CASE PRESENTATION

Mrs R, 44 years old lady with no previous medical or surgical history.

Main complaint was painful red eye for one year.

History of painful eye for one year associated with discomfort, photophobia and blurred vision.

Seen by opthalmologist and diagnosed with bilateral chronic uveitis. She was then investigated to determine etiology.

She has a history of Bells Palsy which resolved spontaneously after one week and a history of hyper-pigmented scaly lesion on forehead.

There is no history of cough or dysnea.

No history suggestive of TB

No history of joint pain.
CASE PRESENTATION

On examination she was a well looking young, not dysnoeic, 
BP 129/ 88 
PR 93/ minute 
No significant lymphodenopathy 
Hyperpigmented lesions on the forehead, 
Chest clear
CVS : NAD
ABDOMEN no organomegaly
Musculoskeletal system: no arthritis and no muscle weakness
CNS: NAD

No cranial nerve palsy, no peripheral neuropathy
INVESTIGATION

FBC: NORMAL
U&E: NORMAL
LFT: Normal
CALCIUM LEVEL: Normal
ESR: 40mm per hour
WR: non reactive
ANF: NEGATIVE
SACE LEVEL: 111 (Normal less than 52)
LUNG FUNCTION TEST: Normal
CHEST X RAY: Bilateral hilar lymphadenopathy
ASSESSMENT: Diagnosed as SARCOIDOSIS on the basis of

Uveitis,

BHL on CXR

Raised SACE level

Possible dermatologic involvement.
TREATMENT

Commenced on Prednisone 50mg daily po and Topical Steroid for Uveitis.

She is being followed up at the Pulmonology Clinic, at Greys
SARCOIDOSIS a diagnostic challenge

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SARCOIDOSIS

INTRODUCTION

- multisystem inflammatory disease of unknown etiology that predominantly affects the lungs.
- manifested by the presence of noncaseating granulomas (NCGs) that may affect any organ system
- the many forms and presentation of this disease and the lack of a single diagnostic test can make the diagnosis challenging.
ETIOLOGY

The exact etiology of sarcoidosis has not been clearly defined. Evidence exists to support
• genetic inheritance,
• infectious transmission, and
• shared exposure to environmental agents that the immune system is unable to clear effectively.
PATHOPHYSIOLOGY

T cells play a central role in the development of sarcoidosis, as they likely propagate an excessive cellular immune reaction. There is an accumulation of CD4 cells accompanied by the release of interleukin (IL)-2 at sites of disease activity. This may be manifest clinically by an inverted CD4/CD8 ratio. There also is an increased production of T\textsubscript{H}1 cytokines, such as interferon and both tumor necrosis factor (TNF) and TNF receptors are increased in this disease.
The importance of TNF in propagating inflammation in sarcoidosis has been demonstrated by the efficacy of anti-TNF agents, such as pentoxifylline and infliximab, in treating this disease. In addition to T cells, B cells also play a role. There is evidence of B cell hyperreactivity with immunoglobulin production.

The histological hallmark of sarcoidosis is the formation of noncaseating granulomas.
These granulomas are in a typical position, adjacent to the pleura (arrowheads). Note giant cells (arrows) within central collections of epithelioid cells and the encircling rim of lymphocytes.
Sarcoidosis is characterized by noncaseating granulomas.

They are different from the caseating granulomas produced by other diseases, especially tuberculosis.

Caseous necrosis is destruction of cells. The term caseous (L. caseus, cheese) refers to the gross appearance of caseous necrosis which resembles clumped, friable cheese.
Cellular destruction in this tuberculous granuloma appears as clumped debris (arrows). This type of necrosis does not occur in sarcoidosis.

Caseous necrosis is most common in tuberculosis, but Gram negative, acid fast bacilli must be identified to make the diagnosis, as in this patient.
Epidemiology

Sarcoidosis affects men and women of all races and ages.

Usually presents in adult younger than forty years, more frequent between 20 - 29 years, and slightly more predominant in women than in men.

Mortality and Morbidity

Course of sarcoidosis is variable, ranging from self-limited acute disease to a chronic debilitatating disease. Spontaneous remissions occur in nearly two thirds of patients.
Presentation depends on the extent and severity of the organ involved.

- Approximately 5% of cases are asymptomatic and incidentally detected by CXR.
- Systemic complaints, fever, anorexia, and arthralgias occur in 45% of cases.
- Pulmonary, dyspnea on exertion, cough, chest pain, and hemoptysis (rare) occur in 50% of cases.
- Löfgren syndrome: Symptoms consist of fever, bilateral hilar lymphadenopathy (BHL), and polyarthralgias.
- This presentation is associated with an excellent prognosis.
ORGANS MOST OFTEN INVOLVED BY SARCOIDOSIS

- Lung
- Skin
- Eye

OTHER ORGANS INVOLVED BY SARCOIDOSIS

- Liver
- Musculoskeletal system
- Heart
- Nervous system
- Kidney
- Gastrointestinal tract
One-third of patients with sarcoidosis have skin lesions.

Cutaneous involvement is either specific or nonspecific.

Histopathologically, specific lesions manifest as noncaseating granulomas, whereas nonspecific lesions do not reveal granulomas on histopathologic examination.
ERYTHEMA NODOSUM (EN) is the main nonspecific cutaneous disease. Tender, erythematous nodules are usually present on the extremities, most commonly on the anterior surface of the tibia.
CUTANEOUS INVOLVEMENT

LUPUS PERNIO is a striking manifestation of sarcoidal skin lesions. It is characterized by red-to-purple or violaceous, indurated plaques and nodules that usually affect the nose, the cheeks, the ears, and the lips, but it can appear on the dorsa of the hands, the fingers, the toes, and the forehead.
LUPUS PERNIO, especially involving the nasal rim, has been associated with granulomatous involvement of the upper respiratory tract (50%) and lungs (75%).
**CUTANEOUS INVOLVEMENT**

**SYSTEMIC PLAQUE** sarcoidosis is characterized by round-to-oval, red-brown to purple infiltrated plaques; the center of the plaque may be atrophic.

Periocular papules and plaques

Plaque of sarcoidosis on the face.
MACULAR or PAPULAR sarcoidosis is the most common lesion seen in cutaneous sarcoidosis. Usually, lesions are asymptomatic, red-brown macules and papules commonly involving the face, the periorbital areas, the nasolabial folds, and/or the extensor surfaces.
CUTANEOUS INVOLVEMENT

**PLAQUES** most commonly occur on the extremities, the face, the scalp, the back, and the buttocks, and they may have an annular appearance. The distribution is usually symmetric. This form of cutaneous involvement is usually chronic; most patients with plaque lesions usually have more severe involvement.

Multiple plaques of sarcoidosis on the trunk.
CUTANEOUS INVOLVEMENT

Some plaques may even appear scaly and can be confused with lesions of psoriasis or lichen planus.
CUTANEOUS INVOLVEMENT

INFILTRATION OF SCAR may occur. Scars from previous trauma, surgery, venipuncture, or tattoo may become infiltrated and show a red or purple color. These lesions may be tender.
OCULAR INVOLVEMENT

One-fourth of patients have eye lesions. The most common symptoms are blurred vision, pain, photophobia and dry eyes.
A patient who presents with findings which have developed over a period of weeks is considered to have acute sarcoidosis.

Acute presentation with the combination of uveitis, parotid gland enlargement, facial palsy, and fever is called uveoparotid fever and also HEERFORDT’S SYNDROME.
Conjunctivitis is common.
Papilledema is often associated with 7th nerve facial palsy.
Peripheral lymphadenopathy is common. The majority of patients have palpable non-tender lymph nodes.

There is thoracic lymphadenopathy in the large majority of patients.
Bilateral symmetric hilar and right paratracheal mediastinal adenopathy, as in this patient, is the most common pattern of lymphadenopathy in sarcoidosis.
The lungs are involved in more than 90 percent of patients, with sarcoid usually presenting as interstitial disease. Symptoms are dry cough, dyspnea, and chest discomfort.

Pulmonary sarcoidosis has an unpredictable course that may result in spontaneous remission or lead to progressive loss of lung function with fibrosis. Airway involvement can occur and may result in airflow limitation, persistent cough and, in severe cases, bronchiectasis.
CARDIAC MANIFESTATION

• Heart failure from cardiomyopathy rarely occurs.
• Heart block and sudden death may occur.
• Approximately 25% of patients may have NCGs at autopsy, but fewer than 5% have clinical cardiac disease.

NEUROLOGIC MANIFESTATIONS (rare)

• Cranial nerve palsies and hypothalamic/pituitary dysfunction may occur.
• Lymphocytic meningitis is the most common neurologic manifestation.
DIAGNOSIS

Because of its nonspecific presentation, the diagnosis of sarcoidosis can be challenging.
The essential factors for diagnosis include:

- **compatible clinicoradiologic features,**
- **histologic proof of noncaseating epithelioid granulomas,** and
- **exclusion of similar diseases.**

- Posteroanterior chest radiographs are useful in staging the disease.
- Transbronchial lung biopsy is recommended in most cases,
- Accessible skin lesions or peripheral lymph nodes also may be sampled.
LAB STUDIES:
Routine lab evaluation often is unrevealing.

Hypercalcemia or hypercalciuria may occur (NCGs secrete 1,25 vitamin D). Hypercalcemia is seen in about 10-13% of patients, whereas hypercalciuria is 3 times more common.
LAB STUDIES:
Angiotensin converting enzyme (ACE) may be elevated.

NCGs secrete ACE, which may function as a cytokine.

Serum ACE levels are elevated in 60% of patients at the time of diagnosis.

Serum ACE levels may correlate with total body granuloma load.
DIAGNOSIS

LAB STUDIES:
Serum ACE levels may be increased in fluid from bronchoalveolar lavage or in cerebrospinal fluid.

Sensitivity and specificity as a diagnostic test is limited (60 and 70%, respectively).

There is no clear prognostic value.

Serum ACE levels may decline in response to therapy.

Decisions on treatment should not be based on the ACE level alone.
DIAGNOSIS
CHEST RADIOGRA PHY

Radiographic involvement is seen in almost 90% of patients. Chest radiography is used in staging the disease.

Stage 0 Normal CXR

Stage I disease shows bilateral hilar lymphadenopathy (BHL).

Stage II disease shows BHL plus pulmonary infiltrates.

Stage III disease shows pulmonary infiltrates without BHL.

Stage IV disease shows pulmonary fibrosis.
DIAGNOSIS
CHEST RADIOGRAPHY

NORMAL CXR
BI LATERAL HILAR LYMPHADENOPATHY

STAGE O
STAGE I
Thoracic lymphadenopathy. Normal lung parenchyma. (50%)

Hilar and mediastinal lymphadenopathy. Abnormal lung parenchyma. (30%)

Abnormal lung parenchyma. No lymphadenopathy. (15%)
DIAGNOSIS
CHEST RADIOGRAPHY: STAGING

STAGE IV

Permanent lung fibrosis. (20%)
DIAGNOSIS

LYMPHADENOPATHY

PATTERNS OF THORACIC LYMPHADENOPATHY

Bilateral hilar lymphadenopathy, usually symmetric (85%)

Unilateral hilar lymphadenopathy (05%)

Mediastinal lymphadenopathy but no hilar lymphadenopathy (rare)

Lymph node calcification (05%)

Marginal "eggshell" lymph node calcification (rare)
When evaluating the hila for lymph node enlargement, special attention should be given to the lateral chest radiograph.

Bilateral symmetric hilar and right paratracheal mediastinal adenopathy, as in this patient, is the most common pattern of lymphadenopathy in sarcoidosis.
At the time of diagnosis there are marked enlarged hilar and mediastinal lymph nodes.

Two years later the lymph nodes are smaller and there is parenchymal lung disease.
DIAGNOSIS

RADIOGRAPHIC PATTERNS OF LUNG DISEASE

Reticular, nodular, or reticulnodular densities
(common)

Acinar type poorly defined nodules, pneumonic appearance (common)

Pulmonary fibrosis, emphysema. Upper lobe predominance (20%)

Multiple large nodules. Some with air bronchograms (unusual)

Miliary lesions (unusual)

Multiple cavitary lesions (rare)
This pattern of widespread interstitial lung disease is a common appearance of sarcoidosis involving the lung parenchyma. Note enlarged hilar lymph nodes.

Note well defined linear and nodular densities characteristic of lung tissue (interstitial) disease.
Extensive pulmonary fibrosis is typically worst in the upper lobes as in this patient. Computed tomography in Stage 4 sarcoidosis shows broad bands of fibrosis in the upper lobes.
ACINAR PATTERN

These poorly defined nodular opacities are the size of pulmonary acini (6mm).

PNEUMONIC APPEARANCE

In this patient confluent acinar opacities look similar to pneumonic consolidation.
Small nodules: peribronchovascular, subpleural including fissures, lobular septae

Small nodules producing thickened or nodular vessels, lobular septae and bronchial walls

Acinar type poorly defined nodules, pneumonic appearance.

Multiple patchy areas of ground glass density.

Multiple large masses, some with air bronchograms.

Late fibrosis, emphysema, bronchiectasis, upper lobe volume loss, honeycomb lung.

Upper lobe predominance.
NODULAR PATTERN

Small 5mm nodules are usually shown by CT in patients with sarcoidosis. Many nodules are subpleural, along fissures, and as in this patient, along bronchovascular bundles. The nodules give the vessels (arrow) and fissures a beaded appearance.

SUBPLEURAL NODULES

The cluster of small nodules here looked like a tumor on a radiograph. Note nodular thickening of the major fissure which is a typical distribution of sarcoid nodules.
Multiple lung masses such as this are an unusual form of sarcoidosis which resembles lung metastases.

This is the rare pattern of multiple cavitary sarcoid lung lesions. There were cavitary lesions in the right lung also. Note lymphadenopathy.
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CT shows innumerable well defined lung nodules less than 5mm in diameter. This is a miliary pattern which is rare in sarcoidosis. These lung lesions are indistinguishable from miliary tuberculosis, fungal disease and a variety of other diseases.
Focal osteolytic lesions in the fingers are the most common abnormality. The lesions in this patient are larger than usual.
Advanced sarcoidosis with numerous osteolytic lesions of the distal forearm, wrist, and bones of the hand cause gross deformity.
The granulomatous process involves the gastric antrum leading to irregular nonspecific narrowing.

Irregular narrowing of the rectosigmoid due to sarcoidosis has the appearance of inflammatory disease or malignancy.
Pulmonary function tests (PFTs) and a carbon monoxide diffusion capacity test of the lungs for carbon monoxide (DLCO) may be performed.
PROCEDURES

BIOPSY

Diagnosis requires biopsy in most cases.

Transbronchial biopsy (TBB) via fiberoptic bronchoscope is often done.

Results may be positive, even in the setting of normal CXR findings.

Endobronchial biopsy is done during bronchoscopy and increases the yield of the procedure.
If therapy is to be given for sarcoidosis, tissue confirmation is essential.

Watchful waiting is indicated only for patients who exhibit a classic presentation, are asymptomatic, and can ensure close follow-up.
The skin is the most easily accessible tissue for biopsy. Biopsy of all cutaneous lesions of sarcoidosis, except EN, is helpful because, histologically, EN is not specific for sarcoidosis.

Obtaining a biopsy specimen is extremely important in confirming the diagnosis of sarcoidosis.
Biopsy specimens need to be sent for histologic examination, and staining and culturing need to be performed to rule out infectious causes of granuloma formation, including mycobacterial and deep fungal infections.

Tissue culture may be appropriate in some clinical settings, especially if fungal or atypical mycobacterial infections are suspected.

A biopsy sample of bronchial mucosa demonstrates the presence of noncaseating granulomas.
TREATMENT

The majority of patients will have spontaneous remission and a generally benign clinical course.
TREATMENT

Treatment is reserved for

- patients with worsening pulmonary function tests
- patients with worsening pulmonary symptoms (cough, shortness of breath, chest pain or hemoptysis) and
- patients with extrapulmonary sarcoidosis including arthritis, neuropathy, cardiac and renal sarcoid, also in,
- patient with intractable fatigue, weakness or fevers.
Corticosteroids are the mainstay of therapy.

Generally, prednisone given daily and then tapered over a 6-month course is adequate for pulmonary disease.
Noncorticosteroid agents are being used more frequently.

Methotrexate has been a successful alternative to prednisone and is a steroid-sparing agent.

Hydroxychloroquine may be used for cutaneous lesions, hypercalcemia, neurological sarcoidosis, and bone lesions.
Anti-TNF agents work to block Tumor Necrosis Factor Alpha, which is thought to accelerate the inflammatory process in sarcoidosis.

Infliximab is a chimeric human-mouse antihuman antibody that specifically blocks TNF-alpha. It is given through intravenous infusion in conjunction with small doses of methotrexate or prednisone to prevent the formation of antibodies to Infliximab. Duration of treatment is not known and may be indefinite.

Infliximab appears to be an effective treatment for patients with systemic manifestations such as lupus pernio, uveitis, hepatic sarcoidosis, and neurosarcoidosis.
Tetracyclines have shown promise for the treatment of cutaneous sarcoidosis.

Topical corticosteroids are effective for ocular disease.

Inhaled corticosteroids are occasionally used, in particular in patients with endobronchial disease.
Lung transplantation is considered for end-stage pulmonary fibrosis from sarcoidosis. Patients with extensive extrapulmonary sarcoidosis are generally excluded from this treatment option.
Many patients do not require therapy, and their conditions will spontaneously improve.

Markers for a poor prognosis include advanced CXR stage, extrapulmonary disease (predominantly cardiac and neurologic), and evidence of pulmonary hypertension.
Because most patients with sarcoidosis do not die of the disease, the medical challenge is to help them live well with their symptoms.

THANK YOU
Anterior Uveitis