DISEASES OF THE RESPIRATORY SYSTEM 2017
DR HEYAM AWAD
LECTURE 6: restrictive lung diseases, part 2: granulomatous diseases

Sarcoidosis and hypersensitivity pneumonia

INTRODUCTION

As we discussed in the previous lecture, restrictive lung diseases can be due to fibrosis or granulomatous reactions.

In this lecture we will cover two important granulomatous diseases: sarcoidosis and hypersensitivity pneumonitis.

Tuberculosis is also an important granulomatous disease which can cause restrictive symptoms. TB will be the topic of our next lecture.

REFERENCE: ROBBINS, 9th edition: 478-482. 10th edition: 512-515

GRANULOMAS

Let's remind ourselves what a granuloma is: it is a pattern of chronic inflammation characterized by aggregates of activated macrophages (histiocytes) and scattered lymphocytes. granulomas occur in infections (TB, fungi) and in immune diseases as well as a reaction to foreign material.

SARCOIDOSIS

Definition:

Sarcoidosis is an example of a restrictive lung disease but it is important to note that sarcoidosis is a **multisystem disease**. It affects many organs in the body, not just the lungs.

So; sarcoidosis is a multisystem disease of unknown etiology characterized by noncaseating granulomas in many tissues and organs.

Please note that : Other diseases, including mycobacterial or fungal infections may also produce noncaseating granulomas; **so the histologic diagnosis of sarcoidosis is one of exclusion.**

Epidemiology:

Sarcoidosis occurs throughout the world, affecting both genders and all races and age groups. There is a consistent predilection for adults younger than 40 years of age

Sarcoidosis is one of the few pulmonary diseases with a higher prevalence among nonsmokers.

Etiology and pathogenesis

etiology of sarcoidosis is unknown, but several lines of evidence suggest that it is a disease of disordered immune regulation in genetically predisposed persons exposed to certain environmental agents

Immunologic abnormalities in sarcoidosis suggest the development of a cell-mediated response to an unidentified antigen and the process is driven by CD4+ helper T cells. These abnormalities include:

1. Intra-alveolar and interstitial accumulation of CD4+ TH1 cells

2. Increases in T cell-derived TH1 cytokines such as IL-2 and IFN-γ, resulting in T cell expansion and macrophage activation, respectively

3. Anergy to common skin test antigens such as purified protein derivative (PPD), that may result from pulmonary recruitment of CD4+ T cells and consequent peripheral depletion

The role of genetic factors is suggested by

a. Familial clustering of cases

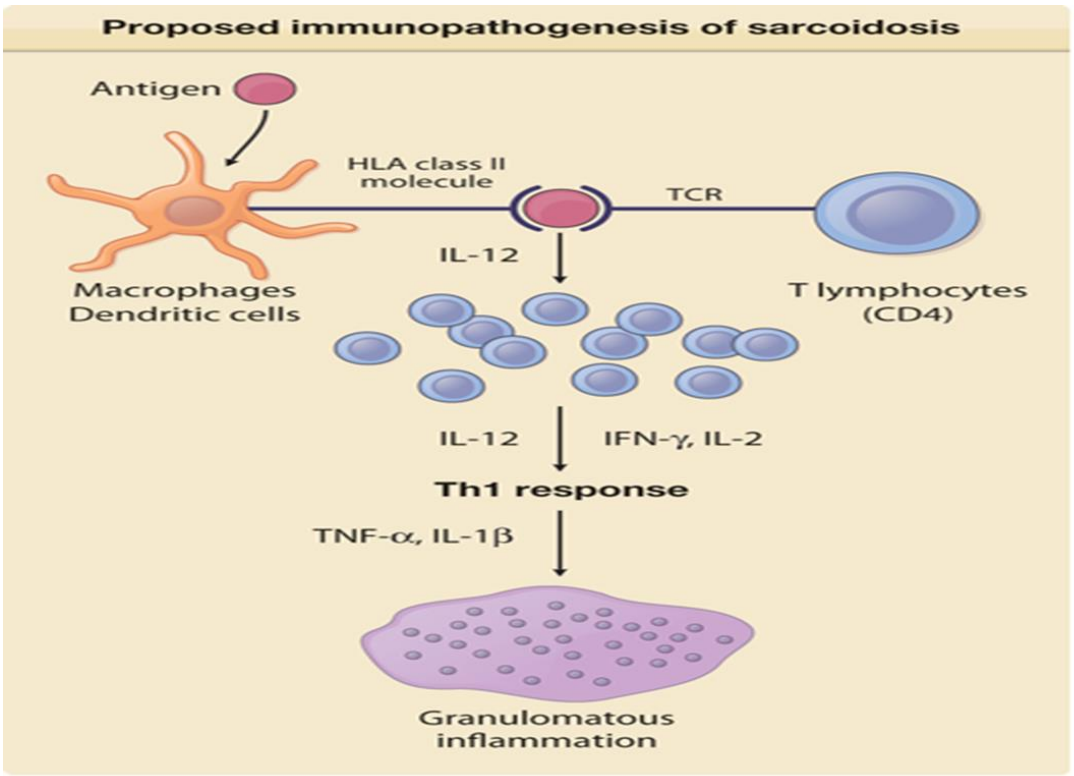
b. Association with certain human leukocyte antigens (HLA) (class I HLA-A1 and HLA-B8)

Pathogenesis of sarcoidosis is similar to type 4 hypersensitivity reaction. It is a cell mediated hypersensitivity.

The proposed scenario in sarcoidosis is that there is an unknown antigen (self antigen or environmental) that stimulates naive T cells to differentiate to Th 1 .If these helpers are subject to the same Ag again they produce powerful mediators (IL2, Interferon gamma) that attract macrophages which also produce cytokines that stimulate T cells. So we will end up with two directional strong activation between macrophages and lymphocytes ending in severe chronic inflammation if the Ag is not eliminated. The usual outcome of such stimulation is granuloma formation.

This is the story of all type 4 hypersensitivity reactions. Examples of this reaction include tuberculin test and contact dermatitis in response to certain poisons (like poison ivy)

NOTE: After lung transplantation, sarcoidosis recurs in the new lungs in 75% of patients.



Source: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K: *Fitzpatrick's Dermatology in General Medicine, 8th Edition*: www.accessmedicine.com

MORPHOLOGY

The diagnostic histopathologic feature of sarcoidosis is the noncaseating epithelioid granuloma, irrespective of the organ involved

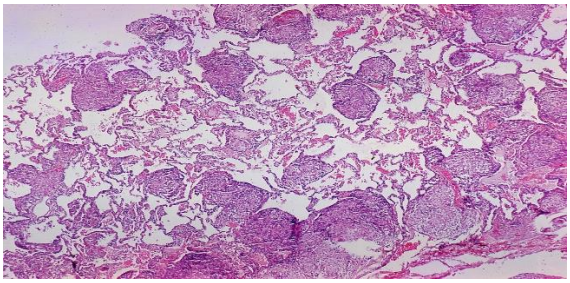
Two other microscopic features are sometimes seen:

1. Schaumann bodies, laminated concretions composed of calcium and proteins

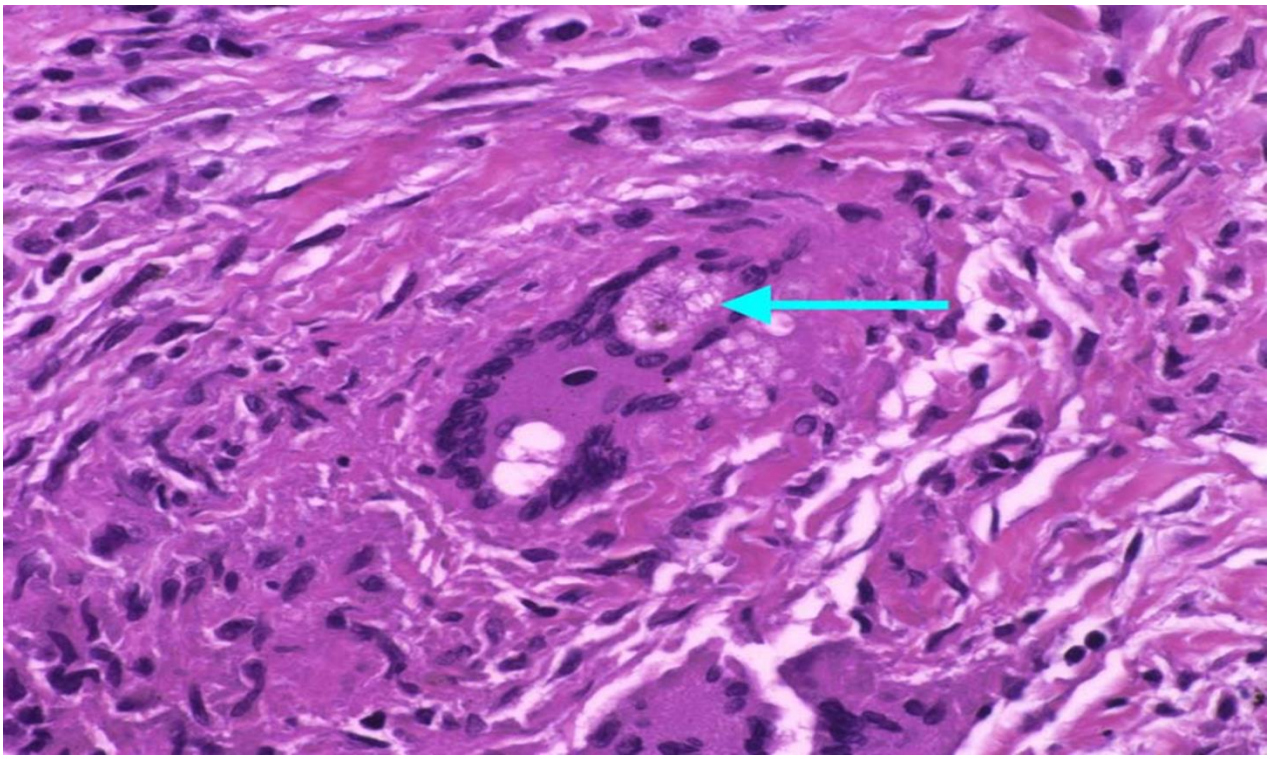
2. Asteroid bodies, stellate inclusions enclosed within giant cells. .

(1&2) above are not required for diagnosis of sarcoidosis-they also may occur in granulomas of other origins.

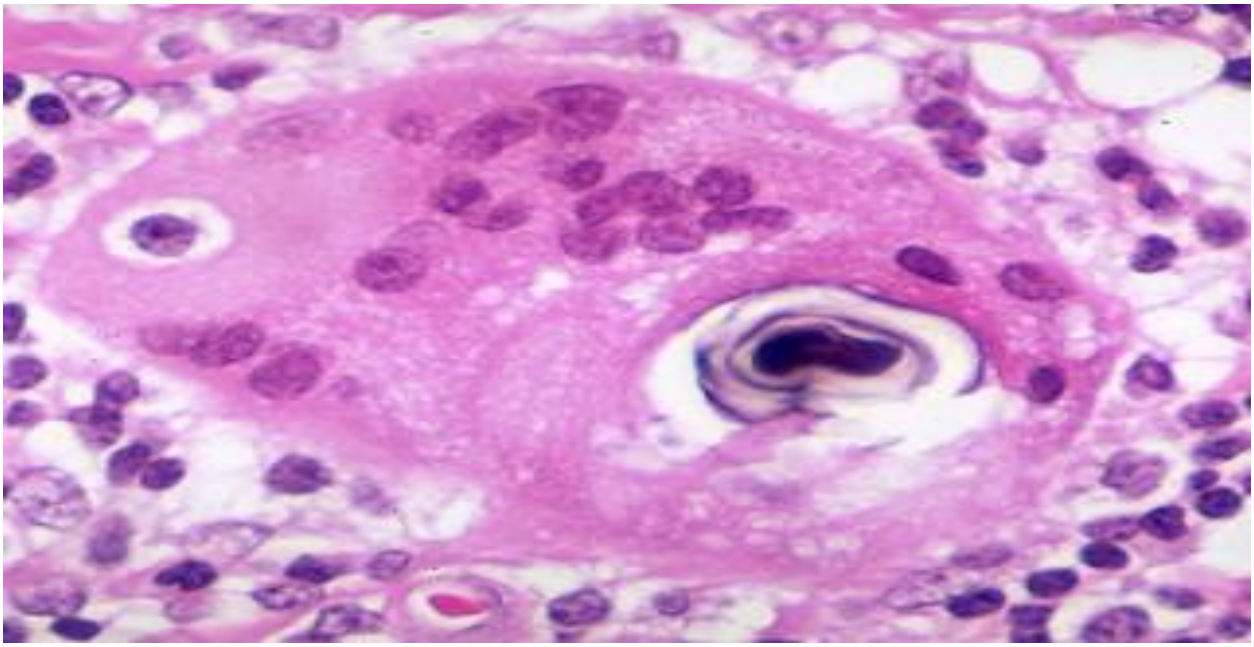
Granulomas:



Asteroid bodies: stellate inclusion within giant cells (arrow below)



Shaumann bodies: laminated concretions composed of calcium and proteins



Involved organs

1. The **lungs** are involved at some stage of the disease in 90% of patients:

The granulomas predominantly involve the interstitium rather than air spaces, with some tendency to localize in the connective tissue around bronchioles and venules and in the pleura .

2. **Intrathoracic hilar and paratracheal lymph nodes** are enlarged in 75% to 90% of patients, while a third present with peripheral lymphadenopathy.

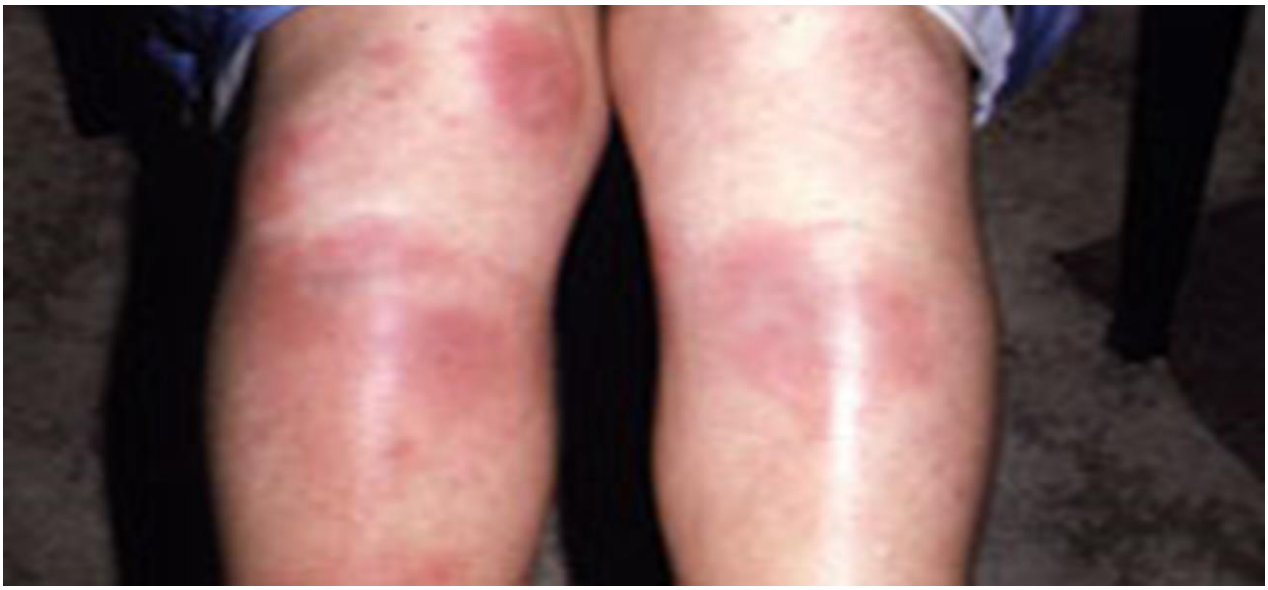
3.**Skin** lesions are encountered in approximately 25% of patients and present with two forms:

a.**Erythema nodosum**, which is the hallmark of acute sarcoidosis. These consist of raised, red, tender nodules on the anterior aspects of the legs.

Sarcoidal granulomas are *uncommon* in these lesions.

b. **Subcutaneous nodules** : Are discrete and painless . they usually reveal abundant noncaseating granulomas.

Erythema nodosum



4. **eye and lacrimal glands** involvement occurs in about one fifth to one half of patients and the ocular involvement takes the form of iritis or iridocyclitis and may be unilateral or bilateral-

As a consequence, corneal opacities, glaucoma, and (less commonly) total loss of vision may develop.

These ocular lesions are frequently accompanied by inflammation in the lacrimal glands, with suppression of lacrimation (sicca syndrome).

5. Unilateral or bilateral parotid inflammation with painful enlargement of the parotid glands-

Note: Combined uveo-parotid involvement is designated Mikulicz syndrome.

Clinical Features

-In many persons the disease is asymptomatic and discovered on routine chest films as bilateral hilar adenopathy or as an incidental finding at autopsy.

- In others, peripheral lymphadenopathy, cutaneous lesions, eye involvement, splenomegaly, or hepatomegaly may be presenting manifestations.

- In about two thirds of symptomatic cases, there is gradual appearance of respiratory symptoms (shortness of breath, dry cough, or vague substernal discomfort) or constitutional signs and symptoms (fever, fatigue, weight loss, anorexia, night sweats)

- Other findings include hypercalcemia and this is not related to bone destruction but rather is caused by increased calcium absorption secondary to production of active vitamin D by the mononuclear phagocytes in the granulomas.

Clinical course

- Sarcoidosis follows an unpredictable course characterized by either progressive chronicity or periods of activity interspersed with remissions The remissions may be spontaneous or initiated by steroid therapy and often are permanent.

- Overall, 65% to 70% of affected persons recover with minimal or no residual manifestations.

- Another 20% develop permanent lung dysfunction or visual impairment.

- Of the remaining 10% to 15%, most succumb to progressive pulmonary fibrosis and cor pulmonale.

HYPERSENSITIVITY PNEUMONITIS

These are a group of diseases that cause granulomas and restrictive disease in the lungs. The pathogenesis and histological features are similar to those of sarcoidosis but here the predisposing factors (the antigens causing the hypersensitivity reaction) are known.

Most of these granulomatous reactions occur due to occupational exposure of certain antigens.

Note: hypersensitivity pneumonitis is also called allergic alveolitis, this is a misnomer becaue these are not allergic conditions (not type 1 hypersensitivity or atopy).

SO: Hypersensitivity pneumonitis is an immunologically mediated inflammatory lung disease that primarily affects the alveoli and is often called allergic alveolitis. Most often it is an occupational disease that results from sensitivity to inhaled antigens such as moldy Hay .

The occupational exposures are diverse, but the syndromes share common clinical and pathologic findings and probably have a very similar pathophysiologic basis. Examples of these are summarized in the table below:

syndrome	exposure	antigen	
Farmer's lung	Moldy hay	micropolyspora	
Maple bark disease	Moldy maple bark	cryptostroma	
Pigeon breeder's lung	Pigeon droppings	Pigeon serum protein	

Diagnosis

With the acute form of this disease, the diagnosis is usually obvious because of the temporal relationship of symptom onset to exposure to the incriminating antigen.

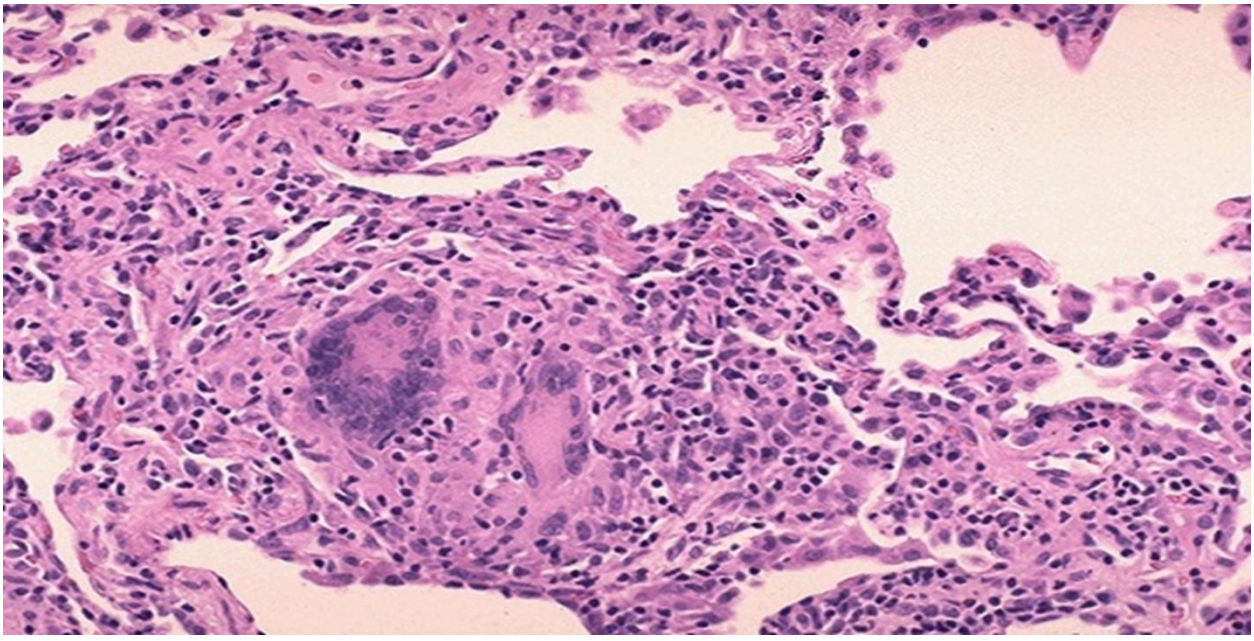
The disease can present as a chronic disease characterized by insidious onset of cough, dyspnea, malaise, and weight loss.

If antigenic exposure is terminated after the acute attacks, complete resolution of pulmonary symptoms occurs within days

Failure to remove the inciting agent eventually results in an irreversible chronic interstitial pulmonary disease

Histology:

Histology shows noncaseating granulomas that look exactly like those of sarcoidosis. So the diagnosis depends on the clinical features and history of exposure to an offending agent.



THANK YOU