Case Reports

Cardiac Involvement in a Patient with Eosinophilia and Inversion of Chromosome 16(p13q22): A Case of Chronic Eosinophilic Leukemia or AML-M4EO?

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Abstract

Any chronic hypereosinophilic state, including eosinophilic leukemia, reactive eosinophilia and idiopathic hypereosinophilic syndrome may be complicated by the end-organ damaging effects of eosinophilic degranulation, especially cardiac involvement. Several cytogenetic abnormalities that have prognostic and even therapeutic implications, have been described in patients with different variants of eosinophilic syndrome as well as different features of cardiac involvement. Here we describe an 11-year-old boy whose clinical and laboratory data met the criteria for chronic eosinophilic leukemia except for the cytogenetic abnormality of inversion of chromosome 16 that represents the strongest argument for AML-M4EO, despite no significant increase in bone marrow blasts. Intramural thrombi in both ventricles, mitral and tricuspid valve regurgitation and congestive heart failure were pathologic cardiac findings in our patient. Cytogenetic and molecular genetic analysis is deemed necessary for determining the definite diagnosis, prognosis and therapeutic strategies ***(Iranian Heart Journal 2007; 8 (1): 46-51)***.

Keywords: cardiac complications■ endomyocarditis ■ intracardiac thrombi■ eosinophilia ■ chromosome 16

Research in cellular and molecular biology has changed the classification criteria in patients with hypereosinophilic syndrome (HES). However diagnostic criteria established by Chusid et al. in 1975 are still in use today. Cardiac and other tissue damage as a consequence of release of eosinophil granule contents can occur in patients with eosinophilic leukemia, reactive eosinophilia and idiopathic hypereosinophilic syndrome. As a matter of fact cytogenetic and molecular genetic analysis for definite diagnosis seems to be helpful. Cardiac damage is a major determinant of overall prognosis.

Different features of cardiac complications in patients with chronic hypereosinophilic state, especially myeloproliferative variants, have been reported.

Case report

An 11-year-old boy previously in good health until 7 months before was admitted to a regional hospital (April 2005) with fever, malaise, left shoulder pain, non-productive cough and dyspnea. Chest-x-ray showed bilateral alveolo-interstitial opacities more pronounced centrally with mild cardiomegaly.

Received Nov. 13, 2005; Accepted for publication Aug. 22, 2006.
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Complete blood count (CBC) showed white blood cell count of 50,300/mm^3 and total eosinophil count of 35,210/mm^3 or 70%. Hemoglobin level was 12.8g/dl and the platelet count was 454,000/mm^3. A bone marrow film revealed marked hypercellular marrow - only eosinophilic hyperplasia. Neither dysplastic feature nor proliferation of blasts was detected.

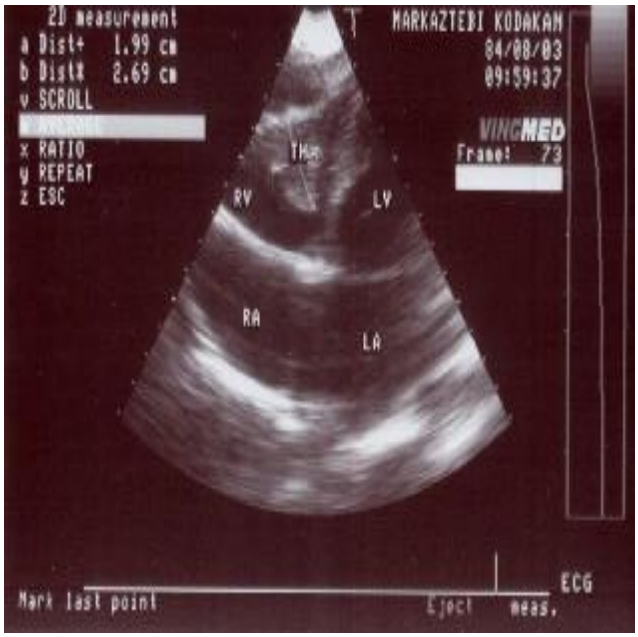
Echocardiography showed moderate to severe mitral regurgitation with no evidence of thrombus formation. After a preliminary work-up for eosinophilia and management of congestive heart failure, he was treated with prednisolone and hydroxyurea. The patient's clinical condition improved. However there was only a partial decline in leukocyte count and peripheral eosinophilia. Seven months later (November 2005) while prednisolone was being tapered, increasing dyspnea and clinical deterioration developed. The patient was transferred to our center for further evaluation and therapeutic measurements.

Table I. Patient's laboratory data at second admission.

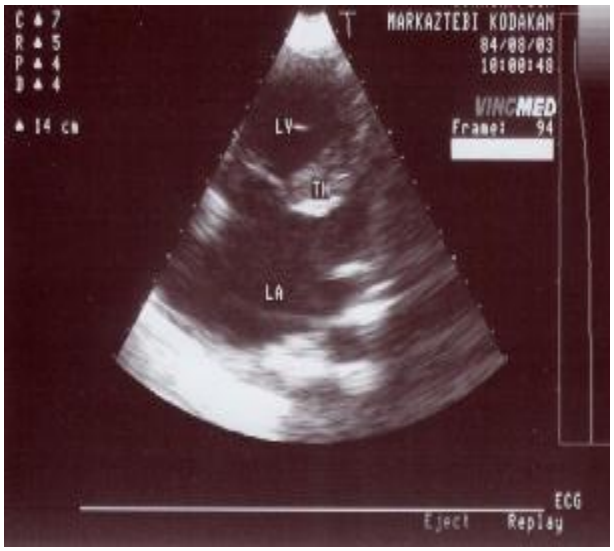
Complete blood count	C3, C4, Total complement	normal	
White blood cell	76400/mm3	Antinuclear antibody	negative
Eosinophil (67%)	51188/mm3	Antineutrophil cytoplasmic antibody	negative
Neutrophil (18%)	13752/mm3	Rheumatic factor	negative
Lymphocyte (13%)	9932/mm3		
Hemoglobin	10.7gr/dl	SGOT,SGPT,Alkaline phosphatase	normal
Platelet	173000/mm3	Lactate dehydrogenase	elevated
ESR	elevated	Serum B12	normal
CRP	elevated	Cardiac troponin T	negative
Leukocyte alkaline phosphatase score			normal
PT, aPTT	normal	Flowcytometry of bone marrow:	
Special coagulation studies	unremarkable	CD10, CD45, HLA-DR, TdT CD19, CD20, CD33 and CD34	Positive weakly positive
Serum immunoglobulin	normal	Cytogenetic examination: [46XY, per inv (16) (p13q22	
Evidence for bacterial, mycobacterial, fungal and viral infection as well as visceral larva migrans and other parasites were negative Bone marrow aspiration showed markedly hypercellular marrow with 70% eosinophils at various stages of maturation with less than 20% blast cells			

On admission the child's general condition was poor. Physical examination revealed tachycardia and S3 gallop. A 3/6 high-pitched holosystolic murmur was heard best at the apex. He had hepatosplenomegaly palpable 2 and 3 cm below the right and left costal margins, respectively. Initial laboratory studies at recent admission are depicted in Table I.

High resolution computed tomography (HRCT) showed bilateral alveolar opacities and ground glass densities but not as the classic pattern of peripheral predominance of idiopathic eosinophilic pneumonia. Electrocardiography showed normal axis, sinus tachycardia with ST-segment and T-wave abnormalities. Two-dimensional echocardiography revealed a round homogenous mass with no mobile components in both ventricles. The right ventricular thrombus (2.69x1.99cm) occupied half of the right ventricle cavity apically. The left one (2.2x1.2 cm) entrapped the posterior leaflet of the mitral valve (Fig. 1).



A.



B.

Fig. 1. A. Two-dimensional echocardiogram showing right ventricular thrombus (2.69x1.99cm) occupying the right ventricle apex (four-chamber view). B. Entrapment of the posterior leaflet of the mitral valve by the left ventricular thrombus (two chamber view). (RA=right atrium LA=left atrium, LV=left ventricle, RV=right ventricle, TH=thrombus).

There was no evidence of inferior or superior vena cava thrombosis. Coronary arteries were intact. Severe mitral regurgitation, moderate tricuspid regurgitation, severe pulmonary hypertension and mild pericardial effusion were other findings of echocardiography. Atrioventricular valve flow studies revealed diastolic dysfunction of both ventricles (restrictive pattern). However the ejection fraction was normal. Spect myocardial perfusion scan showed fairly homogenous radiotracer uptake throughout the myocardium on both phases of the study.

Therapeutic management for congestive heart failure and also anticoagulant therapy with heparin followed by warfarin were started. Despite the slow evolution, clinical features and most laboratory data were in favor of chronic eosinophilic leukemia (CEL), thus we began an induction course of AML therapy with cytarabin due to the evidence of chromosome 16 inversion and progressive deterioration of the patient's condition. There was clinical improvement in signs and symptoms with lowering of the leukocyte and absolute eosinophil counts, in addition to resolution of chest x-ray infiltrations. Close follow-up with serial echocardiography was recommended, and heart surgery consultation for probable surgical resection of thrombi or valve replacement was considered as a part of the therapeutic strategy.

Discussion

An elevated blood eosinophil count may be associated with a number of reactive conditions (secondary phenomenon) or with primary disorders which are classified into two major categories of clonal and idiopathic. Hardy and Anderson proposed the concept of hypereosinophilic syndrome (HES) in1968, stressing damage to organs such as the heart and lungs. However Chusid et al. in 1975 established the diagnostic criteria of idiopathic HES that are still considered valid today: a) blood eosinophilia exceeding 1500/mm3 for more than six consecutive months, b) absence of an underlying cause of hypereosinophilia despite extensive diagnostic evaluation and c) presence of organ damage or dysfunction related to hypereosinophilia.[1]

Factors such as IL3, IL5 and/or GM-CSF prolong the eosinophils survival by preventing apoptosis, stimulation of bone marrow generation and inhibition of peripheral destruction. Whatever its cause, accumulation of eosinophils is deleterious. The organ damage seen in eosinophilia is related to the effect of proteins released upon degranulation, including major basic protein (MBP), cationic proteins, enzymes, proinflammatory cytokines and arachidonic acid-derived factors.[2]

Cardiac involvement in hypereosinophilic state is mainly characterized by endomyocardial fibrosis which is preceded by two other stages. The early - usually asymptomatic - necrotic stage is followed by a thrombotic stage in which intracavitary thrombi develop along the damaged

endocardium of either or both ventricles and occasionally the atria. Large mural thrombi may develop thereby compromising the size of the ventricular cavity and serving as a source of pulmonary and systemic emboli. Typically the ventricular outflow tracts and semilunar valves are spared. Damage to the atrioventricular valves, entrapment of leaflets, chordae tendineae cords and papillary muscle infiltration may cause mitral or tricuspid regurgitation and consequent cardiomegaly and congestive heart failure. Endomyocardial fibrosis is characterized clinically by restrictive cardiomyopathy. It usually occurs 2 years or more after the onset of hypereosinophilia. Some experts believe that prolonged and marked eosinophilia, regardless of its cause may lead to endomyocardial disease. There are also reports of sudden death due to eosinophilic myocarditis (with myocyte necrosis and apoptosis).[3] Giant aneurysm of the sinus of valsalva, multiple coronary artery aneurysms and coronary arterial thrombi with massive myocardial infarction[4] and constrictive pericarditis[5] are other reported cardiac complications of hypereosinophilic state (Table II).

Table II. Cardiac complications in hypereosinophilic state.

Endomyocardial fibrosis	Giant aneurysm of the sinus of valsalva
Fibroplastic endocarditis	Myocardial infarction due to coronary arterial thrombi
Myocarditis	Cardiomyopathy (restrictive and rarely dilated)
Intramural thrombus formation	Conduction disturbances (particularly right bundle branch block)
Constrictive pericarditis	Endomyocarditis simulating a ventricular tumor
Mitral and Tricuspid regurgitation	Arrhythmias (especially atrial fibrillation)
Multiple coronary artery aneurysms	Recurring vertigo and syncope

It seems that cardiac damage is more likely to happen in the presence of: splenomegaly, thrombocytopenia, elevated B12 binding and early myeloid precursors in the blood (features suggestive of myeloproliferation).[6]
Measurement of serum tryptase level may be helpful to predict the development of endomyocardial fibrosis and occurrence of disease related death.[7] Moreover serum concentration of troponin T can be used as a sensitive and non-invasive marker of cardiac involvement.[8]
The most common findings in echocardiography are ventricular apical obliteration and posterior mitral valve leaflet thickening with limited motion. Systolic function is often well preserved as in our case. However in case of endomyocardial fibrosis, Doppler flow imaging may reveal a restrictive pattern. Since imaging findings only suggest the diagnosis of Loeffler's endocarditis, some experts believe that endomyocardial biopsy is necessary in most cases. Endomyocardial biopsy can demonstrate infiltration of eosinophils. Magnetic resonance imaging of the heart may suggest eosinophilic endocarditis by showing a marked signal increase in the subendocardium. Cine MRI may be useful for showing apical thrombus or myocardial wall akinesia.[9]
Hypercoagulation may result in a variety of thromboembolic complications in hypereosinophilic patients. The cause for thrombosis is multifactorial. Vascular cell adhesion molecule (VCAM-1) and platelet activating factor (PAF) may play a role in the pathogenesis of thrombus formation. A mutation in factor V leiden gene has also been reported in a patient with thrombosis and eosinophilia.[2]
Treatment of cardiac complications include supportive management of congestive heart failure, use of anticoagulants (although controversial) or occasionally surgical attention, decortication (endocardiectomy) with or without valve replacement after the fibrotic stage, heart transplantation and chemotherapy for the main pathology.

Various treatment algorithms have been proposed for HES and CEL including corticosteroids, hydroxyurea, IFN-α, vincristin, etoposide, cyclosporine, azathioprine, ARA-C/idarubicin and allo-bone marrow transplantation. Imatinib mesylate - a tyrosine kinase inhibitor - has become the first choice treatment for FIP1L1-PDGFRα clonal eosinophilia.

Chronic eosinophilic leukemia (CEL) is a rare heterogeneous disorder with eosinophil overproduction in the bone marrow which results in marked and sustained peripheral blood eosinophilia. The distinction between chronic eosinophilic leukemia and idiopathic HES is not straightforward. The evidence of an acquired chromosomal abnormality confirms the neoplastic process and excludes categorization as idiopathic HES. Several cytogenetic abnormalities have been documented in multiple cases of CEL in the literature such as: t(5,12), t(2,5) and trisomy 8.[10]

Regarding the WHO classification criteria[11] and the slow evolution of our patient's disease, CEL might be a diagnosis compatible with the clinical and laboratory data except for the existence of cytogenetic abnormality of chromosome 16 [inv (16)(q13p22)] that represents the strongest argument for AML-M4EO diagnosis, despite no significant increase in blasts. The association between abnormal eosinophils, AML and structural rearrangements of chromosome 16(AML FAB subtype M4EO) was confirmed at the Fourth International Workshop on Chromosomes Leukemia (1984). It is now known that most of the patients with AML and inv (16) posses both a blocking mutation (CBF-MYH11 fusion gene) and a proliferative signal (mutations of the receptor tyrosine kinases, C-KIT, FLT3 and RAS genes) as a two-hit hypothesis of leukaemogenesis.[12] Considering our patient's poor condition, disease progression and the cytogenetic abnormality of chromosome 16 [inv (16) (q13p22)] we began an induction course of AML therapy with cytarabin.

Moreover overlap will exist between myeloid disorders associated with hypereosinophilia and the correct diagnosis may not be possible until serial observations and investigations have been carried out. Identification of these variants which helps us in prognosis, and therapeutic measurement should be taken into consideration for adequate management of patients with eosinophilia. Since endomyocardial fibrosis due to persistent hypereosinophilia is irreversible, it is critical that eosinophil counts be controlled before cardiac complications develop. Furthermore as a hunch we should always keep in mind the possibility of malignant progression in these patients.Therefore, close observation and serial examinations are necessary in their follow-up program.

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