

Granulomatous disorders comprise a large family sharing the common histological denominator of granulomatous inflammation and granuloma formation. Granulomatous inflammation is best defined as a special variety of chronic inflammation in which cells of the mononuclear phagocyte system are predominant and take the form of macrophages, epithelioid cells and multinucleated giant cells.

In most instances these cells are aggregated into well demarcated focal lesions called granulomas. In this review, we have discussed etiopathogenesis and few commonly encountered granulomatous diseases.

FUNCTION OF A GRANULOMA

The granuloma has a significant protective function. The replicating or inanimate agents cause chronic tissue irritations and evoke a programmed tissue inflammatory response that isolates and walls off the offender. This is especially useful in the case of replicating intracellular invaders (Mycobacteria, Listeria) that can disseminate throughout the body. The macrophages that converge at the site of bacterial invasion ingest the bacteria and intracellularly kill them. These latent organisms may cause the flare-up of the disease decades later.

PATHOPHYSIOLOGY OF GRANULOMATOUS INFLAMMATION

The granuloma is the end result of a complex interplay between invading organism or antigen, chemical, drug or other irritant, prolonged antigenaemia, macrophage activity, a Th1 cell response, B cell overactivity, circulating immune complexes, and a vast array of biological mediators (Figure 1a).

Historically, the prototype of the lung granuloma is the tubercle induced in infected individuals by *M. tuberculosis* bacilli. Inhalation of the bacilli triggers the non-specific innate immune response expressed chiefly by ingestion (phagocytosis) of the bacilli by alveolar macrophages and dendritic cells.

Cytotoxic T cells can also be activated areas of inflammation or immunological reactivity attract monocyte macrophages which may fuse to form multinucleated giant cells, and a transformation of macrophages to epithelioid cells (Figure 1b).

The Granulomatous diseases exert effect in three ways:

1. Pathogen/invader or foreign body- the intrinsic toxicity of the agents can damage the tissues
2. The vigorous immune-inflammatory T cell-

mediated response and the activated monocyte macrophage system secrete tissue-damaging substances.

3. Beside the local effect of the space occupying granulomatous lesion, some disorders like TB have caseation and there may occur the spread of necrosis to the surrounding tissues.

Infections are the commonest causes of disseminated granulomatous disease. Some experts regard an infection as the root cause of all such disorders, but that it still remains undetected in some (Table 1).

Mycobacterial infections

It is undoubtedly one of the most common cause of granulomatous inflammatory disease in India, and the most prevalent infection cause of the same.

Tuberculosis

It is estimated that one-third of the world's population is infected with TB. This is a disease has pulmonary and extrapulmonary manifestations. Extrapulmonary tuberculosis develops when the bacterium overwhelms the immune system and disseminates by way of the lymphatics or bloodstream. PPD is used for TB screening. PPD test is usually positive in those infected with tuberculosis; however, this may be negative in immunocompromised patients. Sputum stains (Ziehl-Neelsen) and cultures (L-J medium) should reveal acid fast bacilli (after 3-4 weeks). Extrapulmonary TB can be diagnosed by positive blood culture or biopsy. Biopsy will show necrotizing granulomas with acid fast bacilli. First line drugs are ethambutol, isoniazid, rifampin, pyrazinamide and streptomycin. These are available under RNTCP- DOTS programme.

In Indian scenario, one is forced to think : Are all chronic granulomatous lesions tuberculosis?

The polymerase chain reaction (PCR) has uncovered mycobacterial DNA in sarcoid tissue and mycobacterial RNA has been extracted from sarcoid spleen by liquid phase DNA/RNA hybridisation giving rise to false speculations concerning the aetiology of sarcoidosis.

Leprosy

Mycobacterium Leprea is the organism that causes Leprosy (Hansen's disease), a chronic granulomatous infection which involves superficial tissues such as the skin and peripheral nerves. The tuberculoid form is characterized by massive involvement of peripheral nerves resulting in severe pain and muscle atrophy. In lepromatous leprosy,

Table 1: A Non-inclusive List of Granulomatous Diseases and their Causative Agents

Inducers	Diseases	Inducers	Diseases
Bacteria	Tuberculosis Leprosy Brucellosis Syphillis Bartonellosis Lymphogranulomavene- reum	Inanimate agents	Silicosis Asbestosis Bagassosis Granulomatous inflamma- tions to inanimate Surgical sutures Silicone Talc Tattoo pigment Keratin Aspirated material
Fungi	Histoplasmosis Coccidioidomycosis Blastomycosis	Malignancy	Malignant tumor-associ- ated granulomas Hodgkin's disease T cell lymphomas Dysgerminoma - Semi- noma of the testis Large cell lung carcinoma
Protozoa	Leishmaniasis Toxoplasma	Miscellaneous infections	Whipple's disease Cat scratch Lymphogranuloma Kikuchi Buruli ulcer
Helminths	Filariasis Trichinosis Schistosomiasis		
Organic dust	Hypersensitivity pneumo- nitis		
Metals	Berylliosis Zirconium granulomas Sarcoidosis Crohn's disease		
Immunological Aberra- tions	Primary Biliary cirrhosis Wegener's granulomatosis Granuloma annulare Sarcoidosis Crohn's disease Hepatic granulomatous disease Langerhan's granuloma- tosis Hypogammaglobulinae- mia Histiocytosis X Reticulosis Immune complex disease		

cutaneous lesions are more common and peripheral nerve involvement is asymmetric.

Diagnosis is by nasal/skin scraping, which on culture staining show the organism or can reveal granulomatous changes. Treatment for tuberculoid is usually dapson and rifampin, for lepromatous it is usually dapson, rifampin and clofazimine.

GRANULOMATOUS MYCOSES

Aspergillus

Aspergillus fumigatus is ubiquitous in the environment. Transmission is by inhalation of the spores. Those individuals with an underlying pulmonary disease such

as COPD, may harbor a chronic infection with long standing cough and often hemoptysis as a complaint. Mucormycosis is more invasive and can cause vascular occlusion, thrombosis, and necrosis. Diagnosis is by microscopic examination of the secretions, in addition to a culture. The hyphae may be differentiated from other fungi (especially mucormycosis group) by their morphology-septate, bifurcating hyphae. Computerized tomography will demonstrate sinus pathology. Treatment is surgical excision of the involved tissue, and if invasion is evident, treatment with Amphotericin B.

Granulomatous fungal infections mimic Sarcoidosis worldwide. It is important to recognize or exclude fungi localised to one system or disseminated; in particular, granulomatous fungal meningitis needs to be distinguished from Sarcoidosis by all available techniques, like microscopy, culture, ELISA, RIA, etc.

IMUNOLOGICAL ABBERATIONS

Sarcoidosis

Sarcoidosis is a multisystem disorder of unknown cause(s) most commonly affecting young adults, and frequently presenting with hilar lymphadenopathy, pulmonary infiltration, ocular and skin lesions. The diagnosis is established most securely when well recognized clinicoradiographic findings are supported by histological

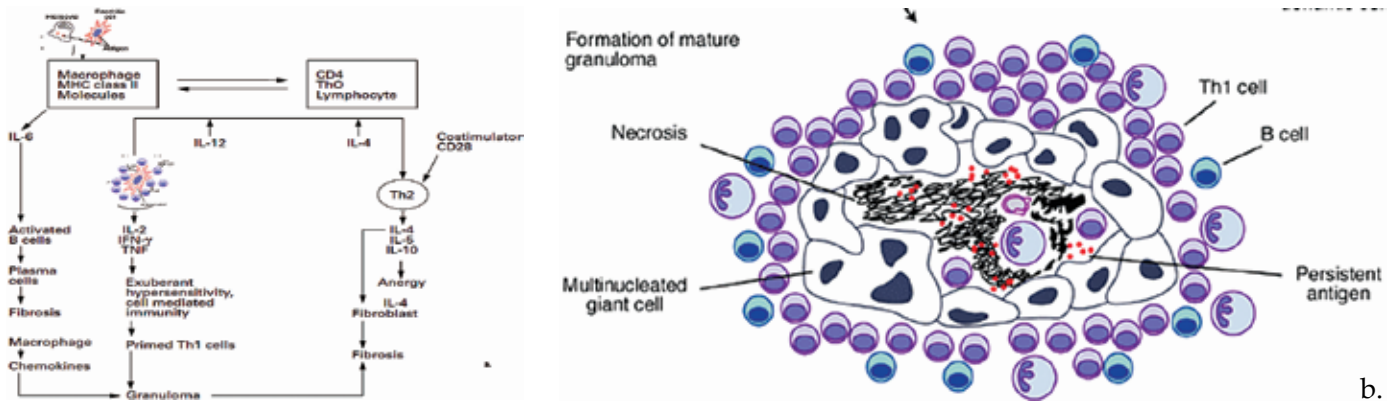


Fig. 1a: The pathogenesis of granuloma formation. IFN- γ = interferon gamma; IL = interleukin; MHC = major histocompatibility complex; TNF = tumour necrosis factor). b :mature granuloma

evidence of widespread epithelioidgranuomas in more than one system.

Diagnosis of sarcoidosis requires a combination of radiographic, clinical, and histologic positive findings (non-caseating granuloma). Angiotensin converting enzyme is also elevated in 80-90% of the patients and is helpful in diagnosis as well as monitoring disease status. Prednisone, or other immunosuppressive agents (Methotrexate) or antimalarial drugs (Hydroxychloroquine and chloroquine) are used for treatment.

Crohn's disease

The commonest cause of granulomatous inflammation in the gastrointestinal tract is Crohn's disease. This reaction seems to centre on the blood vessels of the intestinal wall causing multifocal gastrointestinal infarction. There may be associated lung changes, including pulmonary vasculitis, granulomatous interstitial lymphocytic infiltration, alveolitis, and interstitial fibrosis. Serum antibody increases include antireticulinantibody, antisaccharomycescerevisiae antibody (ASCA), and p-antineutrophil cytoplasmic antibody (ANCA).

Wegener's Granulomatosis

Wegener's Granulomatosis recently known as Granulomatosis with polyangiitis is a systemic disease, thought to be autoimmune, characterized by vasculitis and predominantly epithelioid necrotizing granulomas in the involved tissue. Typically, the patient has a triad of necrotizing granulomas of the upper airway and lungs (cavitating lesions), renal involvement (focal necrotizing glomerulonephritis) and disseminated vasculitis. Diagnosis is based on biopsy of the nasal mucosa. Laboratory evaluation should include a standard chemistry panel (BUN/Creatinine), sedimentation rate, rheumatoid factor, and anti-neutrophilcytoplasmic antibodies (specifically c-ANCA in >90%).

Langerhans Cell histiocytosis

Langerhans cell histiocytosis (LHC) is a granulomatous disease of unknown etiology and commonly affects children. Histology will show proliferation of Langerhans cells, eosinophils, macrophages and lymphocytes. Electron microscopy shows Birbeck granules in cytoplasm of langerhan cells. Immunohistochemistry staining stains positive for S-100.

Neoplastic

There is often a granulomatous component in malignant. There is diagnostic confusion between Sarcoidosis and Hodgkin's disease, in which multisystem granulomas are also observed. Both disorders show depression of cell mediated immunity. In Hodgkin's disease, the Kveim-Siltzbach test is negative and serum angiotensin converting enzyme levels are raised in only about 10% of patients, compared with 60% in Sarcoidosis. The evaluation, in most diseases, requires the tissue biopsy and microscopy, beside biochemical evaluation, to evaluate the cause of granulomatous disease.

REFERENCES

1. Bhatia A, Kumar Y and Kathpalia AS. Granulomatous inflammation in lymph nodes draining cancer: A coincidence or a significant association! *International Journal of Medicine and Medical Sciences* 2009; 1(2) pp. 013-016.
2. James DG. A clinicopathological classification of granulomatous disorders. *Postgrad Med J* 2000; 76:457-465.
3. Zumla A, James DG. Granulomatous infections: etiology and classification. *Clin Infect Dis* 1996; 23:146-58.
4. Guler M, Abdullah S, OfluÖglu R, Erguden HC, Çapan N. Are all granulomatous lesions tuberculosis? *Respiratory Medicine Case Reports* 2012; 5:42-44.
5. Inoue Y, Suga M, Kekkaku. Granulomatous diseases and pathogenic microorganism. 2008; 83:115-30.
6. Mukhopadhyay S and Gal AA (2010) Granulomatous Lung Disease: An Approach to the Differential Diagnosis. *Archives of Pathology & Laboratory Medicine*: 2010; 134:667-690.