CHAPTER 5

SOLITARY LATERAL CUNEIFORM BLADDER CARCINOMA METASTASIS

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This is a report of a biopsy confirmed solitary lateral cuneiform metastasis in a patient with bladder cancer (transitional cell carcinoma). Bone metastases are most commonly located to the axial and appendicular skeleton. Metastatic cancer to the hand or foot is considered rare although metastatic bladder cancer shows a propensity to localize to the foot when it occurs. Non-specific arthritic like pain in the midfoot was the primary manifestation of this particular acrometastasis. This coincided with a rising CEA blood level that was monitored regularly due the patient's history of bladder and breast cancer. Acrometastasis should be considered in the differential diagnosis in any patient with a previous history of cancer and musculoskeletal pain.

Malignant tumors frequently metastasize to bone although it is quite unusual for cancer to metastasize distal to the elbow or knee.[1,2] The overall incidence of metastasis varies in different reports from 20 to 70% of all cancer patients demonstrating microscopic evidence of metastasis at the time of autopsy.[3,4] The most common primary sources of metastatic bone tumors include cancers from the breast, lung, prostate, kidney and gastrointestinal tract.[5] The more typical distribution of metastatic bone tumors include the vertebrae, pelvis, femur, ribs, skull.[2,6] Acrometastases (spread of cancer to the hand or foot) are very rare.[2,7]

Leeson et al reported a 1.7% incidence of foot metastasis in 14 of 827 cancer patients who underwent autopsy.[1] The first reported case of an acrometastasis was described by Bloodgood in 1920. He described multiple metastases to the foot from prostate cancer.[8] Lisbon et al reviewed 290 acrometastases and found a two-times greater prevalence of hand tumors as compared to foot lesions. The most common neoplasm to the hand was bronchogenic carcinoma. Most of the metastases that went to the hand originated superior to the diaphragm (lung, head, and neck). Also noted was a tendency for the pedal tumors to arise from subdiaphramatic areas such as gastrointestinal, genitourinary (renal and bladder), and uterine.[9] Gall et al believe the incidence of metastatic lesions to the feet may have a greater incidence than what is reported. They feel autopsy may not recognize these lesions due to the lack of clinical evidence in non-ambulatory end stage cancer patients.[7] Bunkis and Carter proved the rarity of metastatic tumors after reviewing 948 cancers and found only one metastasis.[10]

Zindrick et al, and later Lisbon et al reviewed large numbers of metastatic tumors and found that the most common tumors that affect the foot originate from the colon and kidney (approximately 17% each). Pedal metastases usually involve the tarsal bones (50-73%).[4,9] The calcaneus is affected primarily (23%) with the cuneiforms being affected 7% of the time.[4]

Bladder metastases are less frequently seen.[4] Although metastatic genitourinary cancer is rare, it appears there is a more frequent incidence in its tendency to show an affinity for metastasis to the bones of the feet.[7] Bright and Wilke in 1969 described the first reported case of a pedal metastasis in a patient with bladder carcinoma.[11] Four of the eight pedal metastases presented by Gall et al suffered from genitourinary cancer.[7] Lisbon et al noted patients with metastatic bladder carcinoma showed a significant predilection for distant spread to the foot. Nine of the ten metastatic lesions from bladder carcinoma were found in the foot and primarily the calcaneus.[9] There have been several other similar isolated reports of bladder cancer metastasizing to the foot.[12-15] The rising number of bladder metastases in the foot warrant definite consideration in the differential diagnosis when evaluating musckuloskeletal pain particularly in patients with this type of cancer.

The pathogenesis of metastatic cancer is still obscure, however, the spread of bladder cancer is believed to be related to the invasion of the bladder wall and the spread is usually by local lymphatics and venous plexus to the vertebral column.[16] A possible explanation of the retrograde spread to the foot is via the vertebral venous plexus down incompetent leg veins.[9] Tumor embolization has also been linked to hemodynamic factors, trauma, temperature differences, hormonal influences, host immune responses.[7,17,18]

CASE REPORT

A 75-year-old female presented with vague dorsal midfoot pain and swelling. She related the pain had been present for approximately 3 months with no history of traumatic injury. The location of the pain was primarily

in the midfoot diffusely spread across the cuneiforms and Lisfranc's joint. The pain had intensified with increasing local inflammation. The symptomatology was worse with prolonged activity and barefoot walking however, the pain remained despite her attempts at decreasing her activity, off-loading the area with braces, making changes in shoe gear and utilizing an over the counter arch support. She described the pain as a chronic ache with occasional sharp stabbing pain if she stepped on the foot wrong.

She had a concomitantly rising CEA tumor marker laboratory value which was monitored periodically by her oncologist for previous bladder and breast cancer. The level went from its normal low signal digit value to over twenty without an explanation. The source of the change in her lab value went undetected with multiple studies (PET scan, CT scans of the abdomen and thorax and a bone scan) turning up negative for metastatic changes. Due to the persistent foot inflammation an appropriate referral was made for podiatric evaluation on 8/13/02.

The patient's past medical history was positive for previous breast cancer (ductal carcinoma) treated with radical mastectomy in January 2001 but, no other treatment was necessary due to negative lymph nodes. She also had from a more severe case of bladder cancer (transitional cell carcinoma) first treated with neoadjunctive MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) before an eventual cystectomy in April 2001. The bladder cancer did extend transmurally and required four cycles of carbo/Gemzar which was complication by thrombocytopenia. She also had a positive history of tuberculosis, asthma, gastroesophageal reflux and hypercholesterolemia. Her medications included inhalers, Brethin, Aciphex, Celebrex, Zoloft, and Xanax. Lower extremity examination revealed the primary focus of pain on palpation was localized in the region of the lateral cuneiform with some pain in the adjacent tissues. There was also pain with tuning fork evaluation over the lateral cuneiform and pain with range of motion of the 2nd-5th tarsometatarsal joints. Radiographs revealed a questionable circumscribed cystic-like lesion within the lateral cuneiform (Figure 1). Considering the patient's history, there was concern for a metastatic lesion, therefore, to more appropriately evaluate this area a MRI was obtained which revealed a one cm "intraosseous ganglion" of the lateral cuneiform with significant marrow edema and inflammation secondary to a pathologic stress fracture (Figure 2). Once these results were obtained there was heavy suspicion for metastatic cancer to the midfoot and surgery was scheduled. A few days later the surgery was performed on 8/17/02. Excision /curettage and allogenic grafting of the lesion was performed and frozen sections were obtained. Cancerous characteristics were noted on the frozen sections however, the source of the cancer was unknown and had to be differentiated between bladder and breast cancer. Figure 3 shows the radiographic postoperative appearance of the tumor.

Initial pathology reports from the frozen section showed poorly differentiated carcinoma. After extensive immunohistochemical stains the tumor was diagnosed as metastatic urothelial (transitional cell carcinoma). This was based on positive tests for antigens CK7, CK20, E-CADHERIN although it was uroplakin negative. Also supporting the diagnosis from a clinical standpoint was that her previous bladder cancer was poorly differentiated

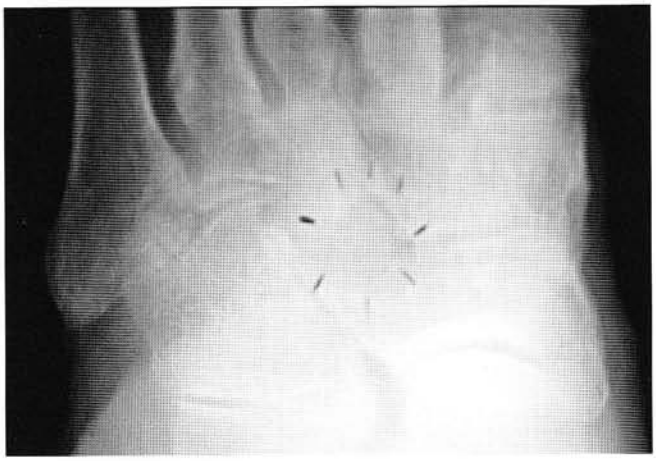

Figure 1. An oblique radiograph of the left foot shows a questionable cystic-like lesion within the lateral cuneiform.

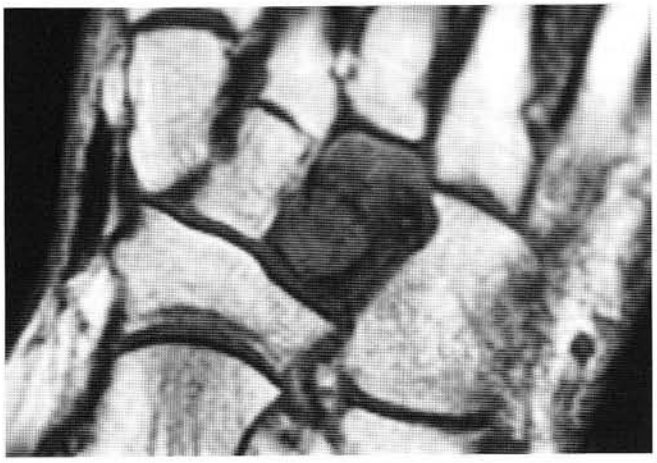

Figure 2A. Magnetic Resonance imaging scans of the foot. Axial T1-weighted image of the left midfoot shows low signal (dark) in the entire lateral cuneiform with a well circumscribed one centimeter lesion area in the proximal cuneiform.

and it had extended transmurally into the prevesicle fat and also invaded the uterus while her breast cancer was high grade ductal carcinoma in situ with negative lymph nodes.

The patient's postoperative course was uneventful. Her incision healed well. Extensive testing post-operatively revealed no evidence of metastatic disease with normal CT scans of the abdomen, thorax, and pelvis. Full body bone scan also showed no evidence of metastasis other than the inflammation noted in the left midfoot and subtle arthritic changes in the knees and shoulders which had been unchanged compared to previous studies. The patient was treated with radiotherapy. Chemotherapy was not necessary. Currently the patient is having minimal discomfort and is ambulating in a fracture walker.

DISCUSSION

A strong clinical suspicion and thorough history and physical examination are necessary when an acrometastasis is in the differential diagnosis. Acrometastasis is usually vague, insidious, non-traumatic and responds poorly to conservative treatment.[2] When an acrometastasis occurs to the foot it usually localizes in the calcaneus.[2,4,9] However, there have been several reports of metastatic cancer to the foot in different locations and from different primary sources.[1-21] Acrometastases could be present at the time of initial diagnosis of cancer and has lead to the identification of primary cancerous lesions.[4,15]

It is uncommon for bladder carcinoma to present as a metastatic lesion without symptoms and a diagnosis of cancer. Metastasis is usually a late feature of the disease because it depends on the invasion of the bladder wall and histologic grade.[15] In the case described, the patient exhibited a poorly differentiated carcinoma that had extended through the bladder wall into the prevesicle fat. When these characteristics are present distant metastases are more common. This is particularly important in transitional cell carcinoma and renal cancer due to the increased incidence of pedal metastasis.[7,12]

Radiographic findings of metastatic bladder cancer to the foot have been described as osteolytic lesions.[4,7,9,12,14,15] However, at the time of early symptoms, radiographic changes may not be evident and special imaging (bone scan, MRI, and CT scans) can play a crucial role in the detection and delineation of osseous pathology.[2] Misdiagnosis has occurred which only delays the eventual treatment.[12,15] These lesions usually respond well to radiotherapy[15] Metastatic lesions can be confused with osteomyelitis, gout, rheumatoid arthritis, Reiter's syndrome, Paget's disease, RSD, and ligamentous strains, which leads to a delay in appropriate diagnosis and treatment.[12,15,19,21]

A delay in treatment of metastatic bladder cancer can have a significantly negative affect on the outcome and long-term survival of these patients. Metastatic transitional cell cancer is a moderately chemotherapy sensitive neoplasm. However, it is an aggressive neoplasm with poor survival rates (median survival less than 12-14 months and frequently less than one year).[10,13,22,23] Poor prognostic factors include bone or liver metastasis and poor performance status.[23]

Treatment modalities in the past had been mainly palliative, and long-term survival was poor. The standard of care for years included MVAC (methotrexate,

Figure 2B. Axial T2-fat suppression image of the left midfoot shows increased abnormal signal (light) at the site of the metastasis as well as throughout the entire cuneiform secondary to the pathologic stress fracture.

Figure 3. An oblique postoperative radiograph of the left foot shows increased bony sclerosis within the lateral cuneiform at the site of the allograft.

vinblastine, doxorubicin, cisplatin). Attempts were also made to control pain with local radiation therapy. Other treatment modalities described include bracing, immobilization, systemic chemotherapy,[4,18] and amputation.[3,15,21] Newer treatment of metastatic bladder cancer includes two- and three-drug combination chemotherapy and molecular therapies regimens with response rates rising to 40 to 80%, although long-term survival is still low compared to other cancers.[22,23] Some promising results have come from adjunctive surgical resection (cystectomy) after aggressive systemic chemotherapy for locally advanced bladder cancer similar to what was performed in this case.[23]

This case emphasizes the predilection of genitourinary tumors for pedal metastasis. A thorough physical examination and detailed history will help increase suspicion for acrometastasis. It is important to consider skeletal metastasis in any patient who has had a history of cancer particularly when they present with musculoskeletal pain.

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