Recurrent pulmonary embolism in a woman with heparin-induced thrombocytopenia

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Abstract: The study presents the case of a 78-year-old woman with recurrent pulmonary embolism, treated with 2 courses of thrombolysis. In this patient, due to heparin-induced thrombocytopenia, fondaparinux therapy was used.

Key words: acute pulmonary embolism, heparin-induced thrombocytopenia

CASE RAPORT

An emaciated, 78-year-old woman (body mass 48 kg) with anorexia, hospitalized because of severe depression, was admitted to the Cardiac Intensive Care Department at the Department of Internal Diseases and Cardiology in the Dental Institute, Medical University, Warsaw, with a suspicion of pulmonary embolism. One day before the admission, she fainted and suffered from severe dyspnoe. On the day of admission to the Cardiac Intensive Care Department, her general condition was good, she did not feel dyspnoe, blood preasure was 130/80 mmHg and pulse rate 100/min. The ECG showed dextrogram, the $S_IQ_{III}T_{III}$ complex and incomplete right bundle branch block; D-dimer level was 4500 μg/ml (normal values <500 μg/ml, Vidas bio Merieux). A cardiac troponin level was not elevated. The transthoracic echocardiography showed paradoxical movement of intraventricular septum. Acceleration time (AcT) was shortened to 55 ms with 32 mmHg transtricuspid pressure gradient value (TRPG). The spiral computed tomography (CT) revealed clots inside proximal pulmonary artery (Fig. 1A). Ultrasonographic examination confirmed thrombosis in the left superficial femoral vein.

The patient was treatment with enoxaparin in a daily dose of 1 mg/kg of body weight, twice a day. After an initial improvement, on the tenth day of the therapy severe dyspnoe, tachycardia 120/min and transient decrease of blood pressure to 70/40 mmHg, were observed. Transthoracic echocardiography showed significant exacerbation of right ventricular failure, and the enlargement of ventricular cavity to the pressure of 40 mmHg with the presence of McConnell sign. The AcT shortening to 37 ms and TRPG of 57 mmHg were also observed. Enoxaparin administration was ceased and the infusion of unfractioned heparin (UH) was started. Because of clinical symptoms and right ventricular failure exacerbation, tissue plasminogen activator (alteplase) was administered, in a 15-minute intravenous bolus, in a dose of 0.6 mg/kg body mass (total 30 mg); intravenous infusion of UH in a dose to prolong activated patrial thromboplastin time 1.5–2.5 times of the control value was continued. The patient general condition was gradually improving. Blood pressure and heart rate were normal. Ultrasound examination of lower extremities veins showed no vein thrombosis. Because of lack of the patient's consent, the vena cava filter was not implanted. Seven days after thrombolysis, hemodynamic parameters deteriorated. The repeat CT scan showed larger amounts of thrombotic mass (Fig. 1B). Because of the poor clinical state of the patient and CT scan results, invasive treatment was considered. However, due to her advanced age and the psychiatric load, alteplase was reintroduced. The general condition of the patient stabilized. Heparin treatment was continued. Platelet counts evaluated after 2 days (on the 9th day from the beginning of the UH therapy and the 19th day from the combined enoxaparin and UH administration) showed thrombocytopenia 113,000/mm^3. Unfortunately, this fact was overlooked and heparin was administered for the next 24 hours. When platelet count was 43,000/mm^3 (on the 10th day of UH therapy, and the 20th day of the combined therapy with enoxaparin and UH), the treatment was discontinued.

After exclusion of other causes of low platelet counts, including disseminated intravascular coagulation, heparin-induced thrombocytopenia was suspected and the administration of heparin was ceased immediately. Heparin-induced thrombocytopenia (HIT) was diagnosed on the basis of anti-platelet heparin-binding antibodies appearance in serum (immunoenzymatic assay GTI-PF4-ELISA).

Treatment with fondaparinux in a dose of 5 mg/24h was started, and increased platelet counts were observed (Fig. 2).

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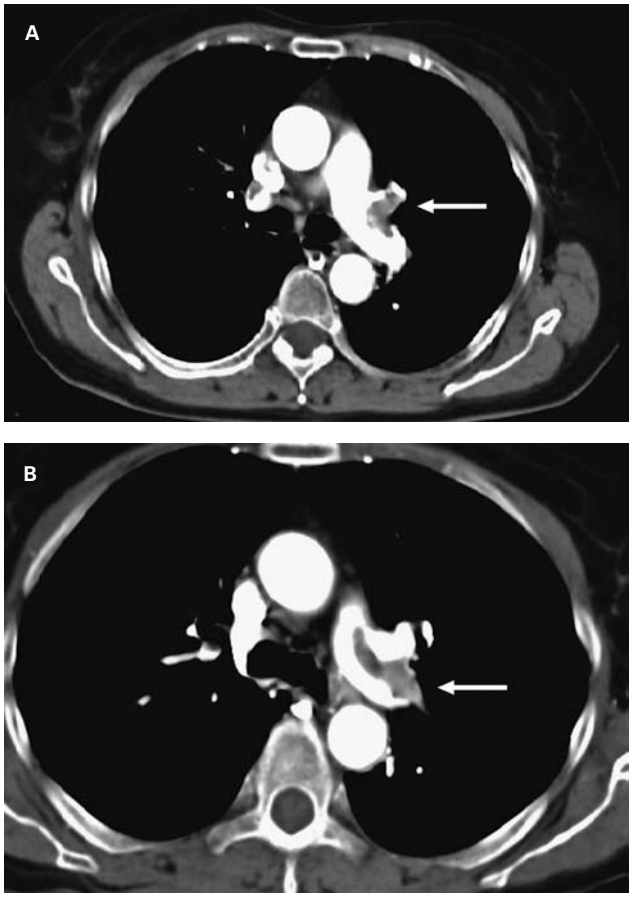

Fig. 1. Computed tomography: thrombus in the vifurcation of the left pulmonary artery (arrows). **A.** First examination. **B.** Control examination, intensity of lesions

After the following 3 days, cardiogenic shock symptoms occurred. The transhoracic echocardiography revealed, besides right ventricular failure, a large free floating thrombus in the right atrium (Fig. 3)

Cardiac surgery intervention was considered. However, eventually, the patient was disqualified from it. After a short time the patient died for cardiac arrest due to electro-mechanical dissociation.

DISCUSSION

Persons with clinically massive acute pulmonary embolism (APE), with low blood pressure or a cardiac shock, need an urgent thrombolytic therapy. In subjects with normal systemic blood pressure, heparin administration is the treatment of choice. In subjects with right ventricular failure on echocardiography, submassive APE ought to be diagnosed. These patients make a moderate risk group, with about 10% mortality during hospitalization [1]. Thrombolytic therapy of submassive APE still remains controversial. Recently, a role of biomarkers in risk stratification of pulmonary embolism was emphasized. Biochemical markers for myocardial injury, for example elevated cardiac troponin serum levels, indicate to higher risk of death and confirm the necessity of aggressive therapy. The patient in the current study at the beginning of the observation had stable hemodynamic parameters, only mild right ventricular failure symptoms were reported, but no biochemical markers for myocardial injury were present. Therefore low molecular weight heparin was administered. Despite this treatment, the clinical condition of the patient deteriorated dramatically. Thrombolytic therapy and then UH were introduced. It must be emphasized that at that time thrombocytopenia was not observed. After 7 days of UH treatment and her stable condition, symptoms aggrevated. Embolectomy or thrombolytic therapy was taken under consideration. A recent study by Meneveau et al. [2] shows advantages of surgical treatment compared to repeated thrombolytic therapy in the cases of ineffective fibrynolytic therapy. Because of the old age and psychatric load of the patient described here, alteplase was eventually readministered and the improvement of the patient clinical condition was observed. The treatment with UH was recommended. While UH treatment continued, severe thrombocytopenia rapidly occurred.

On the basis of the appearance of serum anti-platelet antibodies, heparin-induced thrombocytopenia was diagnosed. Our therapy was conducted in compliance with recommendations concerning the HIT diagnostic test in each case of a decrease in platelet count of at least 50% between the 4th and the 14th day of heparin administration, or a thromboembolic episode, skin necrosis at the site of injection, or an acute side effect after intravenous heparin administration (febrile, acute

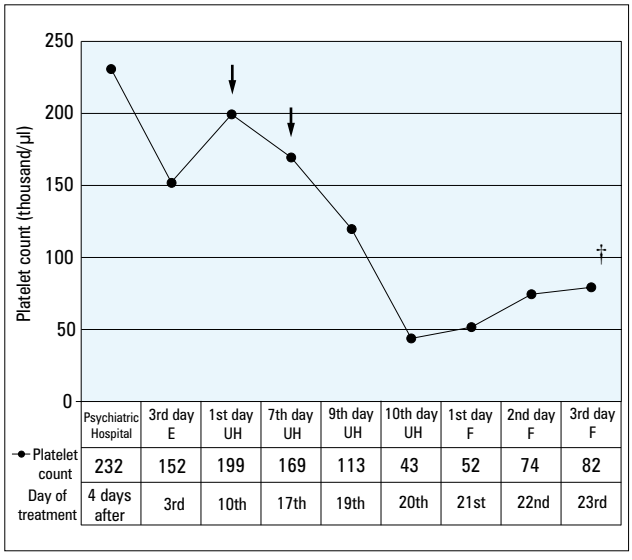

Fig. 2. Medication history. Arrows indicate the day of tissue plasminogen activator administration. Abbreviations: E – enoxaparin *s.c.*, F – fondaparinux *s.c.*, UH – unfractionated heparin *i.v.*, † – the patient death

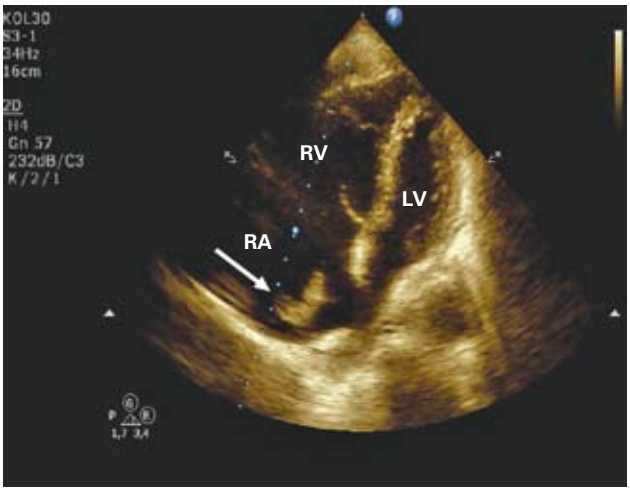

Fig. 3. Thransthoracic echocardiography: four chamber view of the heart. Significant enlargement of the right ventricle. Arrow indicates a free floating thrombus inside the right atrium. Abbreviations: LV – left ventricle, RA – right atrium, RV – right ventricle

respiratory failure, acute heart failure) [3,4]. Pathogenesis of HIT is connected with heparin-binding-platelet factor 4 – antibodies activity. They are responsible for platelets activation and increased thrombin generation [5]. It is known that HIT occurs more frequently in subjects receiving UH in comparison with patients treated with low molecular weight heparins. Its incidence is higher in females than in males [3] and it can occur in as many as 1% of subjects treated with UH. It was emphasized that similarly to the case described here, the thrombotic episode may occur before thrombocytopenia. Thus, after the HIT diagnosis, heparin administration ought to be ceased immediately as it can increase thrombocytopenia and cause thromboembolic episodes. Vitamin K antagonists administration is contraindicated as well because it may enahnce thrombosis. Patients with HIT ought to be treated with direct acting thrombin inhibitors, for example lepirudin. Recently, growing evidence suggest the efficacy of HIT treatment with fondaparinux which acts as an indirect factor-X-inhibitor. Antithrombotic fondaparinux activity is the result of factor X inhibition by antithrombin. This therapy does not affect platelets activity [6,7]. Platelets count monitoring in patients treated with heparins is strongly recommended as the prevention of HIT which is a severe complication in antithrombotic therapy with about 20–40% mortality [8,9].

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