Granulomatosus Disease in an Eye Practice: What makes Granulomatosus vs Non-granulomatous Inflammatory Diseases Different?

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If what defines granulomatous disease for you is Mutton-fat KPs, you are in the right place.
ASSESSING KPs
ARLT’S TRIANGLE
Types of KPs

- Fine, diffuse kps can cover inferior half of cornea and produce edema.
- Distinct, small punctate kps, mostly in Arlt’s triangle, indicative of active non-granulomatous anterior uveitis.
- Pigmented kps indicate that they are old.
- Stellate kps, particularly in a distribution outside of Arlt’s triangle, are typical of Fuchs heterochromic uveitis.
FINE, DIFFUSE KPs, PRODUCING CORNEAL EDEMA
PIGMENTED KPs TELL US THAT THEY ARE OLD
WHEN THE KPS DO NOT FALL WITHIN ARLTS TRIANGLE WE THINK OF FUCHS HETEROCROMIC UVEITIS
BUT WHEN THEY ARE MUTTON-FAT KPs, WE THINK GRANULOMATOUS
BUT WHAT MAKES GRANULOMATOUS INFLAMMATION DIFFERENT?
Non-granulomatous reactions are aggressive inflammation due to an antigen of high virulence that the immune system can eventually clear.

These usually produce all of the cardinal signs of inflammation: RUBOR, CALOR, DOLOR, AND TUMOR.

The principal cells responders, after the first responders have left the scene (poly’s, eosinophils) are lymphocytes and antibody-producing plasma cells.
Granulomatous reactions are a sub-set of chronic inflammation that also manifest lymphocytes and plasma cells.

They are less apt to produce calor, rubor and dolor in the way that non-granulomatous inflammation does.

But, in addition, modified, non-phagocytic macrophages called epithelioid cells are present. These macrophages can merge together to form giant cells that are phagocytic.
Multinucleated Giant Cells

- Foreign Body Type
- Langhan’s type
- Touton type
Th-1 and Th-2 cells are sub-classes of T helper cells. The cytokines of each group tend to inhibit the cells of the other group.

A SUPERB REVIEW IS FOUND AT http://www.antimicrobe.org/e37.asp

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<tr>
<th><strong>Th-1</strong></th>
<th><strong>Th-2</strong></th>
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<tr>
<td>Th-1 cells produce interferon (IFN)-γ and interleukin (IL)-2</td>
<td>Th-2 cells produce IL-4, IL-5, IL-6, IL-10, and IL-13.</td>
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<td>Th-1 cells usually dominate responses against <strong>intracellular</strong> pathogens such as bacteria and viruses.</td>
<td>Th-2 cells usually dominate responses against <strong>extracellular</strong> pathogens.</td>
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<td>Granulomas produced in TB are therefore Th-1 dominated</td>
<td>Granulomas produced in a response to foreign materials are therefore Th-2 dominated.</td>
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On a Cellular and Clinical level, Granulomatous diseases are characterized by the formation of Granulomas.

Granuloma formation is an immune system strategy that has evolved to deal with those pathogens that have learned to evade the host immune system by various means.

These include pathogens being able to resist dying after phagocytosis or masquerading themselves to remain just below the radar for producing an all-out immunological assault.

Epithelioid macrophages, along with giant cells, coalesce to form granulomas to wall off these organisms or antigens to prevent their further growth or spread.

It is a strategy that resigns the system to the continued presence of the antigen, seeking containment rather than a continued effort at total eradication.
Tubercle bacilli can produce and secrete a protein that can pass for the C4-b fraction of the complement cascade that plays such a central role in inflammation.

Activating the complement pathway triggers the cascade and, in the process, the C2a fraction is produced.

The C4-b mimic, produced by the bug, passes for C4-b and can combine with the C2a fragment produced by the host.

That complex forms a C3 convertase enzyme that then deposits C3 onto the surface of the bacillus.
By covering itself with C3, the TB bug is waving its hands in front of the macrophages and screaming EAT ME!!!.

The result is the TB bug is gobbled up by macrophages and put into a phagocytotic vesicle, where almost everything is normally digested away by the harsh enzymes and low pH. Inside this vesicle the bug is below the radar of the immune system.

But the wall of the TB bug is resistant to these enzymes and so it survives just fine. The bug may then go quiescent for periods (in which symptoms are less) or become activated, replicating and ultimately destroying the host cell to then spread to other macrophages, destroying host tissue (e.g. lung, lacrimal gland) along the way.

Or it can be activated by the patient taking steroids that inhibit the macrophages.
Even while the offending agent is travelling just below the radar, the system does know the bug/antigen is there and so it builds a wall of epithelioid cells and giants cells around the bug or the antigen. This is, in turn surrounded by lymphocytes and plasma cells.

This is a GRANULOMA

Caseating Granuloma

Non-Caseating Granuloma

Clinically, these all look like yellow, spherical deposits of various sizes
The Central Role of the Granuloma

Signs and symptoms of granulomatous diseases are almost entirely the result of where and how many of these focal, yellow, granulomas are produced and the amount of destruction of normal tissue that their presence creates.
# Granulomatous Diseases

## Infectious
- tuberculosis
- syphilis
- leprosy
- histoplasmosis
- cryptococcosis
- coccidioidomycosis
- blastomycosis
- cat scratch disease
- Lyme disease

## Non-Infectious
- Sarcoidosis
- Crohn's disease
- berylliosis
- Churg-Strauss syndrome
- pulmonary rheumatoid nodules
- aspiration of food and other particulate material into the lung

We will look at one example from each category:

TB and SARCOID
How do the granulomas relate to the key diagnostic findings in Sarcoid?

- Elevated ACE levels
- Elevated serum calcium levels
- Hilar Adenopathy
- Positive Gallium scan
Elevated ACE (Angiotensin converting enzyme) Levels

ACE is produced by the normal pulmonary endothelium and catalyzes conversion of angiotensin I to angiotensin II – a very potent vasoconstrictor that elevates BP. This process has been targeted by the development of drugs called ACE inhibitors that are commonly used to decrease vasoconstriction as a means of treating systemic hypertension.

ACE levels increase in sarcoidosis because the cells of granulomatous tissue also produce ACE. Increasing ACE does not increase BP in sarcoid since there is not an unlimited source of substrate (angiotensinogen).

Serum ACE activity, expressed in units/L, in normal subjects, is 10-70.
Elevated Serum Calcium Levels

Granulomas develop in bone, producing radiolucent defects that can lead to fractures.

In the process, as bone is destroyed, calcium is released into the blood, explaining why patients with sarcoid often have elevated serum calcium levels.
Adenopathy

Granulomas in the lymph nodes present at the hilus of each lung enlarge them and make them visible on X-ray.
Gallium Scan – injection of citrated Gallium $^{67}$ partitions out with medium to large accumulations of granulomatous tissue.

Destruction of normal lacrimal gland tissue by granulomas accounts for the symptoms of dry eye in sarcoid.
Granulomas in the Iris

**Koepppe nodules**
pupillary margin in both non-granulomaous granulomatous uveitis.

**Bussaca nodules**
pathognomonic for granulomatous uveitis.
Granulomas of the Lid margin and Conjunctiva
Tuberculosis

Again, the signs and symptoms of Granulomatous diseases are almost entirely the result of where and how many of these focal, yellow, granulomas are produced and the amount of destruction of normal tissue that their presence creates.
The initial focus of infection is a small subpleural granuloma accompanied by granulomatous hilar lymph node infection. Together, these make up the Ghon complex.
Cavitary TB of the Lungs

In secondary TB
When resistance to infection is particularly poor, a "miliary" pattern of spread can occur in which there are myriad small millet seed (1-3 mm) sized granulomas, either in lung or in other organs.

28% of those with miliary TB will have choroidal involvement.
Granulomas in the Choroid in TB
Clinical Course of Granulomatous Disease

Because these bugs and antigens are effective at staying just barely above the radar, most granulomatous diseases usually run a long, slow course of exacerbations and seeming remissions. Untreated, some can go away on their own (sarcoid) and, untreated, some eventually lead to death (TB), especially when coupled with immunocompromise, as with AIDS.

They are rarely raging inflammatory processes. Indeed if you look at the list of signs and symptoms of the most common presentation of sarcoid (left), you will notice that FEVER is not even on the list!
Autoimmune Granulomatous Conditions

Giant Cell Arteritis
Granulomatous response to the internal elastic lamina of medium and large sized arteries

Herpetic Corneal Endotheliitis
Includes focal granulomatous responses to Decemet’s membrane
PYOGENIC GRANULOMA
GRANULOMAS THAT ARE NOT GRANULOMAS
GRANULATION TISSUE

When wounds are too large to suture closed, the wound is often left to “granulate in”, that is to allow the normal proliferative connective tissue healing response to replace the void in the tissue. In doing so, a base is created for subsequent epithelialization.

The type of tissue that fills the void is called granulation tissue. Years ago this was also referred to as “proud flesh”
GRANULATION TISSUE

NEW THIN-WALLED, LEAKY BLOOD VESSELS IN A MINIMAL COLLAGEN MATRIX, WITH LOTS OF HYALURONATE TO HOLD WATER AND BUILD TISSUE VOLUME (AS IT DOES IN THE VITREOUS), TOGETHER WITH NON-GRANULOMATOUS INFLAMMATORY CELLS. No epithelioid or giant cells!
IF A BREAK IN THE CONJUNCTIVAL EPITHELIUM OCCURS THAT IS TOO LARGE TO SELF-REPAIR, PROLIFERATION OF NEW PRIMITIVE CONNECTIVE TISSUE (GRANULATION TISSUE) WILL FILL AND EXTRUDE FROM THE OPENING IN THE CONJUNCTIVAL EPITHELIUM
DESPITE ITS NAME, PYOGENIC GRANULOMA IS NOT A GRANULOMA

Pyogenic granulomas are not granulomas. They are granulation tissue, composed of a minimal connective tissue matrix with THIN-WALLED AND FRIABLE BLOOD VESSELS. There is no epithelial covering.

THUS, IF PYOGENIC GRANULOMAS ARE MANIPULATED, IT IS USUALLY VERY EASY TO GET THEM TO BLEED.

indeed, patients with pyogenic granulomas often report blood-stained tears.
Granulomatous diseases are caused by pathogens/antigens with low virulence that can remain barely above the radar system that would normally trigger an aggressive inflammatory response. They are antigens that are hard for the immune system to effectively clear using its usual set of weapons.

The general pattern of signs and symptoms differ in granulomatous vs granulomatous disease, with granulomatous diseases producing less of the classic signs of inflammation (rubor, calor, dolor, tumor). But they also tend to be more chronic, because the immune system cannot effectively eliminate them.
To understand the difference between non-granulomatous and granulomatous inflammation just generalize from the behavior of:

HORDEOLUM VS CHALAZION

+ Rubor -
+ Calor -
+ Dolor +/-
+ Tumor +
Chalazion is the most common granulomatous disease seen in an eye practice.

LIPID

Granulomatous tissue

Lymphocytes and plasma cells