Identifying Two Distinct Previously Undiagnosed Cancers Within a Single Osseous Lesion
A Diagnostic Dilemma

Kathleen J. Maguire, MD, Sigfred Lajara, MD, Esperanza Villanueva-Siles, MD, Ferdinand J. Chan, MD, and David S. Geller, MD

Abstract

A 71-year-old man presented with a distal femur lesion. Workup was positive for elevated prostate-specific antigen, serum protein electrophoresis, and urine protein electrophoresis. He underwent distal femoral resection, and histological evaluation was consistent with concomitant metastatic prostate cancer and multiple myeloma.

The literature notes a link between the treatment of prostate cancer and the development of secondary malignancies. Reports of this simultaneous cancer diagnosis are rare. We present these diagnoses within the same pathologic lesion.

Case Report

A 71-year-old man presented with 3 months of persistent atraumatic knee pain. Pain was aching, localized to the medial knee, and without radiation. It limited his ability to ambulate. He denied weakness, weight loss, and constitutional symptoms. Examination of the knee noted mild fullness of the distal thigh with moderate tenderness. He maintained full motion without pain or limitation. He had no effusion, warmth, skin changes, or other findings indicative of infection. He walked with a limp and required a cane.

Initial radiographs revealed a large lesion in the distal femur with a mixed radiodense and radiolucent appearance. There was erosion of the anterior cortex with soft tissue extension anteriorly and medially. A similarly appearing fibular lesion was also present (Fig. 1). A magnetic resonance image (MRI) of the knee revealed an extensive, confluent tumor with a destructive 9.7 cm distal femur metadiaphyseal lesion with cortical breakthrough and soft tissue extension. These findings were compatible with malignancy. The primary radiographic differential considerations included metastatic disease versus multiple myeloma (MM) or lymphoma.

Bloodwork noted an elevated prostate-specific antigen (PSA) of 90.4 ng/mL (normal: < 6.5 ng/mL). The serum protein electrophoresis was positive for IgA kappa and IgM.
lambda monoclonal proteins (2.4 g/dL), and the urine protein electrophoresis returned with free kappa M protein and elevated IgA of 3,280.

Computed tomography (CT) of the chest, abdomen, and pelvis demonstrated a mass within the prostate as well as diffuse blastic skeletal metastases. A bone scan correlated blastic lesions within the ipsilateral proximal femur, contralateral proximal femur, multiple vertebrae, left sixth rib, right scapula, and left ischium. These findings raised concern for metastatic prostate carcinoma.

A CT-guided core biopsy was performed and the initial pathologic findings from this biopsy were consistent with a plasma cell neoplasm. Some of the neoplastic plasma cells revealed irregular nuclear contour, occasional Dutcher bodies, and binucleation. Immunohistochemical stains were positive for CD138, CD56, lambda, and BCL1 (partial), while negative for CD20, CD117, and kappa. The morphology and the immunoprofile supported the diagnosis of plasma cell myeloma, lambda-restricted.

The patient’s case was presented to the orthopaedic oncology multidisciplinary tumor board. After careful consideration and medical optimization, the patient was indicated for a distal femoral resection and reconstruction due to the extensive bone destruction and associated pain and functional impairment (Fig. 2). Intramedullary nailing with radiation and plating supplemented with cement could be considered. However, in this case, the degree of bone destruction and paucity of quality residual cortical bone raised concern that it would be difficult to contain cement and prevent extravasation. We were also concerned that his distal femur would not provide a reliable, safe, and robust construct.

Figure 2 Anteroposterior and lateral postoperative radiographs.

Figure 3 Coronal section of resection specimen.
On gross dissection, the resected distal femur showed a tan-white fleshy to rubbery tumor mass with central hemorrhage (Fig. 3). The mass predominantly involved the medullary cavity of the femoral diaphysis. It had broken through the cortex and extended into the surrounding soft tissue. Microscopically, the majority of the tumor represented plasma cell myeloma (Fig. 4), but focally a second neoplasm was identified. The second tumor consisted of well-formed glands with abundant, lightly eosinophilic cytoplasm with vesicular chromatin and prominent nucleoli consistent with adenocarcinoma (Fig. 5). Immunohistochemical stains showed that the adenocarcinoma was positive for cytokeratins (Cam 5.2, AE1/AE3), prostate-specific membrane antigen (PSMA), and focally for PSA and CK 20, supporting a prostatic origin. The patient was diagnosed with concomitant metastatic prostate cancer and MM.

The patient underwent a successful distal femur replacement. The patient tolerated this well and at his 2-year follow up was noted to be ambulating without assistive devices or difficulty. He denied pain and tenderness about the involved extremity and achieved full knee extension with flexion to 110°. Imaging demonstrated that the implant remained stable in a good position.

His postoperative medical course ultimately included an autologous stem cell transplantation and treatment with melphalan to manage his multiple myeloma. The prostate cancer was treated with cyclophosphamide, bortezomib, and dexamethasone.

**Figure 4** Atypical plasma cells, HPO (40X objective).

**Figure 5** Prostatic adenocarcinoma, left. Plasma cell myeloma, right. LPO (10X objective). PSMA immunohistochemical stain (insert).
Discussion

We present a case in which two previously unknown primary malignancies were diagnosed simultaneously. The initial core biopsy specimen was consistent with MM. Microscopic evaluation of the resected specimen noted the presence of MM with a coexisting metastatic prostate carcinoma. While there have been reported cases of concurrent disease, this is a rare occurrence. A patient with a known primary disease has a low likelihood of concurrently developing a second malignancy presenting as a metastatic lesion.1

According to the National Cancer Institute Surveillance Epidemiology and End Results (NCI SEER) database, a cancer survivor has a 14% increased risk overall of developing another second malignancy in his or her lifetime.2 Since 1971, the number of cancer survivors in the United States (about 3.5% of the US population) has tripled. Second cancers account for about 18% of new cancer diagnoses annually, making them the third most common cancer diagnosis. There have been cases reported of multiple primary malignancies metastasizing to bone, however these metastases typically appear sequentially years apart rather than simultaneously.1

Multiple myeloma has been known to develop in the presence of other hematologic neoplasms. An association between MM and leukemia was first reported in the 1960s.3 Several case series report the concurrent diagnosis of MM and chronic lymphocytic lymphoma.4,5 Large population-based studies have demonstrated that patients with MM are at increased risk for developing myelodysplastic syndrome (MDS) and acute leukemia. This risk is attributed to a combination of MM related factors (molecular subtypes and bone marrow environment), host genetics, environmental and behavioral factors, and MM treatment. Current therapies (enaladomide and melphalan) may increase a patient’s risk of developing a second primary malignancy in the future.6

Prostate cancer patients have also been known to develop secondary malignancies (about 10% as per the NIC SEER database), most commonly bladder, colon, and rectal cancer. Much of the literature recognizes secondary malignancies that result from prostate cancer treatment.10-12 Radiation therapy is cited as the most common cause of these secondary neoplasms. About 1 in 70 men with prostate cancer treated with external beam radiation therapy (EBRT) develop a secondary malignancy within 10 years. Brachytherapy can reduce the risk of a second primary cancer by delivering direct, localized radiation and avoiding scatter from EBRT.10

Reports of the specific combination of prostate cancer and MM in the literature are rare. Szwed et al.13 described a patient with known prostate cancer who was presumed to have metastatic lesions to bone. Once biopsied, the patient was diagnosed instead with MM. Prostate cancer has also been reported to occur concurrently with bladder and lung cancer.14,15 While these individual case reports present patients with concurrent disease, one notes that these malignancies were diagnosed separately, rather than simultaneously within the same specimen.

Our case describes two cancers presenting with bony manifestations within a single pathologic lesion. Two separate cell lines, previously undiagnosed, were present within the resected specimen while only one was seen in the initial core biopsy. We feel that this illustrates the importance of obtaining representative tissue at the time of biopsy. Bone lesions in particular can have high rates of nondiagnostic results. Malignant tumors have also been known to have high rates of inaccurate results.16,17 Open biopsy, therefore, remains the most accurate method for acquiring adequate and representative tissue, though it remains an expensive and invasive technique.

Looking to the future, open biopsy may have a larger role in the era of patient-specific therapies and targeted treatment approaches. Obtaining tissue samples through open biopsy may allow for the identification of actionable targets and individualized patient-specific treatments. Additionally, larger tumor harvest permits for tissue banking and provides material for translational research.

It is our institutional preference to obtain open biopsies in the operating room to realize a higher degree of representative tissue. However, at times, access to the operating room may not be readily available and a needle biopsy may permit earlier diagnosis and treatment. The accuracy of percutaneous biopsy can be increased with CT or ultrasound guidance.18 Image-guided needle biopsies of musculoskeletal lesions are accurate in 80% to 95% of cases when compared to open biopsy.19 They are safe, easy to perform, and no more time consuming, thus providing a viable alternative.

Our case notes the rare diagnosis of simultaneous malignancies within a single pathologic lesion and highlights the value of a biopsy that is extensive and thorough enough to provide representative tissue.

Conflict of Interest Statement

None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References


