CASE REPORTS

Endomyocardial Disease and Eosinophilia

Report of a Case

BRIAN E. JASKI, EDWARD J. GÖTZL, M.D.,
JONATHAN W. SAID, M.B., CH.B., AND MICHAEL C. FISHEIN, M.D.

SUMMARY While an association between blood eosinophilia and endomyocardial disease has been recognized, the role of the eosinophil in the pathogenesis of the cardiac lesions remains uncertain. In a 69-year-old man with large cell carcinoma of the lung, marked eosinophilia was stimulated by and progressed with the course of the neoplasm which was producing an eosinophil chemotactic factor. Peripheral blood eosinophils were vacuolated and degranulated while those in the bone marrow were morphologically normal. Clinical evidence of cardiac dysfunction developed one month prior to death. At autopsy, 12 months after the onset of symptoms, endomyocardial disease was present. There were numerous eosinophils in the damaged myocardium and surrounding the pulmonary neoplasm. In patients with endomyocardial disease and eosinophilia, the eosinophil may be directly cardiotoxic or a primary mediator of cardiac damage; therapeutic attempts to reduce the number of eosinophils might be of benefit.

SINCE 1893, when Reinbach first described a right ventricular endocardial mural thrombus in a patient with eosinophilia,1 the association between blood eosinophilia and endomyocardial disease has been recognized in various clinical entities including Löeffler’s endocarditis parietalis fibroplastica,2 Davies’ African endomyocardial fibrosis,3 eosinophilic leukemia,4 and eosinophilic collagen disease.5 Although the two latter conditions are characterized by widespread eosinophil infiltration of other tissues in addition to the heart and lung, it has been suggested that all of these diseases are representative of a continuum.6,7 Peripheral blood and bone marrow eosinophils from patients with hypereosinophilic disease manifesting cardiac and other tissue infiltration have shown a degree of degranulation and vacuolization greater than normal subjects or patients with transient eosinophilia.8,9 Labelled autologous eosinophils in such patients disappear from the circulation more slowly than normal cells, after an initial phase of rapid clearance and reappearance, which suggests transient entry into tissue spaces.10 Presumably, massive infiltration of the heart with eosinophils is associated with cardiac dysfunction. In patients with cardiac disease, however, no direct causative role for the eosinophil in the pathogenesis of the cardiac lesions has been established.

Our finding of endomyocardial disease in a patient with chronic peripheral blood eosinophilia and eosinophil infiltration of pulmonary and cardiac tissues secondary to a bronchogenic tumor indicates that profound eosinophilia of diverse causes may be associated with endomyocardial disease. An apparently unique 300–400 molecular weight peptide eosinophil chemotactic factor was recognized in tumor tissue extracts, tumor cell media and urine. Functional chemotactic deactivation of the patient’s eosinophils in association with rising urinary levels of the peptide factor suggests that it or other tumor products induced in vivo alterations in the eosinophils which may contribute to their potential for tissue damage.

Case Report

The patient was a 69-year-old white male with an 80-pack year history of cigarette smoking, who presented for the first time in January 1975 with shortness of breath and a chronic productive cough. Chest X-rays revealed a right lower lobe lung mass. An open lung biopsy established the diagnosis of large cell bronchogenic carcinoma. From January to December his clinical course was characterized by progressive respiratory difficulties and weight loss. During that period of time laboratory investigations revealed a marked progressive blood eosinophilia:

<table>
<thead>
<tr>
<th>Date</th>
<th>WBC</th>
<th>% Eosinophils</th>
<th>% Degranulated, Vacuolated Eosinophils</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/75</td>
<td>12,260</td>
<td>10</td>
<td>Not assessed</td>
</tr>
<tr>
<td>3/75</td>
<td>14,600</td>
<td>28</td>
<td>16</td>
</tr>
<tr>
<td>10/75</td>
<td>27,000</td>
<td>50</td>
<td>34</td>
</tr>
<tr>
<td>12/75</td>
<td>21,200</td>
<td>65</td>
<td>48</td>
</tr>
</tbody>
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The peripheral blood eosinophils were markedly degranulated and many had prominent vacuoles. The extent of both abnormalities increased with progression of the level of eosinophilia during the course of the malignancy.

In November the patient received one dose of Cytoxan, 375 mg, and Adriamycin, 30 mg/m² which did not result in any clinical improvement. By December he had lost 100 lbs, was extremely dyspneic and for the first time developed ankle edema and a persistently irregular cardiac rhythm. The electrocardiogram showed frequent atrial extrasystoles with brief runs of atrial tachycardia, often with aberrant ventricular activation. These cardiac abnormalities were
thought to be due to pericardial metastases and/or myocardial disease. The lung mass and associated pulmonary infiltrates and pleural effusion precluded accurate radiologic assessment of heart size. On December 22, 1975, 12 months after onset of symptoms, the patient died of respiratory failure.

Anatomical Findings

In the lung there was a 7 cm mass originating in the right main bronchus which extended into the lung parenchyma, diaphragm, and parietal pericardium. Microscopically, the tumor was composed of very large pleomorphic cells with bizarre, hyperchromatic, and sometimes multiple nuclei containing prominent nucleoli. Mitoses were common. The main tumor mass was surrounded by a cellular infiltrate composed mainly of eosinophils which had reduced numbers of cytoplasmic granules. Areas of bronchopneumonia also were present in the lung.

The heart weighed 420 g and was free of direct involvement by tumor. The left ventricular cavity contained an apical mural thrombus, 4 cm in diameter, superimposed on a thickened endocardium (fig. 1). Other similar but smaller thrombi were present in the right and left ventricles. Microscopically, there was organization of the thrombi by connective tissue proliferating from the endocardium. The connective tissue, which contained very few elastic fibers, also extended into adjacent myocardium where areas of interstitial and replacement fibrosis were present (fig. 2). There were cellular infiltrates in the myocardium composed almost entirely of eosinophils (fig. 3) with reduced numbers of cytoplasmic granules adjacent to areas of fibrosis. Focal areas of myocardial necrosis were also present and infiltrated by eosinophils (fig. 4). The fibrosis, necrosis and eosinophilic infiltrates tended to involve predominantly the
subendocardial myocardium adjacent to areas with overlying endocardial fibrosis and mural thrombi. The extra and intramural coronary arteries and cardiac valves were normal.

Infiltrates of eosinophils were present in the sinusoids of the liver and spleen but not in any other organs. The bone marrow was hypercellular with a myeloid:erythroid ratio of approximately 10:1. Mature, structurally normal eosinophils were the predominant cells. Unlike the eosinophils in the circulation and those seen in the heart and lungs, the bone marrow eosinophils were filled with their characteristic granules. There were no visceral infarcts or other evidence of embolization of the intracardiac mural thrombi. No renal or vascular lesions were observed.

A peptide of approximately 300-400 molecular weight with preferential chemotactic activity for eosinophil PMN leukocytes in vitro was isolated from extracts of the tumor, appeared in the patient's urine and was elaborated by long-term cultures of dispersed tumor cells. A comparable eosinophil chemotactic factor was isolated from anaplastic large cell tumors of the lung of two other patients with eosinophilia of the peripheral blood as well as tumor and surrounding tissues, but was absent from a pulmonary adenocarcinoma associated with peripheral blood eosinophilia and a renal cell carcinoma metastatic to the lung which evolved only pulmonary and pleural eosinophilia. The eosinophil chemotactic peptide was approximately the same size as the tetrapeptide of the eosinophil chemotactic factor of anaphylaxis (ECF-A), but was distinctly less acidic. Eosinophils from this patient and one other who exhibited high concentrations of the factor in tumor extracts and urine were hypersensitive in vitro to their tumor factor and other chemotactic principles, which is functionally consistent with a state of chemotactic deactivation.

Discussion

Although the association of endomyocardial disease and eosinophilia is well documented,4-7, 12-24 the role of the eosinophils in the pathogenesis of the cardiac lesions is obscure. Many authors feel that the eosinophilia is only an associated phenomenon,5-12-14 while others suggest that the eosinophil itself may be cardiotoxic and have a primary role in causing the endomyocardial lesions.15-17 In our patient, several findings suggest that the cardiac eosinophilia may be associated with cardiotoxicity regardless of the etiology of the eosinophilia. Biochemical studies showed that the pulmonary neoplasm was producing a factor chemotactic for eosinophils. Furthermore, the blood eosinophilia was stimulated by and progressed with the course of the tumor in the absence of other diseases known to stimulate eosinophilia, such as collagen-vascular diseases, hypersensitivity states, dermatoses, or parasitic infestations. In addition, since the eosinophilia preceded the clinical cardiac abnormalities, it seems unlikely to have resulted as a reaction to the myocardial damage.

In a study of patients with Löffler's cardiomyopathy and eosinophilia, Spry and Tai have shown that peripheral blood eosinophils in this disease were vacuolated and degranulated as were those of our patient, who also exhibited comparable changes in the eosinophils of the cardiac and pulmonary lesions. The appearance of chemotactic deactivation in serial in vitro studies of the patient's eosinophils41 implies that the eosinophil chemotactic peptide or other tumor products initially induced in vivo activation of the eosinophils, possibly including degranulation, which may enhance their ability to lead to tissue damage. Spry suggested that the tissue damage in the heart results from prolonged release of products usually present in eosinophil granules. Archer and Hirsch postulated that enzymes such as hydrolases and peroxidases were released from tissue eosinophils and might play a role in inflammatory reactions and tissue damage.25-26 The specific localization of eosinophils near the areas of necrosis and fibrosis in the cardiac lesions of patients with endomyocardial disease suggests that they may be mediators of the cardiac damage. Cardiac involvement with clinical signs can occur early in the course of the eosinophilia. In a prospective study of patients with chronic eosinophilia, Borer et al. have shown that echocardiographic abnormalities may be present before the patients develop signs or symptoms of cardiac disease.27 However, the possibility that eosinophils are regulatory cells brought in to confine or control a deleterious tissue response caused by some other unknown factors cannot be excluded.

If the eosinophil acts as a primary mediator of cardiac damage, then therapeutic attempts to reduce the number of eosinophils in patients with endomyocardial disease and eosinophilia might decrease morbidity and mortality from congestive heart failure, arrhythmias and thromboembolic events. In the past, patients with endomyocardial disease and eosinophilia have received steroid therapy with little improvement.15, 16 This could be because steroids may only increase margination of eosinophils without necessarily reducing their absolute number.10 Barrett and Barrett22 and Blatt et al.,19 however, have reported cases in which therapy caused systematic cardiac improvement in parallel with a reduction in the number of eosinophils. Therapy which has the potential to decrease the number of circulating eosinophils such as radiotherapy,12 vincristine, methotrexate or mercaptopurine,10 leukopheresis,24 hydroxyurea28 or monospecific anti-eosinophil rabbit serum29 might be of benefit in treating patients with cardiac disease associated with eosinophilia.

References

Energy Requirement for Defibrillation of a Markedly Overweight Patient

REGIS A. DESILVA, M.B., F.R.C.P.(C), AND BERNARD LOWN, M.D.

SUMMARY Recommendations have been made recently that the energy output of present-day defibrillators be increased above the 400 wsec limit. These recommendations are based largely on experimental studies in animals. We report a case of a man weighing 190.1 kg (418.2 lb), successfully resuscitated with a single 400 wsec shock after a prolonged episode of ventricular fibrillation. The observation in this patient as well as data derived from cardiovascular experience indicates that weight is not a significant factor in the successful outcome following defibrillation in adults. Many variables primarily related to the clinical condition of the heart influence the results of countershock. There are no valid studies at present to support the claim that high-energy defibrillators are necessary. In fact, implementation of such a recommendation is premature and possibly dangerous.

DIRECT CURRENT DEFIBRILLATION of the heart is a standard method promoted by its procedural simplicity and sanctioned by its high success rate. Recently, Tacker, Geddes and coworkers1-4 presented data in both animal and man indicating that the standard instruments in current use provide insufficient energy for heavy subjects. They concluded that presently available devices are inadequate for defibrillating 35% or more of patients weighing in excess of 50 kg.5,6 This has led to the recommendation that defibrillators be manufactured capable of delivering larger electrical energies.6,7 The very opposite point of view has been reached by Pantridge et al.4,5 and Crampton et al.,6,7 who have counseled the use of lower energies for cardiac resuscitation. The issue is of great importance. If Tacker and coworkers are correct, heavy subjects are denied the chance of resuscitation. On the other hand, if the claims relating to the need for more energy are insubstantial, numerous patients will be subjected to injurious currents, and in some the chance of successful resuscitation will be jeopardized. Because information on the energy requirements for defibrillating patients weighing in excess of 150 kg is not available, we report the following pertinent experience.

Case Report

A 30-year-old white male with acromegaly for six years and atypical chest pain for two years, noted occasional dizzy spells associated with palpitation. He was on hormonal replacement therapy, and warfarin. He was admitted to the Peter Bent Brigham Hospital for weight reduction prior to cardiac catheterization and coronary angiography.

He was massively obese, weighing 198.5 kg (436.7 lb) and 175 cm (68.9 inches) tall. Skull and acral enlargement was obvious. Pulse rate was 75 beats/min with occasional extrasystoles. Blood pressure was 120/80 mm Hg in the supine position. The cardiac findings were within normal limits. The electrocardiogram showed sinus rhythm at a rate of 56/min with frequent unifocal ventricular premature beats (VPBs). PR interval was 0.18 sec, QRS 0.09 sec and the axis was −30°. There were nonspecific ST and T wave abnormalities. Ambulatory monitoring for 24 hours demonstrated frequent unifocal VPBs, couplets and short runs of 3–5 beat ventricular tachycardia. A posteroanterior chest roentgeno-

B E Jaski, E J Goetzl, J W Said and M C Fishbein

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