Architecture of a Native Mitral Valve Thrombus in a Patient with Hypereosinophilic Syndrome

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A 27-year-old male with a six-year history of hypereosinophilic syndrome (HES) presented with a native mitral valve thrombus, despite therapeutic oral anticoagulation. The thrombus was removed, the mitral valve replaced, and subsequent oral anticoagulation maintained at a higher level (INR 3.5). The patient developed two recurrences of mitral valve thrombosis requiring urgent reoperations, and died shortly after the second intervention. A scanning electron microscopy analysis of the native mitral valve thrombus removed during the first cardiac surgery revealed tightly packed thin fibrin strands forming fuzzy irregular structures, with areas of an almost solid fibrin clot. The fibrin networks indicated a heightened thrombin generation, and may account for a diminished susceptibility to intrinsic fibrinolysis. In conclusion, the unfavorably altered compact structure of the fibrin-rich thrombus, which formed despite adequate anticoagulation, might in part explain the recurrent valvular thrombosis. It may also represent a novel prothrombotic mechanism that operates in HES.

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Hypereosinophilic syndrome (HES) is a rare condition defined as persistent eosinophilia (>1500 cells/µl for more than six months) without a primary cause, such as cancer, parasitic or allergic disease, and with evidence of eosinophil-mediated end-organ damage (heart, lungs, gastrointestinal tract, skin, bone marrow, or brain). Patients with HES usually present with endomyocardial fibrosis or eosinophilic endocarditis leading to valvular dysfunction and cardiac mural thrombus. They also have an increased risk of deep-vein thrombosis (DVT). The extent of cardiovascular involvement determines the morbidity and mortality in HES (1).

The mechanisms that underlie the prothrombotic tendency observed in HES are complex, and involve an enhanced thrombin generation induced by a tissue factor that is released from degranulating eosinophils and infiltrated tissues (2,3). The primary stimulus for thrombosis in HES is eosinophil-mediated damage to the endocardium or the vessel wall. Secreted eosinophil cationic proteins, including major basic protein (proteoglycan 2), eosinophil peroxidase and eosinophil cationic protein, also impair the anticoagulant pathways by binding to thrombomodulin (4) and causing inactivation of the anticoagulant polyanions (5).

To the present authors' knowledge, the fibrin structure has not yet been evaluated in patients with HES. Herein are presented details of the architecture of a thrombus formed on a native mitral valve, despite therapeutic oral anticoagulation, in a patient with HES.

Case report

A 27-year-old male with a six-year history of HES (eosinophilia from 14,300 to 7200 cells/µl) was admitted for mitral valve replacement (MVR) because of mitral stenosis combined with regurgitation with concomitant mitral valve thrombus. The patient had experienced three previous episodes of DVT, and was receiving permanent oral anticoagulation with a target International Normalized Ratio (INR) of 2.5 (range 2 to 3). Thrombophilia (antiphospholipid antibodies, factor V Leiden, prothrombin G20210A mutation, protein C, protein S or antithrombin deficiency) and FIP1L1-PDGFRA fusion gene

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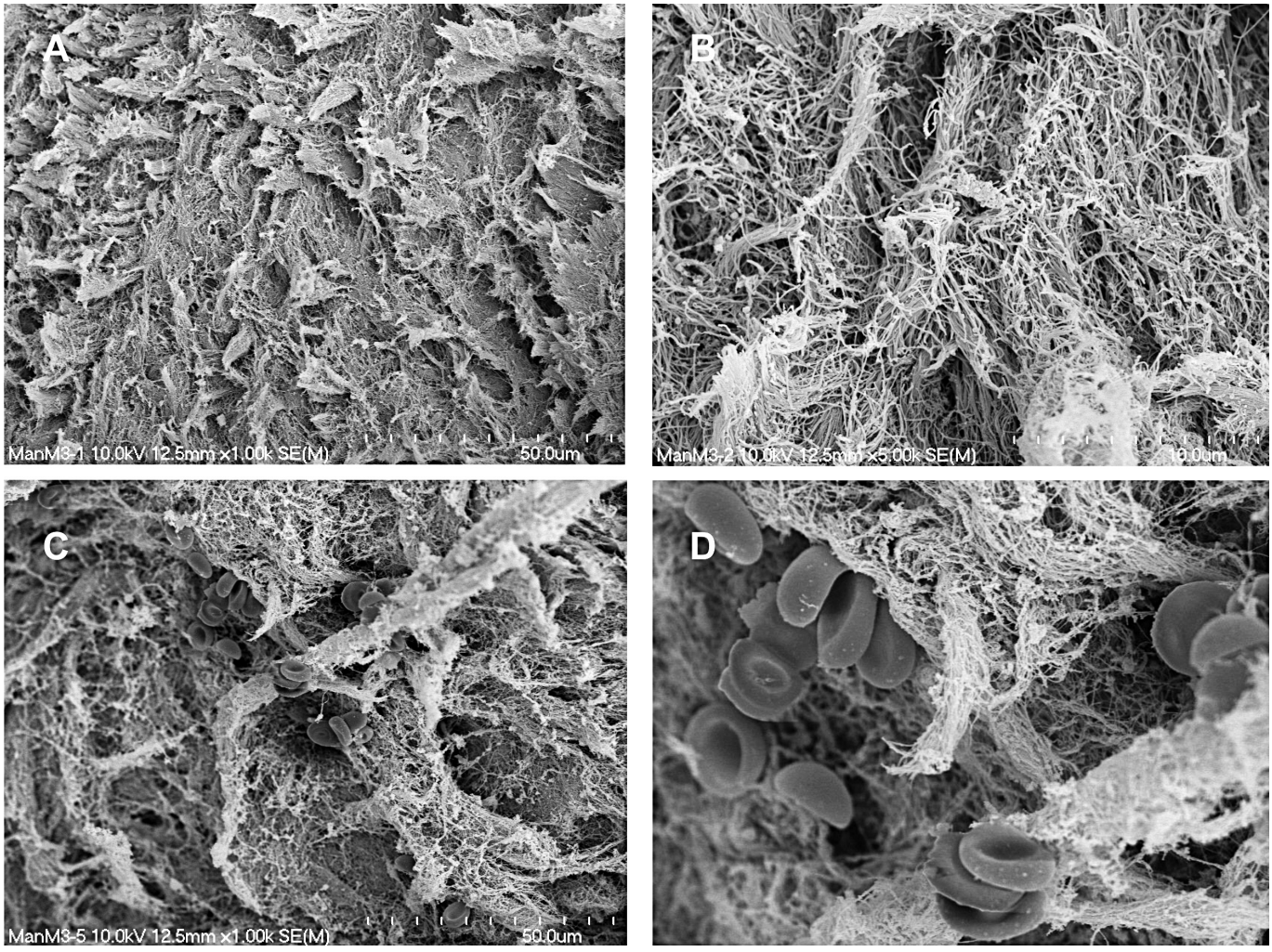

Figure 1: Scanning electron microscopy images of a native mitral valve thrombus formed in a patient with hypereosinophilic syndrome, despite adequate anticoagulation, and removed during the first cardiac surgery. A,B) Inner regions of the thrombus. C,D) Peripheral regions of the thrombus. Original magnifications: panels A and C, ×1,000; panels B and D, ×5,000.

screening yielded negative results. The patient was treated with prednisone, followed by hydroxyurea. On admission, he had normocytic anemia (hemoglobin 10 g/dl) and leukocytosis (15.9 × 10^3 cells/µl, 63% eosinophils, absolute eosinophil count 8,100 per µl), with a normal platelet count. The patient was afebrile, and blood cultures were negative. Ultrasonography revealed mural hyperechogenic thrombi in the left axillary and femoral veins, and also in the right popliteal vein. Echocardiography showed a preserved left ventricular systolic function (ejection fraction 70%), mitral leaflet thickening, and restriction causing severe valve stenosis (mean gradient 21 mmHg) with stage III/IV regurgitation, secondary tricuspid valve regurgitation, and pulmonary hypertension. A mass located on the posterior leaflet of the mitral valve, probably a thrombus, was also observed.

During elective cardiac surgery tricuspid valve annuloplasty, thrombus (Fig. 1) removal and MVR with a 29 mm prosthetic valve (St. Jude Medical, St. Paul, Minnesota, USA) were performed. The perioperative period was uneventful, and anticoagulation with acenocoumarol was continued after surgery (target INR 3.5), along with hydroxyurea treatment. Four weeks later, the patient developed progressive dyspnea due to heart failure. Echocardiography showed a stuck mitral mechanical valve, despite therapeutic oral anticoagulation being continued within the previous month (INR 2.8-3.2). On emergency surgery, the prosthetic valve was shown to be covered by a thrombus, and so was replaced with a new 27 mm prosthetic valve (St. Jude Medical). Anticoagulation was maintained at the same level (target INR 3.5). Two months later, at an INR of 3.9, the patient became hemodynamically unstable following a seven-day period of dyspnea. Echocardiography revealed a similar prosthetic valve dysfunction. At emergency surgery, both leaflets of the prosthetic valve were found to be fixed in the nearly closed position by the enveloping thrombus. The occluded valve was

replaced with a 27 mm biological valve (Edwards Lifesciences, Horw, Switzerland); however, the patient died from cardiogenic shock at 3 h after surgery.

A scanning electron microscopy (SEM) analysis of the thrombus (Fig. 1) was carried out as described elsewhere (6). Briefly, the thrombus was washed, fixed by overnight permeation with 2.5% glutaraldehyde, rewashed with water, and then treated with alcohol. Randomly selected specimens were dehydrated, gold-coated and photographed digitally in six different areas, using a Hitachi S-4700 microscope (Hitachi, Tokyo, Japan). The SEM images showed the center of the thrombus (Fig. 1A and B) to be formed from tightly packed thin fibrin strands, forming fuzzy irregular structures with areas of an almost solid fibrin clot. No erythrocytes or platelets were detected. At the periphery of the thrombus (Fig. 1C and D), red blood cells with small amounts of platelet aggregates were visualized; these were embedded in fibrin fibers of a similar architecture to that observed in the inner regions of the thrombus.

Discussion

The present study is the first to demonstrate the architecture of the thrombus in HES. These novel findings suggest that structure of the thrombus, the final stage of blood coagulation, is unfavorably altered in HES patients. The thrombus is highly abundant in fibrin, and modified fibrin clot features may contribute to the persistence of thrombi in the patient. Thin fibrin fibers forming a tight and irregular meshwork of the thrombus, as demonstrated in the present patient, indicate a heightened thrombin generation (7) and most likely account for the diminished susceptibility to intrinsic fibrinolysis (8). It is known that the fibrin network configuration rather than fiber thickness via an influence on the transport of macromolecules through networks, including proteins involved in fibrinolysis, largely determines the fibrinolysis rate (9). The dense structure renders clots relatively resistant to lysis (9), which might facilitate thrombus growth even in anticoagulated subjects.

HES complicated by mitral prosthetic valve thrombosis, despite therapeutic anticoagulation, has been reported previously in some patients, and was closely related to an increased absolute eosinophil count (10,11). To the present authors' knowledge, the existence of native mitral valve thrombosis despite adequate anticoagulation has not been reported. Moreover, the causes of resistance to oral anticoagulation in some HES patients remain unclear.

In conclusion, a thrombus which is largely composed of densely packed fibrin fibers, as observed in HES, and which is predisposed to resistance to endogenous fibrinolysis, may - at least in part - explain the recurrent valvular thrombosis in the present patient. A tendency to form dense fibrin-rich thrombi may represent a novel prothrombotic mechanism that operates in this disease.

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