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(REVIEW ARTICLE)

The pathophysiology, commonest presentation and diagnosis of bone metastases in breast cancer patients: Overview

Monika Rezacova *

Breast surgery, University Hospital Portsmouth, UK.

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Abstract

Bony metastases in breast cancer patients are a very common presentation anytime between initial diagnosis to many years post treatment. Despite all available research, there have been very controversial theories about discovering the high-risks patients. Although a lot is known about the mechanism of seeding of breast cancer and growth of the cell in the bones on a molecular basis, there is very limited knowledge of which patients should be the ones requiring closer monitoring. Imaging of bony metastases is often dependent on local possibilities and cost of the service.

This review should serve as an overview of current available research and knowledge about pathophysiology, risks factors and diagnostic options of bony metastases.

Keywords: Breast cancer; Pathophysiology; Bone metastases; Imaging of metastases

1. Introduction

Thanks to breast screening and cancer referral pathway, breast cancer is diagnosed in early stages. Despite available cures 20–30% of these patients will present later with metastatic disease. [1] Bone is the most frequent site for metastases and is involved in almost two thirds of metastatic patients. Data shows that even patients diagnosed in stages I-III will develop bone metastasis in 13% of cases at 15 years from diagnosis. [2] Until recently bony metastases of bone cancer were deemed incurable however in recent years, single isolated bony metastasis can be removed considering there is no recurrence at the primary site. Bone metastases alone have better prognosis of overall survival as compared to visceral or bone and visceral together. Several factors influence the metastatic spread, i.e. demographic, clinical, pathological and genetic. Early recognition of the associated factors can help highlight the high-risks patients and in combination with symptoms recognition, early diagnosis can be achieved. This allows clinicians to start further management early and manage symptoms better.

2. Pathophysiology of bone metastasis in breast cancer

Although considered by many as localised disease in the absence of metastases, breast cancer is a systemic disease and can spread at any point. Bony or visceral metastasis can appear as a first presentation or later in the disease, even long after treatment of primary cancer.

Once the breast cancer reaches the basal membrane and becomes invasive, the spread can begin with the epithelial-to-mesenchymal transition (EMT) of carcinoma cells. [3] These enter the blood vessels via intravasation. Once they reach systemic circulation, they are called circulating tumour cells (CTCs). The body has multiple mechanisms to prevent them from reaching the bone marrow or other bodily sites by using matrix detachment, shear forces and immune system. To

* Corresponding author: MUDR. Monika Rezacova

try and overcome these mechanisms, CTCs form relatively large emboli via interactions with blood platelets. [4] Although majority of these clusters are trapped in capillary beds during their first passage through circulation, some of them escape and lodged in the microvasculature of distant organs and initiate intraluminal growth, rupturing the walls of surrounding vessels, and placing cells in direct contact with the parenchyma of a specific organ. This was initially considered a very random mechanism until British pathologist Stephen Paget at the end of 19th century noted a pattern that could not be random. He theorised that although the seeding of tumour cells can occur in any site, it will only truly root and colonise in the environment that provides specific chemokines, trophic factors, and mitogens. Therefore there are preferred sites for some tumours to metastasize into. [5] Later Hoshino et al, described that tumour can prepare favourable sites by exosome integrins. This knowledge provides a great scope for prevention and potential treatment of bony metastases. [6]

The breast cancer related CTCs reach the bone through the vessels feeding the marrow. There they adhere, undergo mesenchymal-to-epithelial transition (MET), and start releasing parathyroid hormone-related peptide (PTHrP). PTHrP causes nearby osteoblasts to increase receptor activator of NF-B ligand (RANKL) and decrease osteoprotegerin (OPG) expression [33]. As a result, osteoclast precursors mature in functional osteoclasts that undertake osteolysis causing bone demineralisation and exposing the extracellular matrix within the bone. During osteolysis transforming growth factor (TGF), calcium, bone morphogenetic proteins (BMPs), fibroblast growth factors (FGF), and insulin-like growth-factor-1 (IGF-1) are released, enabling cancer cell proliferation and survival. Not only acting in the bone itself, but also having systemic effect on the breast cancer cells, encouraging positive feedback loop. Although breast cancer bony metastases result in activation of osteoclast and therefore osteolytic lesions, osteoblastic activation can also be present. The mechanism of osteoclastic and osteoblastic switch is not yet fully understood however from other molecular studies of the bones it is clear that osteoclast and osteoblast activation is always linked. [7]

3. Risk factors of bone metastases

3.1. Demographic and clinicopathological factors

Several studies were collected to try and determine any factors that could be associated with higher risks of bony metastases. Identifying higher risk groups may help to develop closer strategies for monitoring. A lot of the data is retrospective or looks at specific groups of patients which may contribute to conflicting results.

As with any cancer, age has been considered a high risk factor. Although there are studies which suggest that higher age at diagnosis would contribute to development of bony metastases only as compared to younger patients who tend to develop visceral as well as bony metastases. [8] On the contrary, Purushotham et al described that patients above 40 years old at diagnosis had a significant decrease in the risk of developing distant metastasis with increasing age. And specifically, there was a significant decrease in bony metastases. [9] Some studies even described age as a protective factor to developing bony metastases. When considering age, we cannot forget the menopausal status of the patient. Although the subject of menopause and age causation is controversial on its own, it cannot be taken from the equation. It is believed that oestrogens are essential regulators of bone remodelling and could be potentially contributing to a fertile microenvironment that might promote development of bony metastases. If we consider that menopausal status is indeed a risk factor for developing bony metastases, it could explain why adjuvant bisphosphonate treatment seems to have an impact only in postmenopausal women. [10]

Even if age seems like a controversial topic, there is evidence proving the impact of high BMI on recurrence. [11] Patients whose BMI belongs to the obesity category have worse prognosis. Although the effect of high BMI is not yet fully described, it is likely related to higher levels of oestradiol (given the aromatisation of androgens in adipose tissue in postmenopausal women) and/or higher levels of insulin. High BMI has been proven to bear relevance to worse prognosis, there is no established preferred side of metastases.

Histological type of breast cancer seems like an obvious factor for different patterns of metastases, however the studies that have been published report very conflicting results. [12] Some of the latest suggest a higher likelihood of lobular cancer to metastasise to the bone. Several studies relate grade to the risk of developing metastases more than histological type. Bony metastases are often associated with low grade tumours. Although earlier studies show some correlation between tumour size and bony metastases, the most recent Japanese study failed to do so. [13] Out of the initial status of cancer, lymph node involvement seems to be the most consistent. It is a known risk factor for metastases in breast cancer patients. However, there are studies showing lymph node involvement has no significant relationship to bony metastases. [14]

3.2. Genetic factors

Recently changed classification is using five intrinsic subtypes (luminal A, luminal B, HER 2-enriched, basal-like, and normal-like), that are associated with distinct morphologies and clinical implications. Although basal-like tumours have a higher rate of distant metastases, it is mainly in nodes, lungs and brain. Bony metastases are the least common site for basal-like tumours. On the other hand, luminal A subtype is definitely a risk factor for relapse in the bone. Luminal subtypes showed bone as predominant site for metastases in 80.5% of the tumours, while basal-type and HER-2-like tumours 41.7 and 55.6% respectively ($p = 0.001$). In fact, luminal B subtype is more likely to have bone as a first recurrence site when compared to other subtypes. [15] Multiple studies have been performed to try and show relationships between expression of certain receptors or chemokines to provide suitable molecular prognosis. Subsequent studies refuted Kang's bony metastases signature's ability to discriminate tumours prone to develop those. [16] On the other hand, it allowed to distinguish primary breast cancer that preferentially metastasised to bone. To this day, no genomic predictor of bone-specific metastasis was clinically validated.

4. Common presentation

Bony metastases in breast cancer patients can either be present at diagnosis or are discovered on staging imaging. In some cases, fractures or scans generated by persistent pain could be a first presentation of disease. Patients with a history of breast cancer in anamnesis presenting with new onset of pain, should raise a suspicion of metastatic disease. As shown in the studies that were mentioned earlier, this could happen at any point after the initial diagnosis. [17]

The most common symptom is pain in the affected area which is usually worsening while lying down or sleeping. The frequent sites of bony metastases are spine, ribs, skull, pelvis and proximal ends of humerus or femur. Unfortunately, due to the presentation with pain, symptoms can be sometimes overlooked, treated with analgesia or referred to physiotherapy for physical therapy without appropriate imaging. Low threshold should be given to requesting imaging in patients with a history of breast cancer. The best modalities of imaging would be discussed in the paragraphs below. [18]

Other possible presentations of bony metastases in breast cancer are fractures that occurred with minimal or no impact injuries. Severe complications could be caused by spinal cord compression symptoms. However, these are considered emergency and would require urgent imaging. Generally, metastases that presented with fractures or spinal cord compression are often discovered quicker as imaging is required for diagnosis.

The last category of presentation includes incidental findings either on blood tests or surveillance scans (or scans for unrelated complaints). Changes in blood results towards anaemia, low white cell count, or hypercalcaemia could be non-specific but should trigger further investigation. Due to the non-specificity of these results, these tests could not be used for monitoring purposes.

5. Diagnosis

The initial imaging to investigate non-specific pain in breast cancer patients should be CT based. Although simple X-ray may help discover fractures and raise suspicion of metastatic disease, normal looking X-ray should not exclude metastatic disease. Assessment using CT can help discover changes in bone density. Metastases can display different patterns based on their behaviour (lytic, sclerotic or mixed). To be detected by CT, bone metastases need to be at least one cm with a loss of density around 25–50%. However, MSK radiologists are able to describe even more subtle changes. Apart from detection of bony metastases. CT can help to assess soft tissue invasion.

Conventional MRI sequences with T1, T2 and DWI studies, allow to detect breast cancer bone metastases with a sensitivity reported to 100% and a specificity of 90%. They can be used in clinical doubt or to clarify unclear appearance on CT. Some hospitals use whole body MRIs for monitoring (which is usually due to lack of other imaging) but generally MRI is mainly used as a second line investigation. [19] Apart from helping to visualise lesions with high precision, it also allows the study of the integrity of spinal cord.

Bone scintigraphy has a role in staging or during follow-up in detecting bone metastasis in breast cancer. The osteotropic agent used for skeletal imaging is metastable technetium 99 (99mTc) labelled diphosphonates for bone scintigraphy. Bone scintigraphy usually detects bone turnover, so metastasis with a prevalent lytic behaviour can be considered as false negative. [20] Although it is not as specific because of its low cost and effectiveness, it is still widely used. Reported sensitivity and specificity are 78 and 48%, respectively. It is also dependent on nuclear medicine facilities of the hospital which might be a limiting factor in some places.

Positron emission tomography (PET) is a scan that provides excellent spatial resolution with acquisition of tomographic images. It can help to assess treatment response. It relies on nuclear medicine, most commonly 18F labeled sodium fluoride (18F NaF) and 18F labeled fluorodeoxyglucose (18F FDG). Due to fluoride ions collocation in the remodeling skeletal areas, 18F-NaF PET is particularly sensitive to osteoblastic activity. PET images are highly sensitive and specific, 100% and 97% respectively. [21]

6. Conclusion

The bony metastases are common in breast cancer patients. They can appear at any point through their presentation and diagnosis journey. At the initial stages the patients are likely to be scanned as part of their initial staging. Diagnostic challenges come later or after treatment of the disease when back or neck pain could initiate from any possible reasons. Musculoskeletal pain is common occurrence in any patient especially with increasing age however a careful anamnesis and history taking may help to highlight patients that will need further investigation.

The presentation of bony metastases is very nonspecific and there is no single test or imaging modality that would help monitoring to discover these early. However, if there is suspicion, urgent imaging or referral to breast services should be considered.

A lot of research has been performed mainly on the molecular level to help and discover either patients who are more likely to suffer from bony metastases, or to develop early monitoring markers.

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