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Case Challenge
Cocci Are in the Air
Michelle Bergen

A B S T R A C T

The San Joaquin Valley in Central California is a semiarid region that is known to be highly endemic for coccidioidomycosis infections in high-risk groups. Coccidioidomycosis, also known as valley fever, is caused by the fungal spore Coccidioides, which can be found in the soil in arid and semiarid regions in the Southwest United States and parts of Central and South America. When soil is disturbed through excavation, agricultural activities, or with any other soil movement, these activities can release the fungal spores into air; people who are in close proximity can potentially inhale them. The purpose of this clinical case study is to address the need for coccidioidomycosis infection awareness and educate primary care providers to determine the diagnostic reasoning and process. A simple algorithm and template will aid them to accurately diagnose and treat patients with valley fever earlier in the disease process.

Case Presentation

A 64-year-old female patient named S.W. presented to her primary care provider (PCP) for the second time with symptoms of cough, chest congestion, shortness of breath (SOB), wheezing and fatigue for 1 month.

Past Medical History

Approximately 1 month ago, before her second primary care visit, she went to an urgent care clinic with symptoms of cough, chest congestion, SOB, wheezing, and fatigue. At that time, she was prescribed a 5-day course of azithromycin (Zithromax, Pfizer Inc) with no improvement. At her urgent care visit, a chest x-ray and complete blood count (CBC) panel were done.

After her urgent care visit, she returned to her PCP 2 weeks later and was started on doxycycline, 100 mg for 10 days, and prednisone, 20 mg for 5 days. Her symptoms at that time included SOB, cough, and fatigue. She did not have a fever any of the 3 sick visits. Throughout her illness she was also prescribed albuterol and mometasone inhalers. For approximately 1 month, S.W. continued with a cough, SOB, and fatigue after 2 rounds of antibiotics, steroids, and β2 agonists.

S.W. has a history of nontoxic nodular goiter, hypothyroidism, benign paroxysmal positional vertigo, chronic allergic rhinitis, irritable bowel syndrome, microscopic hematuria, fibrocystic breasts, cervical spondylosis, and a family history of breast cancer. S.W. is currently treated with the appropriate medications for her multiple comorbidities and is monitored by endocrine, urology, immunology, and ears, nose and throat specialists. S.W. is up-to-date on all of her vaccinations and had a recent influenza immunization.

Social and Family History

Her social history includes occasional alcohol use, nonsmoker, seasonal allergies, and an occupation that does not involve working around dust or soil disturbing activities, but she lives in Sanger, California, a rural community in Fresno County that is surrounded by agriculture. She is married and is of white ethnicity. The patient did report to her PCP that her husband was diagnosed and treated for valley fever (VF) a few years ago. The patient’s first-degree relatives have no current health problems. Her most recent travel history before she become ill was a vacation to Hawaii in mid-September.

Review of Symptoms

General: The patient reports profound fatigue. She denies any recent weight loss or recent febrile episodes.

Head, eyes, ears, nose, and throat: Reports allergic rhinitis symptoms.

Neurologic: The patient reports intermittent headaches during her course of her illness.

Respiratory: The patient reports SOB, cough, wheezing, and chest congestion. She denies hemoptysis.

Gastrointestinal: The patient denies nausea, vomiting, diarrhea, or anorexia.
Muscloskeletal: The patient denies arthralgias and muscle aches.

Integumentary: The patient reports a localized macular rash to her left lower extremity, but she is unsure on how long the rash has been present.

Genitourinary: Reports no symptoms.

Physical Examination

S.W.’s physical examination findings were blood pressure, 139/81 mm Hg; heart rate, 98 beats/min; respiratory rate, 16 breaths/min; oxygen saturation, 97% on room air; temperature, 99.4°F (ear); height, 160 cm; weight, 80.27 kg; and a calculated body mass index of 30.1 kg/m². On her physical examination the patient appeared to be acutely ill, well-nourished, and well-developed.

- Eyes: Lids and conjunctivae were noninjected, no discharge, and no palor; scleras were noninjected.
- Ear, nose, mouth, throat: External ears were absent of lesions, external ear canals clear, tympanic membranes were intact with good cone of light. No hearing loss evident. Nose was absent of lesions externally, nares patent, nasal passages were clear, no sinus tenderness, no nasal discharge (left naris erythematous). Oropharynx showed moist mucus membranes, no erythema, and no exudates.
- Cardiovascular: Apical pulse not displaced. Heart auscultation regular rate and rhythm, normal S1 and S2, no murmurs, gongs, or rubs.
- Lungs: Expiratory wheezing noted bilaterally to the upper lung fields. Tactile fremitus equal on vibration posteriorly. Percussion equal sounding to all lung fields bilaterally. Absence of crackles and rhonchi on auscultation. Respirations were of normal rate, rhythm, and depth.
- Neurologic: Normal gait and balance. Romberg negative.
- Integumentary: Inspection and palpation of skin showed no evidence of lesions and no jaundice. There was a small area of nonraised macular rash to the left lower extremity; surrounding skin was intact and of normal color.

Imaging Findings

Chest x-ray done at her first urgent care visit showed right lobular infiltrates.

Laboratory Results

CBC and differential: white blood cells, 12.6/L (mild elevation); red blood cells, 14.2/L; hemoglobin, 11.6 g/dL; hematocrit, 35.6%; platelets, 200 × 10⁹/L; neutrophils, 60%; lymphocytes, 40%; monocytes, 7%; and eosinophils, 3% (mild elevation). Erythrocyte sedimentation rate (ESR) was 50 mm/h (elevated).

Coccidioidomycosis (cocci) serology: Enzyme-linked immunosorbent assay (EIA) positive for immunoglobulin (Ig) M and IgG. Complete fixation test using the rapid antigen test based on S.W’s symptoms. One can also use VF as a differential and should strongly consider coccidioidomycosis (cocci), a fungal pathogen that is highly endemic to the Central Valley in California.

One must, however, differentiate these illnesses from the pertinent diagnostic workup and its interpretation. Lymphoma for example, the initial laboratory workup would include CBC with manual differential, comprehensive metabolic panel, HIV, hepatic panel, lactic dehydrogenase, C-reactive protein, chest x-ray, and computed tomography of the chest, abdomen, and pelvis (only done if you truly suspect lymphoma with abnormal cells).

Lung cancer is another reasonable DD, but S.W.’s risk factors are low for this diagnosis. The initial lung cancer workup would include assessment of environmental risk factors and pertinent laboratory tests, which include CBC with differential, comprehensive metabolic panel, psmutum cytology, and chest x-ray.

The novel COVID-19 virus is potential in her case and is a valid DD to consider. Although the 2 illnesses are very similar in symptoms and both are acquired through the respiratory tract, one cannot tell them apart. However, their general patterns are different and can aid in providing clues on when a provider would need to order the appropriate diagnostic tests. Generally, the diagnostic tests for COVID-19 are done with a rapid flu test using the rapid antigen test and direct fluorescent antibody or the viral culture and polymerase chain reaction test. S.W. was not tested for COVID-19.

Lastly, bacterial pneumonia is the most common DD used in the patient’s history and workup. Laboratory and imaging tests include CBC, 2 sets of blood cultures, sputum gram stain and cultures, and chest x-ray imaging. As in S.W’s case, none of this workup was done other than a CBC and chest x-ray imaging, and community-acquired pneumonia may have been the likely DD for S.W. The patient’s chest x-ray image showed right lobular infiltrates, which is a common finding in pulmonary cocci as opposed to bacterial infections, which are more consolidated.

Another symptom that S.W. has is a developing rash to her left lower extremity. This is concerning because it occurred during her respiratory illness. A rash of this type could just be incidental or it could develop into erythema nodosum or erythema multiforme. A rash that is minor in appearance can develop from a delayed-type hypersensitivity reaction to various antigens or it could be an autoimmune reaction. If this rash is accompanied by fever and arthralgias, it may be associated with other etiologies, such as idiopathic, bacterial (streptococcal infections), sarcoidosis, or drugs

**Case Challenge Questions**

1. Based on the patient’s medical and social history and physical findings, what are the differential diagnoses (DDs) for S.W.?
2. What diagnostic test(s) would a provider consider ordering for this patient to confirm a diagnosis of VF as a differential?
3. Once a diagnosis is confirmed, what would be the provider’s next step?
(the patient was on 2 classes of antibiotics but none of them were sulfonamide or amoxicillin derivatives), or it could be fungal (coccidioides immitis, histoplasmosis, blastomycosis). However, dermal manifestations like erythema nodosum and erythema multiforme are not definitive findings of VF, because these skin manifestations can occur in other diseases mentioned above. A provider would need to collaborate with other clinical and objective findings to accurately diagnose S.W.'s rash to a cocci infection.

Now that one has considered a list of DDs, it is then imperative to collect a thorough travel and occupational history, order the correct diagnostic tests, and interpret the findings relative to the patient's clinical presentation. With a cocci infection, the onset of symptoms occur 1 to 3 weeks after inhalation of the spores. The severity of the symptoms often depends on the number of spores inhaled and the person's health status.

**Background on VF**

Approximately 10,000 VF cases are reported to the state health departments each year. VF is reportable in 22 states; 70% of the reported cases are from Arizona and 30% are from California. According to expert opinion, the disease is seasonal, lasting from May through late October, with the autumn season having the highest incidence of cocci infections (Dr. M. Reddy, Dr. M. Fayed, personal communication, October 6, 2018 and October 26, 2019).

People who are at risk are farm and ranch workers, construction workers, firefighters, and individuals with a weakened immune system, such as HIV/AIDS, or on immunotherapy (steroids). Patients with HIV/AIDS are more susceptible to cocci infections if their CD4 T-lymphocytes counts are < 250 cells/mm³. If these patients have a positive cocci serology result without overt symptoms, they will need to start on oral azole therapy, but if their CD4 T-lymphocytes counts are > 250 cells/mm³ and they do not have symptoms, then no treatment is recommended. Additionally, this disease also affects patients with diabetes, older adults, pregnant women, and ethnic and racial minorities, including, Black, Hispanic, Native American, and Filipino. In the case of S.W., she does not fall into the occupational, comorbidity, or ethnic/racial risk categories for VF, but she does live in an agricultural community where soil disturbance activity is high and her spouse was diagnosed with VF a few years ago.

People with mild cocci are asymptomatic, and 60% of infected people recover without treatment. Widespread or disseminated cocci infections can be life-threatening and can affect skin, bones,
The clinical symptoms of VF are fatigue, shortness of breath, fever, muscle and joint pains, rashes to the body and lower extremities, headaches, nocturnal diaphoresis, unexplained weight loss, and cough. In current primary care clinical practices in the Central Valley, there are no standardized guidelines on how and when to test for cocci.

2. What diagnostic test(s) would a provider consider ordering for this patient to confirm a diagnosis of VF?

A variety of cocci serology tests are available; some are highly specific, whereas others are highly sensitive, and false-positive results are also possible. A simple acronym and algorithm that is specific for cocci will be defined later to guide providers on the testing, diagnosing, and treating VF symptoms.

In S.W’s case, once the provider has considered the DD of VF or a cocci infection, and has ruled out other common respiratory illnesses, the next step in the algorithm is to order the correct diagnostics to confirm cocci. A simple blood panel for cocci detecting IgM and IgG antibodies with the EIA, CF, and the immunodiffusion (ID) test are the best screening tools for VF. In addition to a serology panel, a chest x-ray must be ordered to assess for any pulmonary nodules, which is a common finding in cocci infections but is not always present in the acute phase.

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On the contrary, a negative serologic test may not exclude the presence of a coccidioidal infection nor does the absence of pulmonary nodules. In this instance, it is recommended that 1 or 2 repeated serologic tests every 2 to 3 weeks will increase the sensitivity for the diagnosis of cocci. If repeated testing over a 2-month period fails to produce cocci antibodies, it is unlikely that the patient has the disease.

3. Once a diagnosis is confirmed, what would be the provider’s next step?

Once a diagnosis is confirmed with positive serology results for cocci, the provider’s next step is to refer the patient to a pulmonologist or an infectious disease specialist. At this point, the specialties involved will order further testing, such as repeat serology tests and chest imaging, to look for pulmonary nodules or infiltrates. In the meantime, if specialty medicine is not accessible to the patient due to insurance or if pulmonary or infectious disease specialists are difficult to access based on the patient’s geographic location, then the PCP can initiate an antifungal therapy or monitoring, or both. The University of Arizona, College of Medicine...
Tucson, Valley Fever Center of Excellence (2019) recommends starting patients who present with complicated clinical symptoms of VF or who are at high risk, as mentioned above, on fluconazole, 400 mg/d, for 3 to 6 months. Regular monitoring with cocci serology, CF titers, C-reactive protein, and ESR, and chest x-ray are imperative.8

Once treatment is initiated, performing an ESR and C-reactive protein along with the CF titers and cocci serology for IgG and IgM by EIA will determine resolution or progression of the disease.8 With the initial infection with cocci, the ESR will be elevated, and cocci CF and ID antibodies should decrease as the illness progressively resolves; these should be tested weekly.7 If these results do not normalize as expected, there should be concern that complications, such as dissemination of the disease maybe occurring. Another avenue is to collect mycology cultures from sputum sampling, but this collection is often difficult in an ambulatory setting because patients may not be able to produce enough bronchial sputum, and there is a potential risk associated with isolating the cocci spores by the laboratory personnel.3

It is recommended that a follow-up visit be scheduled every 2 to 3 months for 12 months to monitor disease (Figure).8 The follow up visits will include the initial history, review of systems, and the physical examination. The diagnostic studies should be a chest x-ray if the previous x-ray image was abnormal, cocci serology, C-reactive protein, and ESR during and after medical therapy. During the 12-month surveillance, always recheck cocci serology at 3 months and chest x-ray at the initial follow-up visit and again at 12 months.8

Five commercially available oral antifungals are currently on the market for complicated cocci: ketoconazole, fluconazole, itraconazole, voriconazole, and posaconazole.5,8 These antifungals can be initiated at the time of diagnosis by a PCP if specialty referral is inaccessible or delayed. Antifungal therapy is not advised in non-immunocompromised patients or without overt immunosuppression, who are newly diagnosed with uncomplicated cocci; instead, only supportive measures, close observation, and physical therapy for reconditioning are the first-line treatments for fatigue and arthralgia.5 Antifungal treatment will need baseline liver function tests to monitor hepatotoxicity from azoles before treatment, and thereafter routinely at the discretion of the PCP. As with all antifungals, it is essential to educate patients on the abstinence from alcohol while taking these drugs to avoid a disulfiram-like reaction.

As PCPs, knowing what the clinical symptoms are based on the patient’s demographics, and medical, social, travel, and occupational histories are the key points to early diagnosis, but even with these clues, as in the case of S.W., the classic determinants are not always that obvious.

Conclusion

Cocci infections are found in the more vulnerable population, which includes older adults with multiple comorbidities, pregnant women, people with a weakened immune system, and in racial and ethnic minorities. There is currently no vaccine available, but research is being conducted on a possible oral vaccine.9 Early diagnosis of cocci is imperative to prevent dissemination of the disease, reduce health care costs from ongoing unnecessary treatments, and avoidance of persistent infection leading to long term morbidity and disability. It is difficult to diagnose VF; however, with the correct training, PCPs can learn how to recognize and manage VF earlier in the disease continuum. There is an acronym that perhaps will make it easier for the PCPs to use in clinical practice to help them determine a possible cocci infection. The acronym to aid in recognizing VF is:

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\begin{align*}
C & = \text{consider the diagnosis} \\
O & = \text{order the right tests} \\
C & = \text{check for risk factors} \\
C & = \text{check for complications} \\
I & = \text{initiate management}
\end{align*}
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To recognize and treat cocci, one should consider the diagnosis based on the patient’s clinical symptoms, risk factors, occupation, and the patient’s location of residence. Once the risk factors are evaluated, the PCP must order the right tests to confirm or rule out cocci and always check for complications and initiate a referral or management. The 4 main cocci serology tests that should always be on the cocci panel are EIA with IgG and IgM antibodies, ID, CF, and ESR.

To conclude with the case study of S.W., her cocci serology panels came back positive for IgG and IgM, with the panel being done after she completed azithromycin, doxycycline, and prednisone. She was immediately referred to a pulmonologist for further care.

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