Pulmonary Vasculitis

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This is to acknowledge that John Fitzgerald has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Fitzgerald will be discussing off-label uses during this program.

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Areas of interest:
Interstitial Lung Disease
Sarcoidosis
Vasculitis and Collagen Vascular Disease

Introduction

In vasculitis, blood vessels and surrounding tissues become infiltrated by various immune effector cells.[1] This inflammatory process is often systemic in nature, producing constitutional complaints and pathology in multiple systems. Stenosis or necrosis of vascular structures may lead to bleeding, ischemia or infarction in affected organs.[2] Any size and type of vessel may be involved, from the largest muscular artery to the most fragile capillary. The lungs are frequently affected in systemic vasculitis, perhaps owing to their rich vascular supply, and unique exposure to both airborne and blood borne antigens.[3]

Vasculitis in the lung has a varied presentation. Some patients develop pulmonary arterial aneurysms, pulmonary hypertension or diffuse alveolar hemorrhage, while others have lung nodules, masses or infiltrates.[4, 5] These conditions are all uncommon, and the diagnosis may be elusive. Symptoms and imaging patterns are nonspecific, and may suggest other more prevalent differential diagnoses such as infection, malignancy or connective tissue disease.[6] A high index of suspicion is required to avoid dangerous delays in disease recognition. Pulmonary vasculitis occurs most frequently in association with the pauci-immune, small vessel vasculitides.[7] These include Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg Strauss syndrome (CSS). Takayasu arteritis (TA) and Behcet's disease (BD) are other important causes. Necrotizing sarcoid granulomatosis (NSG) is a rare form of vasculitis that is usually limited to the lungs. Rarely, giant cell arteritis (GCA) and classic polyarteritis nodosa (PAN) can involve the lungs; and there are secondary forms of pulmonary vasculitis which are linked to infections or underlying connective tissue disorders.[8]

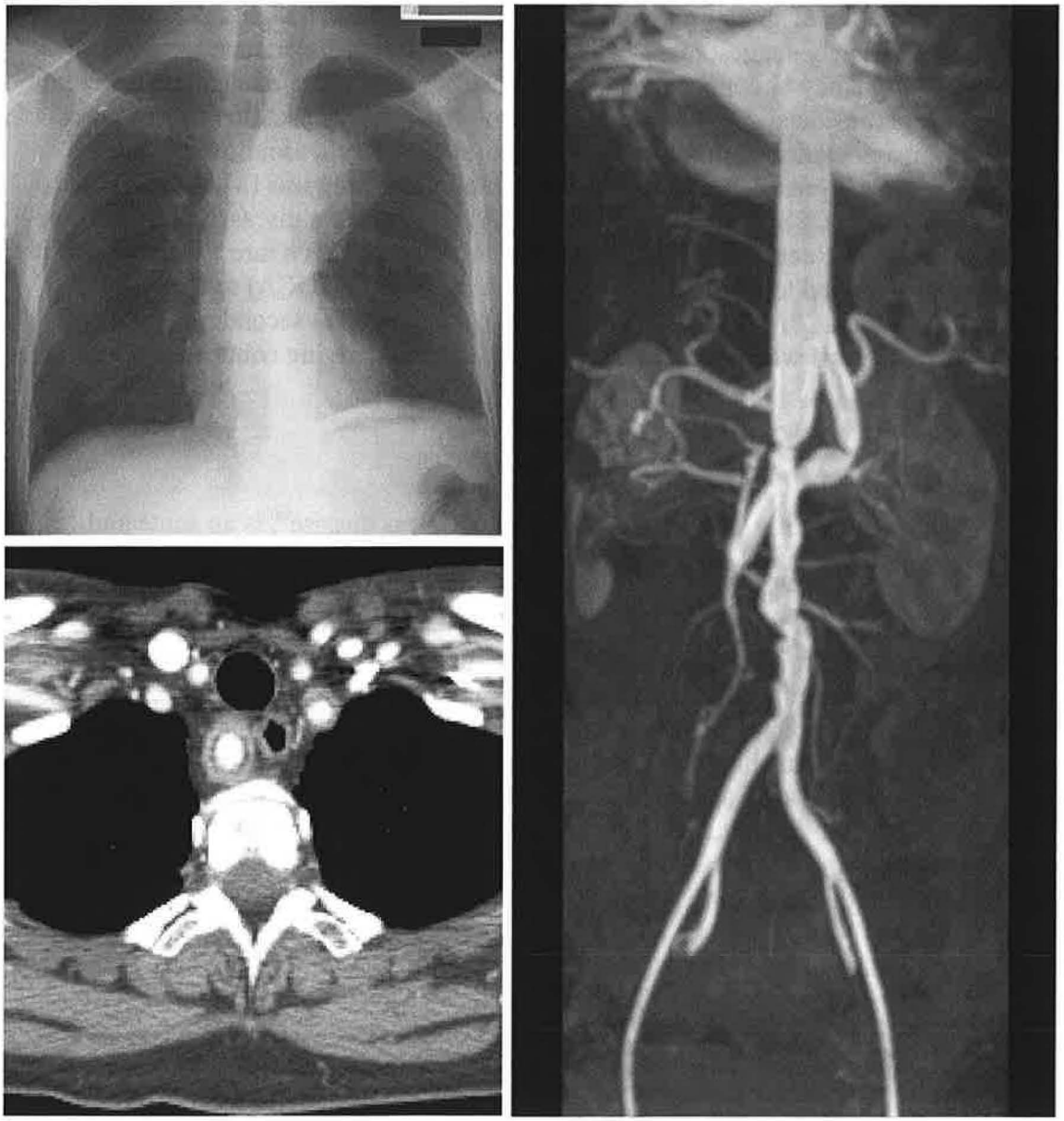
Takayasu Arteritis

Takayasu arteritis (TA), also known as "pulseless disease", is an acute and chronic large vessel vasculitis best known for involvement of the aorta and its major branches.[9] The disease is most prevalent among persons from Southeast Asia, India and Mexico, and there is a strong female predominance. In the West, TA is uncommon, with just 1-3 new cases per million per year.[10, 11] The incidence is fifty times higher in Japan. Takayasu arteritis occurs in persons under 50 years of age, and symptoms usually manifest in the second or third decades of life. The initial inflammatory phase features constitutional symptoms like fever, weight loss, night sweats and general malaise.[12] Patients may report loss of appetite, chronic fatigue and musculoskeletal complaints. Characteristic laboratories include elevated serum markers of systemic inflammation and an anemia of chronic disease. Computed tomography or magnetic resonance imaging will often reveal thickened or enhancing vascular walls during this phase of the arteritis (figure 1).

Eventually, the vascular inflammation regresses, but remodeling of the vessel wall produces stenosis or aneurysmal dilatation.[12] This late "occlusive" phase of the disease features mainly ischemic symptoms. TA is classically described as an "arch syndrome" with limb claudication or symptoms of cerebral ischemia such as visual loss, orthostasis or frank syncope. Headache, vertigo and memory loss may also be seen. Involvement of

the abdominal aorta and iliac arteries is underappreciated, however (figure 1). Stenosis of the mesenteric arteries may cause abdominal pain, diarrhea or gastrointestinal bleeding; and more than half of affected individuals develop hypertension, usually as a result of renal artery stenosis.[13] Ascending aortic aneurysms may develop, along with dilatation of the aortic root (figure 1). The resulting aortic insufficiency can lead to congestive heart failure, especially when paired with poor blood pressure control. In addition, angina or frank myocardial infarction can result from vasculitis involving the coronary arteries or coronary ostia. Such abnormalities are detected in 15 percent of patients.[14]

Figure 1. Three patients with Takayasu arteritis. Large aneurysm of the aortic arch (upper left). Multifocal stenoses of the distal half of the abdominal aorta (right). Note the kinked or stenotic ciliac artery bypass graft, and the zones of infarction in the mid and lower poles of the right kidney. Active arteritis with thickened, enhancing walls above the aortic arch (lower left).



The pulmonary arteries are affected in the majority of TA patients, but it is often clinically silent.[8, 15, 16] Symptomatic pulmonary hypertension occurs in fewer than ten percent, but echocardiography reveals a higher prevalence. Plain films or computed tomography can reveal enlargement of the pulmonary arteries due to pulmonary hypertension or aneurysm formation (figure 2). Increased wall thickness or mural enhancement are commonly identified.[13, 17] In some cases, focal oligemia can result from pulmonary arterial stenosis (figure 2). Lung perfusion scans were abnormal in a remarkable 76 percent of TA patients in one study, mimicking venous thromboembolism (figure 3).[18, 19] Symptoms of pulmonary vasculitis include chest pain, dyspnea and hemoptysis. The most devastating pulmonary complication of TA is rupture of a pulmonary arterial aneurysm, but it is fortunately an uncommon event. Hemoptysis can also result from systemic hypervascularization complicating pulmonary arterial stenosis.[20]

Figure 2. TA patient with left PA aneurysm (upper left). Plain film of the same patient at a later date demonstrates enlargement of the left hilum and extensive lower lobe infarction due to thrombosis within the aneurysm (upper right). CT showing an enlarged ascending aorta and main PA in another patient with TA (lower left). CT image from the same patient revealing enlarged segmental pulmonary arteries indicating pulmonary hypertension, along with a focal area of oligemia due to proximal vascular stenosis.

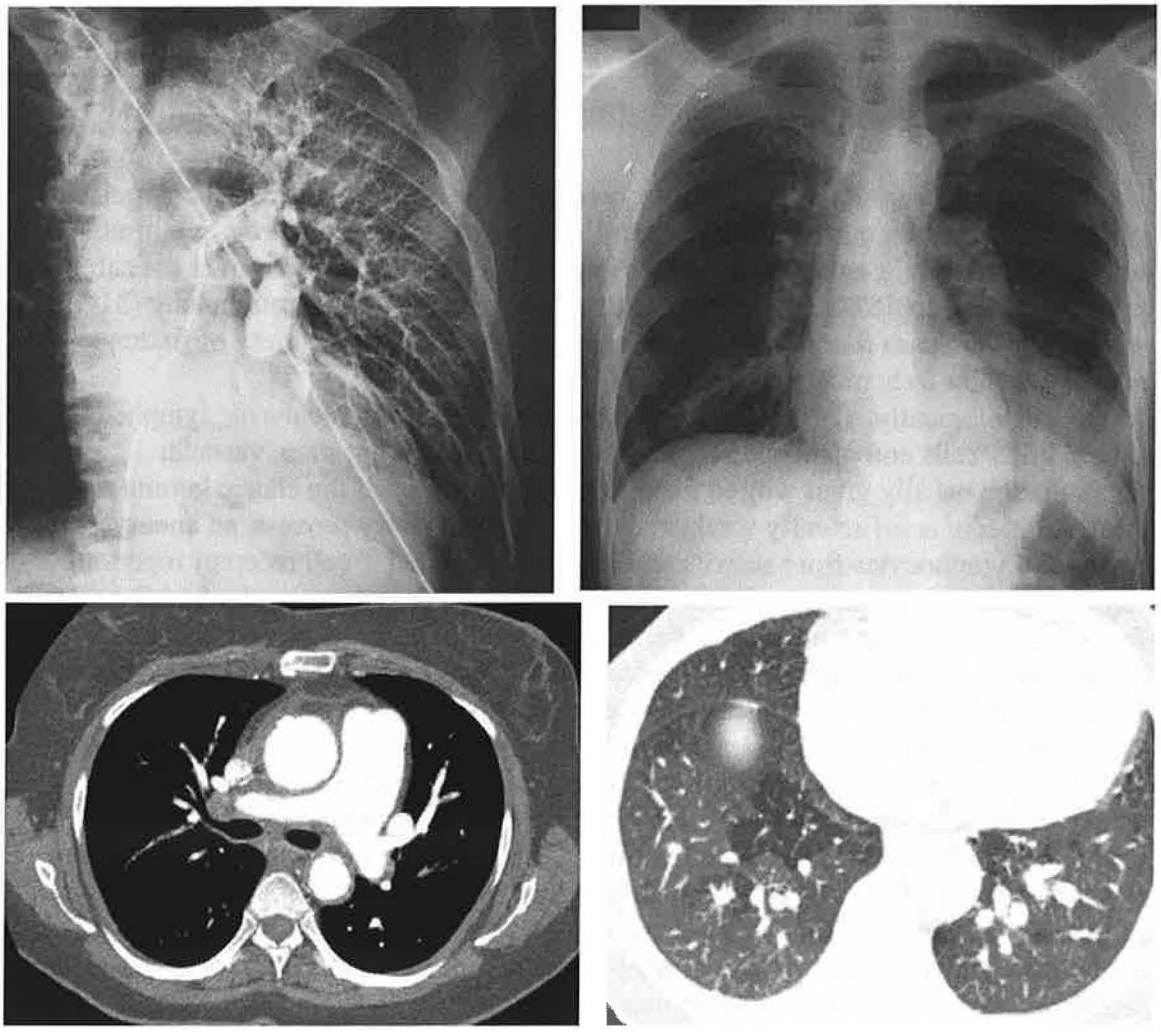
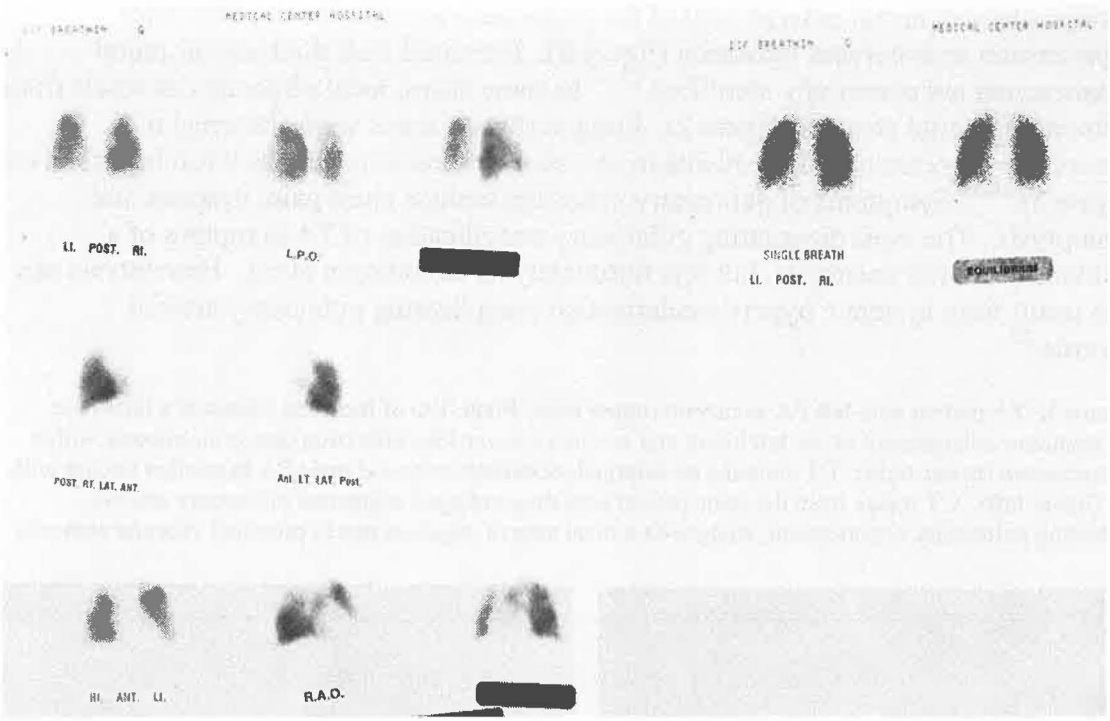


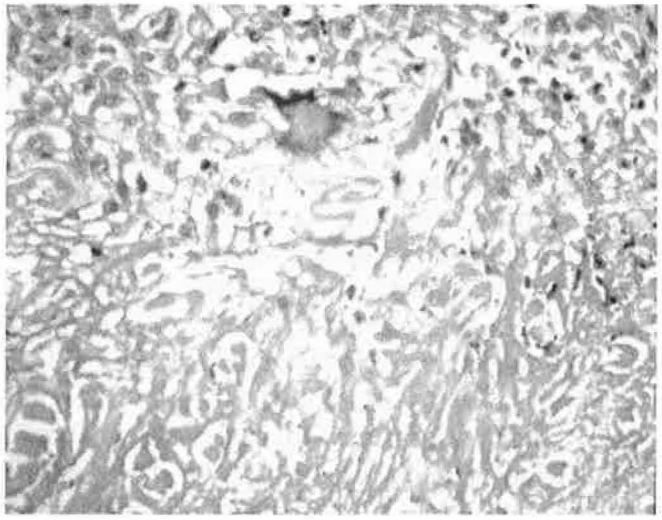
Figure 3. High probability ventilation-perfusion lung scan in a patient with Takayasu arteritis. Multiple unmatched subsegmental perfusion defects are noted due to pulmonary arteritis. Pulmonary arteriography revealed no evidence of thromboemboli.



Physical examination in TA may reveal decreased or absent peripheral pulses, a systolic blood pressure gradient of 10 mm Hg or more between the arms, a murmur of aortic insufficiency, vascular bruits in various locations, or tenderness over the carotid arteries. Fundoscopic examination may demonstrate hypertensive retinopathy (31 percent) or Takayasu retinopathy (14 percent), which includes a variety of findings related to ocular ischemia.[21]

Histologically, TA is a focal granulomatous panarteritis featuring lymphocytes, natural killer cells and giant cells (figure 4).[22] After a period of time, vascular inflammation usually gives way to fibrosis and stenosis, but if the elastic lamina and muscular media is sufficiently weakened by the inflammatory process, an aneurysm may develop. Lymphocytes from active areas reveal a restricted T cell receptor repertoire suggesting an inflammatory response to a specific antigen.[23] A particular 65 kD heat shock protein is strongly induced in the aortic tissue of TA patients, and may be recognized by these lymphocytes.[24] Increased local expression of class I and II human leukocyte antigens and intercellular adhesion molecule-1 suggests a possible role for these molecules in recognition and adhesion of immune effector cells.[24] After being recruited to the vessel wall, infiltrating "killer" cells (gamma delta T lymphocytes, natural killer cells and cytotoxic T cells) secrete large amounts of perforin, a cytolytic substance capable of causing vascular injury.[24] The humoral immune system may also play a role in the pathogenesis of Takayasu arteritis. High titers of anti-endothelial cell antibodies are identified in most patients.[25] This is seen in other vasculitides as well, and it remains unclear whether this is an epiphenomenon of vascular injury, or whether these antibodies are involved in the pathogenesis of vasculitis.[26-28]

Figure 4. Biopsy specimen from a patient with Takayasu arteritis demonstrating infiltration of the vessel wall (media and adventitia) by histiocytes and other mononuclear cells. A single giant is also visible.



Biopsy of involved vessels is risky and generally unnecessary. When the diagnosis is suspected, complete aortography and pulmonary angiography should be performed. Magnetic resonance or CT angiography are preferred since they can delineate both luminal and mural pathology while avoiding arterial puncture.[29-32] Positron emission tomography has been suggested as another option for detecting active sites of vascular inflammation that may be likely to respond to medical therapy.[33-35]

In 20 percent of cases, TA is self-limited, but most patients require immunosuppressive treatment.[13] Corticosteroids are the preferred initial treatment, and are effective in ameliorating disease activity about half the time.[11, 36, 37] An additional 25 percent require concomitant cytotoxic therapy to achieve remission. Methotrexate, azathioprine, leflunomide, mycophenolate and cyclophosphamide have been employed in this setting. Unfortunately, one fourth of patients are refractory to immunomodulating treatment, and half of those who achieve remission later relapse.[13] Limited data suggest a possible role for anti-tumor necrosis factor therapies in patients who require high dose corticosteroids or relapse on other agents.[38-40] Late stage fibrotic, stenotic lesions are much less likely to respond to anti-inflammatory therapies. If patients experience persistent claudication, hypertension from renal artery stenosis, or vital organ ischemia, then surgical bypass or angioplasty with vascular stenting becomes necessary. Unfortunately, such interventions are associated with a high rate of restenosis or vascular occlusion.[41] Restenosis occurs approximately one third of the time, but the risk can be reduced if post-intervention immunosuppressive therapy is employed, and if the procedure is performed during the "stable" stage of the disease.[42] The use of drug-eluting arterial stents may one day prove valuable in this setting. At times, aneurysms of the aorta or pulmonary arteries in TA require open surgical repair.[43, 44]

Survival in this disease is dependent on the presence or absence of major complications, and the pattern of the disease course.[45] Major complications include Takayasu retinopathy, hypertension, aortic regurgitation, and aneurysm formation. In a study of 120 Japanese patients, the 15 year survival was 66 percent for patients with a major complication, but 96 percent for those without one.[45] When patients had a "progressive disease course" (progressively worsening symptoms over years since disease onset), the 15 year survival rate was 68 percent versus 93 percent in subjects without such a preexisting disease pattern. The 15 year survival was only 43 percent for individuals with both a major complication and a progressive course. About three

quarters of patients requiring surgical treatment survived 20 years in one large series.[46] Periodic surveillance for the development of anastomotic aneursyms (incidence 14 percent) is recommended in this patient population.

Giant Cell Arteritis

Giant cell (temporal) arteritis is probably the most common form of systemic vasculitis.[47, 48] It occurs mainly in persons over 50 years of age, especially those of Northern European descent.[49] GCA affects large and medium sized vessels, and has a predilection for involving the cranial branches of the aortic arch.[50] Typical presenting complaints include headache, pain over the temporal arteries, jaw claudication, polymyalgia rheumatica, and systemic symptoms such as fever, weight loss and fatigue.[51] Perhaps 15 percent present with fever of unknown origin.[52] In a minority of cases, high grade spiking fevers initially suggest infection, but leukocyte counts are generally normal. Anemia and elevated erythrocyte sedimentation rates are typical. Loss of vision is one of the most serious complications, occurring in about 15 percent of patients.[53] Fifteen to 25 percent have primarily large vessel involvement manifesting as arm claudication, aortic aneurysm formation or aortic dissection (figure 5).[54-56] Large vessel GCA patients complain of headache and scalp tenderness much less frequently; and temporal artery biopsies are often negative in this setting.[51, 56, 57]

Upper respiratory tract involvement manifesting as a sore throat or persistent, dry cough is seen in about ten percent of patients with GCA.[58] Lower respiratory tract involvement is very uncommon, however. When it occurs, it may take the form of pulmonary nodules, interstitial infiltrates, a lymphocytic alveolitis, subclinical alveolar hemorrhage (prominent hemosiderin-laden macrophages on bronchoalveolar lavage) or pleural effusion.[59-65] GCA rarely affects the large, elastic pulmonary arteries, but in situ vascular thrombosis and pulmonary infarction may result when it does.[66, 67]
The risk for developing GCA is enhanced in persons with HLA-DR and a particular ICAM-1 gene polymorphism.[68, 69] The initiating factor could be a viral or atypical bacterial infection. A possible association has been identified between GCA and infection with parvovirus B19, parainfluenza type 1, and *chlamydophila pneumoniae*.[70-73] Whether infectious or other triggers are involved, the identification of identical T cell clones in multiple vasculitic sites (within a single patient) suggests a response to a specific antigen.[69, 74]

The histology of GCA features chronic inflammation consisting of histiocytes, lymphocytes, plasma cells and giant cells infiltrating the media and adventitia and destroying elastic laminae.[66, 75] Glucocorticoids effectively control the disease process in most cases, and prevent ischemic complications.[76, 77] Death is uncommon as a result of this disorder. Indeed, GCA is usually a self-limited process, with a duration of months to years.[78]

There is a rare condition called idiopathic isolated pulmonary giant cell arteritis which features no lesions outside the lungs, and usually a normal erythrocyte sedimentation rate.[79-82] It is most often an incidental finding in surgical or autopsy specimens, but may cause dyspnea. The histopathology is similar to that seen in classic GCA, and peripheral pulmonary infarcts may be seen.

Behcet's Disease

Behcet's disease is an idiopathic vasculitic disorder featuring recurrent bouts of acute inflammation in many different organ systems, and a tendency toward thrombosis.[83, 84] It is most common in young adults of Middle Eastern or Far Eastern descent. The highest prevalence rates are noted in Turkey.[85] Large and small vessels are affected by an infiltration of lymphocytes and neutrophils. Platelet and endothelial cell activation contribute to the associated hypercoaguable state, which may produce both arterial and venous thromboses, including thrombosis of the vena cava. The diagnosis rests on the identification of recurrent aphthous oral ulceration (figure 6) with at least two of the following clinical findings: recurrent genital ulcers, uveitis, retinal vasculitis, a positive pathergy test, or characteristic skin lesions (papulopustular lesions, palpable purpura, pseudofolliculitis or erythema nodosum).[83, 84, 86] Many other systems can be involved, however. Oligoarthritis is common. In 10-20 percent, the central or peripheral nervous system is affected in the form of chronic meningoencephalitis, dementia, psychiatric disturbances, mononeuritis multiplex or bulbar dysfunction.[87] Nausea, vomiting, abdominal pain, diarrhea or bleeding may indicate gastrointestinal involvement, which tends to favor the ileocecal region, sometimes causing confusion with Crohn's disease. Epididymitis may also occur. Up to 25 percent of patients, particularly young men, may develop large vessel involvement in the form of aortic or pulmonary artery aneurysms (figure 7).[88-90] Behcet's disease is the most common vasculitic cause of pulmonary artery aneurysms.[85, 91, 92] In one series of over 2000 BD patients, however, only 24 actually had PA lesions identified.[93] Rupture is often a terminal event, and one third of patients with these lesions expire within two years. Hemoptysis portends a poor prognosis in Behcet's disease.[93] It is the usual presenting symptom for patients with bronchoarterial fistulas related to PA aneurysms.

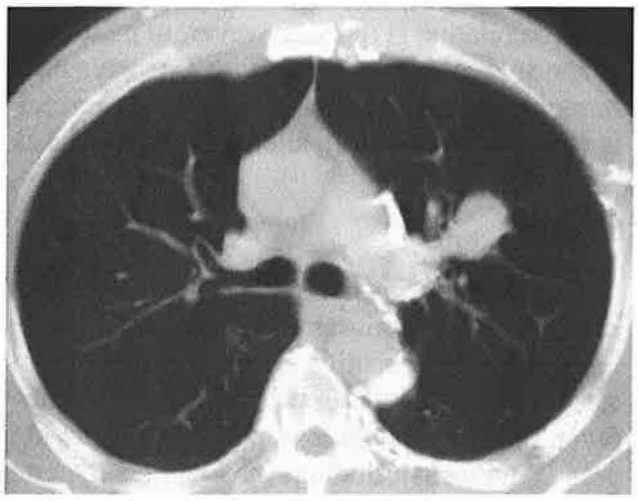


Figure 7. Behcet's disease complicated by pulmonary arterial aneurysm formation.

In patients with BD, diagnostic procedures involving vascular puncture may be complicated by thrombophlebitis or the development of pseudoaneurysms. Consequently, helical computed tomography or magnetic resonance angiography should be utilized to diagnose vascular lesions.[94] Three quarters of patients with PA aneurysms have extrapulmonary venous thrombi or thrombophlebitis.[91] Although deep vein clots are common in Behcet's disease, the thrombi tend to adhere to the inflamed veins and rarely embolize.[93] Nevertheless, lung perfusion scans often reveal patchy blood flow distribution as a result of in situ pulmonary arterial thrombosis.[95, 96] Infarction of lung tissue in BD may result in a variety of radiologic findings typically associated with pulmonary emboli such as atelectasis, subpleural nodules, Hampton's humps, pulmonary cavities and pleural effusions.[97]

Pleural vasculitis and thrombosis of the superior vena cava are other BD complications which may result in the development of pleural effusions. Mediastinal lymphadenopathy, bronchiolitis obliterans with organizing pneumonia, eosinophilic pneumonia, mediastinitis, diffuse alveolar damage, and obstructive airways disease have all been reported.[88, 98-100] Chyloptysis may occur in association with superior vena cava thrombosis.[101] Rarely, Behcet's disease has been associated with pulmonary capillaritis and diffuse alveolar hemorrhage.[88]

Behcet's disease has been associated with both genetic and environmental factors including HLA-B51 and a variety of infections.[83] Traditionally, neutrophil activation and the generation of excess toxic oxygen species has been considered central to disease pathogenesis.[102, 103] Recent studies suggest an important role for T cells in this disease as well.[85] One hypothesis suggests that microbial heat shock proteins stimulate the development of self-reactive T cell clones and autoantibodies in genetically susceptible subjects.[104-106] During periods of disease activity, there is evidence of a Th1 response with increased elaboration of interleukin-1, interleukin-2, and gamma interferon.[107, 108]

Appropriate therapy for Behcet's disease varies depending on the site of disease activity. Skin and mucosal lesions can often be managed with topical steroids, dapsone or colchicine. Sulfasalazine has been used successfully in patients with gastrointestinal involvement. When such treatments are inadequate, or when flares are systemic in nature, thalidomide, oral glucocorticoids, tacrolimus, cytotoxic agents, or biologicals like infliximab and alpha interferon may be required.[83, 84, 109-111] Aneurysms indicate a poor prognosis in BD.[112] Remarkably, though, they may regress completely with aggressive medical therapy.[109, 113, 114] In the absence of major hemorrhage, surgery is best avoided since there is a tendency for aneurysms to recur at anastomotic sites.[115] Endovascular coil or *n*-butyl cyanoacrylate embolization of pulmonary arterial aneurysms has been used successfully to treat massive hemoptysis in patients with BD.[116, 117] Anticoagulation can be used along with short course glucocorticoid therapy in the setting of thrombophlebitis. Anticoagulation is risky, however, in patients with pulmonary vascular involvement. When such patients present with extensive thromboses, an initial period of immunosuppression should precede the careful introduction of anticoagulation. Aspirin is sometimes used as an alternative when the clot burden is not extensive.

Polyarteritis Nodosa

Polyarteritis nodosa is a systemic necrotizing vasculitis affecting small and medium-sized arteries, but not arterioles, capillaries or venules.[118, 119] Some cases are a consequence of hepatitis B (and occasionally other) virus infections.[118, 120] Indeed, HBV-associated vasculitis appears to respond to anti-viral therapy.[121] PAN patients often report fever, malaise, weight loss, polyarthritis, myalgias, weakness, and abdominal or testicular pain.[122] Objective findings may include hypertension, renal insufficiency (and infarction), eosinophilia, livedo reticularis, subcutaneous nodules along the arteries of the lower extremities, and neuropathy (especially mononeuritis multiplex). Angiography is diagnostic when it reveals the pathognomonic arterial microaneurysms.[123, 124] Vascular stenoses or occlusion may also be seen. With regard to thoracic involvement, a coronary arteritis is occasionally identified, but clinically important pulmonary involvement is quite rare. The bronchial arteries are commonly affected based on autopsy evidence, but

it is clinically silent.[125, 126] In one autopsy study of 10 PAN cases, five were noted to have acute or organizing diffuse alveolar damage, and two had interstitial fibrosis with honeycomb change.[125] Five of these patients died of respiratory failure. Most reports of pulmonary disease previously attributed to PAN are now felt to represent cases of microscopic polyangiitis or Churg Strauss syndrome, however.[3] Unlike MPA, classic PAN is not associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA).[127] There have been a few reports of pulmonary arteritis linked to classical PAN, including one that was also associated with bronchiolitis obliterans and organizing pneumonia.[128-130] There have also been three reports of diffuse alveolar hemorrhage in hepatitis B-related PAN.[131-133] Pleural effusions are occasionally recognized.[118]

Necrotizing Sarcoid Granulomatosis

Necrotizing sarcoid granulomatosis is a rare form of vasculitis that is usually limited to the lungs, but occasionally involves the eyes or central nervous system.[134-137] The relationship between NSG and classical sarcoidosis remains unclear. Women are affected twice as often as men. Patients typically have a mixture of respiratory and constitutional complaints such as cough, chest pain, shortness of breath, fever, weight loss and general malaise. Twenty percent have no symptoms, but have incidental abnormalities detected on chest imaging studies. The usual radiographic presentation includes multiple, bilateral pulmonary nodules ranging from a few millimeters to a few centimeters in size (figure 8).[138] They tend to concentrate along bronchovascular bundles in the lower lung zones. Cavitation, or low attenuation centers, may be appreciated on computed tomography scans. Other patterns include peribronchial or subpleural consolidation resembling BOOP, and solitary nodules or masses.[139] Hilar or mediastinal lymphadenopathy may be seen, but is frequently absent. The erythrocyte sedimentation rate is often elevated, but the serum calcium and angiotensin converting enzyme levels are not. Antineutrophil cytoplasmic antibodies have not been reported in necrotizing sarcoid granulomatosis.

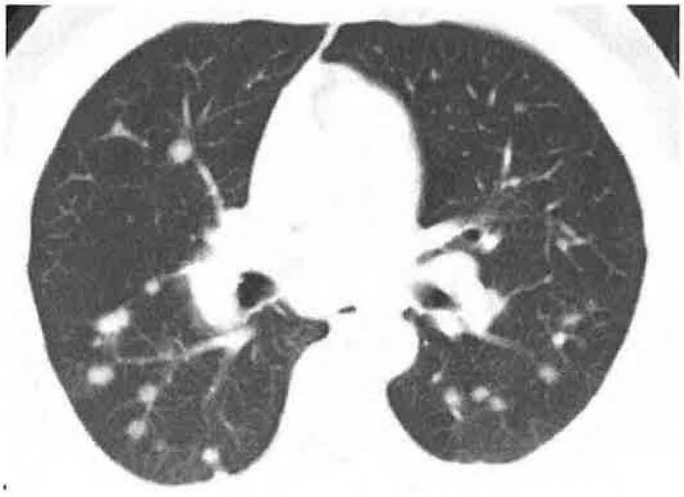


Figure 8. Necrotizing sarcoid granulomatosis featuring multiple pulmonary nodules, many centered on the vascular tree.

The opacities in NSG consist of confluent clusters of sarcoid-like epithelioid granulomas.[75, 135, 140] However, extensive areas of noncaseous necrosis may be identified in the center of these conglomerates. No infectious agents have been identified within these lesions. Vessel walls may be infiltrated by lymphocytes, plasma cells, giant cells and granulomas, but vascular involvement is not the dominant histopathologic feature (figure 9). Since NSG is not generally a

systemic process, debate continues over its classification as a vasculitis.[75] The differential diagnosis includes infectious granulomatous diseases, Wegener's granulomatosis, lymphomatoid granulomatosis, bronchocentric granulomatosis and classical sarcoidosis. A surgical lung biopsy is required to make a definitive diagnosis.

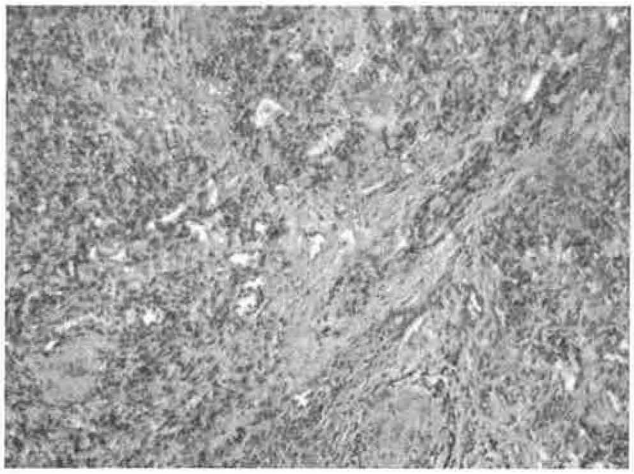


Figure 9. Necrotizing sarcoid granulomatosis. Lung biopsy showing extensive infiltration of epithelioid histiocytes, mononuclear and giant cells with patchy necrosis. Only the remnants of a vessel can be seen extending from the center of the picture toward the upper right corner.

The clinical course of necrotizing sarcoid granulomatosis is generally benign. There is a predictably good response to glucocorticoids, and some cases remit spontaneously. Cytotoxic agents should be avoided as they expose the patient to unnecessary risk.[136] For localized disease, resection is curative.

Table 1. Pulmonary manifestations of the medium and large vessel vasculitides.

TA	BD	NSG	GCA	PAN
PAH	PA aneurysm	Multiple pulmonary nodules	Interstitial infiltrates	Bronchial artery stenosis
PA aneurysm	*in situ* PA thrombosis	Solitary mass or nodule	Lymphocytic alveolitis	DAD
PA stenosis	VTE	Peribronchial or subpleural consolidation	Pulmonary nodules	Pulmonary fibrosis
Focal oligemia	Pulmonary infarction		*in situ* PA thrombosis	
	Pleural vasculitis			
	Pleural effusion			
	BOOP			
	DAD			
	DAH			
	Nodules or cavities			
	Mediastinal LA			

TA = Takayasu arteritis, BD = Behcet's disease, NSG = necrotizing sarcoid granulomatosis, GCA = giant cell arteritis, PAN = polyarteritis nodosa, PA = pulmonary artery, PAH = pulmonary arterial hypertension, VTE = venous thromboembolism, DAD = diffuse alveolar damage, DAH = diffuse alveolar hemorrhage, BOOP = bronchiolitis obliterans with organizing pneumonia, LA = lymphadenopathy

Small Vessel Vasculitis

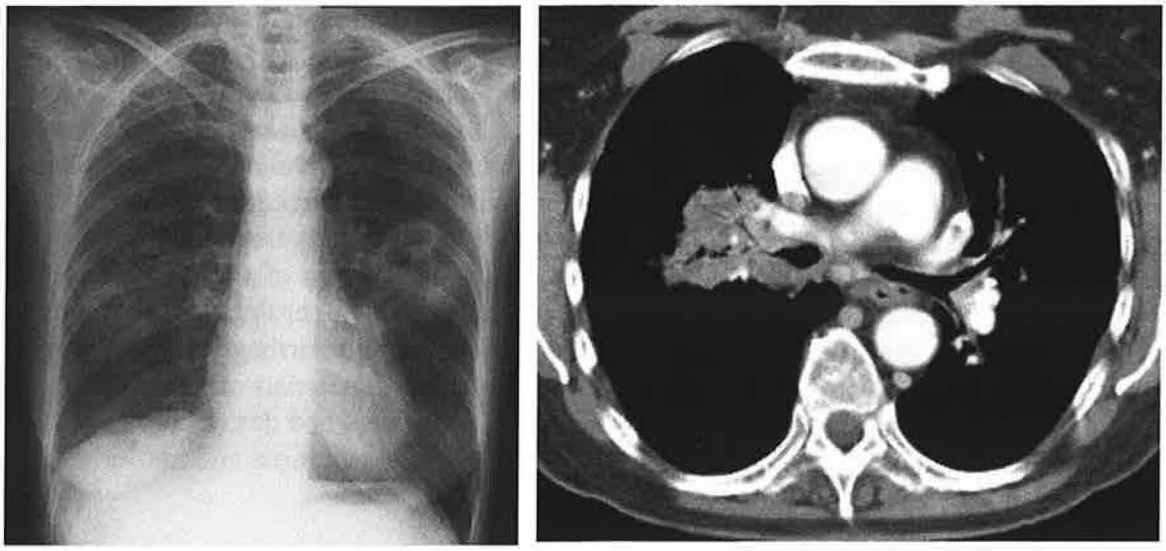
Wegener's granulomatosis, microscopic polyangiitis and Churg Strauss syndrome are closely related forms of small vessel vasculitis. Although medium-sized vessels are involved in these conditions, the inflammatory process is concentrated on arterioles, capillaries and venules.[141] WG, MPA and CSS are idiopathic disorders associated with ANCA, and are the most commonly recognized forms of pulmonary vasculitis.[142, 143] The incidence of ANCA-associated vasculitis is approximately 20 per million.[144] CSS is less common. Diagnosis may be determined by clinical findings and serologic evidence in some cases, but many require biopsy of involved tissues.[141, 145, 146] In patients with suspected vasculitis, the identification of ANCA with specificity for myeloperoxidase (MPO) or proteinase 3 (PR3) indicates a high probability of WG, MPA or CSS.[146]

Clinical Presentation of Small Vessel Vasculitis

Wegener's granulomatosis features a triad of renal, upper respiratory tract and lower respiratory tract involvement.[147, 148] Upper airway disease develops in 90 percent of WG patients, and manifests as chronic rhinosinusitis or epistaxis.[149] Physical examination may reveal nasal crusting or ulceration, and destructive changes such as septal perforation and saddle nose deformity. Other relatively common head and neck manifestations include chronic otitis, sensorineural hearing loss, gingivitis and oral ulceration. Eye involvement is reported in up to 25 percent with disturbances ranging from scleritis or optic neuritis to retroorbital pseudotumors.[150]

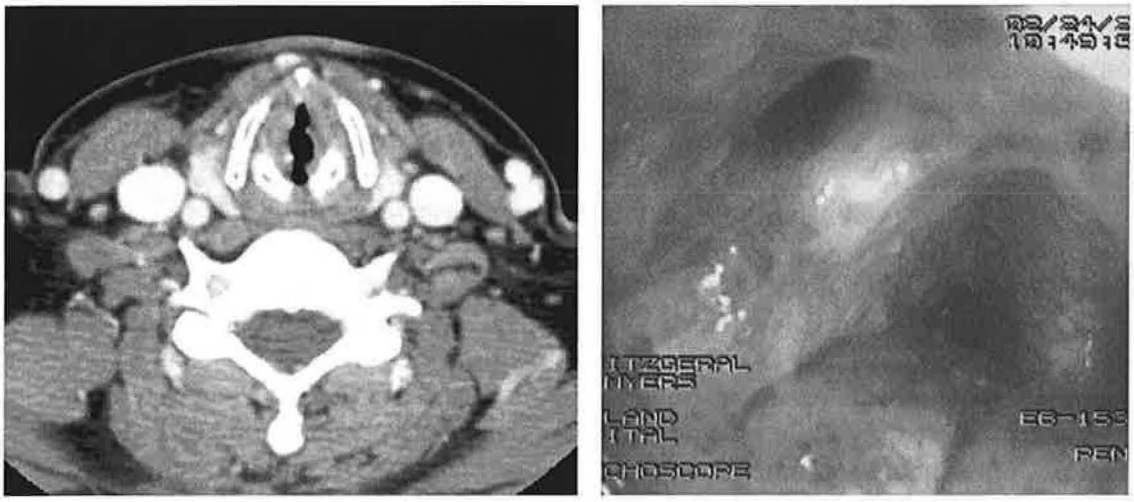
Pulmonary pathology is identified in 65-85 percent of patients with Wegener's granulomatosis.[147, 148, 151] Abnormalities in WG range from single or multiple nodules, masses or cavities, to localized or diffuse airspace disease (figure 10).[4, 152] Diffuse alveolar hemorrhage develops in 5 to10 percent.[147, 153] Subglottic stenosis is seen in 15 percent of WG patients.[154] It presents with dyspnea, hoarseness or weak phonation. Ulcerating tracheobronchitis and bronchial stenosis are other well described complications of this disease (figure 11).[155]

Figure 10. Wegener's granulomatosis. Multiple, bilateral cavitating nodules and masses (left). Right hilar mass enveloping the airways (right).



A minority of Wegener's granulomatosis patients have renal involvement at the time of presentation, but it ultimately develops in 50-90 percent.[147, 148, 151] Urinalysis may reveal proteinuria, hematuria or red blood cell casts reflecting the underlying presence of glomerulonephritis. Early recognition and treatment of WG is essential to avoid considerable morbidity and mortality linked to chronic kidney disease.

Figure 11. Wegener's granulomatosis. CT demonstrating subglottic stenosis (left). Severe ulcerating tracheobronchitis causing stenosis of the right middle and lower lobe bronchi (right).



At some point during the course of their disease, as many as 50 percent of WG patients manifest some type of skin pathology.[156, 157] Palpable purpura is the most commonly recognized lesion in this setting, but vasculitic ulcers, skin nodules, livedo reticularis and signs of digital ischemia (including gangrene) may be seen.

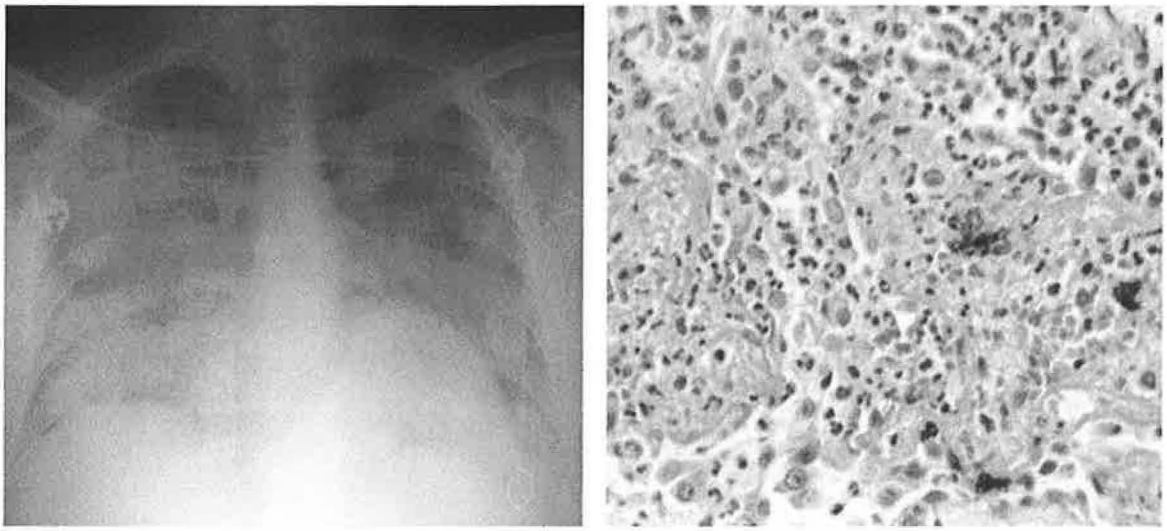
Vasculitic injury to the central or peripheral nervous system occurs in 20 to 50 percent of patients with WG.[158, 159] Mononeuritis multiplex is the most commonly identified neurologic manifestation of ANCA-associated vasculitis, but cranial neuropathies, multifocal cortical strokes, seizures and cerebritis can also occur.

Small vessel vasculitis is a truly systemic disorder, and the gastrointestinal tract is another potential target.[151, 160] In WG, fewer than 15 percent of patients demonstrate symptoms of mesenteric vasculitis such as abdominal pain, diarrhea, or gastrointestinal hemorrhage. Ischemic complications include mucosal ulceration, intestinal perforation and frank bowel infarction.

Microscopic polyangiitis shares many of these same clinical features, with some notable exceptions. Almost all patients with MPA develop renal disease, and it is usually evident at the time of first presentation.[161] Constitutional and musculoskeletal complaints are very common, and the skin is affected in approximately 50 percent of patients, usually in the form of palpable purpura. MPA affects the lung less frequently, perhaps 30 percent of the time. When the lung is involved, it is generally part of a pulmonary-renal syndrome characterized by diffuse alveolar hemorrhage and glomerulonephritis (figure 12).[162, 163] Rarely, patients with chronic or recurrent alveolar hemorrhage may develop pulmonary fibrosis or chronic obstructive lung disease due to necrosis of tethering alveolar walls.[164-166] Cavitating pulmonary nodules (or masses) and destructive head and neck lesions (such as saddle nose deformity, nasal septum perforation, and retroorbital

granuloma) are not a feature of MPA.[167] Mesenteric vasculitis is twice as common in MPA compared to WG, with about 30 percent of subjects being affected.[163]

Figure 12. Diffuse alveolar hemorrhage in a patient with microscopic polyangiitis (left). The patient presented with dyspnea, hemoptysis and acute renal failure. A lung biopsy revealed pulmonary capillaritis consisting of neutrophilic infiltration and fibrinoid necrosis of alveolar walls (right).



Churg Strauss syndrome is characterized by asthma, blood and tissue eosinophilia, and small vessel vasculitis.[168, 169] Patients with CSS often progress over a period of years from a prodromal phase characterized by chronic allergic rhinosinusitis, asthma and nasal polyposis, to a tissue eosinophilia phase.[170] If glucocorticoid therapy is not initiated at this point, further evolution to the vasculitic phase may occur. This is commonly signaled by the development of constitutional symptoms, palpable purpura or vasculitic neuropathy. Peripheral neuropathies, typically mononeuritis multiplex, are noted in two thirds of CSS patients during the course of their illness.[171] The central nervous system may also be affected, and 15 percent of disease-related deaths are due to cerebral hemorrhage.[172] Other commonly affected organs include the lungs, heart, skin, and gastrointestinal tract. In contrast to the other small vessel vasculitides, the kidneys are involved in only about 30 percent of patients, and the disease infrequently progresses to advanced stages of renal failure. Cardiac involvement (eosinophilic myocarditis, coronary arteritis, pericardial effusion) is seen in 40 percent, and is the leading disease-related cause of death in patients with CSS.[169, 172, 173] Lung disease in CSS is fairly distinct among the small vessel vasculitides. Common abnormalities include patchy ground glass or alveolar infiltrates.[174-177] Some patients have peripheral airspace opacities reminiscent of chronic eosinophilic pneumonia (figure 13). Others have lung nodules, but unlike WG, the nodules rarely cavitate. Pleural effusion may be identified in up to 30 percent.[178] Diffuse alveolar hemorrhage is extremely rare in this patient population.[169]

Figure 13. Eosinophilic pneumonia presenting as peripheral airspace disease in a patient with Churg Strauss syndrome.

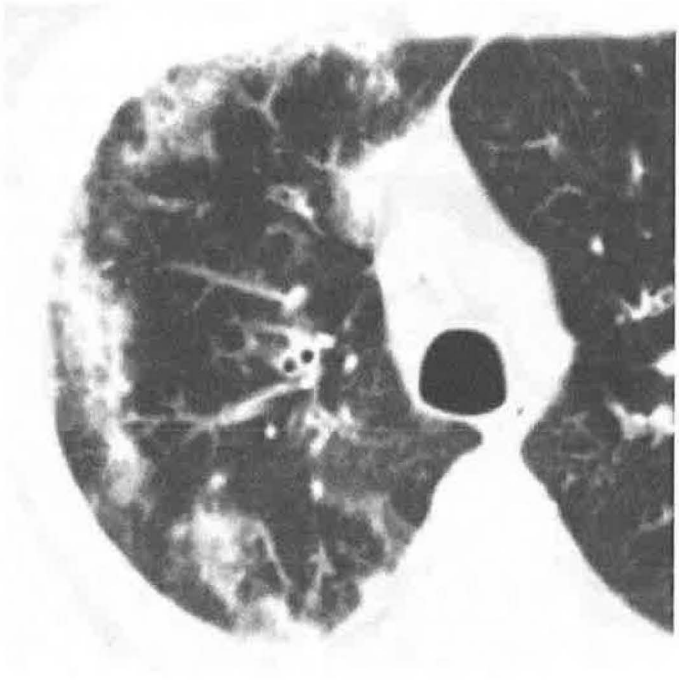


Table 2. Pulmonary manifestations of the common small vessel vasculitidies.

WEGENER'S GRANULOMATOSIS	MICROSCOPIC POLYANGIITIS	CHURG-STRAUSS SYNDROME
Single or multiple nodules, masses or cavities	DAH	Patchy GGO or consolidation
Fixed pulmonary infiltrates	Pulmonary fibrosis	Pulmonary nodules
Tracheal or bronchial stenosis	Emphysema	Pulmonary edema
Mediastinal LA		Pleural or pericardial effusion
DAH		Mediastinal LA
		DAH

DAH = diffuse alveolar hemorrhage, GGO = ground glass opacification, LA = lymphadenopathy

Pathogenesis of Small Vessel Vasculitis

The etiology of WG, MPA and CSS is not known, but anti-neutrophil cytoplasmic antibodies play a central role in the pathogenesis of these disorders.[179-182] Local or systemic infection results in the release of proinflammatory cytokines like tumor necrosis factor. These substances prime neutrophils, and other effector cells, making them susceptible to activation by ANCA.[180] ANCA-binding triggers a respiratory burst, neutrophil degranulation and the production of proinflammatory cytokines.[183-185] ANCA also activate endothelial cells and upregulate the expression of adhesion molecules, facilitating the interaction between inflammatory cells and the vascular surface.[186, 187] ANCA also cause primed neutrophils to undergo dysregulated apoptosis. These cells fail

to express a key consumption signal for scavenging phagocytes. The persistence of dying cells within tissues aggravates inflammation, and may actually result in the development of autoimmunity.[188-191] Self-reactive T cell populations recognizing PR3 and MPO have also been identified in the setting of small vessel vasculitis.[192-194] These lymphocytes assist B cells with ANCA production, and also participate in direct cell-mediated cytotoxicity.[195]

Histopathology of Small Vessel Vasculitis

Lung biopsies in small vessel vasculitis may reveal a variety of histologic patterns. When diffuse alveolar hemorrhage is present, pulmonary capillaritis is the usual finding.[196, 197] This lesion consists of neutrophils infiltrating the interstitial space and enveloping pulmonary capillaries. The release of enzymes and toxic oxygen species from neutrophils causes fibrinoid necrosis of alveolar septae, allowing erythrocytes to spill into the airspaces. Nodules, cavities or focal infiltrates related to WG show a combination of vasculitis, geographic necrosis, and granulomatous inflammation.[198] CSS patients may demonstrate simple eosinophilic pneumonia, or necrotizing vasculitis and granulomatous inflammation along with infiltration by eosinophils.[75, 199] Granulomas are absent from biopsy specimens in MPA. Renal biopsies in patients with these disorders rarely reveal vasculitis. Instead, they demonstrate focal, segmental, necrotizing and crescentic glomerulonephritis.[200] What distinguishes these disorders from lupus or Goodpasture's syndrome is the lack of significant immune deposits within the glomerulus (pauci-immune glomerulonephritis).

Treatment of Small Vessel Vasculitis

Cytotoxic agents and corticosteroids enhance survival and ameliorate organ dysfunction in patients with small vessel vasculitis.[201] Daily, oral cyclophosphamide is preferred for induction of disease remission in patients with multisystem involvement or life-threatening disease.[202] In patients who are less acutely ill, methotrexate is a viable option.[203, 204] After 3 to 6 months of treatment with cyclophosphamide, patients can usually be switched to a less toxic maintenance regimen based on azathioprine or methotrexate.[205] Fewer than half of CSS patients can be managed with corticosteroids alone.[206] Patients with significant cardiac, renal, mesenteric or central nervous system involvement should receive concomitant cytotoxic agents. Biological therapies, such as rituximab or infliximab, can be considered in small vessel vasculitis patients who are intolerant of, or refractory to, conventional immunosuppression.[207-209]

Other Small Vessel Vasculitides

Isolated pulmonary capillaritis and diffuse alveolar hemorrhage may occur without evidence of systemic vasculitis.[210] Such patients may or may not express ANCA. This may simply be a lung-limited form of microscopic polyangiitis. Henoch-Schönlein purpura is a form of vasculitis associated with IgA immune complex deposition.[211] It is best known for producing renal, cutaneous, intestinal and articular symptoms. It is also rarely associated with pulmonary capillaritis and diffuse alveolar hemorrhage.[197, 212]

Goodpasture's syndrome is associated with IgG deposits along basement membranes of the lung and kidney. This produces a characteristic pattern of linear immunofluorescence. In most cases, it produces bland pulmonary hemorrhage, meaning no abnormalities are seen on routine histologic stains. However, capillaritis may be seen.[196, 213, 214] The antiphospholipid antibody syndrome is another recognized cause of pulmonary capillaritis.[215, 216]

Secondary Vasculitis

Pulmonary vasculitis is an occasional complication of drug use, infection and rheumatologic disease. Propylthiouracil is the best known drug associated with the development of ANCA-associated systemic vasculitis.[217, 218] Pulmonary capillaritis and alveolar hemorrhage are also seen in the retinoic acid syndrome.[219] Hepatitis B virus infection may result in the development of PAN, while cryoglobulinemic vasculitis is a sequela of hepatitis C virus infection.[220] This is a rare cause of diffuse alveolar hemorrhage.[221] Certain bacterial pathogens including *Legionella*, *Pseudomonas* and *Staphylococcus* species are known to invade, inflame and destroy blood vessels in the lung.[222, 223] The angioinvasive fungi, Aspergillus and Mucor, may cause pulmonary infarction as a result of vascular occlusion, or massive bleeding due to rupture of mycotic pulmonary arterial aneurysms (figure 14).[224] *Dirofilaria immitis*, the dog heartworm, may be transferred to humans through the bite of mosquitos. The organisms are not viable within human hosts, but they lodge in peripheral pulmonary vessels and incite a granulomatous vasculitis leading to tissue infarction (pleural-based infiltrates or nodules).[225] *Pneumocystis jiroveci* infection is another rare cause of pulmonary vasculitis.[226]

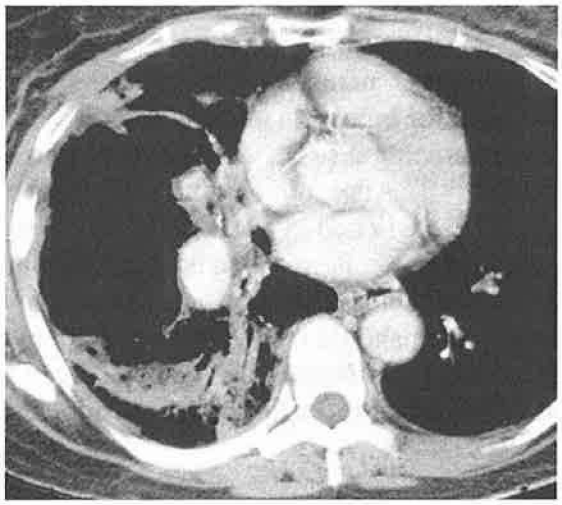


Figure 14. Mycotic aneurysm of the right lower lobe pulmonary artery in a patient with mucormycosis. The aneurysm is contained within a large region of parenchymal necrosis.

Collagen vascular disease is a well recognized cause of pulmonary capillaritis and diffuse alveolar hemorrhage.[197, 216] Systemic lupus erythematosus is responsible for most of these cases.[227] Approximately two percent of lupus patients develop DAH at some time during the course of the illness.[228] Rheumatoid arthritis, mixed connective tissue disease, polymyositis and the related anti-synthetase antibody syndrome are other reported causes.[229-231] Pulmonary vasculitis was seen in five of 65 polymyositis patients in a large autopsy series.[230] Vasculitis affecting the medium and large pulmonary arteries is also a potentially reversible cause of pulmonary hypertension in rheumatoid arthritis.[232, 233] It is important to consider this diagnosis, particularly when pulmonary hypertension develops rapidly in patients with an elevated sedimentation rate, rheumatoid nodules and erosive joint changes. Vasculitic

skin ulcers and peripheral neuropathies are other clues to the presence of rheumatoid vasculitis. Systemic lupus erythematosus patients may also occasionally exhibit pulmonary hypertension which is responsive to immunosuppression, suggesting an underlying inflammatory vascular process.[234]

Summary

Vasculitis in the lung has numerous etiologies and several distinct clinical presentations. Patients with pulmonary vasculitis may complain of constitutional symptoms, chest pain, dyspnea or hemoptysis. Possible radiographic patterns include localized or diffuse infiltrates, nodules, cavities, pulmonary artery enlargement and focal oligemia. Infections, malignancies, and connective tissue disorders can produce similar findings, and are significantly more common. Consequently, a high index of suspicion is required to avoid lengthy and dangerous delays in diagnosis.

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