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MORNING REPORT

Hypercalcemia and Sclerotic Bone Lesions

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A 53-year-old African-American man presents to the emergency department with a six-week history of fatigue, weight loss, and dyspnea. He has lost 60 pounds over the past three months associated with anorexia and is unable to climb stairs due to diffuse weakness. He spends most of the day sitting, whereas he was previously exercising daily. His primary care provider performed PSA testing, which was elevated at 10 ng/mL on two occasions, and he underwent prostate biopsy one week ago showing Gleason 3+3 adenocarcinoma. He endorses dry mouth and intermittent diffuse arthralgias and denies any urinary symptoms, fevers, or change in bowel habits. He has never smoked cigarettes.

The most remarkable aspect of this patient's presentation is profound weight loss. Involuntary weight loss may be defined as 5% or greater weight loss within three to six months, although criteria vary. With a vast differential diagnosis and no subspecialty claiming it, unintentional weight loss is a true general internist's syndrome. In most case series, the top three causes of unintentional weight loss are cancer, gastrointestinal disease, and psychiatric illness.[1]

While this patient has been diagnosed with prostate cancer at a relatively young age, neither his Gleason score nor his PSA is particularly high—suggesting the possibility that his cancer, while very real, is not the main cause of his presenting symptoms. Shortness of breath, unless by downstream illnesses such as pulmonary embolism or metastatic disease, and arthralgias would be unusual. Other causes should continue to be investigated. Of his other localizing symptoms, focusing on his dyspnea is a reasonable next step.

Initial laboratory studies show mild hypercalcemia of 10.8 mg/dL, low-normal albumin (3.5 g/dL), normal leukocyte count (5900/μL) with low-normal lymphocytes (1000/μL), microcytic anemia (Hb 11.8 g/dL), and normal TSH. CT imaging of the chest, abdomen, and pelvis show numerous predominantly sclerotic lesions within the pelvis and ribs, as well as hepatomegaly and extensive mediastinal adenopathy. There are a few scattered pulmonary nodules less than a centimeter in size, with otherwise clear lung parenchyma and no evidence of pulmonary embolism. He is admitted to the hospital for further evaluation.

First, the laboratory studies: Could this patient have hypercalcemia of malignancy? The most common causes of hypercalcemia are malignancy and primary hyperparathyroidism, although many other well-known causes exist. We initially did not want to prematurely attribute his newly diagnosed cancer to his presenting illness, but now we must consider that the hypercalcemia may be another sign of malignancy. With his severe weight loss it is certainly possible. Although he has already been diagnosed with prostate cancer, the incidence of hypercalcemia in prostate cancer is low (8% in one series),[2] *and other cancers more typically cause hypercalcemia, either through lytic lesions (e.g. multiple myeloma, breast cancer) or via PTH-related protein (PTHrP) (e.g. lung cancer, head and neck cancers, lymphoma).*

Again, we must be vigilant for other illnesses that also cause systemic symptoms and hypercalcemia, both malignant and non-malignant. As for other etiologies of hypercalcemia, he may have an unrelated primary hyperparathyroidism or excessive vitamin D intake, but these would not be expected to cause his severe weight loss. We should continue to look for causes of hypercalcemia that also cause severe systemic symptoms. He is euthyroid. Sarcoidosis may cause hypercalcemia, joint pains, hilar adenopathy, and systemic symptoms, with nearly every organ system being potentially affected. In patients with high-volume extrapulmonary sarcoid, marked weight loss and systemic symptoms are not uncommon. African Americans with sarcoid are more likely to develop extrapulmonary disease, and bone lesions are more common in this patient population. In a patient with a relevant exposure history, other granulomatous diseases, including tuberculosis, may cause hypercalcemia and lymphadenopathy. The next step would be to obtain a parathyroid hormone level, which if confirmed to be low would be suggestive of either malignancy or other causes that would down regulate endogenous PTH production.

As for the imaging studies, the hepatomegaly and mediastinal adenopathy could be present in both malignancy as well as sarcoidosis, while the sclerotic bone lesions are concerning for malignancy. Paget's disease is rare and may present with hypercalcemia and sclerotic bone lesions, but it would uncommonly present with profound weight loss.

The patient denies ingestion of calcium or vitamin D. His parathyroid hormone level is low-normal at 20 pg/mL. He has never worked in a foundry and denies heavy metal exposure. He resides in the Northwestern United States and denies

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international travel. He has never been incarcerated or homeless.

At this point we have a patient with weight loss, dyspnea, and arthralgias whose workup has revealed prostate cancer, microcytic anemia, mediastinal adenopathy, hepatomegaly, sclerotic bone lesions, and hypercalcemia not due to hyperparathyroidism. We still need to distinguish whether there is another malignancy or sarcoidosis. A tissue sample would be the next step, and if the mediastinal lymph nodes are accessible by bronchoscopy, that should be pursued next.

Esophagogastroduodenoscopy and colonoscopy are performed without any abnormalities, including biopsy specimens. Endobronchial ultrasound with transbronchial needle aspiration and biopsy are performed. Cytology does not show evidence of malignancy, and flow cytometry does not show evidence of lymphoma. The station 7 subcarinal biopsy reveals multiple non-necrotizing granulomas with acid-fast stain and Grocott's methenamine silver stain negative for organisms. Technetium bone scan demonstrates lack of radiotracer uptake, making metastatic etiology less likely. He is started on high-dose prednisone with gradual improvement in symptoms over several weeks.

This is a remarkable case. First, the team deserves credit for not assuming his symptoms were solely attributable to newly diagnosed prostate cancer, even with sclerotic lesions seen on imaging. Sarcoidosis can cause diffuse arthralgias and systemic symptoms including fevers, malaise, and weight loss—in one series, weight loss was present in 24% of patients and was the most common general complaint.[3] Pulmonary involvement is common in sacrcoidosis. Hypercalcemia from sarcoidosis is thought to be mediated by elevated 1,25 OH vitamin D, although not all patients have elevated levels despite hypercalcemia. A more unusual feature of this case is the presence of sclerotic bone lesions. Imaging alone may not distinguish the etiology of a sclerotic bone lesion. In sarcoidosis, the frequency of bone lesions (not solely sclerotic) is reported between 3% and 13%.[4]

His shortness of breath is most likely from his sarcoidosis; pulmonary function tests should be obtained, and an echocardiogram should be considered as cardiac involvement can occur. Initial treatment for systemic sarcoidosis is with glucocorticoids, often followed by immune modulating therapies such as methotrexate.[5] Hypercalcemia associated with sarcoidosis may resolve with treatment.

Take-home Points

1. Osseous sarcoidosis most often presents as osteolytic lesions, although it can present with a sclerotic appearance, especially in African-American patients.
2. Gleason score of six or less has very low risk of metastatic disease, and technetium radionuclide bone scan is the preferred technique for identifying bone metastases if there is clinical concern.

References

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