Chapter 15
The Diagnostic Approach to Metastatic Bone Marrow Infiltrates

ABSTRACT

The bone and bone marrow are common sites for metastasis due to their high vascularity and niche components. The commonest primaries in adults are the lung, prostate, and breast. Neuroblastoma, osteosarcoma, and Ewing sarcoma are the most frequent in children. The mechanism of tumor spread involves a multistep process with underlying molecular changes involving the interaction between tumor cells and the marrow microenvironment. Sometimes metastatic spread to the bone marrow manifests in peripheral blood changes, including cytopenia and leucoerythroblastic changes, in which case the bone marrow may be the first tissue diagnosis of the tumor. The bone marrow morphology and IHC help identify the primary tumor, though it remains unknown in some cases. The presence of metastasis often implies a poor prognosis.

INTRODUCTION

The bone and bone marrow are frequent sites for metastasis due to their high vascularity and niche components. Metastases are established through a multistep process involving niche formation, tumor seeding, and dormancy. The interaction of tumor cells with bone marrow niche components is a rate-limiting step. Potential strategies to block this interaction are an evolving therapeutic target.

Tumors exhibit a variable propensity to bone metastasis. Lung, prostate, and breast are the common primaries in adults. In children, Neuroblastoma, osteosarcoma, and Ewing sarcoma are the commonest.

The unique features of the bone microenvironment with abundant Vascular Supply and breeding ground for tumor cells are crucial for metastatic spread. Chemo-attractiveness by stromal cells, osteoblasts, osteoclasts, and osteocytes. Secretion of growth factors and prostaglandins recruit and maintain bone metastasis while the microenvironmental niche supports homing and multiplication of tumor cells. (Fan et al., 2018)

Peripheral cytopenia and leucoerythroblastic changes may manifest in metastatic spread. Then, bone marrow examination becomes essential for diagnosis.

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This chapter will explore pathogenic mechanisms, diagnostic approaches, and workups for known and unknown primary neoplasms involving bone marrow.

PATHOGENESIS AND MECHANISMS OF BONE MARROW METASTASIS

Bone metastasis often occurs through a hematogenous route. However, lymphatic spread can also occur, especially in cases like pelvic tumors that spread to para-aortic nodes. The journey of tumor cells from their primary site to distant bones involves complex interactions with the microenvironment. Nearly every bone in the body and multiple sites may host metastatic cells; the commonest are those of the axial skeleton, especially the thoracic spine (70%), the lumbosacral region (20%), and the cervical vertebrae (10%). *(*Ribatti et al., 2006*)*

Bone metastasis is a multifaceted process involving intricate interactions between tumor cells and their microenvironment. Understanding these mechanisms is crucial for developing targeted therapies. *(*Lin et al., 2013*)*

The Bone Metastatic Process Involves the Following Steps

1. epithelial-to-mesenchymal transition (EMT),
2. colonization of the metastatic niche, tumor dormancy,
3. immune evasion and osteo mimicry,
4. bone reconstruction, and
5. progression to overt metastases.

Epithelial-to-mesenchymal mesenchymal transition (EMT) is the acquisition of mesenchymal properties by tumor cells enabling them to invade surrounding tissues and enter the bloodstream. Various pathways can drive EMT, including epidermal growth factor receptor, tyrosine kinases, WNT pathway, nuclear factor kappa B (NF-κB), and transforming growth factor-β.

Tumor cells selectively settle in compatible microenvironments. Bone marrow architecture, with its sinusoid-shaped capillaries and permeable connective envelope, facilitates tumor cell homing. Slow blood flow in red marrow supports tumor cell attachment to the endosteal bone surface.

Primary tumors prepare the target organ's microenvironment for a supportive pre-metastatic niche. Cancer-associated fibroblasts (CAFs) secrete chemokine CXCL12 (SDF-1), attracting tumor cells. Overexpressed CXCL12 receptors (CXCR4 and CXCR7) induce chemotaxis. Proteolytic enzymes (e.g., matrix metalloproteinases) remodel the bone matrix. Tumor-secreted exosomes and microRNAs contribute to bone remodeling. *(*Eldridge, 2021*)*

Specific niches within the bone microenvironment allow tumor cells to settle and proliferate. Some tumor cells remain dormant within their niche for extended periods before overtly progressing. They adapt to resemble bone cells, where they manipulate bone remodeling processes, promoting their survival in the bone environment (*Bussard et al., 2016)*.

During this process, Tumor cells secrete factors that stimulate either osteoclasts or osteoblasts. Excessive osteolysis or osteosclerosis occurs, depending on the tumor type. Most solid tumors exhibit a mixed phenotype of osteolytic and osteoblastic lesions. Endosteal cells, which are quiescent, may support tumor cell dormancy compared to osteoblasts. The diagram in Figure 1 outlines the tumor–microenvironment interactions in bone metastasis. *(*Ban et al., 2021*)*.