Acta Clin Croat 2003; 42:35-39 Professional Paper

METASTATIC BONE TUMORS IN BIOPSY SPECIMENS

Davor Tomas [1], Božo Krušlin [1], Aljoša Matejčić [2], Zoran Kejla [3] and Mladen Belicza [1]

[1]Ljudevit Jurak University Department of Pathology, [2]University Department of Surgery, Sestre milosrdnice University Hospital; [3]University Hospital of Traumatology, Zagreb, Croatia

SUMMARY – Metastatic bone tumors are the most common form of skeletal malignancy. The aim of the study was to present the main characteristics and to highlight the problems encountered in metastatic bone tumor biopsy. Data from the Thanatos database for the period from January 1, 1998 till December 31, 2001, were used. Pathohistologic analysis was done on formalin fixed, paraffin embedded, and hematoxylin-eosin stained tissue. Decalcification was done with nitric acid. There were 78 patients with metastatic bone tumors, 47 (60.3%) male and 31 (39.7%) female. The most common site of metastases was vertebral column (74.4%). Based on the history data, pathohistologic analysis and immunohistochemical staining, the origin of metastatic tumor was identified in 73 (93.6%) cases. The most common origins were cancers of the breast, kidney, lungs and prostate. The main characteristics of metastatic tumors were as expected and consistent with literature data, whereas inadequate cooperation between clinicians and pathologists was identified as the most obvious problem.

Key words: *Bone neoplasms, diagnosis; Bone neoplasms, pathology; Neoplasm metastasis, diagnosis; Bone neoplasms, secondary; Biopsy*

Introduction

Metastatic tumors are the most common bone tumors, with a ratio of one primary tumor *per* 25 metastatic tumors of the bone. According to literature data, the incidence of bone metastases detected on autopsy of malignancy deaths is around 13%[1]. The metastases may occur by lymphogenous, hematogenous or direct tumor dissemination to the bone. Multiple metastases develop in 90% of patients. Solitary metastases are mostly found in thyroid and renal carcinoma, and less frequently in breast cancer. Any tumor can metastasize into the bone, however, carcinoma of the prostate, breast, kidney and lungs, and melanoma account for 75% of all bone metastases. Apart from these, carcinoma of the colon, urinary bladder, cervix uteri and ovary frequently metastasize to the bone[1-4]. Metastatic bone lesions in children are usually induced by rhabdomyosarcoma, Wilms' tumor and neuroblastoma, and Hodgkin's disease[2,5]. As any tumor may metastasize into the bone, so any bone may be involved with metastasis. Bone metastasis is frequently the first sign of malignancy and occurs at the time when the primary tumor localization has not yet been identified or the existence of malignancy has not yet been suspected in the patient. Thus, histopathologic examination of the affected bone can frequently point not only to the existence of a metastatic tumor but may also help determine the primary tumor localization. Therefore, histopathology should immediately follow the radiologic and hematologic examinations, since reaching an accurate diagnosis would thus be greatly facilitated and less expensive. However, determination of the origin of metastasis, and identifying whether it is a bone metastasis or primary bone tumor, may occasionally be very complex and difficult even for an experienced pathologist. The material referred for histopathology usually contains bone fragments, which poses a special problem. Such a material is hard and inappropriate for laboratory testing, requiring softening by the

Correspondence to: *Davor Tomas, M.D.*, Ljudevit Jurak University Department of Pathology, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: dtomas@kbsm.hr

Received August 26, 2002, accepted in revised form January 30, 2003

process of decalcification. Decalcified preparations are not appropriate for additional immunohistochemical examination, thus reaching an accurate diagnosis in vague cases being more difficult[1,2,6,7]. The majority of metastases are found in the head and trunk bones, primarily the spine, followed by the pelvis, ribs and sternum. Long bones, especially proximal aspect of the femur and humerus, are next according to the prevalence of metastatic involvement. A well perfused bone marrow, retarded circulation and nutritive factors make these bones an ideal site for the implantation and growth of tumor cells. Metastases are very rarely seen in small bones of the hand and foot, and they generally derive from carcinoma of the kidney, lungs or colon, however, the occurrence of metastases under the elbow and knee joints is extremely rare. It should be noted that tumors frequently metastasize to the bone first, thereby skipping visceral organs, primarily the lungs and liver[1,2,7,8]. In such cases, the spine is generally involved. One of the attempts at explaining this high rate of spine involvement implies Batson's concept of the verterbral venous system, according to which it is a separate venous network deprived of valves with retarded blood flow, being located around the spinal dura mater and vertebrae, and anastomosing abundantly with the caval, portal and pulmonary venous circulation through which tumor emboli may directly, avoiding visceral organs, reach it and get implanted in the bone[1,8]. Metastatic bone tumors are traditionally classified into osteolytic and osteoblastic tumors, however, many metastases are of a mixed type. Osteolytic metastases are primarily seen in carcinoma of the kidney (hypernephroma), thyroid, breast and bronchi, in carcinoma of gastrointestinal origin, and in malignant melanoma. Osteoblastic metastases are mostly found in prostate carcinoma, however, some 10% of prostate carcinoma give rise to osteolytic metastases. Breast carcinoma and carcinoid may also produce osteoblastic metastases. In osteolytic metastases, tumor cells do not resorb the bone directly but release various active substances such as prostaglandins, interleukins and parathyroid hormone-like protein that stimulate bone resorption. Bone resorption in osteolytic metastases, even in extensive processes, is not accompanied by an increase in serum alkaline phosphatase unless the liver has also been affected along with the bone. In osteolytic metastases, serum calcium and more frequently urine calcium is increased. Osteolysis also occurs in osteoblastic metastases, however, at the same time tumor tissue (tumor cells are considered not to be directly responsible) stimulates osteoblasts for *de novo* bone formation. Serum alkaline phosphatase and bone collagen degradation products such as N-telopeptide are elevated in osteoblastic metastatic processes, the increase rising proportionally to the metastatic process extent. The increase in serum acid phosphatase is highly characteristic of the prostate carcinoma osteoblastic metastases to the bone. Blood withdrawal directly from the bone marrow and determination of acid phosphatase and alkaline phosphatase provide more reliable and sensitive data to differentiate between osteoblastic and osteolytic metastases[1,2,6,7,9,10]. Metastases to the bone are generally diagnosed by radiologic examination. Osteolytic metastases are usually visualized as unsharply demarcated areas of bone destruction with completely destroyed bone without periosteal reaction. Osteoblastic metastases are visualized as sclerozation of the skeleton segment involved. In children, bone metastases are generally seen as osteolytic regions of the metaphysis. As stated above, the majority of metastases are detected in the spine and are easy to diagnose by radiologic examination. Erosion of the pedicle is an early sign of metastasis to the spine, followed by erosion of the vertebral body. However, the entire vertebral body may occasionally be involved with metastasis without any radiologic changes in the vertebral contour, i.e. without any radiologically detectable change in bone density. In such cases, the diagnosis is made by scintigraphy, which is positive in 96% of cases, computed tomography, or magnetic resonance imaging, however, definite diagnosis can only be reached by histopathology. Depending on the primary process characteristics, therapy for bone metastases includes chemotherapy, radiotherapy, immunotherapy, hormonal therapy, bisphosphonate therapy, and various operative procedures[1,5,7,9-12].

Material and Methods

Data on tumor metastases to the bone were retrieved from the Thanatos database of the Ljudevit Jurak University Department of Pathology, Sestre milosrdnice University Hospital, Zagreb, for the period from January 1, 1998 till December 31, 2002. Biopsy procedures were performed at the University Department of Surgery, Sestre milosrdnice University Hospital, and University Hospital of Traumatology, Zagreb. Upon making the diagnosis, the necessary clinical examinations were performed in case of unknown primary tumors. The respective data were subsequently obtained and compared with the pathohistologic diagnosis. Pathohistologic diagnosis was obtained on formalin fixed, paraffin embedded tissue cut on a microtome (3- to 5-micron sections) and stained with hematoxylin-eosin. When required, tissue decalcification was done by

use of nitric acid. The immunohistochemistry tests used in particular biopsy specimens included cytokeratin, epithelial membrane antigen (EMA), prostate specific antigen (PSA), HMB45, carcinoembryonic antigen (CEA), S-100, CD3, CD20, neuron specific enolase (NSE), vimentin and thyroglobulin (MSIP, DAKO, Copenhagen, Denmark).

Results

From January 1, 1998 till December 31, 2002, there were 50481 biopsy findings, 1994 of them indicating metastatic tumors, and 78 of these tumor metastases to the bone. The rate of bone metastases in the total biopsy number was 0.2%, whereas the rate of bone metastases in the total number of metastatic tumors was 3.9%. Bone metastases were detected in 31 (39.7%) female and 47 (60.3%) male patients. The mean age of women and men with metastatic bone tumors was 55.0 and 58.4 years, respectively. Nearly 80% of metastatic bone tumors were diagnosed between 40 and 70 years of age (Fig. 1). Accord-

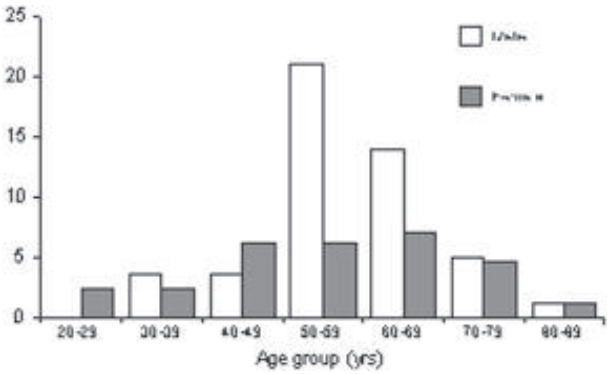

Fig. 1. Age and sex distribution of metastatic bone tumors

ing to localization, the majority of bone metastases were found in the spine (74.4%), most commonly in the thoracic spine, followed by the lumbar spine. According to the rate of involvement, the spine was immediately followed by the femur with 21.7% of metastatic tumors (Table 1). Additional immunohistochemical analysis could only be performed in 20 cases, i.e. on 25.6% of the material, and included cytokeratin, EMA and PSA. Other immunohistochemical markers used in the study were HMB45, S-100, vimentin, synaptophysin, chromogranin, CEA, CD3 and CD20. History data, pathohistology and immunohistochemistry data allowed for identification of the metastasizing tumor origin in 73 (93.6%) cases, whereas the origin of the metastasizing tumor could not be determined in 5 (6.4%) cases. Metastases from cancer of the breast (Fig. 2), kidney (Fig. 3), lungs and prostate were most commonly diagnosed (Table 2). Analysis of referral letters revealed the seat of the primary tumor as one of the referral diagnoses to be listed in 23 (29.5%) cases. Referral diagnosis most commonly referred to breast carcinoma as the primary tumor, followed by carcinoma of the lungs and kidney. History data and previous examinations were reported in 11 (14.1%) referral letters.

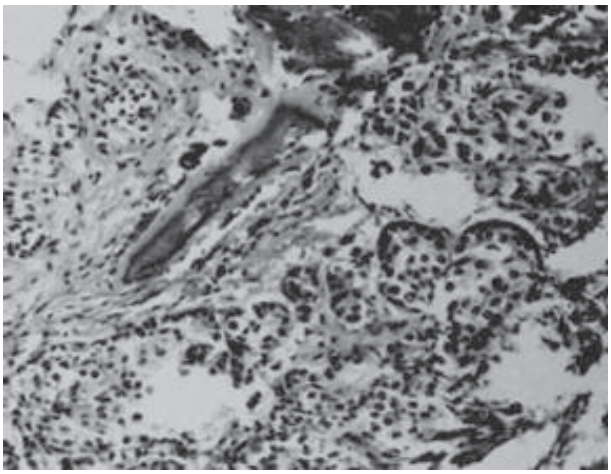

Fig. 2. Breast cancer metastasis to the vertebral column (HE, X200)

Discussion and Conclusion

The aim of the study was to compare some basic data on metastatic bone tumors with literature reports, and to

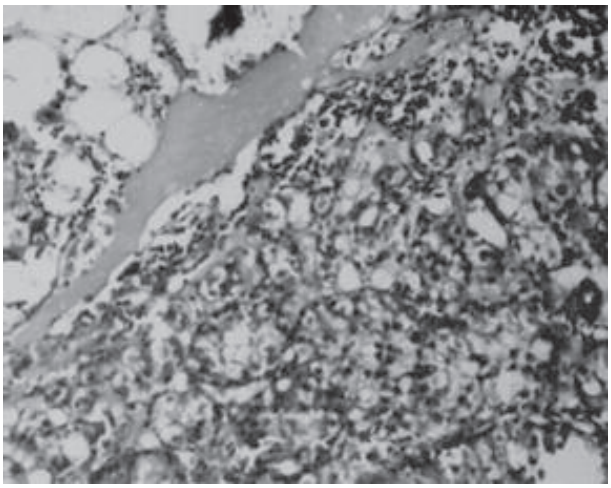

Fig. 3. Renal adenocarcinoma metastasis to the femur (HE, X400)

Table 1. Localization of metastatic bone tumors

Tumor localization	No. of patients	Percentage
Vertebral column	58	74.4
Femur	17	21.7
Humerus	1	1.3
Skull	1	1.3
Unknown	1	1.3
Total	78	100

point to the major problems the pathologist encounters in the diagnosis of metastatic bone tumors. The prevalence, age and sex distribution, and most common localizations of metastatic bone tumors were determined. Also, efforts were made to identify the proportion of the referred material that was eligible for immunohistochemical analysis (the material which required no decalcification prior to laboratory testing), and the ratio of cases where the origin of metastases could be histopathologically determined. In addition, we attempted to determine the percentage of cases in which the clinical data reported were complete enough as to help reach a definite diagnosis.

Our results showed the parameters of bone metastases to be comparable to those from literature reports. Analysis of the results revealed men to be more commonly affected with metastatic bone tumors than women, which was expected because the tumors that most frequently metastasize to the bone are more common in men (carcinoma of the lungs, prostate and kidney)[1-3,8-10]. Among men, bone metastases were most common in the 50-60 age group, which corresponded to the age group with the highest incidence of tumors that show male predominance and highest rate of metastasizing to the bone. In women, the highest rate of metastatic bone tumors was recorded in the 40-50 age group, which also corresponded to the age group with the highest incidence of tumors metastasizing to the bone. As for localization, metastatic bone tumors most commonly involved the spine, precisely its thoracic segment, followed by the femur, which is consistent with literature data[1-7,12,13]. As stated above, the diagnosis of bone metastases was hampered by the general impossibility of performing additional immunohistochemical analyses in the referred material, which required decalcification because of its hardness. Decalcified material is known to be inappropriate for immunohistochemical analyses. In our study, only 25.6% of the biopsy specimens were eligible for immunohistochemical analysis[7,9,10]. On making definite diagnosis, another drawback for the pathologist were inadequate patient history data (only 14.1% of the referral slips contained history data). The lack of insight into x-ray findings and previous test results makes the differential diagnosis of metastatic bone tumors against primary bone tumors, and against some types of sarcoma in particular, more difficult[1,7,11-14]. However, this should be considered with reserve because the surgeon may have contacted the pathologist in some other way (e.g., telephone, telefax) to communicate additional patient data to him. In the present study, the referral diagnosis was very frequently incomplete, without mentioning the primary tumor at all (the seat of primary tumor was reported in 29.5% of the referral letters), which was most probably the reason for the origin of metastases to have remained unknown in five cases. Some data, first of all those referring to collaboration between the clinician (surgeon, oncologist) and the pathologist in the diagnosis of bone metastases could not be correlated with literature data because no such data were found in the literature available. Nevertheless, the results and discussion clearly show that this collaboration is far from the optimal level. Close cooperation and team approach to the patient are needed to upgrade the diagnostic and therapeutic procedures in general. A team consisting of a radiologist, oncologist, cytologist, surgeon and pathologist would be much more efficient in making decisions on therapy and approach to patients with bone

Table 2. Origin of metastatic bone tumors

Primary tumor	No. of metastasizing tumors	Percentage
Melanoma	3	3.8
Adrenal gland	1	1.3
Non-Hodgkin's lymphoma	1	1.3
Ovary	1	1.3
Breast	18	23.1
Colon	3	3.8
Kidney	13	16.7
Prostate	12	15.3
Stomach	5	6.4
Endometrium	1	1.3
Lungs	13	16.7
Larynx	1	1.3
Thyroid	1	1.3
Unknown	5	6.4
Total	78	100

metastases whose prognosis, although greatly improved recently, remains quite poor.

References

1. MARCOVE RC, ARLEN M. A tlas of bone pathology . 1st ed. Philadelphia: JB Lippincott Company , 1992:518-34.
2. ROSAI J. Ack erman's surgical pathology . 8th ed. St. L ouis: CV Mosby, 1996:1975-7.
3. ROSENBERG A. Bones, joints and soft tissue tumors. In: COTRAN RS, KUMAR V, COLLINS T, eds. Pathologic basis of disease. Philadelphia: WB Saunders, 1999:1215-91.
4. JANJAN N. Bone metastases: approaches to management. Semin Oncol 2001;28:28-34.
5. ORLIĆ D. Tumori koštano -zglobnog sustava. In: PEĆINA M, *et al.*, eds. Ortopedija. Zagreb: Naklada Ljevak, 2000:105-23.
6. DEMERS LM, COST A L, LIPTON A. Biochemical mark ers and skeletal metastases. Cancer 2000;88:219-26.
7. COLEMAN ER. Management of bone metastases. Oncologist 2000;5:463-70.
8. OEPPEN RS, TUNG K. R etrograde venous invasion causing ver - tebral metastases in renal cell carcinoma. Br J Radiol 2001;74:759-61.
9. BRAUN S, PANTEL K. Clinical significance of occult metastatic cells in bone marrow of breast cancer patients. Oncologist 2001;6:125-32.
10. MATHIEU MC, FRIDEMAN S, B OSQ J, CAILLOU B, SPILEMANN M, TRA VAGLI JP, CONTESSO G. Immunohistochemical staining of bone marrow biopsies for detection of occult metastasis in breast cancer . Breast Cancer R es Treat 1990;15:21-6.
11. KRAPPEL F A, BAUER E, HARLAND U. Efficacy of MRI whole spine image in diagnosis of vertebral metastases. Z Ortoph Ihre Grenzgeb 2001;139:19-25.
12. ROESSNER A, B OSSE A, WUISMAN P , ERLEMANN R, GRUNDMANN E. P athology of spinal tumors. Orthopade 1987;16:358-70.
13. PATTERSON K. The pathologic handling of sk eletal tumors. Am J Clin Pathol 1988;109:53-66.
14. LAGUNA R, SIL VA F, VASQUEZ -SELLES J, ORDUNA E. FLORES C. Vertebral hemangioma mimicking a metastatic bone lesion in well-differentiated thyroid carcinoma. Clin Nucl Med 2000;25:611-3.

Sažetak

METASTATSKI TUMORI K OSTIJU U BIOPSIJI

D. Tomas, B. Krušlin, A. Matejčić, Z. Kejla i M. Belicza

Metastatski tumori su najčešći tumori kostiju. Svrha rada bila je usporediti nek e osnovne podatk e o metastatskim tumorima kostiju s podacima u literaturi i naznačiti glavne probleme u patohistološkoj dijagnostici metastatskih tumora kostiju. P odaci o biopsijama koštanih metastaza tumora dobiveni su iz kompjutorsk e baze podataka (Thanatos) za razdoblje od 1. siječnja 1998. do 31. prosinca 2001. godine. P atohistološka dijagnoza je napravljena na tkivu fiksiranom u formalinu, uklopljenom u parafin, rezanom na mikrotomu i bojanom hemalaunom i eozinom. Dekalcinacija je napravljena dušičnom kiselinom. Nađeno je 78 koštanih metastaza tumora, 47 (60,3%) u muškaraca i 31 (39,7%) u žena. Najveći broj metastaza bio je smješten u kralješnici (74,4%). Na temelju anamnestičnih podataka, te patohistološk e i imunohistok emijsk e pretrage podrijetlo metastatskog tumora utvrđeno je u 73 slučaja (93,6% biopsija). Najčešće su u kosti metastazirali karcinomi dojk e, bubrega, pluća i prostate. Naši nalazi podudaraju se s onima iz literature, a kao glavni problem nameće se nedovoljna suradnja između liječnika kliničara i patologa.

Ključne riječi: *Koštane neoplazme, dijagnostika; Koštane neoplazme, patologija; Metastaza neoplazme, dijagnostika; Koštane neoplazme, sekundarne; Biopsija*