CASE REPORTS

Endomyocardial Disease and Eosinophilia

Report of a Case

BRIAN E. JASKI, EDWARD J. GOETZL, M.D.,
JONATHAN W. SAID, M.B., CH.B., AND MICHAEL C. FISHBREIN, 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 a direct 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, the association between blood eosinophilia and endomyocardial disease has been recognized in various clinical entities including Löffler's endocarditis parietalis fibroplastica,1 Davies' African endomyocardial fibrosis,8 eosinophilic leukemia,9 and eosinophilic collagen disease.9 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.6,9 Peripheral blood and bone marrow eosinophils from patients with hypereosinophilic disease manifest cardiac and other tissue infiltration have shown a degree of degranulation and vacuolization greater than normal subjects or patients with transient eosinophilia.6,9 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>
</table>

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

From the Department of Pathology, Peter Bent Brigham Hospital and the Department of Medicine, Robert Breck Brigham Hospital and the Harvard Medical School, Boston, Massachusetts.

Supported by NIH Grant HL 06370-16. Dr. Goetzl is the Director of the Laboratories for the Study of Immunological Diseases of the Howard Hughes Medical Institute.

Address for reprints: Dr. Michael C. Fishbein, Department of Pathology, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston, Massachusetts 02115.

Received September 27, 1977; revision accepted November 14, 1977.
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 over- 
lying endocardial fibrosis and mural thrombi. The extra and 
intramural coronary arteries and cardiac valves were nor-
mal. 

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 eosino-
phils 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 character-
istic granules. There were no visceral infarcts or other evi-
dence 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.11 A comparable 
eosinophil chemotactic factor was isolated from anaplastic 
large cell tumors of the lung of two other patients with eo-
sinophilia of the peripheral blood as well as tumor and sur-
rounding tissues, but was absent from a pulmonary 
adenocarcinoma associated with peripheral blood 
eosinophilia and a renal cell carcinoma metastatic to the 
lung which evoked 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.11 Eosinophils from this patient and one other who ex-
hibited high concentrations of the factor in tumor extracts 
and urine were hyporesponsive in vitro to their tumor factor 
and other chemotactic principles, which is functionally con-
sistent with a state of chemotactic deactivation. 

Discussion 

Although the association of endomyocardial disease and 
eosinophilia is well documented,1-7 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.11 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, hyper-
sensitivity states, dermatoses, or parasitic infestations. In 
addition, since the eosinophilia preceded the clinical cardiac 
abnormalities, it seems unlikely to have resulted as a reac-
tion 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 degranulated2 as were those of our patient, who also ex-
hibited 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 
eosinophils11 implies that the eosinophil chemotactic peptide 
or other tumor products initially induced in vitro 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 
causd 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 im-
provement.15 18 This could be because steroids may only in-
crease margination of eosinophils without necessarily reduc-
ing their absolute number.10 Barrett and Barrett22 and Blatt 
et al.,19 however, have reported cases in which therapy 
causd 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,19 leukopheresis,24 hydroxyurea26 or 
monospecific anti-eosinophil rabbit serum27 might be of 
benefit in treating patients with cardiac disease associated 
with eosinophilia. 

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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 joule 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 joule 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.1-3 The very opposite point of view has been reached by Pantridge et al.4,6 and Crampton et al.,4,7 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-

From the Cardiovascular Division, Peter Bent Brigham Hospital and the Cardiovascular Research Laboratories, Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts. Supported in part by Grants HL-05242 and HL-07776 from the NHLBI. Address for reprints: Bernard Lown, M.D., Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, Massachusetts 02115.

Received August 24, 1977; revision accepted November 7, 1977.
B E Jaski, E J Goetzl, J W Said and M C Fishbein

_Circulation._ 1978;57:824-827
doi: 10.1161/01.CIR.57.4.824
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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