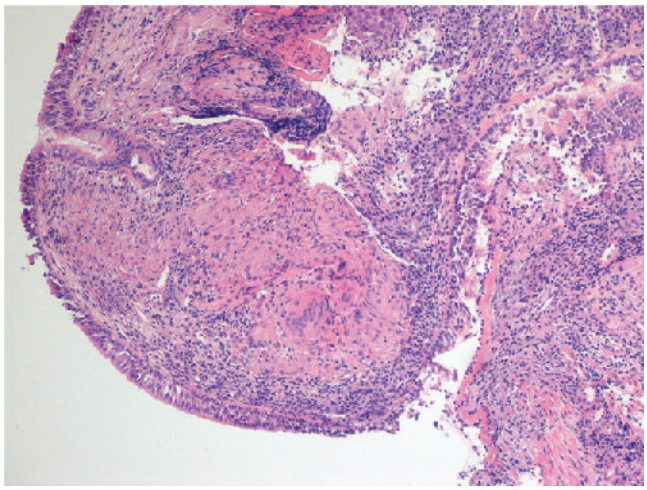

FIGURE 17-5 Subepithelial noncaseating granuloma, which is characteristic of sarcoidosis, from an endobronchial biopsy.

presentation and a mutation in the butyrophilin-like 2 gene *(BTNL2)*, a possible immunoregulatory gene, have been associated with susceptibility to sarcoidosis. A single causative antigen initiating granuloma formation may not exist, and sarcoidosis instead may represent a stereotypical inflammatory reaction to various antigens in a genetically susceptible host.

Sarcoidosis is associated with abnormal immune function as evidenced by cutaneous anergy and as exhibited in lung by an increased ratio of $CD4^+$ to $CD8^+$ T lymphocytes and increased concentrations of pro-inflammatory cytokines such as interferon-γ, interleukin-12, and tumor necrosis factor-α (TNF-α). These derangements can be detected in the bronchoalveolar lavage (BAL) fluid and are consistent with an imbalance in the production of type 1 (T_H1) and type 2 (T_H2) helper T-cell cytokines, favoring the production of the former and promoting persistent inflammation. Sarcoidosis may occur in the setting of immunomodulatory therapy, especially with interferon alfa, or the immune reconstitution syndrome, occurring after initiation of antiretroviral therapy for human immunodeficiency virus (HIV) infection, highlighting the role of immune imbalances in the disorder.

Clinical Presentation

The clinical presentation of patients with sarcoidosis varies. The disease is frequently detected incidentally on routine chest radiographs of asymptomatic individuals. Others may have diverse acute or chronic symptoms. Patients may develop well-described acute syndromes such as Löfgren syndrome, which includes erythema nodosum, fever, arthritis, and hilar adenopathy, or uveoparotid fever (i.e., Heerfordt's syndrome), which exhibits the triad of uveitis, parotitis, and facial nerve palsy. Both syndromes are associated with better outcomes than for other clinical presentations of sarcoidosis.

In many cases, symptoms are vague and chronic, and they may include systemic symptoms such as low-grade fevers, fatigue, night sweats, or joint pains. Respiratory manifestations, including shortness of breath, wheezing, dry cough, and chest pain, occur in one third to one half of patients. Skin manifestations include erythema nodosum, plaques, nodules, and lupus pernio, a violaceous, often disfiguring, nodular lesion of the nose and cheeks. Ocular symptoms are also common, and the onset of uveitis may eventually lead to the diagnosis of sarcoidosis when granulomatous extraocular organ involvement is uncovered. Neurosarcoidosis may manifest with cranial nerve palsies or with headache in the setting of lymphocytic meningitis. Sarcoidosis can involve the heart, resulting in a cardiomyopathy. Arrhythmias and sudden cardiac death can occur as a result of the disruption of the conducting system by granulomatous infiltration. Pulmonary hypertension may result from pulmonary fibrosis or directly from granulomatous vasculitis.

TABLE 17-2 RADIOGRAPHIC STAGING OF SARCOIDOSIS

STAGE	RADIOGRAPHIC FINDINGS
0	Normal radiograph
I	Adenopathy without parenchymal abnormality
II	Adenopathy and parenchymal disease
III	Parenchymal disease without lymphadenopathy
IV	End-stage fibrosis

In 90% of patients, the chest radiograph shows abnormalities that include bilateral hilar adenopathy (E-Fig. 17-2), infiltrates (E-Fig. 17-3), and fibrosis. The radiographic changes characteristic of sarcoidosis have been classified as stages 0 through IV (Table 17-2), but this staging system does not imply a typical chronologic progression. However, stage I patients have a better prognosis for resolution than those with more advanced stages of disease.

As in other ILDs, computed tomography (CT) is more sensitive for the detection of parenchymal abnormalities, and it more clearly demonstrates the extent of mediastinal adenopathy. Parenchymal HRCT findings include nodularity along the bronchovascular bundles emanating from the hila (E-Fig. 17-4). Lung parenchyma involvement in sarcoidosis is more prominent in the upper lobes. Positron emission tomography (PET) or gallium-67 scans may reveal other sites of organ involvement.

Pulmonary function tests show restriction or obstruction. Liver involvement may cause mild elevation of transaminase levels, and cirrhosis and liver failure have been reported, although they are rare. Hypercalcemia and hypercalciuria may be detected and are caused by increased intestinal absorption of calcium as a result of increased conversion of vitamin D to its active form in sarcoid granulomas. Kidney stones may result from the abnormal calcium metabolism. Elevated levels of angiotensin-converting enzyme (ACE) are common but are not specific. The use of ACE levels in the diagnosis or management of sarcoidosis is controversial.

Diagnosis

The diagnosis of sarcoidosis depends on a typical clinical, radiographic, and histologic picture and is a diagnosis of exclusion. Patients with classic syndromes such as the Löfgren syndrome or uveoparotid fever may not require biopsy; however, most patients require tissue biopsy of an affected organ. Tissue samples show noncaseating granulomas, but because this finding is nonspecific, careful attention should be given to ruling out other causes of granulomatous inflammation (e.g., mycobacterial infection) through stains and cultures.