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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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Pulmonary emphysema revisited

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Despite the number of publications generated from the 1950s to the 1960s, the interest of pathologists and clinicians in the pathology of pulmonary emphysema seems to have dissipated over the years. Several reasons can account for this. Pathological lesions are well enough defined to explain the clinical, functional and radiological tindings. The study ot pulmonary emphysema is based on large surgical or postmortem specimens usually by means of rather complicated and "uncomfortable" techniques. The pathological studies rendered data accurate enough to understand and classify experimental emphysema as well as the forms of emphysema associated with inherited metabolic diseases.

However, it is likely that now pathology must be required to update morphological findings and the anatomoclinical correlations within a new scenario involving the introduction of new imaging techniques, namely CTS and high resolution CT scan, the new definition of emphysema, and the need for clearly defined criteria to identify early stages of the disease. Most of these questions were previously formulated by early investigators, but a reconsideration would probably useful. For example, the following should be taken into account when considering the current definition of emphysema:

i) What can be termed "normal size" in alveolar sacs and alveolar ducts? Distal air spaces change in size along fetal, early and late postnatal life. In addition, differences in size between alveoli from upper and lower segments have been described. Therefore, a precise definition of what can be considered normal in the adult lung is necessary. Likewise, a reformulation of the term "ductectasia" must be undertaken.

ii) What are the criteria for destruction? Commonly admitted criteria include the presence of alveolar fenestrae and vascular strands or baffles. Both are easily seen by light microscopy when severe and extensive. However, small size early fenestrae, which precede larger ones, and the development of vascular strands require more sophisticated anatomical techniques and probably the help of quantitative methods.

iii) Is the premise of no fibrosis valid in the current definition of emphysema? It is evident that by definition scar-related irregular emphysema has a component of fibrosis. It is also common that paraseptal emphysema have a component of fibrosis and that most cases of cenfrilobular emphysema also have some fibrous proliferation. This can be important data on the interpretation of imaging techniques.

Current knowledge allows the identification of emphysema in surgical or postmortem specimens, its classification, its quantification and a acceptable correlation with functional studies. These provide a useful tool to investigate the epidemiology of the disease in different countries, and to follow up the prevalence of the disease in the autopsied population. However, these could be considered only marginal aspects in the investigation of the disease. Future prospects of research on emphysema point mainly toward not only the epidemiology but the pathogenesis and prevention. In summary, the pathologist will play a role in developing cooperative work with the radiologist to correlate and gain structure, function and radiology to validate transversal and longitudinal studies on the prevalence and evolution of emphysema in selected population groups, to clarify and correlate the morphological facts with the molecular, inmunohistochemical and clinical studies as far as the elastase-antielastase hypothesis is concerned, and to apply all the results to the prevention of the disease.

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