CASE REPORT

Persistent Eosinophilic Infiltration of the Myocardium in a Child in Complete Remission of Acute Lymphoblastic Leukemia and Eosinophilia. Potential Role in Late Cardiac Disease?

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This report describes the long-term (23 years) follow-up of a pediatric patient with acute lymphoblastic leukemia and eosinophilia who underwent multiple valve replacements. An 8-year-old boy with this complex disease was admitted in January 1984 and treated with 6-week course of vincristine, L-asparaginase, and prednisolone, which induced complete remission. He developed atrioventricular valvular insufficiency and infectious endocarditis at 13.5 and 17.3 years of ages, respectively, with progressive development of congestive heart failure. At 18.6 years of age, he underwent prosthetic valve replacement of both atrioventricular valves; the mitral valve was replaced with a mechanical prosthetic valve and tricuspid valve with a bioprosthetic valve. Histopathological examination of the ventricular endomyocardium showed extensive fibrous degeneration and persistent infiltration of eosinophils and lymphocytes. The right-side prosthesis was replaced twice, at 22.4 and 29 years of ages, due to degeneration of bioleaflets and thrombosis of the mechanical valve, respectively. Although he tolerated all surgical procedures, he developed liver cancer at 31 years of age and died. Autopsy could not be performed. The present study indicates that a subset of patients in complete remission of acute lymphoblastic leukemia and eosinophilia can show persistent myocardial eosinophilic infiltration and are at risk of late cardiac disease. (Keio J Med 59 (2) : 64–68, June 2010)

***Keywords*: acute lymphoblastic leukemia, eosinophilia, eosinophilic infiltration, valvular heart disease**

Introduction

Acute lymphoblastic leukemia (ALL) with eosinophilia is a rare and distinct clinical entity. Patients with this complex disease tend to develop cardiovascular complications related to eosinophilia including valvular and endomyocardial diseases, which frequently lead to restrictive cardiomyopathy. Medical treatment has a limited prognostic value since combination therapy against heart failure, leukemia and eosinophilia has limited effect on the heterogeneous cardiac pathology. Surgical management including prosthetic valve replacement or valve repair again has unresolved questions of thrombus formation or recurring distortion of the repaired valve.[1] In the present study, we describe the long-term (23 years) findings in a pediatric patient with ALL and eosinophilia who developed late atrioventricular (AV) valve disease and underwent repeated valve replacements. Histopatho-

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Table 1 Laboratory data at three time points

	First admission (January 14,1984) 8.1 years	Complete remission of ALL (February 22,1984) 8.2 years	Initial valve replacement (July 17,1994) 18.5 years
CBC			
WBC (μL)	84,000	5,400	7,400
Eosinophil (%)	96	19	5
Neutrophil (%)	1	62	41
Stab cell (%)		6	15
Lymphocyte (%)	3	6	34
Monocyte (%)		1	5
Basophil (%)		6	
Blast cell	+	–	–
RBC (μL)	381×10^4	314×10^4	447×10^4
Hemoglobin (g/dL)	10.9	9.2	13.1
Platelet (μL)	6.4×10^4	13.1×10^4	23.3×10^4
Bone marrow			
NCC (μL)	42.6×10^4	10.4×10^4	
Megakaryocyte (μL)	0		
Lymphoblast (%)	77.6	3.0	
Eosinophil (%)	13.8	2.2	
Others (%)	8.6	94.8	
Blood chemistry			
AST (IU/L)	236	30	24
ALT (IU/L)	353	46	23
LDH (IU/L)	954	648	342
BUN (mg/dL)	12.5	10.0	11.3
Creatinine (mg/dL)	0.69	0.94	0.71
Uric acid (mg/dL)	5.0		6.4

CBC; complete blood count, NCC; nucleated cell count, AST; aspartate aminotransferase, ALT; alanine aminotransferase, LDH; lactate dehydrogenase, BUN; blood urea nitrogen.

logical examination of the ventricular endomyocardium 10 years after complete remission of ALL and eosinophilia showed extensive fibrous degeneration in association with persistent myocardial infiltration with eosinophils and lymphocytes. Based on the unique histopathological features and the long-term follow-up extending over 23 years, we report this case on the assumption that persistent eosinophilic infiltration of the myocardium could explain the late cardiac disease in a subset of patients in complete remission as well as recurrent thrombotic occlusion of the prosthetic valve.

Case Report

An 8-year-old male patient was initially admitted to our hospital in January 1984 because of 2-week history of fever and epistaxis. The past history was negative for parasitic infestation or allergic disease. The initial hemogram demonstrated a platelet count of 64,000/μL and leukocyte count of 84,000/μL (96% eosinophils, 1% neutrophils, and 3% lymphocytes) (**Table 1**). Blood chemistry showed elevated serum levels of transaminases and lactate dehydrogenase. Bone marrow biopsy showed hypercellularity, mainly of lymphoblasts and eosinophils, with marked decrease in erythroid cells and megakaryocytes (**Table 1**). Cytochemical studies of the blasts showed negative staining for myeloperoxidase, sudan black B and alpha-naphtholacetate esterase. Immunological studies were negative result for surface immunoglobulin G and positive result for both anti-1a and anti-common ALL. Additionally, a cytogenetic study showed a normal karyotype, 46XY. The chest radiograph and transthoracic echocardiography (TTE) were unremarkable. Electrocardiography (ECG) showed inverted T wave and depressed ST segment in the left precordial leads. With a diagnosis of L1, precursor acute B-cell ALL (FAB classification) and eosinophilia, he was treated with a 6-week course of vincristine, L-asparaginase, and prednisolone, which induced complete remission of bone marrow findings by termination of the treatment (**Table 1**). Eosinophil fraction of the peripheral blood, on the other hand, returned to the normal level 14 weeks after the treatment and remained normal thereafter. ECG reverted to normal after a brief period of second-degree AV block. The patient was doing well until 13.5 years of age when he developed bilateral AV valvular insufficiency. In addition, at 17.3 years of age, he developed infectious endocarditis and, despite successful management

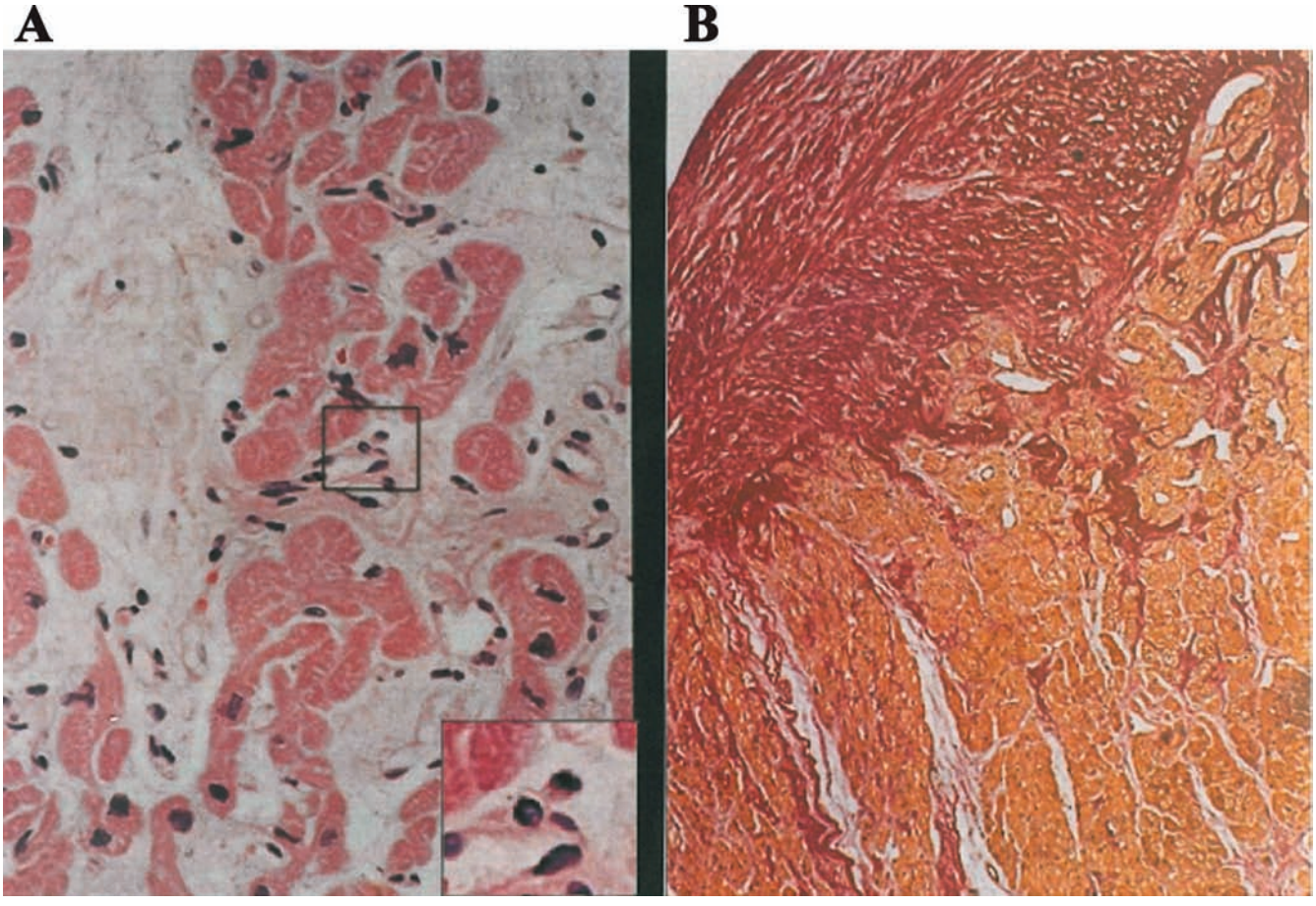

Fig. 1 (A) Left ventricular myocardium shows interstitial edema, increased fibrous tissue, and occasional eosinophils and lymphocytes adjacent to the damaged myocardial fibers (hematoxylin-eosin staining: original magnification x 100). Inset shows a high-power view of the degranulated eosinophil in the square (x 400). (B) Right ventricular endomyocardium is coated with thick fibrous tissue. Note atrophy and fibrosis of myocardial fibers underneath the fibrous tissue (Van-Gieson stain: original magnification x 20).

of the infection, the condition deteriorated progressively to the level of New York Heart Association (NYHA) functional class IV. Cardiac catheterization at 18.3 years of age showed severe regurgitation at both AV valves and pulmonary hypertension with a systolic pulmonary arterial pressure of 52 mmHg. At the age of 18.5 years, he underwent prosthetic valve replacement of both AV valves; the mitral valve was replaced with a mechanical prosthetic valve (model M-29, CarboMedics Inc., Austin, TX) and tricuspid valve with a porcine bioprosthetic valve (Carpentier-Edwards M-29, Edwards Lifesciences, Irvine, CA). Intraoperaive inspection disclosed dilated annuli of both AV valves, fibrous thickening of the valvular leaflets, malformed chordae tendinae, and pearly white fibrous thickening of the endocardia of both ventricles. Excised valves showed myxoid degeneration and extensive fibroelastosis. Histopathological examination of the endomyocardium showed extensive fibroelastosis and atrophic myocardial fibers in the right ventricle (**Fig. 1B**); damaged myocardial fibers, interstitial edema, increased fibrous tissue, and occasional eosinophils and lymphocytes in the left ventricle (**Fig. 1A**); and atrophic or fibrous degeneration of myocardial fibers and vascular degeneration in the papillary muscle. Postoperatively, he remained on conventional warfarin therapy and was well until 22.4 years of age when he developed bioprosthetic valve dysfunction. He underwent a second operation in which the failed bioprosthesis was replaced with a mechanical prosthesis (CarboMedics M-29). The removed bioprosthesis showed diffuse fibrous thickening and bioleaflet deformity with adhesion of the posterior segment to the ventricular septum. Ten months after the second operation, he developed root abscess of the right maxillary first molar, which was subsequently followed by infectious endocarditis. Since TTE demonstrated a verrucous mass protruding into the right-side prosthetic valve, antimicrobial and thrombolytic therapies were administered, which achieved complete resolution of the pathological condition within one month. However, despite the intensive 3-month antimicrobial therapy, one of

the leaflets of the right-side valve became immobile with consequent steno-insufficiency of the valve. Inasmuch as he was rather reluctant to undergo a third operation, he was kept under close observation until 29 years of age, when repeat TTE demonstrated progressive dysfunction of the affected valve. As he developed progressive congestive heart failure (NYHA III), he consented to the third operation with the failed prosthetic valve replaced with a similar mechanical prosthetic model. Although he showed a good postoperative recovery, compiled studies at 31 years of age including laboratory examinations, ultrasonography, and dynamic computed tomography, demonstrated findings compatible with the hepatic cancer. Liver biopsy was excluded from the regular diagnostic study because of the ongoing anticoagulant therapy. He underwent an immediate anticancer chemotherapy, however, with poor response and died at the age of 31.6 years. His family did not consent to autopsy.

Discussion

ALL with eosinophilia, first reported by Spitzer and Garson,[2] is a rare and distinct clinical entity with more than 45 cases documented in the literature.[3] In this complex disorder, eosinophilia is believed to result from a non-neoplastic reaction to the neoplastic lymphoblasts, wherein the tumor-secreting interleukin 5 (IL-5) plays a crucial role in provoking the peripheral eosinophilia and propagating diverse inflammatory responses.[4] While eosinophil-derived toxic granule proteins are known to induce failure of multiple organs, most frequently involved is the heart with consequent high morbidity and mortality.[5] Earlier studies of eosinophils and eosinophilia have made a remarkable progress in elucidating the pathophysiology of the endomyocarditis and the microbiological basis of the myocardial damage. Histologically, the damaging effect of eosinophils on the endomyocardium is often divided into three stages;[6] acute necrotic, later thrombotic, and late fibrotic stages, with the stages evolving with time. In each stage, eosinophil-derived chemokines and chemoattractants play a key role in initiating and propagating the pathological processes. Briefly, in the earlier stage, the tumor cells secrete IL-5, which plays an important role in regulating the production, differentiation, recruitment, activation and survival of eosinophils.[7] In the necrotic stage, eotaxin, a chemokine produced and stored by eosinophils, plays an indispensable role in transmigration of eosinophils from the bloodstream to the endomyocardium,[8] wherein the eosinophil-derived toxic granule proteins induce diverse inflammatory reactions leading to the myocardial necrosis.[5] Furthermore, recent studies have indicated that the majority of eosinophils at the site of cardiac damage can potentially produce IL-5, thereby generating an autocrine pathway for local eosinophil recruitment and activity.[9] In the thrombotic stage, the tissue factor (TF), which is overexpressed in the heart, is known to be the key initiator of the coagulation cascade with ultimate promotion of intramural thrombosis.[10] In addition, TF is detected in the bloodstream in the form of microparticles and also in eosinophils as preformed TF.[11] Another role for eosinophils in this stage is the production of eosinophil-derived cationic proteins, which impair the anticoagulant activity of thrombomodulin.[12] Furthermore, recent studies reported that sepsis accelerates thrombogenesis through excessive endothelial cell production of TF with consequent elevation of the circulating TF and also promotes inactivation of the anticoagulant mechanism.[13] Indeed, the fact that the first and third operations in the present case were preceded by sepsis may be consistent with this theory. In the fibrotic stage, eosinophil-derived granular proteins stimulate fibroblast proliferation, thereby implicating progressive replacement of intramural thrombi with the fibrous tissue. Taking together, the transmigrated eosinophils play critical roles in the entire process of myocardial damage.

The histopathological finding of the present study was unique in that myocardial infiltration with eosinophils and lymphocytes was observed 10 years after complete remission of ALL and eosinophilia. This finding suggests that, in a subset of patient with ALL and eosinophilia, the necrotic stage failed to dissolve but rather persisted for an extended period despite the clinical evidence of complete remission. The underlying reason for the persistent eosinophilic infiltration may be explained by the recent report describing the presence of persistent leukemia cells in a higher proportion of patient who remained in long-term remission.[14] Thus, it seems that residual leukemia cells potentially secrete IL-5 and hence stimulate eosinophil activity, albeit less extensively than that seen in the early stage of the illness. Although further studies are needed to identify whether the long-term infiltration of eosinophils represents an exceptional morphological feature, this finding may partly explain the enigmatic mechanism of late cardiac disease and recurrent thrombotic occlusion of the prosthetic valve.

Considered together, the results suggest that a subset of patients in long-term remission of ALL and eosinophilia can show persistent myocardial eosinophilic infiltration and are at risk of development of late cardiac diseases, among which valvular heart disease predominates the clinical difficulties. The results suggest further that the patients who underwent prosthetic valve replacement need to be kept under close observation because of liability of the replaced valve to the recurrent thrombotic occlusion. Understanding that the single experience does not suffice to draw solid conclusions, the clinical and histopathological features described in the present study warrant further histopathological studies on long-term survivors in order to fully and accurately define the clinical entity of ALL with eosinophilia.

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Addendum

Procedures of the follow-up study and preparation of the manuscript were conducted in accordance with the Helsinki Declaration of 1975, as revised in 1983.

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