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HISTOMORPHOLOGICAL STUDIES OF BONE METASTASIS WITH REVIEW OF LITERATURE

Pathology

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ABSTRACT

Bone metastases are a common complication of various malignancies, with breast and prostate being the most frequent origins. This retrospective study aimed to evaluate histomorphological patterns and aid in identifying the primary malignancy, especially in cases of unknown origin, through biopsy and immunohistochemistry. Ten cases were analyzed,during one year time duration in which female with the majority being metastatic breast carcinoma. Identification of unknown primaries was possible in several cases using imaging and immunoprofiling. The most common site was Femur (60%), followed by humerus, sternum

KEYWORDS

Metastasis, Bone, Unknown Primary

INTRODUCTION

Common type of malignant tumor involving bone are the Metastasis[1]. Tumoral metastasis to the bone is usually a late event in the disease process, where in the primary tumor site is known in a vast majority of cases. about 3%–4% of the patients with metastasis have an unknown primary tumor at presentation, and of these, approximately 10%–15% have skeletal metastasis [2] Bone is the third most common site for metastases after the lungs and liver.[2,3]Any malignant tumor can metastasize to the skeleton, majority of them are epithelial and originate from breast, lung, thyroid, and kidney[4]The most common malignancies are breast in women and prostate in men but secondary lesions from lung cancer have risen in both sexes in the last two decades.

In recent years, with improved imaging studies, advanced diagnostic endoscopic surgeries, new tumor markers,guided percutaneous bone biopsy immunohistochemistry and chromosomal analysis, identifying the primary malignancy at an early stage [5,6,7,8]

However, in cases of occult primary malignancies, diagnosis may be difficult and bone biopsy and histology may be necessary to determine the appropriate treatment and prognosis[9]

The histomorphological pattern of metastases to the bone is usually selective in terms of site of tumor origin and intraskeletal distribution. Require A tripartite approach of clinical, radiological, and pathological findings.[10]

In this study, the clinicopathological features of metastatic bone tumors spanning over a period of year were analyzed and an attempt was made to identify the primary site of malignancy in metastasis of unknown origin.

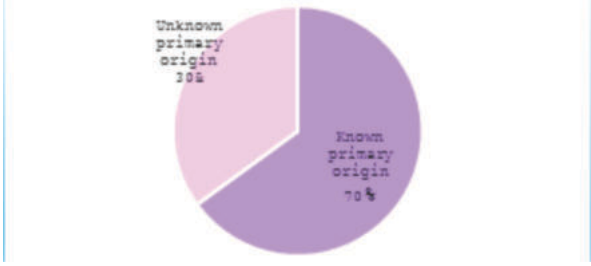
MATERIALS AND METHODS

The present retrospective study was carried out in the department of pathology, government medical college Surat affiliated to tertiary care hospital south Gujarat over a period of one year (January 2024-December 2024). Cases with primary bone tumors, hematolymphoid neoplasms, and patients who had received complete/partial chemotherapy/radiotherapy were excluded from the study. A detailed history, clinical examination, relevant radiological investigations (X-ray, computed tomography [CT] scan,magnetic resonance imaging [MRI] scan, and bone scan) and clinical diagnoses were recorded from the case files in each case. Bone biopsy from the lesional site was performed in all 10 cases. Biopsy was optimally fixed in10% neutral buffered formalin and decalcified using 5% nitric acid. Routine paraffin embedding and 3–5 µm thickness cutting and staining with hematoxylin and eosin stain done.

A correlation between the clinical, radiological, and final histopathological findings was drawn. Furthermore, an attempt was made to decipher the primary site of origin by the organ-specific IHC markers.

RESULTS

Total 10 biopsies of bone metastasis studied over a period of 12 months. Bone metastasis with unknown primary site accounts for 30% while that of known is 70%.



In present study age of the patients ranged from 32-75 (median 55 years). with a female preponderance; Male to female ratio 1:4. Majority of the patient between fifth to seventh decades of life.

Pain, tenderness or pathological fracture was the most common complains noted in all the patient. Pathological fractures noted in 5 out 10 patients. (50%)

Skeleton Distribution

The appendicular skeleton was more commonly involved than axial skeleton of which femur was the most frequent site was biopsied in the present study accounting 06 patients (60%) followed by sternum, humerus and cranium.

The primary site was known in 07 patients and 03 of them being detected after diagnosis of metastasis.

Among 10 patients, 07 presented with breast carcinoma rest three of them are Renal cell carcinoma Thyroid follicular carcinoma and Lung adenocarcinoma.

Majority of the patient shows Osteolytic type of bone lesion.

In our study, 70% of cases in which primary site is known with female preponderance and majority of them is having diagnosed breast carcinoma and on chemotherapy.

Among 7 cases with metastatic breast carcinoma, one of them morphologically Malignant Phyllodes tumour. All of the patient having prior history of Carcinoma Breast. Immunostaining for ER, CK, GCDFP done to confirm primary.

Table 1. Distribution of Cases in Various Groups

Classification of metastatic tumors	Nature of specimen (Bone involved)	Number of cases (%)	Age of patients	IHC markers done to confirm primary	IHC markers done to detect primary
Renal cell carcinoma	Cranium	01	60	-	Vimentin, EMA, PAX-8, CD10

Thyroid follicular carcinoma	Proximal Humerus	01	32	-	CK-7, PAX-8, Vimentin, TTF-1
Breast carcinoma	Femur	06	55	CK-7, GCDFP, ER, PR, TTF, CK20	
Metastatic carcinoma	Femur, Sternum	01	65	CK	
Lung Adenocarcinoma	Humerus	01	70	-	TTF-1, CK-7, NAPSIN

Rest three metastatic carcinoma, primary detected later in both cases these were Thyroid Follicular Carcinoma and Lung Adenocarcinoma involving proximal humerus and Renal cell carcinoma involving cranium. Immunohistochemistry Panel was done to confirm the diagnosis. Later mass detected from imaging which confirmed primary.

A case of 60 year male with complain of headache and palpable swelling since 6 months. CT imaging reveals mass of 85x61x55 mm3 expansile bony lesion with linear calcification (Sun burst appearances) in right parietal bone without dura involvement, and suspected of neoplastic etiology like ? meningioma.

On histopathological examination of resected mass reveals features of Renal Cell Carcinoma which was further confirm by IHC. In which tumour cells are immunoreactive for Vimentin, EMA, PAX8 and CD10. CD31 and CD34 highlights the vascular channels and negative for SMA, CK, PR, GFAP

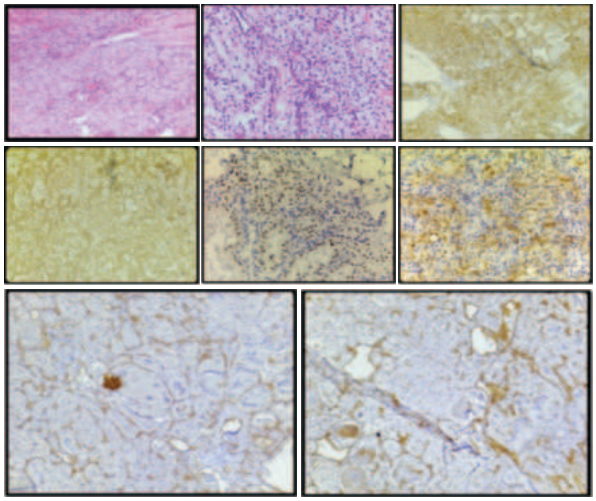
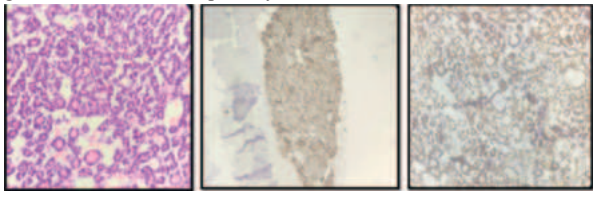


Fig. 1 Metastasis from Renal Cell Carcinoma (a,b) H&E 40X, (c e,f, g) Show Immunoreactive for Vimentin, EMA, PAX8 and CD10. CD31(d) and CD34 (h)(40X) Highlights Vascular Chnnels

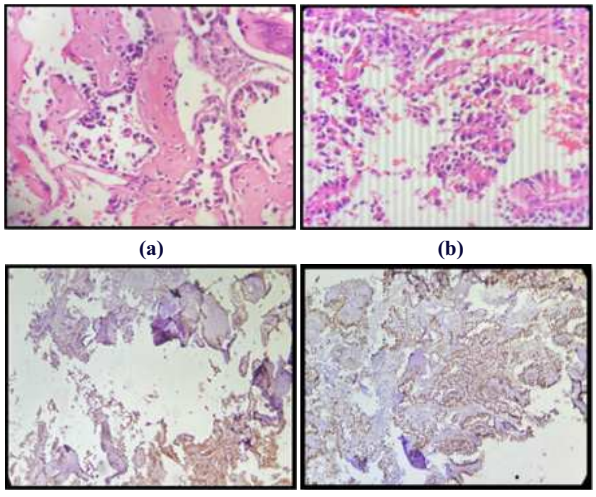
A case 55 year old female with complain of pain and swelling on right shoulder, on radiological findings it was suggested lytic bone lesion - Ewings Sarcoma likely involving proximal humerus. Biopsy from bone was sent for histopathology which was thoroughly examined along with IHC and found to be immunoreactive for CK7, TTF1 & VIMENTIN and suggestive of Metastasis from Thyroid follicular carcinoma. On follow up USG local part revealed nodule in thyroid gland , which confirmed primary site.



(a) (b) (c)

Fig. 2 Metastasis from Thyroid Follicular Carcinoma. (a-c) H&E 40x Shows Thyroid Follicles. (a) Shows Immunoreactive for CK-7(b) and TTF1 (c)

A case of 70 year old female with a complains of unable to lift shoulder associated with pain and swelling since 2 year with decrease range of motion, not responding to analgesics. CT reveals 55x50x100 mm3 sized expansile bony mass lesion in head of humerus & proximal shaft and similar lesion involving scapula, possibility of bone metastasis. Biopsy is taken from left proximal humerus, examined with immunohistochemistry and found to be immunoreactive for TTF-1, NAPSIN & CK-7. While negative for WT1, CDX2, & GCDFP. Overall histological and immunohistochemical findings are suggestive of Metastasis from Lung Adeno Carcinoma

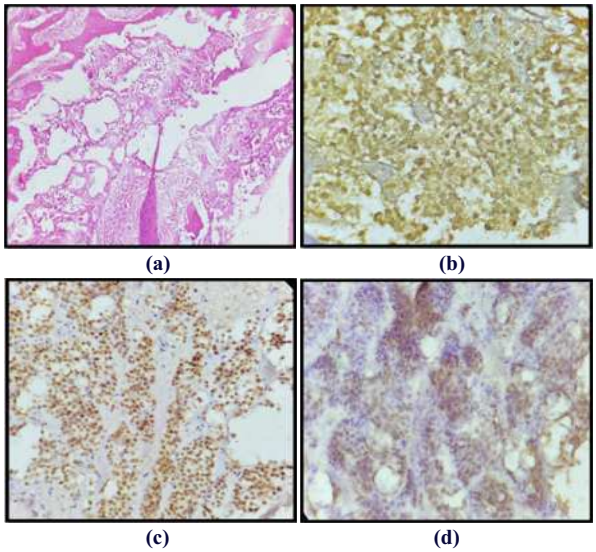


(a) (b) (c) (d)

Fig.3 Metastasis from Lung Adenocarcinoma (Non Mucinous Type). (a, b) H&E 40X Shows Bone Tissue and Trabeculae Infiltrated by Malignant Cells Arranged in Acinar, Lepidic and Micro-papillary Pattern. (c,d) Show Immunoreactive for TTF-1 & CK-7.

Of the 7 cases of metastatic breast carcinoma with bone metastasis median age of the patients were 55 years, vast majority presented with multiple lytic lesions and are on chemotherapy.

- They showed complain of pain and pathological fracture of femur.
- Most common sites are intertrochanteric region, inter-medullary canal, shaft of femur and sternocostal region.
- In our study, the most common molecular subtype of breast cancer patients with bone metastasis was estrogen-receptor positive (ER).
- Bone biopsy has been studied along with IHC to confirm primary revealed metastasis from Carcinoma breast and immunoreactivity for CK, ER, GCDFP, CK-7 (90%), CD20 (10%)and immuno-negative for PR & TTF.(10 %)



(a) (b) (c) (d)

Fig. 4 Metastasis from Breast Carcinoma (a, b, c, d) Immuno-reactivity for CK, ER, GCDFP, CK-7,) H&E 40X Shows Tumor Cells Infiltrated Bony Trabeculae.

DISCUSSION

In our study, Clinically, pain was the main symptom, and it may be accompanied by locacedema and pathological fracture which has also been the experience by other authors. 50% cases presented pathological fracture; however, in most of these patients, the fracture was not the first manifestation of the neoplastic disease, either they presented with long standing pain in bone and restricted movements or

as isolated mass which diagnosed by specific IHC markers[5]. Which is justified in correlation with other studies.

Bone metastasis is the most frequent neoplasm of bone tissue, occurring predominantly in the axial skeleton and proximal limbs. It affects individuals of different age groups; in the present sample, age ranged from 32to 72 years(55% of women and 45% of men).

According to the literature, the most predominant locations are the proximal limbs (humerus and femur) then axial skeletal, rarely occurring beyond the elbow or knee . The present findings were consistent with the literature: the femur was the most affected bone (80%), Extremities (20%) were affected.[4].

In our study, breast carcinoma commonly metastasize to femur which presented as lytic lesion/pathological fracture.

In our study, the most common molecular subtype of breast cancer patients with bone metastasis was estrogen-receptor positive (ER) which was correlate with other studies.[11]

As correlation with other studies, in patients with a known primary tumour, we examined the relationship between the origin of metastases, as suggested by the cytokeratin phenotype, compared with the one indicated by the initial histological diagnosis. We also recorded the efficacy of organ-specific markers to identify the primary tumour origin in epithelial bone metastases in three cases with a immuno-histologically determined primary tumour origin, with those with an undetermined one.[10]Rougraff et al. [12] reported that biopsy alone was unable to identify the primary site of the malignant tumor Immunohistochemistry helps to determine the nature of the primary, most notably when differentiation is minimal

CONCLUSION

Apart from histo-morphological assessment, radiological findings and immunohistochemistry is virtually essential for an accurate diagnosis in identifying the possible primary site in cases with unknown primaries[1]which will help in planning appropriate palliative therapy in these patients.

- More than two-third cases of bone metastases encountered in surgical pathology practice are as initial presentations. Spine, femur, and pelvis are most commonly affected site[1].
- Metastatic adenocarcinomas constitute majority of cases with thyroid, breast, lungs, and kidney being common primary sites. Breast remains the most common primary site, with ER-positive tumors showing predilection for bone.
- IHC provide effective discrimination between carcinomas in bone metastasis specimens. They are often used as part of a panel with other tissue- or organ-specific IHC markers to establish the primary tumor site.

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