Aerospace Medicine Clinic

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You are the rear-detachment flight surgeon for a unit currently deployed. Your forward-deployed unit has medically evacuated a nonaviation service member assigned to your unit from theater to you for further care and evaluation. A 23-yr-old African-American woman presents to the clinic with chest pain and rib pain while running for the past couple months. She states she noticed it "a while ago" and had thought she just pulled a muscle. However, it has not improved and now she noticed a mass in the area of pain. She also reports that she has lost 6.804 kg unintentionally in the past 2 mo along with occasional night sweats. She states coughing and laughing are painful. She has a family history of multiple myeloma, throat, prostate, and stomach cancer on both maternal and paternal sides. The exam you conduct shows a marble-sized firm mass to the medial side of the left breast in the 9 to 11 o'clock position that is tender to palpation. No lymphadenopathy is noted. Ultrasound and mammogram were completed prior to evacuation, but the reports are unavailable.

1. What is your next step?
   A. Magnetic resonance imaging (MRI).
   B. Physical therapy.
   C. Surgical consult.
   D. Biopsy.

ANSWER/DISCUSSION

1. A. Based off exam findings and concern about the soft tissue mass, you order an MRI for further evaluation.[8,14,19] MRI shows a lytic mass measuring 4.5 × 3.2 × 2.5 cm on rib 4, involving the soft tissue of the pectoralis muscle and possible invasion into the pericardium sac, as well as other lytic lesions in the vertebra. You do not place a surgical consult yet as the initial workup has not been fully completed. At this time, you do not know the exact location of the mass and what structures are affected. Without this information, you would not know specifically what type of surgeon to consult. Without proper imaging, a biopsy could be dangerous, as it is unknown if there is vascular supply, how large the mass is, and what structures are involved. Physical therapy is not the next line of evaluation and treatment at this point.

2. Of the differential diagnoses below, which one is least likely to cause the patient's symptoms?
   A. Ewing sarcoma.
   B. Primary non-Hodgkin lymphoma of bone.
   C. Breast cancer.
   D. Gastric cancer.

ANSWER/DISCUSSION

2. D. Gastric cancer would be the least likely to cause the patient's symptoms. She did not have any abdominal pain or loss of appetite. She did have constitutional symptoms, but those can be present in many different types of cancer. Gastric cancer can spread to the bone but is extremely rare.[21] The most common sites are liver, lung, and peritoneum.[22] Given the MRI findings, you are concerned with metastatic cancer, specifically Ewing sarcoma or lymphoma. Ewing sarcoma is a family of tumors that most often arise in the long bones but can occur in the axial skeleton about 54% of the time. Patients with Ewing sarcoma can present with localized swelling and pain.[28] The mass can be tender to palpation and constitutional symptoms occur approximately 10–20% of the time at presentation.[9] The most common site of metastasis is to the lungs and bones and metastasis to the pelvis has a poorer prognosis.[28] Risk factors include being under age 18, Caucasian, and male.[16] Even though our patient does not meet any of the risk factors, her presentation of symptoms and exam findings do fit the criteria. Primary non-Hodgkin lymphoma of the bone usually presents with destructive bone lesions.[20] Typical symptoms present with bone pain even at rest, possible soft tissue swelling, and systemic symptoms of weight loss, fever, and night sweats.[2,20] It occurs more frequently in men

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over age 30.[17] Breast cancer would be unlikely given the MRI showed no masses within the breast tissue.

You consult Oncology and they agree with your differential. They recommend a biopsy, computed tomography (CT) of the chest with contrast, and additional labs. Labs were unremarkable except for a slightly elevated protime at 13.3. CT chest with contrast shows the same findings as with MRI with additional locations of sclerotic/lytic lesions to vertebra, ribs, xiphoid process, distal sternum, and scapula. Following these studies, Oncology took over the patient's care. The oncology team ordered additional imaging, including a head-to-toe positron emission tomography (PET) scan. The PET scan results were consistent with the findings on the CT scan, with additional findings in sacrum, additional rib involvement, and pelvic lesions, as well as extensive reactive lymphadenopathy. She is told she likely has Ewing sarcoma and based off findings is likely stage 4. She undergoes a biopsy to officially confirm diagnosis. The biopsy pathology report is not consistent with metastatic cancer. Much to the surprise of the oncologists, the biopsy shows it was not cancer but an infectious process.

3. You go back to the patient and ask additional history questions. What question would give you the best information for underlying cause?
   A. Were you vaccinated for anthrax?
   B. Have you traveled to a Centers for Disease Control and Prevention Level 3 country recently?
   C. Have you ever been treated for tuberculosis (TB)?
   D. Where have you lived or traveled?

ANSWER/DISCUSSION

3. D. Upon additional questioning of where she has lived, she states she was stationed at Fort Huachuca, AZ, from January to May 2018. She denies any respiratory illness during that time. This information is important to figuring out the source of infection. Her vaccination status to anthrax is irrelevant to her current situation, as she has no known exposure to anthrax and her symptoms are not consistent with anthrax infection. She is not complaining of symptoms related to COVID-19, so travel to a Centers for Disease Control and Prevention Level 3 country would not be important. If she had been treated for TB, one would not expect to find bone lesions, weight loss, or night sweats currently.

4. Knowing she lived in Arizona for a year, what is the most likely cause of her infection?
   A. Histoplasmosis.
   B. Coccidioidomycosis.
   C. Tularemia.
   D. TB.

ANSWER/DISCUSSION

4. B. Her biopsy showed coccidioidomycosis with its characteristic spherule with endospores. Oncology consults Infectious Disease (ID), and they assume care of the patient. Coccidioidomycosis is commonly known as valley fever or San Joaquin valley fever. It typically manifests as a fungal infection in the lungs but can have extrapulmonary manifestations as well. People often are asymptomatic but can present with a flu-like illness. Risk factors for coccidioidomycosis include military trainees, African-American race or Filipino ethnicity, human immunodeficiency virus/acquired immunodeficiency syndrome, use of immunosuppressant medications, diabetes, or pregnancy.[4,5] Coccidiomycosis that is not pulmonary is considered disseminated. It can be lymphatic or hematogenous spread. Disseminated coccidiomycosis to the bones is called osteomyelitis and can affect any bones; however, the lumbar spine is most affected. The southwest United States, particularly southern California, Nevada, New Mexico, and Arizona, is known for having coccidioidomycosis cases.[6] Of note, a single day trip to these states can result in an infection.[18] This is important to know, especially in the military population, as service members may have grown up in these areas or even visited them and there are numerous bases. It is especially important to know because Arizona is an advanced individual training location for unmanned aerial vehicle/unmanned aircraft systems (UAV/UAS) service members. Given her original suspected diagnosis, a biopsy was done in this case. However, serology testing can be done using immunodiffusion, as it is highly specific. Immunodiffusion IgM and IgG tests are essentially diagnostic; however, enzyme-linked immunosorbent assay IgM and IgG tests can cause false positives.[18] If enzyme-linked immunosorbent assays are used, they should be confirmed with immunodiffusion IgM and/or IgG. Histoplasmosis is another fungal infection that can have similar features; however, it does not cause lytic bone lesions. Most immunocompetent people have minor to no symptoms. It is found in central and eastern states where there are large amounts of bird or bat droppings.[3] Tularemia can cause muscle aches, fatigue, and anorexia but often is rapid onset. If left untreated, it can cause unintentional weight loss but does not cause lytic bone lesions.[1,24] Extrapulmonary TB can affect the lymphatic system, bones, joints, liver, central nervous system, and adrenal glands, causing a multitude of symptoms similar to our patient.[10] It can cause respiratory symptoms, unintentional weight loss, musculoskeletal symptoms, and night sweats.[27] Skeletal TB has been known to cause rib pain and breast masses as well as lytic bone lesions.[7] Our patient denies ever being exposed to TB as far as she knows and had a negative purified protein derivative test when she joined the Army last year.

Further exam finds a hyperpigmented nodule along the right medial malleolus less than 1 cm in diameter. Due to the invasive nature of her disseminated fungal infection, she is admitted for further treatment.

5. What is baseline treatment for disseminated coccidioidomycosis with bone involvement?
   A. Fluconazole.
   B. Liposomal amphotericin B (AmB).
   C. Ertapenem.
   D. Itraconazole.

ANSWER/DISCUSSION

5. B. Per Infectious Diseases Society of America guidelines, AmB should be used when severe osseous involvement is diagnosed, with transition to high-dose fluconazole for at least 1 yr, and then lifelong suppression.[15] The patient was started on intravenous (IV) AmB 230 mg daily for 2 wk and closely monitored, especially kidney function. AmB treatment was completed the day of discharge. She was discharged after 2 wk and was started on high-dose fluconazole 800 mg daily with plans to continue for 1 yr. However, 2 d after discharge, she was seen in the ID clinic again as she was unable to tolerate fluids and ended up needing IV rehydration. Labs were repeated and showed her creatinine had doubled in 2 d. They attributed the acute kidney injury to the AmB, which can cause kidney toxicity along with poor oral intake, which had been prevented while inpatient with daily IV hydration. Given the acute kidney injury and decreased glomerular filtration rate, her fluconazole dose was decreased to 400 mg daily. She will remain on fluconazole with close ID follow-up for at least 1 yr. At the 6-wk follow-up, the previously noted nodular skin lesion on her lower extremity had decreased in size and flattened and was now a macular lesion. The breast mass was resolving and the rib/back pain was improving. At the 3-mo mark, she will obtain a repeat PET-CT and coccidioides complement fixation to evaluate early response from her treatment plan. She will continue to be followed by ID for typically 3 yr.

AEROMEDICAL DISPOSITION

The location where this service member, who is not on flight status, contracted disseminated coccidioidomycosis is where the U.S. Army trains UAV/UAS operators. There are many support service members who work within aviation units. It is important to be aware of any disease process occurring in the unit, as it could affect those on flight status as well. The U.S. Army does not specifically address coccidioidomycosis in its aeromedical policies. However, there are policies regarding other infectious diseases and medications used to treat those diseases. The U.S. Army recommendation is to ground the aviator until completion of medication, and a waiver would be required due to long-term use of antifungal medications, which can cause unwanted side effects that could interfere with duties.[26] Serious side effects from AmB are central nervous system difficulties that are incompatible with aviation duty. The U.S. Navy does not have a specific policy for disseminated fungal infections and does not specifically mention AmB as an authorized or unauthorized medication. However, in general, the U.S. Navy's policy is more restrictive on use of antifungal medications. The U.S. Navy Aeromedical Reference and Waiver Guide gives specific instruction that if a medication is not listed it is automatically not authorized while on flight status and the crewmember would be grounded. It also states that flight surgeons at the Naval Aerospace Medical Institute should be contacted to discuss cases such as these and will provide guidance on a case-by-case basis.[23] The Federal Aviation Administration (FAA) states that any history of mycotic lung and skin diseases and medications associated with treatment requires referral to the FAA for issuance of an airman certificate.[11–13] It also states that if the individual is on a medication that could be sedating or cause side effects, an airman certificate should not be issued. If there is any question or concern of whether an individual should be issued a medical certificate, the Aviation Medical Examiner should contact the Regional Flight Surgeon or the Aerospace Medical Certification Division.[11–13] The U.S. Air Force Aerospace Medicine Waiver Guide also does not specifically address coccidioidomycosis or specific medications.[25] As seen in all the previous military services' recommendations, in the absence of clear recommendations or guidance, the most logical and safest course of action is to ground the crewmember and contact the flight surgeons at the service's aeromedical governing body, which for the U.S. Air Force would be the U.S. Air Force School of Aerospace Medicine, for further recommendations and guidance. In general, flight duties in crewmembers of high-performance aircraft and aircraft with ejection capabilities can be affected. If vertebral bodies are compromised, there is an increased risk of spinal injury in ejections and with G-forces. These crewmembers need to be grounded and potentially permanently disqualified.

In conclusion, it is imperative to have a high level of suspicion for fungal diseases in our aviators, crewmembers, and UAV/UAS operators, especially when training in the Southwest United States and presenting with respiratory or bony masses. Coccidioidomycosis can cause spinal cord compromise and/or meningitis and could lead to disastrous results for the crewmember and potentially others in the aircraft or in the vicinity of the aircraft.

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