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Pulmonary Involvement in Systemic Vasculitides

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Pulmonary involvement in systemic vasculitides may manifest as lung hemorrhage, parenchymal necrosis, pulmonary angiitis, and granulomatous disease (Display 70-1).[1–4] The term "pulmonary angiitis" literally means "inflammation of blood vessels in the lung," irrespective of the cause, and leads to destruction of vessel walls, thrombosis, and ischemic injury to the tissue served by the affected blood vessels. The term "pulmonary granulomatosis" refers to inflammatory changes in the lung parenchyma characterized by clusters of lymphocytes, plasma cells, and histiocytes, with or without multinucleate giant cells and tissue necrosis. A definite diagnosis of pulmonary vasculitis requires histologic documentation of the specific lesion, and for this purpose open lung biopsies are infinitely more useful than transbronchial and needle biopsies.

Pulmonary involvement in major types of systemic vasculitis, with the exception of pulmonary vasculitis in collagen-vascular disease (see Chap. 67), is discussed in this chapter. Pulmonary angiitis and pulmonary granulomatosis are discussed in Chapters 68 and 69. In general, pulmonary involvement in systemic vasculitis occurs relatively infrequently, but when present, it is an unfavorable prognostic indicator of the underlying disease.[5,6]

POLYARTERITIS NODOSA

Periarteritis or polyarteritis nodosa (PAN), as described originally by Kussmaul and Maier more than 125 years ago, is a systemic necrotizing vasculitis of medium-sized and small arteries.[7] The vasculitis in PAN is characteristically focal and segmental in distribution, and both active and healing lesions often coexist in the same patient and in the same vascular bed. Virtually any organ in the body may be affected, though not necessarily in a uniform manner.

It is a common misconception that the lungs are spared in PAN.[8] Pulmonary involvement in PAN is a clinically distinct subgroup of systemic vasculitis.[3] Two earlier studies from the Mayo Clinic, in 1949 and 1963, reported 28% and 32%, respectively, of PAN patients with involvement of the lung.[9,10] These statistics are remarkably similar to the 29% pulmonary involvement reported by Rose and Spencer in 1957 in their classic study of 111 autopsy cases of PAN.[11] Many of the PAN cases with pulmonary involvement continue to be misclassified as polyangiitis overlap syndrome by some investigators,[4,8,12] or have been

DISPLAY 70-1. CLASSIFICATION OF PULMONARY VASCULITIS

Vasculitis of Known Cause Confined to the Lungs

Infective vasculitis (*i.e.*, bacterial, fungal, viral, and parasitic)
Reactive vasculitis to embolic material (*e.g.*, cotton, gauze, talc)
Vasculitis of pulmonary hypertensive vascular disease

Vasculitis of Unknown Cause With Lung as Primary Target Organ (Pulmonary Angiitis and Granulomatosis)

Wegener granulomatosis, classic and limited forms
Allergic granulomatosis and angiitis (Churg-Strauss syndrome)
Necrotizing sarcoid granulomatosis

Systemic Vasculitis That May Involve the Lungs

Polyarteritis nodosa
Rheumatoid arthritis
Systemic lupus erythematosus
Systemic sclerosis (scleroderma) and CREST syndrome
Dermatopolymyositis
Mixed connective tissue disease
Hypersensitivity vasculitis
Behçet disease or Hughes-Stovin syndrome
Takayasu arteritis
Disseminated and isolated giant cell angiitis

reclassified as allergic angiitis and granulomatosis (*i.e.*, Churg-Strauss syndrome).[13]

Pulmonary PAN, like its systemic counterpart, has a wide spectrum of histopathologic expressions, including vasculitis with fibrinoid necrosis (Fig. 70-1), polymorphous necrotizing vasculitis (Fig. 70-2), vasculitis with a hint of granulomatous features (Fig. 70-3), and healing or healed vasculitis with intimal fibrosis (Fig. 70-4). Pulmonary PAN can be distinguished from Churg-Strauss syndrome by the absence of tissue eosinophilia or extravascular granulomas,[14] and from Wegener granulomatosis by the absence of geographic-pattern parenchymal necrosis or necrotizing granulomatosis with giant cells.[2] On the other hand, pulmonary PAN may be indistinguishable histologically from rheumatoid vasculitis and from small vessel vasculitis of systemic lupus erythematosus involving the lungs.[15–19]

In a recent autopsy investigation of ten patients with PAN by Matsumoto and colleagues,[19a] seven patients (70%) had evidence of pulmonary vasculitis, but the vasculitis was restricted to bronchial arteries. These authors also noted that six patients (60%) had diffuse alveolar damage (DAD) and interstitial fibrosis; five of their patients died of respiratory failure due to DAD.[19a]

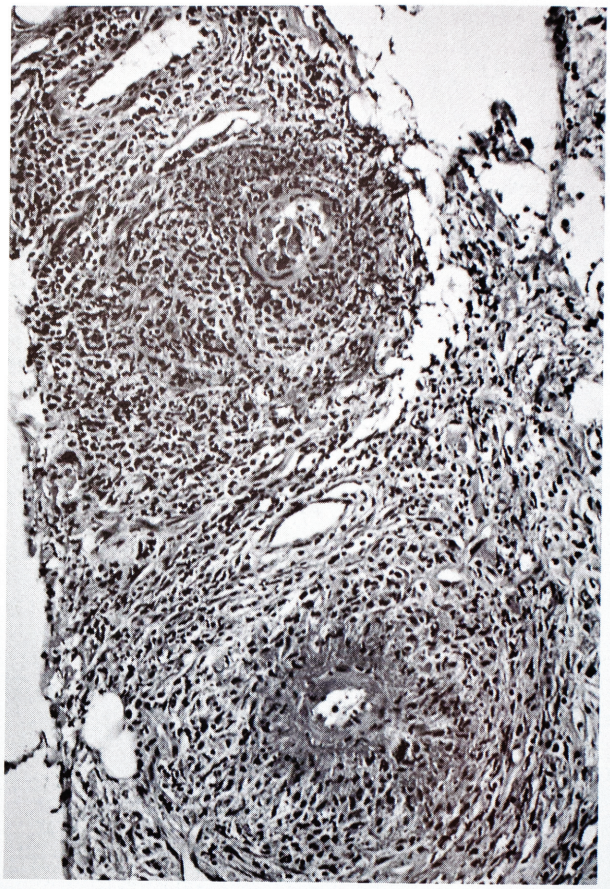

FIGURE 70-2. Polyarteritis nodosa involving the lung. Polymorphous, necrotizing vasculitis–type lesion. (H & E stain; low magnification.)

HYPERSENSITIVITY VASCULITIS

Hypersensitivity vasculitis occurs in association with a variety of different underlying disorders (Display 70-2), and there is ample clinical and experimental evidence pointing to an immune complex mechanism in the pathogenesis of this vasculitis.[20–25] Hypersensitivity vasculitis typically involves the small blood vessels—small arteries, arterioles, and venules—with karyorrhexis of the leukocytic infiltrates, fibrin deposition with vessel wall necrosis, and erythrocyte diapedesis, thus earning the name "leukocytoclastic vasculitis."[21] In sequential biopsies, the character of cellular infiltrates changes progressively from a predominantly polymorphonuclear type at the onset to a predominantly lymphocytic/mononuclear variety over a 5-day period.[22,24]

In most instances, cutaneous lesions dominate the clinical picture of hypersensitivity vasculitis, but virtually any organ system can be affected.[3] Hypersensitivity vasculitis may involve the lungs for the following reasons: the lung has an extensive vascular network; sensitizing antigens have easy access to the lung through

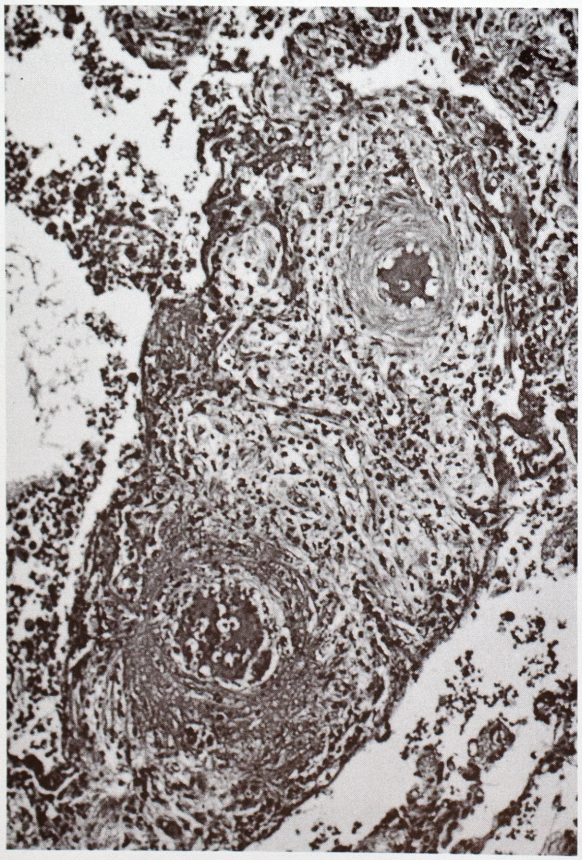

FIGURE 70-1. Polyarteritis nodosa involving the lung. Fibrinoid necrosis–type vascular lesion with dense lymphocytic and neutrophilic infiltrates. (H & E stain; low magnification.)

DISPLAY 70-2. ETIOLOGIC SUBGROUPS OF HYPERSENSITIVITY VASCULITIS

Serum sickness and serum sickness–like reactions
Anaphylactoid purpura (Schönlein-Henoch syndrome)
Related to a preceding infection
Drug or chemical induced
Associated with essential mixed cryoglobulinemia
Associated with malignancies
Associated with other primary disorder
Associated with environmental diseases (*e.g.*, toxic oil syndrome and L-tryptophan–induced eosinophilia-myalgia syndrome)

Adapted from Hunninghake GW, Fauci AS. Pulmonary involvement in the collagen vascular diseases. Am Rev Respir Dis 1979;119:471.

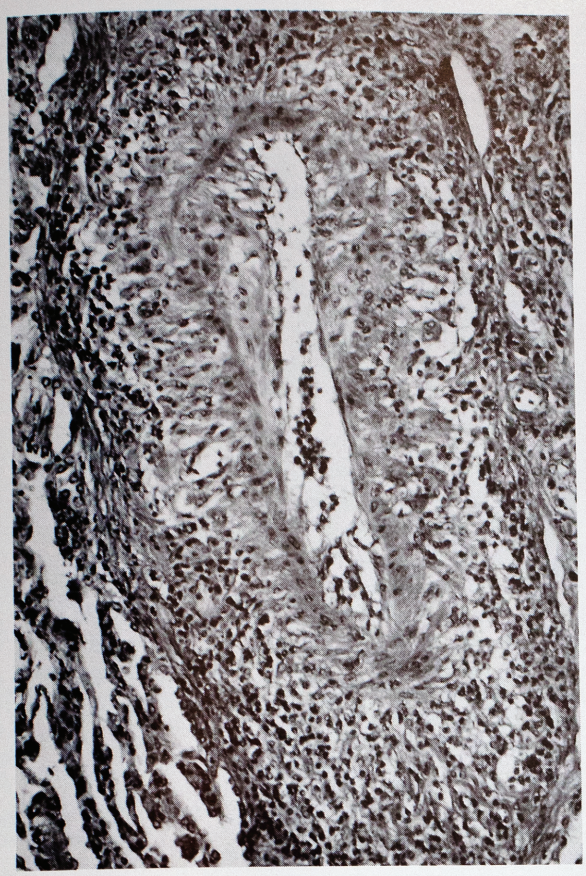

FIGURE 70-3. Polyarteritis nodosa involving the lung with a hint of granulomatous features. (H & E stain; low magnification.)

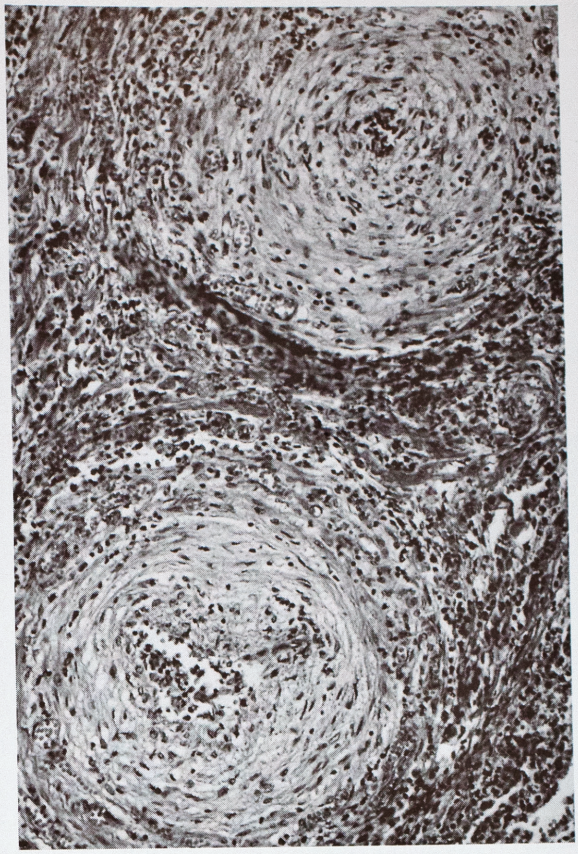

FIGURE 70-4. Polyarteritis nodosa involving the lung. Healing vasculitis with intimal fibrous proliferation (*i.e.*, onion-skinning) and marked luminal occlusion. (H & E stain; low magnification.)

inhalation; and there are large numbers of vasoactive cells in the lung.[4,26]

Nevertheless, compared with the skin and systemic organs, the lungs are an infrequent site of hypersensitivity vasculitis, even though up to 25% of patients may have clinical evidence of pulmonary disease.[26] When present, pulmonary lesions may manifest clinically and radiologically as diffuse, patchy, or nodular infiltrates. Pulmonary hemorrhage may reflect the presence of alveolar capillaritis, which is an expression of microvascular injury from diverse causes.[27,28]

Pulmonary involvement in Schönlein-Henoch syndrome is uncommon, and the reported incidence ranges from 0 to 6.5% in series without histologic documentation.[29,30] However, pulmonary involvement can be a serious complication of Schönlein-Henoch syndrome, including fatal lung hemorrhage.[31] Histologically, in addition to alveolar capillaritis (Fig. 70-5), pulmonary hypersensitivity vasculitis manifests as a necrotizing small vessel vasculitis, usually but not always with a prominent eosinophil infiltrate (Fig. 70-6).

BEHÇET DISEASE AND HUGHES-STOVIN SYNDROME

Although it was originally described by the triple symptom complex of recurrent oral and genital ulceration and relapsing iritis/uveitis,[32] Behçet disease is now recognized as a systemic disorder that may involve virtually any organ of the body.[33–35] Large and small vessel vasculitis or arterial and venous thromboses are common.[36] In the lungs, Behçet disease manifests as thromboangiitis of pulmonary arteries with aneurysm formation; the aneurysms may rupture, resulting in life-threatening hemoptysis.[37–39] Clinically and pathologically, pulmonary involvement in Behçet disease is indistinguishable from the Hughes-Stovin syndrome, which is characterized by multiple pulmonary aneurysms with peripheral venous thrombosis.[40,41] Pulmonary manifestations have been described in more than 80 patients with Behçet disease, about 50 of whom presented with the characteristic pulmonary thromboangiitis.[33–39]

TAKAYASU ARTERITIS

Takayasu arteritis is predominantly an inflammatory disease of large elastic arteries and occurs infrequently in muscular arteries.[42,43] Although most of the cases have been reported from the Orient and Southeast Asia, India, Africa, and South America, the disease has a worldwide distribution. It affects women in the reproductive age group about six to eight times more often than men.[44–50]

The histopathology of Takayasu arteritis varies in different stages of the disease. In the early or active phase of the disease, it is a granulomatous arteritis, indistinguishable from extracranial large vessel giant cell (*i.e.*, temporal) arteritis. The chronic or end-stage lesion is characterized by obliterative fibrosis of the vessel

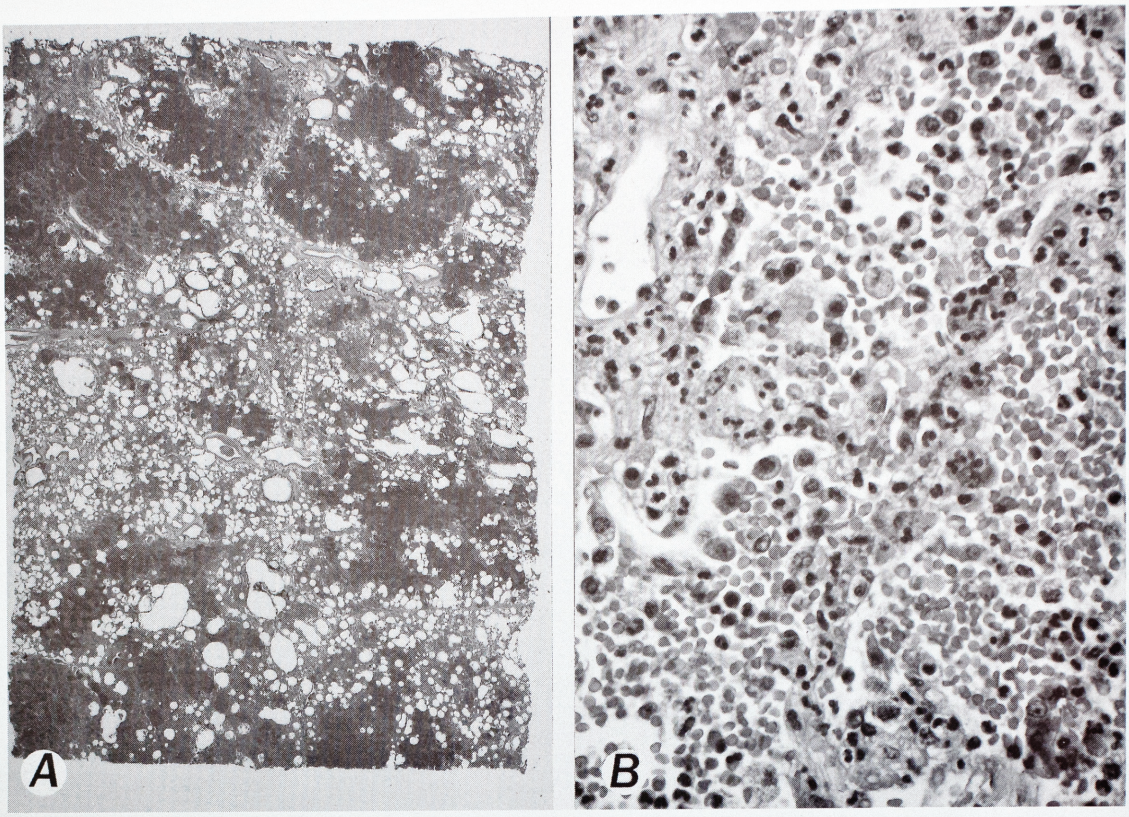

FIGURE 70-5. Pulmonary involvement in Schönlein-Henoch syndrome. (**A**) Diffuse alveolar hemorrhage due to capillaritis. (H & E stain; low magnification.) (**B**) Alveolar capillaritis with extravasated erythrocytes and hemosiderin-laden macrophages. (H & E stain; intermediate magnification.)

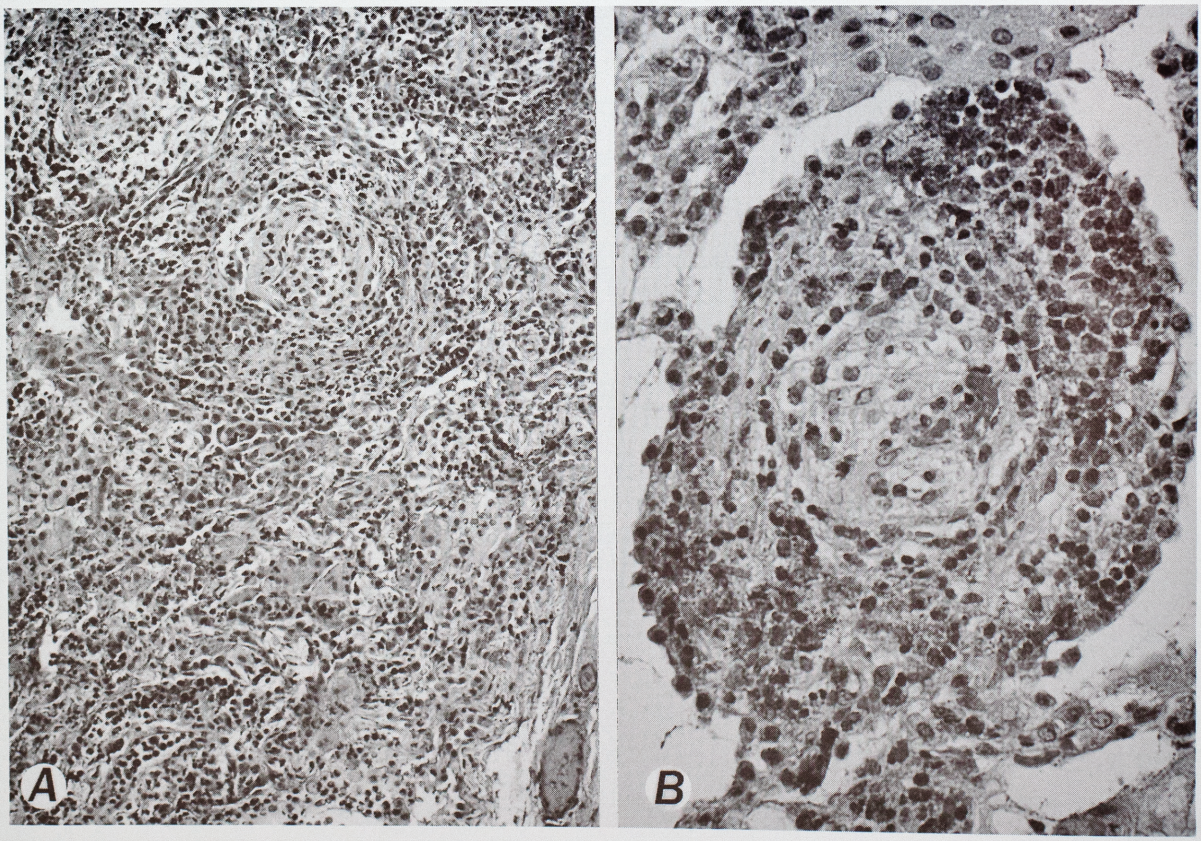

FIGURE 70-6. (**A**) Low-power and (**B**) intermediate-power photomicrographs of hypersensitivity vasculitis (Schönlein-Henoch syndrome). Prominent eosinophilic infiltrate can be seen (**B**). (H & E stains.)

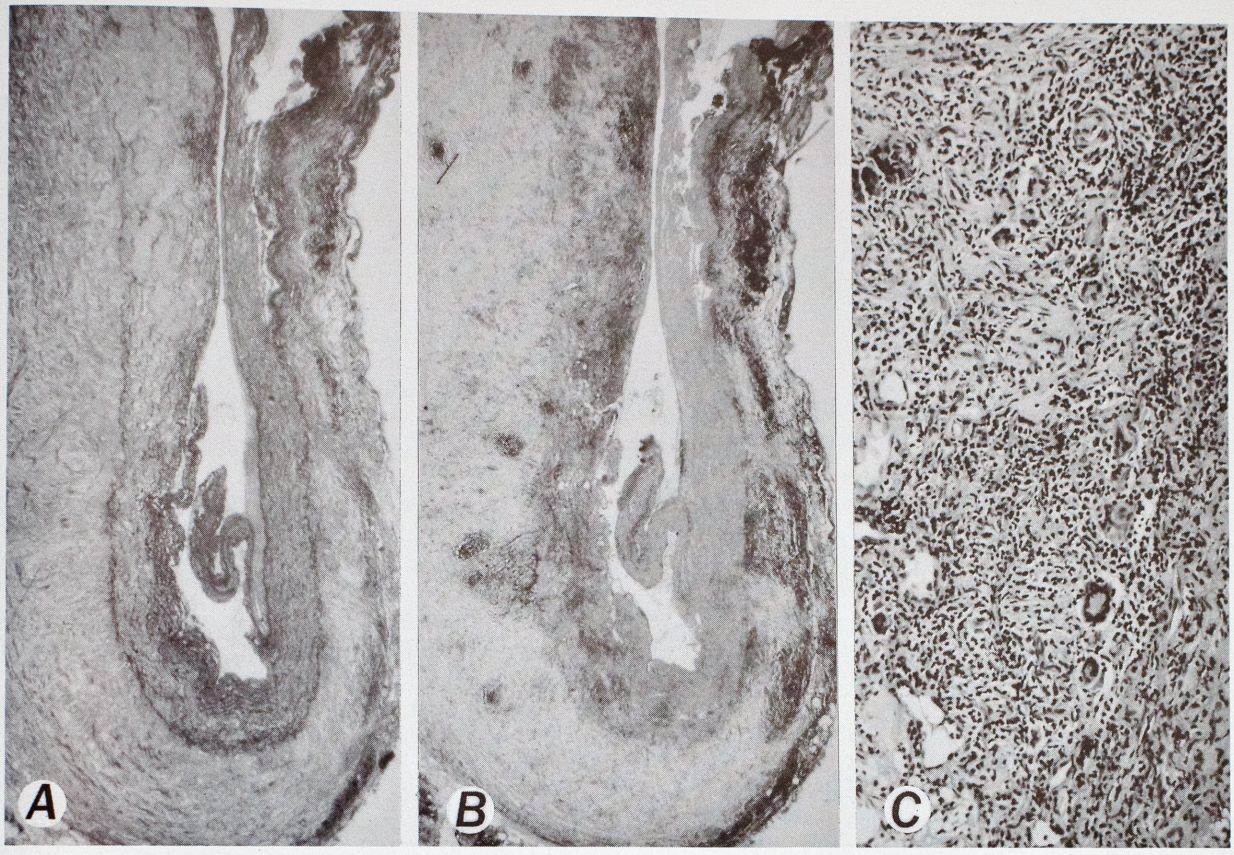

FIGURE 70-7. (**A**) Elastin-stained and (**B**) hematoxylin-eosin–stained sections of a large pulmonary artery in giant cell arteritis (panoramic views). (**C**) Close-up view of the infiltrate with numerous giant cells. (H & E stain; low magnification.)

wall with scanty inflammatory cell infiltrate.[43,47,49] Aneurysmal disease, aortic insufficiency, and renovascular hypertension are common; cerebrovascular manifestations usually result from involvement of the aortic arch and the carotid arteries.[43]

Pulmonary artery involvement by Takayasu arteritis has been reported in as many as 45% to 50% of patients, but the diagnosis is often made angiographically without histologic documentation of the disease.[48,50–53] Most patients with pulmonary involvement are asymptomatic or complain of nonspecific shortness of breath and pleuritic pain, but symptomatic pulmonary hypertension has also been reported in some patients.[48,51] To date, there have been two reports of successful surgical repair of pulmonary artery stenosis in Takayasu arteritis.[52,53] The pulmonary arterial lesion is identical to systemic giant cell arteritis (Fig. 70-7).

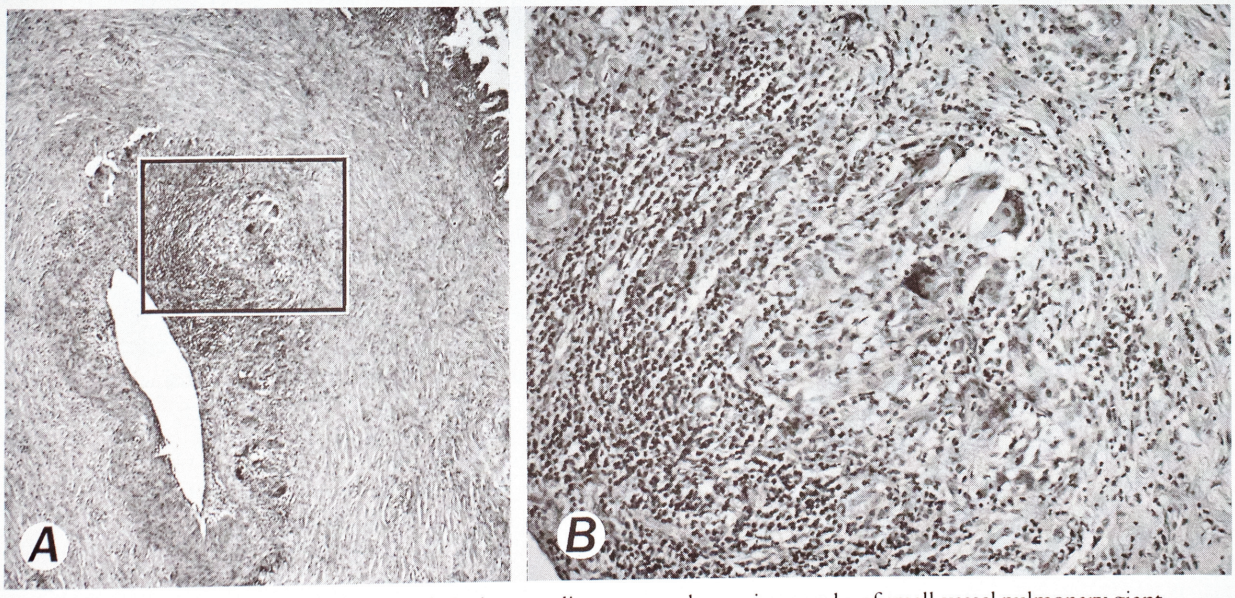

FIGURE 70-8. (**A**) Low-power and (**B**) intermediate-power photomicrographs of small-vessel pulmonary giant cell angiitis. (H & E stains.)

DISSEMINATED AND ISOLATED GIANT CELL ANGIITIS

Disseminated and isolated giant cell angiitis involving large and small pulmonary arteries (Fig. 70-8) is one of the rarest forms of inflammatory vascular disease known in medicine; to date, there have been only seven such cases reported in the English-language literature.[54–59] These seven patients were five men and two women, and their ages ranged from 33 to 77 years.[55,56] Not surprisingly, the giant cell pulmonary angiitis was clinically unsuspected in every case; the diagnosis was made in resected specimens of four patients who underwent a surgical operation,[55–57,59] and at autopsy in three patients.[54,58] In retrospect, the pulmonary giant cell angiitis was clinically significant in all seven patients and not an incidental finding.

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