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A 32-yr-old African-American male active duty Air Force air traffic controller (ATC), with no significant past medical history, presents to the Flight and Operational Medicine Clinic (FOMC) with 4–5 d of nonproductive cough, subjective fever, malaise, and fatigue. He was evaluated in FOMC by the on-duty flight surgeon. On interview, his history of this clinical episode is rather benign, with symptoms gradually worsening over the past 5 d and with no reported exposures or contacts other than his 2-yr-old daughter, who attends the Child Development Center and has occasional upper respiratory infections. He is originally from Georgia, but transferred to an Air Force base in the U.S. southwest region last year where he and his family purchased a new home in a growing housing development. He denies recent travel history. He describes his past medical history as only a few upper respiratory infections, with the last occurrence 1 yr ago, and some minor musculoskeletal back pain that resolved 4 yr ago. Past surgical history, family history, and social history are noncontributory. He takes a daily multivitamin and fish oil, but no prescribed medications, and reports no known drug allergies. On review of systems, the ATC reports the aforementioned complaints, along with a few minor headaches that accompany his fever for the past few days, and decreased appetite, but denies rashes, gastrointestinal symptoms, or genitourinary symptoms. On clinical exam, the ATC is found to be afebrile, with normal vital signs, normal lung exam, and

a benign remainder of the clinical exam. Conservative treatment is prescribed, with ibuprofen for pain and guaifenesin for cough, and the patient is placed on duties not including controlling (DNIC) status for 5 d. The patient is instructed to return to the FOMC for any worsening symptoms or within the 5-d interval for return to status when symptoms are improved. However, after 3 d, the patient returns to the clinic complaining of continued symptoms and describes no relief from the prescribed medication therapy.

1. Given this patient's clinical presentation and history, what is the next appropriate course of action?

- A. Reassure the patient that this is likely a viral etiology and may take more time to improve.
- B. Repeat the patient's history and clinical exam, repeat vital signs, and investigate further any sick contacts or exposures not previously reported.
- C. Redirect the patient immediately to the Radiology Clinic for a contrasted chest computed tomography (CT) scan.
- D. Explain to the patient that he will be rechecked upon follow-up tomorrow morning during the clinic's sick-call hours.

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ANSWER/DISCUSSION

1. B. The most appropriate action to take at this point is to engage in dialogue with the patient to attempt to discover any potential contributory information (such as exposures not previously mentioned, further additional occupational information, hobbies, pet history, sick contacts, or additional medical history) and to thoroughly reevaluate the patient. Although viral etiologies for upper respiratory infections are extremely common and may take up to several weeks for resolution, a repeated history and physical exam are the best options at this point. Accordingly, instructing the patient to travel directly to the Radiology Clinic for imaging without further evaluation of the cause of the patient's illness is not appropriate and would cause unnecessary radiation exposure.

Upon further discussion with the patient, you learn that the ATC has had no known unusual exposures and that his wife and child are healthy, without any of these symptoms. Vital signs are repeated and are all within normal range, except for a mild elevated temperature at 99.6°F. A repeated clinical examination shows clear lung fields, with no wheezes, rales, or rhonchi. Given that this patient has now had symptoms for over 7 d, an antibiotic is prescribed for presumed bronchitis. The patient again is instructed to return to the FOMC if not any better, and his DNIC status is extended for the duration of treatment.

The patient returns to FOMC 3 d later complaining of worsened fatigue, fever, and nonproductive cough despite the antibiotic treatment. This is the third clinic visit for this ATC concerning this episode of illness. The original flight surgeons who have seen this patient in the past are out of the office, so you review his history and perform his exam. A repeat physical exam reveals an ill-appearing, pale, African-American man, with vital signs as follows: heart rate 100, blood pressure 125/76, respiratory rate 16, oxygen 96% on room air, temperature 100.4°F. Head, eyes, ears, nose, and throat exam, heart sounds, lung exam, abdominal exam, musculoskeletal exam, and skin exam reveal no abnormalities.

2. What is the next appropriate course of action you should take?

- Since this patient is not having improvement in symptoms despite therapy, obtain an immediate maxillofacial/sinus CT, as there is new concern for sinusitis rather than bronchitis.
- Discharge the patient from the clinic, as his vitals and physical exam are normal, and advise/reassure patient to follow up in clinic in a few days for recheck, since antibiotic therapy will take some time to show clinical improvement.
- Obtain a chest X-ray due to concerns for other potential etiologies of symptoms.
- Refer this patient to an allergy specialist to determine the etiology of his upper respiratory infection symptoms.

ANSWER/DISCUSSION

2. C. The most appropriate care for this patient at this point is to further investigate why he is worsening. As the patient's clinical symptoms are stable, but proceeding as likely pneumonia, a chest radiograph with posteroanterior and lateral images is the most appropriate next investigatory step. Since the patient's primary complaints are more

upper respiratory in nature, rather than sinus pain with nasal drainage, a CT of the sinuses or referral to an allergist would not be consistent with the presenting symptoms. As previously stated, a high index of suspicion should be afforded this patient since he has returned to the clinic twice after the initial visit, and simply discharging the patient with reassurance is not appropriate.

The chest radiograph obtained reveals a hazy infiltrate in the right middle lung field, substantiating your suspicion of pneumonia. At this point, you decide to modify the patient's medications, since a diagnosis of pneumonia has now been made radiographically and clinically, and you prescribe a different oral antibiotic. The patient is very grateful as he leaves the clinic, and you reassure him of his diagnosis and new treatment, while encouraging him to return to FOMC if there is no improvement in symptoms. Again, his DNIC status is updated on his Air Force Form 2992.

In approximately 4 d, the patient returns to FOMC complaining of much worsened fatigue, cough, and weight loss. Neither of the previous flight surgeons who have evaluated this patient are available, so the on-duty flight surgeon reviews the medical record and evaluates the patient. According to the patient, he states he has lost 20 lb in the past 2 wks, has a cough that cannot be abated, and has extreme fatigue to the point where he cannot perform the assigned administrative duties at his work in the control tower.

Your interview with the patient reveals no new information and is consistent with the previous encounter notes. The patient reports no new symptoms, only a worsening of the fatigue, generally not feeling well, and continued nonproductive cough, but no hemoptysis, chest pain, or rashes. Additionally, the patient denies worsened headaches or stiff neck. On physical exam, the patient continues to appear ill, pale, noticeably thin, and fatigued. Vital signs are consistent with his previous set from 4 d ago, but with temperature elevation of 100.3°F and oxygen saturation of 95%, which is mildly worse from prior recording. The clinical exam reveals normal sounding heart and lung fields, and nothing else has changed on his physical exam.

3. What should you do next?

- Order lab work and a chest CT and have the patient remain in the clinic under observation while awaiting the results.
- Refer the patient to an internist due to weight loss.
- Arrange for hospital admission.
- Discharge the patient with reassurance that the medication needs a while longer to work.

ANSWER/DISCUSSION

3. A. Since this patient has worsened symptoms despite two oral antibiotic medications and a chest radiograph consistent with pneumonia, a further workup is now necessary. A referral for weight loss to Internal Medicine would be inappropriate, as the patient has pneumonia with worsened clinical presentation. Likewise, simply discharging the patient from the clinic without further workup is also inappropriate, as the patient's symptoms are deteriorating, although he remains hemodynamically stable with only slight hypoxia. Alternatively, arrangements to transport the patient to the nearest Emergency Department could also be considered, given his concerning fever and low oxygen

saturation. In this case, lab work and radiology studies are obtainable after speaking with the radiologist on duty. So you decide to keep the patient in your clinic to perform this workup.

A complete blood count, a basic metabolic panel, and a urinalysis are obtained, which reveal a mildly elevated white blood cell count of 11.9, basic metabolic panel within normal range, and normal urinalysis. Chest CT is accomplished, which reveals multiple mediastinal enlarged lymph nodes and confirms the presence of now bilateral pulmonary infiltrates. You receive a call from the radiologist with concerns about the abnormally enlarged mediastinal lymphadenopathy, suggesting a malignant etiology.

An immediate referral to an off-base pulmonologist is made and transportation is arranged for this patient to the local hospital for admission and pulmonary evaluation. The patient undergoes a bronchoscopy several days later and is then discharged from the hospital, awaiting the pathology workup of the biopsied specimens.

After a few days, you receive the faxed pathology report from the pulmonologist. The patient was diagnosed with coccidioidomycosis, more commonly known as valley fever, and is started on oral fluconazole daily. You check with your patient; he is doing well and is extremely grateful for the care he received.

Coccidioidomycosis, also known as San Joaquin Valley fever, is an infection caused by the *Coccidioides* species of dimorphic fungi.^{4,5,7,10,16} Valley fever is considered endemic to Mexico, Central and South America, and the states of Arizona, California, Nevada, New Mexico, and Utah.^{2,5,7,10} In the United States, there are about 150,000 cases of valley fever infections annually, with 60% of these cases occurring in Arizona.^{4,10} According to Blair et al., up to 30% of community-acquired pneumonia in Arizona is actually primary pulmonary coccidioidomycosis.⁴ In the last few decades, there has been an increase in the incidence and prevalence of coccidioidomycosis, contributing to a combined hospitalization cost of over \$2 billion and creating a significant impact on the labor force in these endemic geographic areas.^{4,5,10} The reasons for this increase in incidence remain undetermined, but factors such as precipitation, drought, temperature fluctuations, and soil disturbances at construction sites may potentiate expansive spore dispersal.⁵ Given the opportunity for soil disruption and aerosolization of the arthroconidia (spores), not only has an increase in human cases been observed, but also an increase in rodents, horses, and domestic pets that have tested positive for valley fever.¹⁰

The arthroconidia of *Coccidioides immitis* or *C. posadasii* lie dormant in the soil of arid climates until more favorable weather conditions allow the spores to germinate new mycelia, thus promoting reproduction.¹⁰ If the arthroconidia are inhaled in these dusty, arid climates, particularly where construction sites have disrupted the soil, the warm, moist environment of the terminal bronchioles allows for the fungus to enter the parasitic phase, where it transforms into a spherule with the development of endospores.⁷ These endospores then rupture, disseminating the fungal infection hematogenously.^{10,15} In an immunocompetent host, cellular immunity is activated, typically clearing the infection without residual complications. However, in immunocompromised hosts, and for reasons not completely understood, the infection may remain localized in the pulmonary parenchyma, or may disseminate to other parts of the body, causing noncaseating granulomatous inflammation.^{4,10}

Although about 60% of the *C. immitis* infections are asymptomatic, inhalation of these arthroconidia may produce a mild influenza-like

infection in the remaining 40%, with upper respiratory symptoms that usually are self-limited.² Patients who become symptomatic with valley fever typically demonstrate mild fever, cough, headache, myalgias, skin rashes, arthralgias, and fatigue.^{4,5,10,11} However, some patients develop a more progressive illness or chronic pulmonary disease, requiring hospitalization.⁵ Less than 1% of those with valley fever will develop a more debilitating extrapulmonary disseminated disease, such as meningitis, bone, or joint infections.^{3,10,16} It is estimated that there were 3000 deaths attributed to coccidioidomycosis in the United States from 1990 to 2008, although this number is likely lower because the initial presenting symptoms can be mistaken for other upper respiratory infections.^{13,16} Hospitalization rates for valley fever are highest among African Americans, Filipinos, older men, immunosuppressed patients, outdoor workers, and pregnant patients.¹⁰ Additionally, outdoor exposure to the arthroconidia in dusty, arid climates constitutes an occupational hazard to construction workers, archaeologists, military personnel, and agricultural workers in these endemic environments.^{6,10}

Laboratory tests consisting of enzyme immunoassay testing, immunodiffusion, complement fixation, and sputum testing are available, but tend to have higher false positive rates or require time to show positivity.^{4,10} Of the available tests, sputum culture testing is the most accurate, but requires more invasive procedures for specimen collection.¹⁰

Although most patients do not need clinical evaluation and treatment, those with more pronounced symptoms, chronic pulmonary disease, or disseminated coccidioidomycosis need long-term antifungal therapy.^{4,5,10} Prescription medications such as amphotericin B, ketoconazole, fluconazole, or itraconazole have been shown to be effective in speeding recovery from valley fever.^{4,10} The Infectious Diseases Society of America treatment guidelines recommend antifungal therapy if symptoms have been present for 2 mo, night sweats for greater than 3 wk, a 10% loss in total bodyweight, inability to attend work or school due to fatigue and symptoms, bilateral pulmonary infiltrates or involvement of one-half of one lung, prominent and persistent pulmonary hilar lymphadenopathy, or a serologic complement fixation titer greater than 1:16.⁴

This aeromedical case demonstrates the initial difficulty in diagnosing coccidioidomycosis. The patient presented to the clinic numerous times and was treated with oral antibiotics for more common etiologies before the actual diagnosis was determined to be valley fever. Although this patient had no medical history of a compromised immune system, he did work on a military installation in the southwestern United States, which is known to be endemic for the *Coccidioides* species. Interestingly, he worked primarily indoors in the air traffic control tower; however, there were several areas of construction on this particular installation, which may have contributed to this patient's infection. This case history emphasizes the importance of geographical presentation and travel history when considering differential diagnoses.

4. What treatment and aeromedical disposition are most appropriate for this patient?

- A. Treat with an oral antifungal, continue DNIC status until an idiosyncratic reaction can be safely ruled out, then return to controlling status when symptoms are improved.
- B. Treat with amphotericin B, continue DNIC status until an idiosyncratic reaction can be safely ruled out, then return to controlling status when symptoms are improved.

- C. Treat with an oral antifungal, continue DNIC status for the duration of treatment, then return to controlling status once the patient demonstrates no residual issues that would preclude safe duties as an ATC.
- D. Treat with intravenous amphotericin B and continue DNIC until treatment is completed and the patient is fully asymptomatic.

ANSWER/DISCUSSION

4. C. According to the Infectious Diseases Society of America, the treatment guidelines recommend long-term daily oral antifungal therapy for 4 to 6 mo.^{1,4,10} As it usually takes several months to recover from the fatigue symptoms, aviation duties should be limited until the patient has recovered and has completed the medication course. Although amphotericin B was originally used in the treatment of coccidioidomycosis, the side effects of this medication are significant and include hypotension, electrolyte abnormalities, and renal insufficiency, making this medication no longer recommended as first-line therapy.¹ The patient completed a 6-mo course of oral fluconazole and demonstrated significant improvement in overall appearance and symptoms within 1 mo of starting therapy. Although not specifically addressed in the Air Force Waiver Guide,¹⁷ this patient remained on DNIC status for the entire 6 mo of fluconazole treatment, as this class of antifungal therapy is not approved for active flying status by the U.S. Air Force.^{*} He continued steady improvement without any residual symptoms from the disease or from the therapy that demonstrated any aeromedical implications or compromise. After cessation of treatment, in accordance with his pulmonologist's recommendations, the U.S. Air Force Medical Standards Directory[†] and approved medication list,^{*} and current aerospace medical practice,¹⁴ this ATC was returned to full duty.

It is interesting to note that the corresponding services' regulations vary slightly for flying standards. The Army's Flight Surgeon's Aeromedical Checklists, like the U.S. Air Force Waiver Guide, does not specifically address coccidioidomycosis.¹⁸ Fluconazole is considered a Class 2A medication approved for use during flight as long as the underlying condition does not require a waiver.¹⁸ Given that treatment often extends for 6 mo or longer, and symptoms may vary in severity, valley fever may require a waiver in accordance with Army standards.¹⁸ The Navy, likewise, has no specific waiver guidance for coccidioidomycosis.¹² Fluconazole is not specifically mentioned in the medication standards for Naval aviation. However, a similar drug in the same category is designated as not for chronic use, indicating that per Navy standards, grounding due to chronic medication use would be required.¹² The Federal Aviation Administration Guide for Aviation Medical Examiners outlines the requirements of civilian aviators to refrain from flying duties when a medical condition precludes flight safety⁸ and also requires Federal Aviation Administration review prior to certification for any class of airman for active mycotic disease.⁹ Upon disease resolution and completion of medication therapy, the

airman may receive certification for all aviation classes providing there are no complications or residual symptoms.⁹

This aeromedical case emphasizes several key issues for both aerospace medicine and general medical practice as well. First, this case portrays the importance of patients returning to the clinic for worsening symptoms. Often clinical staff become complacent with patients who return to the department with simple viral complaints. However, as demonstrated in this case presentation, clinic staff must be cognizant in patient reevaluations to prevent missing obscure diseases. Second, this case shows the importance of patient context in clinical presentation. Geographical location was fundamental to this case's clinical diagnosis. Importantly, a transient military population, which changes locations regularly, needs to be mindful of certain diseases that are endemic to geographic areas. Accordingly, it is important to recognize the availability of professional counterparts, such as Public Health and Bioenvironmental Engineering personnel, who can provide excellent insight into complex cases, thus enabling more complete patient care.

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