

A. Sarcoidosis

Sarcoidosis is a multisystem disease characterized by the presence of noncaseating granulomas in multiple organs. The trigger factor is presumed to be the inhalation of a yet unidentified antigen (1). Antigen-presenting cells release IL-1, IL-15, IFN- γ , and TFN- α . They recruit activated T_H1 CD4 T cells, which leads to an oligoclonal T-cell alveolitis. Further release of monocyte chemoattractant protein-1 (MCP-1), monocyte inflammatory protein 1 α (MIP-1 α), CXCL10, and IL-16 induces migration of monocytes and T-cell proliferation. The monocytes produce fibrin, fibronectin, TGF- β , IL-3, IFN- γ , and TNF- α and then transform into epithelioid cells. Some of them coalesce to form multinucleate giant cells and form noncaseating (nonnecrotic) epithelioid cell granulomas. IL-4 and IL-6 lead to polyclonal B cell stimulation, which is reflected as hypergammaglobulinemia.

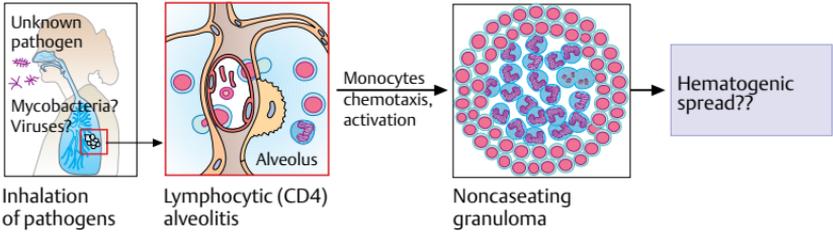
In many cases, the disease is incidentally discovered due to the presence of bilateral enlargement of the mediastinal lymph nodes (bilateral hilar lymphadenopathy) in chest radiograms (4). An acute form of the disease (Loefgren's syndrome) is characterized by bilateral hilar lymphadenopathy, fever, erythema nodosum, and acute arthritis, particularly of the knee and the ankle (2). Bronchoalveolar lavage (BAL) typically reveals the presence of CD4⁺ T-cell alveolitis (3). The BAL fluid often contains up to 10 times as many CD4⁺ T lymphocytes as the peripheral blood because lymphocytes are recruited from the peripheral blood and the skin (anergy to skin antigens) into the lung. In normal individuals, more than 90% of the cells in the BAL fluid are macrophages, and fewer than 1×10^6 lymphocytes are recovered; in sarcoidosis, ten or twenty times more lymphocytes are typically recovered. A decrease in the CD4/CD8 ratio in peripheral blood is also observed. Fever and malaise develop due to increased levels of TNF, IL-1, and IL-6 in serum.

Erythema nodosum, a nongranulomatous inflammation of the subcutaneous tissue, is the most common skin lesion. Eye involvement is common and may range from a harmless conjunctival nodule to blindness as a complication of intermediate and posterior uveitis (see pp. 244, 246). Granulomatous meningitis is a possible manifestation of neurosarcoidosis. Increased intestinal absorption of calcium occurs because the macrophages in the granulomas

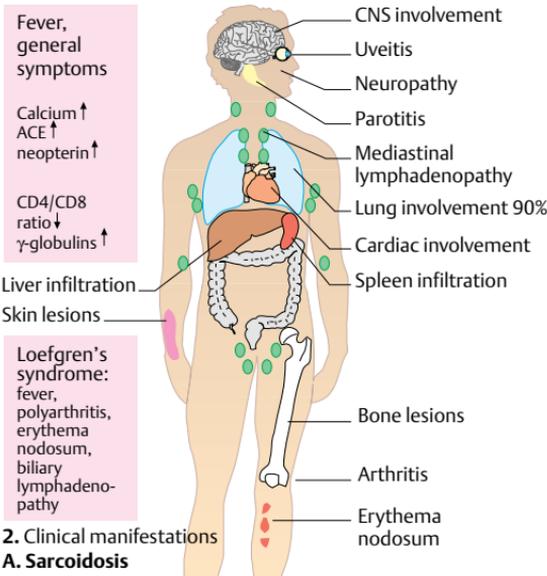
convert 25-hydroxyvitamin D to 1,25-hydroxyvitamin D. Osteolytic bone lesions rarely contribute to hypercalcemia and hypercalciuria. Ventricular tachycardia may occur due to the presence of granulomas in myocardial tissue. Small periportal granulomas or T cell infiltrates exhibiting various degrees of fibrosis are often found in the liver (5). The development of splenic granulomas can cause splenomegaly. The concentration of angiotensin-converting enzyme (ACE) in the serum increases due to the synthesis by granuloma tissue.

B. Idiopathic Pulmonary Fibrosis

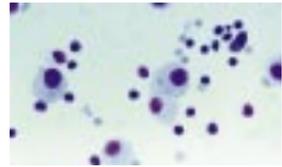
Pulmonary fibrosis may occur in a number of diseases. Hence, idiopathic pulmonary fibrosis (IPF), or cryptogenic fibrosing alveolitis, is a diagnosis of exclusion. Activation of the alveolar macrophages presumably occurs in individuals with a genetic predisposition after contact with a yet unknown pathogen. Viruses or immune complexes are thought to be responsible. T-cell cytokines may also be involved in the activation process. Alveolar macrophages secrete IL-8 and leukotrienes, which recruit and activate neutrophil granulocytes. Granulocytic alveolitis is a typical feature of idiopathic pulmonary fibrosis, whereas lymphocytic alveolitis occurs in sarcoidosis. The alveolar macrophages also secrete fibroblast growth factors, such as TGF- β , insuline-like growth (IGF-1), and platelet-derived growth factor (PDGF). Oxidative processes enable the alveolar macrophages and neutrophils to destroy type I pneumocytes. This induces a compensatory increase in the number of type II pneumocytes, which produce chemotactic and fibrogenic factors. Extracellular matrix deposition occurs. This ultimately leads to the development of fibrotic cicatricial changes, which produce characteristic radiological and histological patterns (honeycomb lung). Corticosteroids have been used to treat this disease, although frequently with disappointing results. Interferon- γ together with corticosteroids may lead to clinical improvement.



1. Pathogenic model



2. Clinical manifestations
A. Sarcoidosis



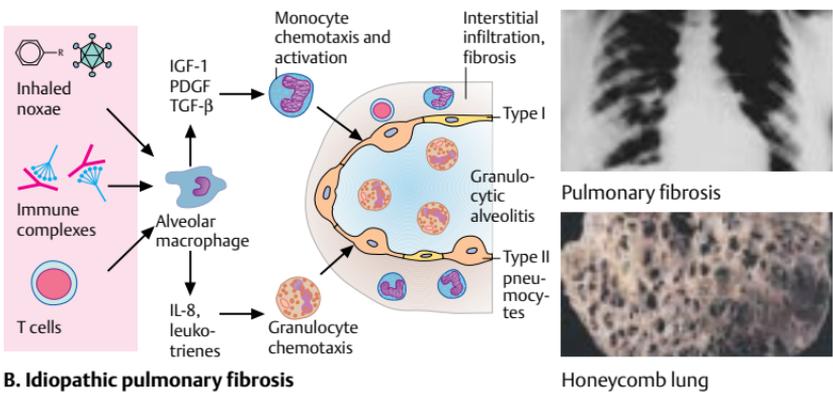
3. BAL



4. Chest radiograph



5. T-cell infiltrate in the liver



B. Idiopathic pulmonary fibrosis