Case Report
Fatal Cerebral Hemorrhage in a Patient with CD19-positive IgM-producing Aggressive Plasma Cell Myeloma, Hyperviscosity Syndrome and Cryoglobulinemia

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Abstract: IgM plasma cell myeloma (PCM) is a rare entity, and CD19 positivity is found in only 1-4% of PCM. Here we report a unique case of IgM PCM, in which the plasma cells are positive for CD19. Clinically, the patient presented with hyperviscosity syndrome, mimicking the clinical manifestation of Waldenstrom's macroglobulinemia. In addition, the IgM para-protein from the patient behaved like cryoglobulins, which interfered with some of the laboratory measurements and resulted in erroneous platelet count, mean platelet volume, and serum IgM level. Despite chemotherapy, the PCM persisted and progressed to plasma cell leukemia, and the patient died of a left frontal hematoma with widespread cerebral hemorrhage extending from left lateral ventricle, third ventricle, fourth ventricle, to cisterna magna. This case represents the first CD19+ IgM-producing PCM and the second case of brain hemorrhage due to plasma cell myeloma/leukemia.

Key Words: IgM plasma cell myeloma, plasma cell leukemia, CD19, Waldenstrom's macroglobulinemia, lymphoplasmacytic lymphoma, hyperviscosity syndrome, cryoglobulinemia, cerebral hemorrhage

Introduction

Plasma cell myeloma (PCM) is a clonal expansion of malignant plasma cells with approximately 15,000 new cases diagnosed each year in the United States [1]. The diagnosis of PCM requires 1 major criterion and 1 minor criterion or 3 minor criteria according to the World Health Organization [2]. More than 99% of PCM patients have a monoclonal paraprotein (M-component) in serum, urine, or both; and approximately 70% have lytic bone lesions, although non-secreting PCM or PCM with sclerotic lesions of the bones do exist [2]. When the M-component reaches a certain level, at which the blood flow is impaired, then a combination of signs and symptoms known as hyperviscosity develops [3]. Clinical features of PCM include bone pain and fractures, easy fatigability due to anemia, nausea, confusion, and polyuria due to hypercalcemia; and renal failure due to Bence-Jones proteins and/or hypercalcemia. Plasma cells from PCM are typically brightly positive for

CD38 and CD138, positive for CD56, but negative for CD19, CD20 and CD45 [4, 5]. In fact, CD19 positive PCM accounts for approximately 1-4% of PCM cases [4, 5].

The main underlying causes of hyperviscosity as a result of hypergammaglobulinemia include Waldenstrom's macroglobulinemia (WM) and PCM, although the former is more frequent than the latter (10-30% vs 2-6%) [3]. The leading cause of WM is lymphoplasmacytic lymphoma (LPL), which is a distinct clinicopathological entity characterized by the presence of monoclonal small mature B-cells, plasmacytoid mature B-lymphocytes and plasma cells in either the bone marrow or extramedullary tissues accompanied by a serum monoclonal IgM, thus giving rise to hyperviscosity syndrome [6]. The manifestations of WM are related to tumor infiltration and/or the properties of the monoclonal IgM paraproteins [6]. For example, tumor cell infiltration can lead to cytopenias, B symptoms (weight loss, fever, night sweats),

Table 1 Relevant laboratory findings

Test	Results	References
WBC	9.6	3.9-10.7 x 10^3/μL
RBC	2.5	4.01-5.31 x 10^6/μL
Hemoglobin	7.3	12.1-16.1 g/dL
Hematocrit	23.1	36.8-48.7 %
MCV	92.4	76.2-98.6 fl
MCHC	31.6	31.6-35.4 g/dL
Platelets	952	174-404 x 10^3/μL
MPV	Cannot be reported	9.4-12.9 fl
RDW	16.1	11.5-15.0 %
Free T4	1.3	0.8-1.8 ng/dL
IgG	55	694-1618 mg/dL
IgA	182	68-378 mg/dL
IgM	180	60-263 mg/dL (day 10)
RF	>130,000	0-15 IU/mL
β2-MG	2.67 μg/Ml	0.7-1.8 μg/mL
Cholesterol	100	120-200 mg/dL
Iron	50	48-180 μg/dL
Ferritin	19	7-282 ng/mL
Transferrin	10	20-50 %
TIBC	495	262-474 μg/dL
LDH	232	140-271 Unit/L
Fibrinogen	456	190-400 mg/dL
Albumin	2.7	3.5-5.2 g/dl
Total bilirubin	0.2	0.2-1.30 mg/dL
Total protein	8.1	6.3-8.2 g/dL
Haptoglobin	244	16-200 mg/dL
ESR	120	0-15 mm/hr
Glucose	82	65-200 mg/dL
PT/INR	10.1/1.0	9.2-12.8 s/0.9-1.3
PTT	21.7	23.5-33.5 s
CRP	<0.4	0.0-0.8 mg/dL
Triglycerides	49	50-150 mg/dL

WBC, white blood cells; RBC, red blood cells; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; MPV, mean platelet volume; RDW, red cell distribution width; TIBC, total iron binding capacity; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate; PT, prothrombin time; INR, international normalized ratio; PTT, partial thromoplastin time; CRP, C-reactive protein; β2 MG, β2-microglobulin; RF, rheumatoid factor

lymphadenopathy, and hepatosplenomegaly; the presence of an M-component of IgM isotype could result in hyperviscosity, amyloidosis, neuropathy, cold agglutinin and cryoglobulinemia [6]. The typical immunophenotype of plasma cells in LPL shows that they are positive for CD19 and CD45, but negative for CD56 [7]. Cytogenetically, 42% of WM/LPL cases have deletion of 6q [8].

IgM PCM is a rare entity, accounting for approximate 1.2% of PCM cases and displaying clinicopathologic features between

PCM and WM/LPL [9], therefore, the diagnosis can be quite challenging. Furthermore, PCM-associated intracerebral hemorrhage has rarely been reported [10]. Here, we report an unusual case of PCM, in which the neoplastic plasma cells secrete IgM and are positive for CD19. Clinically, the patient presented with manifestations of a hyperviscosity syndrome and cryoglobulinemia. The patient was resistant to chemotherapy, later developed plasma cell leukemia, and eventually died of a left frontal hematoma with widespread cerebral hemorrhage. Other autopsy findings include extensive plasma cell infiltrate involving bone marrow, central nervous system (CNS), lymph nodes, liver, spleen, thyroid, adrenal gland, pancreas, and pituitary gland.

Report of the Case

A 45-year-old Hispanic woman with no significant past medical history was referred from an outpatient clinic for evaluation of symptomatic anemia. The patient presented with dizziness of a 3-day duration, light-headedness, palpitations, and excess fatigue; she also had chest pain, which resolved with rest. The patient reported a 10-pound weight loss over the previous 2 months with decreased appetite and early satiety. Vital signs were within normal limits, and the physical examination was unremarkable. Relevant laboratory values are shown in **Table 1**. The patient's liver and renal function tests, serum electrolytes, hepatitis and HIV serologies were all normal. The patient denied rectal bleeding, melena, hematuria, and abnormal menses; and she denied use of alcohol, tobacco, or drugs. Family history was not significant except that her father had an unspecified type of anemia.

On the second day of admission, the patient experienced sudden loss of vision in her left eye. Ophthalmological exam showed engorged vessels, flame hemorrhages, and Roth's spots in the right eye; and hemorrhage directly over the macula in the left eye. Based on the above symptoms, hyperviscosity syndrome secondary to hematolymphoid malignancy was suspected. Serum protein electrophoresis (SPEP) showed an M-spike of 0.09 g/dL (**Figure 1A**). Subsequent immunofixation electrophoresis (IFE) identified the monoclonal protein as IgM kappa and revealed the presence of a nonspecific protein precipitating as a single discrete band in all lanes of the gel
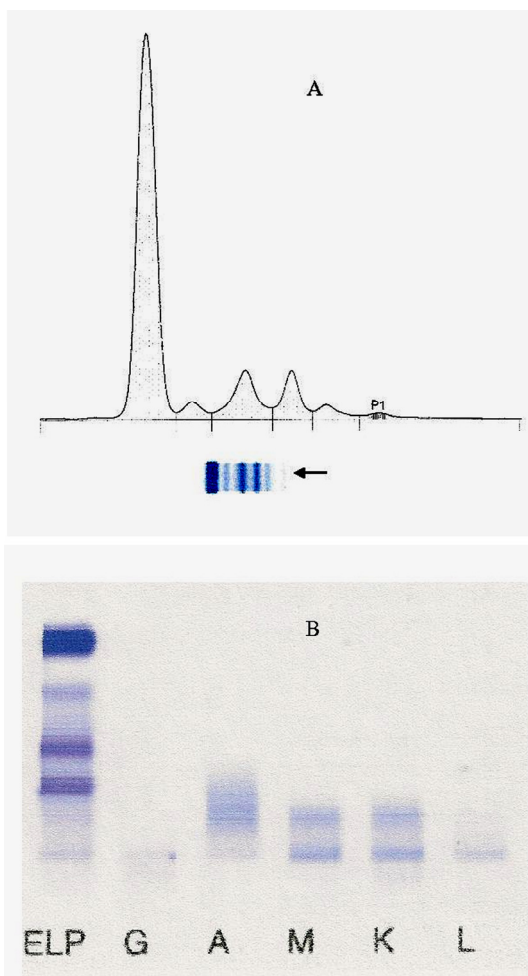
Figure 1 Serum protein electrophoresis (SPEP) and immunofixation (IFE) using immunoglobulin-specific antibodies. **A.** SPEP shows slightly decreased albumin concentration at 3.81 g/dl (normal range 3.90-5.10 g/dL), decreased gamma protein at 0.14 g/dl (normal range 0.40-1.30 g/dL), and presence of a monoclonal protein (M component) at 0.09 g/dL. M refers to the peak produced by the M component and the arrow shows the faint band produced by it. **B.** IFE demonstrates a nonspecific protein precipitated as a single discrete band in all lanes of the gel, consistent with presence of a cryoglobulin. ELP, original serum electrophoresis; G, IgG; A, IgA; M, IgM; K, kappa light chains; L, lambda light chains.

(**Figure 1B**). Urine protein electrophoresis (UPEP) was negative for monoclonal proteins. Computerized tomography (CT) scan showed a non-occlusive deep venous thrombosis in the left common femoral vein, but there was no lymphadenopathy or organomegaly. A skeletal survey revealed multiple lytic lesions in the pelvis. Magnetic resonance imaging showed enlargement and possible infiltration of the right lateral rectus and left medial rectus muscles, and lytic lesions of skull. During this period, the patient's anemia was worsening and she was transfused with two units of red blood cells.

On day 7, the patient had dizziness and syncope while attempting to walk. At this time, her cryoglobulin, cryofibrinogen, and blood viscosity were all elevated (**Table 2**). Despite urgent plasmapharesis, the patient still developed dyspnea and altered mental status and was transferred to the intensive care unit a few hours later. On day 9, the patient started to improve and she was started on steroids and later received her first dose of chemotherapy consisting of vincristine, adriamycin, and dexamethasone. On day 22, the patient was discharged on enoxaparin (levonox), dexamethasone, antibiotics, and iron with scheduled follow-up.

Seven days after discharge, the patient was re-admitted for passing out during a routine hospital visit. In the first day of her second admission, cryocrit, serum viscosity, and serum IgM level were again all elevated (**Table 2**). Another plasmapharesis was performed and her medications were changed to cyclophosphamide, prednisolone, and weekly plasmapharesis. The patient was again discharged with a good clinical condition after a 5-day hospital stay. On subsequent testing, her laboratory results for cryoglobulins, cryofibrinogen, viscosity, and serum IgM were all normal (**Table 2**). Six months later, the patient's bone marrow was replaced with approximately 80% of plasma cells with similar morphologic and immunophenotypic features (see below) to those of the initial specimen, consistent with a substantial residual disease. In addition, the patient had 39% of plasma cells in the peripheral blood with total white blood cells of 33,000/μL, thus giving rise to 12,870/μl plasma cells, consistent with plasma cell leukemia.

On July 12 (6 months after initial diagnosis), the patient was found to be unresponsive. CT scan revealed a large left frontal cerebral hemorrhage (**Figure 2A**) with subfalcine herniation and midline shift, and she was pronounced dead. Relevant autopsy findings include a 3 x 3 cm left frontal hematoma (**Figure 2B**) with hemorrhage within the left lateral ventricle, third ventricle, fourth ventricle and cisterna magna. In addition, there were
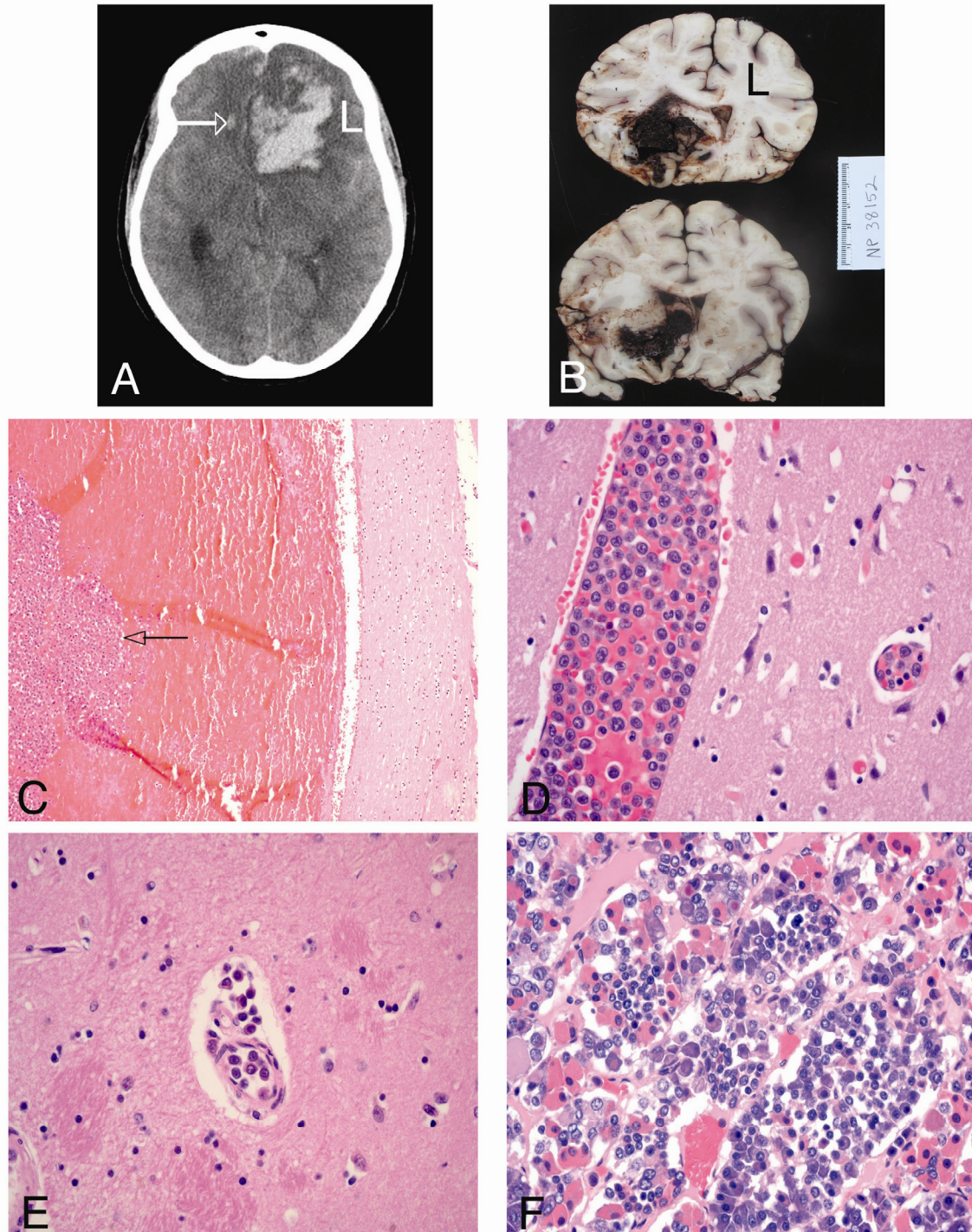
Figure 2 Cerebral hemorrhage and CNS involvement by PCM. **A.** Non-contrast 5 millimeter (mm) contiguous axial CT scan showed a large left (L) frontal hemorrhage and a 6mm subfalcine herniation (arrow) to the right side. **B.** Sections of brain showed a left (L) posterior frontal hemorrhage. **C.** An intra-cerebral hemorrhage with sheets of plasma cells (arrow) (H&E, 200x). **D.** Numerous neoplastic plasma cells are seen in the lumen of the veins of various caliber (H&E, 400x). **E.** Neoplastic plasma cells are seen in and around a small artery in the basal ganglia (H&E, 400x). **F.** Extensive infiltrate of pituitary gland by plasma cells (H&E, 400X)

Table 2 Changes in cryocrit, serum viscosity and total serum IgM after admission or re-admission

Days after admission or readmission	Cryocrit for cryoglobulin (%)	Cryocrit for cryofibrinogen (%)	Viscosity (cp)	Serum IgM (mg/dL)
7†	64	54	3.9	N/A
8	2	2	0.8	N/A
10	N/A	8	0.9	180
13	37	28	N/A	940
15	0	23	3.2	2965
18	50	17	N/A	N/A
19	25	50	N/A	N/A
20	56	40	3.4	N/A
21	59	52	N/A	N/A
1*†	71	54	2.1	4740
2*	18	15	2	N/A
4*	N/A	33	2	3530
6*	38	28	N/A	1200
13*	6	1	N/A	N/A
14*	<1	N/A	N/A	N/A
17*	N/A	N/A	N/A	66

* Days after re-admission; † The day when plasmapharesis was performed. Reference range for cryocrit is < 1%; viscosity < 1.5 cp; serum IgM 60-263 mg/dL. N/A, data not available

widespread plasma cell infiltration involving bone marrow, CNS (**Figures 2C-E**), pituitary gland (**Figure 2F**), retroperitoneal lymph nodes, liver, spleen, thyroid, bladder, adrenal glands, and pancreas.

Results

Morphology and Immunohistochemistry

The prominent features of the peripheral blood smear are profound rouleaux formation and frequent plasma cells (**Figure 3A**) with moderate normocytic and hypochromic anemia. The initial bone marrow aspirate and core biopsy showed numerous plasma cells accounting for approximately 45% of total cellularity with no plasmacytoid lymphocytes seen (**Figures 3B** and **3C**). Some of these plasma cells showed atypical features including conspicuous nucleoli and variation in cell size and shape. In addition, occasional Dutcher bodies were also noted (data not shown). Immunohistochemical stains showed the plasma cells were diffusely and strongly positive for IgM (**Figure 3D**), but negative for IgA and IgG (**Figures 3E** and **3F**). Additional staining revealed the plasma cells were partially positive for CD79a (~40%), but negative for CD20, cyclin D1, and PAX5 (a B-cell specific activator protein).

Multiparameter Flow Cytometry

Flow cytometric analysis from the initial bone marrow specimen showed that the plasma cells were positive for CD38, CD19 (partial), CD56 (low density) (**Figures 4B-D**), and demonstrated surface and intracellular kappa light chain (**Figures 4F** and **4G**); but negative for CD20, CD10, CD45 and CD117 (**Figures 4B, 4C** and **4E**). The immunophenotype from the subsequent bone marrow specimen was similar to the initial one, except that all plasma cells were positive for CD19 (**Figure 4H**).

Conventional and Molecular Cytogenetic Findings

Conventional cytogenetic analysis from the initial bone marrow aspirate showed 47,X,-X,+7,der(14)t(8;14)(q24.1;q32),+21 in 14 out of 20 cells examined (data not shown). Fluorescence *in situ* hybridization using LSI dual-color, break-apart probe set for CMYC and IgH genes (Vysis, Inc, Downers Groves, IL) on interphase nuclei and abnormal metaphase spreads revealed 9% (18/200) of cells having fusion signals (data not shown), confirming t(8;14)(q24.1;q32) involving C-MYC and IgH observed by conventional cytogenetics. However, there was no evidence of t(11;18) involving API2 and MALT1, often associated with marginal zone B-cell lymphoma, or PAX5 rearrangement, often associated with LPL. Conventional cytogenetic analysis on the subsequent bone marrow aspirate showed 47,X,-X,+7,der(14)t(8;14)(q24.1;q32),+21[16 cells]/47,idem,add(2)(q33),del(14)(q24,q32)[2 cells]/47,idem,del(10)(p11.2p15)[2 cells].
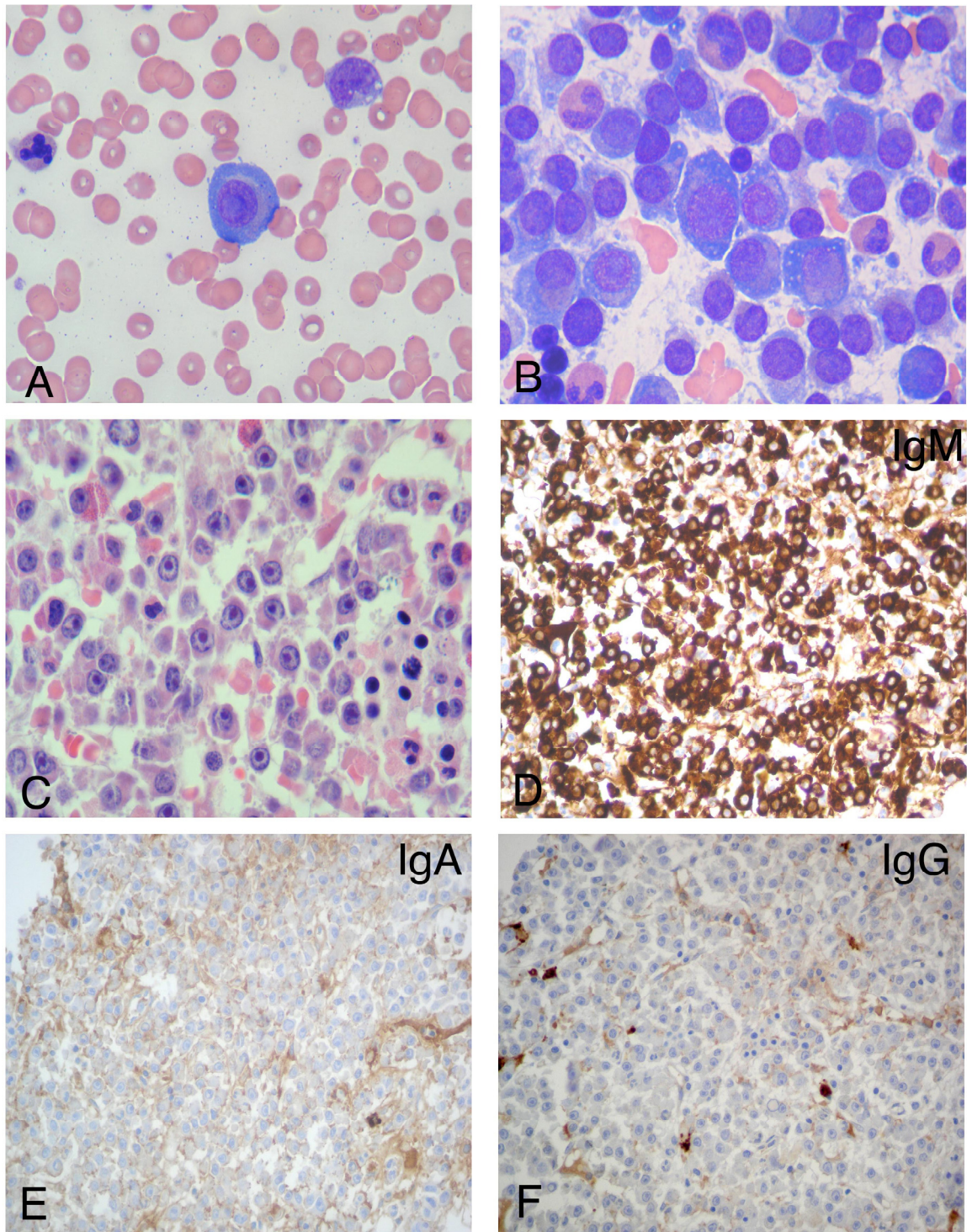
Figure 3 Morphologic and immunohistochemical features of plasma cells. **A.** Plasma cells can be easily identified from the peripheral blood smear (Wright-Giemsa, 1000X); **B.** Numerous plasma cells are easily appreciated from the bone marrow aspirate smear (Wright-Giemsa, 1000X). Many of the plasma cells show morphologic atypia including prominent nucleoli and variation in size; **C.** Sheets of plasma cells with prominent nucleoli are seen in the bone marrow core biopsy (H&E, 1000X); **D-F.** The plasma cells are diffusely and strongly positive for IgM (**D**), but negative for IgA (**E**) and IgG (**F**). (D-F: 400X. Immunohistochemistry staining using avidin-biotin Complex method).
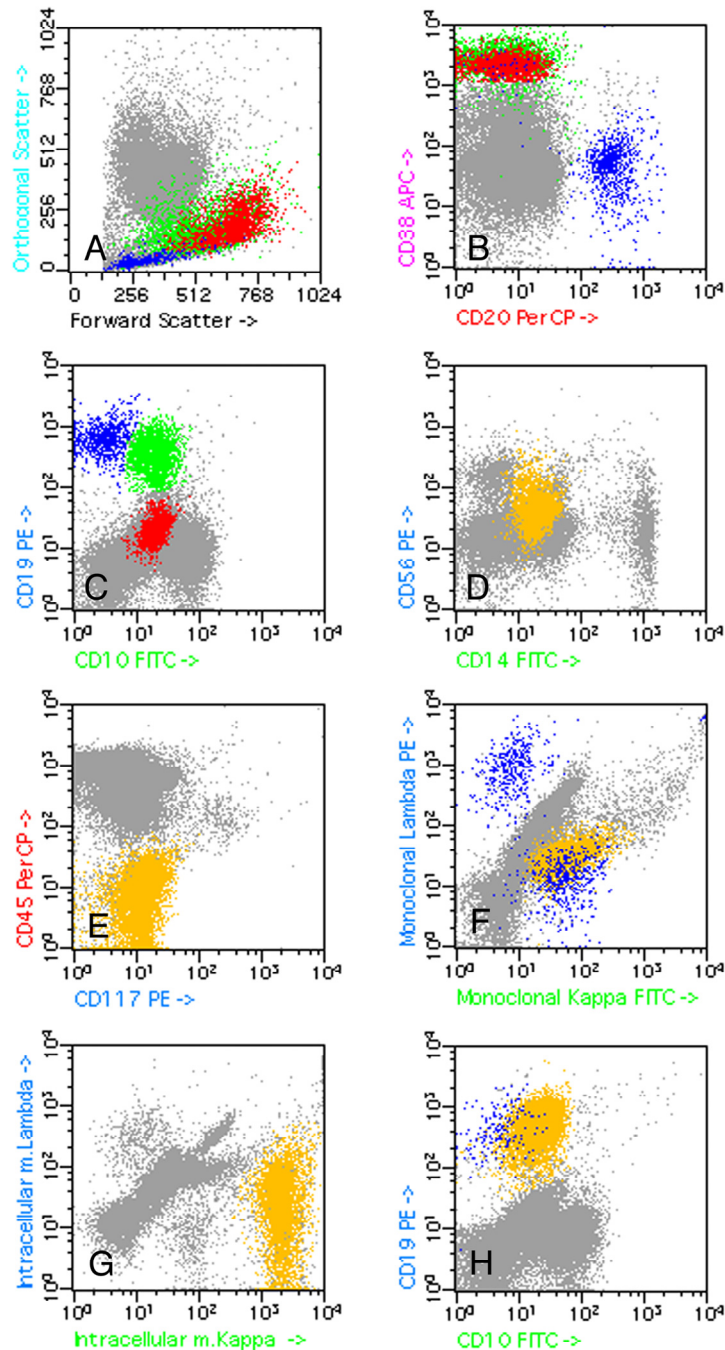
Figure 4 Immunophenotypic profile of plasma cells revealed by multiparameter flow cytometry. Compared to small mature polytypic B-lymphocytes (blue population) (**A-C**, **F-H**), the neoplastic plasma cells from the initial diagnostic specimen (red and green populations from **A** to **C**, and yellow population from **D-G**) are brightly positive for CD38 (**B**), but negative for CD20 (**B**) and CD10 (**C**). Interestingly, approximately 50% of the neoplastic plasma cells are CD19 negative (red population, **C**), which is normally seen in plasma cell myeloma, but the other half of the neoplastic plasma cells are CD19 positive (green population, **C**). The entire neoplastic plasma cell population (the yellow population represent the merge of the red and green populations) are dimly positive for CD56 (**D**), but negative for CD45 and CD117 (**E**). They are dimly positive for surface (**F**) as well as strongly positive for intracellular kappa (**G**) light chain expression. At relapse, the entire neoplastic plasma cell population is positive for CD19 (**H**). (**A** through **G**: initial diagnostic specimen; **H**: plasma cells from relapse). The bone marrow aspirate was processed and stained. The data was acquired with CellQuest software and analyzed using Paint-A-Gate software (Becton Dickinson).

Discussion

There are several unique features of the present case. First, the monoclonal plasma cells are CD19+. Secondly, the paraprotein secreted is IgM, and the patient presents with clinical features of hyperviscosity syndrome. Thirdly, the paraprotein possesses features of a cryoglobulin. Lastly, the patient died of cerebral hemorrhage. The clinical and pathologic differential diagnosis is between an IgM PCM and a WM/LPL with exuberant plasma cell differentiation. However, the presence of multiple lytic bone lesions and t(8;14) translocation, absence of monoclonal small mature B-cell population, lack of plasmacytoid lymphocytes, 6q deletion and chromosome 9 translocation support the diagnosis an IgM PCM.

Hyperviscosity syndrome can be present in both IgM PCM and WM/LPL [3, 6]. Although the correlation between serum viscosity levels and symptoms is often poor, it is generally agreed that most patients with serum viscosity <4-5 cp, which corresponds to a serum IgM level of at least 3 g/dl, will not have symptoms of hyperviscosity [3]. All the viscosity levels in our patient were below 4 cp (**Table 2**), yet the patient showed typical signs and symptoms of a hyperviscosity syndrome. The reasons for the aforementioned finding could be due to the following two possibilities. One possibility is that hyperviscosity-related retinopathy occurs at a viscosity level <3.1 cp as suggested by Menke *et al* [9], and the relationship between the concentration of M-component and the increase of viscosity is not always linear [10]. Another possibility is that the viscosity might be underestimated in our patient due to the nature of her cryoglobulinemia (see discussion below). Similar to most patients with hyperviscosity in which plasmapharesis is effective in the short term but requires frequent exchanges due to the re-accumulation of M-protein in the blood within a few days, our patient's serum viscosity decreased from 3.9 to 0.8 cp but started to increase 2 days after the first plasmapharesis, for which more plasmapharesis procedures were performed [3, 6] (**Table 2**).

Cryoglobulinemia (CG) contains three types and refers to the presence of one or more immunoglobulins in the serum that precipitate(s) at temperatures below 37⁰C and re-dissolve upon warming [11]. CG was suspected in our patient because of the gelling of her peripheral blood at room temperature and the classical pattern of cryoglobulins seen in IFE, in which a single band precipitated in all lanes of the gel and stained with the dye used to detect monoclonal proteins (**Figure 1B**). The distinction between type I and II CG in our patient is difficult, if not possible, to establish since hyperviscosity syndrome and the presence of an M-spike in SPEP are consistent with both types. However, the elevation of rheumatoid factor (RF) activity (**Table 1**) is more consistent with a type II CG.

Cryoglobulins may be discovered incidentally in the laboratory because of interference in other laboratory tests [12]. Our patient presented initially with an IgM concentration of 0.09 g/dL according to the SPEP. It is quite possible that this concentration and the subsequent measurements (0.04 and 0.31 g/dL) were underestimated since some of the immunoglobulins will be bound to and precipitated by cryoglobulins in the gel. The presence of cryoglobulins can also cause falsely elevated cell counts in automated cell counters due to similarity to the size of IgM aggregates [12]. Cryoglobulins mainly cause false elevation of WBCs, platelets, hemoglobin, and MPV [12]. The hematocrit of 23.1%, MCHC of 31.6 g/dL, and MCV of 92.4 fl in our patient suggest a normocytic hypochromic anemia probably due to her chronic illness, given the normal serum iron and ferritin (**Table 1**). However, aggregates of cryoglobulins, which might have been counted as large RBCs may have caused a false elevation of MCV. Other laboratory results that might have been affected by cryoglobulins in the current case include high platelet count (952 x 10³/μL), MPV (cannot be reported), and low serum IgM level (180 mg/dL). The mild elevation of fibrinogen was either due to acute phase reaction or inhibition of the conversion of fibrinogen to fibrin by cryoglobulins. Although this inhibition together with the effect of cryoglobulins on the clotting factors could result in increased clotting times (PT and PTT), these tests were normal in our patient. In contrast to cryoglobulins that are detected in the serum, cryofibrinogen is detected only in plasma. It mainly consists of fibrinogen, fibrin, and fibrin split products.

Several immunophenotypic features revealed by flow cytometry are worth mentioning in the current case. First and foremost, the plasma

cells express CD19, a surface pan-B-cell marker, which is often present in normal polytypic plasma cells [13] and malignant monoclonal plasma cells associated with malignant lymphoma [7], but very rarely in PCM [4, 5]. As shown by Mateo *et al* [5], comparing with CD19-negative PCM, patients with CD19-positive PCM had a clearly worse clinical outcome as measured by both the progression-free survival (PFS) and overall survival (OS). Of interest, the plasma cells from the initial specimen have a heterogenous CD19 expression pattern with half of the population being CD19+, and the remaining half negative (**Figure 4C**); however, the expression of CD19 became homogenous (100% CD19+) (**Figure 4H**), clearly indicating an immunophenotypic evolution and disease progression. Secondly, the plasma cells in our case are CD56-negative, which again is associated with extramedullary spreading, aggressive disease, and poor outcome [7]. The presence of plasma cells in the peripheral blood could be the result of loss of CD56. Thirdly, the plasma cells do not express CD117, which was recently shown to be associated with a significantly shorter PFS and OS [5].

CNS involvement by PCM is a very rare but recognizable phenomenon, and the prognosis is poor [16]. While our patient's CNS symptoms could be due to hyperviscosity; in retrospect, an incipient CNS involvement cannot be completely excluded, since there was no cerebrospinal fluid examination or CT imaging of the head region of this patient prior to her last CT scan. In fact, the unusual immunophenotype (CD19+/CD56-), high tumor burden, atypical morphology, and complex cytogenetic abnormalities all should raise high index of suspicion of CNS involvement [17], therefore, CNS irradiation, intrathecal chemotherapy, or combination could have been life-saving [16]. At autopsy, there is no scalp PCM; instead, presence of aggregates of atypical plasma cells within the hemorrhage (**Figure 2C**), within (**Figures 2D and 2E**) and outside (**Figure 2E**) of vasculature in the cortical gray matter, and plasma cell leukemia, all support the findings that the PCM of the CNS is the result of hematogenous spread rather than a direct extension.

In summary, we present an unusual case of a CD19-positive IgM-producing PCM with clinical presentations of hyperviscosity syndrome and

cryoglobulinemia mimicking WM/LPL. The presence of plasma cells in the peripheral blood, high tumor volume, atypical cytomorphology, unusual immunophenotype, complex cytogenetics, and IgM paraprotein, all point to a CNS involvement and worse clinical outcome. Indeed, the patient died of a cerebral hemorrhage 6 months after the initial diagnosis.

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