Splanchnic Vein Thrombosis as the Initial Manifestation of Lambda Light Chain Multiple Myeloma

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ABSTRACT

We present the case of a 67-year-old man who developed superior mesenteric vein thrombosis (SMVT) as the initial manifestation of IgD lambda and lambda light chain multiple myeloma (LCMM). He initially presented with abdominal pain and was found to have SMVT without identifiable thrombophilic risk factors. Persistent macrocytosis, unexplained renal dysfunction, and mild anemia prompted further evaluation, revealing markedly elevated serum free lambda light chains, suppressed immunoglobulins, and a bone marrow biopsy confirming LCMM. This case highlights the importance of considering plasma cell dyscrasias in patients with unprovoked thrombosis at atypical sites, particularly when accompanied by subtle hematologic or renal abnormalities. Early recognition of LCMM is essential given its aggressive nature and potential for diagnostic delay due to absent or minimal findings on standard serum protein electrophoresis.

KEYWORDS: Splanchnic Vein Thrombosis; Multiple Myeloma

CASE PRESENTATION

A 67-year-old non-smoker man with a history of hypertension, prediabetes, and a remote episode of spontaneous right popliteal vein thrombosis one year prior to presentation, which was treated with a three-month course of anticoagulation, presented with progressively worsening postprandial abdominal pain over three weeks, associated with nausea and vomiting. He denied any melena or hematochezia. On presentation, he was hemodynamically stable. Physical examination revealed diffuse abdominal tenderness without rebound or guarding. Laboratory testing revealed a white blood cell count of 14 $\times 10^3/\mu L$ (reference range [RR]: 4.0–10.8$\times 10^3/\mu L$), hemoglobin 13 g/dL (RR: 13.0–17.5 g/dL), mean corpuscular volume (MCV) 99 fL (RR: 81.0–99.0 fL), platelet count 409 $\times 10^3/\mu L$ (RR: 150–450 $\times$ $10^3/\mu L$), creatinine 1.4 mg/dL (RR: 0.7–1.2 mg/dL), and corrected calcium 10.5 mg/dL (RR: 8.5–10.2). Liver function tests, anion gap, albumin, globulin and albumin/globulin ratio (A/G ratio), and lactate were all within normal limits. Notably, MCV had consistently ranged between 97 and 99 fL over the past four years. Two months prior to presentation, his hemoglobin was 12.8 g/dL. A comprehensive metabolic panel (CMP) performed 10 months earlier was within normal limits, whereas a repeat CMP three months prior showed a mildly elevated creatinine of 1.26 mg/dL.

Contrast-enhanced computed tomography imaging of the abdomen and pelvis revealed long-segment small bowel wall thickening in the right lower quadrant, mesenteric edema, and occlusion of the superior mesenteric vein (SMV), findings concerning for ischemic enteritis. There was no evidence of bowel obstruction or pneumatosis. Surgical and vascular surgery teams were consulted. Hematology team was consulted due to the spontaneous and atypical site of thrombosis. Hypercoagulable testing, including anticardiolipin antibodies, beta-2 glycoprotein antibodies, Factor V Leiden, prothrombin G20210A mutation, JAK2 V617F mutation, and paroxysmal nocturnal hemoglobinuria (PNH) screen, was negative. Testing for lupus anticoagulant, protein C, and protein S testing were initially deferred due to ongoing anticoagulation with heparin and acute thrombotic event. The patient's condition improved with conservative management, thus thrombectomy and thrombolysis were not pursued. He was discharged on therapeutic enoxaparin. At the time of discharge, hemoglobin was 9.8 g/dL, MCV 99 fL, creatinine 1.4 mg/dL, and white cell and platelet counts were within normal limits. He was transitioned to therapeutic enoxaparin and subsequently discharged.

Three weeks after discharge, the patient re-presented with generalized weakness and acute kidney injury. Laboratory findings revealed WBC 5.4 $\times 10^3/\mu L$, hemoglobin slightly improved to 10.4 g/dL, MCV 103 fL, platelet count 274 $\times 10^3/\mu L$, creatinine 2.4 mg/dL, and calcium 10.4 mg/dL. Renal ultrasound and urinalysis were unremarkable. He was diagnosed with non-oliguric acute tubular necrosis. With improved gut function, he was switched to apixaban 5 mg twice daily on discharge. Creatinine at the time of discharge was 2.4 mg/dL.

Two weeks later at outpatient hematology follow-up, his labs showed hemoglobin 11.6 g/dL, MCV 98 fL, creatinine 2.3 mg/dL, mildly elevated calcium 10.5 mg/dL, and normal WBC, platelet count, vitamin B12, and folate levels. Given mild anemia, high-normal MCV, unexplained renal dysfunction, and absence of nutritional deficiencies or alcohol use, a plasma cell dyscrasia was suspected. Serum protein electrophoresis (SPEP) revealed two monoclonal bands:

one at 1.1 g/dL in the beta region (identified as free lambda light chains by immunofixation) and another at 0.3 g/dL in the gamma region (identified as IgD heavy chain). A serum free light chain assay showed kappa light chain of 1.33 mg/dL (RR: 0.33–1.94), lambda light chain of 2850 mg/dL (RR: 0.57–2.63), with a kappa/lambda free light chain ratio of 0.0005 (RR: 0.26–1.65). Beta-2 microglobulin was markedly elevated at 10,957 ng/mL (RR: 1000–2400). Lactate dehydrogenase (LDH) was within normal limits at 243 U/L (RR: 120–246). Immunoglobulin levels were suppressed with IgG 376 mg/dL (RR: 700–1600), IgA 67 mg/dL (RR: 70–400), and IgM 22 mg/dL (RR: 50–300). Bone marrow biopsy demonstrated a plasma cell neoplasm involving 50–60% of marrow cellularity and lambda light chain restriction, confirmed by in situ hybridization and flow cytometry. Congo red staining was negative for amyloid. Cytogenetic testing with fluorescence in situ hybridization (FISH) was normal.

DISCUSSION

Venous thromboembolism (VTE) is a well-recognized complication in patients with multiple myeloma (MM), particularly in those undergoing treatment with immunomodulatory agents (IMiDs) such as lenalidomide, often in combination with high-dose corticosteroids or chemotherapeutic agents. Kristinsson et al. reported that patients with MM have a significantly increased risk of venous thrombosis, with hazard ratios of 7.5, 4.6, and 4.1 at 1, 5, and 10 years post-diagnosis, respectively.[1] The pathophysiology of hypercoagulability in MM has been demonstrated to be multifactorial with evidence of elevated von Willebrand factor (VWF) levels, activated protein C resistance, impaired fibrinolysis, and/or abnormal thrombin generation[2] all being reported. Free lambda light chains, especially in large quantities, can also cause direct endothelial injury and thereby activate coagulation pathways. This is compounded by the presence of procoagulant microparticles and inflammatory cytokines(especially with aggressive subtypes like light chain MM[LCMM] and IgD MM), which further enhance thrombotic risk.[3,4] Furthermore, anti-myeloma therapies, such as immunomodulatory drugs (IMiDs) and high-dose dexamethasone, are known to increase thrombotic potential by inducing endothelial damage and promoting prothrombotic conditions.[5,6] However, VTE as an initial presenting feature of previously undiagnosed MM, is rare with only a few cases reported in the literature.[7] To our knowledge, only one prior case has described MM initially presenting as mesenteric venous thrombosis, highlighting the rarity of our case.[8]

Superior mesenteric vein thrombosis (SMVT) has a broad differential including abdominal infections, inflammatory bowel disease, pancreatitis, trauma, surgical procedures, cirrhosis, portal hypertension, thrombophilic states, and malignancies. At the time of diagnosis of unprovoked SMVT, our patient had none of these risk factors, and he was subsequently diagnosed with LCMM. Multiple myeloma can cause renal amyloidosis, leading to nephrotic syndrome and a subsequent hypercoagulable state. However, our patient had an unremarkable urinalysis, normal serum albumin and lipid panel, and no evidence of pedal edema, essentially ruling out nephrotic syndrome as the cause of hypercoagulability. An important consideration in our case is whether SMVT led to ischemic enteritis or if the enteritis preceded and contributed to thrombosis. Deposition of monoclonal light chains in various tissues, including the gastrointestinal (GI) tract, has been documented and can result in structural changes such as bowel wall thickening.[9] Bonometti et al reported a case of kappa light chain/IgA multiple myeloma presenting with small bowel obstruction caused by circumferential thickening of the terminal ileum, underscoring the potential for light chain deposition to cause significant GI pathology.[10] In our patient, similar bowel wall thickening could have led to local inflammation and edema, contributing to altered venous blood flow and elevated mesenteric venous pressure – factors that may have predisposed to SMVT. Although the affected bowel segment was not biopsied, small bowel light chain deposition remains a plausible explanation in our case.

An additional noteworthy feature in this case was persistent mild macrocytosis in the absence of vitamin B12 or folate deficiency, alcohol use, or liver disease. While anemia in MM is typically normocytic, macrocytosis can be observed, especially in the presence of high levels of free lambda light chains and associated renal dysfunction. Free lambda light chains can interfere with erythropoiesis by direct toxicity to erythroid precursors or by altering intracellular folate metabolism, despite normal serum folate levels. This interference can lead to the production of fewer but larger red blood cells, resulting in macrocytosis.[11] Renal impairment, common in LCMM due to light chain cast nephropathy, can contribute to macrocytosis through reduced erythropoietin levels and altered red cell maturation.[12,13] LCMM and IgD MM often present with higher tumor burden, more aggressive disease, and poorer prognosis.[14,15] Marrow crowding may lead to ineffective erythropoiesis and macrocytosis. Furthermore, multiple myeloma can co-occur with or evolve into myelodysplastic syndrome(MDS). Macrocytosis in MM might reflect early clonal hematopoiesis. Maia et al investigated the presence of dysplastic hematopoiesis in newly diagnosed MM patients and found that 11.6% of cases displayed MDS-associated phenotypic alterations at diagnosis.[16] In our patient, highly elevated lambda free light chains, marrow crowding with neoplastic plasma cell comprising 50–60% of marrow cellularity, and renal dysfunction likely contributed to macrocytosis. There were no dysplastic hematopoietic precursor cells identified in our patient's bone marrow biopsy, making concomitant MDS less likely. It is important to note, however, that the absence of dysplasia does not exclude clonal hematopoiesis, which can occur without overt morphologic abnormalities.[17]

Interestingly, our patient's MCV had been at the upper limit of normal for at least four years prior to his initial presentation with SMV thrombosis, suggesting the possibility

of a smoldering plasma cell dyscrasia. Additionally, mild renal dysfunction was documented approximately three months before SMVT, raising further suspicion that multiple myeloma may have been present but undiagnosed at the time of initial presentation with SMVT. Recent evidence suggests that smoldering multiple myeloma (SMM), despite being an asymptomatic precursor state, may still carry a degree of hypercoagulability. In a study of 123 patients, including 31 with SMM, no thrombotic events were observed in the SMM subgroup however elevated levels of pro-inflammatory TGFβ and microvesicles (MVs), mediators of coagulation activation, were still found in patients prior to overt disease progression. This raises the possibility that even in SMM, subclinical prothrombotic mechanisms exist, highlighting a need for ongoing vigilance as the condition evolves.[18] His remote history of an unprovoked popliteal vein thrombosis one year prior also supports an underlying prothrombotic diathesis, likely related to an evolving plasma cell disorder. Ultimately, the diagnosis of LCMM with an associated IgD component was established. This case highlights the importance of recognizing subtle early signs of MM to facilitate timely diagnosis and treatment.

In conclusion, our case highlights the importance of considering plasma cell dyscrasias in the differential diagnosis of unprovoked thrombosis, particularly when it presents at atypical sites and in the absence of identifiable thrombophilic risk factors. LCMM should also be considered in the evaluation of unexplained macrocytic anemia, given its aggressive nature and potential for renal injury. A key feature of LCMM is the absence of intact monoclonal immunoglobulin production by malignant plasma cells, which can result in a negative SPEP and delay diagnosis.[19] Although our patient's SPEP revealed two monoclonal bands making this concern less relevant in our case, it remains a critical diagnostic consideration. Subtle clinical clues pointing toward LCMM should not be overlooked, as early recognition and a thorough diagnostic workup, including serum free light chain analysis and bone marrow biopsy, are vital for timely initiation of disease-modifying therapy.

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Disclosures

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