Pulmonary capillaritis

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Vasculitis, inflammation, and necrosis of blood vessels can involve any size or type of vessel in the pulmonary vasculature, including the capillaries, so-called capillaritis. Although pulmonary capillaritis is a histopathologic diagnosis that is not pathognomonic of a specific disorder, it usually signals the presence of an underlying systemic vasculitis or collagen vascular disease. Patients with pulmonary capillaritis usually present with bilateral infiltrates on chest radiographs and can be acutely ill with diffuse alveolar hemorrhage that may be life threatening. Therapy depends on diagnosis of the underlying disease that gave rise to the capillaritis. Since many of the disorders leading to capillaritis are treated by immunosuppression with corticosteroids and cyclophosphamide or azathioprine, infection must be excluded early in the course of therapy.

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Abbreviations

ANCA	antineutrophil cytoplasmic autoantibodies
SLE	systemic lupus erythematosus

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Pulmonary capillaritis is a histologic pattern of lung injury rather than a specific disease entity [1,2]. It has been reported as a manifestation of systemic vasculitis, most often Wegener granulomatosis [3–5] and microscopic polyangiitis [6–8], and collagen vascular disease, particularly systemic lupus erythematosus (Table 1) [9]. Less frequent associations include antiglomerular basement membrane disease (Goodpasture disease) [10–12], collagen vascular disease other than systemic lupus erythematosus [13,14], idiopathic pulmonary hemorrhage [2], idiopathic pulmonary-renal syndrome [2,15–18], Churg-Strauss syndrome [19], Henoch-Schönlein purpura [20–22], cryoglobulinemia [4], Behçet syndrome [21,23,24], IgA nephropathy [4,25], idiopathic pulmonary fibrosis [8], acute pulmonary allograph rejection [26], antiphospholipid syndrome [27–29], diphenyhydantoin use [30], retinoic acid syndrome [31], and administration of propylthiouracil [32]. Since therapy and prognosis for these disorders varies, it is important to accurately diagnose the disease giving rise to the capillaritis. Still, diagnosis may be problematic because of the protean clinical manifestations of the systemic disorders and the nonspecific features of capillaritis. Accurate diagnosis requires evaluation of the data from the clinical history; physical examination; radiographs; routine laboratory tests; ancillary laboratory tests, such as antinuclear antibodies, antineutrophil cytoplasmic antibodies, and antiglomerular basement membrane antibodies; and biopsies from sites other than the lung, such as kidney, nasal sinuses, or skin, using light, immunofluorescence, or electron microscopy.

Clinical findings

Although pulmonary capillaritis has been reported as a manifestation of a variety of systemic disorders, it is most commonly associated with the systemic vasculitic syndromes and collagen vascular disease. The studies by Mark and Ramirez [1], Travis *et al.* [2], and Jennings *et al.* [8] reviewed a total of 76 patients with pulmonary capillaritis and alveolar hemorrhage. In this group, capillaritis was most frequently associated with Wegener's granulomatosis or probable Wegener's granulomatosis (21 cases; 28%), systemic vasculitis otherwise unclassified (9 cases; 12%), systemic lupus erythematosus (7 cases; 9%), and microscopic polyangiitis (6 cases; 8%). Eight of the 29 patients with diffuse alveolar hemorrhage and pulmonary capillaritis in the study by Jennings *et al.* [8] lacked clinical, serologic, or histologic evidence of an associated

Table 1. Disorders reported to be associated with pulmonary capillaritis

Most common associations
Wegener granulomatosis
Microscopic polyangiitis
Systemic lupus erythematosus (SLE)
Less frequent associations
Antiglomerular basement membrane disease
Collagen vascular disease other than SLE
Idiopathic pulmonary hemorrhage
Idiopathic pulmonary-renal syndrome
Churg-Strauss syndrome
Henoch-Schönlein purpura
Cryoglobulinemia
Behçet syndrome
IgA nephropathy
Idiopathic pulmonary fibrosis
Acute pulmonary allograph rejection
Antiphospholipid syndrome
Diphenylhydantoin use
Retinoic acid syndrome
Propylthiouracil

systemic illness. Capillaritis is the typical microscopic finding in 88% of patients with diffuse alveolar hemorrhage, and the extent of the capillaritis depends on the underlying disorder [2].

Most patients with pulmonary capillaritis present with acute alveolar hemorrhage characterized by dyspnea, cough, pleuritic pain and hemoptysis, and diffuse bilateral infiltrates on chest radiographs [1,2,8,33]. Patients can be acutely ill with respiratory failure requiring mechanical ventilation or with renal failure. Mark and Ramirez [1] found that whatever the cause of the pulmonary capillaritis, the resulting pulmonary hemorrhage was life-threatening in all of their patients. Of 13 patients in their study, 4 patients died 1 to 21 days after lung biopsy and 2 patients died of Wegener granulomatosis and the diagnosis was made at autopsy.

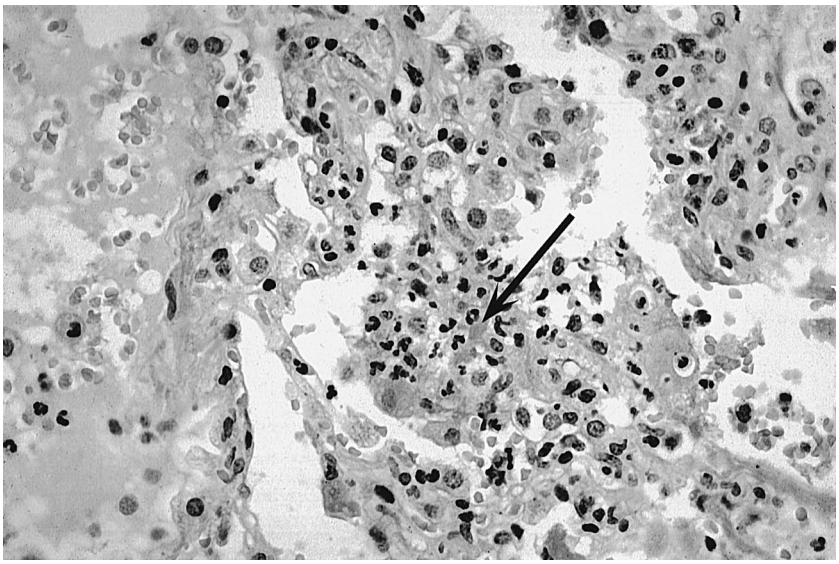
Pathology

In 1985, Mark and Ramirez [1] described the following histologic features in pulmonary capillaritis: (1) fibrin thrombi occluding capillaries in interalveolar septa; (2) fibrin clots attached to interalveolar septa in a sessile manner; (3) fibrinoid necrosis of capillary walls; (4) neutrophils and nuclear dust in the fibrin, in the interstitium, and in the immediately adjacent alveolar blood; and (5) interstitial red blood cells and interstitial hemosiderin. Although not all of these features are present in every patient, the number of interstitial neutrophils and the amount of nuclear dust are always in excess of intra-alveolar neutrophils and nuclear dust [1]. This difference is an important feature in distinguishing capillaritis from hemorrhagic infectious pneumonia. In the latter, intra-alveolar neutrophils and nuclear dust usually exceed those in the interstitium (Fig. 1).

Pulmonary capillaritis is a subtle pathologic finding that may be difficult to recognize, particularly in areas of extensive alveolar hemorrhage [3]. Mark and Ramirez [1] suggest several factors that contribute to this difficulty. First, the ease of recognizing vasculitis is inversely related to vessel size, so that capillaritis may be both focal and subtle [1]. Also, while capillaritis may coexist with more readily identifiable inflammation of larger vessels, it may also be the only pulmonary vascular manifestation of a systemic disorder. Second, unlike leukocytoclastic vasculitis in the skin, in which the diagnosis of vasculitis is facilitated by the accumulation of extravasated red blood cells in the connective tissue surrounding the blood

Figure 1. Capillaritis as the sole biopsy finding in a patient later diagnosed with Wegener granulomatosis

Note the increased numbers of polymorphonuclear leukocytes and fibrinoid necrosis in the interstitium (arrow).



vessel, the red blood cells that escape from alveolar capillaries in the alveolar wall enter the alveolar space and are not confined to the site of damage to act as a marker for capillaritis. Third, the alveolar wall is narrow and neutrophils escaping damaged capillary walls immediately enter the alveolar space, decreasing the chance of identifying them within the interstitium. Finally, capillary necrosis leaves behind an area of hemorrhage without an inflamed capillary in which capillaritis can be identified. In addition to these features, there is the problem of distinguishing acute tissue hemorrhage induced by the biopsy itself from hemorrhage caused by capillaritis.

Wegener granulomatosis

Wegener granulomatosis is a distinct systemic vasculitic syndrome characterized by necrotizing granulomatous inflammation of the upper and lower respiratory tracts, necrotizing glomerulonephritis, and a variable degree of small-vessel vasculitis [21,34–37]. Disease involving organs other than the kidney, such as the lung, is known as limited or localized Wegener granulomatosis [38,39]. Although middle-aged adults are usually affected, pediatric and geriatric cases are reported [40,41]. The onset of Wegener granulomatosis is typically insidious, with nonspecific symptoms of fever, malaise, weight loss, and fatigue combined with symptoms referable to the nose, paranasal sinuses, ear, or chest [42–45]. Necrotizing granulomatous inflammation, necrotizing small vessel vasculitis, parenchymal necrosis, and multinucleated giant cells are the most common and classic pathologic manifestations of Wegener granulomatosis [46–48]. Less common histologic variants include alveolar hemorrhage and capillaritis, interstitial fibrosis with patchy vasculitis, the eosinophilic variant, the bronchocentric variant, and the variant that resembles bronchiolitis obliterans-organizing pneumonia [47]. The alveolar hemorrhage and capillaritis variant is the most difficult to diagnose pathologically [47]. Since patients with this variant may present with massive pulmonary hemorrhage and pursue a fulminant clinical course with a high mortality rate, rapid diagnosis and prompt institution of therapy are essential [2–4,49–52].

Antineutrophil cytoplasmic autoantibodies (ANCA) were first observed in vasculitis approximately 15 years ago [53]. They are useful serologic markers for the diagnosis and management of Wegener granulomatosis as well as other ANCA-associated vasculitides such as microscopic polyangiitis and Churg-Strauss syndrome [35,54]. Additionally, ANCAs may be involved in the pathogenesis of these disorders [55–57]. ANCAs are autoantibodies specific for components of neutrophil primary granules and monocyte lysosomes [58,59]. Two major subtypes of ANCAs have been identified by indirect immunofluorescence microscopy using alcohol-fixed neurophils as a substrate: cANCAs producing cytoplasmic staining, and pANCAs producing perinuclear staining [59]. Most cANCAs are specific for proteinase 3 (anti-PR3 cANCA), whereas pANCAs are generally specific for myeloperoxidase (anti-MPO pANCA); proteinase 3 and myeloperoxidase are both found in the primary granules of neutrophils and the peroxidase-positive lysosomes of monocytes [59]. cANCA induced by PR3-ANCA are highly sensitive and specific for Wegener granulomatosis [57]. cANCAs induced by proteinase 3 occur in more than 90% of patients with generalized Wegener granulomatosis and approximately 75% of patients with the limited form of the disease [60]. Evidence suggests that cANCA can be used to follow the course of Wegener granulomatosis and to guide therapy. Decreases in ANCA titers have been reported during induction therapy [61], while other investigators report increases prior to relapse [62,63]. False-positive ANCA test results have been reported in diseases without obvious association with vasculitis [64].

Microscopic polyangiitis

The microscopic form of polyarteritis nodosa, now called microscopic polyangiitis, is defined as a systemic necrotizing vasculitis affecting small vessels—that is, arterioles, capillaries, or venules—without necrotizing granulomatous inflammation [34]. The definition requires few or no immune deposits to allow differentiation from other small vessel vasculitides with immune complex deposits such as Henoch-Schönlein purpura and essential cryoglobulinemic vasculitis, immune complex-mediated small vessel vasculitis as seen in lupus vasculitis and serum sickness, and from antiglomerular basement membrane disease [34]. Microscopic polyangiitis is differentiated pathologically from polyarteritis nodosa by the presence or absence of vasculitis in arterioles, capillaries, and venules, in addition to small or medium-sized arteries. By definition, this usually means the presence of renal capillaritis (glomerulonephritis) and pulmonary capillaritis. Classic polyarteritis nodosa, by contrast, affects small and medium-sized arteries but lacks capillary, arteriolar, and venular inflammation [34]. Owing to the involvement of arterioles, capillaries, and venules, the term *microscopic polyangiitis* is preferred over the term *microscopic polyarteritis* [34].

Microscopic polyangiitis presents, on average, in the fifth decade, with ages ranging from 3 to 80 years [65,66]. The male to female ratio quotient varies from 1 [65] to 1.8 [67]. Renal involvement, characterized by rapidly progressive glomerulonephritis, is the major clinical feature of microscopic polyangiitis and is present in over 90% of cases [35,65–68]. Microscopic polyangiitis is also the most common cause of pulmonary-renal syndrome [69]. After renal involvement, the most common organ-system manifestations due to small vessel vasculitis are musculoskeletal, pulmonary, gastrointestinal, and cutaneous (Table 2) [35].

Pulmonary manifestations vary from transient infiltrates on chest radiographs to hemoptysis with massive pulmonary hemorrhage, the most life-threatening manifestation of small vessel vasculitis and the major contributory factor to morbidity and mortality [35,70]. The majority of ANCA detected in microscopic polyangiitis are anti-MPO pANCA [70]. However, since pANCAs are found in a variety of inflammatory disorders and are not specific for vasculitis or glomerulonephritis, the diagnostic usefulness of anti-MPO pANCA, although well established in microscopic polyangiitis [71], is not as great as that of anti-PR3 cANCA in Wegener granulomatosis [70].

Bosch *et al.* [72] suggest that the distinction between microscopic polyangiitis and polyarteritis nodosa may be a source of misinterpretation. In their study, 1250 patients with different forms of systemic vasculitis, connective tissue disease, and renal and pulmonary disorders were screened for ANCAs. Sixty-eight patients with pauci-immune idiopathic narcotizing and crescentic glomerulonephritis and five patients with isolated pulmonary hemorrhage and biopsy-proven narcotizing alveolar capillaritis were identified and diagnosed with microscopic polyangiitis. Five of 68 patients with idiopathic narcotizing and crescentic glomerulonephritis (three with PR3-ANCA and two with MPO-ANCA) and one of five patients with idiopathic pulmonary hemorrhage (MPO-ANCA) developed clinical and histologic features of Wegener granulomatosis with increased serum titers of ANCA 20 to 72 months after initial diagnosis (mean of 42.3 months). None of the six patients had signs or symptoms of Wegener granulomatosis, other systemic vasculitides, or collagen vascular at initial diagnosis. Admitting the limitation of a small number of patients (six), Bosch *et al.* suggest that microscopic polyangiitis may be a dynamic rather than static condition in which clinical and histopathologic features evolve over time to other well recognized forms of small vessel vasculitis, particularly Wegener granulomatosis.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease primarily affecting young women that is characterized by a bewildering array of autoantibodies and widely variable clinical presentation. Updated in 1997, the revised classification system for SLE delineates 11 criteria for the diagnosis of this disorder [73]. Although SLE is typically characterized by injury to the skin, joints, kidney, and serosal membranes, it can involve any organ, including the lungs. In fact, SLE involves the lung more than any other collagen vascular disease [74]. Pleuropulmonary disease in patients with SLE may be the direct result of immune complex deposition (pleuritis, pleural effusion, acute lupus pneumonitis, usual interstitial pneumonia pattern, bronchiolitis obliterans-organizing pneumonia, respiratory muscle or diaphragmatic dysfunction, alveolar hemorrhage and capillaritis). It may also be secondary to therapy (infection, drug reactions), anticardiolipin or lupus anticoagulants (thrombosis, pulmonary hypertension), or systemic disease (uremia, congestive heart failure, infection, amyloidosis) [75]. Pleuritis with or without effusion is the most common pleuropulmonary manifestation of SLE and is reported in up to 60% of patients [76].

Table 2. Organ system involvement in microscopic polyangiitis

Organ system	Involvement, %	Symptoms
Kidney	90	Glomerulonephritis
Musculoskeletal	60	Myalgias, arthralgias, arthritis
Lung	50	Infiltrates, hemoptysis
Gastrointestinal tract	50	Abdominal pain, gastrointestinal bleed
Skin	40	Purpura, splinter hemorrhages
Ear, nose, and throat	35	Sinusitis
Neurologic	30	Peripheral neuropathy

Clinically important pulmonary hemorrhage is a rare but potentially catastrophic complication of SLE [1,2,33,76]. Mortality rates exceed 50% [9,12,77–79]. Diffuse alveolar infiltrates, hypoxemia, dyspnea, and anemia are nonspecific but characteristic clinical features. Pulmonary hemorrhage typically occurs in patients with clinically active SLE but rarely it may be the initial manifestation of the disease [9]. Microscopically, pulmonary hemorrhage is characterized by extensive filling of the alveolar spaces with red blood cells and fibrin and capillaritis may be present [2,9,78]. Granular deposits of IgG or C3 have been identified in the alveolar walls and small pulmonary arteries of some but not all patients with pulmonary hemorrhage complicating SLE [9,78].

Conclusions

The majority of articles on the subject of pulmonary capillaritis are written from the clinical perspective of diffuse alveolar hemorrhage or to illustrate associations between capillaritis and specific clinical situations (Churg-Strauss, allograft rejection, retinoic acid syndrome). Although little is written in the annual period of review, several older and recent articles are noteworthy. The 1996 paper by Green *et al.* [33] is an excellent review of the diagnosis and management of pulmonary capillaritis and alveolar hemorrhage, including five cases illustrating the most common associated diseases. The retrospective review by Jennings *et al.* [8] of 29 patients with diffuse alveolar hemorrhage and biopsy-proven pulmonary capillaritis delineated the most commonly associated diseases and characterized eight patients lacking an accompanying systemic illness. Travis *et al.* [2] and Mark and Ramirez [1] present excel-

lent studies on the pathologic features of diffuse alveolar hemorrhage and capillaritis. Since several of the small vessel vasculitides comprise the majority of diseases associated with capillaritis, the articles by Jennette and colleagues [34,35] are highly recommended.

Pulmonary capillaritis is a pathologic diagnosis of a histologic pattern of lung injury, the presence of which should initiate investigation for an underlying systemic disorder. Since patients may be critically ill with life-threatening injury to major organs, such as the lung and kidney, it is important for clinicians and pathologists to be familiar with the key clinical, laboratory, and pathologic features of the most common causes of pulmonary capillaritis, especially Wegener granulomatosis, microscopic polyangiitis, and systemic lupus erythematosus so that the diagnosis can be established quickly and therapy instituted promptly. Diagnosis of the specific underlying systemic disorder may not be possible based on lung biopsy alone and may require correlation with the clinical history, radiographs, laboratory tests for antineutrophil cytoplasmic antibodies, antinuclear antibodies, and antibasement membrane antibodies, and results of biopsies from kidney, nasal sinuses, or skin with light, immunofluorescence, or electron microscopy.

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