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A short-term retrospective analysis of the clinical, histopathological and immunohistochemical aspects of bone metastases

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Abstract

Bone is a typical location of metastasis that usually reflects a negative outcome in oncologic patients. Once cancer has spread to the bones, it can rarely be cured, but sometimes it can be treated to minimize its rate of proliferation. Most skeletal metastases are produced by tumors originating in the breast and prostate. Osseous metastases are actually much more frequent than primary bone tumors, especially in adults. The diagnosis relies on signs, symptoms, and imaging techniques. This paper is a review of all cases of bone metastasis from our unit and a comprehensive review regarding the clinical approach and treatment of patients with such lesions.
Keywords: bone metastasis, management

Introduction

Bone metastases are far more common than primary bone tumors [1]. The most common primary sites for bone metastases are the lung, breast, prostate, kidney, and thyroid. Other tumors include lymphoma, melanoma, neuroendocrine and hepatocellular carcinoma [2]. Besides the lung and liver, skeleton is the third most frequent site of metastatic disease.

In general, bone metastases are more common in the elderly population and most cases show a predilection for the red marrow. Commonly involved bones include the skull, spine, ribs, pelvis, humerus, and femur [3]. Metastases distal to the knee and tibia are rare. Distal metastases are typically from the lung. In long bones, metastatic deposits tend to involve the metaphysis. Solitary metastasis in long bones may mimic primary sarcoma [4].

Clinical presentation and therapeutic management

Pain is the typical presentation symptom of metastatic tumors to the bone. Pathologic fracture may also occur in advanced stages of the disease. In patients with extensive metastasis, laboratory tests reveal hypercalcemia [5].

Isolated bone metastases can be resected surgically and radiation may be effective in controlling symptoms. If the patient is asymptomatic, then observation with repeated radiographs may suffice [6]. The usage of bisphosphonate or RANKL inhibitors should be considered to reduce skeletally related events or fractures.

Management of bone metastases differs significantly from the management of primary bone tumors. With primary bone tumors, every attempt is made to resect the entire lesion with negative margins [7]. Frozen section is often requested in order to exclude the diagnosis of metastatic carcinoma. When distinction cannot be made, judicious deferral to permanent sections is prudent.

Radiographic findings

Lesions may be entirely sclerotic, entirely lytic or a combination of both sclerotic and lytic [8]. Based on this observation, prostate, breast and neuroendocrine tumors produce typically sclerotic metastases, while renal cell carcinoma and thyroid produce typically lytic metastases. Moreover, metastases of renal cell carcinoma have been described as having soap bubble appearance and may show aneurysmal bone cyst-like changes [9]. PET/ CT is very sensitive for the detection of bone metastases. Bone metastases appear hot on bone scan. The technique has 80-90% sensitivity and it is more sensitive than the plan film or CT [10].

Histologic features

In general, the morphology of bone metastases resembles the primary tumor. However, the histologic grade of cell differentiation or immunophenotype may vary greatly between the primary tumor and the metastatic lesion [11]. Another problematic situation is that sarcomatoid carcinoma may resemble primary sarcoma of the bone. Osteoblastic metastases show abundant reactive woven bone. Unlike in osteosarcoma, reactive bone is lined by plump, benign-appearing osteoblasts. Secondary changes, including hemorrhage, fibrosis, and osteoclast-type giant cell reaction are common.

The main differential diagnoses of bone metastases include osteosarcoma and epithelioid vascular tumors. Osteoblastic metastases such as prostatic metastases may mimic osteosarcoma. Moreover, osteosarcoma may be focally positive for keratin, making the differential diagnosis even more difficult [12]. However, osteosarcoma cells are negative for PSA and PSAP. Epithelioid hemangioma, epithelioid hemangioendothelioma, and angiosarcoma may all be diffusely positive for keratins. All these 3 vascular tumors are positive for endothelial cell markers such as CD31, CD34, FLI-1 and ERG.

Materials and methods

This retrospective analysis aims to evaluate the clinical, histopathological and immunohistochemical aspects as well as the short-term evolution of bone metastases in a series of cases investigated and diagnosed at the University Emergency Hospital in Bucharest, Romania. The study has been elaborated as a descriptive-quantitative analysis performed over a period of three years (January 2017 – December 2019) and includes 26 patients histopathologically diagnosed with bone metastasis in the Department of Pathology of the University Emergency Hospital in Bucharest, Romania. Each case was thoroughly reviewed through the digital database of our hospital, taking into account

the clinical setting, medical history, prior investigations, diagnoses and treatments, all performed within their respective departments of our clinic. Data collection and processing was performed using Microsoft Office Excel 2010.

Biological samples have been processed using the conventional method of paraffin embedding and hematoxylin and eosin (HE) staining. Tissue samples were initially fixed for 24 hours in 10% buffered formalin and afterwards processed and embedded in paraffin. Hematoxylin and eosin staining was performed on three-micron thick sections cut from these blocks. Immunohistochemical staining was performed on fresh paraffin sections using an indirect tristadial Avidin-Biotin complex method. Sections were first deparaffinized in toluene, dehydrated in alcohol series, then rehydrated and washed in phosphate buffered saline. Afterwards, they were incubated with primary antibody overnight, washed with carbonate buffer and developed in 3,3'-diaminobenzidine hydrochloride/ hydrogen peroxide nuclear counterstaining with Mayer's Hematoxylin. Also, immunohistochemical (IHC) tests were performed, using the following antibodies: pan-cytokeratin (CK), clone AE1/AE3 (Thermo Fisher Scientific Inc., USA, 1:100 dilution); CK 19, clone D5/ 16 B4 (Thermo Fisher Scientific Inc., USA, 1:50 dilution); p53 protein, clone DO-7 (Thermo Fisher Scientific Inc., USA, 1:100 dilution); Ki-67, clone SP6 (Thermo Fisher Scientific Inc., USA, 1:200 dilution); bcl-2, clone 8C8 (Thermo Fisher Scientific Inc., USA, 1:100 dilution); p16, clone G 175- 405 (Thermo Fisher Scientific Inc., USA, 1:50 dilution); proliferating cell nuclear antigen (PCNA), clone PC10 (Thermo Fisher Scientific Inc., USA, 1:200 dilution).

Results

The study included a total of 26 patients histopathologically confirmed with bone metastases. As expected, clinical features of the studied population were not specific. Most patients addressed our clinic for imaging staging after oncologic treatment. A low number of patients presented particular diagnostic circumstances, including: tumefaction, pain, or pathologic fracture.

Demographic analysis revealed that the vast majority of patients (80,77%) came from urban areas. All patients were adults and the mean age at presentation was 71,07, ranging from 43 to 86 years (Fig. 1). Distribution of cases according to gender, revealed a predominance of bone metastases in females (Fig. 2).
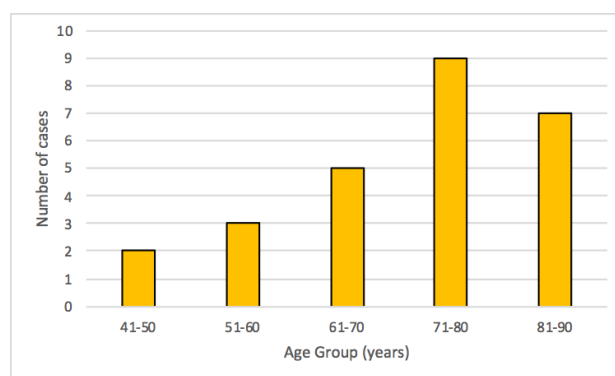

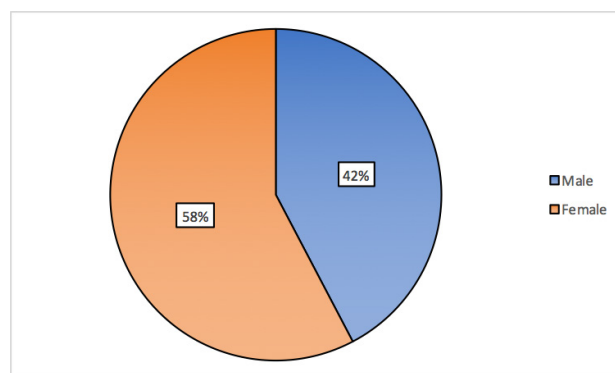*Fig. 1 Distribution of cases according to age groups*

Fig. 2 Distribution of cases according to gender

Hospital database queries revealed that 23 out of all 26 patients received previous oncologic treatment in our hospital. The distribution of cases according to the origin of the primary tumor (Fig. 3) revealed that the most frequent organ of origin was the breast (n=7), with the most frequent neoplasia being breast carcinoma of no special type (NST). Other frequent organs of origin were lung (n=4), prostate (n=3) and uterine cervix (n=3).
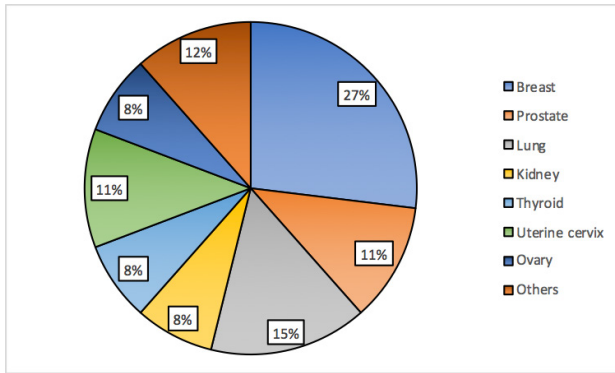
Fig. 3 Distribution of cases according to the origin of the primary tumor

Most patients presented with multiple metastases (n=24) and almost all of those had polyostotic metastases (n=21). Other organs involved were lung (n=6), liver (n=5), brain (n=3) and kidney (n=1). Most patients had bone metastases affecting the spine (n=10) or pelvis (n=5).
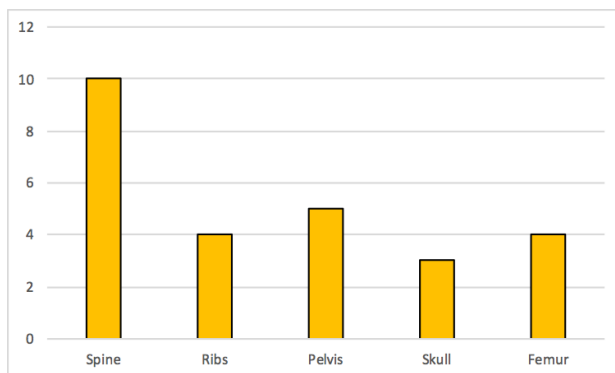

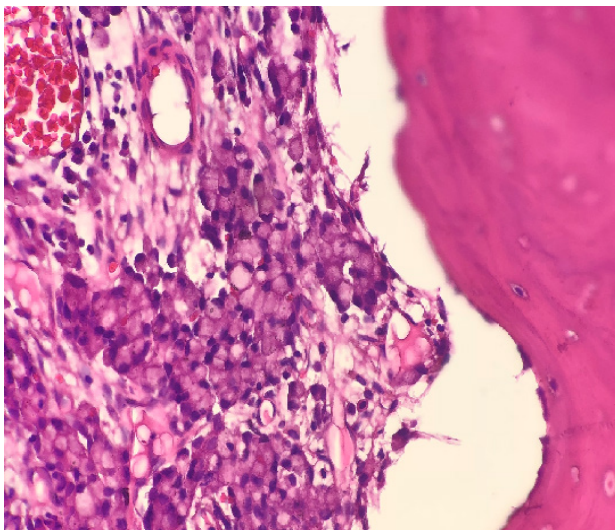Fig. 4 Distribution of cases according to the location of bone metastasis

Fig. 5 Bone metastasis from gastric signet ring cell carcinoma, showing a proliferation of polygonal epithelial cells with intracytoplasmic vacuoles and semilunar nuclei (H.E. 200x)
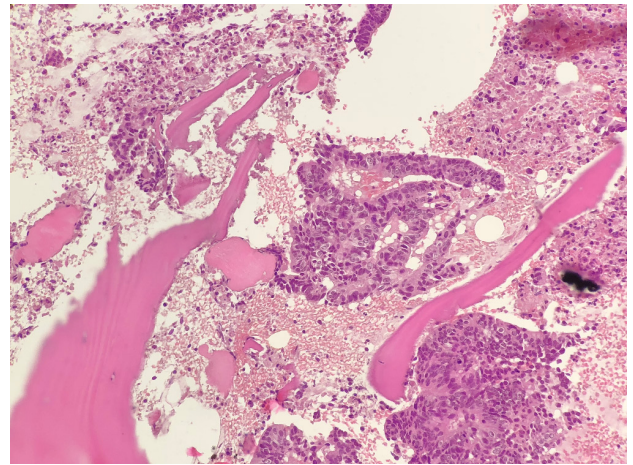

Fig. 6 Bone metastasis from an endometrial endometrioid carcinoma, showing a proliferation of tubular and cribriform structures with hyperchromatic, elongated nuclei and eosinophilic cytoplasm (H.E. 200x)
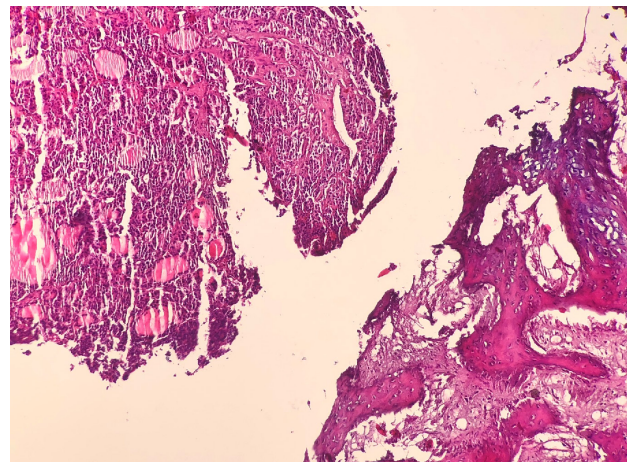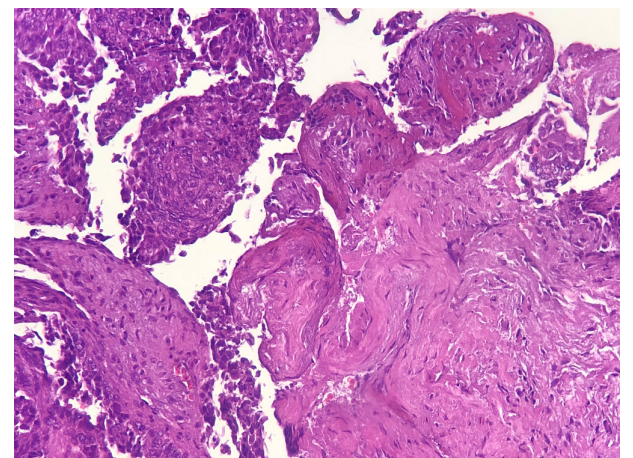
Fig. 7 Bone metastasis from thyroid follicular carcinoma, showing a proliferation of thyroid follicles with abundant intraluminal colloid (H.E. 200x)

Fig. 8 Bone metastasis from a squamous cell carcinoma of the uterine cervix, showing a solid proliferation of epithelial cells with vesicular nuclei and abundant eosinophilic cytoplasm (H.E. 100x)

Discussion

Bone metastasis represents a major cause of morbidity in patients with cancer, as they may cause disability by the presence of pain and bony tenderness, as in the cases investigated in our hospital, which negatively impact mobility, ability to carry out daily tasks, quality of life and patient mental state; also, in the late stages of cancer, tumor masses may damage the skeleton by compression of vascular system and consequent ischemia that can rapidly lead to motor and sensory dysfunction, incontinence, loss of function, radicular pain or even paralysis [13]. In cases with multiple metastases, hypercalcemia of malignant cause can be severe and may lead to lethargy, nausea, anorexia, constipation, muscle weakness, cardiovascular or renal dysfunction and in late stages even coma [14].

For the most part, primary bone cancer is prevalent among young people as in children or adolescents whereas secondary bone cancer appears especially from carcinomas of the breast, lung, prostate, kidney, and thyroid in older patients, consistent with our results in which the mean age was 71 years old. Most often, the diagnosis is easy to be determined but confusion may appear particularly for older patients, in whom osteoporosis or degenerative disease are common.

Initiation of metastatic spread is starting to be considered an early event, occurring before the primary tumor becomes clinically detectable, rather than being associated with high tumor volume. After leaving the primary site, tumor cells are attracted to particular "metastatic niches" in the hematopoietic bone marrow, and these tumor cells may further spread from the bone to other organs [15]. The metastatic cells in the red bone marrow from the axial skeleton level suggest that the slow blood flow in these sites could support the attachment of metastatic cells. However, most definitely, the molecular properties of the malignant cells and the tissue in which metastases develop are of critical importance [16]. When established in the bone marrow niches, disseminated tumor cells may remain dormant for many years because of complex interactions among tumor cells, bone cells and the bone microenvironment.

Bone remodeling represents a dynamic process regulated by many biochemical factors, essential for bone integrity and structure. When tumor cells interfere, they disrupt the fine balance between the osteoblast, derived from mesenchymal, fibroblast-like cells and osteoclast, a multinucleated cell derived from granulocyte-macrophage precursors' activity, resulting in excessive bone resorption, increased bone formation or both [17]. For instance, in breast cancer, the most frequent one to cause metastatic bone lesions, also considered a standard example for osteolytic lesions, involves many factors such as parathyroid hormone-related protein (PTHrP), interleukin (IL)-11, IL-8, IL-6, and receptor activator of nuclear factor-nB ligand (RANK) and also others factors, independent of tumor, such as sex steroid deficiency. In the case of the patients with prostatic cancer, the prototype for osteoblastic tumor, based on the radiographic appearance of the lesion, the growth factors involved in osteoblastic lesions, are platelet-derived growth factor, insulin-like growth factors and adrenomedullin [18]. However, recent clinical evidence indicated that both type of processes, bone resorption and bone formation, contribute to the metastatic phenotype even in the same patient [19]. The same prostate cancer patient often has evidence of osteolytic and osteoblastic disease as shown in the histologic examination [20]. At the same time, tumor cells within the bone may remain dormant for prolonged periods under the control of micro-environmental signals as cancer patients can follow a relatively long course over several years. The two types of cancers were also the most frequent in our group of study.

In some cases, even in the presence of advanced disease, the metastatic bone lesions are the only place of present metastatic disease. While the lethality of carcinogenic disorder consists most often of metastasis to visceral organs, bone metastases are the most common [21]. Approximately 70% of the patients dying from breast cancer have radiologic evidence of

skeletal metastases before death, and bone is the first metastatic site in more than 40% of the persons with distant relapse [22].

The vast majority of bone metastases are currently first diagnosed when symptoms such as pain are present, at which point they are detectable by radiological investigations that reveal bone lesions. Therapeutic interventions at this late stage are mainly aimed to reduce bone destruction, as bones become more fragile and at a greater risk of fracture, but with limited impact on survival.

Conclusion

Most skeletal metastases are produced by tumors originating in the breast and prostate. Osseous metastases are actually much more frequent than primary bone tumors. The management of patients with bone metastases requires a multi-disciplinary approach.

Disclosure
None of the authors has a conflict of interest.
All authors have participated equally in developing this study.

Conflict of Interest statements
Authors state no conflict of interest.

Informed Consent and Human and Animal Rights statements
Informed consent has been obtained from all individuals included in this study.

Authorization for the use of human subjects
Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies, is in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent commitee.

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