Year 1, FOUNDATIN BLOCK - PATHOLOGY

Granulomatous inflammation – one lectures

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**Objectives:**

Upon completion of this lecture, students should be able to:

* Understand the pathogenesis of granuloma formation.
* Recognize the microscopic appearance and aetiology of granuomatous inflammation
* Know the clinical differential diagnosis of granulomatous diseases, especially those that are common in Saudi Arabia ( e.g. tuberculosis, schistsomiasis, lieshmaniasis)

**Background:**

Neutrophils ordinarily remove agents that incite an acute inflammatory response. However, there are circumstances in which neutrophils cannot digest the substances that provoke acute inflammation. Instead, a distinctive pattern of chronic inflammation characterized by aggregates of activated macrophages that assume a squamous cell-like (epithelioid) appearance is present. This type of reaction is called granulomatous inflammation. Granulomas are encountered in relatively few pathologic states; consequently, recognition of the granulomatous pattern is important because of the limited number of conditions (some life-threatening) that cause it.

**Key principles to be discussed:**

* Definition and morphological features of granulomas.
* Pathogenesis of granulomatous inflammation.
* Clinical differential diagnosis of necrotizing and non-necrotizing granulomatous inflammation

**Summary:**

Granuloma is a nodular collection of *epithelioid macrophages* surrounded by a rim of lymphocytes. It is encountered in certain specific pathologic diseases, most of them are infectious. Tuberculosis is an excellent example of necrotizing granulomatous inflammation which mostly affect the lung, but can affect any organ in the body.

**Take home messages:**

* Recognition of the granulomatous inflammation is very important as granulomas are encountered in relatively few diseases, some of them are life-threatening if untreated
* In Saudi Arabia, if granulomatous inflammation is encountered in a patient , tuberculosis must seriously considered, investigated, and excluded.

**Further reading (Prescribed book):**

Vinay Kumar, Abul K. Abbas, Nelson Fausto, & Richard Mitchell , Robbins Basic Pathology, 8th Edition

**Key words:**

Granuloma, granulomatous inflammation, epitheliod histiocytes, giant cells. tuberculosis.

**GRANULOMATOUS INFLAMMATION**

Granulomatous inflammation is a distinctive pattern of chronic inflammation characterized by **aggregates of activated macrophages that assume an Epithelioid appearance.**  Granulomas are encountered in certain specific pathologic states; consequently, recognition of the granulomatous pattern is important because of the limited number of conditions (some life-threatening) that cause it. Granulomas can form in the setting of persistent T-cell responses to certain microbes (such as Mycobacterium tuberculosis, T. pallidum or fungi), where T-cell derived cytokines are responsible for chronic macrophage activation. Tuberculosis is the prototype (classical example) of a granulomatous disease caused by infection and should always be excluded as the cause when granulomas are identified. Granulomas may also develop in response to relatively inert foreign bodies (e.g. suture or splinter), forming so-called foreign body granulomas. The formation of a granuloma effectively “walls off” or separate the offending agent and is therefore a useful defense mechanism. However, granuloma formation does not always lead to eradication of the causal agent, which is frequently resistant to killing or degradation, and granulomatous inflammation with subsequent fibrosis may even be the major cause of organ dysfunction in some diseases such as tuberculosis.

**MORPHOLOGY**

In the usual H & E preparations, Epithelioid cells in granulomas have pink, granular cytoplasm with indistinct cell boundaries. The aggregates of Epithelioid macrophages are surrounded by a collar of lymphocytes secreting the cytokines responsible for continuing macrophage activation. Older granulomas may have a rim of fibroblasts

and connective tissue. Frequently, but not invariably, **multinucleated giant cells 40 to 50 μm in diameter are found in granulomas.** They consists of a large mass of cytoplasm and many nuclei, and they derive from the fusion of 20 or more macrophages. In granulomas associated with certain infectious organisms (most classically the tubercle bacillus), a combination of hypoxia and free-radical injury leads to a central zone of necrosis. Grossly, this has a granular, cheesy appearance and is therefore called caseous necrosis. Microscopically, this necrotic material appears as an amorphous, structureless, granular debris with complete loss of cellular details. Healing of granulomas is accompanied by fibrosis that may be quite extensive.

**Examples of Diseases with Granulomatous Inflammation**

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| **Disease** | **Cause** | **Tissue Reaction** |
| Tuberculosis  Leprosy  (tuberculoid type)  Syphilis  Cat-scratch disease  Sarcoidosis  Crohn’s disease (inflammatory bowel disease) | Mycobacterium tuberculosis  Myocobacterium leprae  Treponema pallidum  Gram-negative bacillus  Unknown etiology  Immune reaction against  Intestinal bacterial, self-  Antigens | Non-caseating tubercle (granuloma prototype): a focus of Epithelioid cells, rimmed by fibroblasts, lymphocytes, histiocytes, occasional giant cells.  Caseating tubercle: central amorphous granular debris, loss of all cellular detail; acid fast bacilli.  Acid-fast bacilli in macrophages; non caseating granulomas.  Gumma: microscopic to grossly visible lesion, enclosing wall of histiocytes; plasma cell infiltrate, central cells are necrotic without loss of cellular outline.  Rounded or stellate granuloma containing central granular debris and recognizable Neutrophils; giant cells uncommon.  Non-caseating granulomas with abundant activated macrophages.  Usually no surrounding chronic inflammatory cells are seen.  Occasional non-caseating granulomas in wall of intestine, with dense chronic inflammatory infiltrate. |