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Review

Plasmacytoma (Solitary bone plasmacytoma, extramedullary plasmacytoma)

Sean Rowell, Matthew Ho Zhi Guang, Giada Bianchi, Kenneth C. Anderson

LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, 02115.
smr250@georgetown.edu; matthew_ho@dfci.harvard.edu; giada_bianchi@dfci.harvard.edu; kenneth_anderson@dfci.harvard.edu

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Abstract

Plasmacytoma is a rare hematological malignancy characterized by a discrete, solitary mass of neoplastic monoclonal plasma cells that occurs either (1) inside (solitary bone plasmacytoma - SBP) or outside (extramedullary plasmacytoma - EMP) the bone. Plasmacytoma mainly affects people in the 5th to 6th decade of their lives, and the incidence of the disease is higher in men than in women. It also affects African Americans more often than Caucasians, with the lowest incidence being reported in Asian populations. Unlike MM, plasmacytoma is not a systemic disease and lacks the characteristic CRAB abnormalities such as hypercalcemia, renal failure, anemia, and bone disease, excluding the plasmacytoma itself. The median time to progression of plasmacytoma to MM is 2-3 years, with progression more likely to occur in SBP than EMP. SBP commonly presents in the axial skeleton and mostly manifests as local pain, pathological fractures nerve compression, while EMP is usually seen in the head and neck and typically manifests as space-occupying lesions. Therapeutically, local therapy such as radiotherapy (RT) is the gold standard and is able to achieve long-term disease-free survival in approximately 30% and 65% of patients with SBP and EMP respectively. Surgery (and adjuvant RT), on the other hand, is mostly reserved for easily resectable plasmacytomas.

Keywords
Plasmacytoma, solitary bone plasmacytoma, extramedullary plasmacytoma

Clinics and pathology

Disease

Plasma cell neoplasms can present as single lesions (plasmacytoma) or as multiple lesions in the context of end organ damage (active multiple myeloma (MM)).
Plasmacytoma is a rare, infrequent plasma cell neoplasm that represents approximately 5-10% of all cases of this malignancy (Kilciksiz et al, 2012) and is characterized by the monoclonal proliferation of mature plasma cells that synthesize monoclonal immunoglobulins or free light chains (FLC).
The disease, first described in 1905 by Schridde, exists in two forms known as solitary bone plasmacytoma (SBP) and extramedullary plasmacytoma (EMP) (Chang et al, 2014). SBP originates in the bone marrow, whereas EMP arises out of the bone marrow (Corvo et al). They are further distinguished by the location of their occurrence: SBP mainly presents as a single, typically painful bone lesion mainly occurring in the axial skeleton (83%), in such places as the vertebrae, with the other 17% of cases occurring in the appendicular skeleton, in such places as the pelvic bones.

EMP involves the soft tissue and usually manifests itself in the head and neck region (80% of cases; commonly of respiratory origin), and in the mouth and pharynx (Dores et al, 2009). The symptoms of each vary depending on the site of the malignancy. For SBP, the most common symptom is pain, with motor and sensory deficits occurring if the spine is involved. For EMP, the symptoms are nonspecific and usually secondary to space-occupying lesions (Guo et al, 2013). Plasmacytoma and MM are cytologically and immunophenotypically identical. However, unlike MM, plasmacytoma is not a systemic disease and lacks the characteristic CRAB abnormalities such as hypercalcemia, renal failure, anemia, and bone lesions (with the exception of SBP). Recent studies have shown that there might be small cytogenetic differences as well (Bink et al, 2008).

Phenotype/cell stem origin

Monoclonal proliferation of plasma cells.

Etiology

The etiology of plasmacytoma remains largely unknown. Factors such as viral pathogenesis and irritation from inhaled irritants have been noted. Genetic factors may also play a role; however, no specific loci for the origin of this disease have been identified. (Chang et al, 2014) (Cozen et al, 2006).

Epidemiology

Plasmacytoma generally occurs more frequently in men than in women. Incidence rates anywhere from 2 to 3 times higher in men than in women have been reported (Kilciksiz et al, 2012.) (Corwin et al, 1979.) (Chang et al, 2014).

The role that gender plays in incidence rates is especially prominent in Caucasians (Corvo et al).

Age and race also impact the incidence of plasmacytoma.

The median age of diagnosis is 55-65 years old, and the incidence rate of plasmacytoma is approximately 9 times higher in people over the age of 60 than those under the age of 60, indicating that plasmacytoma is especially prevalent in older populations (Dimopoulos et al, 2000) (Dores et al, 2009).

Also, incidence is approximately 30% higher in African Americans than in Caucasians, and Asians have a 50% decreased lifetime risk of the disease (Dores et al, 2009). An increased risk of the disease amongst family members of patients with SBP/EMP has also been reported (Cozen et al, 2006).

Clinics

Plasmacytoma is a diagnosis of exclusion, as active MM must be ruled out.

The diagnostic criteria for SBP and EMP are as follows (Rajkumar, Lancet Oncology, 2014).

Biopsy proven, single infiltrate of clonal plasma cells in bone (SBP) or soft tissue (EMP).

A bone marrow biopsy showing no evidence of infiltration by clonal plasma cells.

Negative skeletal survey plus MRI/CT spine and pelvis except for the solitary lesion.

Lack of **CRAB**, which would suggest MM.

1. Increased Calcium
2. Renal failure
3. Anemia
4. Bone lesions (with the exception of SBP)

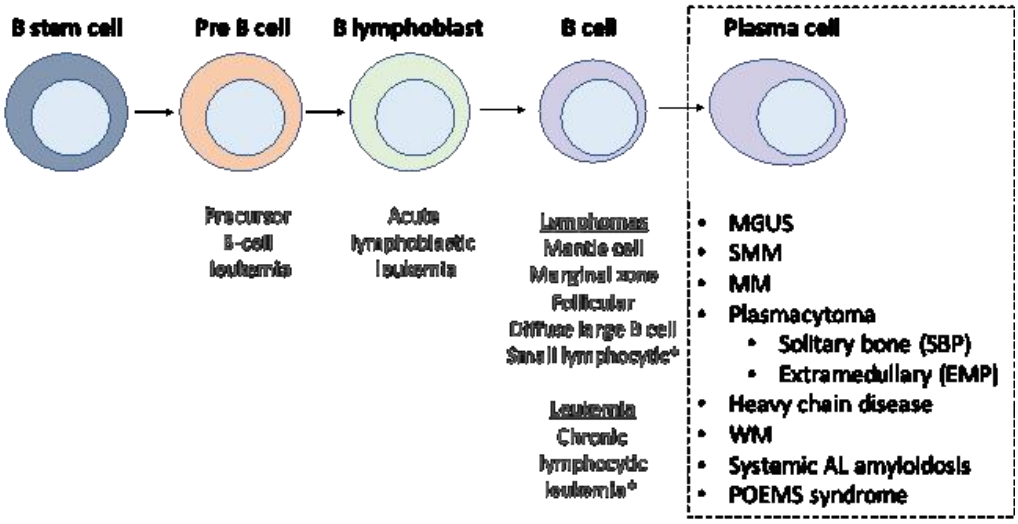

Figure 1: Stem cell origin of plasmacytoma. This figure demonstrates the origin of the monoclonal proliferation of plasma cells that characterizes plasmacytoma and all other plasma cell neoplasms.

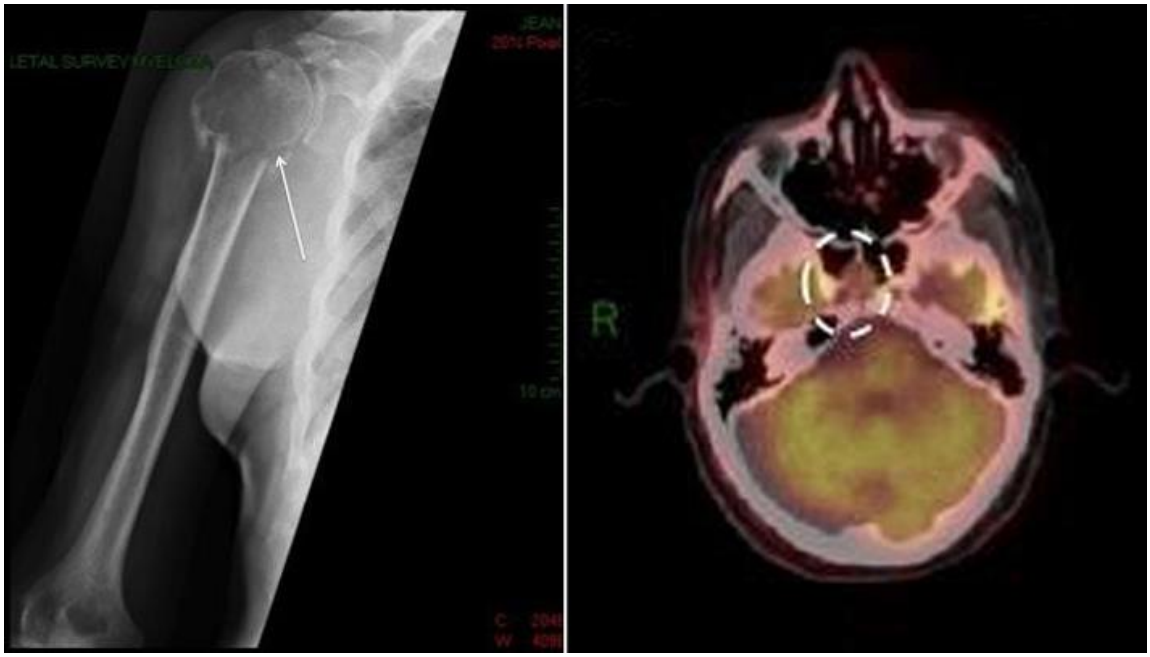

Figure 2: Left: Shoulder X-ray showing solitary bone plasmacytoma located in the right shoulder complicated by pathological fracture of the head of humerus. Right: Positron emission tomography-computed tomography (PET-CT) scan showing a mass occupying the anterior clivus, later identified to be an EMP tumor.

Solitary plasmacytoma carries a risk of transformation in MM of 10% in 3 years. If bone marrow aspirate/biopsy shows less than 10% involvement by clonal plasma cells, then the disease is defined as solitary plasmacytoma with minimal marrow involvement, which carries a 60% (SBP) or 20% (EMP) risk of transformation in MM within 3 years. As space occupying lesions, the symptoms of plasmacytoma vary based on the location of the tumor. Plasmacytomas located in the brain (e.g. solitary craniocerebral plasmacytoma or EMP of the brain) can cause headaches, seizures, and paralysis while plasmacytomas in the rib may cause pain while breathing.

Generally speaking, a common yet nonspecific clinical symptom of SBP is pain. Motor and sensory deficits can also occur, secondary to nerve impingement from compression fractures (Guo et al, 2013). Complications of SBP include pathological fractures due to lytic bone disease. EMP, on the other hand, usually manifests itself in the upper respiratory tract and oral cavity; symptoms often include epistaxis, sore throat, rhinorrhea, and hemoptysis (Chang et al, 2014) (Galieni et al, 2000).

Cytology

Plasmacytoma cells are positive for the extracellular matrix receptor CD138, and negative for CD20, CD3, CD5, BCL-1, and PAX-5 (Feldman et al, 2015). The expression of CD138 is restricted to normal and malignant plasma cells, and is commonly used as a marker for identification and quantification of plasma cells (O'Connell et al, 2004).

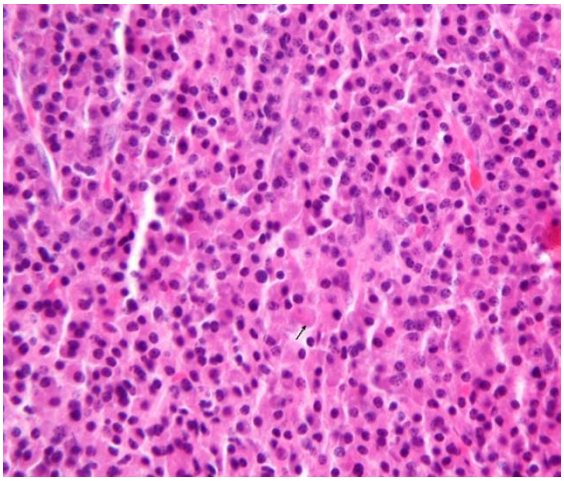

Figure 3: Light microscopy image of a plasmacytoma showing malignant plasma cells and the presence of Mott cells containing intracytoplasmic Russell bodies (eosinophilic staining membrane bound body containing immunoglobulin) (Image taken from https://commons.wikimedia.org/wiki/File:Plasmacytoma1.jpg)

Treatment

Radiotherapy (RT) is generally considered to be the best form of treatment for plasmacytoma. While the most effective dose has been debated in the literature, usually a dose of 40-45 Gray (Gy) is required for the best local control without adverse toxicity (Dimopoulos et al, 2000). However, it has also been reported that there is no dose-response relationship for RT of doses greater than 30 Gy (Knobel et al, 2006). Plasmacytoma is a particularly radiosensitive tumor, and rates of local control in EMP from 90-100% have been reported for this

treatment alone (Galieni et al, 2000) (Chang et al, 2014). Surgical resection has proven to be beneficial in some cases, though surgery alone is usually not recommended as it results in lower rates of local control and higher rates of recurrence (Kilciksiz et al, 2012, 2012). It shows promise in localized tumors that are easily resectable, but is a treatment that is often avoided in cases of EMP, as a result of the majority of tumors being located in the head and neck region with mutilation from surgery being a significant risk (Galieni et al, 2000) (Kilciksiz et al, 2012). Orthopedic surgery for the stabilization or reduction of pathological fractures (e.g. open reduction, internal fixation) or the restoration of vertebral structure (e.g. kyphoplasty) may also be of benefit. The use of chemotherapy for this disease has also been reported, but is usually reserved for cases in which the plasmacytoma has progressed (Corvo et al). Particular promise for chemotherapy is seen in antiangiogenic compounds such as thalidomide. Angiogenesis is highly correlated to progression of plasmacytoma to MM, so compounds such as thalidomide may play an important role in halting this progression (Knobel et al, 2006). Bortezomib has also been reported to stimulate bone formation and could be of benefit in patients with bone disease (Pennisi et al, 2009).

Evolution

There are three patterns of failure in the case of either SBP or EMP. These are:

The development of MM,

The development of a new bone lesion without progression to MM,

A local recurrence.

Of these three, the progression to MM is the most common, with a median time to progression of 2-3 years for SBP with minimal BM involvement (Dimopoulos et al, 2000) (Kilciksiz et al, 2012). While varying rates of progression for SBP and EMP have been reported, the one commonality is that there is a sharp distinction to be drawn between SBP and EMP with minimal BM involvement. SBP progresses to MM at far higher rates than does EMP, with SBP progressing in the range of anywhere from 30-75% of cases, and EMP progressing in the range of 10-35% of cases (Feldman et al, 2015) (Dores et al, 2009.)

Prognosis

The median survival time for plasmacytoma averages 10 years (Dimopoulos et al, 2000). There are a variety of factors that affect the prognosis for this disease, and either shorten or lengthen the survival time. Higher-grade angiogenesis has been shown to lead to a higher rate of progression to MM as well as a shorter progression free survival (Kilciksiz et al, 2012). A major factor in the prognosis of this disease is also which type of plasmacytoma is present in the patient. There is a large body of literature that shows that EMP carries with it a favorable prognosis over SBP (Galieni et al, 2000) (Corwin et al, 1979) and that the overall and median survival rate for EMP is higher than for SBP (Dores et al, 2009). It has been demonstrated that EMP progresses to MM at a much lower rate than SBP. Galieni et al notes that this favorable prognosis might point to EMP having a different origin and biological aspects than MM or even SBP despite the diseases sharing multiple histologic and immunohistochemical similarities. Other factors that affect prognosis are age and size of tumor. People over the age of 60 with plasmacytoma have the least favorable prognosis, whereas those under the age of 40 have the most favorable (Thumallapally et al, 2017), and tumors larger than 5 cm were shown to be an unfavorable prognostic factor (Knobel et al, 2006). Interestingly, one study shows that tumors were larger in the observed SBP group than in the EMP group, pointing to a possible explanation for the higher rates of progression in SBP (Guo et al, 2013). Another study also notes that, while the occurrence of plasmacytoma is higher in men than in women, men have a significantly higher chance of survival. Race, on the other hand, did not affect survival in this study, despite playing a role in the incidence of the disease (Thumallapally et al, 2017).

Cytogenetics

Cytogenetics morphological

Unlike MM, there have only been a few molecular studies done on plasmacytoma specifically. Bink et al. conducted a study of 38 cases of plasmacytoma in an attempt to uncover differences between plasmacytoma and MM, and discovered that while the two diseases are cytogenetically very similar, they differ in the distribution of immunoglobulin heavy locus (IGH) translocation partners, with a notable lack of t(11;14) in EMP. They found that breaks in the 14q32 region were less frequent in EMP than MM, and that EMP completely lacked the t(11;14)(q13;q32) translocation that occurs in 15-25% of MM patients. This translocation leads to a strong overexpression of CCND1 (cyclin D1), so the absence of the translocation in EMP was confirmed by complete negativity for cyclin D1 by immunohistochemistry. An IGH/FGFR3 fusion indicating a t(4;14)(p16;q32) translocation was detected in 6/38 (16%) cases. Bink et al. concludes that this data may point to the t(11;14) translocation being linked to bone marrow involvement, and that EMP and MM are likely more than just different tissue manifestations of the same plasma cell malignancy.

Genes involved and proteins

FGFR3

Location
4p16.3

IGH

Location
14q32

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