pathogenesis. Following immunosuppression, a rising PR3-ANCA titer is often a harbinger of relapse; most patients in remission have a negative test or falling titers.

MORPHOLOGY

Upper respiratory tract lesions range from inflammatory sinusitis with mucosal granulomas to ulcerative lesions of the nose, palate, or pharynx, rimmed by **granulomas with geographic patterns of central necrosis and accompanying vasculitis** (Fig. 11-27*B*). The necrotizing granulomas are surrounded by a zone of proliferating fibroblasts associated with giant cells and leukocytic infiltrate, reminiscent of mycobacterial or fungal infections. Multiple granulomas can coalesce to produce radiographically visible nodules that can also cavitate; late stage disease may be marked by extensive necrotizing granulomatous involvement of the parenchyma (Fig. 11-27*C*), and alveolar hemorrhage may be prominent. Lesions may ultimately undergo progressive fibrosis and organization.

A spectrum of renal lesions can be seen (Chapter 20). In early stages, glomeruli exhibit only focal necrosis with isolated capillary loop thrombosis (**focal and segmental necrotizing glomerulonephritis**); there is minimal parietal cell proliferation in the Bowman capsule. More advanced glomerular lesions are characterized by diffuse necrosis with exuberant parietal cell proliferation resulting in crescent formation (**crescentic glomerulonephritis**).

Clinical Features. Males are affected more often than females, at an average age of about 40 years. Classic features include persistent pneumonitis with bilateral nodular and cavitary infiltrates (95%), chronic sinusitis (90%), mucosal ulcerations of the nasopharynx (75%), and evidence of renal disease (80%). Other features include rashes, myalgias, articular involvement, neural inflammation, and fever. Left untreated, the disease is usually rapidly fatal, with 80% mortality within 1 year. Treatment with steroids, cyclophosphamide, and more recently TNF antagonists have turned this formerly fatal condition into a chronic relapsing and remitting disease.

Thromboangiitis Obliterans (Buerger Disease)

Thromboangiitis obliterans (Buerger disease) **is characterized by segmental, thrombosing, acute and chronic inflammation of medium-sized and small arteries, principally the tibial and radial arteries, with occasional secondary extension into the veins and nerves of the extremities.** It is a distinctive disease that often leads to vascular insufficiency, typically of the extremities. It occurs almost exclusively in heavy cigarette smokers, usually before age 35.

Pathogenesis. The strong relationship with cigarette smoking may stem from either a direct idiosyncratic endothelial cell toxicity caused by some component of tobacco, or an immune response to components of tobacco smoke that modify host vascular wall proteins. Most patients have hypersensitivity to intradermally injected tobacco extracts, and their vessels exhibit impaired endothelium-dependent vasodilation when challenged with acetylcholine. There is an increased prevalence in certain ethnic groups (Israeli, Indian subcontinent, Japanese) and an association with particular HLA haplotypes.

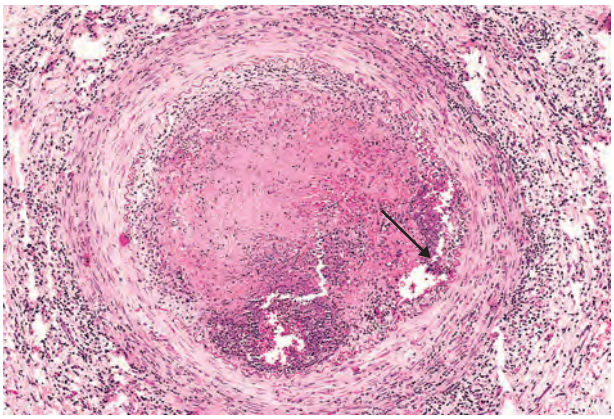

Figure 11-28 Thromboangiitis obliterans (Buerger disease). The lumen is occluded by a thrombus containing abscesses *(arrow)*, and the vessel wall is infiltrated with leukocytes.

MORPHOLOGY

Thromboangiitis obliterans is characterized by a **focal acute and chronic vasculitis of small- and medium-sized arteries,** predominantly of the extremities. On histology, there is acute and chronic inflammation, accompanied by luminal thrombosis. The thrombus can contain small **microabscesses** composed of neutrophils surrounded by granulomatous inflammation (Fig. 11-28); the thrombus may eventually organize and recanalize. The inflammatory process extends into contiguous veins and nerves (rare with other forms of vasculitis), and with time all three structures can be encased in fibrous tissue.

Clinical Features. Early manifestations include cold-induced Raynaud phenomenon (see later), leg pain induced by exercise that is relieved on rest (*intermittent claudication*), instep foot pain induced by exercise (*instep claudication*), and a superficial nodular phlebitis (venous inflammation). The vascular insufficiency of Buerger disease tends to be accompanied by severe pain—even at rest—undoubtedly due to the neural involvement. Chronic extremity ulcerations develop, progressing over time (occasionally precipitously) to frank gangrene. Smoking abstinence in the early stages of the disease can often ameliorate further attacks; however, once established, the vascular lesions typically do not respond to smoking abstinence.

Vasculitis Associated with Other Noninfectious Disorders

Vasculitis resembling hypersensitivity angiitis or classic polyarteritis nodosa can sometimes be associated with other disorders, such as rheumatoid arthritis, systemic lupus erythematosus, malignancy, or systemic illnesses such as mixed cryoglobulinemia, antiphospholipid antibody syndrome (Chapter 4), and Henoch-Schönlein purpura. *Rheumatoid vasculitis* occurs predominantly in the setting of long-standing, severe rheumatoid arthritis and usually affects small- and medium-sized arteries, leading to visceral infarction; it may also cause a clinically significant aortitis. Identifying the underlying pathology has therapeutic significance. For example, although