

# Plasma Cell Myeloma: Literature Review and Case Study

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## LEARNING OBJECTIVES

1. Explain the pathophysiology of multiple myeloma.
2. Outline the different subsets of presentation.
3. Correlate the immunophenotype with the clinical and genetic aspects of myeloma.
4. List the results of the laboratory tests routinely evaluated in multiple myeloma.

**ABBREVIATIONS:** PCM – plasma cell myeloma, PC – plasma cell, PB – peripheral blood, BM – bone marrow, NCAM - neural cell adhesion mutation, VDC – cyclophosphamide, dexamethazone, bortezomib

**INDEX TERMS:** Plasma cell Myeloma, Immuno-electrophoresis, Myeloma subtypes

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## Introduction

Plasma cell myeloma (multiple myeloma, myelomatosis, medullary plasmacytosis, Kahler's disease) is a B-cell neoplasm resulting from the expansion of a single clone of plasma cells (PC). The PCs synthesize a monoclonal immunoglobulin (paraprotein), a monoclonal immunoglobulin light chain (Bence-Jones protein) or both.<sup>1</sup> The Bence-Jones proteins may lead to renal failure and the paraproteins can lead to peripheral blood (PB) hyperviscosity.<sup>2</sup> Plasma cell myeloma (PCM) is clinically heterogeneous and may present with no symptoms or as an extremely aggressive disease.<sup>3</sup> PCM is usually confined to the bone marrow (BM), with extramedullary involvement seen only in end stage

cases.<sup>4,5</sup>

## Epidemiology and Etiologies

PCM constitutes 10-15% of all hematologic malignancies and 1% of all malignancies.<sup>6,7,8</sup> PCM incidence increases with age with 40% of patients presenting under 60 years and only 2% occurring under the age of 40. The median age at diagnosis is 70. Incidence is greater in men than women (1.4:1), and occurs twice as frequently in African Americans than in Caucasians. The risk of PCM increases by 3.7 fold for individuals with a first degree relative with the disease.<sup>9,10</sup> In 2007 approximately 20,000 new cases were diagnosed and 11,000 patients died from the disease.<sup>11,12</sup>

## Clinical Features/Diagnostic Criteria

The patients usually present with bone pain and pathologic fractures (due to lytic bone lesions). Anemia (due to bone marrow replacement of clonal PCs), recurrent infections (decreased normal immunoglobulin levels), and renal failure (Bence Jones deposition in kidneys) are common findings. Other clinical findings include hyperviscosity syndrome, hypercalcemia (increased osteoclastic activity), and epidural masses causing spinal cord compression.<sup>13</sup>

The 2008 World Health Organization (WHO) revision to the classification for lymphoproliferative disorders states three diagnostic criteria for PCM. Symptomatic PCM in a patient is defined by the incidence of an M-protein in the serum or urine, the demonstration of clonal bone marrow PCs or plasmacytoma and the presence of end-organ damage (CRAB: hypercalcemia, renal insufficiency, anemia, bone lesions). A specific level of serum or urine M-protein is not defined. However, the M-protein in most cases is >30g/L of IgG or >25g/L of IgA or >1g/24 hour of urine light chain. The monoclonal bone marrow PCs usually exceed 10% of all nucleated cells in the marrow but a minimal level is not defined as approximately 5% of patients with

symptomatic PCM have fewer than 10% PCs.<sup>14</sup> Clinical and laboratory features are summarized in Table 1.<sup>15</sup>

**Table 1.** Clinical and laboratory findings in PCM

Laboratory Features	% patients*
Anemia (Hemoglobin <12g/dL)	72
Bone lesions (lytic lesions, pathologic fractures, severe osteopenia)	80
Renal failure (serum creatinine >2mg/100ml)	19
Hypercalcemia (>11mg/100ml)	13
Monoclonal protein on serum protein electrophoresis	82
Monoclonal protein on serum protein immunofixation	93
Monoclonal protein on serum plus urine protein immunofixation†	97
Increased >10% clonal BM plasma cells	96
Type of M-protein	
IgG	52
IgA	21
Light chain only	16

\* proportion of patients with laboratory finding

† or serum immunofixation plus serum free light chain assay

### Clinical Variants

#### *Monoclonal gammopathy of unknown significance (MGUS)*

MGUS is a common condition, occurring in 3% of individuals over 50 years of age and 5% of individuals over the age of 70.<sup>16,17</sup> There are no clinical features and the diagnosis is usually made incidentally when a serum protein electrophoresis is performed on an asymptomatic patient.<sup>18</sup> The 2008 WHO revised classification defines MGUS as the presence of a serum M-protein <30g/L and the identification of <10% monoclonal BM PCs but with no end-organ damage and no evidence of a B-cell lymphoma or other condition known to cause an M-protein. The monoclonal PCs rarely exceed 10%; the median is 3%. In MGUS the monoclonal plasma cells usually co-exist with reactive polyclonal plasma cells in the BM, making the flow cytometric analysis challenging.<sup>19,20</sup> MGUS is not considered neoplastic as it does not always progress to overt malignancy. The presence of a small IgM paraprotein (IgM MGUS) may be associated with a clone of lymphoplasmacytic cells that may progress to a lymphocytic lymphoma or Waldenstrom macroglobulinemia. Conversely a small IgG or IgA paraprotein may progress to a malignant plasma cell disease.<sup>21</sup> One study of over 1300 MGUS patients showed the rate of progression to multiple myeloma or other related neoplasms was 12% by 10 years, 25% by 20 years and

35% at 25 years.<sup>22</sup>

#### *Asymptomatic (smoldering) plasma cell myeloma*

In asymptomatic PCM the characteristic serum or urine M-protein, and clonal BM PCs or plasmacytoma are present but there is no related organ or tissue impairment. By definition, the serum level of M-protein must exceed 30g/L and/or  $\geq 10\%$  monoclonal PC must be identified in the bone marrow.<sup>23,24</sup> Asymptomatic PCM is quite similar to MGUS clinically, but is much more likely to progress to symptomatic PCM. Approximately 8% of all myeloma patients initially present with no symptoms.<sup>25</sup>

#### *Non-secretory myeloma*

In 1-3% of PCM cases an M-protein is not detected. Cytoplasmic M-protein is present in 85% of these cases, suggesting impairment of secretion. Of interest, in 66% of cases, elevated serum free light chains are detectable. The clinical features of non-secretory myeloma are similar to other plasma cell myelomas except for a lower incidence of renal insufficiency and hypercalcemia, and less depression of normal immunoglobulin.<sup>26</sup>

#### *Plasma cell leukemia (PCL)*

By WHO guidelines, for PCL, the number of clonal PB plasma cells exceeds  $2 \times 10^9/L$  or is 20% of all PB white blood cells.<sup>27</sup> PCL represent approximately 2% of plasma cell neoplasms.<sup>28</sup> Primary PCL represents initial presentation of disease and constitutes less than 5% of newly diagnosed cases of myeloma. Secondary PCL is peripheralized myeloma at the terminal stage of disease as a result of excessive tumor growth and proliferation.<sup>29</sup> Unlike PCM, most PCL neoplastic PCs are negative for CD56.<sup>30</sup> Of interest CD56 (NCAM) normally functions to anchor plasma cells to the bone marrow stroma, therefore lack of CD56 may explain why these plasma cells escape to the PB.<sup>31,32</sup>

### Morphology

#### *Peripheral blood*

Clonal plasma cells are rarely seen in the PB, except for cases of plasma cell leukemia.<sup>33</sup> However, the PB smear classically shows marked rouleaux formation and increased background staining (bluish tinge), due to the presence of the paraprotein.<sup>34</sup>

#### *Bone marrow biopsy*

The bone marrow biopsy is valuable to assess the extent

and pattern of plasma cell infiltration.<sup>35</sup> Normal plasma cells are found in small clusters around bone marrow arterioles, but myeloma cells occur in interstitial clusters, focal nodules, or diffuse sheets. With interstitial or focal involvement, oftentimes there is sparing and preservation of normal hematopoiesis. However, with diffuse involvement normal hematopoiesis may be almost completely suppressed. There is usually a progression from interstitial/focal to diffuse involvement as the disease advances. As a rule, when 30% of the marrow is replaced by plasma cells, the diagnosis of myeloma is likely.<sup>36</sup> There is often increased osteoclastic activity which results in the lytic bone lesions and hypercalcemia observed in these patients.<sup>37,38</sup> Increased microvascular density and angiogenesis are also observed in the biopsy specimens.<sup>39</sup> Immunohistochemical stains are routinely performed on bone marrow biopsies. CD138 is useful for quantifying the number of plasma cells present, while stains for kappa and lambda light chains will identify the clonal nature of the myeloma cells.<sup>40</sup>

*Bone marrow aspirate*

Plasma cell enumeration is generally based on a 500 cell differential count on Wright stained bone marrow aspirate smears. This may become difficult if the plasma cell infiltration is patchy or associated with fibrosis. Additionally the high background protein in these specimens may sometimes obscure the morphology. The number of plasma cell is variable from just barely increased (>4 % of all marrow nucleated cells) to upwards of 90%. Morphology ranges from small mature plasma cells that are indistinguishable from normal, to immature, plasmablastic, pleomorphic and bizarre forms. Dysynchronous nuclear to cytoplasmic maturation, high nuclear to cytoplasmic ratio and prominent nucleoli are characteristics of immaturity. Multinucleated and polylobated forms (evidence of anaplasia) are prominent in some cases. These morphologic changes rarely occur in normal plasma cells; therefore they are reliable indicators of neoplastic plasma cells. The cytoplasm of myeloma cells is enriched with increased endoplasmic reticulum, which often contains condensed or crystallized Ig. This immunoglobulin gives rise to a number of distinct inclusion bodies and descriptive terms such as:

- Mott/Morular cells: contain multiple pale bluish-white, grape-like accumulations of Ig
- Russell bodies: plasma cells containing round,

cherry red refractive bodies

- Flame cells: glycogen rich IgA plasma cells staining vermilion
- Thesaurocytes: gaucher-like plasma cells with overstuffed fibrils
- Crystalline rods: plasma cells containing needle-like crystallized Ig
- Dutcher bodies: plasma cells containing nuclear immunoglobulin inclusions

Of interest, normal or reactive plasma cells may have the morphology of Mott cells, Flame cells, Theaurocytes or contain Russell bodies, but only neoplastic myeloma cells will demonstrate the nuclear Dutcher bodies or contain crystallized Ig.<sup>41-43</sup>

**Immunophenotyping by Flow Cytometry**

Flow cytometric analysis is not only useful to demonstrate the monoclonal nature of the plasma cells, but is also a valuable tool to detect aberrant marker expression, and to identify prognostic markers. Although malignant plasma cells represent the end-stage of B-cell differentiation, they are typically negative for the pan B-cell markers CD19, CD20 and CD22. Myeloma cells from a minority of patients retain CD19 or CD20 (2.5% and 14% of cases respectively) but never both.<sup>44</sup> Plasma cells characteristically express monotypic cytoplasmic kappa or lambda light chain restriction; the surface light chains are negative. The monotypic heavy chain is usually IgG while IgA is positive in fewer cases.<sup>45</sup> Both normal and malignant plasma cells express both CD38 and CD138; however, myeloma cells express higher levels of CD138 and lower levels of CD38 than do normal polyclonal plasma cells. CD56 (neural cell adhesion molecule), normally a marker for natural killer lymphocytes, is aberrantly expressed in 67-79% of cases of PCM.<sup>46-48</sup> Other aberrantly expressed markers include CD117, CD20, CD10 and the myeloid markers CD13 and CD33. The lack of CD56 expression is associated with a poorer outcome, whereas the expression of CD117 is associated with a more favorable outcome. Of interest patients with CD56 negative phenotype have fewer, if any osteolytic lesions. CD45, the leukocyte common antigen broadly expressed on hematopoietic cells, is consistently weak or negative on malignant PCs, but brightly expressed by proliferating or reactive PCs. CD45 negative patients have a poor survival prognosis when compared to CD45 positive patients. This may be due to the fact that CD45 down-regulation is associated

with increased maturation and proliferation arrest.<sup>49-52</sup>

**Genetics**

Conventional cytogenetic analysis only detects numerical or structural abnormalities in 30-40% of newly diagnosed myeloma cases, most likely due to the low rate of proliferation of these cells.<sup>53-56</sup> Additionally, as mentioned previously, the number of plasma cells present in a bone marrow sample is highly variable ranging from < 2% up to 100%. Therefore, it is critical to restrict the analysis to the myeloma cells (eliminating normal myeloid elements) which is done by cell purification (CD138 magnetic beads) or co-labeling immunofluorescent in order to positively identify the myeloma cells.<sup>57,58</sup> Modern molecular techniques, such as comparative genomic hybridization (CGH) and fluorescence *in situ* hybridization (FISH), allow the detection of genetic abnormalities independent of proliferating cells and with positive identification of lesional myeloma cells. These modern methods detect chromosomal abnormalities in almost all patients with PCM and MGUS.<sup>59-62</sup>

There are two well documented cytogenetic pathways that contribute to the pathogenesis of PCM. Nonhyperdiploid (chromosome number is less than or equal to 46/47; hypodiploid and pseudohypodiploid, respectively)<sup>63</sup> tumors have a high incidence of IgH gene rearrangement (heavy chain locus found on chromosome 14q32) translocations, involving five recurrent partners [11q13, 6p21, 4p16, 16q23, and 20q11) and a high frequency of chromosome 13/13q14 loss. Conventionally these IgH associated translocations have been associated with the dysregulation of specific genes, namely *cyclin D1*, *MUM1*, *FGFR3*, *c-maf* and *MAFB* respectively. Inasmuch as the IgH locus is transcriptionally active in B-cells, transfer of an oncogene to this region results in upregulation of these genes.<sup>64-67</sup> Overall, IgH translocations are considered an early immortalizing event which confers survival and proliferative advantage for the tumor clone.<sup>68</sup> These translocations involving the heavy chain locus are found in 55-70% of tumors and are generally considered to be indicators of a poor prognosis; t(11;14) is the only translocation associated with a favorable prognosis.<sup>69-72</sup>

There are four main secondary chromosomal aberrations reported in PCM that are associated with disease progression. These include *MYC* translocations,

deletion of chromosome 13, deletion or amplification of chromosome 1, and deletion of chromosome 17p13.<sup>73,74</sup> Hyperdiploid tumors (chromosome number is between 48 and 74)<sup>75</sup> are more often associated with multiple trisomies involving chromosomes 3, 5, 7,11,15,19, and 21.<sup>76-78</sup> This karyotype confers advantage to the clone through other mechanisms such as chromosomal duplication. The hyperdiploid PCMs do not generally show the IgH translocations.<sup>79</sup>

**Prognosis/Treatment**

The median survival of myeloma patients is three years. The median survival is related to the stage of disease. Features of a more aggressive clinical course and worse prognosis include anemia, renal failure, increased  $\beta_2$ -microglobulin, increased lactate dehydrogenase, increased C-reactive protein, high plasma cell labeling index, high Ki-67 labeling index, and low serum albumin. Additionally, hypodiploidy, t(4;14), t(14;16), 13q14 on conventional cytogenetic analysis and 17p13 by FISH are consistent with a worse prognosis. Morphologic features predicting poor outcome are plasmablastic morphology and increased microvascular density in the bone marrow. Greater than 10% circulating plasma cells is considered an adverse indicator, reflecting an increased tumor burden.<sup>80-82</sup>

Survival is related to the stage of the disease. The Durie Salmon staging system (which essentially measures the tumor burden) stratifies patients into three risk groups. (Table 2). Reported in 2007, the median survival is approximately 6.5 years for Stage 1, 5 years for stage 2, and 2 years for stage 3.<sup>83</sup>

Table 2. Durie-Salmon staging system

Stage 1: Low myeloma cell mass	Stage 2: Intermediate myeloma cell mass	Stage 3: High myeloma cell mass
<b>All criteria must be met</b>	<b>Neither stage 1 nor stage 3</b>	<b>One or more needed criteria</b>
Hemoglobin > 10.0g/dL		Hemoglobin < 8.5g/dL
Normal serum calcium		Serum calcium >12mg/dL
Normal bone x-ray or single bone plasmacytoma		Multiple lytic bone lesions
Small amounts of monoclonal Ig		Large amounts of monoclonal Ig
IgG <50g/L		IgG >70g/L
IgA<30g/L		IgA>50g/L
Urine light chain<4g/24hr		Urine light chain>12g/24hr

Historically, the combination vincristine-doxorubicin-dexamethasone (VAD) was the standard induction treatment for PCM for patients eligible for autologous stem cell transplantation (ASCT). The regimen was VAD for 4-6 cycles prior to transplant, leading to a partial response rate ranging from 52-63% with a 3-13% complete response rate. The availability of new drugs such as thalidomide, lenalidomide, and bortezomib, has dramatically changed the treatment of this disease. After determining a patient's autologous bone marrow transplantation eligibility, the first step is high dose induction therapy to induce remission. For transplant eligible individuals this chemotherapy involves treatment with immunomodulatory drugs, proteasome inhibitors and the steroid dexamethasone. The immunomodulatory drugs thalidomide, lenalidomide and pomalidomide have antiproliferative activity against hematopoietic tumors and patient cells. Additionally, they cause increased inhibition of tumor necrosis factor secretion from activated monocytes, and increased activation of T-cells and natural killer cells.<sup>84</sup> The proteasome inhibitors bortezomib and carfilzomib protect proteins that inhibit cell division.<sup>85</sup>

Despite the efficacy of high dose chemotherapy with stem cell transplantation as well as recent progress with aforementioned novel treatments, PCM remains an incurable disease and eventually all patients relapse and become refractory to treatment. The median survival post high-dose chemotherapy followed by autologous stem cell transplantation is 5-7 years.<sup>86,87</sup>

**Case Study**

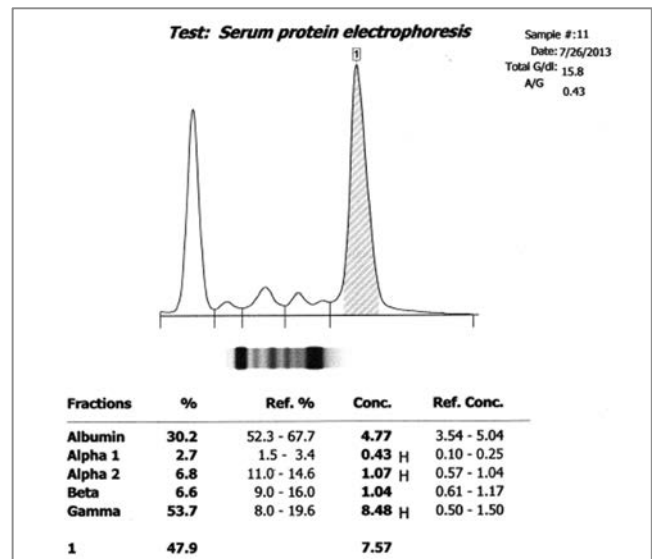
*History*

A 38 year old male presented with chief complaint of back pain over the past two months which progressed to bilateral lower extremity paresthesias which brought him immediately to his primary care physician. His primary care physician referred him to a neurologist. An MRI of the spine disclosed an epidural soft tissue mass most pronounced at T10 (causing the spinal cord compression). CT scans of the chest, abdomen and pelvis revealed numerous lytic osseous lesions distributed throughout the axial and proximal appendicular skeleton. There were no other masses to suggest a primary site. Serum protein electrophoresis demonstrated a prominent paraprotein in the gamma region (see Figure 1), which was identified as an IgA

kappa by immunofixation (Figure 2). Quantification of the serum immunoglobulins showed IgG 552mg/dL, IgA 6440 mg/dL, IgM 27 mg/dL. Bence Jones proteins were not identified. The patient was anemic and thrombocytopenic. The peripheral blood smear showed rouleaux formation, but no plasma cells were seen. His serum calcium level was 11mg/dL and beta-2 microglobulin level was 6.66 mg/L. The creatinine was 1.32 mg/dL. Table 3 summarizes the patient's pertinent laboratory results.

**Table 3.** Patient's pertinent laboratory results

Test	Patient Results	Normal range
Creatinine	1.32 H	0.64-1.27 mg/dL
Albumin	2.6 L	3.5-5.0 g/dL
Calcium	11.0 H	8.5-10.5 mg/dL
Uric Acid	9.7 H	3.5-8.5 mg/dL
Hemoglobin	9.4 g/dL	13.5-16.0 g/dL
Hematocrit	28.1 L	37.0-47.0 %
Platelet	112 L	150-400 x 10 <sup>9</sup> /L
Total protein SPEP	15.8 H	6.0-8.0 g/dL
IgG	552 L	562-1585 mg/dL
IgM	27 L	30-246 mg/dL
IgA	6440 H	73-372 mg/dL
Beta-2 microglobulin	6.66 H	0.7-2.50 mg/L



**Figure 1.** Serum protein electrophoresis pattern showing monoclonal M-spike in the gamma region.

The bone marrow biopsy is hypercellular (100%). The plasma cell tumor extensively replaces normal hematopoietic marrow. Megakaryocytes are decreased. The bone trabeculae have focal osteoclastic activity. The bone marrow aspirate smears are remarkable for a

neoplastic plasma cell population consisting of medium to large sized mono- or –multinucleated plasma cells with conspicuous nucleoli. Some plasma cells have intracytoplasmic needle shaped crystals, others contain Dutcher bodies. The erythroid, neutrophilic and megakaryocytic cell lines comprise less than 30% of the total cell population. The morphologic features of the peripheral blood, bone marrow aspirate and biopsy are illustrated in Figure 3A-F.

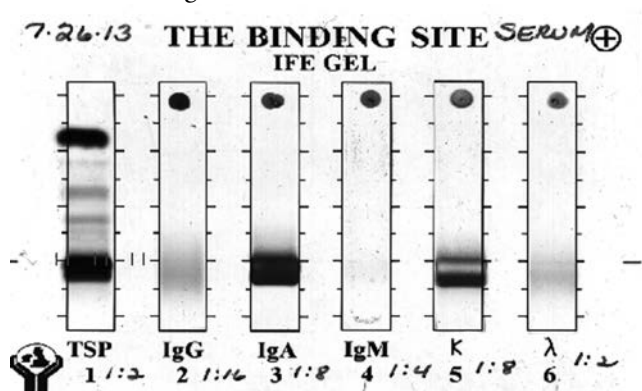


Figure 2. Immunofixation electrophoresis identifies an IgA kappa paraprotein.

#### Cytogenetics

A near-tetraploid complex karyotype with rearrangements leading to a gain of chromosome 1q and other abnormalities was detected in 4 metaphase cells analyzed. As mentioned previously, duplication of all or part of a 1q chromosome and whole arm translocation of 1q can result from unbalanced derivative translocation chromosomes, isochromosomes, or jumping translocations; these structural rearrangements are reported as secondary aberrations and associated with tumor progression and advanced disease.<sup>88</sup>

#### Further Testing

Flow cytometric analysis on the bone marrow aspirate demonstrated a population of cytoplasmic Ig kappa light chain restricted plasma cells expressing CD38, CD138, CD56 and CD45. Figure 4A-D shows the flow cytometry results.

Immunohistochemical stains on the bone marrow biopsy demonstrated a large CD138 positive plasma cell population, with a subset showing cyclin D1 positivity. The plasma cell population is in its majority kappa light chain restricted and negative for CD20. Figure 5A-B shows immunohistochemical stains. A Congo red stain for amyloid deposition appears negative.

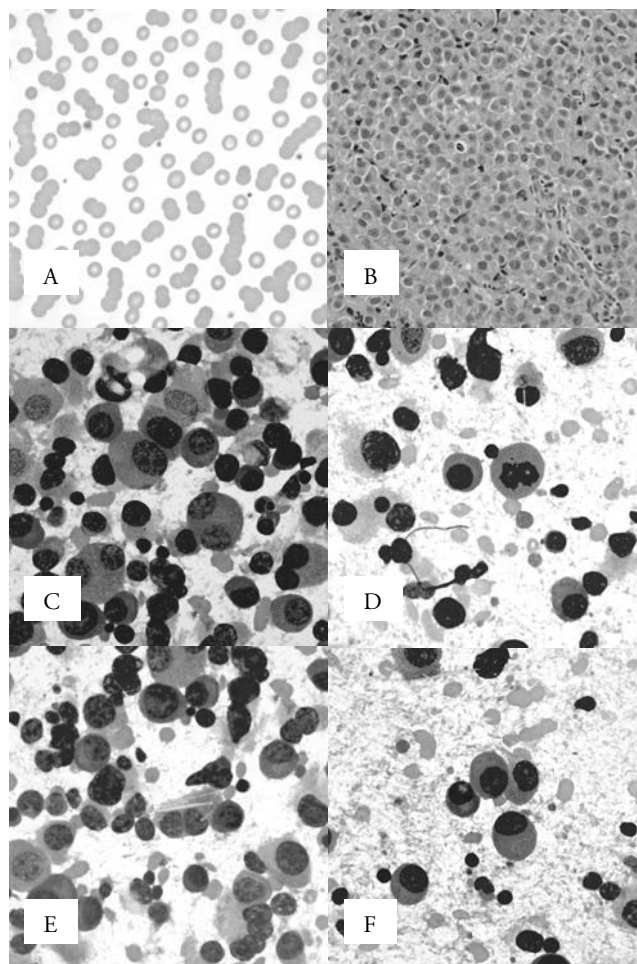
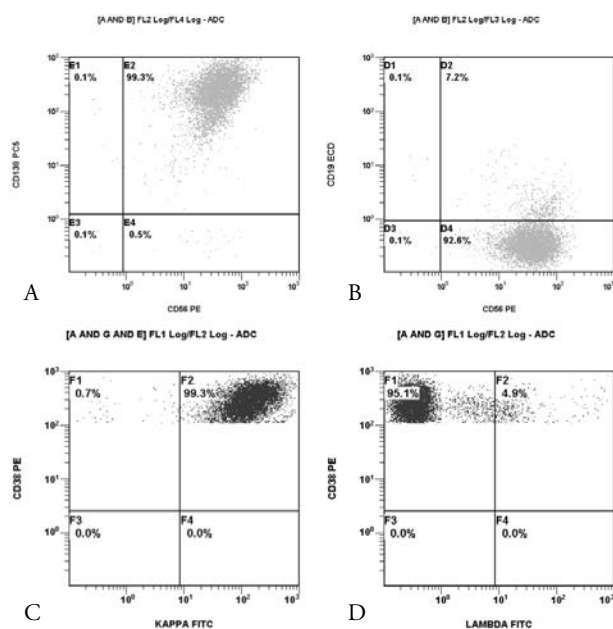


Figure 3. A, Peripheral blood smear showing rouleaux formation. (Wright stain, x100) B, Bone marrow biopsy showing a monotonous population of plasma cells replacing the normal marrow elements. (Wright stain, x50). C, Bone marrow aspirate smear showing numerous bi-lobed plasma cells. (Wright stain, x50). D, Bone marrow aspirate showing mitotic plasma cell indicating a high proliferation rate (Wright stain, x50). E, Bone marrow aspirate smear showing a plasma cell with numerous cytoplasmic Ig crystals (Wright stain, x50). F, Bone marrow aspirate smear showing a plasma cell with Dutcher bodies (Wright stain, x50).

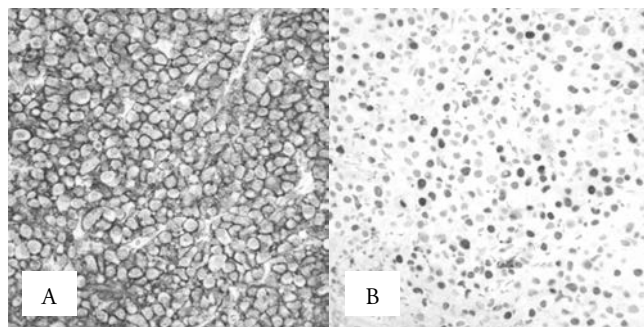
#### Diagnosis/Discussion

The patient has a history of multiple lytic bone lesions. His peripheral blood is remarkable for rouleaux, anemia and thrombocytopenia. There is evidence of renal insufficiency (increased creatinine) and hypercalcemia. The bone marrow biopsy is hypercellular for age and remarkable for a large neoplastic monoclonal plasma cell population extensively replacing the bone marrow. Dutcher bodies and intracytoplasmic needle shaped crystals are present in the plasma cells. Additionally, the patient has an IgA paraprotein. Taken together the

morphologic, immunophenotypic and clinical findings are consistent with plasma cell myeloma (Stage 3 of Durie-Salmon staging system).



**Figure 4** A-B. Flow cytometry identifies a bright CD138 plasma cell population coexpressing CD56 and showing absence of CD19. C-D, The neoplastic plasma cell population (bright CD38 positive) is exclusively cytoplasmic Ig kappa positive.



**Figure 5** A-B. Immunohistochemical stains on bone marrow biopsy shows A, overwhelming CD138 positivity and B, overexpression of cyclin D1.

### Treatment

The patient received a total of ten days radiation to the T11-T12 region of the spine. Concomitantly, he received 20mg dexamethasone twice per week. Although he experienced adverse reaction to the steroid therapy requiring a reduction in the dosage, he acknowledged improvement in pain level and much reduced lower extremity weakness. At this point his creatinine and calcium normalized to 0.89 mg/dL and

8.9 mg/dL respectively. After radiation therapy was completed, he started systemic modified VDC therapy as outlined in the Phase II Evolution study.<sup>89</sup> Modified 21 day cycle VDC therapy includes cyclophosphamide and dexamethasone on days 1, 8, 15 and bortezomib on subsequent days 1, 4, 8 and 11. Upon completion of systemic chemotherapy, the patient will undergo autologous bone marrow transplantation.

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