

# Multiple Myeloma With Multiple Extramedullary Plasmacytomas

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## Introduction

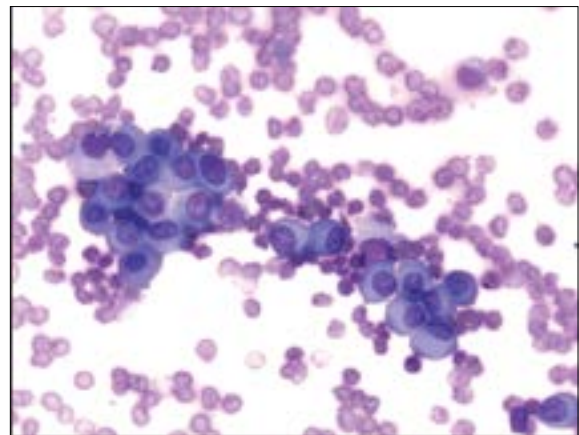
Multiple myeloma (MM) is a neoplastic proliferation of a single clone of plasma cells producing a monoclonal immunoglobulin. Active MM is defined by the presence of an M-protein in the serum or urine, plasma cell infiltration of the bone marrow (at least 10%), and the presence of related tissue or organ impairment. The latter can be remembered by the acronym CRAB: *C* is elevated calcium, *R* is renal insufficiency, *A* is anemia, and *B* is bone lesions. It is estimated that in 2011 there will be 20,520 new cases of MM and 10,610 deaths. MM accounts for 1% of cancers and 10% of hematologic malignancies.<sup>1</sup> The etiology is unknown, though exposure to radiation, benzene, and other organic solvents may be involved. Chronic inflammatory diseases may also play a role, as plasma cell dyscrasias with prolonged stimulation of the reticuloendothelial system have been noted. This disease is highly treatable but rarely curable. It is well known that solid plasmacytomas of the bone and soft tissues can be the initial presentation in patients. Solitary plasmacytoma of the bone (SBP) will often evolve into systemic MM with time; however, plasmacytoma of the soft tissues, oropharynx, and other non-osseous presentations less often evolve into systemic MM. Our patient is an extraordinary example of multiple plasmacytomas occurring as the terminal phase of disease.

## Case Report

The patient is a 68-year-old retired teacher with a medical history of hypertension, osteoarthritis, osteoporosis, and glaucoma. She presented to the hematology clinic in May 1999 for a workup of a monoclonal gammopathy. She was found to have immunoglobulin (Ig)A lambda MM.

Her bone marrow examination was normocellular with 20% plasma cells; serum creatinine, albumin, calcium, and hemoglobin were normal, and no lytic lesions were seen on skeletal survey.

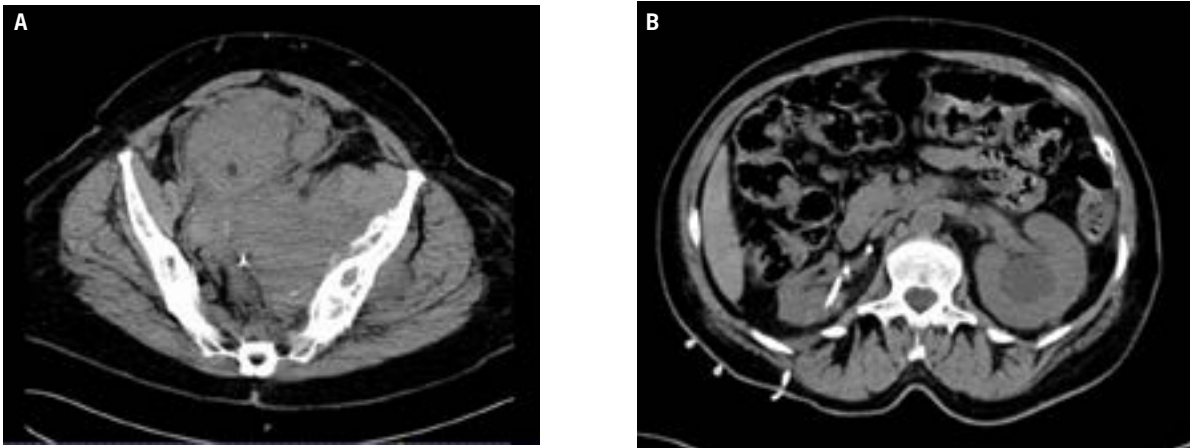
She was initially observed, and had stable smoldering myeloma for many years. In 2003, she required treatment secondary to anemia, and was started on zoledronic acid, epoetin alfa, and pulse steroids. Ten months later the disease progressed, and she was treated with bortezomib (Velcade, Millennium Pharmaceuticals), which was intermittently administered until April 2006. Bone marrow biopsy in April 2006 showed 87% plasma cells (Figure 1). The patient initially declined further treatment with lenalidomide (Revlimid, Celgene). However, she developed renal insufficiency and symptomatic anemia in February 2007, thus melphalan and prednisone were started and stopped in August 2007 secondary to side effects. Zoledronic acid was discontinued in October 2007 secondary to a tooth extraction that was complicated by osteonecrosis of the jaw. Bortezomib was



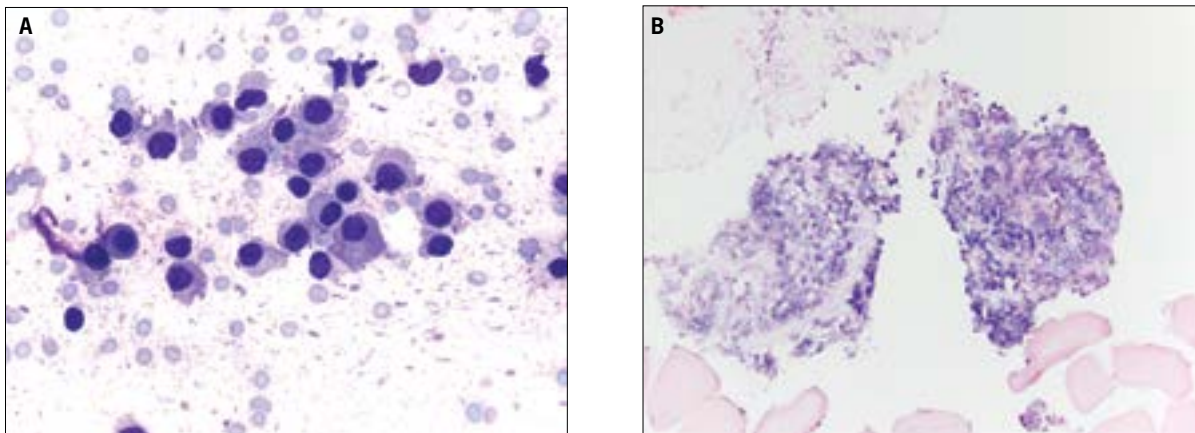
**Figure 1.** Bone marrow aspirate done in April 2006 showing 87% plasma cells.

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**Figure 2.** (A) Computed tomography image of the abdomen showing a complex cystic structure in the pelvis. (B) Computed tomography image of the abdomen displaying hydronephrosis.

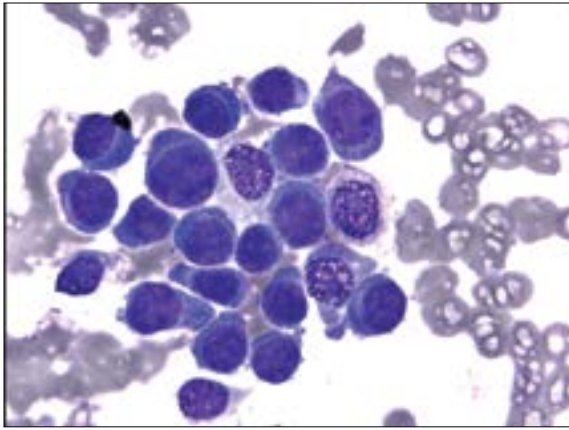


**Figure 3.** (A) Fine needle aspirate of iliac bone lesion. Dif-Quik stain showing plasma cells. (B) In situ hybridization for lambda light chain of the cell block was positive.

restarted in January 2008 and given until March 2008. The patient did well throughout the treatments and was very functional.

In April 2008, the patient was seen in the clinic and found to be in acute renal failure. Renal ultrasonography revealed bilateral hydronephrosis and a complex cystic structure in the pelvis. Computed tomography (CT) showed a large, left-sided pelvic mass measuring  $9.9 \times 6.7$  cm in diameter, involving the left iliac bone (Figure 2). Bilateral urethral stents were placed to relieve the obstruction, and a biopsy of the iliac bone mass was consistent with plasmacytoma (Figure 3). The plasmacytoma was irradiated, but despite the stents and radiation therapy, the patient's renal function did not improve and she was placed on hemodialysis.

In June 2008, she presented to the hematology clinic for routine follow-up. On review of systems, it was noted that she was having syncopal episodes during hemodialysis. On exam, she was found to have a large right neck mass, a large left upper quadrant mass, and multiple subcutaneous nodules. CT showed a large enhancing soft tissue mass, which appeared to arise in the subcutaneous tissues of the neck, extending to the sternocleidomastoid muscle. Multiple enlarged lymph nodes were observed, as well as bilateral pleural effusions and innumerable masses and nodules in the chest, abdomen, and pelvis. Fine needle aspiration of a subcutaneous nodule and the right neck mass showed plasmacytoma (Figure 4). The patient was treated palliatively with cyclophosphamide and steroids. One month later, she presented to the hos-



**Figure 4.** Subcutaneous skin nodule fine needle aspirate. Diff-Quik stain shows plasma cells. When compared to the bone marrow aspirate (Figure 1), these cells are more immature with less cytoplasm; a few cells may be plasmablasts, but they are not anaplastic.

pital with worsening dyspnea on exertion, and was found to have progressive disease with enlarging plasmacytomas and pleural effusions. Thoracentesis revealed a malignant effusion containing plasma cells. The patient passed away soon thereafter.

## Discussion

MM has been linked to plasmacytomas, though the vast majority of plasmacytomas have been solitary, presenting as an initial event. It was previously believed that the solitary plasmacytoma of the bone, extramedullary plasmacytoma, and MM were different manifestations of the same process. Most extra-osseous solitary plasmacytomas are now thought to be marginal zone lymphomas with extensive plasmacytic differentiation. Wiltshaw classified soft tissue plasmacytoma into 3 clinical stages: (I) limited to an extramedullary site, (II) involvement to regional lymph nodes, and (III) multiple metastasis.<sup>2</sup> A thorough review of PubMed and Ovid found 9 papers describing 62 patients from 1965 to the present—similar to our patient—with multiple extramedullary plasmacytomas as the terminal event of their MM.<sup>3-12</sup>

Requena looked at 40 patients similar to our patient. The type of monoclonal immunoglobulin produced by the neoplastic plasma cells in the skin was determined in 39 patients: 18 had IgA (5 kappa, 13 lambda), 19 had IgG (15 kappa, 4 lambda), and 2 had IgD lambda MM.<sup>9</sup> Although not seen in our patient, it has been noted in several reports that patients who present with multiple plasmacytomas often have a reduced immunoglobulin level when compared with the original levels. This may be due to selection of a very immature, dedifferentiated clone that is incapable of adequately secreting immunoglobulin.<sup>11</sup> Sanal and colleagues believe that this acquisition of a new malignant phenotype during the clinical course suggests that the malignant clone in MM is not derived from a terminally differentiated B cell, but from a B-cell precursor that shows a continuous clonal evolution.<sup>10</sup>

Due to the rarity of multiple plasmacytoma metastases, no specific treatment plan has been defined. This is always a terminal event, with poor prognosis and minimal response to treatment.

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# Review

## Plasma Cell Myeloma With Multiple Plasmacytomas

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### Plasma Cell Myeloma With Multiple Plasmacytomas

Solitary bone plasmacytomas (SBP) are defined as a single area of bone destruction due to clonal plasma cells without bone marrow clonal plasmacytosis or related organ or tissue impairment (ROTI). Solitary extramedullary plasmacytomas (EMP) consist of clonal plasma cells of any organ without bone marrow plasmacytosis or ROTI. Multiple plasmacytomas involve more than one localized area of bone destruction or extramedullary tumor of clonal plasma cells without bone marrow plasmacytosis or ROTI.<sup>1</sup> SBP and EMP can evolve into plasma cell myeloma (PCM) in more than 75% and less than 30% of cases, respectively.<sup>2</sup> In the Surveillance, Epidemiology and End Results (SEER) program (1992–2004), the incidence of PCM was 16-fold higher than solitary plasmacytomas, and the incidence of SBP was 40% higher than solitary EMP.<sup>3</sup> EMP are variably defined in the published literature, with some studies considering plasmacytomas and PCM in combination or plasmacytomas also extending from bone as EMP, making it difficult to determine the true incidence. In addition, variable use of screening studies such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) makes it difficult to know whether there is a true change in the incidence of EMP over time.

### Incidence of Extramedullary Plasmacytomas in Plasma Cell Myeloma

In 2 recent studies, 68% and 85% of cases of EMP seen at diagnosis of PCM consisted of soft tissue masses extending from bone lesions, with 32% and 15% of cases due to hematogenous spread to the organs.<sup>4,5</sup> Extramedullary plasmacytomas are rare at diagnosis of PCM. In 1,027 patients with new onset PCM, only 4 patients (0.4%)

presented with EMP.<sup>6</sup> Using a strict definition of EMP (not arising from a bone lesion), the incidence of EMP at diagnosis of PCM was found to be 2%, and the rate of EMP in the first 3 years after diagnosis of PCM was 3%, occurring at a median of 48 months (range 16–183 months).<sup>7</sup> The incidence of treatment-emergent EMP was 7.5% during the course of PCM after a median of 6 prior lines of chemotherapy (range 1–12) consisting of immunomodulatory drugs (IMiDs) in all patients and bortezomib (Velcade, Millennium Pharmaceuticals) in 78% of patients. Treatment-emergent EMP occurred at a median of 28 months (range 7–119 months) after start of therapy for PCM.<sup>7</sup> Using a broader definition of EMP as soft tissue masses extending from bone or from hematogenous spread, other series have found the incidence of EMP at diagnosis of PCM to be 15–20%, with an additional 15% occurring during the course of PCM indicative of relapsed or refractory PCM.<sup>8,9</sup>

### Prognosis

In the SEER analysis, older age beyond 60 years significantly reduced overall survival of PCM, BP, and EMP, but overall survival was superior for solitary plasmacytomas compared to PCM.<sup>3</sup> SBP of the axial or appendicular skeleton had a similar 5-year survival, 65% and 59%, respectively.<sup>3</sup> The 5-year survival rates of solitary EMP were 92%, 98%, and 48% with skin, lymph node, or central nervous system involvement, respectively.<sup>3</sup> This may be due to differences in disease biology of the plasma cells according to the primary site. Hematogenous spread of PCM can be to any organ, including the skin, lung, or liver. Risk factors for development of EMP in PCM are younger age, male gender, Bence Jones PCM, lambda light chain, extensive skeletal involvement, nonsecretory PCM, or advanced stage.<sup>4,5</sup> Gastrointestinal tract presentation is rarely reported in the published literature (5%), as is myelomatous pleural effusion (6%) or pleural involvement (0.8%).<sup>10,11</sup> A myelomatous pleural effusion has been associated with a survival of less than 4 months.<sup>12</sup> In the severe combined immunodeficiency (SCID)-human chimeric animal model, injection of plasma cells from patients with EMP into fetal bone grafts also results in growth into soft tissues.<sup>13</sup>

Autologous hematopoietic cell transplantation (HCT) is an established therapy in PCM, with improved event-free survival and overall survival compared to chemotherapy alone.<sup>14</sup> Relapse after autologous HCT was in the form of EMP in 14% of cases in a Spanish registry study.<sup>15</sup> Plasmacytoma relapses (both bone and extramedullary) can occur after autologous HCT for PCM without evidence of systemic progression.<sup>16</sup> It is unknown if high-

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dose chemotherapy and autologous HCT increase the risk of EMP due to the selection of more resistant clones with altered homing.

### Imaging Techniques to Diagnose Extramedullary Plasmacytomas

Use of CT and MRI has increased the detection of EMP in PCM. The incidence of EMP increased during the 2000–2007 time period compared to the 1971–1993 and 1994–1999 time periods both at diagnosis and follow-up of 1,003 PCM patients.<sup>7</sup> EMP at diagnosis of PCM was associated with a shorter progression-free survival (18 vs 30 months;  $P=.003$ ) but not overall survival compared to PCM without EMP at diagnosis. Development of EMP during the course of PCM was associated with a significant reduction in both progression-free and overall survival.<sup>5</sup> Uptake of <sup>18</sup>F-fluorodeoxyglucose (FDG) by plasma cells correlates with the metabolic activity of PCM.<sup>17</sup> PET scan provides not only morphologic assessment but also functional assessment of PCM, and differentiates treated lesions versus active tumor, whereas CT and MRI provide mainly morphologic assessments. The mean values of the maximum standardized uptake value ( $SUV_{max}$ ) in EMP lesions were higher in stage III than in stage I or II PCM (6.23 vs 2.85;  $P=.023$ ). The 5-year overall survival rate was 61% for those with FDG-avid EMP lesions by PET compared to 100% in those with any FDG-avid lesions.<sup>17</sup> The  $SUV_{max}$  of EMP lesions with the highest FDG avidity showed a significant correlation with overall survival. However, FDG avidity of bone marrow or bone marrow involvement detected by MRI had no association with overall survival. A multivariate analysis of age, creatinine level, International Staging System, and Durie-Salmon stage showed only the  $SUV_{max}$  of extramedullary plasmacytoma lesions to independently predict overall survival.<sup>17</sup> Since early detection of EMP lesions may lead to better survival, the International Myeloma Working Group has recommended the use of PET/CT scans at diagnosis and follow-up of PCM as an added modality.<sup>18</sup>

### Therapy

Although IMiDs and bortezomib are of proven efficacy in PCM, their use in EMP with or without PCM is based on case reports. Some case reports show the anti-angiogenic agent thalidomide (Thalomid, Celgene) to be ineffective in EMP compared to PCM perhaps due to differences in the microvasculature of these 2 entities or due to inherent resistance. Despite serologic response to thalidomide, progression of EMP was seen in 4 PCM patients.<sup>9</sup> Tha-

lidomide and dexamethasone had synergistic action in resolving EMP in a PCM presenting as a myelomatous pleural effusion despite resistance to both drugs given as single agents.<sup>19</sup> In a study of 13 PCM patients with EMP receiving pomalidomide 2–4 mg/day and low-dose dexamethasone 40 mg/week, complete response was achieved in 2 patients, including resolution of EMP, and 2 patients had partial response with more than 50% reduction in the size of EMP, for an overall response rate of 31%.<sup>7</sup> Overall survival for those PCM patients with EMP in this study was significantly shorter (median, 16 months vs not yet reached;  $P=.002$ ) compared to those without EMP.<sup>7</sup> Half of these patients were diagnosed with EMP by imaging alone.<sup>7</sup>

There are case reports of selected patients with plasmacytomas (bone and extramedullary) without PCM benefiting from autologous HCT, in particular those with large plasmacytomas greater than 5 cm or with rapid relapse after first-line therapy.<sup>20</sup> There are no data that suggest autologous HCT prevents plasmacytomas from evolving into PCM, and so further study is needed. PCM evolving from prior plasmacytomas have a similar outcome to high-dose chemotherapy and autologous HCT to PCM without an antecedent plasmacytoma diagnosis.<sup>21</sup> There are few data on the role of autologous HCT in PCM associated with EMP, perhaps due to the overall poor prognosis of this presentation, but this should be the subject of further study.

### Conclusions

This case report by Nangia and colleagues highlights the development of treatment-emergent EMP presenting as a myelomatous pleural effusion and renal failure from an obstructive pelvic mass after bortezomib therapy in PCM.<sup>22</sup> Therapy with thalidomide and dexamethasone can be used in the setting of renal failure and has been shown to be effective in case reports of extramedullary plasmacytomas.<sup>19,23</sup> It is unknown if the use of novel agents such as IMiDs or bortezomib for PCM or high-dose chemotherapy and autologous HCT increase the risk for development of EMP due to the selection of more resistant clones with altered homing. This emphasizes the need for longer follow-up with the novel agents and autologous HCT to understand their full impact on outcomes of PCM despite their efficacy in PCM. Whether EMP is associated with adverse cytogenetics or a poor prognosis gene expression signature that is different from those associated with bone marrow plasmacytosis, and whether these cytogenetic and gene expression signature abnormalities affect outcomes is unknown and requires further study.

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