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Histopathologic review of granulomatous inflammation

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ABSTRACT

Granulomatous inflammation is a histologic pattern of tissue reaction which appears following cell injury. Granulomatous inflammation is caused by a variety of conditions including infection, autoimmune, toxic, allergic, drug, and neoplastic conditions. The tissue reaction pattern narrows the pathologic and clinical differential diagnosis and subsequent clinical management. Common reaction patterns include necrotizing granulomas, non necrotizing granulomas, suppurative granulomas, diffuse granulomatous inflammation, and foreign body giant cell reaction. Prototypical examples of necrotizing granulomas are seen with *mycobacterial* infections and non-necrotizing granulomas with sarcoidosis. However, broad differential diagnoses exist within each category. Using a pattern based algorithmic approach, identification of the etiology becomes apparent when taken with clinical context.

The pulmonary system is one of the most commonly affected sites to encounter granulomatous inflammation. Infectious causes of granuloma are most prevalent with mycobacteria and dimorphic fungi leading the differential diagnoses. Unlike the lung, skin can be affected by several routes, including direct inoculation, endogenous sources, and hematogenous spread. This broad basis of involvement introduces a variety of infectious agents, which can present as necrotizing or non-necrotizing granulomatous inflammation. Non-infectious etiologies require a thorough clinicopathologic review to narrow the scope of the pathogenesis which include: foreign body reaction, autoimmune, neoplastic, and drug related etiologies. Granulomatous inflammation of the kidney, often referred to as granulomatous interstitial nephritis (GIN) is unlike organ systems such as the skin or lungs. The differential diagnosis of GIN is more frequently due to drugs and sarcoidosis as compared to infections (fungal and mycobacterial).

Herein we discuss the pathogenesis and histologic patterns seen in a variety of organ systems and clinical conditions.

1. Introduction

Granulomatous inflammation is a distinctive form of chronic inflammation produced in response to various infectious, autoimmune, toxic, allergic, and neoplastic conditions (Table 1). It is defined by the presence of mononuclear leukocytes, specifically histiocytes (macrophages), which respond to various chemical mediators of cell injury. This pattern of injury response occurs in all age groups and within all tissue sites. Through light microscopy, the activated histiocytes appear as epithelioid cells with round to oval nuclei, often with irregular contours and abundant granular eosinophilic cytoplasm with indistinct cell borders (Fig. 1). They may also coalesce to form multinucleated giant cells. Identification and classification of the granulomatous inflammation pattern can be helpful in narrowing a clinical differential diagnosis. In a study of pulmonary granulomas, 23% of diagnoses could not identify the specific etiology via hematoxylin and eosin (H&E) at the time of biopsy. In this series, etiology identification improved to 90.8% with clinical features, radiographic findings, and improved laboratory methodologies, including molecular techniques, culture, immunohistochemical profiles, and serologic values [1].

1.1. Pathogenesis

The origin of the epithelioid histiocytes begins within the bone marrow as myeloid precursors mature into monocytes, which enlarge and enter peripheral circulation. When recruited into tissues, mature monocytes are renamed as histiocytes. The activation of histiocytes, via the innate immune response, gives the cells their characteristic epithelioid appearance (Fig. 1) as compared to the

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Table 1
Patterns of granulomatous inflammation and commonly associated etiologies.

Pattern of Inflammation	Associated Etiology
Foreign Body	Talc, starch, suture, hyaluronic acid (and other injectable fillers)
Necrotizing Granulomas	**Infectious:** *Coccidioides immitis/C. posadasii, Cryptococcus neoformans/C. gattii, Histoplasma capsulatum, Blastomyces dermatitidis, Aspergillus* spp., Mucorales, *Mycobacterium tuberculosis*, Non-tuberculous mycobacteria, *Brucella* spp., *Nocardia* spp., *Yersinia* spp., *Bartonella henselae, Pneumocystis jiroveci, Echinococcus granulosus, xanthogranulomatous pyelonephritis*[+] **Autoimmune**: Rheumatoid nodule, granuloma annulare, necrobiosis lipoidica, granulomatosis with polyangiitis
Non-Necrotizing Granulomas	**Infectious**[*]**:** *Candida albicans* (hepatosplenic candidiasis), *C. immitis/C. posadasii, Coxiella burnetii,* cytomegalovirus, *M. tuberculosis,* non-tuberculous mycobacteria including *M. leprae* (tuberculoid forms), *Schistosoma* spp., *Toxoplasma gondii, Rickettsia* spp., *Salmonella typhi, hepatitis A & C virii,* **Autoimmune**: Sarcoidosis, Churg Strauss, giant cell arteritis, systemic lupus erythematous, Crohn disease, primary biliary cirrhosis, orofacial granulomatosis, rosacea, granuloma annulare **Toxic:** actinic granuloma, berylliosis, zirconium, hot tub lung **Drug:** Bacillus Calmette-Guérin, Non-steroidal anti-inflammatory drugs, antibiotics, methotrexate **Other:** Lymphoid interstitial pneumonia, hypersensitivity pneumonitis, chronic lymphocytic leukemia
Suppurative Granulomas	**Infectious**: *Actinomyces* spp., *Dirofilaria* spp., *Acanthamoeba* spp., *Balamuthia mandrillaris, B. henselae, B. dermatitidis, Brucella* spp., *Chlamydia trachomatis* (serotypes L1, L2, L3 causing lymphogranuloma venereum), dematiaceous fungi causing chromoblastomycoses and phaeohyphomycosis, non-tuberculous mycobacteria, *Francisella tularensis, Prototheca* spp., *Sporothrix schenckii, Paracoccidioides brasiliensis, Yersinia* spp., *Enterobius vermicularis*
Histiocytic response,no granulomas	**Infectious**: *Tropheryma whipplei, Listeria monocytogenes,* non-tuberculous mycobacteria including *M. leprae* (lepromatous forms), *H. capsulatum, Leishmania* spp., *Rhodococcus* spp. (with malakoplakia) **Other**: Langerhans cell histiocytosis, granulomatous mycosis fungoides, juvenile xanthogranuloma, reticulohistiocytoma, Rosai Dorfman, pineal germinoma, seminoma/dysgerminoma, dendritic cell sarcoma, Erdheim-Chester disease, hemophagocytic lymphohistiocytosis, histiocytic sarcoma, interdigitating cell sarcoma, Langerhans cell sarcoma

[*]Entities may appear as well formed granulomas or histiocytic response.[+]Can present as necrotizing or non-necrotizing.

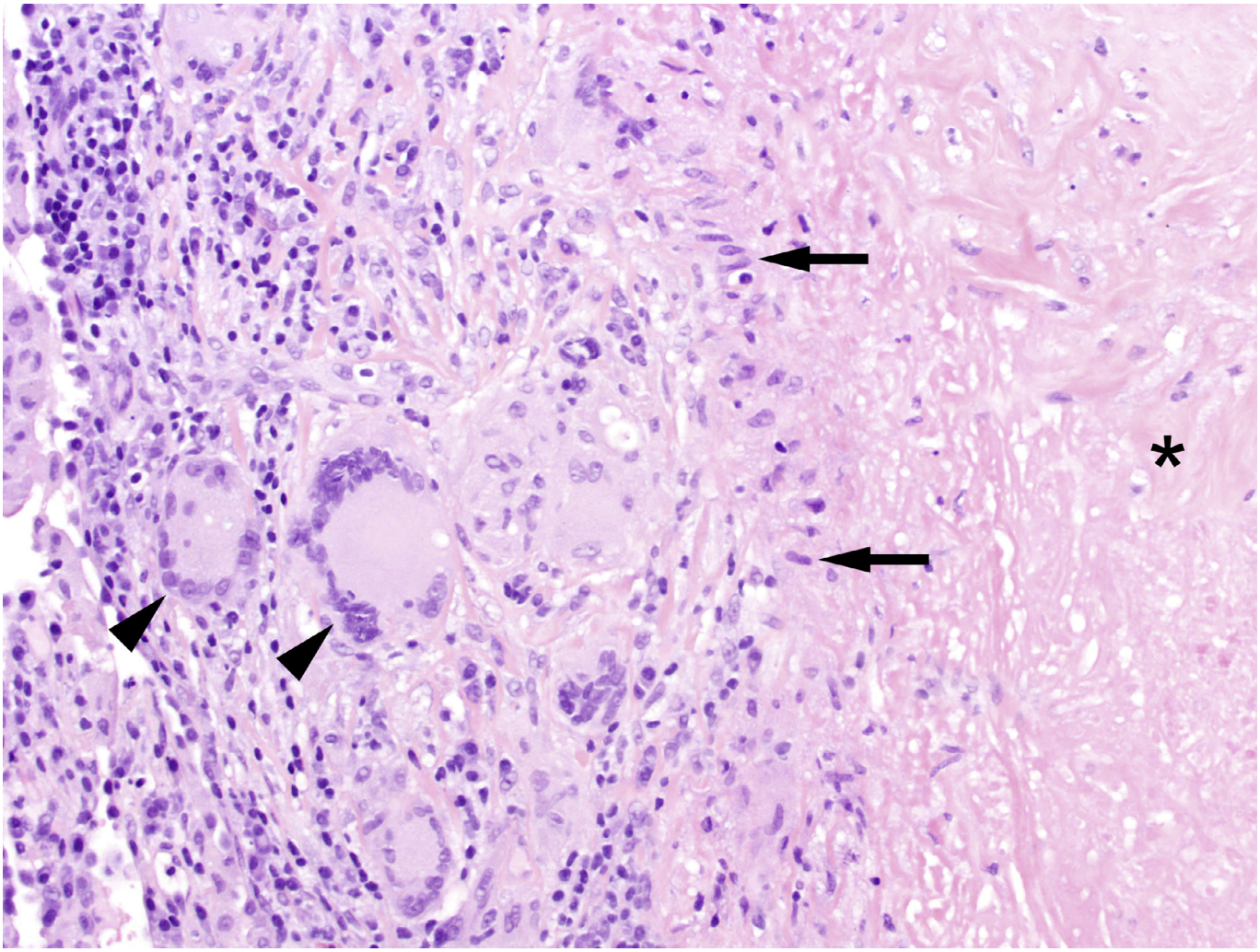

Fig. 1. Edge of a necrotizing granuloma seen in mycobacterial tuberculosis showing a peripheral rim of epithelioid histiocytes (arrows) surrounding the central necrotic region (asterisk; H&E, 200x). Some histiocytes are also forming multinucleated giant cells (arrow heads). External to the rim of histiocytes is an outer rim of lymphocytes and plasma cells.