CHAPTER 19

The Eosinophil in Cardiac Disease

Lambert A. Wu, M.D., Leslie T. Cooper, Jr., M.D.,
Gail M. Kephart, B.S., and Gerald J. Gleich, M.D.

EOSINOPHILIC DEVELOPMENT
AND CELLULAR COMPOSITION

EOSINOPHIL-ASSOCIATED MYOCARDIAL DISEASES
  Eosinophilic Myocarditis: Association With Systemic Diseases
  Hypersensitivity Myocarditis
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SUMMARY
Eosinophils were first described by Wharton-Jones\(^1\) as coarse granule cells in 1846. It was not until Ehrlich\(^2\)'s 1879-1880 paper that these cells became known as "eosinophils." The association between eosinophils and clinical diseases has been known for many years, but only recently, through more detailed analyses, has their role in the pathogenesis of disease been elucidated.

The first section of this chapter discusses the development and pathophysiology of the eosinophil, and the remainder focuses primarily on eosinophil-associated myocardial diseases.

## EOSINOPHILIC DEVELOPMENT AND CELLULAR COMPOSITION

In the bone marrow, eosinophils develop from CD34\(^+\) precursor cells containing cell-surface interleukin (IL)-5 receptors. The actual stimulus for the expression of these receptors is unknown. IL-5 stimulates these precursors to produce several granule proteins. Chief among these is major basic protein (MBP).\(^3\) The direct precursor of MBP produced in translation of MBP mRNA transcripts is proMBP.\(^4,\!^5\) As the eosinophil matures and differentiates, proMBP aggregates into large, uncondensed granules where it undergoes post-translation processing into MBP.\(^6\) MBP then condenses into dense granules that appear to form the core of the mature eosinophil. In addition to stimulating the synthesis of MBP, IL-5 stimulates the eosinophil precursor cell to synthesize other granule proteins.\(^3,\!^7\)

Migration from the bone marrow through the sinusoidal endothelium requires IL-5.\(^8\) During this migration process, eosinophils increase their expression of \(\beta_2\) integrin, thereby increasing IL-5-mediated eosinophil release. Another protein, eotaxin, is required for the mobilization of eosinophils from bone marrow and appears to have synergistic effects when combined with IL-5.\(^9\) Eotaxin may also induce the migration of eosinophil progenitor cells to peripheral tissues.\(^10\)

Once in the circulation, eosinophils can migrate selectively into diseased tissues. To do so, they must first go through a complex process that includes contacting, tethering, and rolling along the endothelial cells of the vessel wall. In vitro studies have shown that during this process, tethering and adhesion require interaction between P-selectin and vascular cell adhesion molecule (VCAM)-1 on the endothelial cell and very late activation antigen-4 on the eosinophil.\(^11-\!^13\) IL-4 stimulates expression of P-selectin and VCAM-1 on endothelial cells.\(^14\) Blocking of P-selectin, VCAM-1, and very late activation antigen-4 with antibodies abolished tethering of eosinophils to endothelial cells; antibodies to \(\alpha_4\) and \(\beta_2\) integrins on eosinophils blocked firm binding of eosinophils. However, in vivo experiments with mice showed that IL-4 increases VCAM-1 expression but does not alter P-selectin expression. Additionally, mice treated with IL-4 and deficient in P-selectin still show leukocyte recruitment and this is blocked by antibodies to \(\alpha_4\) integrin.\(^15\) Thus, in
IL-4–mediated tethering and adhesion, VCAM-1 and very late activation antigen-4 appear to play more important roles than P-selectin.

Once firmly bound, the eosinophil changes morphology to migrate between endothelial cells and extrude into the extravascular space. At the cellular level, C5a anaphylatoxin activates eosinophil adhesion and assists in the transmigration of eosinophils, whereas C3a is specific for eosinophil chemotaxis.\textsuperscript{16,17} In addition, specific eosinophil eotaxins—eotaxins 1, 2, and 3—are important eosinophil chemoattractants.\textsuperscript{18-27} After migration between endothelial cells, the eosinophil must cross the basement membrane. This requires that the eosinophil express matrix metalloproteinases (MMP), particularly MMP-9.\textsuperscript{28-30} The tissue inhibitor of MMP prevents this migration.\textsuperscript{30} Once in the extravascular space, the eosinophil is guided to its destination by chemoattractants, chiefly eotaxin. Eotaxin was initially discovered in a guinea pig model of asthma.\textsuperscript{31} Murine and human eotaxins have been found.\textsuperscript{18,32} The expression of eotaxin mRNA in endothelial cells is stimulated by tumor necrosis factor-\(\alpha\) and IL-1.\textsuperscript{20}

Once at its intended site, the eosinophil is activated by cytokines and immunoglobulin receptors\textsuperscript{33,34} and this activation depends critically on \(\beta_2\) integrins, especially MAC-1 (\(\alpha M\beta 2\)).\textsuperscript{35} For example, \(\beta_2\) integrins, cytokines, and immunoglobulins mediate an increase of the eosinophil life span and eosinophil degranulation.\textsuperscript{33,36-38} Additionally, these stimulants promote eosinophil superoxide anion production. Platelet-activating factor may also serve as an endogenous eosinophil stimulant.\textsuperscript{39} In studies utilizing platelet-activating factor antagonists, IgG- and IL-5-induced eosinophil superoxide production and degranulation were inhibited.\textsuperscript{39}

Once at the site of inflammation, eosinophils can promote proinflammatory and cytotoxic effects. The granules stored within the eosinophil contain the MBP dense core surrounded by the eosinophil matrix, which is composed of the other granule proteins—namely, eosinophil peroxidase, eosinophil cationic protein, and eosinophil-derived neurotoxin.\textsuperscript{40} These granule proteins have various effects, including ribonuclease activity,\textsuperscript{41,42} formation of toxic pores in target cells,\textsuperscript{43} and degranulation of other cells, including basophils and mast cells. Eosinophils are also capable of chemoattractant production, such as platelet-activating factor and eotaxin, and cytokine production.\textsuperscript{35,44} Eosinophilic proteins such as eosinophil peroxidase are also capable of producing cytotoxic substances, including hydrogen peroxide and hypohalous acids.\textsuperscript{40}

**EOSINOPHIL-ASSOCIATED MYOCARDIAL DISEASES**

Various terms are used to categorize eosinophilic endomyocardial diseases, resulting in a large number of descriptors—for example, hypereosinophilic myocarditis, Löffler endocarditis,
endomyocardial fibrosis, tropical obliterative endomyocardial fibrosis, and eosinophilic endomyocardial disease.

In this section, the eosinophilic myocarditides are grouped according to general categories, such as those associated with systemic disease (hypereosinophilic syndrome, Churg-Strauss syndrome, and malignancies); those associated with drugs (hypersensitivity eosinophilic myocarditis); those associated with parasitic infections; and the specific entity of acute necrotizing eosinophilic myocarditis.

EOSINOPHILIC MYOCARDITIS: ASSOCIATION WITH SYSTEMIC DISEASES

Eosinophilic Myocarditis in the Hypereosinophilic Syndrome (HES)

HES is a general term encompassing a disease state characterized by a marked increase in peripheral eosinophils, infiltration of multiple organ systems with mature eosinophils, and resultant multiorgan dysfunction.\(^\text{45,46}\) Organ systems involved may include the skin, liver, intestinal tract, nervous system, and lung. However, it is involvement of the heart that is most critical for morbidity and mortality.\(^\text{46}\)

Case reports describing eosinophilic myocarditis in the setting of HES have been published. The first description was from Löffler\(^\text{47}\) in 1936, in which he presented 2 patients with eosinophilia and heart failure due to fibrous thickening of the endocardium. In 1948, Davies\(^\text{48}\) reported a case series consisting of 36 Ugandan patients with heart failure and endocardial thickening. This latter entity became known as Davies' tropical endomyocardial fibrosis and is not consistently associated with eosinophilia.

Different clinical and pathologic manifestations of HES myocarditis include endocardial fibrosis, valvular regurgitation due to endocardial fibrosis of the valvular apparatuses, right- and left-sided congestive heart failure, and systemic thromboembolization due to thrombus formation on the endocardial surface.\(^\text{45}\)

Myocarditis Associated With Churg-Strauss Syndrome

In 1951, Churg and Strauss first described allergic angiitis and granulomatosis, now commonly referred to as the Churg-Strauss syndrome.\(^\text{49}\) This syndrome is characterized by necrotizing vasculitis, extravascular granulomata, and tissue infiltration with eosinophils. The annual incidence has been estimated at 2.4 cases per 1,000,000 people,\(^\text{50}\) and case reports and case series have been published.\(^\text{51-55}\) Criteria were published by the American College of Rheumatology to increase the sensitivity and specificity of distinguishing Churg-Strauss from other vasculitides.\(^\text{56}\) The 6 criteria include peripheral eosinophilia of 10% or more in the leukocyte differential, biopsy-proven extravascular eosinophils, asthma, paranasal sinus abnormality, mononeuropathy or polyneuropathy, and nonfixed pulmonary infiltrates.

As in other diseases with eosinophilic infiltration of multiple organs, cardiac involvement can be the major cause of morbidity and mortality. Numerous clinical signs and
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symptoms of cardiac involvement may be seen. These include presentation with heart failure, pulmonary embolism, myocardial infarction, and signs and symptoms associated with constrictive pericarditis.

**Eosinophilic Myocarditis Associated With Cancer**

Reports in the literature demonstrated the association of tissue and blood eosinophilia with cancer of the lung, the gastrointestinal tract, the genitourinary tract, and the skin. Eosinophilic myocarditis in this setting has been described.

**Endomyocardial Fibrosis: Eosinophilic Versus Tropical**

Endomyocardial fibrosis is a pathologic diagnosis, describing the replacement of endocardium with thick collagen tissue overlying a looser framework of connective tissue in the involved endomyocardium. Although pathologically descriptive, the term “endomyocardial fibrosis” belies the dynamic pathophysiology, especially that of the eosinophil, which contributes to this “end result” and to the debate in distinguishing the 2 entities frequently associated with this pathologic finding: Löffler endomyocardial fibrosis and Davies endomyocardial fibrosis (tropical endomyocardial fibrosis).

As alluded to above, Löffler initially described endomyocardial fibrosis in the setting of myocardial eosinophil infiltration within the context of the hyper eosinophilic syndrome. The patients in whom this type of endomyocardial fibrosis develops (Löffler endomyocardial fibrosis) are generally male; from geographic regions with temperate climates; and clinically demonstrate fever, rash, weight loss, congestive heart failure, restrictive physiology, and systemic embolization. Eosinophilia and myocardial infiltration with eosinophils are the rule. However, by the time of necropsy or endomyocardial biopsy, the eosinophilic infiltrations may have already stopped, leaving only the remaining endomyocardial fibrosis.

The pathophysiology of endomyocardial disease in HES is associated strikingly with cardiac deposition of eosinophil granule protein initially onto the endocardium and later on the mural thrombi and on myocardial cells. Analyses of cardiac tissue from 18 autopsies and biopsies of patients with HES-associated endomyocardial disease revealed dramatic MBP and eosinophil cationic protein deposition, especially during the acute phase of the disease. Surprisingly, MBP deposition in subendocardial fibrous tissue may persist and provide a signal indicative of eosinophil involvement. Because MBP causes platelet activation, it inhibits the capacity of endothelial cell surface thrombomodulin to generate the natural anticoagulant (activated protein C), and activates cardiac mast cells, its deposition may stimulate clot formation directly, with subsequent embolization and encroachment on the ventricular cavity.

Tropical endomyocardial fibrosis (Davies endomyocardial fibrosis) is distributed geographically along the tropical and subtropical regions of Africa, India, and South America. The sex distribution is approximately equal, and children and young adults
are affected most. Eosinophilia and eosinophilic infiltration of myocardium are not distinct features of this disease.

**HYPERSENSITIVITY MYOCARDITIS**

With the increasing use of medications, iatrogenic causes of hypersensitivity myocarditis from drugs need to be understood and considered. The incidence of hypersensitivity myocarditis is unknown. One series reported 16 cases of hypersensitivity myocarditis in 3,373 consecutive autopsy cases.

The first series of patients describing the association of myocarditis with drug therapy was published in 1942 by French and Weller. They reported on 126 patients who developed eosinophilic infiltration and interstitial myocarditis after sulfonamide administration. Subsequently, numerous published case reports have had similar findings in patients treated with various medications. These are listed in Table 19-1. The mechanism of hypersensitivity myocarditis is thought to be a delayed hypersensitivity reaction. Hypersensitivity myocarditis associated with eosinophilia is generally independent of drug dosage, and drugs can also have a direct, dose-related toxic effect on myocardium, causing a myocarditis unassociated with eosinophils.

Clinically, patients may present with symptoms characteristic of a drug hypersensitivity reaction, including nonspecific skin rash, malaise, fever, and eosinophilia. More specific signs and symptoms referable to the heart include conduction abnormalities and tachyarrhythmias, sudden death, and increased concentrations of cardiac enzymatic markers such as creatine kinase and the creatine kinase-MB isozyme. Acute fulminant myocarditis with hemodynamic instability has also been described. The onset of hypersensitivity myocarditis after initiation of the offending medication is highly variable, with onsets hours to months after a medication is started.

Further evaluation with noninvasive testing, including echocardiography, may show a dilated cardiomyopathy with regional or global wall motion abnormalities. Endomyocardial biopsy may be performed for histologic evidence. However, if endomyocardial biopsy is used, the procedural risks versus benefits must be understood.

Treatment mainly consists of withdrawal of the suspected offending medication, which should not only be therapeutic but also diagnostic. Perhaps most importantly, a high level of clinical awareness is required to diagnose this entity.

**ACUTE NECROTIZING EOSINOPHILIC MYOCARDITIS**

A few patients have been reported who presented with an aggressive form of hypersinophilic-associated myocarditis: acute necrotizing eosinophilic myocarditis. All 3 patients with acute necrotizing eosinophilic myocarditis without extracardiac abnormality had viral prodromes, allergic diatheses, and rapidly deteriorating courses ending in death. These
Table 19-1
Drugs Associated With Hypersensitivity Myocarditis

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Anti-inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Oxyphenbutazone</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Phenylbutazone</td>
</tr>
<tr>
<td>Penicillin</td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td></td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Sulfisoxazole</td>
<td>Chlorthalidone</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide</td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Others</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Methyldopa</td>
</tr>
<tr>
<td></td>
<td>Sulfonyleas</td>
</tr>
<tr>
<td>Antituberculous</td>
<td>Tetanus toxoid</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Para-aminosalicylic acid</td>
<td></td>
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</tbody>
</table>


cases differed from prior reports of eosinophilia-associated heart disease in which a more chronic myocarditis occurred in the setting of systemic disease and extracardiac involvement. As its name implies, this form of eosinophilic heart disease is characterized by an acute onset and rapid progression of hemodynamic compromise and systolic ventricular failure. Mortality is high, with patients typically dying within days to weeks.

On histopathologic study, extensive inflammatory infiltration with eosinophils is seen in the setting of extensive myocyte necrosis (Fig. 19-1; see color plate 37). Analyses of 2 children who died of this disease showed massive eosinophil infiltration and degranulation with deposition of MBP onto necrotic myocardial cells.128 Electron microscopic study showed extensive areas of myocardial necrosis in the presence of degenerating eosinophils, the latter characterized by loss of the cytoplasmic membrane with release of eosinophil granules to the extracellular milieu. Immunosuppressive therapy, especially intravenous glucocorticoids in massive doses, may be beneficial in these patients,130 although they usually present acutely ill and often die.

EOSINOPHILIC MYOCARDITIS ASSOCIATED WITH PARASITIC INFECTIONS
Parasites that cause myocarditis associated with eosinophilic infiltration are listed in Table 19-2. Eosinophilia may occur in patients infected with helminthic parasites as an immune
response during which cytotoxic granule proteins may kill these organisms and damage cardiac tissues as bystanders. Additionally, protozoal disease may be associated with eosinophilic myocarditis. Chief among these is Chagas myocarditis caused by the protozoan Trypanosoma cruzi. The prevalence of trypanosomiasis is highest in Central and South America; an estimated 20 million people are infected with this parasite. The disease is transmitted to humans through the reduviid insect acting as the vector. Once the reduviid bug bites the human host, trypanosomes present in the reduviid bug feces gain entry by breaks in the skin or mucosa, particularly the conjunctiva.
Clinical, infected patients undergo acute, latent, and chronic phases. During the acute phase, patients present with myalgia, fever, diaphoresis, hepatosplenomegaly, and myocarditis with congestive heart failure. These symptoms may last for months and generally resolve. During the latent phase, symptoms usually are not present, although there can be a subclinical progression of cardiomyopathy. As cardiomyopathy progresses, patients may develop overt heart failure, thromboembolic phenomena from apical aneurysms, conduction abnormalities such as right bundle branch block and left anterior fascicular block, arrhythmias (atrial and ventricular), and sudden cardiac death.

Gross cardiac pathologic features may include dilated and hypertrophied cardiac chambers and left ventricular or apical aneurysm formation with thrombus. On histologic examination, extensive fibrosis is seen in the setting of a chronic mononuclear cellular infiltrate. The mononuclear cell infiltrate is composed chiefly of lymphocytes, macrophages, and plasma cells.

Eosinophils have been associated with these lesions, and activated eosinophils with their extruded granule constituents have been reported in the disrupted myofibrillar lesions. Finding actual parasites in these lesions is unusual and has brought into question whether the cardiac disruption is due to autoimmune phenomena.

**TREATMENT**

Treatment for the eosinophilic myocarditides depends on the underlying cause. In patients with eosinophilic myocarditis in the setting of systemic disease (such as hypereosinophilic syndrome and Churg-Strauss syndrome), high-dose corticosteroid therapy is beneficial. Mural thrombus may be an additional feature that requires anticoagulation therapy. In patients with endomyocardial fibrosis, surgical treatment may be required, involving myocardial
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stripping, valve replacement, and thrombectomy. For patients with hypersensitivity myocarditis, the offending medication must be withdrawn and treatment with high-dose corticosteroids is recommended. For patients with eosinophilic myocarditis associated with parasitic infections, treatment with antiparasitic medications may be of benefit. Use of immunosuppressive therapies specifically for eosinophilic myocarditis is still experimental.

SUMMARY

In this chapter, we have discussed the elegant mechanisms by which the eosinophil develops from its conception in the bone marrow, through its maturation, and finally to its attachment, extrusion, and homing into areas of inflammation in the myocardium. We have also discussed the role of the eosinophil in myocardial diseases, including eosinophilic myocarditis associated with systemic diseases such as HES, Churg-Strauss, and cancer; hypersensitivity myocarditis; acute necrotizing eosinophilic myocarditis; and eosinophilic myocarditis associated with parasitic infections. Although treatment currently consists of corticosteroids or therapies specifically directed toward underlying primary diseases (or both), the future may hold possibilities for alternative immunosuppressive regimens for the eosinophilic myocarditides.

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