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Granulomatous inflammation: The overlap of immune deficiency and inflammation

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A B S T R A C T

Pediatric granulomatous diseases constitute a heterogenous group of conditions in terms of clinical phenotypes, pathogenic mechanisms, and outcomes. The common link is the presence of multinucleated giant cells in the inflammatory infiltrate. The clinical scenario in which a tissue biopsy shows granulomatous inflammation is not an uncommon one for practicing adult and pediatric rheumatologists. Our role as rheumatologists is to develop a diagnostic plan based on a rational differential diagnostic exercise tailored to the individual patient and based mainly on a detailed clinical assessment.

This chapter presents a comprehensive differential diagnosis associated with a classification developed by the authors. We describe with some detail extrapulmonary sarcoidosis, Blau syndrome, and immunodeficiency associated granulomatous inflammation, which in our view are the paradigmatic primary forms of granulomatous diseases in childhood. The other entities are presented only as differential diagnoses listing their most relevant clinical features.

This chapter shows that almost all granulomatous diseases seen in adults can be found in children and that there are some entities that

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are essentially pediatric at onset, namely Blau syndrome and most forms of immunodeficiency associated granulomatous diseases.

Introduction

Granulomas are organized inflammatory infiltrates characterized by a core of macrophages, epithelioid, and multinucleated giant cells and a corona of lymphocytes and a few to many fibroblasts. Giant cell formation in turn is the result of macrophage fusion via a mechanism that is highly dependent on membrane-bound signaling and which is not completely understood [1]. Formation of granulomas is observed across most multicellular organisms; it occurs within a diverse myriad of clinical conditions and is the result of a highly orchestrated process involving numerous cellular types, cytokines, chemokines, and cell surface receptors [2].

Antigen persistence in tissue resulting from inability of individual phagocytes to carry on antigen digestion and processing is a time-honored notion that provides a rationale to the biologic function of granuloma formation; in fact, data suggest that multinucleated giant cell formation may enhance degradative activity perhaps at the expense of phagocytic capacity [1]. Lipid-rich mycobacterium, large multicellular parasites, or inert non-digestible inorganic material like silica and beryllium are well-known inducers of macrophage fusion and granuloma formation, in both in vivo and ex vivo experimental conditions [3]. Yet, no antigen has been identified in many human granulomatous diseases, and these are likely the result of deregulation of the immune system ultimately leading to macrophage fusion and giant cell formation. Blau syndrome and a number of immunodeficiency syndromes are inheritable monogenic diseases with prominent granulomatous inflammation. Sarcoidosis, primary biliary cirrhosis, Crohn's disease, and granulomatous necrotizing vasculitis are also examples of immune deregulation, yet their genetic mechanisms remain less defined.

The purpose of this chapter is to provide the consulting pediatric rheumatologist with a tool to assist in the differential diagnosis when a granulomatous disease is found on a biopsy material or is suspected on clinical bases. We will review the classification of granulomatous diseases (in broad categories) and focus our attention on clinically definable forms of granulomatous disease, namely granuloma associated with immunodeficiency, sarcoidosis, and Blau syndrome, limiting our description to the main and defining features. The reader is referred to specific reviews for a comprehensive account of the clinical entities [4–6]. We will also briefly review the mechanism of granuloma formation and discuss possible pathogenic mechanisms in selected diseases. There are several ways in which granulomatous diseases can be classified. We prefer to follow a combination of pathologic findings and etiologic factors, recognizing that this is still a work in progress (Table 1).

Granulomatous inflammation with known triggers

Infections

Rheumatologists may be involved with the care of patients who are eventually diagnosed with an infection. Two distinct scenarios are likely. (1) The finding on histology of granulomas due to infection of lymph node, liver, bone, or bone marrow in the setting of a systemic illness or (2) inflammatory syndromes 'reactive' to a granulomatous infection commonly characterized by arthritis, erythema nodosum, uveitis, and constitutional symptoms. Examples of the latter infections are caused by *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Yersinia enterocolitica*, and *Coccidioides immitis* (valley fever, desert rheumatism, or San Joaquin valley fever). Clinically, granulomatous infections can present in the context of skin and mucosal lesions, pulmonary and mediastinal disease, bone marrow dysfunction, or hepatic granulomas. Adenitis is still the most frequent presentation in children for all granulomatous infections and the location of the inflamed lymph node will determine the clinical features (cervical, abdominal, or inguinal adenitis). Although infectious disease specialists are more likely to be consulted in these cases, occasionally the histology may be unclear because of lack of obvious