CASE REPORTS

Surgery for Cardiac Complications Caused by Endocardial Mural Fibrin Deposits in a Hypereosinophilic Syndrome

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SUMMARY A 31-year-old man presented with rapid onset of intractable congestive heart failure during the course of chemotherapy for eosinophilic leukemia. Patients with a hypereosinophilic syndrome usually die from complications of eosinophilic infiltration and fibrosis in target organs. The resulting cardiac lesions are a cause of death among these patients. Surgical intervention enabled our patient to survive the immediate medical crisis and has prolonged his life.

Case Report

A 31-year-old white male was referred to the outpatient clinic of the Department of Hematology at Purpan Hospital in December 1976 with the chief complaint of weakness. A peripheral blood study had shown a leukocytosis of 39,000 and an eosinophilia of 61%. He had no history of allergy or travel outside France. He was admitted to the hospital on January 5, 1977. On physical examination, the patient was asthenic and pale. An enlarged spleen could be palpated 5 cm below the left costal margin. The inguinal lymph nodes were enlarged. The heart and lungs were normal. The liver was not palpable. Bone tenderness was elicited by the palpation of spinal processes between T-1 and T-4. A complete blood count confirmed a leukocytosis with eosinophilia, and revealed circulating immature white cells and normochromic, normocytic anemia. The erythrocyte sedimentation rate was 63 mm/hour. The free vitamin B-12 serum level was 6500 pg/ml (normal 300 ± 10 pg/ml) and the leukocyte alkaline phosphatase score (LAP) was 23 (normal 80-100). A search for the Philadelphia chromosome was negative. Bone marrow aspiration and biopsy showed increased cellularity with marked granulopoietic activity. Treatment for an atypical form of chronic myelocytic leukemia was begun using 6-mercaptopurine and, later, hydroxyurea. The anemia was compensated by two whole blood transfusions. He was discharged on January 20, 1977. The progress of the chemotherapy was followed by monthly outpatient visits over 6 months.

In April 1977, he began to experience exertional dyspnea. In July, he complained of paroxysmal constrictive chest pain. A grade 2 pansystolic murmur was heard at the apex. Roentgenograms of the chest showed an enlarged cardiac shadow. The ECG demonstrated nonspecific ST-segment abnormalities. On further examination, frank hepatomegaly and enlarged cervical, axillary and inguinal lymph nodes were discovered.

By October 1977, the liver showed further enlargement clinically, was tender to palpation and was accompanied by pedal and facial edema; there was a hepatosplenic reflex. The spleen and peripheral lymphadenopathy were unchanged. He was readmitted on December 19, 1977. His temperature was 38°C, the pulse 100 beats/min and the respirations 22. The blood pressure was 120/85 mm Hg.

The patient was extremely weak and could not perform any activity without provoking marked dyspnea. He had two-pillow orthopnea. The systolic murmur was accentuated during inspiration. The liver was tender, vertically spanned 17 cm and was accompanied by a hepatosplenic reflex. The ECG showed signs of right ventricular hypertrophy with a mean frontal plane axis of +35°. The erythrocyte sedimentation rate (ESR) was 83 mm/hour. A trial treatment with thiabendazole was begun in an effort to eliminate trichinosis, which had reached epidemic proportions in France. The patient’s condition did not improve and the drug was discontinued. The bone marrow aspiration and biopsy were repeated, demonstrating frank eosinophilic hyperplasia. The elevated serum levels of vitamin B-12, a consistently low LAP score, the presence of immature white blood cells in the blood stream and a hypochromic microcytic anemia associated with the narrow findings and symptoms, led to the diagnosis of a variant of chronic myelocytic leukemia, eosinophilic leukemia.

An echocardiogram showed an image that might have been caused by a mass, but this echocardiogram...
was of very poor quality and cannot be reproduced. A right cardiac catheterization demonstrated increased end-diastolic pressure. Cineangiography revealed the global reduction in right ventricular wall motion (fig. 1) and a filling defect in the right ventricular outflow tract (table 1). Global angiography permitted the calculation of the left ventricular ejection fraction, which was 59% (normal 63–73%). Pulmonary function studies were normal. Flow rates and arterial blood gas determinations, drawn while the patient was breathing room air, were normal. These findings are compatible with the possibility of a right intraventricular tumor, right ventricular thrombosis or eosinophilic endomyocardial heart disease.

The patient had an exploratory thoracotomy in February 1978. The approach to the heart was by median sternotomy. The pericardium was incised. No external abnormalities were observed. Digital examination of the tricuspid valve revealed that the valve opening was restricted, permitting the passage of only the small finger through the anterosuperior aspect of the valve. The patient was placed on extracorporeal circulation, with hypothermia maintained at 26°C.

The tricuspid valve was visible after right atriotomy. The valve was partially immobilized by a soft tissue mass occupying the entire atrioventricular orifice, which allowed an opening of 4 mm in diameter in the anterior commissure as the only pathway between the right atrium and ventricle.

An infundibulotomy was performed below the pulmonary ring, disclosing a gelatinous matrix adhering to the wall of the right ventricle. The right ventricle outflow passage and the endocardium were progressively freed of the mass. The chordae tendineae of the tricuspid valve could not be salvaged. The valve was removed and a Hancock #31 heterograft was inserted. The mass, along with biopsies of the diaphragm and endocardium, were sent for pathologic examination.

On the third postoperative day, the patient developed pedal edema, ascites and hepatomegaly, and gained more than 2 kg in less than 24 hours. On examination, there was a grade I midsystolic murmur heart at the apex. The liver was enlarged; there was no hepatojugular reflux or spontaneous tenderness over the liver. The splenomegaly and lymphadenopathy were unchanged from preoperative examination. The patient responded to combined treatment with digitalis, furosemide and an infusion of 250 ml of human albumin. His condition rapidly improved.

### Table 1. Cardiac Catheterization Hemodynamic Values

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th></th>
<th></th>
<th>Postoperative</th>
<th></th>
<th></th>
<th>Control 4/17/79</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A wave V wave Mean S/D</td>
<td>A wave V wave Mean S/D</td>
<td>A wave V wave Mean S/D</td>
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<tr>
<td>Right atrium (mm Hg)</td>
<td>18</td>
<td>10</td>
<td>14</td>
<td>18</td>
<td>12</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Right ventricle (mm Hg)</td>
<td>15/14 ± 5</td>
<td></td>
<td></td>
<td>26/0 ± 3</td>
<td></td>
<td></td>
<td>35/20 ± 2</td>
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<tr>
<td>Pulmonary artery wedge pressure (mm Hg)</td>
<td>14</td>
<td>16/12</td>
<td></td>
<td>20</td>
<td>25/15</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyn-sec-cm⁻²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Arterial</td>
<td>351.84</td>
<td></td>
<td></td>
<td>266</td>
<td></td>
<td></td>
<td>332.99</td>
</tr>
<tr>
<td>Arteriolar</td>
<td>51.32</td>
<td></td>
<td></td>
<td>80</td>
<td></td>
<td></td>
<td>106.55</td>
</tr>
<tr>
<td>Cardiac index (l/min)</td>
<td>1.7</td>
<td></td>
<td></td>
<td>3</td>
<td></td>
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<td>3</td>
</tr>
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</table>

Pulmonary vascular resistance (PVR) was calculated using the following formulas:

\[
\text{Arterial} = \frac{\text{mean PAP}}{\text{flow rate}} \times 1332 \times 60 \text{ (normal 90–300)};
\]

\[
\text{Arteriolar} = \frac{\text{PAP} - \text{WP}}{\text{flow rate}} \times 1332 \times 60 \text{ (normal 20–200)}.
\]

Abbreviations: PAP = pulmonary artery pressure; WP = wedge pressure; S/D = systolic/diastolic.
By the fifteenth postoperative day, chest roentgenograms showed a progressive reduction in the cardiac silhouette. However, the liver remained enlarged and there was no change in the splenomegaly or lymphadenopathy.

He remained under treatment for heart failure with digitalis, furosemide, spironolactone and a salt-free diet. Various antihistamines and hydroxyurea were administered prophylactically to prevent endocardial fibrin formation. Heparin was also given to prevent thrombosis due to the valve prosthesis.

In early April 1978, the first postoperative studies were performed. Cardiac catheterization showed a reduction in right ventricular end-diastolic pressure (table 1). Cineangiocardiography demonstrated normal blood flow across the valve prosthesis, improved ventricular wall motion compared with the preoperative results, but still hypokinetic, and an improved pulmonary ejection pathway (fig. 2). The left-sided ejection fraction was 66%. The echocardiogram revealed the persistence of ventricular wall thickening with some degree of intraventricular fibrosis. The valve prosthesis appeared normal.

An echocardiogram taken in March 1979 showed the absence of new cardiac lesions and fibrosis. Between the two echocardiograms, done at an 8-month interval, there was no evidence of a recurrence of mural fibrosis (fig. 3). On April 17, 1979 cardiac catheterization and cineangiocardiography were performed (table 1). The results were similar to the first postoperative examination.

The patient is seen every 6 months by a cardiologist and a hematologist. Digitalis, furosemide, spironolactone and a salt-free diet have controlled the cardiac symptoms. Anticoagulant therapy, which was begun postoperatively with heparin, has been continued using dicumarol with satisfactory results. The combination of antihistamines, allopurinol and hydroxyurea has been very effective in stabilizing the hypereosinophilia. He has experienced no new symptoms. As of March 1981, his condition was stable.

Discussion

Eosinophilia is most often caused by allergy, parasitosis, certain malignancies and blood dyscrasias. Recently, a syndrome characterized by an eosinophilia with secondary systemic manifestations has been described. Despite its relative rareness, it must be considered among the possible differential diagnoses of eosinophilia.

In this patient, we were most immediately concerned with only certain forms of the hypereosinophilic syndrome, entities characterized by an eosinophilia and an endomyocardiopathy that would result in heart failure. These were eosinophilic leukemia, disseminated eosinophilic collagen disease, Loeffler’s endocarditis with eosinophilia, endomyocardial fibrosis and endomyocardial fibroelastosis. Each of these diseases can partially obliterate a ventricular cavity by fibrinous tissue deposits. The ECG

![Figure 2. Postoperative cineangiogram of the right chambers shows tricuspid valve bioprosthesis and subnormal ventricular outflow pathway.](image1)

![Figure 3. Postoperative echocardiogram on March 12, 1979. The right and left cardiac chambers are of normal size. There are no images of obstruction in the right ventricle. The posterior wall (PW) of the right ventricle shows some residual akinesia. The echo of the endocardium is flat at the beginning of diastole followed by a sudden deflection to a more posterior position during the protodiastolic phase, giving a “dip” aspect to the posterior wall (arrows). S = septum.](image2)
in those cases shows nonspecific ST-segment deviations. Chest roentgenograms demonstrate progressive cardiomegaly. Cardiac catheterization reveals a decrease in cardiac output and an elevation in left or right end-diastolic pressure.

We ruled out the more common causes of eosinophilia except for parasitosis. During the summer of 1977, a contaminated shipment of pork from Eastern Europe caused an epidemic of trichinosis in France. Before becoming ill, the patient had eaten pork purchased from a store known to have received a contaminated shipment. At the same time, an article by Andy et al. linked trichinosis to endocardial mural fibrosis. Diagnostic procedures to recover the parasite were initiated. A therapeutic trial of thiabendazol as well as muscle biopsies were tried. The patient's condition did not improve and the biopsies were negative, eliminating parasites from further consideration.

Endomyocardial fibrosis is principally seen in Africa and only occasionally in temperate climes. Mural fibrosis is found in all four chambers, principally in the left ventricle and right atrium. The ultrasonic examination in our case revealed mural fibrosis only in the right ventricle. Endomyocardial fibroelastosis occurs in infants, children and adults, but is far more often encountered before age 3 years. Because of the respective peculiarities that did not correspond to this case, they were not considered as possible diagnoses.

The remaining entities, disseminated eosinophilic collagen disease, Loeffler's endocarditis and eosinophilic leukemia, have been described as being the same disease seen at different stages of its elaboration. If so, then the absence of generalized vasculitis and antinuclear antibodies, coupled with frank hematologic signs, situate our case at the leukemoid stage of the hypereosinophilic syndrome. However, these same hematologic signs — very high concentration of free vitamin B-12, very low LAP score, persistent splenomegaly and bone marrow showing increased cellularity with marked granulopoietic activity — lead us to believe that this is in fact an atypical form of chronic myelocytic leukemia, eosinophilic leukemia.

Furthermore, we base our diagnosis of eosinophilic leukemia on criteria established by Bentley et al. in 1961 and Benvenisti and Ultmann in 1969. Bentley divided the disease into three categories: blastic, immature and mature based on the cell type found in the blood stream. Benvenisti and Ultmann specified that the eosinophilia must be accompanied by hepatosplenomegaly and peripheral lymphadenopathy. As early as July 1977, our patient had all criteria of having immature eosinophilic leukemia.

The surgical management of a hypereosinophilic syndrome with endocardial mural fibrosis causing intractable heart failure is a new approach, insomuch as the patient did not succumb to the acute medical crisis before surgery. The mortality once the patient enters the period of congestive heart failure is very high. In a review of 48 cases of eosinophilic leukemia, Benvenisti and Ultmann stated that 80% of the patients had cardiac involvement and died within 12 months of diagnosis due to hemodynamic complications. In this case, surgery enabled him to survive the medical crisis.

The results of the biopsies taken during surgery were similar to autopsy findings in other studies. The matrix, taken from the right ventricle, was composed of highly organized fibrin and altered eosinophils that completely covered the endocardium (figs. 4 and 5). The endocardium was normal; however, there was a nonspecific leukocyte infiltration of the myocardial interstices. Light and electron microscopy of the eosinophils demonstrated abnormal vacuolization, which was metachromatically different from normal eosinophilic vacuoles. The extent of our biopsies was limited, so we are unaware of the extent of the myocardial involvement of ventricular wall thickening.

The long-term prognosis must be guarded because of several considerations. If this is a chronic leukemoid process, it may recur, change its course and become the rapidly fatal acute myeloblastic leukemia. Second, since the true extent of the myocardial lesions is uncertain and there is no guarantee against the recurrence of endocardial mural fibrosis and intractable heart failure, the prognosis in this case cannot be predicted.

This study is based on one case; thus, the conclusions that can be drawn are limited. However, the clinical problems encountered in other studies dealing with the hypereosinophilic syndrome were identical.
We know that surgery might be considered in treating endocardopathies due to the presence of a hypereosinophilic syndrome.

To the best of our knowledge, this is a unique case. The heart failure was due to an obstruction rather than restrictive endomyocardial disease, which is usually seen in the other forms of the hypereosinophilic syndrome. We feel that the combination of surgery and chemotherapy improved the prognosis in this case.

Acknowledgment

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References

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