Multiple Myeloma

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Definition: Multiple or plasma cell myeloma (PCM) is a bone marrow-based multifocal plasma cell neoplasm, usually associated with secretion of a single homogeneous monoclonal immunoglobulin called M protein. The bone marrow is the site of origin of nearly all PCMs. Multifocal bone marrow involvement is frequently observed. In advanced disease, extramedullary involvement can be appreciated.

Epidemiology: PMC accounts for about 1% of malignant tumor with an incidence of about 20 cases/million/year. Male predominance is observed. PMC is almost never found in children and extremely rare in young adults (mean age at diagnosis: ≈70 years). In elderly patients, PMC represents the most common primary bone malignant neoplasm.

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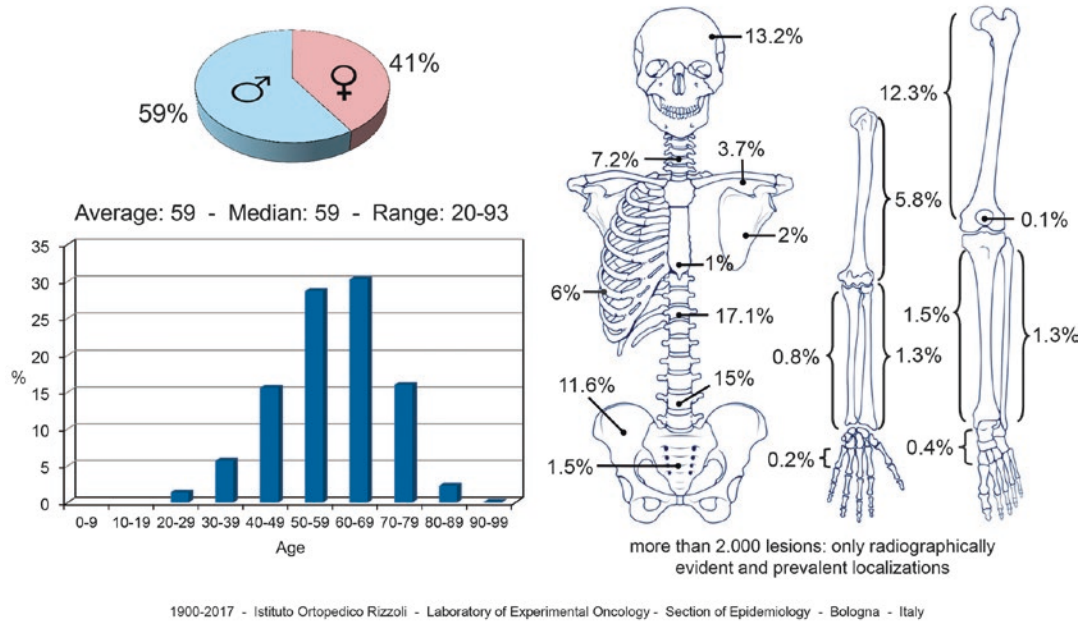


Localization: The axial skeleton is the preferred site. In the appendicular skeleton, the metaphysis is favored. It is very rare in bones of the hand and foot.

Clinical: In most patients, the symptomatology includes local pain (usually relieved by rest), hypercalcemia, and occasionally pathologic fracture (more often at a later stage) resulting from lytic lesions and/or osteoporosis. In advanced stages, there may be local swelling, weight loss, anemia, bleeding diathesis, and propensity to infections. Renal failure and hyperuricemic syndromes occur due to tubular damage resulting from monoclonal light chain proteinuria. In 90% of cases, serum and/or urinary immunoelectrophoresis shows a spike due to the excess of the monoclonal protein. Congestive heart failure, peripheral neuropathy, and carpal tunnel syndrome may be frequently observed. Erythrocytes sedimentation rate is usually elevated. Elevated serum creatinine and hyperuricemia are rather frequent. Anemia, leukopenia, and thrombocytopenia are seen due to substitution of bone marrow.

Imaging: Radiographic skeletal changes include:

- Diffused osteoporosis (osteopenia), particularly seen in the spine; (2) "punched-out" round lytic areas without associated osteoblastic changes and absence of sclerotic rim; (3) large or massive osteolytic tumors (trabeculated, honeycombed, or even bubbly).

The cortex is thinned or broken, with frequent extension of the tumor in the soft tissues, particularly in ribs and spine. Occurrence of pathologic fractures is frequent. Periosteal reaction is absent.

Rarely (1–2%), PCM generates osteosclerotic lesions. Sclerotic changes are observed in younger patient, generally associated with hypocellular tumors, lower levels of monoclonal proteins, and more elevated serum alkaline phosphatase. It reflects a less aggressive infiltrative process, which allows time for osteoblastic reaction. MRI is the most sensitive to discover diffused and nodular disease in cancellous bone. Isotope bone scan is usually negative or scarcely positive.

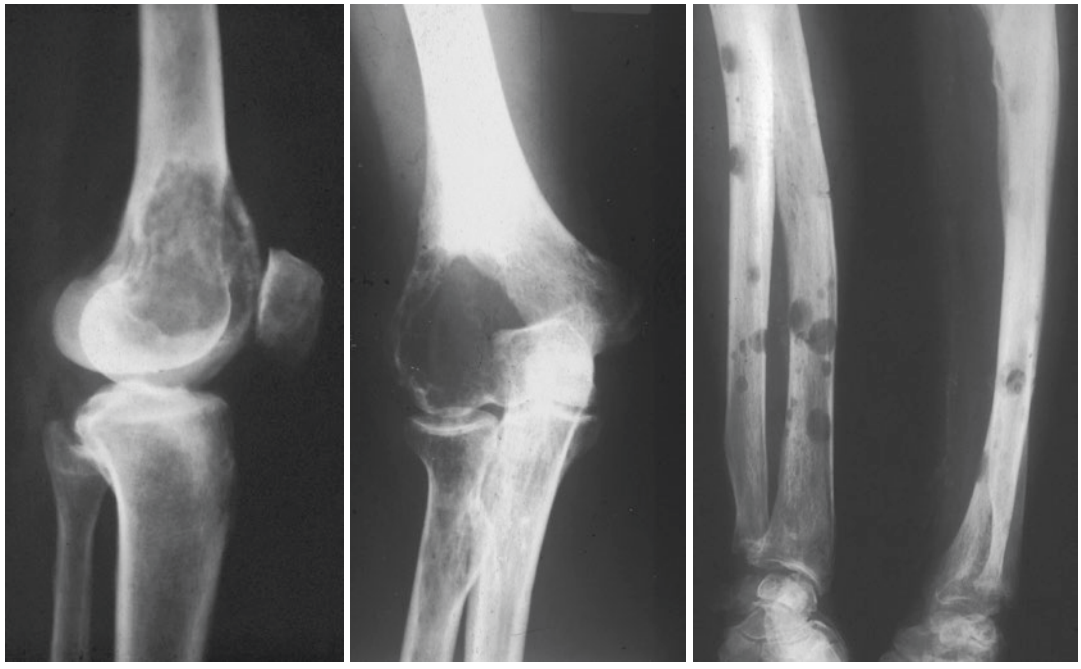
Bone marrow aspiration. If necessary, it should be repeated from multiple sites. It is diagnostic in about 90% of cases. Aspirate smears may contain a different proportion of monoclonal plasma cells that varies from bare increase to >90%.

Histopathology: Macroscopically the tumor appears as a soft, fleshy hemorrhagic tissue that replaces the affected bone marrow. Histologically the tumor is composed of either easily recognizable or highly pleomorphic malignant or blastoid-type plasma cells. The tumor cells may be organized in small clusters, focal nodules or in diffuse sheets into bone marrow. In focal patterns of involvement, foci of interposed normal hematopoiesis were observed, whereas they may be markedly decreased in advanced disease. In differentiated forms, the tumor is composed of mature plasma cells, featuring a round, eccentric nucleus showing a distinctive "cartwheel" chromatin, harbored by basophilic cytoplasm with a perinuclear hof. In contrast, immature forms have a more dispersed nuclear chromatin, a higher nuclear-cytoplasmic ratio, and prominent nucleoli. In almost 10% of cases, the plasmablastic morphology is observed. Pleomorphism is extremely rare. Intracytoplasmatic cherry-red, refractile round bodies, so-called Russell bodies, can be frequently observed. Immunohistochemically, neoplastic cells are strongly positive for CD138 and MUM1. Clonality of neoplastic plasma cells can usually be demonstrated with staining for Ig Kappa and Lambda light chains. On core biopsy, at least 30% of the bone marrow volume should be replaced by monoclonal plasma cells in order to formulate a diagnosis of myeloma. Prominent osteoclastic activity is observed in some cases.

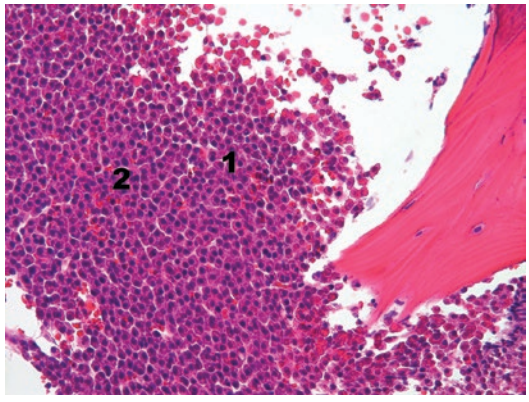
Treatment and Prognosis: Treatment is based on chemotherapy, particularly using alkylating agents (cyclophosphamide, melphalan, nitrosourea BCNU). Molecular targeted therapy with bortezomib is also currently available. Prednisone, thalidomide, and biphosphonates can also be used. In younger patients, allogenic marrow transplantation has been employed. Radiation treatment is used, to relieve pain, decrease spinal cord compression, and prevent pathologic fractures. Surgery may be indicated to decompress the spinal cord or stabilize the spine with internal fixation, to treat or prevent pathologic fractures (internal fixation) and occasionally manage destructive lesions or fractures in the long bones (resection with endoprosthesis). PMC is an incurable progressive disease, with a 5-year survival rate of 30%. Median survival is around 5.5 years. Systemic spread is very frequent, even occurring 8–12 years after the diagnosis. Adverse prognostic factors are the extent of bone involvement and the severity of anemia, hypercalcemia, impaired renal function, circulating monoclonal proteins, hyperuricemia, and alkaline phosphatase.

Key points	
Clinical	Elderly, most common primary malignant bone neoplasm
Radiological	Pure lytic lesion frequently multifocal. Bone scan usually negative
Histological	At least 30% of the bone marrow volume is composed of plasma cells secreting a monoclonal immunoglobulin
Differential diagnosis	Metastasis of carcinoma and melanoma, lymphoma primary of the bone and chronic osteomyelitis

Immunohistochemical panel	
CD138	+
MUM1	+
Kappa	±
Lambda	±



Radiograph. Multiple well-defined purely osteolytic lesions



The bone marrow is entirely constituted of a very thick mat of cells with no intercellular matrix (1). The tumor is composed of sheets of mature plasma cells with oval, eccentric nucleus showing a typical "cartwheel" chromatin (2)

53.1 Solitary Plasmacytoma of Bone

Definition: Solitary plasmacytoma of bone (SPB) is a rare localized tumor consisting of monoclonal plasma cells with no clinical features of PCM. In some cases, flow cytometry identifies minimal (<10%) clonal bone marrow plasma cell. Most often osteolytic lesions are identified in the axial skeleton.

Epidemiology: It is more common in men and median patient age at diagnosis is 55 years.

Imaging: Radiological studies show a localized and often massive homogeneous, trabeculated, or bubbling osteolysis with frequent destruction or inflation of the cortex.

Histopathology: Histologically, plasmacytoma has the same morphology described in PCM. The immunophenotype is also similar to that of PCM.

Treatment and Prognosis: It is based on radiation therapy and/or surgery and sometimes chemotherapy. Two-thirds of cases evolve to PCM, mostly in patients with minimal bone marrow involvement at diagnosis. Median overall survival is about 10 years.

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