ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

CLINICAL MYCOLOGY COURSE

A MAN WITH LONG-TERM ABDOMINAL DISCOMFORT PRESENTING WITH FEVER

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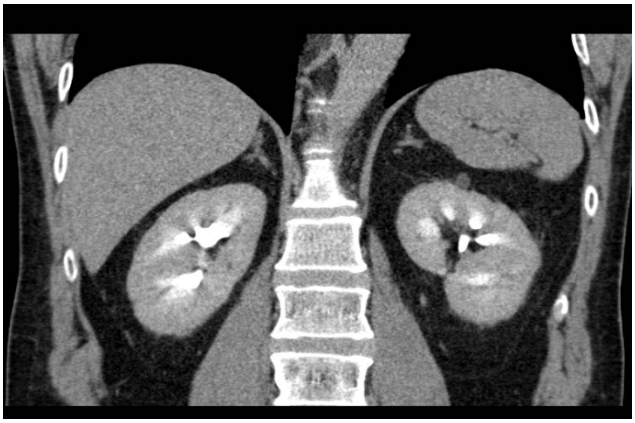
Initial Presentation

A white man in his 60s presents with a 2-month history of fevers, fatigue, night sweats, and unintentional weight loss. The patient's medical history is significant for Crohn's disease, managed for many years with the tumor-necrosis factor-alpha (TNF-α) inhibitor infliximab. The patient works a desk job. He enjoys travel and spends several months each winter in Arizona, where he owns a condominium.

He experienced vague abdominal discomfort over the past year. A routine colonoscopy 5 months preceding the admission was normal. Four months preceding the admission, a routine surveillance computed tomography (CT) enterography was performed because of his history of inflammatory bowel disease and was remarkable only for a 2.5-cm left adrenal nodule that had not been observed during a study the year prior. An adrenal protocol CT (see Figure 1), performed 3 months preceding the admission, found the nodule to be unchanged in size and characterized the lesion as indeterminate for possible adenoma.

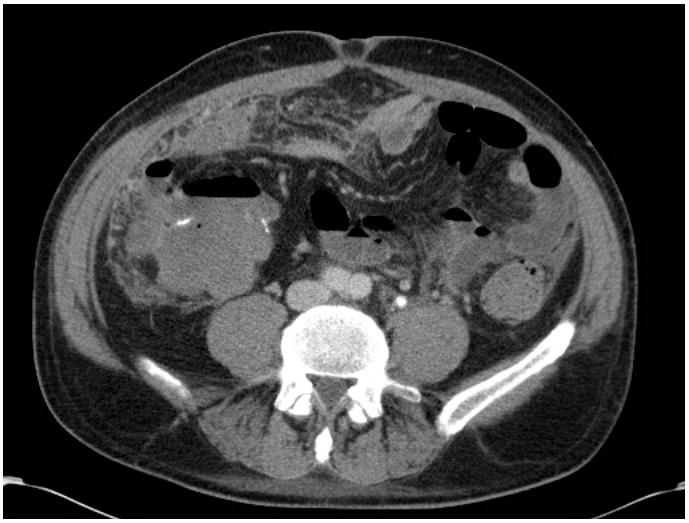
Figure 1. Protocol CT showing the 2.5-cm left adrenal nodule. Courtesy of Ilan S. Schwartz, MD, PhD.



Two months preceding the admission, the patient developed fevers, drenching sweats, and weight loss—eventually losing 15 lbs—in addition to worsening abdominal pain and an increased sense of abdominal distention.

A CT abdomen, as shown in Figure 2, was performed 1 month preceding the admission. The CT scan found that the adrenal nodule was unchanged and noted stranding of the greater omentum, which was not observed on the previous imaging. There were small-volume ascites and small bilateral pleural effusions. The general impression was of a likely malignancy, or less likely, tuberculosis. Because of persistence of fever, the patient was admitted to a hospital 1 month later.

Figure 2. Abdominal CT scan showing stranding at the greater omentum. Image courtesy of Ilan S. Schwartz, MD PhD.



Case Work-up

On examination, vitals were normal. There was no palpable peripheral lymphadenopathy. Chest examination was unremarkable. The abdomen felt bulky, firm, and tender. There were no cutaneous lesions.

A chest X-ray demonstrated small pleural effusions. A CT chest demonstrated several small, sub-centimeter nodules with internal calcification in the lungs, and a mild, right-sided pleural effusion. CT abdomen demonstrated anterior omental thickening.

As seen in Figure 3, CT/positron emission tomography (PET) of the abdomen demonstrated bilateral, metabolically active hilar lymphadenopathy, enlargement and hypermetabolic activity at the adrenals bilaterally, and intense metabolic activity at the thickened, nodular omentum. An ultrasound-guided omental biopsy was performed, and the pathology is shown below in Figure 4.

Figure 3. CT-PET of abdomen showing the omental mass with hypermetabolism (left) and intense hypermetabolism of the adrenals bilaterally (right). Image courtesy of Ilan S. Schwartz, MD, PhD.

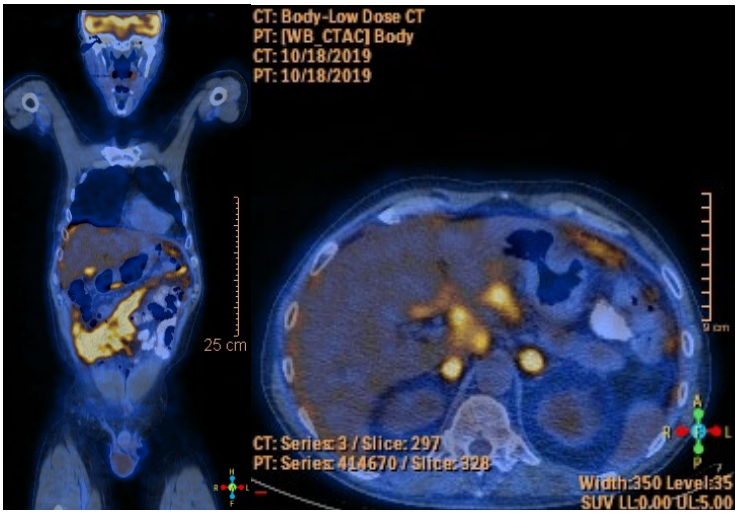
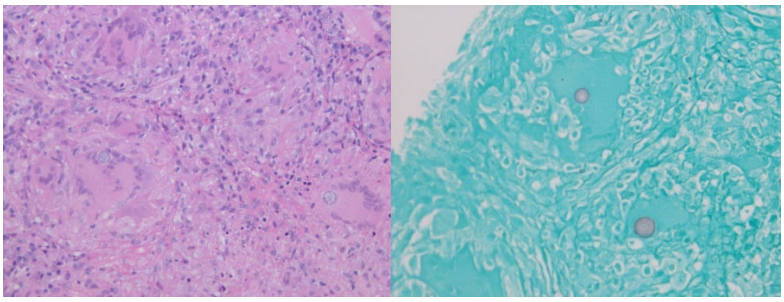


Figure 4. Omental biopsy using hematoxylin and eosin (H&E) stain, 20x, showing necrotizing caseating granulomas with spherules (left) and using Grocott's methenamine silver stain, 40x, with spherules highlighted (right). Images courtesy of Julinor Bacani, MD.



Diagnostic Tests

Bacterial, mycobacterial, and fungal cultures on tissue had no growth after 4 weeks. Serology tests were:

- *Coccidioides* immunodiffusion immunoglobulin M (IgM) positive
- *Coccidioides* enzyme immunoassay (IgM) and immunoglobulin G (IgG) positive

Challenge Question 1. TNF-α inhibitors are associated with which diseases?

A. Tuberculosis (TB)
B. Histoplasmosis
C. Coccidioidomycosis
D. Listeriosis
E. All of the above

Discussion

A. **Tuberculosis (TB).** TNF-α inhibitors carry a black-box warning for risk of reactivation of latent TB infection. All patients started on a TNF-α inhibitor should first be screened for latent TB infection by either skin test or interferon gamma release assay, and latent TB should be treated when present.

B. **Histoplasmosis.** Histoplasmosis is also a disease strongly associated with TNF-α inhibitor use. Infections are more likely to be disseminated[1]. In one large series of 98 patients with histoplasmosis complicating TNF-α inhibitor therapy, the median time from TNF-α inhibitor initiation to diagnosis of histoplasmosis was 15.5 months, suggesting that most cases occurred as new rather than reactivated infections[1]. There are no guidelines for screening patients who are candidates for TNF-α inhibitor therapy for histoplasmosis. TNF-α inhibitors carry a black-box warning for histoplasmosis.

C. **Coccidioidomycosis.** TNF-α inhibitors are associated with coccidioidomycosis. Patients who develop symptomatic coccidioidomycosis while on TNF-α inhibitors have high rates of hospitalization, disseminated disease, and death[2]. In a retrospective study from Arizona, 3.4% of patients not screened and treated for latent *Coccidioide*s infection prior to TNF-α inhibitor initiation developed symptomatic coccidioidomycosis. In contrast, screening resulted in pre-treatment and fewer cases of symptomatic disease (1.3%), confirming a role for screening prior to TNF-α blockade in patients living in endemic areas. The role of screening in patients outside these areas with travel histories is less clear. TNF-α inhibitors carry a black box warning for coccidioidomycosis.

D. **Listeriosis.** A few case reports have identified a potential association between TNF-α inhibitor use and the development of listeriosis. TNF-α inhibitors also carry a black box warning for risk of listeriosis.

E. **All of the above.** The United States (US) Food and Drug Administration (FDA) has warned that TNF-α antagonists increase the risk of tuberculosis, invasive fungal diseases (including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, pneumocystosis), hepatitis B virus infection, listeriosis, and legionellosis[3]. Infliximab, a monoclonal antibody against TNF-α, is associated with a higher risk of invasive fungal disease and TB than etanercept, a soluble TNF-α receptor[4].

Correct answer: E.

Challenge Question 2. Coccidioidomycosis has been acquired in all but which of the following locations?

A. California
B. Arizona
C. Washington State
D. Canada
E. Mexico

Discussion

A. **California.** California is a region of geographic risk for coccidioidomycosis, and most cases are acquired in central California.
B. **Arizona.** Arizona is a region of geographic risk for coccidioidomycosis and has the highest incidence of disease. The region of highest risk is the Sonoran Desert, which includes Phoenix and Tucson.
C. **Washington State.** Coccidioidomycosis has been acquired in Washington State, and *C immitis* was isolated from soil in eastern Washington, an arid part of the state[5].
D. **Canada.** Coccidioidomycosis has not been reported to have been acquired in Canada.
E. **Mexico.** Coccidioidomycosis is endemic to parts of Mexico.

Correct answer: D. *Coccidioides* species exist in the environment in arid soils, and the geographic range includes the Southwestern USA, Mexico, and parts of Central and South America. The incidence of coccidioidomycosis is highest in Arizona, followed by California. *Coccidioides* is also known to be present in Nevada, New Mexico, Utah, and Washington, but the cumulate incidence of coccidioidomycosis is much lower in these regions[6].

Challenge Question 3. Which of the following findings is encountered LESS often in patients with clinically evident coccidioidomycosis than in patients with clinically evident blastomycosis or histoplasmosis?

A. Extra-pulmonary dissemination
B. Erythema nodosum
C. Eosinophilia
D. Severe fatigue

Discussion

A. **Extra-pulmonary dissemination.** Extra-pulmonary dissemination is relatively rare in coccidioidomycosis, occurring in fewer than 1-3% of clinically symptomatic cases[7]. In contrast, extra-pulmonary disease occurs in 25-40% of patients with clinically evident blastomycosis[8] and $\geq$33% of patients diagnosed with histoplasmosis[9].
B. **Erythema nodosum.** Erythema nodosum is a reactive panniculitis that manifests as painful, erythematous nodules, usually of the legs, which occurs in several infectious and non-infectious conditions. It is common in primary coccidioidomycosis and can be present in 19% of cases[10]. Erythema nodosum also can occur with histoplasmosis. Among 435 laboratory proven cases of histoplasmosis diagnosed in an epidemic in

Indiana in 1978, 11 patients (4%) had erythema nodosum[11]. Although reported, it is an uncommon finding in blastomycosis[12].

C. **Eosinophilia.** Eosinophilia is common in primary coccidioidomycosis, occurring in as many as 71-88% of patients[13,14]. In contrast, while eosinophilia has been reported in histoplasmosis, it is uncommon. It is not a common feature of blastomycosis.

D. **Severe fatigue.** Severe fatigue is a notable manifestation in patients with coccidioidomycosis and occurs in up to two-thirds of patients with primary pulmonary disease[15]. Fatigue usually improves to that comparable with the general population by 12 weeks, and resolution does not seem to be affected by treatment[16]. Severe fatigue is not typically noted in patients with histoplasmosis, with the exception of patients with hypoadrenalism secondary to adrenal involvement, in whom it is common[17]. Fatigue was reported by 92-95% of patients with pulmonary blastomycosis patients[18,19], but it has not been quantified.

Correct answer: A.

Challenge Question 4. Which of the following is TRUE regarding serological diagnosis of coccidioidomycosis?

A. Complement fixation (CF) assays are most sensitive in immunocompromised patients
B. CF titer can identify patients at risk of dissemination and can be useful to monitor disease activity
C. Enzyme immunoassay (EIA) has modest sensitivity but excellent specificity for *Coccidioides* infection
D. Immunodiffusion (ID) has high sensitivity but only moderate specificity for *Coccidioides* infection
E. Detection of antibodies from cerebrospinal fluid (CSF) have no role in the diagnosis of coccidioidal meningitis

Discussion

A. **Complement fixation (CF) assays are most sensitive in immunocompromised patients.** All serological tests for coccidioidomycosis (CF, ID, and EIA) are less sensitive in immunocompromised patients[7,20]. Sensitivity is improved by repeating the test a second time[21].

B. **CF titer can identify patients at risk of dissemination and can be useful to monitor disease activity.** CF titer during primary uncomplicated coccidioidal pneumonia can be useful to identify patients at higher risk of disseminated disease. Traditionally, a cut off of 1:16 has been used, but more recent data suggest that a cut off of 1:32 may be more appropriate[22]. However, it should be noted that dissemination can still occur at low serum CF titers. Notably, coccidioidal meningitis can occur with low serum titers and high CSF titers. CF titer can also be useful to monitor disease activity.

C. **Enzyme immunoassay (EIA) has modest sensitivity but excellent specificity for *Coccidioides* infection.** EIA is a useful first test because it can be performed locally and has high sensitivity. Samples with positive results are often reflexively tested with ID or CF tests because these are more specific. However, the specificity of EIA is reduced because it can cross react with other endemic mycoses[20,23].

D. **Immunodiffusion (ID) has high sensitivity but only moderate specificity for *Coccidioides* infection.** Both ID and CF have lower sensitivity and higher specificity compared to EIA. For this reason, and the fact that

EIA is often available in local laboratories whereas the others are send-out tests, EIA is frequently used as an initial screening test, with subsequent confirmatory testing by CF or ID[20].

E. **Detection of antibodies from cerebrospinal fluid (CSF) have no role in the diagnosis of coccidioidal meningitis.** With few exceptions, the detection of *Coccidioides* antibodies is considered diagnostic for coccidioidal meningitis. The exceptions are low titer IgG in CSF that may represent spillover from high serum titers or parameningeal disease. In these cases, CSF indices can help determine which patients have meningitis: the presence of high cell counts and protein and low glucose is strongly suggestive of meningitis[24,25]. IgG, detected by CF, is present in CSF in 95% of patients with coccidioidal meningitis[24]. On the other hand, IgM is infrequently detected but is invariably associated with meningitis[24].

Correct answer: B.

Challenge Question 5. Which of the following variables is a risk factor for disseminated coccidioidomycosis?

A. Use of immunosuppressants and TNF-α inhibitors
B. Black race
C. Pregnancy
D. All of the above

Discussion

A. **Use of immunosuppressants and TNF-α inhibitors.** Patients who are immunocompromised (including those with advanced HIV), use immunosuppressants, or use TNF-α inhibitors are at higher risk of disseminated coccidioidomycosis[26].
B. **Black race.** Several studies have found Black race to be a risk factor for disseminated coccidioidomycosis[26-28].
C. **Pregnancy.** Pregnant women, especially those in the third trimester, are at higher risk of disseminated coccidioidomycosis[29,30]. It is possible that dissemination is more likely in pregnancy because of a decrease in Th1 immune response, which is important in *Coccidioides* immunity[29].
D. **All of the above.** This is the correct answer.

Correct answer: D.

Challenge Question 6. Does this patient need a lumbar puncture (LP) to exclude coccidioidal meningitis?

A. Yes, all immunocompromised patients with coccidioidomycosis should have an LP
B. Yes, all patients with disseminated (extrapulmonary) coccidioidomycosis should have an LP
C. Only if central nervous system (CNS) symptoms are present
D. Only if high complement fixation (IgG) antibody titers are present
E. No, because it would not affect management

Discussion

A. **Yes, all immunocompromised patients with coccidioidomycosis should have an LP.** Not all immunocompromised patients with coccidioidomycosis require CSF examination, although this would be indicated if there are any symptoms of neurologic involvement (eg, headache, ataxia, focal signs or symptoms, intractable vomiting, etc.).
B. **Yes, all patients with disseminated (extrapulmonary) coccidioidomycosis should have an LP.** Not all patients with extrapulmonary coccidioidomycosis require CSF examination if neurological signs or symptoms are absent.
C. **Only if CNS symptoms are present.** Until recently, patients with coccidioidomycosis considered at high risk of dissemination routinely had CSF examinations[31]. However, a multicenter retrospective study reviewed 58 patients with coccidioidomycosis who underwent CSF examination and found that of the 14 patients with meningitis, all had at least one symptom of CNS infection (most commonly headache), whereas no patients without CNS symptoms had meningitis. This remained true even in the subgroup of patients with HIV infection[31]. The presence of headache, however, is not specific for meningitis in patients with coccidioidomycosis, and in fact, headache was reported in up to 81% of patients with uncomplicated primary coccidioidal pneumonia[32]. Infectious Diseases Society of America (IDSA) guidelines recommend that if headache is modest and improves in approximately 1 week, then CSF examination is not required[33].
D. **Only if high complement fixation (IgG) antibody titers are present.** High *Coccidioides* complement fixation is associated with disseminated disease but is not specific for CNS disease.
E. **No, because it would not affect management.** Coccidioidal meningitis is a serious complication of coccidioidomycosis. Management of coccidioidomycosis with meningitis is different from that without meningitis because the latter is currently considered incurable and requires lifelong azole therapy. The first line of therapy is fluconazole—like for other forms of the disease—but treatment should be continued indefinitely. In addition, treatment failure may require intrathecal amphotericin B[33,34].

Correct answer: C.

Challenge Question 7. How should this patient be managed initially?

A. Liposomal amphotericin B
B. Fluconazole
C. Itraconazole
D. Posaconazole

Discussion

The IDSA clinical management guidelines for coccidioidomycosis address the question of whether immunosuppressed patients, including those on TNF-alpha inhibitors, should be treated differently than non-immunosuppressed patients. Because of the risk for complicated disease, including dissemination, IDSA guidelines recommend treatment of primary uncomplicated pulmonary coccidioidomycosis in

immunosuppressed patients, including those on TNF-α inhibitors. Other groups at high risk of complicated disease who warrant treatment of primary coccidioidomycosis—especially when extensive pulmonary disease is present at diagnosis—are pregnant women, especially those in the third trimester, patients with diabetes, and patients who are frail due to old age and comorbidities. The guidelines do not make a specific recommendation for whether Black or Filipino patients with early, uncomplicated coccidioidomycosis require treatment, but note that some experts do treat such patients routinely[33].
Beyond the decision of whether to treat early uncomplicated disease, the IDSA guidelines recommend that patients who are on TNF-α inhibitors or other biological response modifiers be treated similarly to other patients. In other words, amphotericin B should be used up front only if disease is severe[33].

A. **Liposomal amphotericin B.** Liposomal amphotericin B is indicated for severe coccidioidomycosis. For other forms of disease, initial treatment with an oral azole is recommended. Limited data suggest that the penetration of amphotericin B into peritoneal tissue is variable[35].
B. **Fluconazole.** Fluconazole is an appropriate option for primary therapy in this patient. Fluconazole achieves good penetration into the peritoneal cavity[35].
C. **Itraconazole.** Itraconazole is effective for the treatment of coccidioidomycosis. However, it does have some problems with absorption and bioavailability[36], although a new formulation of itraconazole that is highly bioavailable is now available (SUBA-itraconazole)[37]. However, the cost of itraconazole is higher than fluconazole, and there are more drug-drug interactions. It can be considered in patients who are intolerant of or who fail to respond to fluconazole[34].
D. **Posaconazole.** Posaconazole is effective for the treatment of coccidioidomycosis but is expensive and is not recommended over fluconazole. Posaconazole can be considered for salvage therapy in patients with non-meningeal coccidioidomycosis who fail to respond to fluconazole[34].

Correct answer: B.

Antifungal Treatment
The patient is started on fluconazole 400 mg by mouth daily. The patient's gastroenterologist suggests that the infliximab cannot be discontinued because the patient has previously not responded to alternative treatments.

Challenge Question 8. What do you recommend?
A. Insist that infliximab be changed to an alternative, non-TNF-α inhibitor treatment
B. Continue fluconazole as long as infliximab will be continued, possibly indefinitely
C. Treat with fluconazole for a finite duration then stop and monitor clinically
D. Any of the above are reasonable with appropriate clinical follow-up

Discussion
The management of biological response modifying treatment such as TNF-α inhibitors in patients with coccidioidomycosis is uncertain. There are some limited data from case series to suggest that it is reasonable

to resume or continue these medications if necessary[38]. Recurrences were not observed in a small retrospective series of patients who continued biological response modifying treatment, even after discontinuing fluconazole (median follow up was 30 months)[38].
Correct Answer: D.

Case Follow-up
During a follow-up visit at 8 weeks, the patient complains that his hair is falling out and wonders if it is because of fluconazole.

Challenge Question 9. Which of the following is true regarding fluconazole adverse effects?
A. Fluconazole is extremely well tolerated and rarely discontinued because of toxicities
B. Fluconazole-associated toxicities are common and frequently require dose modification or treatment interruption
C. Fluconazole is a negative inotrope and can cause or precipitate congestive heart failure
D. Long term use of fluconazole can result in fluorosis and periostitis
E. Fluconazole is safe during pregnancy

Discussion
A. **Fluconazole is extremely well tolerated and rarely discontinued because of toxicities.** Fluconazole is often thought of as a benign medication, but long-term, high-dose fluconazole as used for coccidioidomycosis is associated with frequent toxicities[39]. In fact, in a large retrospective study, 64 out of 124 (51.6%) patients receiving fluconazole for coccidioidomycosis reported at least one toxicity; therapeutic modification such as dose reduction or treatment substitution or discontinuation was required in two-thirds of affected patients[39]. The most frequent toxicities were fatigue, alopecia, and xerosis.
B. **Fluconazole-associated toxicities are common and frequently require dose modification or treatment interruption.** As stated above, fluconazole is associated with toxicities–especially at higher doses (400 mg daily or greater) over prolonged periods – and can require treatment modifications.
C. **Fluconazole is a negative inotrope and can cause or precipitate congestive heart failure.** Fluconazole is not a negative inotrope. This is an adverse effect of itraconazole.
D. **Long term use of fluconazole can result in fluorosis and periostitis.** Fluconazole does not result in fluorosis or periostitis, which are adverse effects of long-term voriconazole.
E. **Fluconazole is safe during pregnancy.** High-dose fluconazole, like that used for coccidioidomycosis, is teratogenic when administered in the first trimester of pregnancy. It is associated with pregnancy loss, trapezoidocephaly, mid-facial hypoplasia, cartilage abnormalities with multiple synostoses and skeletal fractures, and results in a set of congenital deformities resembling Antley-Bixler syndrome[40]. For this reason, fluconazole and other systemic azoles are contraindicated in the first trimester of pregnancy.

Correct answer: B. Fluconazole-associated toxicities are common and frequently require dose modification or treatment interruption.

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