Oncology Tips and Tricks: Pathologic Fractures in Metastatic Cancer: Presentation and Workup Considerations

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Introduction

Cancer remains one of the world's leading causes of mortality with an estimated 19.3 million new cases and approximately ten million cancer-related deaths in 2020.[1] The vast majority of cancer-associated deaths occur in those with metastatic disease. With longer survival time in patients with advanced cancers in light of recent advances in treatments, there have been increases in morbidity and disability related to cancer-associated complications.[2]

Among these complications are pathologic fractures, which occur in areas of weakened bone secondary to either primary or metastatic lesions, the latter of which are seen far more frequently. Bone is among the top three most frequent sites of metastases, which include lung and liver. The most common primary cancers to metastasize to bone are breast, prostate, thyroid, lung, and renal cell carcinoma. The relative incidence of bone metastasis by type of tumor is: 65-75% in breast cancer; 65-75% in prostate; 60% in thyroid; 30-40% in lung; and 20-25% in renal cell carcinoma.[3] Multiple myeloma also manifests frequently as lytic bone lesions. Pathologic fractures have been reported in 8 to 30% of patients with bone metastases.[4]

Pathologic fractures cause considerable morbidity and cost to quality of life. A 2020 retrospective study published in JOA comparing pathologic hip fractures to native hip fractures showed that patients with pathologic fractures experience significantly higher rates of death (6.3% vs 4.3%) serious adverse events (17.3% vs 13.5%), extended lengths of stay (30.2% vs 25.9%), readmissions (11.9% vs 8.4%), thromboembolic complications (3% vs 1.6%) and perioperative transfusions (31.5% vs 26.4%).[5]

Level 1 evidence shows that the use of bisphosphonates such as zoledronic acid or bone-modifying agents such as denosumab is associated with a significant decrease in skeletal-related events (SREs) including pathologic fractures.[6] Additionally, in the metastatic breast cancer population, the American Society of Clinical Oncology guidelines recommend treatment of cancer-related bone pain with these agents as part of adjunctive therapy for cancer-related bone pain in addition to additional analgesic therapy, chemotherapy, radiotherapy, or hormonal therapy.[7]

When approaching a patient with a suspected malignancy who presents with new-onset musculoskeletal pain or fracture, a high degree of suspicion and an experienced multidisciplinary team are necessary to accurately diagnose and treat the underlying process.

Presentation and Workup

Pathologic lesions can be discovered in various ways—incidentally found on imaging, in the outpatient clinic during evaluation for hip pain, or as pathologic fractures in the emergency setting. Patients may report progressive pain with inability to bear weight on their affected lower extremity, and often report prodromal pain prior to sustaining a fracture. Workup of pathologic lesions require a thorough history, review of systems, exam, imaging and labwork.

History and Exam

Initial history should include personal and family history of malignant tumors and related treatment, risk factors for cancer including prior smoking history, onset of pain, and mechanism of injury (bone weakened especially by lytic metastatic lesions fracture with much less force than benign bone). A full review of systems should assess for systemic symptoms such as fatigue, fevers, night sweats, shortness of breath, dark urine or hematuria, early satiety and weight loss. Metastatic hypercalcemia occurs when osteolytic metastases cause excessive release calcium from bone, which can cause symptoms such as confusion, muscle weakness, polyuria and polydipsia, gastrointestinal distress, nausea and dehydration.[8] A full physical exam may reveal other signs of metastatic disease such as scleral icterus and jaundice, lymphadenopathy, lung crackles, hepatosplenomegaly, skin lesions, breast masses, enlarged prostate, musculoskeletal tenderness including along the vertebral column, or neurologic abnormalities.

Imaging

Pathologic lesions are most frequently diagnosed on plain radiographs. Metastatic lesions frequently affect proximal aspects of

long bones, and fractures through these lesions often occur commonly in the proximal femur due to the stress from forces placed on the lower extremities during weightbearing. Initial biplanar x-rays should include the joints above and below the lesion, including the pelvis, hip, femur, and knee. Aggressive features suggestive of a pathologic process include lesion diameter > 5cm, cortical interruption, periosteal reaction and associated pathologic fracture.[9] Plain radiographs have high specificity for bone lesions, especially those that appear lytic, and may also reveal osteoblastic lesions which appear sclerotic on imaging.

More advanced imaging such as CT can be used on a case-dependent basis and can be useful in disease staging; they allow for high-resolution cross-sectional views of the bone cortex and periosteum.[10] CT scans of the chest, abdomen and pelvis can help identify possible sources in cases of metastatic cancer with an unknown primary. In women, mammography can be used to evaluate for occult breast masses. The spine is one of the most common sites for metastatic disease to spread, and when physical exam is concerning for neurologic deficit or hyperreflexia, an MRI of the spine can be used to evaluate for neurologic compromise.

Laboratory analysis

A comprehensive laboratory workup is helpful in characterizing the disease process, distinguishes infectious etiologies from cancer, and establishes a baseline from which the disease course can be followed over time. Screening lab studies include a complete blood count with differential and peripheral blood smear, comprehensive metabolic panel, liver function tests, coagulation studies, inflammatory marks (ESR/CRP), electrolyte panel (calcium, phosphorous, alkaline phosphatase), LDH, beta-2 microglobulin, and prostate specific antigen. Other studies include serum protein electrophoresis with quantification of immunoglobulins, 24-hr urine protein electrophoresis, immunofixation, and serum monoclonal light chains for myeloma screening. Tumor markers such as alpha-fetoprotein, carcinoembryonic antigen, CA-19-9, and CA-125 may be useful as a screening test to distinguish skeletal metastases of carcinoma from primary bone tumors.[11]

In patients with an unknown primary carcinoma with a solitary bone lesion, a biopsy is needed prior to any surgical fixation in order to rule out a primary bone lesion such as osteosarcoma, which could jeopardize the chance of limb salvage. Patients who undergo needle biopsy for impending fractures should maintain protected weight bearing status after the procedure. The biopsy should be performed in a location that will permit excision of the biopsy tract should a primary sarcoma be diagnosed.[12] Fixation may precede final biopsy results when metastatic disease may be presumed based on widespread disease to multiple bones and solid organs. Ideally, primary bone sarcoma should be ruled out on pathology prior to the introduction of any internal fixation or instrumentation.

Criteria for prophylactic fixation

In patients with metastatic lesions to long bones that are concerning for impending pathologic fracture, the risk of fracture within 6 months can be predicted using Mirel's criteria, a weighted scoring system based on four objective clinical and imaging risk factors, which include location, size and type of lesion and pain.[13] The system was first established in 1989 following a retrospective study of 78 pathologic lesions that received radiation therapy without prophylactic fixation. Clinical and imaging data were obtained related to each of Mirel's four criteria prior to the follow-up period of 6 months, during which 27 cases sustained fractures and 51 did not. The average score was 7 in the non-fracture group and 10 in the fracture group, which led to the conclusion that lesions with scores higher than 7 have a higher risk of fracture and may be good candidates for prophylactic fixation prior to irradiation.

Internal fixation of pathologic fractures is considered a palliative procedure, to reduce pain and improve mobility by providing stabilization that will outlast the patient's expected survival time. The choice of fixation suited for various types of lesions in each area of bone is a broad and complex topic which is beyond the scope of this discussion. Instead, we will briefly review a case below which discusses one of the most common types of pathologic fractures.

Table 1. Mirel's Classification Scoring System.

Criteria	1 Point	2 Points	3 Points
Site of lesion	Upper limb	Lower limb	Trochanteric region
Size of lesion	<1/3 of bone diameter	1/3-2/3 of bone diameter	>2/3 of bone diameter
Nature of lesion	Blastic	Mixed	Lytic
Pain	Mild	Moderate	Functional limitation

Table 2. Recommendation for fixation based on Mirel score.

Mirel score	Fracture Risk at 6 months post-irradiation	Recommendations
≤7	0-4%	Safe to irradiate with minimal risk of fracture
8	15%	Consider prophylactic fixation
≥9	>33%	Candidate for prophylactic fixation

Radiation Therapy

Radiation therapy has become standard in treatment after internal fixation of a complete or impending pathologic fracture, with evidence supporting that radiotherapy can promote remineralization and bone healing, alleviate pain, improve functional status, and reduce the risk of subsequent fracture or loss of fixation.[14] Compared to surgery alone, radiation therapy is associated with increased regain of use of the affected extremity, fewer reoperations to the same site, and increased overall survival.[15] The area of radiation should include the entire fixation device Radiation therapy can also be used for palliative measures to reduce pain in patients with metastatic disease that are not candidates for surgery.

Brief Case Report

A 38-year-old female with a history of asthma and uterine fibroids was brought to the emergency department after a ground level fall while attempting to get out of a car. She reported severe hip and thigh pain and was unable to bear weight on her right leg. On further history, the patient reported progressively worsening right-sided hip pain for the past four months which had required her to start using a cane. Imaging showed diffuse lytic lesions in the pelvis and femur, especially prominent in the right proximal femur, with a pathologic fracture adjacent to the lesser trochanter. On additional questioning, the patient endorsed early satiety and constipation mixed with loose stools, as well as a mass over her left breast. Exam was notable for significant pain with log roll and palpation of the right hip localizing to the groin, and an 2cm mobile mass in the left upper quadrant of the left breast.

A non-contrast CT of the right hip and femur with axial, sagittal and coronal reconstructions redemonstrated the fracture inferior to the right lesser trochanter, and showed cortical breakthrough and diffuse marrow infiltration of the distal femur concerning for impending pathological fracture. The visualized peritoneum had multiple areas of thickening and nodularity concerning for peritoneal carcinomatosis. Additional CTs of the head, chest, abdomen and pelvis revealed osseous metastases to the clivus, mandibular condyles and upper cervical spine, multiple bilateral pulmonary nodules, numerous hepatic and renal lesions, and widespread lytic and blastic osseous metastases involving the axial skeleton and all visualized long bones. A thorough workup was initiated by a multidisciplinary team including hematology-oncology, radiation oncology, palliative care, and orthopedic surgery.

After discussion with the patient and care teams, the patient was taken to the OR for a right intramedullary nail (Smith & Nephew Meta-Nail) with two proximal and two distal interlocks. Femur reamings were sent for pathology. There were no intraoperative complications. Final pathology results were consistent with HER2-positive metastatic breast cancer.

Final Remarks

Metastatic cancer with skeletal metastasis can cause severe pain and morbidity, reduction in quality of life, and early mortality. The goal for patients with end stage cancer is primarily palliative. Pathologic fractures can be approached

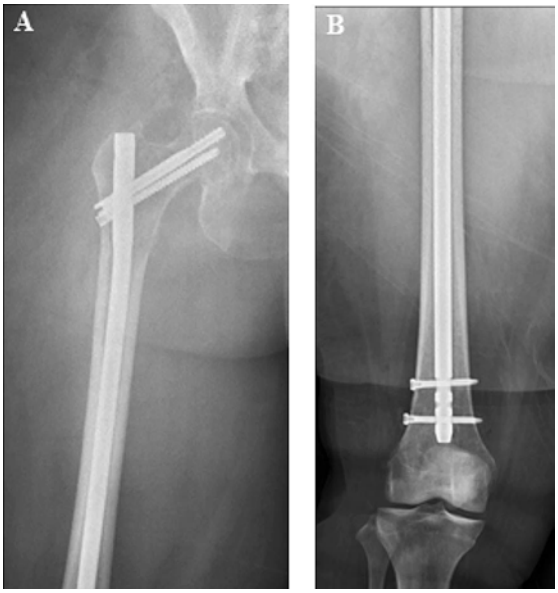

Figure 2. AP Right hip **(A)** and distal femur **(B)** status post right intramedullary Smith and Nephew Meta-Nail.

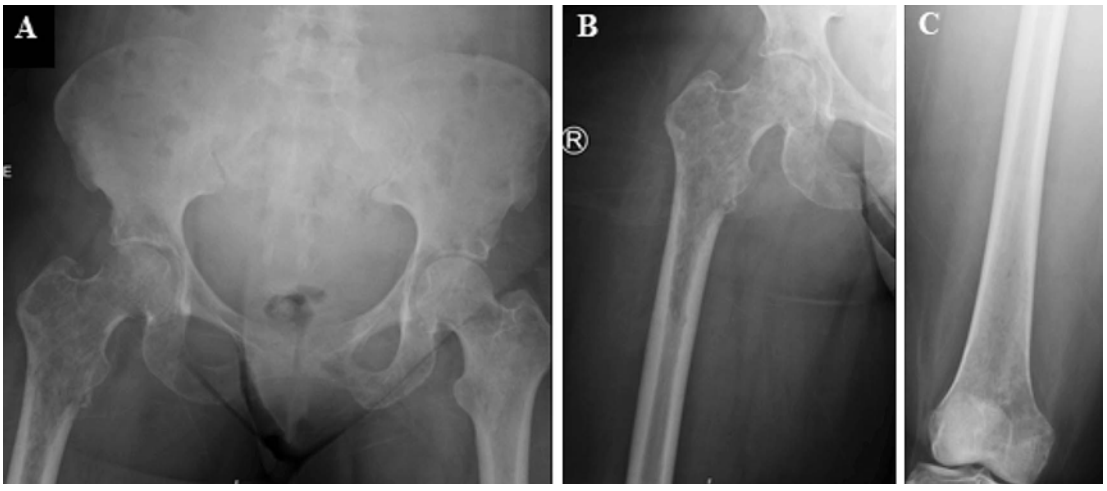

Figure 1. AP Pelvis **(A)** AP right hip **(B)** and AP distal femur **(C)** demonstrating pathologic lytic lesions of the pelvis and right proximal and distal femur.

with a combination of internal fixation and radiation therapy; however, the patient's overall medical course can become unpredictable especially in those with advanced metastases as witnessed in this case. This reiterates the importance of a thorough evaluation and workup and the combined efforts of an experienced multidisciplinary team in order to provide the best possible outcomes for these complex cases.

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