Case report - Vascular general

Heparin induced thrombocytopenia in a patient with factor V Leiden following cardiac surgery

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Abstract

We report a patient who died as a result of heparin induced thrombocytopenia (HIT) and arterial thromboses following cardiac surgery. The onset was three days after exposure to low molecular weight heparin on the eighth postoperative day. The patient was heterozygous for the factor V Leiden mutation. We have reviewed 15 patients previously diagnosed as HIT on clinical and laboratory criteria and found an incidence of 6.7% (1/15) activated protein C resistance. This second patient had a pulmonary embolus and HIT after only three days exposure to low molecular weight heparin. We postulate that factor V Leiden hastens the onset and magnifies the severity of HIT.

Keywords: Heparin induced thrombocytopenia; Factor V Leiden; Complication

1. Background

Heparin induced thrombocytopenia (HIT) is a severe complication of heparin anticoagulation and occurs in about 1–3% of patients exposed to heparin for an appropriate time [1]. HIT (type II) is an immune mediated reaction in which a substantial fall in the platelet count is seen, usually below 100 × 10^9/L. It is associated with complications involving arterial and venous thromboembolism. Antibodies to heparin-platelet factor 4 are found in ~50% of patients receiving heparin but only 1–2% go on to develop thrombotic complications. The pathogenesis is not fully understood.

Factor V Leiden, a single point mutation, has been identified as a risk factor for venous thrombosis [2]. It has a high prevalence, about 3–8%, in Europeans, but it is not clear whether it adds to the risk of developing HIT.

We describe here a patient who died from HIT (type II) with thrombotic complications, following cardiac surgery who was found to be heterozygous for factor V Leiden. We also describe a review of the factor V Leiden status of 15 patients diagnosed as having HIT at The Royal Brompton Hospital.

2. Case report

The patient was a 68-year-old white male with a history of diabetes (type II), hypertension, hypercholesterolaemia, asthma and rheumatic fever. He had worsening exertional dyspnoea for the past 5–6 years. On examination, he had an ejection systolic murmur loudest at the second right intercostal space and radiating to his neck. He had peripheral oedema up to his thigh and demonstrable ascites. His liver was palpable 2 cm below his costal margin. His prothrombin time was prolonged by 1 s and his liver enzymes were raised (Alkaline phosphatase 306 U/l normal range 80–250, γ-GT 72 normal range 11–51). He was not known to have been exposed to heparin in the last three months before admission.

Coronary angiography showed diffuse coronary artery disease with a significant narrowing of the left anterior descending artery (LAD). Echocardiography demonstrated an aortic stenosis with a peak gradient of 71 mmHg. The tricuspid valve was regurgitant while the mitral valve was stenotic. No significant carotid lesions were seen on Doppler imaging. Preoperative respiratory assessment showed a significant chronic obstructive pulmonary disease.

In theatre, he was given 30,000 IU of unfractionated heparin before the commencement of cardiopulmonary bypass (CPB). The left internal thoracic artery was anastomosed to his LAD and a perimount pericardial tissue valve was exchanged into the aortic position. An open valvotomy was performed on the mitral valve.

The patient was started on low molecular weight heparin on the fifth postoperative day after going into atrial fibrillation. Three days after starting low molecular weight heparin, on the eighth postoperative day he developed widespread necrotic lesions on the lower limbs and his hands (Figs. 1 and 2). This change in clinical status coincided with a fall in the platelet count from 93 to 45 × 10^9/L. Initially, under vascular teams advice, he was treated with unfractionated heparin and low molecular weight heparin was withdrawn. The following day the diagnosis of HIT was...
made clinically. All heparin therapy was withdrawn and anticoagulation substituted with danaparoid. The lowest platelet count was $19 \times 10^9/l$ on the ninth postoperative day. It subsequently rose to $132 \times 10^9/l$, on the fourteenth postoperative day, five days after heparin had been withdrawn. However, the patient’s general condition deteriorated as he became confused and eventually died.

3. Results of laboratory investigations

The patient had antibodies to heparin-PF4, as tested by ELISA, and a positive HIT platelet aggregation activity assay was seen with unfractionated heparin, low molecular weight heparin but not with danaparoid.

At the time of these thrombotic complications his daughter announced that she was homozygous for factor V Leiden and had suffered a deep vein thrombosis (DVT) and pulmonary embolus whilst pregnant; we therefore tested the patient and other family members for activated protein C resistance (factor V Leiden). The patient was heterozygous for factor V Leiden. Antithrombin, protein C, free protein S, homocysteine were all normal and the prothrombin mutation 20210A was not detected. His wife was heterozygous for factor V Leiden. Two of the four children, the daughter already known and a son were homozygous. One daughter and one son were normal.

We analysed stored samples from 15 patients who had been diagnosed with HIT on clinical and laboratory criteria. One patient was found to have activated protein C resistance. We were unable to perform DNA analysis to confirm the existence of the factor V Leiden mutation.

4. Discussion

HIT is a clinical diagnosis and is based on appropriate exposure to heparin and associated thrombocytopenia. This diagnosis is more difficult in patients after cardiac surgery because a fall in the platelet count is often seen after CPB. In a retrospective analysis of 127 patients with serologically confirmed HIT, approximately half of all HIT cases were recognised only after they developed a thrombotic event [3]. Although a large proportion of patients exposed to unfractionated heparin develop antibodies to heparin-PF4, only a small proportion develop thrombocytopenia and even fewer thrombotic complications [1]. There is, however, a very high rate of morbidity and mortality associated with thrombotic complications. A prospective randomised double blind clinical trial comparing heparin and danaparoid for off-pump coronary artery bypass grafting found danaparoid to be a valuable alternative to heparin [4].

The patient reported here showed thrombocytopenia and severe thrombotic complications. The platelet count recovered five days after heparin was stopped. What was unusual was the apparent rapid onset and the finding of factor V Leiden. There was no documented previous exposure to heparin.

A review by Lee et al. from Canada reported results in 165 patients diagnosed as HIT over a 14-year period and found no associated risk between factor V Leiden and severity of HIT. However, in this study no distinction was made between patients positive for heparin-PF4 antibodies and those with clinically overt HIT [5].

There have been three reports of the association of factor V Leiden with HIT [5–7]. The first by Lee et al. described a young woman with HIT and heterozygous for the factor V Leiden defect who died. A second patient reported by Gardyn et al. from Israel died from HIT. The patient was heterozygous for factor V Leiden [6]. A third report by Pizzolo et al. from Verona describes an elderly man with HIT and factor V Leiden who suffered extensive venous and arterial thrombosis but survived. Our review of patients diagnosed as HIT on clinical and laboratory criteria found one out of 15 had activated protein C resistance. This patient also had a rapid fall in the platelet count after only three days exposure to low molecular heparin. We speculate that factor V Leiden would contribute to the thrombotic risk in HIT in accelerating the rate at which thrombocytopenia and thrombosis develop.

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References

2% go on to develop thrombotic complications of heparin-induced thrombocytopenia (HIT). Among genetic risk factors for venous thrombosis is 2% in patients with proven deep venous thrombosis (n=60) [4]. Five percent of the children with thromboses (n=40) have positive test resistance to activated protein C caused by factor V:Q506 (factor V Leiden) mutation (unpublished data). Hence, low frequency of genetic anomalies of factor V and of HIT, along with many other risk factors for thrombohemorrhagic complications in patients after heart surgery makes it difficult to interpret the relation between these two events in the development of complications presented in this article.

The presented information sets one thinking about the equipment of cardiosurgical centers with modern tools for timely antibody diagnostics, including in patients undergoing repeated heart surgery using ELISA technique, and alternative anticoagulants, in particular, with Danaparoid.

References

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