
CLINICAL PRESENTATION AND BIOCHEMICAL EVALUATION OF BONE SECONDARIES

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Abstract

The skeleton is one of the commonest sites for metastasis. Bone secondaries account for more than one third of the malignant disease of bone.

Seventy-six patients with bone secondaries were admitted in the orthopaedic department of Basrah Teaching Hospital from February 2000 to June 2002, age range 14-86 years; 34 were males and 42 were females. The dominant sites of bone metastases were spine, 60 patients (79%) and pelvis, 16 patients (21%). The common primary sites were breast, 19 patients (25%) and lung, 11 patients (14.4%); 9 patients (11.2%) had undetected primary site. Most secondaries (90%) were osteolytic in type and the most common histopathological type was adenocarcinoma, 47 patients (63%). In 63 patients (83%), pain was the dominant presenting feature. Late presentation was a major problem; it ranges between 4-8 months. Another problem was lack of clinical awareness in the early stage of the illness.

Serum and urinary biochemical markers of bone metabolism were significantly high in patients with bone secondaries than control group, no difference whether the metastasis was single or multiple and whichever the primary site or histopathological subtype. Special interest with urinary hydroxyproline, it was significantly elevated in patients with bone secondaries, some of them had negative radiography. Prognosis was poor with short life expectancy.

Introduction

Bone tumors vary widely in clinical presentation, biology, and histology, there is nothing typical of bone tumors¹. The development of bony metastasis is a catastrophic complication for most patients with cancer and indicates that the malignant process is incurable and

only palliation is available. Metastatic destruction of bone reduces its load bearing capabilities, resulting in trabecular destruction and microfracture and subsequently in loss of bony integrity. Bone metastasis thus causes considerable morbidity, including pain, impaired mobility, hypercalcaemia, compression of spinal cord or nerve roots, and particularly with osteolytic lesion, pathological fracture². The skeleton is the most

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common site to be affected by metastatic cancer³, and metastatic deposits are the most common malignant tumors affecting the skeleton and it is more common than all primary tumors together in patients above 70 years of age⁴.

However the incidence of bone metastasis to the skeleton by carcinoma in general, from whatever primary sites is probably greatly underestimated⁵. It has been estimated that up to three fourths of the patients that succumb to cancer, have bone metastasis at the time of death⁶.

Although bone metastasis has been reported with nearly all cancers, carcinoma of the breast, prostate, lung, kidney, and thyroid have particularly high predilection for bone involvement⁷. The bones most often afflicted by secondary deposits are vertebral bodies, pelvis, ribs, and upper ends of femur & humerus⁸.

Clinically, patients with bone secondaries are divided into 4 groups^{8,9}:

1. Patients give history of previous disease and its treatment, e.g., mastectomy for a breast lump.
2. Patients complaining of symptoms related to the primary growth such as cough, haemoptysis, or difficulty of micturition.
3. Patients develop bony metastasis with no signs or symptoms to indicate the site of the primary lesion. They are further subdivided into:
 - a. The primary site detected thereafter.
 - b. The primary site is not detected after exhaustion of all investigations (carcinoma of unknown primary syndrome).
4. Patients present with bone Metastasis many years after the primary tumor has been successfully removed (tumor dormancy).

Typically the patient with bone metastasis is an adult in middle or late in

life with a lesion in the proximal portion of the extremities or in the spine, present because of pain, localized tenderness, swelling, pathological fracture, or the development of hypercalcaemia³. They may be found on routine screening of the skeleton for patients known to have malignant disease¹⁰.

Bone metastases are most often associated with abnormalities of the skeletal matrix and mineral compartment homeostasis. Measurement of these components (or their byproducts) in the serum or urine might be of diagnostic and prognostic guidance¹¹. Accordingly, this report is an attempted to study and assess the clinical and biochemical changes associated with bone metastasis.

Subjects and methods

This is a prospective study that was carried out over the period from February 2000 till 2002. Seventy six patients with bone secondaries proved by histopathology and /or radiography were evaluated clinically, radiologically, and biochemically.

Detailed history, through physical examination, radiographic skeletal survey, abdominal ultrasound, and common laboratory tests were done routinely. M.R.I. and C.T. scan of the spine and other regions were done in most of cases with symptoms relevant to these areas. For patients with bone secondaries of unknown primary site, thyroid ultrasound, bronchoscopy, I.V.U., barium study, chest and abdominal C.T. scans were requested only if clinically indicated. Certain biochemical markers were estimated in all the patients and the results were compared with fifty persons with no apparent musculoskeletal disease or malignancy as a control group.

Serum and urine samples were obtained from patients and control group. Ten ml of blood was obtained and 24-hour urine

collection for biochemical analysis. The serum parameters that had been estimated are calcium, phosphorous, acid phosphatase and alkaline phosphatase. Liver enzymes (SGPT & SGOT), serum albumin, blood urea, and serum creatinine also measured to assess hepatic and renal function status. Urinary parameters are calcium, phosphorous, and hydroxyproline. Urinary creatinine also was measured to assess the accuracy of urine collection.

All procedures were done in lab of biochemistry department of college of medicine were followed according to the instructions of the manufacturers or the authors¹², using special kits from either bioMerieux France or Randox UK.

Biopsy from the primary lesion and/or the secondary deposits was done in sixty-five patients, although some patients were known to have primary malignant tumor.

Statistical Analysis: The results were expressed as mean \pm SD. The data were analyzed statistically by Student's "t" test and one-way analysis of variance (ANOVA). $P < 0.05$ was considered to be the lowest limit of significance.

Results

Bone secondaries constitute about 39% of all malignant bone tumors (170) during the period of the study. Of them 34 (45%) were males and 42 (55%) were females. The commonest age group was above 60 years (45%). (Table I).

The common primary sites of the tumor were breast (19cases, 25%) followed by lung (11 cases, 14.4%) and prostate (7 cases, 9%). The primary site remains undetected in 9 cases (11.8%).

The most common sites for secondary deposits were vertebrae (60 cases, 79%) followed by pelvis (16 cases, 21%) and femur (12cases, 15%). Only one case had secondary deposit in the tibia.

Bone pain was the dominant presenting complain in 63 patients (82.9%); the backache (with or without neurological deficit) constitute the majority of them (47cases, 61.8%), but complete paraplegia with sphincters disturbance was the main presenting feature in 8 cases (10.6%) while pathological fracture of long bones was reported as the presenting symptom in 3 cases only (4%).(Table II).

Forty patients (52.6%) gave history of trauma. Thirty-nine patients presented with poor general health, the majority of them (29 cases, 75%) have positive liver ultrasound for bone metastasis.

The bone secondaries were mainly osteolytic (69 cases, 90.7%), and only few cases were with osteoblastic or mixed deposits.

Histopathological evaluation revealed that the adenocarcinoma was the most common type (47 cases, 62%), followed by squamous cell carcinoma (13 cases, 17%). (Table III).

Eighteen patients (23.6%) were hypercalcaemic (serum $Ca^{+2} > 2.7$ mmol/L, 10.5mg/dl), serum phosphorous was higher than upper normal limit (4mg/dl) in 32 patients (42%), alkaline phosphatase was raised (more than King Armstrong units %) in 60 cases (78.9%). Urinary calcium excretion

was higher than normal (350 mg / day) in 60 patients (78.9%), urinary phosphorous was elevated (>1300 mg/day) in 8 patients (10.5%), urinary hydroxyproline excretion in an abnormally high value (> 535 μ mol/day) was reported in 61 patients (80.2%). These readings were significantly elevated in comparison with the control group (p value <0.05)(Table IV).

Within patient's groups, comparative studies were also done. Statistical

analysis showed that there were no significant differences among these groups (p value >0.05): in different primary sites, single vs. multiple secondary deposits, and among patient's groups with tumors of different histopathology.

Figures 1-6 showed some radiographs of bone secondaries and their origin.

Table I: Age and sex distribution of skeletal secondaries

Age(year)	Males		Females		Total	
	No	%	No	%	No	%
0-20	1	1.3	3	3.9	4	5.2
20-40	3	4	6	8.8	9	12.8
40-60	11	14.4	17	22.3	28	36.7
Above 60	19	25	16	20.3	35	45.3
Total	34	44.7	42	55.3	76	100

Table II: Clinical Presentation

Clinical feature	No. of cases	%
Pain	63	82.9
Paraplegia	8	10.6
Mass	2	2.6
Long bone fracture	3	3.9

Table 3: Histopathological Classification:

A. Epithelial tissue tumors	= 68 cases
1. Columnar (Adeno (Ca.))	=47
2. Squamous cell Ca.	=13
3. Transitional cell Ca.	=3
4. Follicular cell Ca.	=4
5. Small cell Ca.	=1
B. Specialized connective tissue:	
*Bone	=4
C. Lymphoid tissue	=4

Table IV: Biochemical markers in patients versus control group.

Biochemical marker	Patients N=76	Control N=50	P value
Serum Calcium (S. Ca.) mg/dl	9.7±1.5	8.8±0.97	.007
Serum phosphorous (S. Pi.) mg/dl	4.4±1.6	3.8±1	.024
Serum alkaline phosphatase (S. Alk .Pase.) KAU%	20±7.1	6.2±1.6	.000
Urinary calcium (U. Ca) mg/day	517±218	116±51	.000
Urinary phosphorous (U. Pi.) mg/day	860±404	566±212	.000
Urinary hydroxyproline (U. OHP) µmol/day	384±236	175±58	.000

Results were expressed as mean ±SD

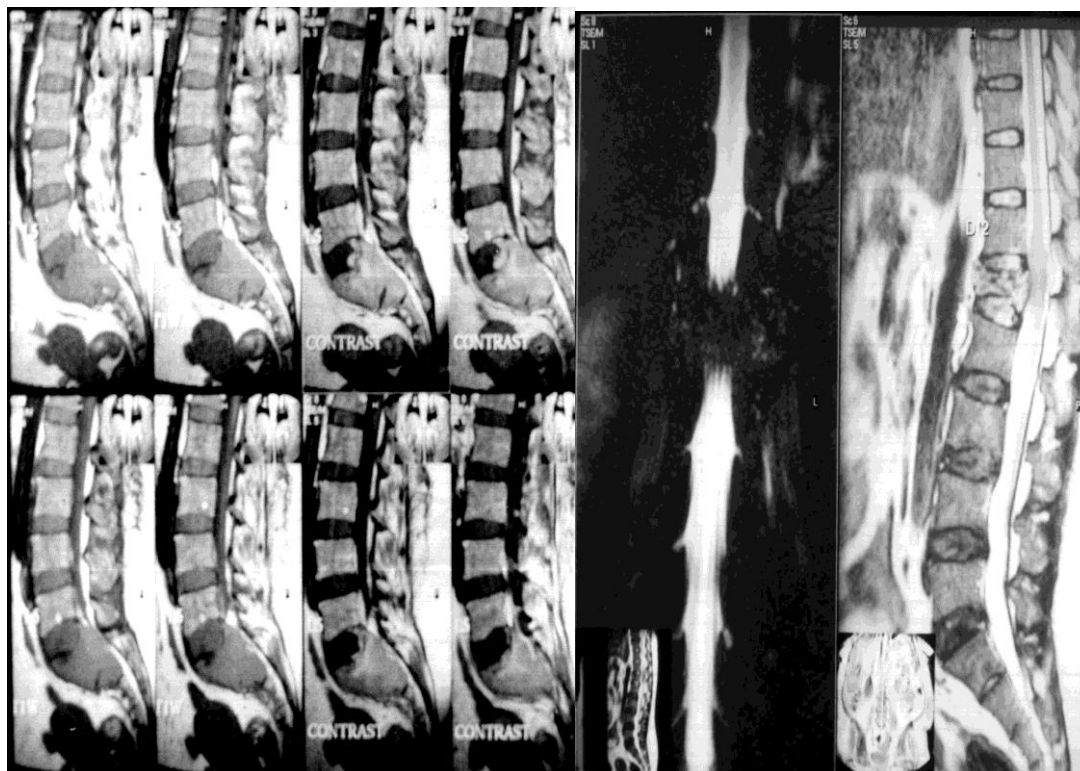


Fig.1&2 : Secondaries in the spine and sacrum.



Fig.3:Ca.bladder & Path. fracture



Fig.4:Osteoblastic lesion-Ca.prostate



Fig.5:Ovarian cancer & tibial deposit



Fig.6:Ca.Bladder& Path.fracture femur

Discussion

Although, it is well known fact that the metastatic deposits are the most common malignant tumors affecting the skeleton³ and it is more common than all primary tumors together in patients above 70 years of age⁴, surprisingly in our locality the primary malignant tumors are more common than bone secondaries, probably this is related to admission of patients with bone secondaries in other departments and the absence of a central tumor registry. The bone metastasis usually affect old age patients, often above 70 year old^{3,11}, however in our study, there is high percentage in younger age group, this might be explained by lack of mass screening for primary tumors, in addition to high overall incidence of cancer in our locality, which could be due to a widely spread contamination with depleted uranium at Basrah city borders, proved by Gamma spectrometric analysis of soil samples¹³.

Breast cancer metastasizes frequently to the skeleton and leads to considerable morbidity and deterioration of the quality of life. Breast cancer cells may release factors that stimulate bone resorption, angiogenesis and selective increase in the attraction of cancer cells to the bone¹⁴. Further more the breast cancer is quite common, it is mentioned that every 12th woman suffers in her life time from mammary cancer^{15,16}.

The axial bones-especially vertebrae- is the commonest site for bone secondaries, because these bones contain red marrow and have a good blood supply⁷. Spine metastasis accounts for as many as 70% of patients with disseminated cancer¹⁷.

The metastatic lesions are frequently osteolytic. Osteoblastic metastases

occur most frequently in metastatic cancer of the prostate⁷. In our study 2 out of 7 cases (28.5%) of bone metastases of prostatic origin are purely osteolytic. This might be explained by the predominance of the mechanisms of bone destruction, and the radiographic appearance merely indicating the net balance between the different types of bone formation and the simultaneous progressive bone destruction¹⁸. Pure osteolysis might be a marker for aggressiveness of the tumor and probably carries a bad prognosis if compared with those of pure osteoblastic or mixed deposits.

We have noticed an obvious change in tumor behaviour as the patients had apparently good general health, although they were carrying an advanced lesion. Bone secondaries were the first marker of tumors in 39 cases (51.3%), particularly with breast, lung, and genitourinary system tumors. Rickard-Wedin et al¹⁹ felt that lung and kidney cancers are inaccessible to physical examination, and grow to large size before there are symptoms, in addition to their propensity to metastasize early to the skeleton. So once the physician faces such cases, he most look for these primary sites, although they are relatively uncommon causes for carcinoma of unknown primary syndrome⁶. Insisting to identify the primary site or not in patients with carcinoma of unknown primary syndrome is still a matter of discussion as the strategy used may be costly and/or uncomfortable for the patient and the effect of precise identification of the primary site of origin on the patient's treatment and prognosis is questionable^{6,20}. Further-more we found the prognosis of those patients dose not differ significantly from those with detected primary site and maybe better for the patient to live long without evidence of the disease. However, the

physician's approach should involve reasonable efforts to identify the primary site or to determine the histology or subcategory of the metastatic tumor to decide on the optimal therapy.

The history of trauma was reported in 40 cases (52.6%), which could be a direct trauma at site of metastasis or indirect as lifting heavy weight. Higher figure was reported in other study¹. Ewing⁵ said that trauma merely draw attention to the site of tumor. Galasko¹⁸ suggested that a traumatized bone is more liable to bone secondaries. Trauma may affect the host-tumor balance²¹.

Although bone pain was the dominant presenting complain, it is unreliable marker for bone metastasis as secondary deposits may be totally asymptomatic or symptoms may be confined only to few sites²².

Spinal cord compression with complete paraplegia and sphincters disturbance are also reported as the presenting complaint. Kevin & Harrington²³ suggested that the most common cause of this syndrome is the extrusion of tumor tissue and detritus of bone or disk into the spinal canal following partial collapse of a vertebral body that has been infiltrated and weakened by metastatic deposits.

Pathological fracture of long bones usually occurs with lytic metastases. It is rare sequel of osteoblastic metastases²⁴. It is extremely debilitating and often results in diminished survival for otherwise stable patient.

The diagnosis of bone metastasis may be difficult, both clinically and radiologically. Reliable biochemical markers could, and in some instance do, contribute significantly to the diagnosis, staging, and assessment of treatment and follow-up evaluation of patients with metastatic carcinoma¹⁵. Hypercalcaemia is commonly associated with bone metastases; due to release of factors from these tumors that stimulate bone

resorption, such as polypeptides with parathormone-like activity²⁵. It is less common in solid neoplasm without bone metastases and its appearance may suggest spreading of the tumor and poor prognosis²⁶. Relatively low percentage in our study (23.5%) and Coomb's study (14%)²⁷ could be explained by absence of renal impairment in those patients. Consequently patients with hypercalciuria (80%) are more than those with hypercalcaemia. So, hypercalciuria may be more sensitive marker for progression of bone secondaries. Campbell²⁶ said that calcium excretion provide a reliable indicator of early changes of calcium homeostasis than hypercalcaemia.

Contrary to general notion, that serum phosphorous is only raised when there is associated renal failure¹⁰, we found hyperphosphataemia in 40% of cases despite the absence of overt renal failure. This could be due to the statistically significant relationship between an excess of phosphorous and an excess of alkaline phosphatase²⁸, which was reported in 80% of patients in our study.

Acid phosphatase appear totally unreliable marker for diagnosis of metastasizing carcinoma of the prostate to the bone, this could be due in part of variations in the amount of the enzyme produced by the tumor in different patients and even in the same patient at different times, in addition this enzyme is very unstable affected by heat, haemolysis, sample storage, P-R examination, and catheterization^{15,28}. Bishop's²⁹ study demonstrated that plasma alkaline phosphatase is a much more reliable marker of bone metastasis in prostatic cancer than acid phosphatase, provided that the liver function tests (SGPT & SGOT) are normal.

Alkaline phosphatase is also highly elevated in patients with breast and lung

cancer as well as those with undetected primary site.

Urinary hydroxyproline has been shown to be a non-specific but informative marker for bony metastasis, we found its sensitivity is superior to plain radiography. A finding in agreement with that of Grant et al³⁰ and Erol et al³¹, so it can be used to decrease the need for repetitive skeletal surveys and bone scans³². However newly formed metastases, small foci or deposits with minor activity could be responsible for normally detected urinary hydroxyproline³¹.

Surprisingly, there was no statistically significant difference in the level of these markers among patient's group with bone secondaries. Galasko¹⁸ and Campbell²⁶, feel that the changes in the level of markers of bone metabolism could be related more to the rapidity and aggressiveness of skeletal involvement by secondary deposits rather than the number of deposits, the site of the primary tumor, or the site of secondary deposits.

The prognosis is generally poor with short life expectancy, particularly in those with associated liver involvement, despite normal liver function tests. O'Donoghue²⁴ considered four factors affecting the prognosis and survival in patients with bone metastases: the development of liver metastasis, age less than 35 years, the development of pathological fracture, and hypercalcaemia due to disease progression.

The value of biochemical markers in assessment of the prognosis usually completed by clinical evaluation and other parameters such as survival³³. The problem with biochemical evaluation is the relative change of these markers and not the absolute level should be used,

because the later reflects the rate of bone turnover, which may be increased due to metastatic activity and bone healing as well, thus repeated measurements are usually required, which unfortunately were difficult to be done in our study.

In conclusion we can say that:

- 1- Biochemical markers together with clinical assessment may be appropriate alternative for reported skeletal surveys and bone scans for early detection of bone secondaries as they are simple, available in almost all general hospitals, will give results within few days and also there are economic advantages, as marker estimations amount to only a small proportion of the costs of limited skeletal surveys.
- 2- Patients with polystatic disease (proved by radiography) and known primary neoplasm with significantly increased levels of bone biomarkers can be treated without obtaining biopsy. However careful observation is needed, with needle biopsy being reserved for patients who do not respond predictably to treatment.
- 3- Although our results do not allow us to assess the real importance of hydroxyproline in the evaluation of response to treatment and prediction of prognosis, we believe that if those patients excreting the highest hydroxyprolinuria levels were monitored by serial measurements, more information could be obtained.

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