Challenges in managing a patient with multiple primary malignancies

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An 81-year-old African American man presented to the emergency department with right flank pain for 3 days. He had first noticed the pain after lifting a heavy box. He described the pain as sharp, nonradiating, and worsening with movement. He denied nausea, vomiting, diarrhea, fever, chills, cough, abdominal or back pain, dysuria, hematuria, or increased urinary frequency.

The differential diagnosis for flank pain is broad. In this case, the pain started after lifting a heavy box, suggestive of musculoskeletal etiology such as muscle strain or rib fracture. Although less likely, both nephrolithiasis with passage of a stone and pyelonephritis must be ruled out. Other genitourinary pathologic processes to be considered would include renal infarct or hemorrhage, ureteral obstruction, and malignancy. The pain may also be of hepatic or biliary origin. Diverticulitis and colitis need to be considered. Finally, the pain may be referred from a pulmonary process such as right lower lobe pneumonia. Further history and a thorough physical exam are needed to narrow down these possibilities.

The patient's medical history included prostate cancer treated with brachytherapy and external beam radiation therapy 4 years previously (total prostate specific antigen (tPSA) at diagnosis, 24 ng/mL; at 2-year follow-up, 0.07 ng/mL). Other comorbidities included hypertension, type 2 diabetes mellitus, end-stage renal disease (ESRD) and on hemodialysis for 5 years, chronic anemia treated with erythropoietin and intravenous iron (baseline hemoglobin, 10-11 g/dL). His social history was notable for smoking 3 cigars daily for 50 years. He had an ECOG performance score of 1. Both his cardiopulmonary and abdominal examinations were unremarkable. He had reproducible tenderness over the right 7th rib. Urinalysis demonstrated 1+ proteinuria and it was negative for leukocyte esterase, nitrite, or blood. A computed tomography (CT) of the abdomen and pelvis without contrast was ordered for further evaluation of flank pain and it revealed diffuse osteolytic bone lesions throughout the pelvis and lumbosacral spine (Figure 1).

In discovering these lytic bone lesions in a patient with a prior history of malignancy, tumor recurrence with metastatic spread to the bone is of great concern; however, bone metastases from prostate cancer are classically osteoblastic (sclerotic). Although a prostate neoplasm may rarely present with osteolytic metastases, an alternative explanation for the bone pathology must be explored. Multiple myeloma or other second primary malignancies are the most likely explanation for these bone lesions. Of note, in elderly patients with osteoporosis, "osteolytic" areas on CT may represent baseline osteoporotic bone, whereas "normal-appearing" spots may actually be diffuse osteoblastic lesions. A bone scan will be helpful in identifying osteoblastic metastases.

The patient's relevant laboratory values were as follows: white cell count, 6.1 $\times$ 10^3/L; hemoglobin, 11.3 g/dL; mean corpuscular volume, 100.6 fL; blood urea nitrogen, 18 ml/dL; creatinine, 2.89 mg/dL; calcium, 9.4 mg/fL; phosphorus, 4.4 mg/dL; alkaline phosphatase, 91 U/L; parathyroid hormone, 41 pg/mL (normal, 15-65 pg/mL); 25-hydroxyvitamin D, 33 ng/mL (normal, 25-80 ng/mL); and tPSA, $<$ 0.1 ng/mL. Serum protein electrophoresis identified an M-spike of 0.73 g/dL with IgA-kappa monoclonal protein on immunofixation. Serum immunoglobulin levels revealed an IgA of 1,184 mg/dL (normal, 81-463 mg/dL),

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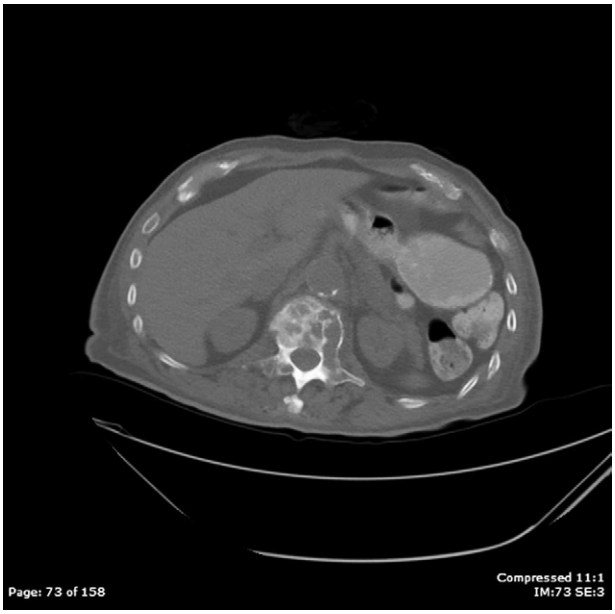

FIGURE 1 CT of abdomen/pelvis without contrast demonstrating incidental osteolytic lesions of the spine.

IgG of 963 mg/dL (normal, 964-1,618 mg/dL), and IgM of 40 mg/dL (normal, 48-271 mg/dL). Bone marrow biopsy demonstrated 10%-15% of plasma cells with marked kappa predominance, consistent with a plasma cell neoplasm. Cytogenetic and chromosomal analysis identified a normal karyotype. A bone scan revealed multiple areas of increased activity throughout the pelvis and spine, all of the findings were diagnostic of a plasma cell neoplasm.

Monoclonal protein disease is a spectrum that ranges from monoclonal gammopathy of undetermined significance (MGUS), through smoldering myeloma, and finally symptomatic myeloma. The distinguishing feature of the latter is evidence of symptom burden, a group of findings referred to as CRAB (hyperCalcemia, Renal insufficiency, Anemia, and/or Bone involvement). Other diagnostic criteria that can be used to identify myeloma include isolation of a monoclonal paraprotein in the serum or urine with 10% or more clonal plasma cells in the bone marrow. Of note, monoclonal protein disease does not always progress to symptomatic myeloma, although patients should be monitored for the development of signs or symptoms of CRAB, which would serve as an indication to begin treatment for myeloma. The decision to treat is determined by the presence of CRAB. Our patient did not have hypercalcemia, and his stable anemia predated the newly diagnosed plasma cell neoplasm. There was, however, new osteolytic bone disease on CT imaging, which may have been due to his monoclonal disease.

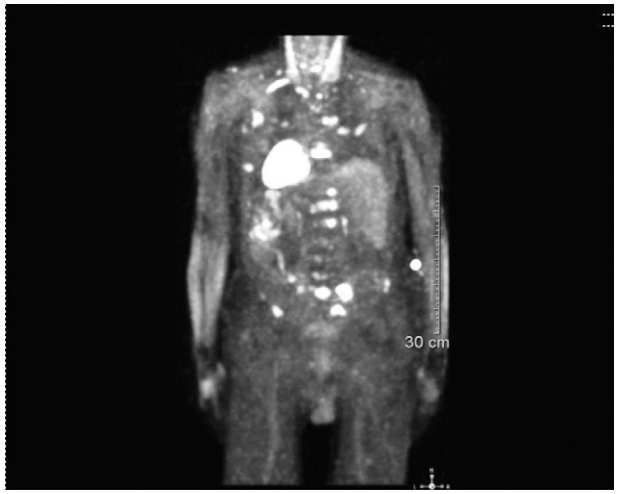

FIGURE 2 PET scan demonstrating increased activity within the left breast and throughout the skeleton including bones of the spine, pelvis, ribs, and sternum.

The diffuse osteoblastic uptake seen in the bone scans may have been due to significant bone destruction from myeloma, which had caused adjacent reactive bone formation seen as nuclear uptake on the scan. Although bone scans may reflect inflammation, infection, or osteoblastic activity induced by cancer, the pattern of activity made metastatic cancer the most likely culprit. Rarely, metastatic prostate cancer presents with mixed osteolytic and osteoblastic bone lesions (with osteolytic lesions identified by CT). In the current case, recurrence of prostate cancer remained within the differential, however, another primary cancer had to be considered given the normal serum PSA at that time. Other neoplasms such as lung, colon, kidney, bladder, and breast commonly metastasize to bone. His diagnosis required a biopsy of one of these bone lesions. We deemed that positron emission tomography (PET) scan would be useful in detecting metabolic activity that might represent a primary malignancy as well as locate other areas of metastatic involvement. Although the patient's flank pain had subsided, there was still no explanation for it. A PET scan might also have identified a plasmacytoma or additional previously undetected bone lesions, which could impact therapy (ie, potential need for local radiation for refractory/recurrent pain).

The patient declined a biopsy of his bone lesions. The results of a PET scan showed increased uptake throughout the skeleton, including a small lesion in the right posterior 7th rib. It also identified a 2.1-cm × 3.3-cm mass in the left breast (Figure 2). Mammography confirmed this irregularly shaped mass with spiculated margins and pleomorphic calcifications, suspicious for malignancy. A left mastectomy with sentinel node biopsy was

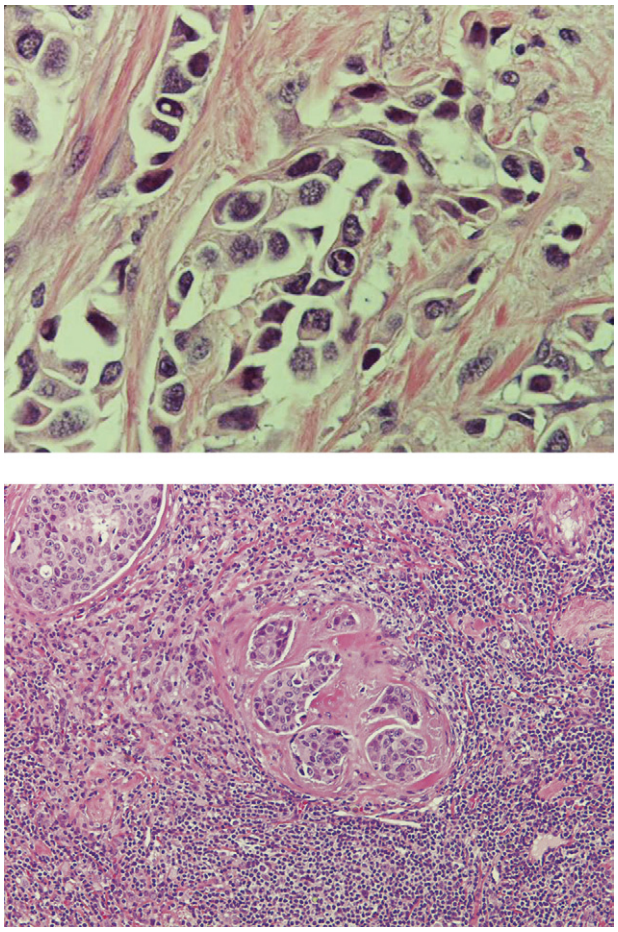

FIGURE 3 High-power view of moderately differentiated, infiltrating duct carcinoma of mammary origin (top); high-power view of a lymph node infiltrated by metastatic carcinoma cells (bottom).

performed. Pathology results revealed a moderately differentiated, infiltrating ductal carcinoma with 19/19 lymph nodes positive for metastatic breast cancer (Figure 3A and B). Immunohistochemical staining for hormone receptor positivity showed 70% of cancer cells expressed estrogen receptors (ER+), though none of the cancer cells stained positive for progesterone receptors (PR−). Immunohistochemistry stains were negative (0) for human epidermal growth factor receptor 2 (*HER2*) overexpression.

Breast cancer can yield both osteolytic and osteoblastic bone metastases. The incidental discovery of breast cancer in our patient provided yet another possible explanation for his bone lesions. If the lesions were due to breast cancer, that would downgrade his plasma cell neoplasm to smoldering myeloma and eliminate the need for therapy at that time. He was started on tamoxifen for treatment of ER-receptor positive male breast cancer (MBC). He was also started on a bisphosphonate, although denosumab, a RANK-ligand targeting agent, could also have been given if it were established that his bone disease was due to metastatic breast cancer and not secondary to a plasma cell neoplasm, for which at the time of publication of this report did not have an indication. Hormonal therapy (tamoxifen) was likely to be a more tolerable treatment option over systemic chemotherapy, especially in this patient with such significant comorbidities—that is, advanced age, multiple comorbidities including ESRD, and two newly diagnosed primary malignancies.

The patient continued on tamoxifen until a follow-up CT of the chest, abdomen, and pelvis 4 months later showed significantly increased, mostly osteolytic and some new osteosclerotic lesions scattered diffusely through the axial skeleton. The patient agreed to a biopsy of a mixed sclerotic/lytic lesion in the left iliac crest. The results were consistent with metastatic cancer of mammary origin without evidence of prostate cancer or clonal plasma cells. As his disease burden has rapidly advanced on tamoxifen, it is unlikely that he would benefit much from an aromatase inhibitor. A discussion is scheduled to determine goals of care as chemotherapy will likely be needed to attempt control of this advanced breast cancer.

The iliac crest biopsy revealed that the metastatic breast cancer was the cause of his bone lesions. The patient had been started on tamoxifen, which inhibited the stimulant effects of circulating estrogens on tumor cell growth via estrogen receptor binding. The reason for the rapidly advancing disease burden is most likely due to the aggressive nature of this malignancy, although compliance with therapy must be confirmed. That the breast cancer advanced this quickly makes chemotherapy the logical next step in his management. The patient is unlikely to get a significant response from an aromatase inhibitor with this malignancy progressing so quickly on tamoxifen. Though his performance score is an asset, his end-stage renal disease is a considerable liability in weighing chemotherapeutic options.

Discussion

Bone metastases may occur through direct extension, lymphatic dissemination, or hematogenously.[1] It is seen in 70% of advanced breast and prostate neoplasms as well as 15%-30% of lung, colon, bladder, and renal carcinomas.[2] Cancers that spread to bone may form either osteolytic or osteoblastic lesions. Osteolytic lesions are classically described in multiple myeloma.[3] They also predominate in breast cancer, although 15%-20% of cases present with osteoblastic disease.[4] Osteoblastic lesions predominate metastatic prostate cancer, and although purely osteolytic disease may occur, this is considered a rarity.[5] Metastatic disease to bone is a dynamic process involving dysregula-

tion of normal bone remodeling. Adjacent areas of osteoblastic and osteolytic metastases or mixed disease may be seen, as well as purely isolated lytic or sclerotic lesion.[2] These areas may be truly mixed disease or may represent reactive bone formation in response to increased bony destruction in an osteolytic process such as myeloma, seen as nuclear uptake by bone scan.[4]

In a patient with a history of malignancy, newly discovered bone lesions are of concern because of the risk of tumor recurrence. Cancer survivors are also at increased risk for developing a second primary cancer, with an incidence as high as 16%, compared with 3.5% within the general population.[6] The highest rates of secondary tumors follow an initial diagnosis of melanoma (21.6%), colorectal (12.9%), prostate (12.7%), and female breast (12.6%) cancer.[7] Each primary malignancy is further linked to a specific group of secondary neoplasms. Primary prostate cancer is associated with a higher risk of secondary MBC, melanoma, and small bowel endocrine tumors.[8] Although secondary solid neoplasms in patients with multiple myeloma are rare, associations with carcinomas of the lung, colon, prostate, breast, bladder, uterus, and liver have been reported.[9,10] Data on secondary cancers following male breast cancer is variable, but one study suggested an increased incidence of tumors of the small intestine, prostate, rectum, pancreas, and lymphohematopoietic system.[11] To our knowledge, there are no prior reports of concurrent secondary multiple myeloma and MBC associated with history of primary prostate carcinoma. The overall increased risk of developing a second primary malignancy may be attributed to high-risk behaviors, inherited susceptibilities, therapy received for prior cancer treatment, or underlying immune defects from a prior or concurrent malignancy.[7,12]

In cases in which multiple malignancies are identified, there are unique challenges in initiation of therapy, including potentially compounded chemotherapeutic drug interactions and the inability to use certain therapies based on the type of concurrent cancer. For instance, denosumab is a RANK-ligand targeted therapy approved for prevention of skeletal-related events in patients with bone metastases from solid tumors, but it has not been approved in bone disease secondary to multiple myeloma, as of the time of publication of this article.[13] Likewise, bisphosphonates must be used with caution in patients with renal disease, which may be the initial presentation of multiple myeloma.[14] Treatment for each cancer is also highly individualized based on age, performance status, comorbidities, stage, and features of the disease. As such, a patient may not be able to tolerate simultaneous treatment for multiple malignancies, with consideration to that which is most aggressive or most likely to cause immediate harm. Myeloma is unique in that it often may be observed until signs or symptoms of the disease develop. In the case of a contaminant solid tumor, it should be treated as a primary target of therapy in the setting of MGUS or smoldering myeloma, as these stages of monoclonal disease require only observation, and may in fact hold a better long-term prognosis than that of an advanced solid tumor.[9]

Management principles in MBC are generalized from those of female breast cancer due to its rarity and lack of randomized controlled trials.[15] Mastectomy with sentinel lymph node biopsy or axillary dissection remains the standard of care.[16] The role of postmastectomy radiation in MBC is not well defined but should be used in patients at high risk for local recurrence.[17] For advanced disease, adjuvant treatment is based on tumor hormone receptor status and *HER2* status. Because most men have hormone-positive disease, hormonal therapy consisting of tamoxifen (a selective estrogen receptor modulator) or aromatase inhibitors is the mainstay of treatment.[18] We were unable to identify in the literature trials comparing the efficacy of tamoxifen against aromatase inhibitors in MBC, but tamoxifen is more commonly used.[19] Data is also limited regarding optimal therapy in MBC after tamoxifen failure though second-line options include orchiectomy, luteinizing hormone-releasing hormone agonists, or anti-androgens.[18] Fulvestrant, an estrogen receptor antagonist, was found effective in hormone-positive female breast cancer,[20] but no studies exist for efficacy in men. In patients with hormone-negative pathology or hormone-resistant disease, systemic chemotherapy with the same agents used in treatment of female breast cancer is appropriate.[16]

As far as we can ascertain, this is the first reported case of concurrently diagnosed multiple myeloma and MBC in a patient with a history of primary prostate carcinoma. It highlights the complexities of the diagnostic work-up and the approach to treatment.

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