CASE #1: “A hospitalized patient with sudden shortness of breath”

CLINICAL HISTORY: A 30-year-old woman presented to the emergency department with fever, chills, and shortness of breath for 24 hours. She was well until 4 days earlier, when she noted pain on urination, followed shortly thereafter by pain in her left flank. She has a diagnosis of diabetes mellitus that is being treated with insulin.

On arrival, the patient’s blood pressure is 120/80 mm Hg, heart rate is 90/min, respiratory rate is 18/min and temperature is 39 °C. Heart and lung auscultation are unremarkable. Patient is admitted with a diagnosis of pyelonephritis for IV antibiotic treatment.

On hospital day 3 you are paged by the floor nurse because patient has difficulty breathing. On arrival to her bedside, patients blood pressure is 70/40mmHg, pulse is 120 beats/min and respiratory rate is 30/min.

Patient shows significant respiratory distress. On chest auscultation, coarse crackles are present bilaterally and there is tenderness in the left flank. Chest x-ray revealed bilateral diffuse pulmonary infiltrates.

Laboratory results were as follows: WBC 14,000, 82% PMNs, 7% bands; hematocrit 26% with fragmented red blood cells on peripheral blood smear; platelets 25,000; prothrombin time 18 sec (reference range 9.8-11.9 sec), partial thromboplastin time 80 sec (reference range 23-32.5 sec); arterial blood gases pH 7.25, PCO2 36 mm Hg, PO2 28 mm Hg; creatinine 4.8 mg/dL, glucose 600 mg/dL; urine cloudy with protein and PMNs.
The patient was intubated and placed on levophed (norepinephrine), 100% O2, and intravenous antibiotics. She experienced progressive hypotension, upper gastrointestinal hemorrhage, and intractable acidosis; blood cultures grew gram-negative rods. She died on the second hospital day. At autopsy, her lungs were heavy, firm, red, and boggy.

References (from mandatory readings) for this case:
   a. Robbins Pathologic Basis of Disease (9th edition), ARDS (Diffuse Alveolar Damage), pages 672-674 (chapter 15)
   b. Lecture: Non-Neoplastic Lung Pathology, Dr. Beissner, Online lectures June 7.

Clinical Features relevant from this clinical history:

1. What are the main symptoms present in this patient? **Acute UTI, with high respiratory rate (dyspnea), tachypnea, hypoxemia, fever, bilateral rales on chest auscultation.**
2. What would you see on chest X-ray? **Bilateral diffuse pulmonary infiltrates.**
3. What is the difference between acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and diffuse alveolar damage (DAD)?

   **ALI:** Non-cardiogenic pulmonary edema, clinically it presents as abrupt onset of significant hypoxemia and diffuse pulmonary infiltrates in the absence of cardiac failure.

   **ARDS:** refers to severe ALI.

   **DAD:** is the histological manifestation of the above clinical disease.

   The majority of acute lung injury is secondary to infection/sepsis. In the absence of any etiologic association, those cases are called acute interstitial pneumonia (AIP).

4. List the conditions associated with Acute Respiratory Distress Syndrome (ARDS) (Table 15-2 Robbins)

<table>
<thead>
<tr>
<th>TABLE 15-2</th>
<th>Conditions Associated with Development of Acute Respiratory Distress Syndrome</th>
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<tbody>
<tr>
<td>Infection</td>
<td>Sepsis*</td>
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<td></td>
<td>Diffuse pulmonary infections*</td>
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<td></td>
<td>Viral, Mycoplasma, and Pneumocystis pneumonia; mycobacterium tuberculosis</td>
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<td></td>
<td>(acute aspiration)</td>
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<td>Physical Injury</td>
<td>Mechanical trauma, including head injuries*</td>
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<td></td>
<td>Pulmonary contusions</td>
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<td></td>
<td>Near drowning</td>
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<td>Fractures with intravascular</td>
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<td></td>
<td>Burns</td>
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<td></td>
<td>Ionsizing radiation</td>
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<td>Inhaled Irritants</td>
<td>Oxygen toxicity</td>
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<td></td>
<td>Smoke</td>
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<td></td>
<td>Irritant gases and chemicals</td>
</tr>
<tr>
<td>Chemical Injury</td>
<td>Heroin or methadone overdose</td>
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<tr>
<td></td>
<td>Acetylsalicylic acid</td>
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<td></td>
<td>Barbiturate overdose</td>
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<tr>
<td></td>
<td>Paroxysm</td>
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<tr>
<td>Hematologic Conditions</td>
<td>Transfusion associated lung injury</td>
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<td></td>
<td>(TRALI)</td>
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<td></td>
<td>Disseminated intravascular coagulation</td>
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<tr>
<td>Pancreatitis</td>
<td>Uremia</td>
</tr>
<tr>
<td>Contraindicated Hypoxia</td>
<td>Hyperositivity Reactions</td>
</tr>
<tr>
<td></td>
<td>Organic solvents</td>
</tr>
</tbody>
</table>
|             | Drug}
5. How did this patient develop ARDS? She is a diabetic patient and developed an UTI. From this infection, she developed gram-negative sepsis and septic shock. The condition gave rise to ARDS.

6. What is the clinical course of the disease and what are the consequences at short term and long term? Individuals who develop ALI are usually hospitalized for one of the predisposing conditions listed before. Patients present with profound dyspnea and tachypnea with subsequent cyanosis, hypoxemia and respiratory failure. There are diffuse bilateral infiltrates on radiographic examination. The process may resolve with minimal changes or progress to end stage honey comb lung (interstitial fibrosis)

7. What is the treatment during the acute presentation? Antibiotics for treatment of sepsis, mechanical ventilation and supportive care. Deaths are attributable to sepsis or multiorgan failure and in some cases direct lung injury.

Autopsy findings show heavy, firm, red and boggy lungs (see picture bellow):

Picture description: The lung(s) are diffusely firm, heavy, red and rubbery /boggy.

Gross Questions:

8. Describe the gross appearance of the lungs. Is there a mass lesion, or does the process affect the lungs diffusely and uniformly? Gross: Lungs are heavy, firm, red and boggy. The have congestion

9. If you didn't know this was a case of Adult Respiratory Distress Syndrome, could you have guessed how the patient might have presented clinically, given the gross appearance of the lung tissue? NO

10. Can we make a definitive diagnosis of ARDS based only on gross specimen evaluation? If not, what else is needed for diagnosis? Clinical, X-ray and microscopic examination.
Microscopic Description and Orientation to Slide #656:

This is a slide from the left upper lobe of lung obtained at autopsy. The tissue is rather congested. At low power, you see large blood vessels and some larger airways with adjacent cartilage. In some of the airways, the respiratory type epithelium is partially or completely denuded. One edge of the tissue demonstrates pleura, while the other edges are cut. Find the largest portion of cartilage in the section, which is partially calcified. Go to a higher power and look at the alveolar parenchyma nearby. You will see alveoli with "white" air spaces, but then along the alveolar septa, you should see dense, pink material lining the alveolar septal walls. These are hyaline membranes, indicating recent acute alveolar damage. You may also see some cells within alveoli that have enlarged nuclei and prominent nucleoli with eosinophilic cytoplasm. These represent sloughed type II pneumocytes which are activated and/or reactive. The nearby alveolar capillaries are congested and filled with blood. Additionally you may be able to identify neutrophils and some intra-alveolar macrophages.

Check list (have you seen the following structures):

- Bronchi
- Larger pulmonary blood vessels
- Hyaline membranes
- Reactive type II pneumocytes

Microscopic Questions:

11. What is the pathogenesis of hyaline membrane formation? **Alveolar hyaline membranes consist of fibrin-rich edema fluid mixed with the cytoplasmic and lipid remnants of necrotic epithelial cells.**

12. How does the pathogenesis differ in hyaline membrane disease of the newborn? **The mechanism of newborns is a deficiency of surfactant.**

13. After resolution of acute damage, what type of lung disease develops in these patients? **Hyperplasia of type II alveolar pneumocytes plus intra-alveolar fibrosis.** Marked thickening of the alveolar walls and interstitial fibrosis may persist giving rise to restrictive lung disease. What is the clinical course of the disease and what are the consequences at short term and long term?
CASE #2: “A female with bilateral hilar lymphadenopathy”

CLINICAL HISTORY: A 43 y/o female presented with dyspnea. A chest x-ray demonstrated bilateral hilar adenopathy. Due to concern for pulmonary neoplasia, mediastinal lymph node biopsy was performed.

References (from mandatory readings) for this case.

a. Robbins Pathologic Basis of Disease (9th edition), Sarcoidosis (Granulomatous diseases) pages 693-694 (chapter 15)
b. Lecture: Non-Neoplastic Lung Pathology (Dr. Beissner), Wed June 14, 2017, 10-12am
c. Sarcoidosis. The new England Journal of Medicine, November 22, 2007;357:2153-65. Michael C Iannuzzi, M.D., Benjamin A Rybicki, PhD., and Alvin S. Teirstein, M.D.

Clinical Features relevant from this clinical history:

1. Using the sarcoidosis paper and your Robbins textbook, describe the epidemiology of sarcoidosis.
   
   a. What is the sex predilection? Higher in women
   b. What racial and ethnic groups are most commonly affected? It is 10 times higher in blacks than whites.
   c. Is there a tendency for sarcoidosis to occur in certain populations throughout the world? If so, which ones? Northern European Countries. In contrast the disease is rare among Chinese and Southeast Asians. In US the rates are highest in the southeast
   d. What age has the highest incidence? It usually develops before the age of 50 years (20-39 years)

2. According to sarcoidosis paper, what environmental findings have been found to be associated with sarcoidosis? Exposure to irritants found in rural settings, such as emissions from wood-burning stoves and tree pollen. More recently associations with exposure to inorganic particles, insecticides, and moldy environments have been reported. Occupational studies have shown positive associations with service in the U.S. Navy, metal working, firefighting and the handling of building supplies.
3. What genetic factors have been found to be associated with sarcoidosis? Evidence of genetic influences include familial and racial clustering of cases and the association with certain HLA genotypes (e.g., HLA-A1 and HLA-B8).

4. Describe the immunopathogenesis of sarcoidosis (Robbins)? Although the etiology of sarcoidosis remains unknown, several lines of evidence suggest that it is a disease of disordered immune regulation in genetically predisposed individuals.

There are several immunologic abnormalities in the local milieu of sarcoid granulomas that suggest the involvement of a cell-mediated immune response to an unidentified antigen. These abnormalities include:

- Intra-alveolar and interstitial accumulation of CD4 T cells, resulting in CD4/CD8 T-cell ratios ranging from 5:1 to 15:1, suggesting pathogenic involvement of CD4+ helper T cells. There is oligoclonal expansion of T-cell subsets as determined by analysis of T-cell receptor rearrangement, consistent with an antigen-driven proliferation.
- Increased levels of T cell derived TH1 cytokines such as IL-2 and IFN-γ, which may be responsible for T-cell expansion and macrophage activation, respectively.
- Increased levels of several cytokines in the local environment (IL-8, TNF, macrophage inflammatory protein 1alpha) that favor recruitment of additional T cells and monocytes and contribute to the formation of granulomas. TNF in particular is released at high levels by activated alveolar macrophages, and the TNF concentration in the Bronchoalveolar fluid is a marker of disease activity.
- Impaired dendritic cell function.

Additionally, there are systemic immunologic abnormalities in individuals with sarcoidosis:

- Anergy to common skin tests antigens such as candida or tuberculosis purified protein derivative (PPD)
- Polyclonal hypergammaglobulinemia, another manifestation of helper T-cell dysregulation

5. How do patients with sarcoidosis first present? Sarcoidosis often first comes to attention when abnormalities are detected on a chest radiograph during a routine screening examination (Bilateral hilar lymphadenopathy on chest X-ray)
6. Besides an unexpectedly finding on routine chest X-ray, what other signs and symptoms can raise the possibility of sarcoidosis? Because of its varying severity and inconstant tissue distribution, sarcoidosis may present with diverse features. It may be discovered unexpectedly on routine chest films as bilateral hilar adenopathy or may present with peripheral lymphadenopathy, cutaneous lesions, eye involvement, splenomegaly or hepatomegaly. In the great majority of cases, however, individuals seek medical attention because of the insidious onset of respiratory abnormalities (shortness of breath, cough, chest pain, hemoptysis) or of constitutional signs and symptoms (fever, fatigue, weight loss anorexia, night sweats).

7. Describe clinical symptoms, for each of the following organs?
   a. Lungs: The lungs are common sites of involvement. Respiratory symptoms often include dyspnea, cough, vague chest discomfort, and wheezing. About 65% of patients have airflow limitation at presentation, and spirometry usually indicates restrictive ventilator dysfunction, with reduced forced vital capacity (FVC) and reduced forced expiratory volume in 1 second (FEV1). At least 50% of patients also have concurrent obstructive airway disease, with a reduced ratio of FEV1 to RVC. Airway hyperreactivity occurs in 5-83% of patients. Pulmonary hypertension is a well described complication of sarcoidosis. Fibrosis, and the resulting obliteration of the pulmonary vessels is the most common mechanism for pulmonary hypertension in sarcoidosis, although granulomatous infiltration of the pulmonary arterioles can cause pulmonary hypertension in the absence of pulmonary fibrosis. Lesions may also appear on the mucus membranes of the oral cavity, larynx, and upper respiratory tract.

   a. Lymph nodes: Lymph nodes are involved in almost all cases, particularly the hilar and mediastinal nodes but any other node in the body may be involved. Nodes are affected in about one fourth to one third of cases.
b. **Spleen and Liver:** Just over 10% of all patients with sarcoidosis have elevated serum aminotransferase and alkaline phosphatase levels. A cholestatic syndrome characterized by pruritus and jaundice, hepatic failure, or portal hypertension can develop; yet liver involvement is usually clinically silent. Detection of hepatic and splenic lesions on CT is described in 5% and 15% of patients respectively. Nearly 60% of patients with hepatic manifestations of sarcoidosis have constitutional symptoms such as fever, night sweats, anorexia, and weight loss. Liver involvement is at least twice as common in black Americans as in white Americans. Portal hypertension with variceal bleeding, a hepatopulmonary syndrome with refractory hypoxemia, and cirrhosis leading to liver failure occur in only 1% of patients with sarcoidosis.

c. **Cutaneous involvement:** Skin lesions, encountered in one fourth of cases (25-35%), assume a variety of appearances, including discrete subcutaneous nodules; focal, slightly elevated, erythematous plaques; or flat lesions that are slightly reddened and scaling, resembling those of systemic lupus erythematosus. Lesions commonly involve the nape of the neck, upper back, extremities, and trunk, and may appear in scars and tattoos. Erythema nodosum occurs in about 10% of patients with sarcoidosis and usually lasts for about 3 weeks.
Neurologic involvement: The central nervous system is involved in up to 25% of patients with sarcoidosis who undergo autopsy, but only 10% of all patients with sarcoidosis present with neurologic symptoms. The most common problems, listed in decreasing order of frequency, are cranial-nerve palsies, headache, ataxia, cognitive dysfunction, weakness, and seizures. Neurologic involvement precedes the diagnosis of sarcoidosis in up to 74% of patients and is the only manifestation in 10 to 17% of patients with neurosarcoidosis. Analysis of cerebrospinal fluid in patients with central nervous system involvement indicates non-specific lymphocytic inflammation. The diagnostic value of measuring ACE levels in cerebrospinal fluid is controversial, since ACE levels are neither sensitive nor specific for the diagnosis. In a third of patients, oligoclonal immunoglobulin bands in the cerebrospinal fluid are elevated, making it difficult to differentiate sarcoidosis from multiple sclerosis. MRI is useful for detecting central nervous system involvement and guiding therapy.

Ophthalmologic complications: Ocular involvement, seen in one fourth cases, takes the form of uveitis, iritis or iridocyclitis, either bilaterally or unilaterally. Consequently, corneal opacities, glaucoma, and total loss of vision may occur. These ocular lesions are frequently accompanied by inflammation of the lacrimal glands and suppression of lacrimation. Anterior uveitis is the most common manifestation, occurring in 65% of patients with ophthalmologic involvement.

Cardiac sarcoidosis: Cardiac sarcoidosis is clinically apparent in 5% of all patients. Cardiac sarcoidosis is manifested clinically as a cardiomyopathy with loss of muscle function or tachyarrhythmias and bradyarrhythmias (palpitations, syncope and death).

Kidney involvement: Hypercalciuria occurs in 40% of patients with sarcoidosis, Hypercalcemia in 11% and renal calculi in 10%. Therefore, 24-hour urinary excretion of calcium should be measured in all patients with sarcoidosis. Intrarenal calcium deposition may be so severe that renal failure ensues. Renal failure due to granulomatous nephritis rarely occurs.

Bone, joints and muscular involvement: With new imaging techniques (MRI and PET), bony lesions scattered throughout the skeleton are often detected in patients with sarcoidosis and may be confused with metastatic bone lesions. Muscle involvement is underdiagnosed, since it may be asymptomatic. Muscle weakness, aches, tenderness, and fatigue should prompt consideration of occult sarcoid myositis. Chronic arthralgias are more common than frank arthritis.

Salivary glands: Bilateral sarcoidosis of the parotid, submaxillary, and sublingual glands constitute the combined uveoparotid involvement designated as Mikulicz syndrome.
j. **Bone marrow**: The bone marrow is involved in about one fifth cases. Radiological visible bone lesions have a particular tendency to involve phalangeal bones of the hands and feet, creating small circumscribed areas of bone resorption within the marrow cavity and a diffuse reticulated pattern through the cavity, with widening of the bony shafts or new bone formation on the outer surfaces.

Review Figure 3, Clinical features of sarcoidosis from sarcoidosis paper
8. How do you make the diagnosis of sarcoidosis? The diagnosis of sarcoidosis is established on the basis of compatible clinical and radiologic findings, supported by histologic evidence in one or more organs of non-caseating epithelioid –cell granulomas in the absence of organisms or particles. A biopsy specimen should be obtained from the involved organ that is most easily accessed, such as the skin, peripheral lymph nodes, lacrimal glands, or conjunctiva. If diagnosis requires pulmonary tissue, transbronchial biopsy by means of bronchoscopy has a diagnostic yield of at least 85% when multiple lung segments are sampled. If the results of lung biopsy with bronchoscopy are negative and other organs are not obviously involved, biopsy of intrathoracic lymph nodes, which are often enlarged in patients with sarcoidosis, may be necessary to confirm the diagnosis.

9. True or False: When you see non-necrotizing granulomas, a diagnosis of sarcoidosis can be made without the need of additional studies. False, sarcoid granulomas have no unique histologic features to differentiate them from other granulomas. Special stains for acid-fast bacilli (AFB special stain) and fungi (GMS and PAS special stains), as well as cultures of such organisms are essential.

10. What is the Kveim-Siltzbach test? It is a test that has been used for many years in the diagnosis of sarcoidosis. The test is performed by injecting homogenate of human sarcoid tissue extract intradermally; 4 weeks later, the papule that develops at the site of injection is biopsied. This test is now used less often for several reasons:
   First no commercially available preparation of the antigen exists.
   Second, the use of human tissue extracts for clinical purposes presents many constrains.
   Third, each new Kveim-Siltzbach preparation requires validation in vivo.
   Kveim-Siltzbach testing, if available is most useful in patients whose lesions are not easily accessible by biopsy.

11. What is the value of testing for serum ACE levels when testing for sarcoidosis? Sarcoid granulomas produce angiotensin converting enzyme (ACE), and ACE levels are elevated in 60% of patients with sarcoidosis.

12. In general terms, what is the treatment used on patients with sarcoidosis? Corticosteroids
13. What is the prognosis on a patient with a diagnosis of sarcoidosis? Sarcoidosis follows an unpredictable course. It may be inexorably progressive, or marked by periods of activity interspersed with remissions, sometimes permanent, that may be spontaneous or induced by steroid therapy. Overall, 65% to 70% of affected patients recover with minimal or no residual manifestations. Twenty percent have permanent loss of some lung function or some permanent visual impairment. Of the remaining 10% to 15%, some die of cardiac or central nervous system damage, but most succumb to progressive pulmonary fibrosis and cor pulmonale.
GROSS EVALUATION

The following finding are seen on an autopsy case of a patient with same pathology:

Sarcoidosis is a systemic disease of unknown cause characterized by non-caseating granulomas in many tissues and organs. Bilateral hilar lymphadenopathy is visible on chest X-ray in 90% of cases. Eye and skin lesions occur next in frequency.

14. Describe gross findings, for each of the following organs?
   a. **Lungs**: Macroscopically there is usually no demonstrable alteration, although in advanced cases the coalescence of granulomas produces small nodules that are palpable or visible as 1 to 2 cm, non-caseating, non-cavitated consolidations. The lesions are distributed primarily along the lymphatics around bronchi and blood vessels, although alveolar lesions and pleural involvement are also seen. The relatively high frequency of granulomas in bronchial submucosa accounts for the high diagnostic yield of bronchoscopic biopsies. There seems to be a strong tendency for lesions to heal in the lungs, so varying stages of fibrosis and hyalinization are often found.
b. **Spleen and Liver:** The spleen is affected in about three fourths of cases, but it is enlarged in only one fifth. On occasion, granulomas may coalesce to form small nodules that are visible macroscopically.

![Image of the spleen]

The liver is affected slightly less often than the spleen. It may be moderately enlarged and typically contains scattered granulomas, more in portal triads than in the lobular parenchyma. Needle biopsy can be diagnostic.

c. **Heart:** Cardiac granulomas are found in about 25% of patients with sarcoidosis who are examined at autopsy. The most common location for granulomas and scars is the left ventricular free wall, followed by the intraventricular septum, often with involvement of the conducting system. Endomyocardial biopsy has a low diagnostic yield (less than 20%) because cardiac involvement tends to be patchy, and granulomas are more likely to be located in the left ventricle and basal ventricular septum than in the right ventricle, where endomyocardial biopsies are usually performed.
MICROSCOPIC DESCRIPTION AND ORIENTATION TO SLIDE # 655:  Fragments of lymph node are present.  You can see some adjacent mature adipose tissue and portions of the fibrous lymph node capsule.  The architecture of the lymph node is relatively preserved, with rare reactive germinal centers.  In a few areas, you can see some brown-black pigment, which represents anthracotic pigment.  In many fragments, discrete nodular aggregates of pale eosinophilic cells are seen.  On closer inspection, these cells have round to oval nuclei, focally visible nucleoli and abundant cytoplasm, consistent with histiocytes.  These aggregates of histiocytes represent granulomas.  Note that there does not appear to be central necrosis within these granulomas, so these are non-necrotizing (or non-caseating).  Special stains to detect fungus (GMS) and acid fast organisms (AFB) were performed in this case, but were negative.  (They are not included in the study set). Molecular PCR based tests to detect mycobacteria were also performed, and were also negative.  These features were felt to be clinically and pathologically most consistent with a diagnosis of sarcoidosis.

**Check list (have you seen the following structures):**

- Lymphoid parenchyma with reactive germinal centers
- Non-necrotizing granulomas

**Microscopic questions:**

15. What is the classical histological lesion present in lung, lymph nodes, spleen, bone marrow and skin in patients with sarcoidosis? **Non-caseating granulomas**

16. Define granuloma (sarcoidosis paper): **Granulomas are compact, centrally organized collections of macrophages and epithelioid cells encircled by lymphocytes. Macrophages in the face of chronic cytokine stimulation, differentiate into epithelioid cells, gain secretory and bactericidal capability, lose some phagocytic capacity, and fuse to form multinucleated giant cells. In more mature granulomas, fibroblasts and collagen encase the ball-like cluster of cells, and in some cases, sclerosis ensures, altering organ architecture and function.**
17. Are Schaumann bodies and asteroid bodies “pathognomonic for sarcoidosis? **NO, they may be present in other granulomatous disease like TB.**

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**Key Concepts**

**Sarcoidosis**

- Sarcoidosis is a multisystem disease of unknown etiology; the diagnostic histopathologic feature is the presence of noncaseating granulomas in various tissues.
- Immunologic abnormalities include high levels of CD4+ T cells in the lung that secrete T,1-dependent cytokines such as IFN-γ and IL-2 locally.
- Clinical manifestations include lymph node enlargement, eye involvement (sicca syndrome [dry eyes], iritis, or iridocyclitis), skin lesions (erythema nodosum, painless subcutaneous nodules), and visceral (liver, skin, marrow) involvement. Lung involvement occurs in 90% of cases, with formation of granulomas and interstitial fibrosis.
CASE #3: “A 27-year old male with SOB”

CLINICAL HISTORY: A 27 y/o male presented with sudden onset of shortness of breath. A chest x-ray revealed air in the pleural space, consistent with a pneumothorax. The patient was clinically stabilized, but ultimately went to surgery for resection of subpleural bullae.

References (from mandatory readings) for this case:


Clinical Features relevant from this clinical history:

1. Define emphysema (Dr. Beissner lecture). **Permanent enlargement of airspace distal to the terminal bronchioles with destruction of alveolar walls.**
2. List some etiologic associations with emphysema. **Smoking (emphysema is the 4th leading cause of morbidity and mortality in the United States. Alpha-1-antitrypsin deficiency: Panacinar emphysema**
3. What is a bulla? **Spaces more than 1cm in diameter in the distended state**
4. Briefly describe the classification of various types of emphysema. The picture below should help you to classify the 3 types.

![Diagram of lung structures](image)

**Centriacinar (centrilobular) Emphysema:** The central or proximal parts of the acini (respiratory bronchioles) are affected, and the distal alveoli are spared (B). Thus, both emphysematous and normal airspaces exist within the same acinus and lobule. The lesions are most commonly located on the upper lobes. Occurs predominantly in heavy smokers.

**Panacinar (panlobular) Emphysema:** The acini are uniformly enlarged from the respiratory bronchiole to the terminal blind alveoli. “pan” refers to the entire acinus NOT the entire lung. Is more commonly present on the lower zones. This type of emphysema is associated with alpha-1 antitrypsin def.

**Distal (Paraseptal) Emphysema.** The proximal portion of the acinus is normal and the distal part is predominantly involved. The emphysema is more striking adjacent to pleura. It occurs adjacent to areas of fibrosis, scaring or atelectasis.
5. What type of emphysema is present in patients with alpha-1 antitrypsin deficiency? **panacinar**
(Compare the centriacinar vs the panacinar type on the diagram)

**Gross findings:**

![Image of emphysema](image1.jpg)

**Picture description:**

Left/Right: Numerous large bullae apparent on the surface of the lungs in a patient dying with emphysema (similar to our case). Bullae are **large dilated airspaces that bulge out from beneath the pleura**. Emphysema is characterized by a loss of lung parenchyma by destruction of alveoli so that there is permanent dilation of airspaces.

Center: dilated airspaces with emphysema. In contrast with pic on left, here you can see the airspace damage within the lung parenchyma.
**Gross questions:**

6. Describe the gross appearance of the lung, including the pleural and cut surfaces, as well as the airways and intervening parenchyma. **Advanced emphysema produces voluminous lungs, often overlapping the heart. Generally the upper two thirds of the lungs are more severely affected.**

7. How do these gross features relate to findings you might see on a chest x-ray of a patient with emphysema? **X-ray will show increased lucency, flattened diaphragms, increased anteroposterior (AP) diameter (Barrel chest) and increased retrosternal clear space.**

**SLIDE TO REVIEW: #650**

**MICROSCOPIC DESCRIPTION AND ORIENTATION TO SLIDE #650:** This specimen represents a wedge resection of lung tissue. You will see the pleural surface as well as some larger airways lined with respiratory type ciliated epithelium. Blood vessels filled with blood are also seen on low power. Look at the pulmonary parenchyma in the areas immediately underlying the pleural surface. You will notice that there are patchy areas where the normal alveolar architecture is destroyed and a larger air space is present instead. This change represents bullous emphysema.

Check list (have you seen the following structures):

- __Sub pleural enlarged air spaces
- __Normal-appearing alveoli in areas away from pleura
When there is emphysema, the size of terminal air spaces is increased. This is caused by a dilation and/or destruction of interalveolar septums and other respiratory structures. The integrity of the alveolar walls is preserved when two substances are balanced: surfactant and ceroidins. In chronic smokers, this balance is altered in favor of emphysema.
CASE #4: “13 years of chronic cough and dyspnea”

CLINICAL HISTORY: A 54 year old female has had mild chronic cough that comes and goes for over 13 years that she attributed to allergies. Recently she has felt a marked gradual increase on her cough and she can barely perform her daily activities due to shortness of breath.

References (from mandatory readings) for this case:

a. Robbins Pathologic Basis of Disease (9th edition), Usual Interstitial pneumonia (UIP) as an example of fibrosing lung disease pages 684-687 (chapter 15)
b. Lecture: Non-Neoplastic Lung Pathology, Dr. Beissner, Online lectures June 7.

Clinical Features relevant from this clinical history:

1. What is the typical clinical presentation of a patient with suspected UIP?
   Clinical Course.
   IPF begins insidiously with gradually increasing dyspnea on exertion and dry cough. Most patients are 55 to 75 years old at presentation. Hypoxemia, cyanosis, and clubbing occur late in the course. The progression in an individual patient is unpredictable. Usually there is a gradual deterioration in pulmonary status despite medical treatment with immunosuppressive drugs such as steroids, cyclophosphamide, or azathioprine. Other IPF patients have acute exacerbations of the underlying disease and follow a rapid downhill clinical course. The median survival is about 3 years after diagnosis. Lung transplantation is the only definitive therapy.

2. Regarding the pathogenesis of Idiopathic Pulmonary Fibrosis, which molecule is believed to be the "driver" of the process? Idiopathic pulmonary fibrosis (IPF) refers to the clinicopathologic syndrome. Usual interstitial pneumonia (UIP) is the histologic definition of the injury. An unidentified insult gives rise to chronic inflammation resulting in fibrosis. Abnormal epithelial repair gives rise to exuberant fibroblastic/myofibroblastic foci that are so characteristic of IPF. TGF-B1 is probably the driver of the process. TGF-B1 is known to be fibrogenic and is released by injured type I alveolar epithelial cells. It favors the transformation of fibroblasts into myofibroblasts and deposition of collagen and other extracellular matrix molecules.

3. What is the prognosis on patients with this diagnosis? Most patients have gradual deterioration of their pulmonary status. The mean survival is 3 years or less.
**Gross findings:**

Additional gross examples of patients with similar pathology:

**Picture description:** Grossly, the pleural surfaces of the lung are cobblestoned as a results of the retraction of scars along the interlobular septa. The gross appearance is known as "honeycomb" lung because of the appearance of the irregular air spaces between bands of dense fibrous connective tissue.

**Gross Questions:**

4. Describe the gross appearance of the lung. Is this lung normal? Why or why not? **Gross: Pleural surfaces are cobblestoned as a result of the retraction of multiple scars. Honeycomb fibrosis.**
SLIDE TO REVIEW: #651

ORIENTATION TO SLIDE #651: This specimen represents a wedge biopsy of lung tissue. You will see the pleural surface on some fragments, as well as obvious airways lined with respiratory type epithelium. You will notice that the normal alveolar architecture is not maintained and there is focal loss of alveolar walls with air space enlargement. In other areas, the alveolar walls are expanded with what appears to be fibrous tissue, with some accompanying chronic inflammatory cells and intra-alveolar macrophages. This specimen is included in your study set as an example of a fibrosing lung disease. This case was diagnosed as being consistent with usual interstitial pneumonia (UIP). Given the abnormal architecture, you can imagine that this patient had reduced diffusion capacity (restrictive picture), which correlated clinically with her shortness of breath.

NOTE: While we do not expect you to be able to specifically diagnose these exact etiologies in these cases, we hope you appreciate the abnormal nature of this tissue with alternating enlarged air spaces and foci with more dense fibrosis and chronic inflammation.

Check list (have you seen the following structures):

- Enlarged cystic air spaces
- Patchy interstitial fibrosis
- Chronic inflammatory cells

Microscopic questions:

5. List some of the common histologic features seen in a patient who suffers from UIP or IPF. **Micro:** patchy interstitial fibrosis. Proliferation of fibroblasts and interstitial fibrosis. Coexistence of both early and late lesions.

Key Concepts

**Chronic Interstitial Lung Diseases**

- Diffuse interstitial fibrosis of the lung gives rise to restrictive lung diseases characterized by reduced lung compliance and reduced forced vital capacity (FVC). The ratio of FEV₁ to FVC is normal.
- Idiopathic pulmonary fibrosis is prototypic of restrictive lung diseases. It is characterized by patchy interstitial fibrosis fibroblastic foci and formation of cystic spaces (honeycomb lung). This histologic pattern is known as usual interstitial pneumonia.
- The cause of idiopathic pulmonary fibrosis is unknown, but genetic analyses point to roles for senescence of alveolar epithelium (due to telomere shortening), cell stress related to protein misfolding, abnormal signaling in alveolar fibroblasts, and altered mucin production. The resulting injury to alveolar epithelial cells set in motion event that lead to increase local production of fibrogenic cytokines such as TGF-β.
- The other diseases that cause diffuse interstitial fibrosis are heterogeneous poorly understood, but most have better prognoses that idiopathic pulmonary fibrosis.
Morphology

Grossly, the pleural surfaces of the lung are cobblestoned as a result of the retraction of scars along the interlobular septa. The cut surface shows firm, rubbery white areas of fibrosis, which occurs preferentially in the lower lobes, the subpleural regions, and along the interlobular septa. Microscopically, the hallmark is patchy interstitial fibrosis, which varies in intensity (Fig. 15-14) and age. The earliest lesions contain exuberant fibroblastic proliferation (fibroblastic foci). With time these areas become more collagenous and less cellular. Quite typical is the coexistence of both early and late lesions (Fig. 15-15). The dense fibrosis causes the destruction of alveolar architecture and formation of cystic spaces lined by hyperplastic type II pneumocytes or bronchiolar epithelium (honeycomb fibrosis). With adequate sampling, these diagnostic histologic changes (i.e., areas of dense collagenous fibrosis with relatively normal lung and fibroblastic foci) can be identified even in advanced IPF. There is mild to moderate inflammation within the fibrotic areas, consisting of mostly lymphocytes admixed with a few plasma cells, neutrophils, eosinophils, and mast cells. Foci of squamous metaplasia and smooth muscle hyperplasia may be present, along with pulmonary arterial hypertensive changes (intimal fibrosis and medial thickening). In acute exacerbations diffuse alveolar damage may be superimposed on these chronic changes.
**CASE #5: “Multiple cases of fever and cough”**

References (from mandatory readings) for this cases.


b. Lecture: Upper and Lower respiratory infections, mycobacterial diseases, fungal Pulmonary disease. Dr. Mc Murray, Thursday June 2, 10-12am and Friday June 3, 8-10am.

**CLINICAL HISTORY:** A 33 y/o male presents with bilateral pulmonary infiltrates and cough. No other clinical history is available. A bronchoscopy with transbronchial biopsy is performed.

![Radiograph Image]

**SLIDES TO REVIEW:** #646 and #660 (GMS of 646)

**MICROSCOPIC DESCRIPTION AND ORIENTATION TO SLIDE #646/ #660 (GMS):** This specimen represents fragments of respiratory mucosa and pulmonary alveolar parenchyma. The respiratory mucosa shows pseudostratified ciliated respiratory type epithelium, and there is some chronic inflammation and edema within the submucosa. You may also see that some fragments contain blood with aggregates of neutrophils. Find a fragment that shows alveoli with their intact septal walls. In these areas, you will notice that some alveoli are not air-filled, but rather contain pink proteinaceous bubbly material with a few admixed brown-pigmented macrophages. This bubbly intra-alveolar material suggests an intra-alveolar process. The accompanying acute inflammation suggests the possibility of an infection. Go to the accompanying GMS stain (#660), which has a green background. As you navigate within the tissue fragments, find alveolar tissue, and you will discover silver or GMS positive circular structures. Some of them have a "punched in" appearance like a partially deflated ping-pong ball. These represent *Pneumocystis jiroveci* organisms.

Check list (have you seen the following structures):

- Fluffy pink intra-alveolar material on H&E stain
- Organisms, highlighted on GMS stain
QUESTION

1. Under which clinical circumstances, in general, will you find that patients are infected with Pneumocystis jiroveci organisms? Immunocompromised (opportunistic infection)

CLINICAL HISTORY: An 85 y/o Chinese male presented with a history of tuberculosis that was treated 50 years ago. He now has hemoptysis and a right upper lung cavitary mass. A CT guided needle biopsy of the mass is attempted.

Picture explanation: This is a fungal granuloma produced by Aspergillus. An infectious process is suggested by the fact that the lesion has crossed the fissure as though it weren’t there. A neoplasm usually is initially impeded by an anatomical barrier. This granuloma has an irregular, red margin and a firm, tan-orange center. Fungal infections are more common in patients who are immunosuppressed.

SLIDES TO REVIEW: #648 and #649 (GMS of 648)

MICROSCOPIC DESCRIPTION AND ORIENTATION TO SLIDE #648/ #649 (GMS): This is a rather fragmented biopsy in which you will find it difficult to recognize normal pulmonary parenchyma. You may recognize a few blood vessels and fragments of fibrous tissue, along with distorted lymphocytes. However, close inspection of most fragments shows filamentous, red to faint purple material. Even on an H&E stain, this suggests a type of fungal infection. An accompanying GMS stain, which has a green background, highlights the numerous filamentous fungal elements. Take some time to drive around and determine the morphologic features of the fungus. You should see some structures that have 45 degree angle branching and discrete septal walls. The
morphologic features are consistent with *Aspergillus* species. This patient's cavitary mass lesion of the lung turned out to be a necrotic cavity containing fungus.

**Check list (have you seen the following structures):**

- Filamentous structures on H&E stain
- Fungal elements highlighted on GMS stain with branching

**QUESTION**


**CLINICAL HISTORY:** A 23 y/o male presented with mucopurulent sputum production. No other clinical history was available at the time. A bronchoscopy with bronchial biopsy is performed.

**SLIDES TO REVIEW:** #657 and #658 (AFB of 657)

**MICROSCOPIC DESCRIPTION AND ORIENTATION TO SLIDE #657/ #658 (AFB):** This specimen consists of fragments of tissue, a few of which show overlying ciliated pseudostratified respiratory type epithelium. This tissue derived from the bronchus. No bronchial cartilage is seen, however. You don't see typical submucosal structures. Rather, sheets and aggregates of moderately sized cells with round regular nuclei are seen. Their cytoplasm is gray-tinged and granular, and relatively abundant. This is not a normal finding in bronchial tissue. Although not neoplastic, these cells are abnormal and have features most consistent with histiocytes. An accompanying stain for acid-fast bacilli is present for your review. On this stain, note that within the cytoplasm of these histiocytes, numerous positive staining acid-fast organisms are noted. For this particular patient, molecular PCR based studies were performed and were positive for *Mycobacterium avium* - *intracellulare*.

**QUESTION**

3. For this patient, what serologic test would you want to order and why? *Mycobacterium avium intracellulare complex. Clinically significant infection with MAC is uncommon, except among people with AIDS and low numbers of CD4+ lymphocytes. (serology to detect HIV)*
CLINICAL HISTORY: A 42 y/o HIV positive male presents with a 3 week history of productive cough and low grade fever. Fever appears predominantly at night, is associated with sweats and partially resolves with acetaminophen. Within the last 2 days he started to develop hemoptysis.

*Picture explanation: Pulmonary Tuberculosis.* This is the gross appearance of a lung with tuberculosis. Scattered tan granulomas are present; mostly in the upper lung fields (The pattern of smaller nodules which have a propensity for upper lobe involvement suggests a granulomatous process rather than metastatic disease). This pattern of multiple caseating granulomas primarily in the upper lobes is most characteristic of tuberculosis. However, fungal granulomas (histoplasmosis, cryptococcosis, coccidioidomycosis) can mimic this pattern as well.

*Slide(s) to review: Aperio #137*

At low-power observe this section of lung with an extensive architecture distortion due to granulomatous reaction. At high power focus on tubercles and observe central caseation, surrounded by epithelioid cells and multinucleated giant cells. The granulomas are enclosed within a rim of lymphocytes an plasma cells. No special stains are available for review.

**QUESTION**

4. What test(s) should be performed on this patient should be performed if suspicious for tuberculosis? 

   on patients with signs and symptoms suggestive of tuberculosis (chronic, productive cough, fever, nigh sweats, weight loss) and/or history of contact with TB case the following tests can be performed:

   **Blood tests:**
   - Purified protein derivative (PPD) skin test
   - IFN-γ release blood test (IGRA)

   **Imaging studies are suggested:**
   - Chest X-ray
   - Chest CT

   If HIV status is unknown, remember to confirm with serologic tests.
Can you highlight the hyaline membranes of this case?

What are the membranes composed of? **Fibrin-rich edema fluid mixed with the cytoplasmic and lipid remnants of necrotic epithelial cells.**

What is the definition of bronchiectasis? **Bronchiectasis is a disease characterized by permanent dilation of bronchi and bronchioles caused by destruction of the muscle and elastic tissue, resulting from or associated with chronic necrotizing infections. To be considered bronchiectasis, the dilation must be PERMANENT.**
Can you point to the **caseating** granuloma and the **non-caseating** granuloma?

Examples of diseases with caseating granulomas? **TUBERCULOSIS, SYPHILIS, CAT-SCARTHC DISEASE.**

Examples of diseases with NON-caseating granulomas? **SARCOIDOSIS, CROHN DISEASE, LEPROSY**

What is the Robbins definition of “granuloma”: **A granuloma is a focus of chronic inflammation consisting of a microscopic aggregation of macrophages that are transformed into epithelium-like cells, surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells.**

Aspergillus is an example of a **septated** (septated/ non-septated hyphae) while Mucor is an example of a **Non-septated** (septated/ non-septated hyphae).

They are both transmitted by ________________
1) A 61-year-old female smoked cigarettes for 10 years but stopped smoking 5 years ago. She has experienced increasing dyspnea for months along with a non-productive cough. A chest radiograph shows prominent hilar lymphadenopathy. A transbronchial biopsy is performed, and the microscopic findings include interstitial fibrosis and non-caseating granulomas. One of the granulomas contains an asteroid body and a giant cell. This disease is believed to be caused by:

(A) Diffuse alveolar damage (DAD)
(B) Immune complexes formed in response to inhaled antigens
(C) Smoke inhalation for many years
(D) Delayed hypersensitivity response to an unknown antigen
(E) Infection with atypical mycobacteria

2) A 74-year-old woman was found comatose in her apartment by her family and brought to the hospital. Three years previously, she had undergone uncomplicated replacement of both the mitral and aortic valves by porcine prostheses, and had done well until the current event.

PHYSICAL FINDINGS: Vital signs: Temp. - 38.5 deg. C; blood pressure - 88/56 mm Hg; heart rate - 102/min.; respiratory rate - 21/min. Skin was warm and flushed, and several ecchymosis were noted. Auscultation of the heart revealed a pan systolic murmur that radiated to the base.

LABORATORY RESULTS:
WBC: 14,300/cu mm. (N: 4,300-10,800/cu mm), with 68% neutrophils, 12% bands, 3% monos, 15% lymphs, and 2% basophils.
Blood culture: Positive for Streptococcus viridans and Staphylococcus epidermidis.
Urinalysis: Many rbc's, wbc's and rbc casts.
Platelets: 56,000/ml. (N: 150,000-350,000/ml.)
Prothrombin time: 21.5 sec. (N: 8.8-11.6 sec.)
Partial thromboplastin time: 51 sec. (N: 24-37 sec.)
Creatinine: 3.8 mg/dl (N: 0.6-1.5 mg/dl)
BUN: 52 mg/dl (N: 8-25 mg/dl)

CLINICAL COURSE: The patient remained comatose and in high-output heart failure despite antibiotics and other supportive treatment, and she developed guarding in the right upper quadrant. Oozing from intravenous and phlebotomy sites was noted. She became increasingly hypoxic and chest x-ray revealed a marked bilateral reticulonodular pattern. She died 5 days after admission. Autopsy noted vegetations on both the mitral and aortic valves, among other findings.
As depicted in this image, the pulmonary lesions are most consistent with
(A) bronchopneumonia
(B) florid pulmonary edema
(C) granulomatous pneumonitis
(D) hypersensitivity pneumonitis
(E) adult respiratory distress syndrome

3) A 40 year-old woman has had malaise and an 11-kg weight loss over the past 3 years. She has had fever and a non-productive cough with increasing dyspnea for the past 3 days. On physical examination, her temperature is 37.8 C, pulse is 82/min, respiratory are 22/min, and blood pressure is 100/60 mm Hg. There is dullness to percussion over the lungs and diffuse crackles on auscultation. A chest radiograph shows extensive bilateral infiltrates. Bronchoalveolar lavage is done, and the fluid is stained with Gomori methenamine silver. The high-power microscopic appearance is shown below. Which of the following underlying conditions is most likely present?

(A) Diabetes mellitus
(B) Systemic lupus erythematosus
(C) AIDS
(D) Sarcoidosis
(E) Severe combined immunodeficiency
(F) Centrilobular emphysema
4) Which of the following structures in the lung is likely to be affected the most in a patient who smoked a pack and a half of cigarettes per day for 30 years and developed centrilobular emphysema?
   (A) Alveolar sac
   (B) Terminal bronchiole
   (C) Respiratory bronchiole
   (D) Alveolar duct
   (E) Capillary

5) After a hemicolectomy to remove a colon carcinoma, a 53-year-old man develops respiratory distress. He is intubated and receives mechanical ventilation with 100% oxygen. Three days later, his arterial oxygen saturation decreases. A chest radiograph shows increasing opacification in all lung fields. A transbronchial lung biopsy specimen shows hyaline membranes lining distended alveolar ducts and sacs. Which of the following most likely represents the fundamental mechanisms underlying these morphologic changes?
   (A) Reduced production of surfactant by type II alveolar cells
   (B) Disseminated intravascular coagulation
   (C) Aspiration of oropharyngeal contents with bacteria
   (D) Leukocyte-mediated injury to alveolar capillary endothelium
   (E) Release of fibrogenic cytokines by macrophages

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**Answers to multiple choice questions**

1) D
2) E
3) C
4) C
5) D
1) Aperio Spectrum Website http://aperio.ad.tamhsc.edu

Login: student1 (or student2/3/4) the number corresponds to the work-station number
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3) Select Courses

4) Click on the folder for Pathology Phase II.

5) Look for cardiovascular folder and click on the book

6) Select the slide number (third column) and click on the image (second column), a window will open with a message “Do you want to open or save this file?”, select open.

7) The slide will open