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Spectrum of Eosinophilic End-Organ Manifestations

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Synopsis

Eosinophil-associated disorders can affect practically all tissues and organs in the body, either individually or in combination. This article provides an overview of end-organ manifestations of eosinophilia, discussing selected organ systems including the upper and lower respiratory, cardiovascular, gastrointestinal, nervous, dermatologic, and renal systems. Mechanisms by which eosinophilia leads to end-organ damage are also considered.

Keywords

Eosinophils/pathology; Eosinophils/immunology; Humans; Pulmonary eosinophilia; Eosinophilic esophagitis; Hypereosinophilic syndrome; Churg-Strauss syndrome; Eosinophilic granulomatous vasculitis

Introduction

The purpose and function of eosinophils in health and disease are complex and cannot be readily crystallized into a single summary statement. This has become increasingly true as myriad potential immunoregulatory behaviors of eosinophils have been uncovered in recent years.^{1, 2} However, the traditional characterization of eosinophils as end-organ effectors cells, causing tissue damage through release of cationic granule proteins, is borne of the observation of a spectrum of eosinophil-associated disorders encompassing practically all organ systems of the body. These disorders may affect one organ alone, as in the eosinophilic pneumonias or eosinophilic esophagitis, or affect multiple organ systems simultaneously, as in the hypereosinophilic syndromes or eosinophilic granulomatosis with

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polyangiitis (EGPA, formerly known as Churg-Strauss syndrome).^{3–6} The chapter provides an overview of eosinophilic end-organ manifestations, setting the stage for the organ-specific chapters that follow. Table 1 provides a partial tabulation of organs and organ-systems that may be affected by eosinophilia and potential diagnostic tests and assays that have the ability to reflect end-organ dysfunction.

Mechanisms of End-Organ Manifestations

While the specific mechanisms by which tissue eosinophilia results in end-organ dysfunction require further investigation, some general themes can be constructed based on current knowledge. These themes may be overlapping in specific disease processes, but can be useful in parsing the pathologic effects of eosinophils in disease.⁷

The first is that the infiltration of eosinophils in tissue can in and of itself be pathologic if it is extensive enough. For example, in the eosinophilic pneumonias, the main finding observed on lung biopsy is often simply extensive infiltration of eosinophils into the lung parenchyma.^{3, 8, 9}

Second, eosinophils may also cause organ damage mediated through associated fibrosis.¹⁰ Several *in vitro* studies have demonstrated the potential of eosinophils to promote fibroblast activation, proliferation, and extracellular matrix production, likely through their secretion of TGF- β and IL-1 β .^{11–15} Eosinophil cationic protein (ECP), one of the granule-stored proteins of eosinophils, has itself been observed *in vitro* to promote fibroblast migration and TGF- β release, potentially implicating granule protein deposition as a mechanism for eosinophil-mediated tissue fibrosis.^{16, 17} As discussed later in this chapter, eosinophil-associated tissue fibrosis is observed in the heart, specifically the endocardium, in hypereosinophilic syndromes, as well as in the subepithelial fibrosis that is characteristic of eosinophilic esophagitis and asthma.^{18–20}

Third, allergic mechanisms are a substantial driving force behind a subset of eosinophil-associated diseases and their resulting end-organ manifestations.²¹ The Th2 inflammation that is characteristic of allergic-mediated disease creates an IL-5 rich environment, promoting eosinophil infiltration and survival.^{22–24} Additionally, eosinophils themselves have immunoregulatory functions that may promote further inflammation in these tissue environments.¹ Cardinal examples include allergic asthma and atopic dermatitis.^{25, 26}

Finally, eosinophils have in certain conditions been observed to promote hypercoagulability, which may in turn promote end organ damage.²⁰ This effect may be mediated through hypercoagulable and platelet-activating effects of eosinophil granule proteins.^{27, 28} Such a phenomenon has been reported in the form of thrombotic microangiopathic kidney disease in hypereosinophilic syndromes.²⁹

Gastrointestinal

Eosinophils are normally present in all portions of the gastrointestinal tract, with the exception of the esophagus.³⁰ However, their presence may be pathologic in the gastrointestinal tract when they are present in excess and are the defining feature of a set of

diseases known as the eosinophilic gastrointestinal disorders (EGID).⁴ These include eosinophilic esophagitis, eosinophilic gastritis and gastroenteritis, and eosinophilic colitis. The degree of end-organ dysfunction in EGID is dependent on the location and extent of disease. In the esophagus, for example, functional manifestations may include food impaction and general dysphagia, with eosinophilic inflammation and epithelial hyperplasia seen on tissue specimens.^{30–32} In progressing distally down the gastrointestinal tract, end-organ manifestations can be characterized by defects in nutrient and calorie absorption, as well as frank protein losing enteropathy.³⁰ On endoscopic examination, the examined portions of the gastrointestinal tract are commonly visually abnormal in appearance, emphasizing the functional consequences of tissue eosinophilia.³³

Eosinophilia involving the gastrointestinal tract may be part of the spectrum of systemic illness in EGPA.⁶ The small bowel is most commonly affected and can lead to abdominal pain and gastrointestinal bleeding. In severe cases, bowel ischemia can occur.⁶

Tissue eosinophilia may be seen in the liver and in particular be associated with frank hepatitis and hepatic injury in systemic eosinophilia associated with severe drug reactions, known as DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome.³⁴ In this condition, liver injury can be detected by elevation in serum transaminases.³⁵ Though quite rare, eosinophilic infiltration resulting in pancreatitis has been described as well.³⁶

Pulmonary

The lungs are perhaps the organ where tissue eosinophilia intersects most distinctly with organ infiltration to result in a set of specific disease entities. These include allergic asthma, acute and chronic eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, EGPA, as well as a host of infectious entities that are predominantly parasitic in nature.³ From a functional perspective, eosinophilic infiltration can be thought of as affecting two separate but intimately related compartments, the airways and alveolar spaces (along with accompanying interstitium).

Tissue eosinophilia of the airway wall contributes to the obstructive physiology characteristic of asthma, promoting subepithelial fibrosis and airways hyperresponsiveness.¹⁹ Similar physiology associated with tissue eosinophilia may be found in related disorders that can mimic traditional asthma, principally EGPA and allergic bronchopulmonary aspergillosis. The resulting obstruction is manifest in dyspnea and wheeze that are often experienced by patients and may be quantified by a characteristic pattern on pulmonary function testing.³

Eosinophilic infiltration of the alveolar spaces and associated interstitium are characteristic of the eosinophilic pneumonias and may be seen in EGPA as well. Involvement of these areas of lung responsible for gas exchange not only result in dyspnea but in hypoxemia as well.^{37, 38} Gas exchange abnormalities can result in respiratory failure in severe cases with extensive parenchymal involvement.^{37, 38} In acute eosinophilic pneumonia, diffuse alveolar damage may accompany eosinophilic infiltration on pathologic specimens.³⁷ In EGPA, eosinophilic vasculitis in the pulmonary interstitium can be observed (though not necessarily so), as the name of the disorder implies.⁶ Eosinophilic inflammation of the alveolar spaces

may be detected by the observation of eosinophils in bronchoalveolar lavage specimens taken during bronchoscopy.³

Eosinophilic effusions can also form in the pleural space, affecting lung function through extraparenchymal compression, leading to shortness of breath and impaired gas exchange.³⁹ Eosinophilic pleural effusions may be idiopathic in nature, although they are also associated with other specific processes, including pathologic drug reactions, malignancy, and parasitic infections.³⁹

Upper Airway and Sinuses

As a disease entity, chronic rhinosinusitis is strongly associated with tissue eosinophilia.⁴⁰ In particular eosinophilia is associated with rhinosinusitis that is accompanied by nasal polyposis.⁴¹ Chronic rhinosinusitis can occur independently in atopic individuals or in close association with allergic asthma or EGPA. From an end-organ dysfunction perspective, loss of smell can occur, along with sinus pain and pressure, mucous production, and nasal blockage.⁴⁰ While no specific functional studies are characteristic of eosinophilic infiltration of the sinuses and nasal tissue, eosinophilia may be noted in pathologic specimens obtained in therapeutic surgical procedures.

Cardiovascular

Eosinophilic inflammation affects the heart in systemic eosinophilic processes such as hypereosinophilic syndromes and EGPA, as well as in concert with helminthic processes and tropical eosinophilia.^{20, 42, 43} End-organ damage to the heart occurs through multiple pathways, including endocardial necrosis, fibrosis, intraluminal thrombosis, and ischemia due to epicardial vascular involvement.^{7, 20}

In the hypereosinophilic syndromes, endocardial damage occurs initially as necrosis and progresses to endocardial fibrosis.^{44, 45} Endocardial damage can affect the systolic and diastolic functionality of the heart.⁴⁶ When fibrosis affects the chordae tendinae, valvular function can potentially be impaired. The endocardial damage and eosinophilia in hypereosinophilic states also promote intraluminal thrombosis, which has the potential to further impair cardiac function through impairment of filling and flow through the ventricular outflow tract.^{20, 28} These end-organ cardiac manifestations lead to dyspnea when symptomatic. While endocardial inflammation is also seen as the primary cardiac pattern in EGPA, small vessel coronary vasculitis and pericarditis may both be seen and represent additional patterns of cardiac end-organ dysfunction related to eosinophilia.^{42, 43}

Echocardiography may detect impairment of cardiac and valvular function and visualize thrombus, while cardiac magnetic resonance imaging is emerging as a useful modality to detect endocardial fibrosis before functional consequences are readily apparent.^{47–49} Electrocardiogram is non-specific but is also abnormal with endocardial, pericardial, and ischemic eosinophilic cardiac processes.⁵⁰ Serum troponin is a useful clinical tool in eosinophilic disorders to detect any possible active cardiomyocyte cell damage and death.⁵¹

Neurologic

The idiopathic hypereosinophilic syndromes and EGPA both have the potential to demonstrate end-organ neurologic manifestations, with the ability to affect both the peripheral and central nervous systems.⁵² The peripheral neuropathies that occur with hypereosinophilic syndromes may have motor and sensory components of varied distributions.⁴⁴ Direct eosinophil infiltration is often not seen on pathologic examination, making the exact mechanism of end-organ dysfunction somewhat unclear.⁵² In EGPA, mononeuritis multiplex is commonly seen and is used as a criterion in diagnostic schema, including often-cited 1990 American College of Rheumatology criteria.⁵³ Eosinophilic vasculitis may be seen on nerve biopsy specimens in EGPA.⁵⁴

The central nervous system and cranial nerves can be affected in the hypereosinophilic syndromes. However, as with peripheral neuropathy, pathology does not necessarily reveal eosinophilic infiltration.^{52, 55} Central nervous system and cranial nerve involvement have been reported in EGPA as well.^{6, 54}

As discussed above, hypereosinophilia is associated with thrombosis, providing an additional thromboembolic mechanism for end-organ neurologic injury.

Skin

Dermatologic eosinophilia is varied in nature, can involve all layers of the skin, and can be associated with both local and system disease.⁵⁶ While it is challenging to categorize eosinophilia of the skin into patterns of end-organ damage, highlighting dermatologic disorders that are characterized by eosinophilia, as will be done in a later chapter, can be illustrative. Skin biopsy is the key modality in diagnosis of this diverse group of conditions, including atopic dermatitis, eosinophilic cellulitis (Wells' Syndrome), eosinophilic fasciitis, eosinophilic panniculitis, bullous pemphigoid, urticaria, and drug reactions.⁵⁶⁻⁶⁰

In systemic disorders such as EGPA, skin lesions demonstrating eosinophilic vasculitis can be part of the spectrum of disease.⁵⁴ Hypereosinophilic syndromes, particularly lymphocytic variants, can demonstrate urticaria and angioedema, or alternatively, erythematous papules and nodules.⁵² Episodic angioedema with eosinophilia, known as Gleich's Syndrome, represents another distinct entity with its own dermatologic end-organ manifestation.⁶¹

Renal and Genitourinary

Eosinophiluria can be indicative of eosinophilic end-organ pathology of the kidney in acute interstitial nephritis related to drug exposure, with common offenders including non-steroidal anti-inflammatory medications and antibiotics.⁶² Acute interstitial nephritis may also be seen in systemic infections and inflammatory conditions such as Sjogren's syndrome and sarcoidosis.^{63, 64}

The kidneys can be involved in EGPA, in particular in patients with circulating anti-neutrophil cytoplasmic antibodies.^{6, 54} End-organ dysfunction of the kidney is reflected in elevated serum creatinine.

Eosinophilic cystitis and eosinophilic prostatitis both have the ability not just to cause end-organ damage to the bladder and prostate, respectively, but to lead to renal failure as well.^{65, 66}

Summary

The discussion above does not represent an exhaustive list of the potential end-organ manifestations of eosinophilia. Many other entities, such as eosinophilic myositis and localized eosinophilic vasculitis of the skin, among others, belong on the full roster of eosinophilic conditions with end-organ consequences.^{67, 68} While eosinophilic disorders encompass a broad range of conditions that are not easily categorized other than the common characteristic of the presence of eosinophils, whether they be present in the blood, in tissues, or in combination, it is clear that eosinophilia can cause significant dysfunction of virtually any organ or organ system.

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Key Points

- Eosinophilia may affect any organ and cause end-organ damage.
- Mechanisms by which eosinophilia promotes tissue damage include infiltration, fibrosis, thrombosis, and allergic inflammation.
- Patterns of eosinophil-mediated end-organ dysfunction are particularly well characterized for the lungs, heart, and gastrointestinal tract.

Table 1

Detection of Eosinophilic End-Organ Dysfunction

Organ System Affected by Eosinophilia	Selected Studies
Cardiac	Serum troponin Electrocardiogram Echocardiogram Cardiac MRI
Gastrointestinal	Endoscopy with tissue biopsy Serum liver function testing Serum amylase, lipase
Pulmonary	Chest X-ray Chest CT Pulmonary function testing Bronchoscopy with bronchoalveolar lavage Lung biopsy
Neurologic	Head MRI Head CT Nerve conduction studies Nerve biopsy
Skin	Skin biopsy
Renal	Serum creatinine Urine eosinophils Kidney biopsy