Review Article

Metastatic Bone Disease

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ABSTRACT

Bone metastases are frequent complication of carcinoma, occurring in approximately 70% of patients with advanced breast and prostate carcinomas, and 15-30% of patients with lung, colon, uterus, rectum, thyroid or kidney cancer approximately. Metastatic bone by tumor is a frequent cause of destructive lesions in mature bone. Osteolytic metastases induce spinal cord compression, other nerve compression, pathological fractures, hypercalcemia, and acute pain. For the identification, diagnosis, prognosis, therapy, and follow-up planning of bone metastases, imaging investigations are crucial. Imaging tests are useful for bone screening, describing metastases, and confirming their existence in individuals with non-skeletal malignancies. In patients with malignancy, the diagnosis of bone metastases is confirmed by radiography. If bone metastases are suspected, advanced imaging techniques may be required to confirm the diagnosis and locate the primary tumor. This article aims to review the clinical manifestations, advanced and imaging studies, and therapy of bone metastases in cancer.

Keywords: clinical manifestations, metastatic bone disease, imaging studies, therapy
INTRODUCTION

Bone metastases are a frequent consequence of carcinoma, occurring in 15–30% of patients with lung, colon, stomach, bladder, uterine, rectum, thyroid, or kidney carcinomas, as well as in around 70% of patients with advanced breast or prostate carcinomas. Furthermore, once the tumor has metastasized to the bone, it is usually difficult to heal, only about 20% of breast cancer patients survive up to 5 years after being diagnosed with Metastatic Bone Disease (MBD). Bone metastases cause straining complaints. Severe pain, pathologic fractures, hypercalcemia, compression of the spinal cord, and other nerve compression are all effects of osteolytic metastases. Due to the poor quality of bone formed by osteoblasts in patients with osteoblastic metastases, they usually have discomfort and pathological fractures. Because of this, MBD is regarded as a major issue in complications of cancer (1).

The primary cause for destructive lesions in mature bone is tumor metastases to the bone. About 1.2 million new cases are reported each year in the US. According to these examples, there are around 600,000 individuals with cancers including breast, lung, kidney, and prostate tumors that frequently metastasize to bone. In a previous research, 498 patients with breast cancer who developed bone metastases suffered 9% bone marrow failure, 10% spinal cord compression, and 19% pathological fractures or hypercalcemia (2).

Bones are often affected by cancer metastases. For the identification, diagnosis, prognosis, therapy, and follow-up of bone metastases, imaging investigations are crucial. Imaging is crucial for screening the bone, describing metastases, and confirming their occurrence in individuals with non-skeletal malignancies. Radiography is used to confirm the diagnosis of bone metastases in patients with cancer. More advanced imaging methods may be necessary to find the source tumor and confirm the disease’s diagnosis if there are probable bone metastases (2). The goal of this article is to examine the clinical signs, radiologic findings, and treatment of bone metastases in cancer.

Metastatic Bone Disease

After the lungs and the liver, bone metastases have the third-highest incidence. Approximately 70% of all individuals with cancer develop bone metastases. The type of tumor the patient has typically determines where the damaged bones are located, however the axial skeleton is most commonly impacted, including the vertebrae, pelvis, ribs, and proximal limbs (proximal femur), where pathological fractures frequently occur (3). Visceral cancers often travel through the circulation, but rarely they do so directly to virtually bony structures (such as the pelvis or ribs) (4).

Figure 1. Osteoblast and Osteoclast in normal bone (A) and bone metastases (B,C)
roughly 15-20% of breast cancer cases were osteoblastic, the majority of individuals with breast cancer have a significant osteolytic process (1).

Several variables can influence the occurrence of bone metastases. High blood flow in the red marrow region, resulting in a high tendency for metastases. Tumor cells also create adhesion molecules, which attach tumor cells to bone marrow stromal cells and bone matrix. This binding relationship leads tumor cells to produce more angiogenic and bone resorption factors, resulting in increased tumor development in the bones (1).

Growth factors such as insulin-like growth factors I and II, fibroblast growth factor, platelet-derived growth factors, bone morphogenetic protein, and calcium are all stored in bone. These growth factors, which are produced and activated during bone resorption, create a conducive environment for tumor cells to thrive. Paget popularized the “seed-and-soil hypothesis” in 1889, which defined the process of bone metastases (1).

On the trabecular surface and in the haversian system, human bone undergoes a continual cycle of osteoclast and osteoblast activity. Normal bone undergoes balanced remodeling, in which osteoclasts resorb bone and osteoblasts rebuild bone at the same place. In bone metastases, however, there is an imbalance between osteoblasts and osteoclasts, which results in lesions. This process is affected by the bone microenvironment, which plays a significant role in osteoclast development via stromal cells or osteoblasts producing macrophage colony-stimulating factor and receptor activator of nuclear factor-kB (RANK) ligand (RANKL) (1).

Clinical Manifestation

Back discomfort is the most prevalent complaint. The history of pain should contain information about the pain that the clinician needs to analyze, such as the onset, radiation, precipitating and relieving causes, and the patient’s report on the severity of the pain. MBD pain can be somatic (musculoskeletal), neuropathic (with somatic or epicritic aspects produced by irritation or nerve injury from tumor invasion), or mixed pain, which is the most prevalent. MBD pain develops gradually, gets increasingly severe, is generally localized, and happens often at night and/or during weight-bearing. The vertebrae, pelvis, ribs, head, humerus, and femur are the most prevalent sites for skeletal spread (5).

Although the vertebral multilevels are involved in around 80% of metastases, they are more common in the thoracic area, followed by the lumbosacral and cervical regions. Atlas (C1) degeneration may be indicated by pain in the occipital region or the nuchal area spreading posteriorly to the skull and escalating with neck flexion. Pain in the interscapular area may be related with C7-T1 syndrome owing to tumor invasion of the vertebrae. Epidural compression, an emergency involving oncology and neurological conditions, may be indicated by pain that worsens quickly and radiates in a band-like pattern across the chest or belly. The typical symptoms of spinal cord compression include sensory loss, aberrant reflexes, weakness, and autonomic dysfunction. The thigh joint might be the source of knee or thigh discomfort (5).

Patients with skeletal metastases may experience (and frequently fail to recognize) symptoms of hypercalcemia. Anorexia, nausea, dizziness, thirst, polyuria, back pain, weakness, and sadness are a few of them. Adrenal neuroblastoma is the most typical metastatic lesion in children under the age of six (4).

Radiological Examination

Plain X-Rays

The starting point of a radiological examination is a simple x-ray examination. A pure lytic lesion, a pure blastic (sclerotic) lesion, or a mixed lesion may be the only radiographic manifestation of metastatic disease. Blastic lesions resemble metastases from bronchial carcinoid, prostate, bladder, and medulloblastoma cancers. Lytic lesions typically develop as a result of cancers of the kidney, lung, thyroid, uterus, adrenal, melanoma, or gastrointestinal system. Primary malignancies of the breast, ovary, testicles, cervix, or lymphatic tissue present a mixed picture (6).

The majority of skeletal deposits are moth-eaten-looking in the cortex or rarefied patches in the medulla, which indicate osteolytic deposits. Sometimes, whether or not there is a pathological fracture, it might be a sign of bone degeneration. Prostate cancer is suspected when there are osteoblastic deposits; the pelvis may have increased density (4).

Radioscintigraphy

Radionucleotide bone scanning, often employing
99mTc-methylene diphosphonate (99mTc-MDP). The absorption of radionucleotides into calcium hydroxyapatite is influenced by elevated regional blood flow and osteoblastic activity. Although it is the most accurate approach (with a sensitivity of 95%) for finding metastatic deposits in bone, it lacks specificity (7).

CT Scan

To seek for the main disease, a CT-Scan can be used on the chest, abdomen, and pelvis. It may be required to do a CT scan to determine the local status of a metastatic location since it provides a more thorough image of the bone structure (6).

Magnetic Resonance Imaging (MRI)

At the location of a metastatic lesion, MRI is frequently used. When the bone scan is negative but the clinical picture is alarming an MRI is very helpful. Additionally, early marrow abnormalities can be seen using MRI, making it more sensitive than a technetium bone scan. The gold standard for assessing soft tissue masses is MRI. MRI in the spine is helpful for identifying spinal cord or nerve root compression involvement (6).

Therapy

General management

Individualized MBD treatment and interventions are typical. The treatment of MBD in both vertebral and non-vertebral systems is described in the following method. Goals of therapy include minimizing discomfort, enhancing function, and avoiding consequences such as spinal cord compression and pathological fractures in the majority of patients who are handled palliatively. With a multidisciplinary approach, the provision of analgesics/pain management, systemic therapy, radiation, and surgical treatment might present options for reaching the therapeutic objectives for each patient. RANKL inhibitors and bisphosphonates are used in medical treatment. Pain treatment is addressed based on the requirement for analgesics (NSAIDs, opioids, corticosteroids) (8).

Special Management

Patients should still be carried gently, allowed to enjoy the rest of their lives, and die softly and sweetly despite their dire prognosis. Skeletal metastases are difficult to actively control. Patients also require understanding guidance and helpful assistance with their daily routines.

Pain Control and Metastatic Activity

The majority of patients need analgesics, although extremely potent narcotic analgesics should be administered for severe pain. Unless there are particular contraindications, radiotherapy is used to manage pain and slow the spread of the metastatic process. Internal fixation is one example of a treatment that frequently includes radiotherapy. According to the World Health Organization (WHO), the analgesic ladder, which has stages dependent on the intensity of pain, is most frequently used to manage pain in cancer patients (5).

Non-opioid analgesics are used as the initial step in treating minor pain. This group includes acetaminophen, adjuvants, non-steroidal anti-inflammatory medications (NSAIDs), COX-2 inhibitors, topical analgesics, and NSAIDs. Numerous debates around NSAID use indicate...
that it should be done with caution, especially in the elderly. Drugs used in adjuvant therapy are typically not analgesics but may be in certain circumstances for the control of pain. First-line treatment for neuropathic pain includes a number of antiepileptics and antidepressants; the most popular ones are gabapentin, pregabalin, and tricyclic antidepressants (such as amitriptyline, nortriptyline) (5).

The second step involves treating mild to moderate pain with weak opioids such hydrocodone, codeine, and low-dose oxycodone. Tramadol and tapentadol are examples of other medications that are receptor agonists with numerous modes of action. These medications have enhanced benefits on neuropathic pain while reducing many of the negative effects of pure opioids. Due to its impact on cardiac arrhythmia, propoxyphene (Darvocet Darvon) has been taken off the market (5).

Strong opioids including morphine, hydromorphone, fentanyl, heavy dosages of oxycodone, meperidine, and methadone are used in the third step. A mix of short-acting and long-acting opioids is advised for individuals with persistent cancer pain. The mainstay of the treatment for chronic cancer pain is the use of long-acting opioids, either pharmacologically long-acting (like methadone or levorphanol) or long-acting formulations (slow-release systems like morphine, oxycodone, oxymorphone, or hydromorphone). Repeated doses of short-acting opioids are needed to relieve acute pain (5).

**Treatment of Fractures**

Surgery is necessary for patients with MBD fractures. The major objectives of this procedure are to lessen discomfort, enhance function and mobility, and enhance the patient’s psychological state. Surgery for fracture reduction and fixation involving tumors differs from non-tumor instances. These individuals hardly tolerate surgical treatments, thus fixation must happen as quickly as feasible (9).

Capanna R and Campanacci DA classified MBD patients into 4 groups in order to determine the need for surgical intervention:

- **Class 1**, patients with single metastatic lesions from primary tumors with good prognosis, such as well-differentiated thyroid, prostate, breast (sensitive to hormones and chemotherapy), clear cell renal, and colorectal carcinoma, and where the time between the occurrence of the primary tumor and the emergence of the MBD is greater than three years.
- **Class 2**, patients have pathological long bone fractures.
- **Class 3**, patients have long bones or the periacetabular region symptoms that are radiologically and clinically suggestive of an imminent fracture.
- **Class 4**, Patients with: (a) Osteoblastic lesions anywhere, (b) Lesions that are osteolytic or mixed in non-weight-bearing bone (sternum, ribs, clavicle, or fibula), (c) Bone having osteolytic lesions but no signs of imminent fractures, (d) Scapular, anterior pelvic, or iliac wing lesions (9).

Referrals to an orthopedic oncologist for surgery for all patients falling under classifications 1, 2, and 3 should be given first priority. If necessary, the patient is sent back to the oncologist or radiotherapist after surgery for adjuvant therapy. Class 4 patients are managed conservatively with chemotherapy, hormonal therapy and/or irradiotherapy according to the diagnosis. Response to pain management and control should be carefully evaluated at follow-up. In cases of pathological fractures or in cases of pain that does not go away after 2 months of treatment or radiologically there is local progression this patient should be referred to an orthopedic oncologist for surgery and assigned to class 2 or 3 (9).

In the most cases, intramedullary nailing is the most effective method for fractures near joint (e.g. distal femur or proximal tibia). Sometimes it requires fixation with plates or blade-plates, and sometimes using endoprostheses. The best treatment of femoral neck fractures is prosthetic replacement: hemiarthroplasty if the pelvis is intact, or total joint replacement if the acetabulum is involved. If the pelvic wall is destroyed, it can be reconstructed with a large bone graft, reconstructing the cage with a custom-made prosthesis. Postoperative irradiation/radiotherapy is very important to prevent further expansion of metastases. Common surgical techniques for metastatic tumors include: tumor excision, mixed osteosynthesis, joint replacement, segmental reconstruction, cryosurgery and amputation (4).

**Prophylactic Fixation in Impending Pathological Fractures**

Even when the bone is intact, internal fixing must be performed on large deposits that provide a fracture risk.
A pathological fracture cannot be avoided if 50% of the single cortex of a long bone has been damaged (on radiography). The same fundamental fracture care techniques apply to fixation. In order to determine whether more bone lesions necessitate postoperative irradiation and more extensive fixation, radionuclide scanning is used prior to surgery (4).

The principles of managing impending pathological fractures include preoperative embolization in cases of suspected vascular tumors, perioperative antibiotic administration, correction of hypercalcemia, transfusions to treat anemia, thrombocytopenia, and the presence of blood clotting deficits, and modification of the standard surgical approach to avoid previous radiation areas and ensure closure. Adequate soft tissue, curettage to remove diseased tissue, rigid fixation with PMMA or prosthetic replacement with cement, filling the defect with PMMA, good postoperative nutrition to speed wound healing, and adjuvant radiotherapy with or without adjuvant chemotherapy are all necessary (6).

CONCLUSION

A frequent consequence of cancer is bone metastases. Osteolytic and osteoblastic metastatic lesions are distinguished. Spinal pain is the most typical clinical symptom of bone metastases. It may also result in hypercalcemia symptoms and pathological fractures. Bone metastases can be diagnosed with the use of appropriate radiographic studies. The patient’s outlook and quality of life can be enhanced by choosing the right therapy.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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REFERENCE