Diagnosis of Bone Metastases

Evaluation of the Patient With Carcinoma of Unknown Origin Metastatic to Bone

Bruce T. Rougraff, MD

Metastatic carcinoma to bone of uncertain primary origin is a common clinical diagnostic scenario. I present a simple and effective staging system to identify primary malignancies. The role of clinical history, physical examination, laboratory studies, and limited radiographic studies are critical to the success of this diagnostic strategy. Needle or open biopsy frequently is needed yet usually is more effective as a confirmatory study for carcinoma or to rule out primary bone sarcomas. Patients who present with a displaced pathologic fracture require an urgent diagnostic and treatment plan that does not compromise future treatment options and provides durable skeletal reconstruction.

The skeleton is a common metastatic site for several visceral carcinomas. In patients who have a known primary carcinoma site, the breast and prostate are the most common malignancies that metastasize to bone. Metastatic disease in these patients usually occurs late in the disease process, long after the primary disease has been identified. However, 3% to 4% of patients with metastatic carcinoma have an unknown primary site at the time of presentation. Ten percent to 15% of these patients have skeletal involvement as the cause of their presenting symptoms. In the patient older than 40 years with a poorly marginated bone lesion on plain radiographs, the diagnosis of skeletal metastasis of unknown origin is more likely than a primary bone malignancy. Because these patients typically are evaluated initially by an orthopaedic surgeon for musculoskeletal complaints, it is imperative that the treating physician have a rational and effective approach to the diagnostic evaluation and treatment of these patients.

Before the use of CT scanning, the success rate of identifying an occult primary carcinoma was very poor. Rougraff et al reported the results of a prospective evaluation of a simple diagnostic strategy that included CT scanning to identify the primary carcinoma. They were able to find the primary site of disease in 85% of the patients, and ultimately identified an additional 5% before the death of the patient. The primary site of the carcinoma has serious medical and surgical treatment implications, and is of prognostic significance.
This review article attempts to revisit the diagnostic issues in evaluating patients who present with a metastatic carcinoma to bone in light of newer diagnostic and staging methods. Expanding on this issue, the appropriate clinical approach to patients who initially present with pathologic fracture through a metastatic carcinoma of unknown origin requires discussion because very little direction is offered in the current literature.

**DISCUSSION**

Metastatic carcinoma of bone must be considered in patients older than 40 years who present with a poorly marginated bone lesion in the proximal skeleton and spine. Metastatic carcinoma is more likely than a primary bone sarcoma in this group of patients. The most likely visceral primary carcinomas that spread to bone include the lung, kidney, prostate, breast, and thyroid. However, many other malignancies can spread to bone and may include melanoma, liver carcinoma, gastrointestinal carcinoma, metastatic lymphoma, and uterine carcinoma. Primary malignancies of bone that occur in this older age group of patients include malignant fibrous histiocytoma of bone, primary lymphoma of bone, chondrosarcoma, and plasmacytoma. The first and most important part of the diagnostic strategy to evaluate these patients includes a thorough clinical patient history. Patients who have had a previous malignancy in the distant past may not volunteer that information on a cursory medical history. Despite a long disease-free interval, any patient with the history of a previous carcinoma and a new skeletal lesion must be considered to have metastatic carcinoma until proven otherwise.

The second part of the diagnostic strategy involves a physical examination, which includes a breast examination in female patients, and a prostate examination in male patients. The thyroid and abdomen were examined in all patients. Unfortunately, these patients typically have small primary tumors that are not easily identifiable on physical examination. Rougraff et al reported that only 8% of the patients had a primary carcinoma found on physical examination.

The third part of this evaluation should include laboratory analysis to accomplish two goals: to assess the medical condition of the patient before surgical intervention, if needed; and to exclude the diagnostic possibility of multiple myeloma, which usually does not need a biopsy for diagnosis. The laboratory analysis should consist of the determination of a complete blood cell count, ESR, levels of electrolytes, liver enzymes, prostate specific antigen, and ALP and serum and urine protein electrophoresis. Laboratory findings usually are non-diagnostic in patients who have a normal prostate specific antigen, and serum and urine protein electrophoresis.

The next part of the diagnostic strategy should involve a radiographic evaluation. A plain radiograph of the chest and involved skeleton should be obtained. Any painful extremity should be evaluated, and any radiographs of the skeleton should include the entire bone, with adequate markers to be able to plan a skeletal reconstructive procedure if necessary. Radiographs of the chest identified the lung as the primary site in 43% of the patients in the study by Rougraff et al. The typical radiographic appearance of a metastasis is a lytic, permeative lesion of the diaphysis or metadiaphysis of a proximal long bone or bone of the axial skeleton. If the lesion seems to involve mostly the cortex of a bone or is located distal to the knee or elbow, it is more likely to be from an occult lung primary carcinoma than other sites. A bone scan of the entire skeleton (technetium 99m-phosphate scintigraphy) should be obtained to identify whether there are multiple skeletal lesions. A patient with multiple skeletal lesions is unlikely to have a primary bone malignancy. In addition, another skeletal lesion may be found with bone scintigraphy that is more amenable to a biopsy or that may require prophylactic skeletal fixation.

Next, a biopsy is required if the diagnostic strategy fails to identify a primary carcinoma, or before internal fixation if indicated. The placement of the biopsy incision is critical in case the
final diagnosis is a primary malignancy of bone, which may require a subsequent resection and reconstruction. A poorly planned and executed biopsy in a patient with a primary bone malignancy could result in an amputation for a patient who otherwise might be a candidate for limb salvage surgery. The biopsy may be accomplished by needle biopsy if there is an accessible soft tissue mass, or an incisional biopsy. Good communication with the pathologist before the biopsy is critical so that enough tissue is obtained for special testing and so that the tissue is processed appropriately. The pathologist may be able to gain information concerning the primary site by using immunohistochemical tests or monoclonal antibodies as markers. Occasionally, a bone lesion such as lymphoma can be misdiagnosed as an undifferentiated adenocarcinoma, resulting in significant mistreatment of the patient. If the pathologist is informed as to the prebiopsy information and the remaining questions that are to be addressed, this type of mistake can be avoided. The biopsy material, although it confirms the diagnosis of metastatic disease, only infrequently identifies the primary site of malignancy.

This simple diagnostic strategy using CT scanning (Table 1) is able to identify the primary site of malignancy in most patients at the time of presentation. Using followup CT, Rougraff et al9 were able to identify two additional primary sites (of the six patients who originally had negative CT studies), 3 months after the initial evaluation. Clinical judgment should be used to decide whether additional testing is warranted in patients with an unidentifiable primary malignancy. Several reports have shown that postmortem examinations rarely are able to identify the primary site in patients whose carcinoma was not identified before death.1,2,11

Unlike skeletal metastasis of known origin (most often of the breast or prostate), a metastasis of unknown origin usually originates from the lung or kidney (although almost any visceral carcinoma can be the source of an occult malignancy). This could be attributed to the inaccessibility of these organs to physical examination, to the large size to which tumors in the kidney or lung can grow before becoming symptomatic, or to the tendency of these tumors to metastasize to bone earlier than breast or prostate carcinoma. Because the breast is a distinctly uncommon site for a metastatic malignant tumor when the patient has a skeletal metastasis of uncertain origin, mammography should not be included as part of the evaluation unless the history or physical examination reveals an abnormality in the breast, or in women who, after the diagnostic strategy has been completed, still have an unknown primary site.9,10

A difficult clinical scenario is the occasional patient who presents to the orthopaedist with a fracture that seems to be pathologic, yet the patient has no prior cancer history. The problem here is to provide skeletal fixation, identify the tumor type, and not eliminate a limb-sparing

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**TABLE 1. Diagnostic Strategy for a Bone Metastasis of Unknown Origin**

<table>
<thead>
<tr>
<th>History and physical examination</th>
<th>Normal</th>
<th>Abnormal</th>
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<tbody>
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<td>focus on thyroid, breast and prostate</td>
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<tr>
<th>Laboratory studies</th>
<th>Normal</th>
<th>Abnormal</th>
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<tr>
<td>Serum and urine protein electrophoresis</td>
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<td>Prostate specific antigen</td>
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<td>Multiphasic chemistry</td>
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<th>Imaging</th>
<th>Normal</th>
<th>Abnormal</th>
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<td>bone scintigraphy</td>
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<tr>
<td>chest radiograph</td>
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<tr>
<th>Chest CT</th>
<th>Abdominal CT</th>
<th>Biopsy of the most accessible lesion</th>
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operation if the tumor is a primary bone sarcoma. Depending on the fracture location and pain level of the patient at the time of presentation, blood testing and CT scans can be obtained before surgical intervention. A needle biopsy of the lesion is needed before additional contamination of the soft tissues and bone occurs. If the needle biopsy is not diagnostic, an open or incisional biopsy is necessary. It is not appropriate to place internal fixation before a primary bone sarcoma is ruled out by biopsy. Referral to an orthopaedic oncologist before biopsy is an appropriate consideration.

Because most patients with skeletal metastasis of unknown primary site have a short life expectancy, it is tempting to limit the number of diagnostic tests, thereby limiting the cost to these patients. It may seem logical to proceed directly to a biopsy in these patients, without a prebiopsy evaluation. There are at least six reasons for not starting the evaluation with a biopsy in these patients: (1) the lesion may be a sarcoma of bone, and an ill-planned biopsy compromises the ability to do a limb salvage procedure and obtain high-quality imaging studies of the osseous lesion; (2) another lesion may be identified that would be easier and safer to sample; (3) renal cell metastasis can be very vascular, and it is helpful to know before the biopsy whether the osseous lesion is most likely to be renal in origin. This allows the surgeon to consider embolization before the biopsy, or to consider the use of a needle biopsy to limit the blood loss from the procedure; (4) an unnecessary biopsy in a patient who has multiple myeloma can be avoided by obtaining the appropriate laboratory test; (5) the histologic analysis alone identifies the primary site in only a small percentage of patients. It is unlikely that a biopsy alone would identify the primary site without an appropriate prebiopsy evaluation; and (6) the surgeon and the pathologist will be more confident in making a histologic diagnosis based on frozen section if a primary malignant site is identified before the biopsy. This allows internal fixation of impending fractures to be done more often at the time of biopsy, and can eliminate the need for a second operation after a final histopathologic diagnosis has been obtained.

The prognosis of these patients is related to the primary site that was identified. Patients with primary tumors of the lung usually have a very poor prognosis, with few surviving more than 12 months after the diagnosis. Likewise, patients whose primary site cannot be identified survived an average of 11 months. However, patients with kidney and thyroid carcinomas may have a very long survival, especially if they have isolated skeletal metastasis at the time of presentation. The technique of skeletal reconstruction used for these patients should be durable.

Skeletal metastases of unknown origin usually are painful, poorly-marginated lesions of the proximal part of the skeleton. Ninety percent of these patients are older than 40 years at the time of their diagnosis. Using a simple diagnostic strategy, almost all occult primary carcinomas can be identified. Careful attention to the details to the approach and care of these patients can prevent an irreversible error in their treatment.

References

