

# Obstructive Prosthetic Mitral Valve Thrombosis in Idiopathic Hypereosinophilic Syndrome: A Case Report and Review of the Literature

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**Idiopathic hypereosinophilic syndrome (HES) is an uncommon condition characterized by an unexplained elevation of absolute eosinophil count (AEC) to  $\geq 1.5 \times 10^9/l$  for at least six months, and is frequently associated with eosinophil-mediated end organ damage. Idiopathic HES, as with secondary HES and primary hypereosinophilic clonal hematopoietic disorders, has a high incidence of myocardial, pulmonary, neurological and other organ injury. Myocardial fibroelastosis and valvular lesions are common, and successful treatment with valve replacement or resection of fibrotic myocardium has**

The idiopathic hypereosinophilic syndrome (HES) is an uncommon condition characterized by an unexplained elevation of absolute eosinophil count (AEC) to  $1.5 \times 10^9/l$ , or above, for period of at least six months. The condition is frequently associated with eosinophil-mediated end organ damage (1). Idiopathic HES, as with secondary HES and primary hypereosinophilic clonal hematopoietic disorders (2), has a high incidence of myocardial, pulmonary, neurological and other organ injury. Myocardial fibroelastosis and valvular lesions are common, and successful treatment with valve replacement or resection of fibrotic myocardium has been reported. Herein is described the case of a patient with idiopathic HES and multi-organ complications, including severe mitral valve disease, in whom a functionally obstructive thrombosis of a newly inserted prosthetic mitral valve occurred despite adequate warfarinization, at a time when the AEC was profoundly elevated. Recurrent thrombosis has not occurred over a substantial period following reduction of the AEC with corticosteroid treatment, and subsequent maintenance of the AEC at normal levels.

been reported. The case is described of a patient with idiopathic HES and multi-organ complications including severe mitral valve disease, in whom a functionally obstructive thrombosis of a newly inserted prosthetic mitral valve occurred despite adequate anticoagulation, when the AEC was profoundly elevated. Recurrent thrombosis has not occurred over a substantial period following AEC reduction with corticosteroids, and subsequent maintenance at normal levels.

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## Case report

A 32-year-old asthmatic female presented with cough and dyspnea due to moderate cardiac failure. Over the previous 12 years she had experienced five episodes of facial palsy which was diagnosed as multiple sclerosis, in spite of negative investigations. She had been admitted to hospital eight weeks previously for a similar episode of dyspnea that had responded to anti-asthma treatment, including corticosteroids. A full blood examination at the time of admission showed a mild hypereosinophilia (eosinophil count  $1.5 \times 10^9/l$ ).

Echocardiography and cardiac catheterization on admission showed severe mitral stenosis (mean gradient  $>20$  mmHg) and severe pulmonary hypertension (right ventricular systolic pressure 70 mmHg), but excluded coronary artery disease. Transesophageal echocardiography (TEE) revealed restriction of the posterior leaflet of the mitral valve, and fusion of anterior and posterior leaflets at the posteromedial commissure. The patient was commenced on therapy with frusemide, metoprolol and digoxin as treatment for cardiac failure.

On admission to the authors' institution, the AEC was normal, but two days later the patient developed a self-limiting widespread urticaria, which was attributed to a drug reaction. Despite replacing the patient's drugs with alternative agents, and resolution of the

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rash, the AEC rose progressively from  $0.6 \times 10^9/l$  on day 2 to  $2.1 \times 10^9/l$  by day 7. Magnetic resonance imaging of the brain at this time showed multiple lacunar infarcts, but no evidence of demyelination.

A presumptive diagnosis of cardiac failure secondary to rheumatic mitral valve stenosis was made, and a semi-elective mitral valve replacement was undertaken. A 27 mm St. Jude Medical mechanical prosthesis (St. Jude Medical, Inc., St. Paul, Minnesota, USA) was inserted during an uncomplicated procedure. Intraoperatively a small nodule was seen on the posterior leaflet, and subsequent histological examination revealed diffuse fibrosis and chronic inflammation of the valve tissue with myxoid change and focal calcification. No vegetations were identified, and no organisms were either seen or cultured. The ventricular endocardium was normal at the time of surgery.

Warfarin treatment was commenced postoperatively and was therapeutic by day 5 (International Normalized Ratio 2.8). On postoperative day 9, the patient became acutely dyspneic and hemodynamically unstable. Echocardiography demonstrated a functioning mitral valve, and the chest sepsis was thought to be the cause of her deterioration. *Haemophilus influenzae* was cultured from sputum samples, and bilateral lung field infiltrates were evident on imaging. The patient was commenced on antibiotic therapy, by which time the AEC had risen to  $15.7 \times 10^9/l$ .

By postoperative day 11 the AEC had risen to  $40.6 \times 10^9/l$ , at which point cardiogenic shock developed suddenly. Immediate TEE showed the prosthetic mitral valve to be almost fixed in the closed position due to masses within the valve, with an appearance typical of thrombus. The valve gradients were 50 mmHg (peak) and 22 mmHg (mean). The patient suffered a cardiac arrest, but resuscitation with internal cardiac massage en route to the operating room was successful, and immediate valve revision was performed. At surgery, both leaflets of the prosthetic valve were found to be fixed in the closed position by enveloping thrombus. The occluded valve was replaced with a second 27 mm St. Jude Medical mechanical valve. Histology revealed eosinophilic pannus covering the valve, but no organisms were either seen or cultured.

Intraoperatively, the patient was administered 1 g methylprednisolone intravenously, after which the AEC count fell over 24 h to  $0.5 \times 10^9/l$ . Subsequently, the AEC began to rise two days later and reached  $15.6 \times 10^9/l$ , indicating the need for further corticosteroids to maintain suppression. Prednisolone (75 mg daily) was commenced and the AEC was again normalized after 48 h. A bone marrow biopsy revealed an increase in myeloid series, 22% eosinophils, and no evidence of hematologic malignancy. A bone marrow

cytogenetic analysis revealed cells only of normal karyotype. PCR analysis for the FIP1L1-PDGFR fusion gene was negative, and thus failed to provide evidence of the primary clonal form of HES (2). Screening for autoantibodies, and antibodies to organisms associated with hypereosinophilia, was negative, and a review of the patient's clinical course failed to identify any cause of reactive eosinophilia. She was consequently considered to have idiopathic HES. Nonetheless, she made a full recovery, and has remained complication-free on a slowly reducing dose of oral prednisolone, which ultimately was ceased. Currently, a normal AEC has been maintained for 12 months since the second valve insertion.

## Discussion

### Definition, incidence, clinical presentation and diagnosis

Idiopathic HES was first described by Löffler in 1936 (3), but was later more clearly defined by Chusid et al. (1) as a prolonged (six months), unexplained elevation in AEC to  $1.5 \times 10^9/l$  or above, with eosinophil-mediated end organ dysfunction (1,4). HES is a heterogeneous group of conditions with an elevation of AEC and predictable complications (1,5-8). Other causes of hypereosinophilia include allergic disorders, parasitic infections and malignant disease (4,5,7,9). Cardiac and neurological complications are the most common extra-hematologic manifestations, and are the major contributors to morbidity and mortality (8,10).

HES is a rare condition, the exact incidence of which is unknown. It occurs predominantly in males (male:female ratio 9:1) between the ages of 20 and 50 years (5,7,8,11-13). The clinical presentation is variable, though patients commonly are diagnosed with cardiac failure or neurologic symptoms. Other symptoms include anemia, weight loss, lethargy, anorexia, and night sweats (5-8,11). Some patients may have hypereosinophilia without symptoms (8). The highest reported eosinophil count was  $174 \times 10^9/l$  (5).

Idiopathic HES is a diagnosis of exclusion, and extensive investigation is important to exclude secondary hypereosinophilia. All patients should undergo serial blood counts, urinalysis, liver and renal function tests, serologic tests for infective and connective tissue disease, stool analysis for parasitic infestation, assessment of cardiac and pulmonary function and bone marrow analysis (4,14). Biopsy of individual organs may also be indicated.

### Pathogenesis and pathology

The exact pathogenesis of eosinophil-mediated end organ damage is unknown, but the direct tissue damage is thought to result from cytotoxic mediators

released from eosinophilic granules (4,7,11,15). Eosinophilic major basic protein and eosinophilic cationic protein are cytotoxic to splenic, cutaneous, and other mammalian cells (7), while degranulated eosinophils are seen in blood films and tissue biopsy in HES (1,5-8,15,16). Other unknown mechanisms are thought to play a role in determining the distribution and degree of injury seen with this disorder (4).

The distribution of organ damage has been well reviewed (Table I) (1,4,5,7,8,15). In an analysis of over 100 patients, Weller and Bubley found that in, addition to hematologic abnormalities, the most common systems involved were cardiac (58%), cutaneous (56%), neurologic (54%) and pulmonary (49%) (8). A similar pattern of organ involvement occurs in secondary hypereosinophilia (5).

Cardiac involvement is the most common extra-hematologic manifestation of HES (58-93% of patients) (1,8,17). Fauci et al. showed that endothelial cells of the endocardium are a primary target of activated eosinophils (4). Platelet thrombi form over the damaged endocardium, and subsequent fibrotic changes lead to a restrictive cardiomyopathy (8). Although both ventricles are affected (7,18), there is often a sparing of the outflow tracts. Propagation of the mural thrombus commonly involves the posterior leaflets of the mitral or tricuspid valves and results in valvular insufficiency (4,5,8,15,19). Involvement of the fibrous cardiac skeleton can also result in mitral or tricuspid regurgitation, and involvement of the valves themselves causes stenotic lesions (5,7,12,17). Most commonly affected is the posterior mitral leaflet, which is often found adherent to the fibrotic endocardium of the ventricle.

The clinical presentation of cardiac involvement includes chest pain, arrhythmias, cardiac failure, cardiogenic shock, and peripheral embolism (5-8,11,20); such involvement with HES is a poor prognostic indicator and the major cause of mortality (8). Cardiac involvement is predicted by male gender,

splenomegaly, HLA-Bw44 presence, thrombocytopenia, raised serum vitamin B<sub>12</sub> levels, hypogranulated or vacuolated eosinophils, and bone marrow fibrosis (10). Investigations reveal t-wave inversion on electrocardiography, and wall thickening, increased pressures and valve lesions on echocardiography and angiography (8,18,20,21). The diagnosis is confirmed by endomyocardial biopsy.

Current cardiac interventional techniques have improved the prognosis of HES (1,8), there being multiple reports of successful treatment of endomyocardial and valvular pathology (4-6,13,16,17,19,21-25). Cardiac failure due to constrictive fibrous endocarditis can be treated by endocardectomy (11), with improvement in exercise tolerance, reduction in left ventricular cavity dimensions and improved hemodynamics after surgery (4,6,16,17,19,21-25). Recurrence of infiltrative disease in the myocardium is infrequent after surgery. Arrhythmias, including ventricular extrasystoles and tachyarrhythmias, are common in HES due to altered cardiac metabolism or mechanical changes secondary to valvular dysfunction or infiltration. Cohen et al. have also reported the resolution of these following successful cardiac surgery (20).

### Cardiac valve replacement

Symptomatic valve disease is best treated with valve replacement, which has improved outcome compared with historical controls (4-6,13,16,17,19,21-25). There is inadequate evidence to establish whether bioprosthetic or mechanical valves are superior (6,13,19,23). Postoperative acute valve obstruction has been reported, and can recur despite adequate anticoagulation. Thrombosis can occur within hours, days, months or years following surgery, often profoundly interfering with function, and usually requiring urgent valve replacement (16,19,21,23). In some reports, thrombosis occurred in conjunction with a rising or marked elevation of the AEC. In survivors of such episodes the AEC is suppressed by therapeutic means. Supportive data

Table I: Extra-cardiac organ involvement seen in hypereosinophilic syndrome (HES).

Organ system	Nature of pathology
Hematologic (73-100%)	Anemia, thrombocytopenia, leukophilia, vitamin B <sub>12</sub> and folate abnormalities, hypercoagulability.
Cutaneous (56-64%)	Angio-edema and urticarial lesions. Pruritic papules and nodules, dermatographism.
Neurologic (23-64%)	Ischemic events - thrombotic and embolic disease, local intravascular thrombosis. Diffuse encephalopathic changes. Peripheral neuropathies, both sensory and motor.
Pulmonary (38-49%)	Pulmonary embolic phenomena from right ventricle, primary eosinophilic infiltration, pleural effusions (eosinophilic) pulmonary fibrosis.
Splenic (29-46%)	Splenomegaly - contributing to anemia and thrombocytopenia, splenic pain (capsular distention) and splenic infarcts.
Embolic	Embolic phenomena common. Including splinter hemorrhages, retinal microemboli, cerebral, renal, splenic, and femoral emboli.

on the course of the AEC has generally not been reported in detail.

Released products from eosinophils have thrombogenic potential. In particular, the major eosinophil basic protein, released during degranulation of eosinophils, inhibits the capacity of thrombomodulin to activate protein C, and this results in an enhanced activity of the thrombotic cascade (26). Both eosinophil basic protein and eosinophil peroxidase interfere with the anticoagulant effect of heparin on antithrombin III, the result being an additional increase in thrombogenic activity (27). It is possible that a substantial rise in AEC, as seen in the present patient, can increase thrombogenic activity by mechanisms of this type to predispose to the development of thrombosis on the implanted prosthetic valve. A lack of further thrombotic complications after sustained normalization of the AEC by corticosteroid administration in the present patient also provided further support for an association between a substantial elevation of the AEC and a risk of thrombosis. This also suggests that prosthetic mechanical valves are a reasonable option, provided that adequate anticoagulation and suppression of hypereosinophilia can be ensured (16,19,21,25). Bioprosthetic valves may be subjected to an accelerated deterioration of function in HES due to thrombus formation, fibrosis and tearing (particularly in children) (13). Some authors believe, however, that there is a reduction in early thrombotic occlusion (6,13,19,21,22).

### Treatment of HES

The medical management of HES is directed at lowering the eosinophil count, minimizing organ involvement, and the symptomatic treatment of organ failure (7). In hypereosinophilia without organ involvement, close observance without intervention is advocated (8,14,18). Symptoms of cardiac involvement respond to standard anti-failure treatment and can be further improved by the concurrent use of prednisolone (1 mg/kg, up to 60 mg per day). Corticosteroids are recommended as first-line treatment (4,5,7,8,14), but failure to control eosinophilia with a single agent is common. Hydroxyurea is normally used as a second-line agent (4, 14), while other case reports have supported the use of busulphan, 6-mercaptopurine, vincristine, cyclophosphamide, azathioprine and interferon- $\alpha$  (4,5,7,8,14,19). Eosinophilic release products are responsible for organ damage, so there is a rational basis for the long-term suppression of eosinophilia (4,6-9,19,21,23). Recurrence of hypereosinophilia and associated complications once medication is ceased is common (5,7,12,13,17), and maintaining a low count without necessarily inducing disease remission probably improves the prognosis (4,7-9,14,19,21,23).

Other medical treatment is directed at reducing the high risk of embolic disease. Where possible, anticoagulation and anti-platelet agents are prescribed, although emboli and thrombosis still occur (4,6-8,13,14,17). Most authors recommended lifelong anticoagulation with warfarin and an anti-platelet agent, especially following cardiac surgery.

### Prognosis

Early reviews reported an average survival of nine months, and a three-year survival of between 12 and 23% (1,4,14). Currently, with aggressive treatment - particularly of cardiac disease - survival exceeding 15 years (8), as well as 96% three-year survival (14), has been reported. Poor prognostic indicators are cardiac and neurological involvement, leukocyte counts exceeding  $90 \times 10^9/l$ , myeloblasts in the peripheral blood, and congestive heart failure (1,7,8,14).

*In conclusion*, idiopathic HES is an uncommon condition associated with widespread organ damage that causes significant morbidity and mortality. Valvular and myocardial damage is common, and associated with potentially lethal complications due to an increase in thrombotic risk, as well as functionally restrictive thrombosis of implanted valves. HES is amenable to surgical treatment. The present subject had neurologic, cutaneous, pulmonary and cardiac damage due to idiopathic HES that was recognized late in the course of the disease. Prosthetic valve replacement was complicated by the rapid development of thrombosis of the mechanical valve, despite adequate anticoagulation, and the patient survived only because of immediate valve replacement and high doses of intravenous corticosteroids. This thrombotic event occurred at a time of rapid escalation of the eosinophil count to very high values, which indicated an association between the high circulating eosinophil count and thrombus generation on the valve surface. A rising eosinophil count after prosthetic valve insertion may therefore be an indicator of increased risk of valve thrombosis and indicate a need for medical measures to suppress eosinophilia. Treatment with corticosteroids in the present patient successfully reduced the eosinophil count to normal for an extended period, during which time no further thrombotic events occurred.

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