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Bone Metastases—The Clinical Problem

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INTRODUCTION

CANCER-INDUCED BONE diseases include primary osseous tumours, non-metastatic effects of malignancy on the skeleton and the effects of anticancer treatment on bone, but by far the most important problem clinically is metastatic bone disease. Cancers of the breast and prostate are particularly likely to spread to bone; approximately 70% of patients who die from these diseases have evidence of skeletal involvement at autopsy (Table 1). Carcinomas of the thyroid, kidney and bronchus also often cause bone metastases with a postmortem incidence of 30–40%, but, by contrast, tumours of the gastro-intestinal tract do so rarely affecting only about 5% of patients dying from these malignancies [1].

The variability in metastatic patterns from different primary cancers, while probably reflecting molecular and cellular biological characteristics of both the tumour cells and the tissues to which they metastasise, is also likely to be a consequence of other mechanisms. The predominant distribution of bone metastases in the axial skeleton, in which most of the red bone marrow resides, suggests that sluggish blood flow at these sites might facilitate the attachment of metastatic cells. However, slow blood flow alone does not account adequately for metastatic patterns. The high incidence of bone metastases from cancers of the breast and prostate without corresponding lesions in the lung makes it unlikely that malignant cells spreading to bone pass through the pulmonary circulation. Even if lung tissue is not receptive as a site for the establishment of metastatic disease from a particular cancer, tumour cells are still unlikely to pass through its narrow capillaries, particularly when aggregated as tumour emboli. A satisfactory explanation for the predilection of metastatic disease from these cancers to the skeleton has been provided through studies in animals and human cadavers which demonstrated the vertebral-venous plexus of veins [2]. Venous blood from both the pelvis and the breast flows not only into the venae cavae, but also directly into the vertebral-venous plexus. Flow into the vertebral veins predominates when intrathoracic or intra-abdominal pressure is elevated. This work has provided a good explanation for the high frequency with which prostatic and breast cancers, as well as those arising in the kidney, thyroid and lung, produce metastases in the axial skeleton and limb girdles.

INCIDENCE AND PROGNOSIS

Given the high prevalence of carcinomas of the breast, prostate and lung, it is estimated that these cancers probably account for more than 80% of cases of metastatic bone disease (Table 2). In geographical areas having the highest incidence of breast cancer, this tumour accounts for 10% of all malignancies and is the one most often associated with metastatic bone disease. Because of the long clinical course breast cancer may follow, even after the development of metastases, morbidity from bone secondaries makes major demands on resources for health care provision. Bone metastases from breast cancer usually have a mixed osteolytic and osteosclerotic appearance radiologically, with osteolysis predominating and predisposing these lesions to serious complications, particularly pathological fracture and hypercalcaemia. By contrast, in prostatic cancer, osteosclerotic disease predominates, although computerised tomography often identifies lytic areas within these sclerotic lesions. This characteristic results in a lower predisposition to hypercalcaemia and pathological fracture re-emphasising the particular importance of metastases from breast cancer as a cause of morbidity from bone metastases.

In a study of 587 patients dying from breast cancer, it was observed that 69% had radiological evidence of skeletal metastases before death [3]. This compared with 27% each for lung and liver metastases. In that study of 2240 patients who had presented with breast cancer over a 10 year period, 681 (30%) relapsed after a median follow-up of 5 years, of whom 395 (58%) had distant metastases. The first relapse was in bone in 184, accounting for 47% of all those with first distant relapse, 27% of the total with any relapse (local and/or distant) and 8% of the whole study population. Survival of patients with metastases confined to the skeleton was markedly different from that in patients with visceral involvement. After first relapse in bone, median survival was 20 months, compared with only 3 months after first relapse in liver. If metastatic disease remained confined to the skeleton, the median duration of survival increased to 24 months, 20% of patients still being alive 5 years after the development of metastases. These results emphasise the prolonged clinical course metastatic breast cancer can follow. Survival in prostatic cancer can similarly be prolonged after the development of bone metastases [4].

Table 1. *Postmortem incidence of bone metastases in different cancers (after Galasko* [1]*)*

Primary tumour	Postmortem incidence (%)
Breast	73
Prostate	68
Thyroid	42
Kidney	35
Lung	36
Alimentary tract	5

The problem of bone metastases in lung cancer is different. The incidence of bone metastases with this tumour at the time of primary diagnosis is highest with the small cell variety and lowest with squamous cell tumours, but at autopsy the incidence of bone metastases is similar for all four main histological types of lung cancer (squamous cell, small cell, large cell anaplastic and adenocarcinoma) at approximately 30% [5]. Less than 10% of patients with lung cancer survive 5 years after diagnosis and, when metastatic disease becomes apparent, most die within a few months. Hence, although bone metastases from lung cancer are usually osteolytic, the shorter survival means that morbidity from skeletal complications is far less of a long-term health care problem compared with either breast or prostatic cancer.

COMPLICATIONS OF BONE METASTASES

Pain

Bone metastases are the most common cause of pain from cancer, which results from either mechanical or chemical stimulation of pain receptors in the periosteum and endosteum [6]. Pressure effects from an expanding tumour mass, cytokine release, the formation of microfractures, mechanical instability and pathological fracture may all be contributory. Spread of tumour from bone to surrounding neurological structures, such as the spinal cord, nerve roots and brachial and lumbosacral plexuses, are other important causes of pain and neurological disability.

The spine is the commonest site for metastatic spread from breast and prostatic cancer. Pain at the site of bone involvement is common and may be associated with radicular pain if the tumour involves adjacent nerve roots. Extension of the tumour into the epidural space may lead to spinal cord compression with associated motor, sensory and autonomic signs. Certain distinct referred pain patterns are recognised. Damage to the lower cervical and upper thoracic spine may be referred to the interscapular region, while involvement of the lower thoracic and upper lumbar spine may cause unilateral or bilateral pain in the region of the iliac crest or sacroiliac joints. Upper cervical lesions should be suspected in any patient with neck pain and neurological symptoms or signs in the arms or legs. At other sites of vertebral body metastases, local or radicular pain may be the only symptom heralding impending spinal cord compression. A careful neurological examination is, therefore, essential in such patients with appropriate imaging as prompt intervention with high-dose steroids, radiotherapy or surgical decompression may prevent the establishment of severe and permanent disability.

Bone pain may be poorly localised. It often has a deep boring quality which aches and may be accompanied by episodes of stabbing discomfort. Pain worsened by movement, weight bearing or changes in body position or posture often occurs when metastases involve the pelvis, femora or vertebrae. This so-called incident pain may be poorly controlled by analgesics and sometimes requires surgical stabilisation.

Measurement of pain is difficult because of its subjective nature. Nevertheless, its evaluation is important in order to estimate the effectiveness of treatment. Various instruments have been developed, both linear analogue scales and categorical systems. The latter take into account the described intensity of the pain, analgesia consumption and mobility. Scoring can be applied to these recordings to enable a semiquantitative assessment of pain which can be particularly useful in the interpretation of clinical trials [7].

Pathological fracture

Pathological fracture is a major complication of metastatic bone disease, causing severe pain and often prolonged disability. Fractures of long bones have the most serious consequences and occur in approximately 10% of patients with bone metastases [3]. The addition of fractures at other sites, particularly the ribs and vertebrae, raises the incidence of pathological fracture to approximately 50% in patients with skeletal metastases. Although survival after pathological fracture can be prolonged following appropriate orthopaedic surgery, radiotherapy and/or systemic treatment, the median survival after a long bone fracture is only approximately 12 months. In a large series of 1800 patients with metastatic bone disease, 150 (8%) had fractures of either the femur or humerus [8]. Carcinoma of the breast was responsible for 53% of the fractures, compared with kidney 11%, lung 8%, thyroid and lymphoma each 4% and prostatic cancer 3%; a variety of other cancers accounted for the remainder.

To distinguish benign from pathological fractures radiologically is usually straightforward as the latter normally occur in the context of obvious bone metastases. However, occasionally, a pathological fracture in a solitary metastasis may be the first presentation of metastatic bone disease irrespective of whether or not a primary diagnosis of cancer elsewhere has been made. Even in these instances, the pathological nature of the fracture is normally apparent on plain radiographs as they occur through rarefied bone with trabecular destruction and endosteal scalloping. In these circumstances, histological material obtained at the time of surgical fixation of the fracture usually confirms the diagnosis.

Table 2. *Comparison of survival after the diagnosis of bone metastases in breast, prostate and lung cancer in relation to the epidemiology of these cancers in the U.K.*

Carcinoma	Incidence No. per annum	Estimated prevalence	Deaths No. per annum	% 5 year survival	Median survival from bone metastases (months)
Breast	26 000	105 000	16 000	64	24
Prostate	14 000	28 000	10 000	46	20
Lung	42 000	30 000	37 000	<10	3

After pathological fracture of a long bone, pain is severe, admission to hospital is urgent and surgery is often needed at a time when the general condition of the patient is poor and not ideal for general anaesthesia. Furthermore, because of the greater difficulty in stabilising an established, as opposed to an impending, fracture, perioperative morbidity is increased. Hence, an important aim in the management of metastatic bone disease is prophylactic surgical fixation of a bone at risk before the occurrence of a fracture. Identification of such lesions is, therefore, important, those not at risk of fracture being relatively safely irradiated or treated medically.

The prediction of impending pathological fracture has been controversial [9]. Factors which have been taken into account include pain, the anatomical site of a lesion, its radiological characteristics and its size. Although intensity of pain, which is difficult to quantify, is not clearly associated with fracture risk, pain that is aggravated by function appears to be an important factor in predicting impending fracture. Presumably such functional pain indicates diminution in the mechanical strength of a bone and in one series was invariably followed by fracture. As far as radiological appearances are concerned, there is a general consensus that lytic lesions give the patient a much higher risk of fracture than either mixed or osteosclerotic lesions. Accordingly, a particularly high fracture rate is found in association with metastases from lung cancer. However, given the poor prognosis of this tumour, such fractures rarely lead to prolonged disability. By contrast, in breast cancer, which follows a much more prolonged course, pathological fracture constitutes a major cause of prolonged disability. In prostatic cancer, with its predominantly sclerotic picture, pathological fracture is relatively unusual.

Radiological assessment also gives information on the size of a lesion and the extent to which the bone is destroyed. When less than two thirds of the diameter of a long bone is affected, pathological fracture is relatively unusual, but above this size the fracture rate increases markedly with an incidence of approximately 80% for such lesions. A practical scoring system incorporating the above factors has been described to give valuable guidance in the selection of patients for prophylactic fixation [10].

Rib fractures are a common cause of chest pain, which may be pleuritic in character. Their location is often indicated by a well-localised area of severe tenderness on palpation. Such fractures, although extremely unpleasant, rarely give rise to serious sequelae and can effectively be treated by analgesics and a single fraction of radiotherapy. Rarely, multiple rib fractures can impair the integrity of the chest wall and result in impairment of respiratory function. Rib fracture may occasionally follow radiotherapy to the chest wall as a consequence of radionecrosis.

Vertebral body fractures are common in patients with bony metastases leading to loss of height of, often several, vertebrae. Acute vertebral collapse is associated with severe pain which usually remits following radiotherapy. The pain is frequently a combination of localised bony pain associated with a radicular component as a consequence of compression of spinal nerve roots. A serious sequel to vertebral fractures is extension of tumour into the theca with resultant spinal cord compression (see below).

Vertebral fracture from metastatic disease is sometimes difficult to distinguish from osteoporotic collapse. This is particularly so in middle-aged and elderly women with breast cancer who are coincidently at physiological risk of osteoporosis. Moreover, treatments which may have been prescribed for breast cancer can also aggravate a tendency to osteoporosis; they include ovarian ablation, chemotherapy-induced ovarian failure and corticosteroids.

Spinal cord compression

Compression of the spinal cord or cauda equina in patients with metastatic disease of the spine is a medical emergency necessitating prompt diagnosis and treatment. Its causes include pressure from an enlarging extradural mass, spinal angulation following vertebral collapse, vertebral dislocation following pathological fracture or, rarely, pressure from intradural metastases. The standard diagnostic test for many years was myelography, but this has largely been superseded by magnetic resonance imaging (MRI), which may reveal multiple levels of compression.

Back pain is a common symptom at presentation and affects the majority of patients with spinal cord compression. Two types of pain occur, local spinal and radicular. Radicular pain varies with the location of the tumour, being particularly common in the cervical and lumbosacral regions and less so with thoracic lesions. Both local spinal and radicular pain are experienced close to the site of a lesion identified at myelography or MRI. Motor weakness, sensory loss and autonomic dysfunction are all common at presentation of spinal cord or cauda equina compression. The most common primary tumours producing this complication are, in order of decreasing frequency, carcinoma of the breast, lung cancer, prostatic cancer, lymphoma and renal carcinoma [10].

A detailed study of spinal cord compression complicating breast cancer in 70 patients has been reported [11]. Over the period of this study 1684 patients had presented with metastatic disease, giving an incidence of cord compression of 4%. The median time to the development of spinal cord compression from diagnosis of breast cancer was 42 months. All patients had radiological evidence of bone metastases and only 5 of them were not known to have bone metastases previously. The most frequent symptom was motor weakness (96%), followed by pain (94%), sensory disturbance (79%) and sphincter disturbance (61%). Ninety-one per cent of patients had had at least one symptom for more than a week. Radiotherapy was given as primary treatment to 43 patients, whilst 21 had decompressive surgery, 7 of whom had subsequent postoperative radiotherapy; 6 patients were too unwell for either treatment. Following treatment, 96% of those who were ambulant before treatment maintained the ability to walk. In those unable to walk, 45% regained ambulation, radiotherapy and surgery being equally effective in achieving this result. Median survival following cord compression was 4 months with no significant difference being seen between those treated by either radiotherapy or surgery. The most important predictor of survival was the ability to walk after treatment. The conclusion from the study was that the majority of patients had had prior warning symptoms of cord compression and nearly all had previous evidence of spinal bone metastases before the complication occurred. These findings stress the importance of prompt presentation, diagnosis and treatment and they suggest that earlier diagnosis and intervention should improve outcome.

Hypercalcaemia

Hypercalcaemia is common in patients with malignant disease of bone. It is seen particularly frequently in multiple

myeloma, approximately a third of patients with this disease developing this metabolic complication. It is also common in breast cancer, in which it affects approximately 20% of patients with bone metastases. Hypercalcaemia can also develop in the absence of metastatic involvement of the skeleton, the mechanism being the production of parathyroid hormone-related protein (PTHrP) by the tumour. Irrespective of its cause, either metastatic deposits or humoral, osteoclastic bone resorption is the final common path for the development of hypercalcaemia. Whereas with bone metastases urinary calcium excretion is markedly elevated, in humoral hypercalcaemia it is inappropriately low as a consequence of increased renal tubular re-absorption of calcium under the influence of PTHrP.

Hypercalcaemia may initially be asymptomatic, but as the blood calcium level rises a variety of symptoms appear. Although this is usually a gradual process, its development may occasionally be rapid and imminently life-threatening. Common symptoms include lassitude, anorexia, nausea and constipation. Thirst and polyuria frequently develop and as the condition advances, vomiting, dehydration, severe constipation and impairment of concentration may progress to drowsiness, psychosis, coma, renal failure and cardiac arrest. Despite the variety of symptoms, physical signs are relatively few but signs of dehydration are likely to be present. The condition can be rapidly reversed by treatment comprising rehydration and bisphosphonates.

Bone marrow suppression

Extensive infiltration of the bone marrow by metastatic cells can lead to impaired haematopoiesis and the development of leucoerythroblastic anaemia characterised by the appearance of immature red blood cells and granulocytes in the peripheral blood. Associated leucopenia and thrombocytopenia predispose patients to infection and haemorrhage, respectively. In its severest form, diffuse involvement of the bone marrow by metastatic cells can result in either marrow fibrosis or necrosis which may be associated with splenomegaly and immature cells of all lineages being seen in the peripheral blood [12]. Radiotherapy, often needed in the treatment of metastatic bone disease, can exacerbate this problem. Hence, the presence of bone metastases, particularly when irradiation has been administered, may compromise significantly the ability to give effective chemotherapy. Moreover, animal experiments have shown that cytotoxic drugs can interfere with osteoblast function and new bone formation [13].

CONCLUSION

Metastatic bone disease is a major cause of morbidity in patients with cancer. The principal problems that arise are pain, pathological fractures, spinal cord compression, hypercalcaemia and bone marrow suppression. Together, these problems are responsible for a particularly high proportion of days spent in hospital as a result of cancer [14]. To some extent, it is possible to predict which patients with bone metastases are at high risk of developing the most serious complications and this can assist in the selection of patients for optimal treatment and towards the prevention of serious morbidity. Although the recent introduction of the bisphosphonates is reducing the complication rate from bone metastases, much more progress still needs to be made to lessen this problem as a major cause of suffering and disability in patients with cancer.

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