moconiosis consisting predominantly of MDF-type nodules with or without silicotic nodule or massive fibrosis. Classic silicosis is meant in cases where almost all lesions are silicotic nodule. Silicosis and mixed dust pneumoconiosis are distinct entities clinicopathologically (18). Massive fibrosis, active tuberculosis and alveolar proteinosis are more common in cases with silicosis. Mixed dust pneumoconiosis tends to be associated with DIE more frequently.

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Perspectives of cellular sociology in chronic interstitial lung diseases

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The development and outcome of chronic interstitial lung diseases is still subject of intensive scientific investigations. In particular, factors which are related to occurrence and prognosis are still missing. Similar to investigations in lung cancer, the analysis of basic structure elements in combination with the involved inflammatory cell types seems to be appropriate for the characterization of chronic interstitial lung diseases. Therefore, transbronchial lung biopsies taken from patients with chronic interstitial lung diseases were incubated with the following antibodies: CD3, CD2O, macrophage migration inhibitory factor (MIF), galectin-1, galectin-3, galectin-8, CD-34; and the biotinylated substances galectin-1, galectin-3, sarcolectin, and carrier-immobilized cortisone. Cases with various of the following rare interstitial lung diseases were analyzed in relation to the HR-CT findings: sarcoidosis, usual interstitial pneumonia, lymphoid interstitial pneumonia, pulmonary hemosiderosis, carbohydrate deficiency syndrome, systemic lupus erythematodes, pulmonary ossification, alveolar proteinosis, bronchiolitis obliterans, acute and chronic eosinophilic pneumonia, and inflammatory lung reaction due to various cytostatic drug regimes. The expression of binding capacities was measured by use of a semiautomated image analyzing system, and the spatial relation of the binding and nonbinding cells was calculated. The amount of fibrosis was measured by use of Sirius-red stain.

As a result, the expression of the analyzed determinants differs not only in the percentage of specific cells but also in the spatial arrangement. For example, the alveolar spaces of alveolar proteinosis are characterized by rare populations of B-cells and macrophages (and absence of macrophage migration inhibitory factor). Missing presence and binding capacities of MIF were, in addition, noted in sarcoidosis and cytostatic drug reactions. Vascularization was disturbed in cases with usual interstitial pneumonia (UIP) and lymphocytic interstitial pneumonia (LIP), whereas in cases with eosinophilic pneumonia the vascular arrangement was notably preserved. These investigations are derived from similar measurements of structure features and entropy of primary and metastatic lung tumors (1-3), and confirm the practical use of the analysis of tissue structures. In addition, the expression of binding capacities of immobilized sugar-binding substances (lectins) and their antibodies can be used to determine specific interactions of involved inflammatory cells in altered lung parenchyma due to various agents (4-6). Thus, modern image analyzing techniques in combination with immuno- and ligand histochemistry permit detailed insight into the arrangement of various cellular subpopulations and the underlying interstitial and vascular matrix. The response of the idiopathic lung diseases to corticosteroids is related to the amount of irreversible fibrosis (collagen IV) and the expression of binding capacities of cortisone. The spatial arrangement of the different cell types and cells with the different functional states seems to be of importance for the outcome of the various diseases.

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Etiology, pathogenesis and differential diagnosis of lung granulomatosis. An update

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Slowly dissolving or even insoluble particles or organisms generally cause the formation of granulomas in the lung as elsewhere in the body. These might enter the lung by inhalation or by circulation via blood vessels. Living organisms or organic and inorganic particulate matter might cause granuloma formation. This can both be driven and regulated by immune mechanisms or by the older phylogenetic mechanism of phagocytosis and lysosomal degradation, with few or no participating lymphocytes.

The granuloma is defined as a nodular, well-circumscribed inflammatory lesion composed of either histiocytes (histiocytic granuloma), epitheliold and giant cells (epitheliold cell or sarcoid granuloma), Langerhans' cells (Langerhans' cell granulomatosis, histiocytosis X), foreign body giant cells (toreign body granuloma), or fibroblasts with hyalinization (hyalinizing granuloma), respectively. These granulomas can have an additional mixture of neutrophils, eosinophils, or lymphocytes. Additional structural features might be encountered, such as vasculitis or necrosis.

Formation of granulomas by immune mechanisms can either progress along a T-helperl -lymphocyte profile, ruled and regulated by cytokines such as tumor necrosis factor-ct (TNF-ca), interleukin (IL)-3, IL-12, interteron--y(IFN-y), orbyaT-helper2-lymphocyte profile and the respective cytokines IL-4, and IL-5, or even by a T-cytotoxic-suppressor-lymphocyte profile, for which predominant cytokines are not well known.

Granulomas might develop central necrosis by many different mechanisms, such as thrombosis or vasculitis, followed by infarct-like necrosis. Mediator induced platelet aggregation and coagulative necrosis, by apoptosis, or by performs released by natural killer cells.

The differential diagnosis of granulomatosis starts at the cellular level, by tirst differentiating the granulomas by their predominant cell types into the forms found below.

Epithelloid cell granulomatoses are further divided into necrotizing and non-necrotizing. From this point special techniques are required to define the causing agent. By acid fast stains or polymerase chain reaction (PCR), mycobacteria are proven, while silver impregnation or immunohistochemical stains are necessary to define fungi, and other special stains are necessary to prove various parasitic infections. If living organisms are excluded, autoaggressive or allergic diseases have to be considered. The former can be proven by additional features, such as necrosis and granulocytic vasculitis in Wegeners granulomatosis, or by additional palisading histiocytic granulomas, necrosis and disruption of collagen as in rheumatoid arthritis. Additional lymphocytic bronchitis, bronchiolitis and lymphocytic interstitial infiltrates with or without follicles characterize the latter, as in exogenic allergic alveolitis (EAA). Non-necrotizing sarcoid granulomas with or without granulomatous vasculitis are seen in sarcoidosis/necrotizing sarcoid granulomatosis! nodular sarcoidosis-complex, as well as in chronic allergic metal disease. Eosinophilic or neutrophilic bronchiolitis is a characteristic feature in bronchocentric granulomatosis/allergic bronchopulmonary mycosis. Indistinguishable from sarcoidosis, epithelloid cell reaction in tumor draining lymphatics requires clinical information or an additional biopsy showing the causative tumor.

Histiocytic granulomatosis can be induced by inorganic dust, such as silicium oxides and silicates, coal dust, toner dust, etc. The causing mineral can be proven by polarized light microscopy, EDAX analysis or laser mass spectrophotometry (LAMA). The immune system in immunocompromised patients might not be able to exhibit a sarcoid reaction and therefore histiocytic granulomas or even loose aggregates of histiocytes and macrophages are formed. This implies that in histiocytic granulomatosis without visible dust particles, special stains have to be performed to rule out infection. Often *Mycobacterium* other than tuberculosis complex, such as *M. leprae* in endemic areas, are the causing agents. A combination of histiocytic and epithelloid cell granulomas is seen in lungs affected by rheumatoid arthritis and in bronchocentric granulomatosis. The former contain destroyed collagen, while the later shows remnants of fungi and eosinophilia (allergic variant) or microorganisms and neutrophilia (infectious variant).

If particles, either inhaled or recirculated to the lungs, cannot be easily dissolved by the first line of defense *(i.e.,* the macrophages), the host forms foreign body granulomas. Although some cytokines, such as IL-ib, which are secreted by macrophages and probably also by a few bypassing lymphocytes, are necessary for giant cell formation by fusion and/or nuclear division, with the process of granuloma formation not being regarded as immunologic. Phylogenetically, this mechanism can already be found in primitive multicellular organisms. A wide variety of inhaled materials can be found and are most often food. Material entering the lungs through the blood stream can be shedded particles from dialysis membranes or other medical devices, and inorganic chemicals like talcum in drug abusers.

Foreign body granulomas are also seen in different forms of pulmonary amyloidosis and in the very early phases of some pneumoconiosis (silicosis, asbestosis, and hard metal lung disease). Pulmonary microlithiasis is a very rare disease causing foreign body granulomatis. In this condition, many large and small alveoliths can be found, surrounded by foreign body giant cells, sometimes forming granulomas. Some of the alveoliths may be free in the alveoli, but most of them are within the alveolar walls.

The characteristic features of hyalinizing granulomas are their sharp delineation and their acellular centers. Usually a dense yinphocytic and plasmocytic infiltration is seen at the rim of the hyalinized nodules, but also within the nodule. Most patients are either children or patients in their second decade of life. The typical features of collagen fibers can be seen under polarized light.

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