A rare case of a minimally secretory plasma cell leukemia with a hemorrhagic gastric plasmacytoma

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1. Introduction

Plasma cell leukemia(PCL) is a rare and aggressive plasma cell neoplasm characterized by clonal plasma cells comprising more than 20% of the leukocytes in the circulation and/or an absolute clonal plasma cell count of more than 2×10^9 [1,2]. PCL accounts for 2–4% of plasma cell dyscrasias [3]. PCL is more common in African Americans, compared to Caucasians [3], with more male preponderance [4]. PCL arising de novo without prior evidence of multiple myeloma (MM) is termed primary PCL(PPCL), and PCL evolving from a preexisting MM is termed as secondary PCL(SPCL). According to the literature, 60–70% of PCLs are primary, and 30–40% are secondary [3,5]. The chances of refractory and relapsed MM progressing to SPCL is 1–2% [3,6]. PCL is a rare disease and the precise information regarding its incidence, clinical presentation, and pathological features are unfolding gradually [7].

Primary extra medullary plasmacytomas of the gastrointestinal tract represents < 5% of all extra medullary plasmacytomas [8]. Any segment of the gastrointestinal tract may be the site of plasma cell infiltration. The small bowel is the most commonly involved site, followed by stomach, colon and esophagus [9]. The most common presenting symptoms are abdominal pain and gastrointestinal bleeding. A few case reports of solitary gastric plasmacytomas have been described in literature [10,11]. A case reported a solitary gastric plasmacytoma in a 46-year-old male who presented with melena and was treated with partial gastrectomy, progressed to having local recurrence and respiratory obstruction due to large mediastinal deposits after 18 months. Eventually transforming into lambda light chain type multiple myeloma with multiple visceral plasmacytomas within a few months

[11]. There is only one case reported in literature of a non-secretory PCL with gastric involvement, where a 49 year old male was diagnosed with non-secretory Ig A PPCL, co-expressing CD38 and CD13 on immunophenotyping. He presented with epigastric discomfort and was found to have multiple submucosal masses with ulcerations in the body of the stomach on endoscopy. On biopsy confirmed to be gastric involvement by PCL and he eventually died of cerebral hemorrhage [12].

Here we present a case of a 79-year-old Caucasian male who presented with symptomatic anemia, and was diagnosed with an aggressive type of plasma cell leukemia and a large ulcerated and hemorrhagic gastric plasmacytoma.

2. Case presentation

A 79-year-old Caucasian male with past history of hypertension, prostate cancer post brachytherapy 10 years prior to presentation, laminectomy for spinal stenosis 6 months before presentation, chronic kidney disease stage 3 (CKD-3) due to previous unrecovered acute kidney injury from nonsteroidal anti-inflammatory drugs postoperatively presented with 2 weeks of worsening shortness of breath and 3 days of right sided chest pain. On further questioning he endorsed having night sweats for 6 months, anorexia for 1 month but denied any weight loss. He lived alone and performed activities of daily living independently with a good performance status. His vital signs were within normal limits and were maintaining normal oxygen saturation on room air. Physical exam was unremarkable except for splenomegaly. On labs he was found to have hemoglobin of 9.9 g/dl, white blood cell count of 23.3×10^9/L and a platelet count of 45×10^9/L. On the
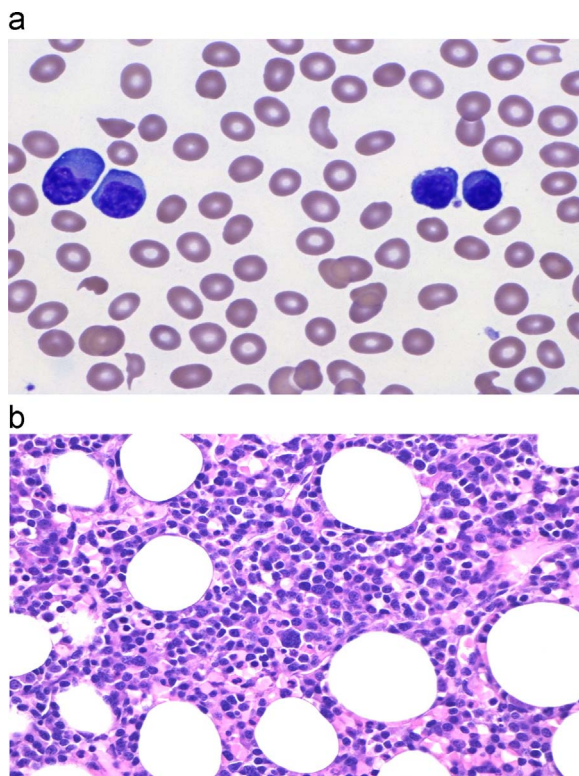
Fig. 1. a: Circulating plasma cells in the peripheral blood (Wright-Giemsa stain, original magnification ×1000). b: Bone marrow diffusely infiltrated by a population of neoplastic plasma cells (Hematoxylin & Eosin stain, original magnification ×400).

Fig. 2. a. b: CT abdomen without intravenous contrast and with oral contrast showing an irregular 6 cm soft tissue density mass in a non-dependent position in the stomach with an ulcerated and irregular surface.

differential the lymphocytes were found to be predominating being 75.9% and neutrophils found to be only 20.4% of the whole white blood cell count. On reviewing old labs his white blood cell count with differential and platelet count were normal 3 weeks prior to this presentation. He had persistent normocytic normochromic anemia with elevated red cell distribution width for 1.5 years without any additional work up performed. Comprehensive metabolic panel showed a calcium of 13.9 mg/dL (last normal being 3 weeks ago), creatinine of 3.34 (baseline being 1.8–2). Other labs included an undetectable prostate specific antigen, uric acid of 11.5 mg/dl, normal phosphorus and potassium. Computed tomography (CT) chest was done without contrast to evaluate the dyspnea which showed an enlarged spleen, lymph nodes in the gastrohepatic ligament measuring 2.8 × 1.8 cm and 8 mm to 1.5 cm lung nodules.

Further work up of the above findings was pursued. Peripheral blood smear showed atypical lymphoplasmacytoid cells being > 20%, some rare blasts with no evidence of hemolysis (Fig. 1a). Flow cytometry revealed 30% kappa light chain-restricted plasma cells that were CD45+ (partial), CD38+ and CD138+. They were negative for CD19 and lambda. Regarding his anemia work up he had normal levels of vitamin B12, folate, haptoglobin, elevated LDH of 483 U/L, elevated ferritin, low transferrin and reticulocyte index was 0.21 showing a combination of anemia of chronic disease and hypoproliferative bone marrow. The bone marrow revealed 80% cellularity with markedly decreased erythroid, myeloid and megakaryocytic cell lines. It showed numerous circulating atypical plasma cells and plasmablasts (> 50%) (Fig. 1b). Urine 24 h protein electrophoresis showed a gamma M-spike of 53% and on immunofixation showed kappa chains. Urine protein/creatinine ratio was 4855.42. Total serum protein was 6.8 g/dL and albumin was 4.7 g/dL. Serum protein electrophoresis showed M spike of 0.1 g/dL. Serum light chain analysis showed 10,314 mg/L of kappa light chains and 3.64 mg/L of lambda light chains. Serum immunofixation showed polyclonal Ig G, Ig A, lambda chains but monoclonal kappa chains and no Ig M were detected. Immunoglobulin
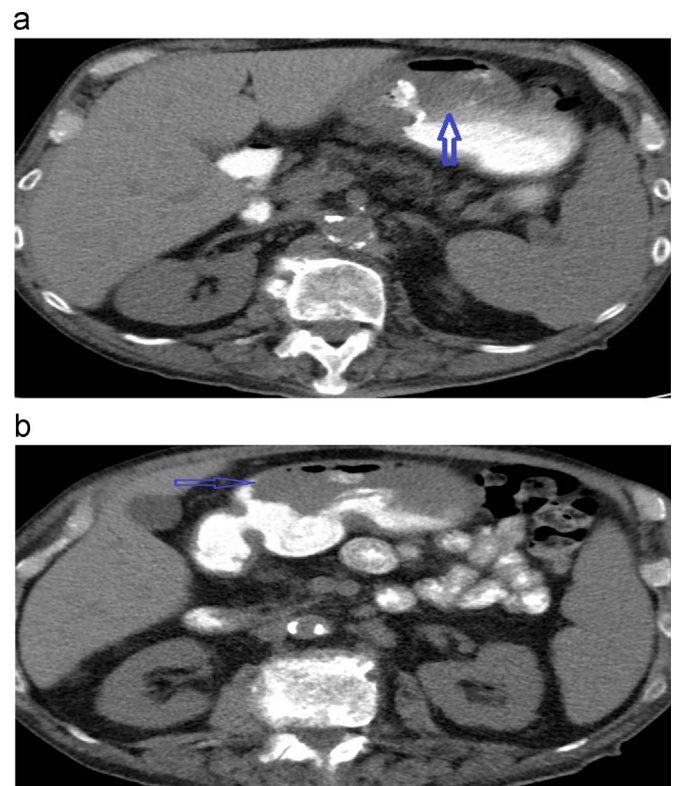
analysis showed low Ig G, Ig A and IgM. Hence he was diagnosed with a minimally secretory plasma cell leukemia (PCL) as per the WHO 2008 guidelines. Cytogenetic study showed out of 15 available metaphases, 10 were normal and 5 had a very complex karyotype which included a structural abnormality of 1q resulting in duplication of 1q, among numerous other structural abnormalities. Karyotype being 44,XY, + add(1)(p13),add(2)(q11.2), add(3)(q25),add(4)(q21),add (6)(q11), add(7)(q22), − 10, − 12, − 13,add(16)(q22),add(17)(q25),add(18)(q21.1), − 21, − 21, + 2mar[5]/46,XY[10].

While above work up was ongoing due to his CT chest showing gastrohepatic ligament lymphadenopathy a CT abdomen /pelvis with oral contrast was obtained to evaluate for the extent of the adenopathy. This revealed an irregular soft tissue density in a non-dependent position in the stomach (Fig. 2a,b). Keeping the differential of a second primary malignancy, fungal infection, or a plasmacytoma in mind gastroenterology was consulted. An esophagogastroduodenoscopy (EGD) was performed which revealed a 6 cm ulcerated gastric mass with raised edges along the lesser curvature extending into the body and pylorus. The mucosa was friable and oozing blood. Biopsies were taken and it was not thought to be amenable for endoscopic therapy or resection (Fig. 3a-e). Due to the high risk of gastrointestinal bleed or perforation from the appearance and the extent of the ulcer he was prophylactically started on intravenous proton pump inhibitors. The biopsy from the gastric mass showed same immunophenotype as his PCL being positive for CD20, CD45, CD138, kappa and negative for CD3, CD10, CD30 and lambda confirming it to be a plasmacytoma with his co-existing kappa chain PCL. Proliferation index as assessed by Ki-67 staining was 80%.

His chest pain was thought to be musculoskeletal since other cardiopulmonary causes were ruled out and progressed to developing generalized body pain. He developed melena 24 h after the endoscopy procedure and was supported by blood transfusions for his anemia of acute blood loss. The left gastric artery was embolized by interventional
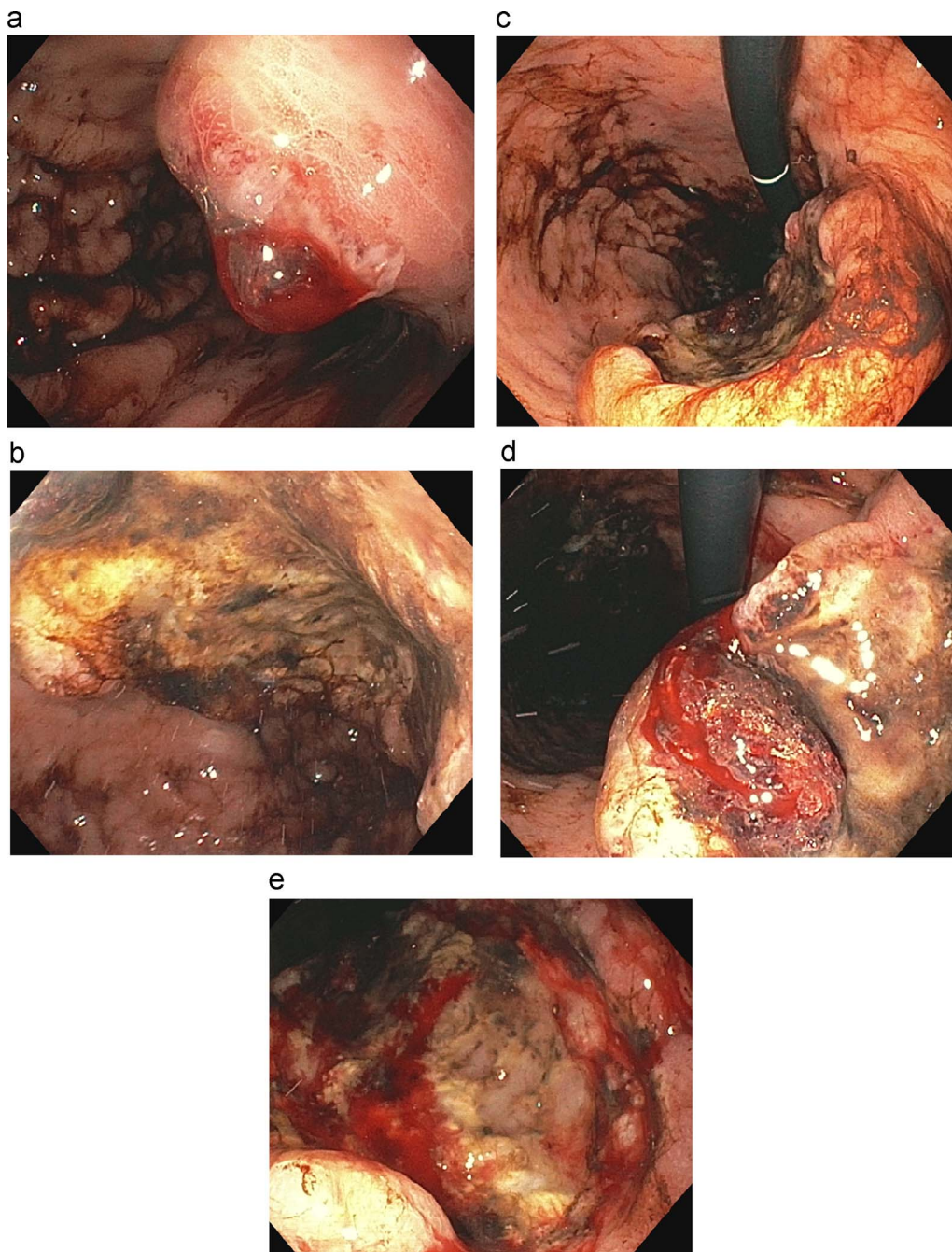
Fig. 3. a: Endoscopy showing a large gastric mass attached to lesser curvature with a bleeding surface. b: Endoscopy showing ulcerated, irregular and hemorrhaging surface of the gastric mass. c: Endoscopy showing lower edge of the gastric mass extending into the pylorus. d: Endoscopy showing necrotic, friable, ulcerated and bleeding surface of gastric mass. e: Endoscopy confirming evidence of active gastrointestinal bleed from the mass.

radiology in an attempt to stop the bleed and treatment for plasma cell leukemia was planned with bortezomib, lenalidomide and dexamethasone (VRd). However, lenalidomide was not able to be obtained in time during the hospitalization stay. Thus, one dose of cyclophosphamide was given, according to the CyBorD regimen. His WBC did respond to treatment and decreased from 30.4×10^9/L to 18×10^9/L. Allopurinol and rasburicase were also started to prevent tumor lysis syndrome. However, his mental status continued to decline and he became progressively encephalopathic attributed to his gastrointestinal bleed, uncontrolled severe pain, elderly age and long hospital stay. Goals of care discussion was held in a multidisciplinary meeting with the patient and family. Patient made his wishes clear that he did not want to die in the hospital. The decision was thus made to discharge the patient home with hospice care and forgo further transfusion support. His melena did stop 3 days after discharge with home hospice but he died 4 days later at home.

3. Discussion

Extramedullary involvement of spleen and liver are most commonly seen in plasma cell dyscrasias [13]. Other visceral sites of involvement include kidneys, lungs, heart, pleura, testes, skeletal muscles, central nervous system, and, very rarely, skin [13]. Involvement of the gastrointestinal tract by plasma cell neoplasia is rare and its association in PCL is quite uncommon [14]. Our patient had a unique presentation in terms of being atypical for his race and age, as well as having a very

rapid onset of leukocytosis, thrombocytopenia and hypercalcemia within 3 weeks. Gastric involvement with his PCL with the lesion being ulcerative, necrotic and hemorrhagic is extremely uncommon. His disease characteristics make him very atypical of being a PPCL. It is our hypothesis that he had an underlying gastric plasmacytoma and possibly undiagnosed light chain multiple myeloma corresponding with his chronic anemia which rapidly transformed into an aggressive SPCL over 3 weeks, presenting as symptomatic anemia.

Since SPCL is a leukemic evolution of MM, there are no major differences in the clinical profiles of MM and SPCL. On the contrary, PPCL usually presents a decade earlier (median age, 52–65 years) unlike our patient who presented later on in life, and PPCL patients have been documented to show a higher prevalence of hepatosplenomegaly, lymphadenopathy, pleural effusion, neurological deficits, anemia, thrombocytopenia, hypercalcemia, and extra medullary plasmacytomas, while osteolytic lesions are relatively few [3]. In addition, PPCL is associated with significant leukocytosis, markedly elevated lactate dehydrogenase levels, high beta-2-microglobulin levels, and a higher incidence of tumor lysis syndrome [3]. Light chain disease is considered to be more frequent [15], with higher lambda light chain restriction than kappa light chain restriction [7,16] in contrast to our patient who had a kappa light chain restricted PPCL. As per previous studies the frequencies of IgG, IgA, light chain, and non-secretory PCL are in the ranges of 28–58%, 4–17%, 23–44%, and 0–12%, respectively [3,4,7]. No M protein is detected in the serum or urine of non-secretory type of PCL [17]. Serum-free light chain assay in such cases would suggest the majority of patients with conventional non-secretory PCL do have evidence of clonal immunoglobulin production [18].

CD13 expression on neoplastic plasma cells has been related to gastric involvement in literature. CD13 antigen is expressed by granulocyte-monocyte progenitors cells, leukemic blasts of acute myeloid leukemia [19]. The CD13 cDNA sequence has been found to be identical to that of amino peptidase N, a membrane-bound glycoprotein expressed by the brush borders of the small intestine and renal tubules [20]. Furthermore, specific inhibitors or antibodies of amino peptidases N have been shown to inhibit the penetration of metastatic melanoma cells in vitro [21], indicating that amino peptidases N plays a role in the process of tumor invasion. However, our patient's immunophenotype lacked the expression of CD13. Also as per literature the lack of CD56 on the malignant PCs explains the reason for their spread into extra medullary sites as CD56 is considered to have an important role in anchoring PCs to the bone marrow stroma [22], our patient demonstrated negative expression for CD56 as well.

The presence of p53 deletions, 13q deletions, karyotypic complexity, hypodiploidy, and 1q gains could confer an advanced stage on PCL disease progression characterized by therapy resistance and a dismal prognosis [23], in concordance with our patient whose cytogenetics showed abnormalities with 1q, perhaps contributing to the aggressive tumor behavior. On a molecular level, PCL can be differentiated from multiple myeloma by fluorescent in situ (FISH) analysis looking for IgH translocations and chromosome 13q deletions [24].

Till date, there is no curative treatment for PCL and the median survival is merely 7–13 months for PPCL and 2–7 months for SPCL [5,25]. The disease still remains largely unexplored due to its rarity. Due to the rare nature of PCL, there is no standard treatment as randomized studies are not available and treatment data are extrapolated from MM studies [26]. No prospective series have been published and only seven reports including > 20 patients have been identified.

Despite the younger age of patients with PPCL, we have not obtained, in this rare and aggressive disorder, the same important therapeutic progress seen during past years in multiple myeloma (MM) [3]. Nevertheless, a registry study of 445 patients with PPCL showed a modest, but statistically significant improvement in overall survival (OS), which has increased from 5 months in patients diagnosed between 1973 and 2005 to 12 months in those diagnosed between 2006 and 2009 after the introduction of the so-called novel agents (thalidomide,

lenalidomide, and bortezomib) in the upfront setting [27]. The most significant benefit was observed in older patients in whom the early mortality rate decreased from 26% to 15%. Moreover, because of the high rate of recurrence and poor outcome with chemotherapy alone, consolidation with hematopoietic stem cell transplant provides the best hope for remaining in complete remission [28].

4. Conclusion

In the setting of hepatosplenomegaly, soft tissue mass and hypercalcemia, serum and urine protein electrophoresis with immunofixation should be obtained to identify the presence of monoclonal immunoglobulins. Although bone marrow biopsy is the mainstay of diagnosing multiple myeloma and plasma cell leukemia, any soft tissue mass identified should also be biopsied to evaluate for possible extra medullary involvement. As evident in this case, although gastric involvement is uncommon, it can lead to life threatening hemorrhage. Early diagnosis and timely initiation of therapy can potentially prevent or reverse hemorrhagic complications, although the overall prognosis of this aggressive disease remains poor.

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