Hematopoietic Tumors Primarily Presenting in Bone

Arjen H.G. Cleven, MD, PhD*,
Pancras C.W. Hogendoorn, MD, PhD

KEYWORDS

• Plasma cell myeloma • Lymphoma of bone • Langerhans cell histiocytosis

Key points

- Plasma cell myeloma cells typically secrete a monoclonal immunoglobulin.
- The clinical and pathologic features of primary lymphoma of bone overlap with osteomyelitis, Langerhans cell histiocytosis, and other malignant tumors.
- Diagnosing acute lymphoblastic leukemia/lymphoma requires the integration of aspirate and flow cytometry findings.
- *BRAF* mutations are a frequent finding in Langerhans cell histiocytosis.

ABSTRACT

Plasma cell myeloma is the most common primary malignant bone neoplasm and diffuse large B-cell lymphoma is the most frequent type of non-Hodgkin lymphoma primarily presenting in bone. Because clinical and morphologic features may overlap between primary malignant hematologic tumors in bone and other malignant tumors, as well as benign proliferations, a final diagnosis in bone lesions can be challenging. We discuss the differential diagnosis of plasma cell myeloma, solitary plasmacytoma of bone, primary non-Hodgkin lymphoma of bone, acute lymphoblastic leukemia/lymphoma, and Langerhans cell histiocytosis.

OVERVIEW

Plasma cell myeloma is the most common primary malignant bone neoplasm and diffuse large B-cell lymphoma (DLBCL) is the most frequent type of non-Hodgkin lymphoma primarily presenting in bone. Because clinical and morphologic features may overlap between primary malignant hematologic tumors in bone and other malignant tumors as well as benign proliferations, a final diagnosis in bone lesions can be challenging. Therefore, in the diagnostic workup, it is important to correlate clinical features with morphology, immunohistochemistry, and sometimes additional molecular analysis for a definitive diagnosis. Most malignant hematopoietic tumors primarily presenting in the bone are treated with systemic chemotherapy, with a relatively good prognosis compared with their nodal counterparts in case of DLBCL.

PLASMA CELL MYELOMA

Plasma cell myeloma is a plasma cell-based neoplasm composed of a clone of immunoglobulin-secreting, terminally differentiated B cells that typically secrete a monoclonal immunoglobulin.[1,2] Plasma cell myeloma is defined as a bone-marrow–based, multifocal plasma cell neoplasm associated with M protein in serum and or urine.[3]

Conflict of Interest: All authors declare that they have no conflict of interest.

Department of Pathology, Leiden University Medical Center, PO Box 9600, L1-Q, Leiden 2300 RC, The Netherlands
* Corresponding author.
E-mail address: a.h.g.cleven@lumc.nl

Surgical Pathology ■ (2017) ■–■
http://dx.doi.org/10.1016/j.path.2017.04.011

Plasma cell myeloma is the most common primary malignant bone neoplasm with a median age at diagnosis of 70 years and males being affected more frequently than females.[1,3] The thoracic vertebrae, ribs, skull, pelvis, femur, clavicle, and scapula are most commonly involved.[3] Most patients have pain or a pathologic fracture at first presentation.

Disease progression from normal plasma cell to plasma cell myeloma includes several steps of disease. Translocations in 14q32 and deletion of chromosomal 13 transform normal plasma cells into monoclonal neoplastic cells, which give rise to an early stage of disease, named 'monoclonal gammopathy of unknown significance' (MGUS). Additional oncogenic events such as *N-RAS*, *K-RAS,* and *TP53* mutations, inactivation of p16 via methylation, *MYC* dysregulation by complex chromosomal abnormalities, and nuclear factor-kappa Beta pathway activating mutations result in further progression of the disease and manifestation of plasma cell myeloma.[4,5]

Key Features
Plasma Cell Myeloma

- Most common primary malignant neoplasm presenting in bone
- Neoplastic plasma cells secrete a monoclonal immunoglobulin
- CD138 positive

Pitfalls
Plasma Cell Myeloma

! Carcinomas are frequently confusingly positive by immunohistochemistry for the plasma cell marker CD138

! Plasma cell myeloma may be positive for epithelial membrane antigen

RADIOLOGIC AND GROSS FEATURES

Radiographic findings in plasma cell myeloma include lytic bone lesions centered in the bone marrow without identifiable matrix and approximately 44% show a multiloculated appearance (**Fig. 1**).[6] Plasma cell myeloma localizations in the long bones are usually well-circumscribed and may be encompassed by periosteal new bone formation, giving the appearance of expansion and only rarely plasma cell myeloma generates sclerotic lesions.[6] In case of a pathologic fracture followed by surgery, gross specimen of the involved bone will show a friable, soft, and red appearance in which the underlying bone is eroded or fragile.[6]

MICROSCOPY

The morphology of plasma cell myeloma may vary from sheets of easily recognizable plasma cells to only scattered clusters of plasma cells to a highly pleomorphic malignant or blastoid type of morphology in which the plasma cell origin of the tumor cells is not recognized at first glance (**Fig. 2**A, C).

Mature-looking plasma cells show an eccentric nucleus with "spoke wheel" or "clock-face" chromatin without nucleoli and basophilic cytoplasm and perinuclear hof. The more immature plasmablasts-type of cells have a more dispersed nuclear chromatin, higher nuclear:cytoplasmic ratio, and often prominent nucleoli (see **Fig. 2**A). Nuclear immaturity and pleomorphism rarely occur in reactive plasma cells and are reliable indicators of neoplastic plasma cell myeloma (see **Fig. 2**C). Cytoplasmic Ig may produce a variety of morphologically distinctive findings like round eosinophilic bodies named Russell bodies in the cytoplasm or round eosinophilic bodies called Dutcher bodies in the nucleus (see **Fig. 2**C).

DIFFERENTIAL DIAGNOSIS

The most common differential diagnosis among plasma cell neoplasms is early myeloma versus monoclonal gammopathy of undetermined significance (MGUS) or reactive plasma cells in conditions such a chronic osteomyelitis. Normally, this differential diagnosis is not difficult for a pathologist, because clinical and pathologic findings such as lytic bone lesions and myeloma-related symptoms required for the diagnosis of plasma cell myeloma are lacking in MGUS or reactive plasma cell conditions.

Plasma cells of plasma cell myeloma can look like reactive plasma cells, which is a common finding in chronic osteomyelitis, but restriction for lambda or kappa light chain by performing immunohistochemistry is only observed in plasma cell myeloma and not in osteomyelitis. Furthermore, MGUS shows typical normal looking plasma cells in bone marrow with only a mild increase of clonal plasma cells of less than 10%.

Metastasis of poorly differentiated carcinoma to the bone can show overlapping morphologic features with the more pleomorphic type of plasma cell myeloma. Because both entities are CD138