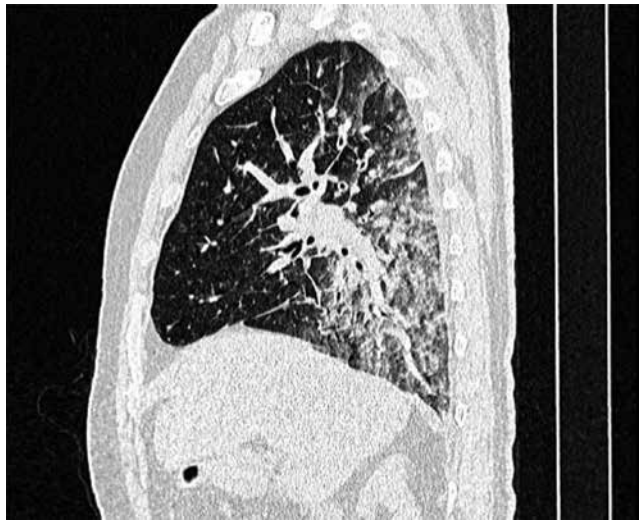

Figure 2. Transverse view of thoracic contrast-enhanced computed tomography showing ground glass opacities of posterior segment of lungs.

bilateral ground glass opacities of the lungs (Figure 1,2). Careful analysis of CT findings revealed that ground glass opacities of the lungs were accumulated in the posterior sides of the lungs, which was appropriate considering the lying position of the patient (Figure 3). For the first time, DAH was taught to be cause of the clinical condition of the patient. Repeated complete blood count (CBC) and activated clotting time (ACT) tests were performed. The haemoglobin level dropped from 14.8 g/dL to 11.1 g/dL and the maximal ACT was 227 s, as observed in the catheter laboratory. Bronchoscopic examination showe d clots and blood in the trachea and bronchial tree without active bleeding, which was confirmed the diagnosis of DAH a day later. Clopidogrel was stopped because it was an aetiological agent

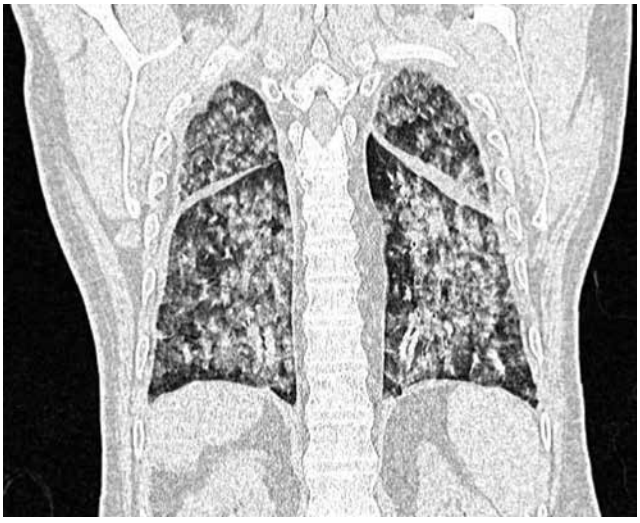

Figure 3. Sagittal view of thoracic contrast-enhanced computed tomography showing ground glass opacities of posterior segment of lungs.

of this complication. We followed up the patient for a week under aspirin and low-molecular-weight heparin (LMWH), and no further complication was observed. The patient underwent cardiovascular surgery for the revascularisation of CX and RCA.

DISCUSSION

DAH is active bleeding into the alveolar space. It is usually associated with connective tissue disorders such as microscopic poliangitis, Goodpasture syndrome, anti-phospholipid antibody syndrome and Wegener's disease, in which the bleeding is caused by injured vessel walls due to immune reactions.

DAH, which is associated with anti-thrombotic drug use, is not common. Current guidelines suggest a combination of different anti-thrombotic drugs in thrombosis for their additive effect[3,4]. However, bleeding risk also increases.

Clopidogrel and glycoprotein IIb/IIIa inhibitors are recommended in the treatment of patients with unstable angina pectoris and non-ST segment elevation myocardial infarction (NSTEMI), and current treatment guidelines for STEMI recommend that clopidogrel should be administered for at least 12 months[3,4]. DAH is commonly observed in patients under glycoprotein IIb/IIIa inhibitor therapy. A study conducted by Ali et al. revealed that the prevalence of pulmonary haemorrhage was 0.5% with eptifibatide, 0.7% with abciximab and 0.9% with tirofiban[5]. Only 10 of the 5.382 patients (0.19%) who received abciximab in 4 clinical trials developed pulmonary haemorrhage[6]. Ikeda et al. reported a case of a patient who developed DAH after coronary stent implantation for STEMI due to aspirin and ticlopidine therapy[7]. Kilaru et al. reported the first case of a patient who developed DAH after the placement of a coronary stent due to clopidogrel therapy[8]. When the clinical situation of a patient is suggestive of DAH, adjunct laboratory tests and imagining must be performed as soon as possible for confirming the diagnosis. Contrast-enhanced chest CT scans and bronchoscopic examination of airways are preferred tools for diagnosis.

Here we present a case of a patient who was admitted to our institution with anterior MI and in whom DAH was diagnosed after 2 hours of 600 mg of clopidogrel administration. In this case, this side effect was attributed to clopidogrel use because the patient was already taking aspirin and ACT was in the normal therapeutic range. Yet, the time interval from ingestion to bleeding was also suggestive of clopidogrel-associated DAH. This must be third case report of DAH associated with clopidogrel use, following the reports of Kilaru et al. and Kim et al[8,9].

CONCLUSION

DAH is a bleeding complication associated with anti-thrombotic drug use and can be fatal if misdiagnosed. Clinical findings such as a drop in haemodynamic parameters, dyspnoea, decrease in arterial oxygen saturation, haemoptysis, infiltration observed on chest X-Ray, ARDS-like chest CT findings, unexplained drop in haemoglobin levels, and use of anti-thrombotic or anti-coagulant drugs may help in diagnosing DAH. DAH is a very rare complication of clopidogrel use. If DAH occurs, discontinuing the use of the causative drug is advised.

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