VASCULITIS

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KEYWORDS

• Vasculitis • Lung • Wegener granulomatosis • Churg-Strauss • Necrotizing sarcoid
• Microscopic polyangiitis • Diffuse alveolar hemorrhage • Capillaritis

ABSTRACT

Vasculitic syndromes involving the lung present a unique challenge for pathologists because of the histologic overlap with other disorders and the clinical implications of the diagnosis in regard to clinical management. This article reviews the more common vasculitic syndromes involving the lung, concentrating primarily on Wegener granulomatosis, Churg-Strauss syndrome, necrotizing sarcoid, microscopic polyangiitis, and diffuse alveolar hemorrhage syndromes. The article focuses on a review of the recent literature, diagnostic approach, and differential diagnosis.

OVERVIEW

Vasculitic syndromes involving the lung often pose unique challenges for the surgical pathologist, and a diagnosis of vasculitis carries serious implications from a clinical standpoint in prognosis and treatment. Most of the vasculitic syndromes involving the lung are immune mediated. Vasculitic syndromes are relatively rare, with an estimated annual incidence of just under 40 cases per million.[1] The most common vasculitic syndromes involving the lung, which are the focus of this article, are Wegener granulomatosis (WG), Churg-Strauss (CS) syndrome, and microscopic polyangiitis (MPA), whereas other vasculitic syndromes involving the lung are rare. Diffuse alveolar hemorrhage with capillaritis is a particular histologic type of pulmonary vasculitis that occurs most commonly in a relatively narrow range of immune-mediated disorders. Vasculitic syndromes involving the lung are

(1) Wegener granulomatosis
(2) Churg-Strauss syndrome
(3) Microscopic polyangiitis
(4) Diffuse pulmonary hemorrhage syndromes (**Box 1**)
(5) Necrotizing sarcoid granulomatosis
(6) Polyarteritis nodosa
(7) Takayasu arteritis
(8) Henoch-Schönlein purpura
(9) Behçet syndrome.

of which (5) to (9) are rare. Disorders associated with diffuse alveolar hemorrhage are presented in **Box 1**. It is important to note that inflammation may involve the vessel walls secondarily in infections and other inflammatory lung diseases, and it is generally recommended that the term ''pulmonary vasculitis'' as a diagnostic entity should be restricted to those disorders in which the vasculitis is a major or primary component of the pathology given the clinical implications. As with most lung diseases, pulmonary vasculitic syndromes should be diagnosed in a multidisciplinary fashion taking into account radiographic and clinical findings, particularly serologic studies.

Key Points
WEGENER GRANULOMATOSIS

Most patients are positive for cytoplasmic antineutrophilic cytoplasmic antibodies (C-ANCAs) by serologic testing

WG typically shows irregular areas of basophilic necrosis containing abundant neutrophils surrounded by histiocytes and scattered giant cells

Vasculitis may be neutrophilic or granulomatous and typically involves small arteries and/or veins. Some cases may show prominent or exclusive capillaritis.

Other findings may include neutrophil microabscesses, microgranulomas, organizing pneumonia, or foamy macrophage accumulation

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Box 1
Disorders associated with diffuse alveolar hemorrhage with capillaritis

Wegener granulomatosis[a]
Microscopic polyangiitis[a]
Collagen vascular disease[a]
Antiphospholipid antibody syndrome
Mixed cryoglobulinemia
Goodpasture syndrome[b]
Behçet syndrome
Henoch-Schönlein purpura
Drug induced
Infections: Listeria, endotoxin associated

[a] Most common
[b] May occur without capillaritis

WEGENER GRANULOMATOSIS

WG is a systemic inflammatory disease characterized by pulmonary, upper respiratory, and renal involvement. Although involvement of these 3 systems constitutes what has been considered the "classic triad," frequently only 1 or 2 of these systems is involved.[2,3] "Limited WG" often refers to WG involving the lung without involvement of the kidneys[4]; however, the term has also been used to describe disease that does not threaten the function of a vital organ.[5]

CLINICAL FEATURES

WG may occur at any age, including childhood, but is primarily seen in adults, with an average age at presentation of 50 years.[6–8] The clinical presentation and symptoms depend on the site and extent of organ involvement. More than 90% of patients experience head and neck involvement during the course of their disease, which manifests most commonly as sinusitis. Some patients may experience otitis media, hearing loss, or subglottic stenosis. Progressive nasal inflammation may result in the so-called saddle nose deformity. Pulmonary involvement occurs is 85% of patients, usually in conjunction with head and neck disease. The pulmonary disease is often manifested by cough, hemoptysis, or pleuritic chest pain. Renal involvement occurs in 75% of patients. WG may potentially involve almost any other organ, although involvement of the heart and nervous system is uncommon. Ocular disease occurs in roughly half the patients with WG.[6,9–11] Left untreated, WG is a progressive and ultimately fatal disease with almost 90% of patients dying within 2 years of diagnosis. Treatment with cyclophosphamide and prednisone has greatly improved disease outcome. With appropriate treatment, nearly 75% of patients achieve remission, although relapses are common.[12] Rituximab and tumor necrosis factor α are also under evaluation for treatment of WG, particularly in patients with refractory disease.[13,14]

Radiographically, patients with pulmonary WG have multiple opacities or nodules of variable size, which may be cavitary (**Fig. 1**). The nodules are more common in the lower lobes, and a "feeding vessel" may be observed in association with the nodules. Patients presenting with diffuse pulmonary hemorrhage show diffuse pulmonary infiltrates and airspace opacities. Pleural thickening or effusion is seen in up to 50% of cases, but mediastinal adenopathy is unusual. WG only rarely presents as a solitary pulmonary nodule or opacity.[15–18]

DIAGNOSIS

The clinical diagnosis of WG is greatly aided by the evaluation of serum antineutrophilic cytoplasmic antibodies (ANCA). Two major immunofluorescence patterns are associated with ANCA:

(1) Cytoplasmic pattern, or C-ANCA, associated with proteinase 3
(2) Perinuclear pattern, or P-ANCA, associated with myeloperoxidase.

Expression of C-ANCA is fairly sensitive and specific for WG, but expression is not restricted to this entity, and the absence of C-ANCA expression does not exclude a diagnosis of WG. C-ANCA is positive in 85% of patients with systemic WG, in 50% to 70% with limited disease, and in 30% to 40% in remission. P-ANCA is present in 5% to 20% of WG cases. The histologic findings appear to be the same in both C-ANCA and P-ANCA positive cases.[19–22] Although the pathogenesis of WG is not fully understood, it is thought that ANCA, either directly or indirectly, is involved in the tissue damage.[23,24]

MICROSCOPIC FEATURES

Pathology of WG

WG is characterized by necrotizing granulomatous inflammation and vasculitis. Low power microscopy typically shows areas of necrosis that have irregular outlines (geographic necrosis) and have a basophilic appearance owing to the presence of abundant neutrophils (**Fig. 2**). The areas of necrosis are surrounded by histiocytes, which may be palisaded, and a mixture of inflammatory