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Development of Eosinophilic Endomyocardial Disease in a Patient with Episodic Angioedema and Eosinophilia

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Clinical Implications

Episodic angioedema and eosinophilia (Gleich syndrome) has been distinguished from other hypereosinophilic syndromes by the absence of cardiac involvement. Here we report a case in which eosinophilic endomyocardial disease developed in a patient with episodic angioedema and eosinophilia.

Keywords

Gleich syndrome; hypereosinophilia; hypereosinophilic syndrome; Loeffler's endocarditis

To the Editor

We report the long-term follow up of a previously reported patient with episodic angioedema and eosinophilia (Gleich syndrome). The patient became ill at seven years of age with recurrent cyclical attacks of urticaria, fever and angioedema of the face and extremities every 4–6 weeks¹. She was evaluated at age eleven and had splenomegaly, peripheral blood hypereosinophilia (WBC 46,000 per microliter, 85% eosinophils; calculated eosinophil count of 39,100 per microliter) and decreased serum levels of C4. A bone marrow aspirate was hypercellular with increased eosinophils (est. 75%). Interleukin-5 levels were increased prior to an attack and decreased spontaneously before prednisone administration². The patient had no clinical evidence of cardiac involvement with normal echocardiograms from

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age eleven through fourteen years. Cyclical attacks with weight gain were controlled with intermittent prednisone dosing (5-25 mg) and diuretics.

The patient returned for further evaluation at age twenty-three years with frequent attacks of angioedema and weight gain, occurring as often as once every two weeks. Laboratory analysis revealed hypereosinophilia (WBC 16,300 per microliter, 58.5% eosinophils; calculated eosinophil count of 9,535 per microliter). An echocardiogram showed mitral valve regurgitation with mild thickening of the posterior leaflet as well as some retraction and reduction in mobility. The patient was started on 1.5 million units of interferon-alpha 2b, and the dose was increased to 3.0 million units thrice weekly with improvement in her eosinophil count and angioedema; however, the patient experienced side effects from the interferon alpha 2b and discontinued it after one month of therapy.

Three months later, the patient developed blurred vision, left lower extremity weakness and severe dyspnea. She was diagnosed with congestive heart failure secondary to acute mitral regurgitation requiring placement of a prosthetic St. Jude Valve. Intraoperative inspection of the mitral valve revealed prolapse of the anterior leaflet and near total destruction of posterior leaflet with papillary muscle involvement. Gross inspection of the left ventricle revealed thrombus formation and myocardial thickening requiring endocardectomy of the left ventricular apex. Pathological examination revealed severe eosinophilic endomyocardial fibrosis. Sections from the mitral valve showed adherent thrombus with numerous degenerating eosinophils and deposition of eosinophil granule major basic protein. In addition, sections of the papillary muscle showed evidence of severe endocardial fibrosis with eosinophil infiltration. Immunofluorescence staining of the intraventricular thrombus was floridly and diffusely positive for eosinophil major basic protein.

Within one month after valve replacement, during which time the patient was off treatment for eosinophilia, she was readmitted with severe congestive heart failure due to an acute occlusion of the valve. At surgery, the valve leaflets were nearly fixed in the closed position and covered in organizing thrombus; pathology revealed a thrombosed prosthetic valve encased in fibrous connective tissue with marked eosinophil infiltration around the valve. The patient's prosthetic valve was replaced with a Starr-Edwards Silastic ball valve. She was treated with 0.8 million units interferon-alpha 2b thrice weekly with normalization of eosinophil counts and excellent symptom control. Presently, at age 46, she continues on weekly treatments with interferon alpha 2B; she is well and has trained to run a marathon.

Molecular testing was not available at the time of initial diagnosis or ensuing cardiac disease; current analyses for FIP1L1/CHIC2/PDGFRA, PDGRFB, FGFR1 and CBFB were negative by fluorescent in situ hybridization. PCR testing of T-cell receptor rearrangement patterns by next generation sequencing showed no evidence of T-cell clonality. Moreover, flow cytometric analysis of leukemia/lymphoma phenotypes showed no evidence of monoclonality, acute leukemia, or lymphoproliferative disorder.

In the initial report, we observed that this syndrome is characterized by its episodic nature, the severity of angioedema, acute weight gain, and its relatively benign course¹. The apparent absence of cardiac disease in this syndrome^{4, 5} was in contrast to the common

presence of cardiac disease in primary (neoplastic) and idiopathic forms of the hypereosinophilic syndromes³. This patient remained free of cardiac disease for approximately 16 years, but then developed eosinophilic endomyocardial disease with severe mitral insufficiency. Since age 23, the patient has not suffered from episodes of angioedema, and she recalls that the episodes stopped around the time of the second valve replacement when she was treated with methylprednisolone and restarted on interferon-alpha 2B.

Cyclic elevations of IL-5 have been associated with the periodicity of eosinophilia in patients with this syndrome², which has been shown to be a multilineage cell cycling disorder⁶. During peaks of eosinophilia, Khoury et al⁶ recently described an increase in aberrant CD3⁺CD4⁺ T-cells. Given excellent control of our patient's symptoms with interferon-alpha 2B, we have not assessed cycling of aberrant T-cell populations; however, T-cell receptor rearrangement studies did not show evidence of T-cell clonality. Aside from the patient's splenomegaly at age 11, she does not have any known distinctive clinical or molecular features that would increase her risk for severe end organ complications; in retrospect, splenomegaly may have been a warning of future morbidity. The occurrence of valvular disease in our patient's native mitral valve and in the replacement valve indicates that the stimulus for destruction is not the nature of the valve itself, but likely the activation status of eosinophils.

Eosinophilic endomyocardial disease is a major cause of morbidity and mortality in the hypereosinophilic syndromes. This is the first report of eosinophilic endomyocardial disease in a patient who suffered from episodic angioedema and eosinophilia. Our patient's course indicates the need for continued surveillance for cardiac disease and control of eosinophilia in all patients with hypereosinophilic syndromes regardless of clinical categorization.

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