Educational Case

Educational Case: Histoplasmosis

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see https://www.journals.elsevier.com/academic-pathology/pathology-competencies-for-medical-education-pcme.1

Keywords: Fungal pneumonia, Histoplasmosis, Organ system pathology, Pathology competencies, Pulmonary infection, Respiratory system, Systemic mycosis

Primary objective

Objective RS2.10: Fungal Pneumonia. Compare and contrast the causative agents, geographic locations, clinical presentation, and pathologic findings in chronic pneumonia caused by fungal organisms.

Competency 2: Organ System Pathology; Topic: Respiratory System (RS); Learning Goal 2: Pulmonary Infection.

Patient presentation

A 44-year-old woman presents to her primary care physician with two days of fever, chills, nonproductive cough, and dyspnea. She took her temperature at home, and it has reached up to 102°F. The dyspnea initially started when she was walking up stairs but occurred without activity today. The patient denies headaches, loss of smell or taste, gastrointestinal symptoms such as nausea or diarrhea, nasal discharge, and muscle aches. She does mention that several of her extended family members also currently have a flu-like illness. She has no significant past medical history and is not currently on any medications other than acetaminophen for her fever. She does not smoke cigarettes and drinks 2 glasses of wine per week. Both of her parents and her two brothers have no chronic illnesses or history of malignancy.

Diagnostic findings, Part 1

Vital signs include a blood pressure of 128/72 mmHg, temperature 101.7°F, pulse 88 beats per minutes, and respirations 18 per minute. Auscultation of the chest reveals diffuse crackles in all lung fields bilaterally. The remainder of the physical exam is normal.

Questions/discussion points, Part 1

What additional information would be useful to request from the patient in this case?

Given that multiple members of the same family are ill, additional information regarding potential causes should be sought. This includes contact with sick persons outside the family, current living conditions, travel history (both within the United States and abroad), and potential environmental exposures. Depending on the time of year, questions about influenza, including vaccination status, and knowledge of current local infection rates would also prove useful. Information regarding the patient's COVID-19 vaccination status and potential contacts should also be sought, as should possible interaction with individuals at high risk for tuberculosis.

Diagnostic findings, Part 2

Further questioning reveals that no other ill contacts are known, and no one has been near persons at high risk for tuberculosis. The patient is fully vaccinated for COVID-19 and has received her annual influenza vaccine. The sick family members all helped clean out an abandoned barn approximately 10 days ago on the local family farm in western Kentucky. A flock of birds had been roosting in the barn, and a large amount of bird excrement had accumulated. They used brooms to sweep the debris out of the barn; no cleaning or other chemical agents were used. The farm is no longer active...
and has not intentionally housed any animals for the past 4 years, and no manure was present in the barn. The patient and her family have not recently traveled to any other locations, including out of the country.

Questions/discussion points, Part 2

Given this additional information, what infectious organisms should be strongly considered in the differential diagnosis and why?

While the new information cannot rule out common viral respiratory infections (such as COVID-19), it does provide details that guide development of the differential diagnosis. The new information supports a potential environmental cause rather than a community transmitted infection. The timing of the presentation with the family sharing similar symptoms after a common experience and no recent travel or ill contacts leads to this conclusion. The development of a differential diagnosis would incorporate the location of the event into the analysis. The setting of the farm and an enclosed space with a high volume of bird droppings leads to the consideration of Cryptococcus neoformans, Coxiella burnetii, Chlamydia psittaci, and Histoplasma capsulatum as etiological agents.

Cryptococcosis is caused by two species: Cryptococcus neoformans and C. gattii. These organisms are encapsulated fungi, with C. neoformans commonly found in pigeon droppings versus C. gattii of arboreal origin. It can be acquired through inhalation; and, although infection is common, illness primarily affects only immunocompromised patients. While any part of the body can be affected by cryptococcosis, pneumonia and meningoencephalitis are the most common disorders, with skin and soft tissue infections also seen. A patient with pulmonary infection may experience a productive cough and chest pain. Only a minority of patients are febrile; and, in fact, many are asymptomatic altogether. Symptoms of central nervous system (CNS) infection may be of extended duration and may include headache, fever, and problems with memory. Given that the presentation is found in several family members, including this otherwise healthy patient, this is unlikely to be the causative agent.

Coxiella burnetii is a pleomorphic coccobacillus prokaryote and the causative agent of Q fever. An acute infection can present with variable signs and symptoms which may depend on geographic location. General symptoms include fatigue, fever, and chills and may be accompanied by retro-orbital headache, photophobia, and cough. It can be acquired by inhalation of aerosolized organisms from ruminants (e.g., sheep, goats, cattle, and cats) undergoing parturition due to localization of the organism in the uterus of mammals. Since no farm animals were present on the property and no contact with manure, Q fever is less likely.

Psittacosis is an infection caused by the bacterium Chlamydia psittaci and is characterized by systemic symptoms such as fever and chills as well as muscle aches, gastrointestinal symptoms, and headaches. A severe pneumonia may also develop. C. psittaci is found in avian reservoirs, and thus frequently implicated sources of psittacosis include domestic birds such as parrots and parakeets as well as poultry such as ducks and turkeys. Pigeon excrement could potentially harbor C. psittaci, although the described patient did not have many of the signs or symptoms typically associated with this infection.

Based on the history of cleaning a barn with probable aerosolization of bird excrement and the geographic location, histoplasmosis should be strongly considered. Histoplasmosis is caused by infection with Histoplasma capsulatum, a dimorphic fungus. Two variants of H. capsulatum exist, H. capsulatum var. capsulatum and H. capsulatum var. duboisii. H. capsulatum var. capsulatum will be the focus of this case's discussion, as it is the type endemic to the United States; it will henceforth be referred to simply as H. capsulatum. H. capsulatum var. duboisii is endemic to equatorial Africa and should be considered if travel to or residence in this area is reported.

In the United States, H. capsulatum is found within the Mississippi and Ohio River valleys; it can also be encountered in southern parts of the Americas (Mexico, Central and South America). Infection is typically acquired through inhalation after aerosolization of contaminated soil. A high nitrogen content to the contaminated soil is conferred by bird or bat droppings, which contain the infectious microconidia of H. capsulatum. The probable source of infection may be elicited with a careful history, and some exposures more commonly associated with a large inoculum include the disturbance or cleaning of areas with a large amount of bird droppings (e.g., barn, chicken coop) or bat droppings (e.g., cave) or renovation or demolition of old structures.

What additional physical exam findings may be identified in patients with acute histoplasmosis? What potential findings may signal infection with other entities in the differential diagnosis?

Depending on the severity of the clinical manifestations, the following signs of acute histoplasmosis may be observed by careful physical examination: ulcerations of the oral mucosa, hepato-splenomegaly, erythema nodosum, and pulmonary infiltrates. Evidence of localized or diffuse infiltrates may be seen on a chest radiograph as well as mediastinal and/or hilar lymphadenopathy. Erythema nodosum, a type of panniculitis causing symmetrical tender erythematous nodules and plaques on the shins, is a non-specific sign of infection and only appears in 5%-10% of acute histoplasmosis patients.

Signs of infection with one of the other organisms previously listed in the differential diagnosis follow:

- Cryptococcosis may result in pulmonary abnormalities on exam or a chest x-ray that are consistent with pneumonia. Signs of CNS infection may be detected as sensory, cranial nerve, or vision deficits. Findings of meningismus such as a stiff neck, confusion, and photophobia may or may not be present. Additionally, a wide variety of skin lesions can be found.
- Some patients with acute Q fever develop a non-specific rash. Thrombocytopenia and/or positive autoimmune markers may be detected with lab testing. A chest x-ray may reveal opacities consistent with pneumonia.
- A patient with psittacosis may have detectable hepatomegaly and/or splenomegaly on physical exam. If a severe pneumonia develops, auscultation of the chest may reveal rales with consolidation on a chest x-ray.

What laboratory tests could be used to support a diagnosis of acute histoplasmosis? What tests could be performed to rule out other infections in the differential diagnosis?

Antigen testing, performed on urine and/or serum, should be remembered as showing high clinical utility for both the diagnosis of acute histoplasmosis and for follow-up of therapeutic efficacy. Antigen detection through skin testing should not be used clinically, although it does have value in epidemiologic studies. Serologic antibody testing is available through several methods, although the time delay (2–6 weeks for antibody formation following exposure) and problems with sensitivity and specificity are limitations in an acute infection. In some cases, the diagnosis may be made from histology or cytology specimens taken from lymph nodes, bone marrow, peripheral blood, and tissue (biopsy) or fluid (bronchoalveolar lavage, BAL) from the lungs. If the patient has a disseminated infection, blood cultures can be obtained. Tissue cultures can also be performed, although H. capsulatum takes approximately 1.5–2 weeks to grow and often requires molecular (nucleic acid) testing for confirmation. If histoplasmosis is suspected, the lab should be notified to assist with appropriate handling of the material, both to increase the potential for success of the culture as well as to ensure the safety of laboratory personnel. The patient material requires plating on appropriate fungal culture media or inoculation of specific tubes. The cultures are incubated at room temperature (25–30°C). One could also consider a culture at 37°C to demonstrate the dimorphic nature of the organism,
although molecular testing has mostly replaced this confirmation technique. While tissue specimens pose no risk of airborne spread since the tissue phase is not transmitted in this manner, mold cultures should be contained and manipulated within a biosafety level 3 environment (appropriate personal protective equipment worn, work performed in a biologic safety cabinet, exhaust air is not recirculated, etc.).

If common viral infections are a consideration, a PCR panel for common respiratory infections could be considered. PCR and/or antigen testing for COVID-19 should also be considered for any patient with a fever and respiratory symptoms during the ongoing pandemic. If cryptococcosis remains in the differential diagnosis, it can be proven by identifying the causative yeast or obtaining a positive antigen test from cerebrospinal (CSF) fluid or blood. The antigen test is both sensitive and specific, although it is more likely to be negative in pulmonary disease. The India ink test for CSF which identifies cryptococcal organisms based on the exclusion of ink by their capsules is a rapid method for diagnosis. Other findings in the CSF may include increased mononuclear cells and protein levels. Q fever can be suspected with detection of high IgG antibody levels, but a definitive diagnosis requires evidence of seroconversion, an increase in IgG titers by a factor of 4 between samples drawn in the acute and convalescent phases. PCR of blood or tissue can also detect the organism, but this test suffers from low sensitivity (blood) and frequent lack of available material (tissue). Psittacosis can be diagnosed through serologic testing, although the availability of some tests and specificity for C. psittaci versus other chlamydial infections may limit their utility. Culture is not recommended due to the potential risk for infection of laboratory personnel.

Diagnostic findings, Part 3

Histoplasma urine antigen is positive in this patient and her family members, even in some individuals who were not symptomatic.

A chest x-ray shows patchy bilateral pulmonary infiltrates and hilar lymphadenopathy.

Questions/discussion points, Part 3

A mediastinal lymph node biopsy was performed on a patient with a similar illness. Describe the cytologic and histologic features as seen in Figure 1

Fig. 1 On the touch preparation slide (Fig. 1A), several macrophages contain organisms within their cytoplasm. The remaining cells are lymphoid cells of varying sizes, implying a reactive (non-neoplastic) pattern. The histologic section in Fig. 1B shows lymph node tissue containing a large area of necrosis. Gomori methamine silver (GMS) staining (Fig. 1C) reveals many small (3–5 μm) yeast. Some of the yeast display narrow-necked budding. Note that no hyphae or pseudohyphae are seen. Histoplasma organisms are not typically seen with hematoxylin-and-eosin staining.

What pattern of chronic inflammation is typically associated with infection by this organism?

Like many fungal organisms, Histoplasma typically incites a granulomatous inflammatory response. Recall that granulomas are a pattern of chronic inflammation composed of macrophages and surrounded by lymphocytes (Fig. 2). Cellular immunity develops within 1–2 weeks of Histoplasma infection. Th1 helper T cells produce interferon gamma which activates macrophages. Histoplasma additionally induces macrophages to make tumor necrosis factor, which recruits additional macrophages. Some of the macrophages may coalesce to form multinucleated giant cells. Other fungal organisms and some bacteria such as Mycobacterium spp. may also cause this prolonged T cell stimulation, and the cytokine production by these T cells with the resulting macrophage activation leads to granuloma formation over time. In the case of histoplasmosis, the granulomas are often caseating (contain central necrosis) and in healthy patients will eventually resolve with residual fibrosis and/or calcification. It is not uncommon to identify calcifications in the lungs, mediastinal lymph nodes, liver, and spleen of persons from

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Fig. 1. The lymph node touch preparation (A) contains many yeast within macrophages (arrows), as well as numerous lymphocytes. Histologic sectioning (B) shows necrosis at the top center portion of the image (appears pink) and residual lymphocytes (appear purple). A Gomori methamine silver (GMS) stain (C) of the lymph node reveals numerous small budding yeast (appear black) (A, Diff-Quik stain, original magnification ×1000; B, hematoxylin and eosin, original magnification ×100; C, GMS, original magnification ×400).
Disseminated histoplasmosis may develop in persons who are immunocompromised due to AIDS, immunosuppressive or immunomodulatory medications, and/or the extremes of age. A severe, and even fatal, acute systemic disease can occur. Others may experience a subacute process that is organ-based (e.g., gastrointestinal ulceration, meningitis, adrenal insufficiency, etc.).

Chronic pulmonary histoplasmosis occurs most commonly in the setting of emphysema or other structural lung diseases. The clinical and radiologic findings are similar to those of tuberculosis and may cause diagnostic confusion. Symptoms can include weight loss, night sweats, a productive cough, dyspnea, and a low-grade fever. Cavitary lesions, an infiltrate of the upper lobe(s), and pleural involvement may be demonstrated on a chest radiograph. Serologic testing is more useful for chronic histoplasmosis than for acute, and culture of BAL fluid or sputum is also of use.

Of note, histoplasmosis differs from tuberculosis in that once it becomes inactivated, it does not reactivate.

**How is histoplasmosis treated?**

When treatment is indicated, typically with chronic or disseminated infection, amphotericin B and/or itraconazole are most frequently prescribed, with other antifungals used when needed. The duration of treatment and monitoring for disease are dependent on the type of disease and the patient’s underlying medical condition. Because this patient had acute pulmonary disease and was not immunocompromised, she was not treated with antifungal medications. Her symptoms improved and resolved completely approximately seven days after they began.

**Which other endemic fungal organisms commonly cause chronic pneumonia? Why are these organisms called dimorphic fungi? Describe the geographic localization, clinical findings, and histomorphology for each**

Other endemic fungal organisms that may cause chronic pneumonia (and their associated mycoses) include Blastomyces dermatitidis (blastomycosis), Coccidioides immitis/C. posadasii (coccidioidomycosis), and Paracoccidioides brasiliensis (paracoccidioidomycosis). These are referred to as dimorphic fungi because they have two distinct forms depending on the environmental conditions. They grow in a mold form at 25–30°C as found in nature or in the laboratory but grow as a yeast or spherule in vivo or on media in the laboratory when incubated at 37°C. These organisms are generally acquired through inhalation and may sicken immunocompromised or immunocompetent individuals.

The typical geographic localization, clinical findings, and histomorphologic descriptions for each of the above organisms is summarized in [Table 1](#). Knowledge of organisms endemic to one’s practice location is essential so that the potential infections can be included in the differential diagnosis when appropriate. However, knowledge of all these

**Describe the various clinical symptoms and anatomic sites of involvement in patients with histoplasmosis. What factors affect the clinical manifestations?**

*H. capsulatum* infection can produce a variety of clinical presentations, ranging from clinically silent to life-threatening, and may be acute or chronic. The factors affecting a patient’s clinical status include the amount of exposure, underlying lung architecture, and status of the immune system. Persons who are otherwise well and contact a small number of organisms are often asymptomatic, with evidence of infection only indicated by positive serology or by the detection of lung nodules during chest imaging performed for other reasons. A mild, self-limited illness may also occur. When exposure levels are higher, patients may experience a flu-like illness. Other findings in this setting can include erythema nodosum and/or pericarditis. Mediastinal or hilar lymphadenopathy, sometimes mass-forming, may be identified on radiology due to necrosis and coalescence of involved lymph nodes. Infrequently, the acute illness is followed by fibrosis around the lymph nodes, which can impinge upon nearby vascular and pulmonary structures. This is called fibrosing mediastinitis.

**Fig. 2.** Most of this image is composed of a granuloma containing many macrophages and several multinucleated giant cells as well as small lymphocytes and a few plasma cells (hematoxylin and eosin, original magnification ×200).

**Table 1**

| Organism (disease) | Endemic locale | Clinical features | Histomorphology (at 37°C) |
|--------------------|----------------|------------------|--------------------------|
| *Histoplasma capsulatum* (histoplasmosis) | Ohio and Mississippi River valleys, Central and South America | Wide variety of clinical features, ranging from asymptomatic to flu-like symptoms to disseminated disease | Budding yeast (narrow neck), 3–5 μm, typically within macrophages |
| *Blastomyces dermatitidis* (blastomycosis) | Mississippi and Ohio River valleys in U.S., Canada near Great Lakes, Africa | Pulmonary and systemic symptoms as well as joint and muscle aches; can have skin or bone involvement | Budding yeast (broad base), visible nuclei, thick wall, 8–15 μm, within granulomas or microabscesses |
| *Coccidioides immitis/C. posadasii* (coccidioidomycosis) | Southwestern U.S., parts of Central and South America | More than half are asymptomatic, others mostly with pulmonary symptoms (fever, cough, chest pain); can cause erythema nodosum | Endospores (2–5 μm) within spherules (up to 250 μm), within macrophages |
| *Paracoccidioides brasiliensis* (paracoccidioidomycosis) | Southern Mexico, parts of Central and South America | Acute, subacute, or chronic course; primary infections are typically self-limited; can disseminate; may cause painful ulcers on the oral mucosa | Multiples buds (4–60 μm), lending a “ship’s wheel” appearance |
infections is advisable so that one may correlate findings with a patient’s travel history or previous residency locale. The clinical manifestations associated with these endemic infections may be isolated to the pulmonary system, or they may disseminate to other areas of the body. Notable extrapulmonary involvement includes skin and bone infection in blastomycosis and mucosal ulceration in paracoccidioidomycosis. Immune reactions may also play a role such as with development of erythema nodosum or erythema multiforme in coccidioidomycosis.6

A diagram representing relative size and shape of the yeast forms is provided in Fig. 3, with representative histologic images in Figs. 4–6. Distinctive histologic features of the yeast forms in tissue include the broad-based budding and presence of nuclei in B. dermatitidis; relatively large (mean 20–60 μm) spherules of C. immitis that do not bud but can contain endospores7; and yeast with one or more buds of various sizes, likened to a “mariner’s wheel” appearance, in P. brasiliensis.5 Several additional pathologic features are of note for these organisms. B. dermatitidis and C. immitis may elicit a neutrophilic inflammatory response in addition to granulomas. Also, striking epithelial hyperplasia induced by blastomycosis involving the larynx and/or skin may resemble squamous cell carcinoma.7

**Teaching points**

- Fungal organisms that can cause chronic pneumonia and their corresponding diseases include *Histoplasma capsulatum* (histoplasmosis), *Blastomyces dermatitidis* (blastomycosis), *Coccidioides immitis/C. posadasii* (coccidioidomycosis), and *Paracoccidioides brasiliensis* (paracoccidioidomycosis).
- The aforementioned organisms are termed dimorphic fungi because they grow in a mold form in nature (25–30°C) but in a yeast or spherule form in the body (37°C).
- Histoplasmosis is endemic in the Ohio and Mississippi River valleys and may have a variety of clinical manifestations ranging from asymptomatic to fatal. Exposure to soil containing bird or bat droppings is the typical source. Exposure to soil containing bird or bat droppings is the typical source.
- Urine and/or serum antigen testing can help confirm the diagnosis of histoplasmosis. If a biopsy is performed, the organism may be found within granulomas and can be visualized as a small yeast with narrow-necked budding using a special stain for fungal organisms.
- Blastomycosis is acquired in the central and eastern United States, overlapping in areas with *H. capsulatum*. B. dermatitidis displays broad-based budding and is larger than *H. capsulatum*, at about the size of a red blood cell. Blastomycosis can disseminate to the skin.
- Coccidioidomycosis is endemic to the southwestern United States and forms a spherule (not a yeast) in the body tissue. The spherule is larger than a red blood cell, and endospores can be observed inside. Coccidioidomycosis may be asymptomatic or manifest as pulmonary disease, but it may also involve other sites such as the skin, causing erythema nodosum.
- *P. brasiliensis* has a characteristic “captain’s wheel” shaped construction which is significantly larger than a red blood cell. It is endemic to South America. While primary infection is often self-limited, chronic and disseminated forms can occur. Some patients develop ulcers of the oral mucosa.
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Declaration of competing interest

The Authors declare that there is no conflict of interest.

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Fig. 6. Paracoccidioides yeast contain multiple buds, which has been described as similar to a ship's wheel, as seen in the center of each image (A and B) taken from a lymph node biopsy. The yeast in B are more clearly seen to be within a multinucleated giant cell of a granuloma (A and B, hematoxylin and eosin, original magnification ×1000).