

Unique Presentation of Hypereosinophilic Syndrome: Recurrent Mitral Prosthetic Valve Thrombosis without Endomyocardial Disease

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Hypereosinophilic syndrome (HES) is defined as a prolonged, unexplained peripheral eosinophilia in a patient presenting with end-organ damage. The heart is frequently involved, resulting in eosinophilic endomyocardial disease, which is characterized by mural thrombus formation and endocardial fibrosis. Thromboembolic complications in HES are mediated by material released from eosinophilic granules. Herein is reported the case of a patient who presented, 15 years after valve replacement with a mechanical prosthesis, with clinical signs of recurrent

In 1975, Chusid and colleagues defined hyper-eosinophilic syndrome (HES) as an unexplained eosinophilia lasting more than six months in the presence of end-organ involvement (1). Cardiac involvement is the major source of morbidity and mortality in patients with the syndrome (1-3). Herein is reported a case of HES, which caused recurrent prosthetic valve thrombosis, but without endomyocardial involvement.

Case report

A 59-year-old Caucasian man was referred to the 3rd Department of Medicine at Semmelweis University Medical School on the 1st August 1996, after recurrent surgery of the mitral prosthetic valve due to valve obstruction. Previously, in 1981, the patient had undergone valve implantation with a St. Jude Medical prosthesis because of significant rheumatic mitral valve stenosis. In 1991 he was hospitalized with paroxysmal atrial fibrillation and transient cerebral ischemia; at this time, the mitral valve function was normal, but the International Normalized Ratio (INR) was subtherapeutic (1.5). The INR became therapeutic after increas-

prosthetic valve thrombosis that was caused by missed hypereosinophilia. The unique feature of the case was that the mitral prosthetic valve obstruction was the result of an eosinophilic thrombus, though no tissue infiltration or inflammation had been detected by random biopsy of the left ventricular myocardium. After nine years of effective treatment of HES there were no cardiac or extracardiac complications.

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ing the dose of acenocoumarol. In October 1992 the patient was shown to have permanent atrial fibrillation, and in August 1995 was admitted to the regional general hospital with a one-month history of progressive dyspnea. Transthoracic echocardiography (TTE) demonstrated mitral valve obstruction, while transesophageal echocardiography (TEE) showed a severely restricted mitral leaflet motion and thrombus, the mobile portion of which was at the atrial surface of the mitral valve prosthesis. The mean mitral valve gradient was 15 mmHg, and the area 0.7 cm². The patient's INR was subtherapeutic (1.5). Following intravenous thrombolysis with streptokinase for 48 h, the mitral valve obstruction was resolved, the leaflet motion normalized, and the mean gradient fell to 3.5 mmHg.

In December 1995 the patient presented again with signs and symptoms of mitral valve obstruction, though his INR level at this time was therapeutic (2.5). Thrombolysis with streptokinase was again successful, and he was discharged with combined acenocoumarol and aspirin therapy. In March 1996, prosthetic valve obstruction was identified (INR 3.3), but thrombolysis was unsuccessful, and the patient was transferred to the Institute of Cardiology. Coronary arteriography revealed a left main coronary artery stenosis. A saphenous vein bypass graft and valve replacement using a CarboMedics 25 valve were carried out. At surgery, a thrombus, which had caused the obstruction, was found on the artificial valve.

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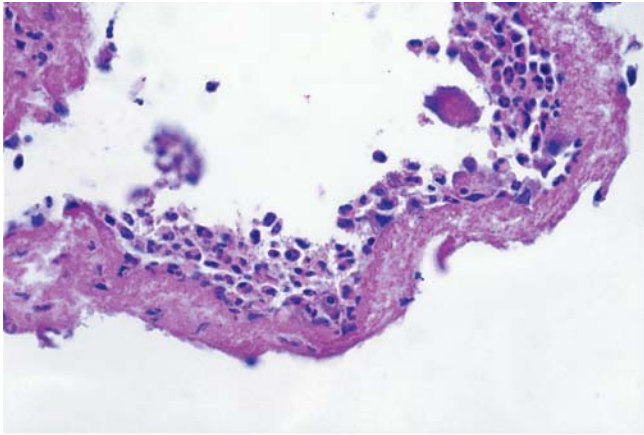


Figure 1: High-power view of the obstructive thrombus, containing many eosinophils.

In May 1996 the patient was asymptomatic, with TTE showing normal mitral artificial valve movement with a mean gradient of 4 mmHg. On 18th July 1996, however, the patient was readmitted to the Institute of Cardiology with a one-month history of progressive dyspnea and recurrent angina. TTE showed mitral valve obstruction with a mean gradient of 31 mmHg, and coronary arteriography detected graft occlusion. At surgery, a vermiform mass which had caused the obstruction was found on the artificial valve, but the endocardium was intact. Histology of the obstructive mass, and of a random biopsy specimen from the left ventricular myocardium, was performed. An Intact 25 bioprosthesis was implanted and a new saphenous vein bypass graft inserted on the left anterior descending coronary artery. Histology revealed the obstructive mass to be a thrombus containing many eosinophils (Fig. 1). There was no tissue infiltration or inflammation in the myocardial biopsy specimen. The patient's leukocyte count was 14×10^9 cells per liter (30% eosinophils), and he was transferred to the authors' department with suspected HES.

Subsequently, the possibility of secondary eosinophilia including asthma, allergic conditions, vasculitis, metastatic cancer or parasitic infections was ruled out. A clonal cause of eosinophilia was also excluded after examination of the peripheral blood and bone marrow biopsy. A review of the patient's medical reports revealed a previously increased eosinophil count in December 1995, and progressive eosinophilia had been documented retrospectively (Table I) but was missed, presumably due to the emergency situations. Therapy was commenced with vincristine (1.5 mg per month, intravenous) and prednisolone (25 mg per day). In November 1996, subcutaneous interferon- α (3×10^6 units, three times weekly) was added to the treatment, and the prednisolone

Table I: White blood cell and eosinophil counts of the patient between August 1995 and May 1996.

Date	White blood count (G/L)	Eosinophil count (G/L)
August 1995	7.5	NA
December 1995	12.6	1.3
March 1996	30.0	15.0
May 1996	37.1	29.6

NA: No data available.

dose was reduced to 10 mg per day. This regime allowed the absolute eosinophil count to be controlled at $<1500/l$. Vincristine therapy was ceased in February 1998 as it caused peripheral neuropathy, but hydroxyurea (1 g/day) was added to the prednisolone and interferon- α . During a nine-year period of therapy there were no cardiac or extracardiac complications of the disease. At the most recent follow up examination, conducted in December 2005, the patient's leukocyte count was 5.1×10^9 cells per liter (20% eosinophils), and the mitral valve mean gradient 5 mmHg.

Discussion

Hypereosinophilic syndrome is characterized by the triad of prominent eosinophilia (absolute eosinophil count $>1,500/l$, chronic course (>6 months) and eosinophil-mediated tissue injury (e.g., cardiomyopathy, pneumonitis, dermatitis, sinusitis, gastrointestinal inflammation, stroke, etc.) (1-6). Among patients with HES, cardiac disease is the major source of morbidity and mortality (1-4).

The common clinical manifestations of eosinophilic endocardial disease include cardiomegaly, congestive heart failure (right- or left-sided, or both), atrioventricular valve regurgitation, arrhythmias, and restrictive cardiomyopathy (1,2,5,7). The most common pathological findings are endocardial fibrosis, myocardial inflammation with necrosis and scarring and mural thrombus formation (1-3,6,7), though valvular damage (1,8), myocardial necrosis associated with thrombi in the smaller coronary vessels and eosinophilic infiltration of the myocardium itself can also occur (1). Some atypical cases have also been reported in the literature, when eosinophilic endomyocarditis was detected without peripheral eosinophilia (9,10).

The mechanism of tissue damage by eosinophils has not been delineated, though the cytotoxic effects of proteins produced by eosinophils are most likely important (11,12). Tissue injury in HES is mediated by material released from eosinophilic granules, including major basic protein and eosinophil-derived neuro-

toxin (11,13-15). These eosinophil-derived molecules contribute to thromboembolic complications associated with HES (5,16,17).

To date, four cases of HES with prosthetic valve obstruction have been reported in the literature (8,18-20), each of which also had endomyocardial disease. In one case the obstruction was caused by pannus (8), but in the other three cases the cause was thrombus, despite adequate anticoagulation (18-20), though the presence of eosinophils was not reported. Replacement of the obstructed valves was performed in all cases, but three patients died postoperatively at 14 months (18), eight months (19), and 12 days (8), respectively. The eosinophil count of one 11-year-old child was controlled with prednisolone therapy (20).

The unique feature of the present case was that, after 15 years of valve replacement with a mechanical prosthesis, HES presented with clinical signs of recurrent prosthetic valve obstruction, though the primary operation was not performed for Löffler's endocarditis. Histologically, thrombus containing numerous eosinophils proved to be the cause of the obstruction. Neither tissue infiltration nor inflammation was detected by random biopsy of the left ventricular myocardium, though eosinophil-induced endothelial damage is known to serve as an initiator of the thrombosis in the early phase of HES. The younger, less-organized thrombi were found to contain greater numbers of eosinophils (3).

Thrombolysis represents an alternative to surgery, with 84% success and low complication rates (21). Indeed, thrombolysis was successful twice in the present patient, but failed at the third episode, most likely due to a significant rise in antistreptokinase antibody titers (22). Consequently, a bioprosthesis was implanted at the last operation.

Current experience of HES is insufficient to determine which type of artificial valve should be used to treat significant valve disease, there being very few data available to evaluate the thrombotic potential and long-term structural integrity of valve prostheses to treat this condition. All thrombotic valve obstructions in HES occurred in patients fitted with mechanical prostheses. Consequently, knowledge that these valves are thrombogenic, and that mural thrombi are characteristic of HES-associated heart disease, has led some authors to prefer porcine heterografts in patients with HES when prostheses are required, and to administer anticoagulant therapy (19,23).

In HES, the major aim of therapy is to debulk the tissue eosinophil burden, as the tissue injury and thromboembolic complications are mediated by eosinophil-derived molecules. Prednisone, hydroxyurea and interferon- α constitute first-line therapy of the disease, while imatinib, cladribine and monoclonal

antibodies to either interleukin-5 or CD52 are considered investigational (24). In the present case, the eosinophil count was well controlled by first-line combination therapy, and this led to a nine-year survival, without recurrent cardiac complications. To the present authors' best knowledge, there has been no reported case with such severe cardiac complications and long-term survival until very recently (25).

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