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Type 1 Cryoglobulinemia Secondary to Primary Plasma Cell Leukemia: A Rare Presentation of a Rare Entity

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Abstract

Primary Plasma Cell Leukemia (pPCL) is a rare and aggressive form of plasma cell dyscrasia that comprises 1% of plasma cell dyscrasias. It is characterized by the presence of more than 20% plasma cells in the peripheral blood or an absolute peripheral blood plasma cell count of greater than 2.0 x 10^9 cells/L. Symptoms are similar to Multiple Myeloma (MM) but develop in a shorter period of time. A case of secondary plasma cell leukemia associated with type 1 cryoglobulinemia was reported in the literature. To our knowledge, this is the first case of pPCL with associated necrotizing lesions and cryoglobulin level up to 81%.

Case Presentation

A 63-year-old African American male with no past medical history presented to the hospital with severe burning pain in his legs, progressive necrotizing rash of 10-day duration, 6.8 kg unintentional weight loss and decreased appetite over a one-month period. He was noted to have a necrotizing retiform purpuric rash predominantly in the distal upper and lower extremities (Figure 1), ears, and tip of the nose highly suspicious for cryoglobulinemia. Complete blood count with differential and peripheral smear revealed leukocytosis with neutrophilia, plasma cells, and Rouleaux formation. He was also noted to have elevated total serum protein, acute kidney injury, and normocytic anemia. Infectious work up including HIV, hepatitis B and C came back negative. Autoimmune work-up for possible vasculitis was unrevealing. Serum electrophoresis revealed an M-spike of 5.67. IgG level was significantly elevated at free lambda was 152.10 and free kappa/lambda was 0. Cryoglobulin level was 81%, Table 1. A computed tomography of the chest, abdomen, and pelvis without IV contrast was obtained that revealed extensive lytic lesions throughout the spine as shown in Figure 2. Skin biopsy revealed thrombotic vasculopathy with intraluminal fibrinogen deposition and no evidence of vasculitis as shown in Figure 3. Bone marrow biopsy revealed 80% dysplastic plasma cells as shown in Figure 4. Flow cytometry of peripheral blood was consistent with lambda restricted neoplastic plasma cells, 72% of which had high expression of CD38 and CD138 but were negative for CD19, CD20, CD56 and CD117. FISH revealed t(11;14) (q13;q32) resulting in IGH/CCND1

Figure 1: Necrotic skin lesions classic of type 1 cryoglobulinemia in primary plasma cell leukemia. Note the severity of the lesions in the setting of a cryocrit of 80%.

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Table 1: Laboratory data.

Variable	Reference Range	Admission	At discharge after a course of 6 PLEX	One Month Follow-up
Complete blood count with differential				
White cell count (bil/L)	3.5-10.1	**18.7**	8.2	10.9
Red blood cell count (tril/L)	4.31-5.48	3.48		
Hemoglobin (g/dL)	13.5-17	**9.9**	7.8	8.6
Mean corpuscular volume (fL)	80-100	80		
Mean corpuscular hemoglobin (pg)	28-33	28		
Mean corpuscular hemoglobin concentration (g/dL)	32-35	36		
Red cell width (%)	12-15	15		
Platelets (bil/L)	150-400	162	104	377
Nucleated RBC	0/100 white blood cell	5		
Neutrophils (bil/L)	1.6-7.2	**11.4**		
Lymphocytes (bil/L)	1.1-4	3.4		
Monocytes (bil/L)	0.0-0.9	0.9		
Eosinophils (bil/L)	0.0-0.4	0		
Basophils (bil/L)	0.0-0.1	0		
Metamyelocytes		**0.19**		
Myelocytes		**0.19**		
Plasma cells (bil/L)		**2.6**		
Vacuolization		**Present**		
Roleaux		**Present**		
Red blood cell morphology		**Leukoerythroblastosis**		
Chemistry				
Sodium (mmol/L)	135-145	**127**	135	
Albumin corrected calcium	8.5-10.5	9.5		
Rest of electrolytes		Within normal limit		
Urea (mg/dL)	7-25	**63**	**44**	**49**
Creatinine (mg/dL)	0.6-1.3	**2.85**	**1.75**	**1.27**
GFR (mL/min/1.73 m2)	>59	**26**	**40**	**60**
Total protein (g/dL)		**12.8**	**7.7**	**6.1**
Albumin (g/dL)	3.5-4.9	**2.9**		
Globulin (g/dL)	6.2-8.1	**9.9**	**3.2**	**2.6**
Alkaline phosphatase (U/L)	33-120	40		
Aspartate aminotransferase (U/L)	0-34	31		
Alanine aminotransferase (U/L)	9-47	38		
Total bilirubin (mg/dL)	0.3-1.2	0.4		
Protime (s)	9.2-13.5	**15.8**		
INR		**1.4**		
aPTT (s)	25-37	22.9		
Fibrinogen (mg/dL)	200-400	312		
Infectious Workup				
HIV-1 p24 antigen/HIV-1/2 antibody screen		Nonreactive		
Hepatitis C virus antibody		Nonreactive		
Hepatitis B surface antigen (HBsAg)		Nonreactive		
Total Hepatitis B core antibody		Nonreactive		
Rheumatologic Workup				
Erythrocyte sedimentation rate (mm/hr)	0-15	**130**		

C reactive protein (mg/L)	0.0-7.9	**27.4**		
Cryoglobulin (%)		**81%**	**Negative**	**Negative**
Serum viscosity (cP)	1-2	**3.1**		
Anti neutrophil cytoplasmic antibody (ANCA)	<1:20	Negative		
Myeloperoxidase antibodies	≤ 20 U	Negative		
Proteinase 3 antibody	≤ 20 U	Negative		
Antinuclear antibody (ANA)	<1:160	Negative		
Rheumatoid factor (IU/mL)	0-15	Negative		
Cyclic citrullinated peptide (U)	0-19.9	Negative		
Antiphospholipid antibody panel		Negative		
Sjogren SSA antibody (AU/mL)	0.0-99.9	Negative		
Sjogren SSB antibody (AU/mL)	0.0-99.9	Negative		
Complement, C4 (mg/dL)	10-43	**4**		
Complement, C3 (mg/dL)	82-193	106		
Monoclonal Gammopathy Workup				
Gamma M-peak in serum protein electrophoresis (g/dL)	0.60-1.45	**5.67**		**0.76**
IgG (mg/dL)	550-1,650	**7,239**		
IgA (mg/dL)	70-365	**37**		
IgM (mg/dL)	40-293	**26**		
Free kappa (mg/dL)	0.33-1.94	0.7		
Free lambda (mg/dL)	0.57-2.63	**152.1**		**7.07**
Free K/L Ratio	0.26-1.65	**0**		**0.18**
Serum beta 2 microglobulin (mg/dL)	0.00-2.49	**7.96**		
Urine Studies				
Urinalysis		Within normal limits		
Total urine protein (mg/24 hours)	0-150	**4368**		
Free lambda monoclonal protein (mg/24 hours)		**3560**		

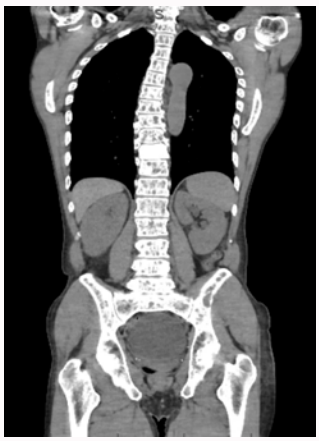

Figure 2: Coronal view of a chest/abdomen/pelvis CT scan without contrast. Note the extensive lytic lesions throughout the spine and pelvis secondary to primary plasma cell leukemia.

gene rearrangement that was identified in 55% of patient's myeloma cells. Patient was diagnosed with plasma cell leukemia. The diagnosis of type 1 cryoglobulinemia secondary to IgG/lambda primary plasma cell leukemia was made.

Hospital course

Acute kidney injury improved with administration of crystalloids. Severe lower extremity pain was managed by the pain specialist with a methadone infusion that was eventually weaned to an oral methadone regimen. Early decision was to hold plasmapheresis (cryoglobulin level was a send-out test). However, the patient's skin lesions increased in size and new eruptions appeared in other parts of the body, so plasmapheresis was initiated 3 days after presentation as a bridge to chemotherapy. After six plasmapheresis sessions, the skin lesions stabilized, no new lesions appeared, and pain medication weaning was possible. Cryoglobulin levels became undetectable after four plasmapheresis sessions. VRD (bortezomib, lenalidomide, dexamethasone) was started 9 days after presentation. No evidence of tumor lysis syndrome was noted. Patient was successfully discharged 3 weeks after presentation. Three months later, the patient achieved a very good response as he was alive, feeling well, tolerating chemotherapy, renal function was improving, skin lesions were healing but lambda chains continue to be elevated.

Discussion

Plasma cell leukemia

Plasma Cell Leukemia (PCL) is a rare and aggressive form of plasma cell dyscrasia. Although it is characterized by the presence of more than 20% plasma cells in the peripheral blood or an absolute peripheral blood plasma cell count of greater than 2.0×10^9 cells/L, this definition may change as plasma cell counts >5% have shown to be equally aggressive [1]. PCL is classified as primary (pPCL) when

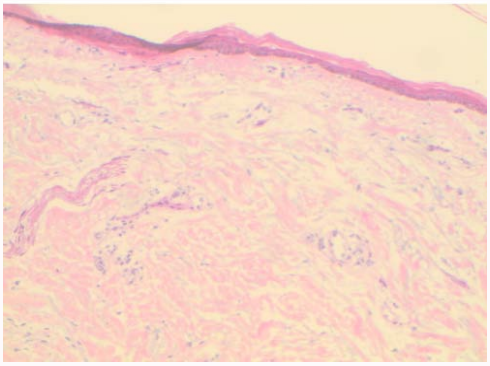

Figure 3: Skin biopsy of necrotic lesions. Note thrombotic vasculopathy from type 1 cryoglobulinemia.

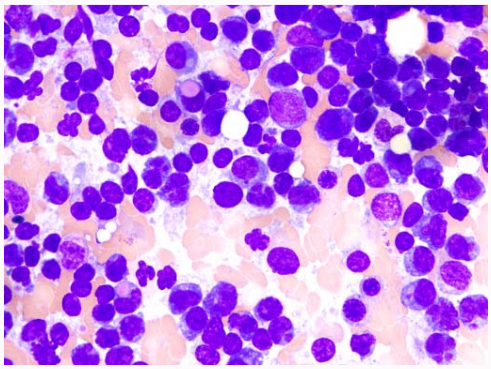

Figure 4: Bone marrow biopsy revealed extensive infiltration of the bone marrow by plasma cell leukemia.

it presents de novo in patients with no evidence of previous Multiple Myeloma (MM) and as secondary (sPCL) in patients with previously diagnosed MM, typically with relapsed or refractory disease, who develop leukemic transformation. 60% to 70% of PCL are primary (1% of all plasma cell dyscrasias), and the remaining 30% to 40% are secondary (2% to 4% prevalence in MM) [1].

Presentation of plasma cell leukemia

Compared to MM, pPCL has a more aggressive clinical presentation and the progression of the disease is very rapid (weeks), as exemplified by our case. Furthermore, patient frequently presented with extramedullary disease including organomegaly with involvement of the liver, spleen, lymph nodes, and disseminated plasmacytomas [1,2]. This propensity of plasma cells for extramedullary invasion is considered secondary to the decreased adhesion to the bone marrow stoma due to lack of CD56 expression resulting in increased peripheral circulation dissemination mediated by the expression of CD54 and VLA-4 that facilitate capillary wall adhesion and migration, and cell proliferation mediated by IL-6 [1]. Moreover, PCL is characterized by elevated lactate dehydrogenase and b2-microglobulin serum levels, reflecting the high cell burden that demands monitorization and prophylaxis for tumor lysis syndrome. In addition, light-chain disease ranges from 26% to 44% in PCL compared to 15% in MM. Flow cytometry can be obtained from peripheral blood or bone marrow samples that typically show positivity for CD38, CD138, negativity for CD19 and CD45, and variable expression of CD20 and CD56 [3]. Caveat, the small cell variants of PCL may resemble mantle cell lymphoma in immunohistochemistry and flow cytometry, but the strong expression of CD138 and lack of expression of CD45 are diagnostic of PCL [3].

Cytogenetics

Bone marrow sample cytogenetics and FISH are recommended. Cytogenetic will frequently reveal poor prognostic features such as complex karyotypes and hypodiploid or diploid cells. Deletion of 17p has been detected in almost 50% of pPCL and in 75% of secondary forms and results in allelic loss of TP53, which is associated with treatment resistance [5]. P53 loss due to mutation or deletion was observed in 56% of patients with pPCL and in 83% of patients with the secondary form [1]. Furthermore, a biallelic t53 mutation associated with ISS 3 has been denominated "double hit" and has been associated with extremely poor prognosis [4]. Finally, around 60% of patients with pPCL (compared to 15% in MM) harbor t(11;14), which is a marker of bcl-2 driven disease that has treatment implications [4,5].

Management of plasma cell leukemia

Management of PCL is extrapolated from MM. Bortezomib-based regimens constitute the first-line therapy for PCL. Bortezomib-based regimens have shown to result in response rates as high as 90% in relapsed pPCL and sPCL and up to 80% in untreated pPCL with a progression-free survival of 14 months and overall survival of 25 months [1]. Although the initial response to induction therapy is high, relapse and refractory disease will invariably develop. Newer agents have been used to manage relapse/refractory cases. For example, daratunumab is a monoclonal antibody that binds the CD38 receptor on the neoplastic plasma cell surface leading to its destruction. Daratunumab-based combination therapy improved survival in untreated, Autologous Stem Cell Transplant Ineligible (ASCT) patients with MM but at the expense of more grade 3 and 4 adverse events [7]. Another agent is venetoclax, a BH3 mimetic which releases BH3 and allows for activation of pro-apoptotic mechanism in the mitochondria [5]. Concomitant use of bortezomib has been advocated to sensitize neoplastic cells to venetoclax *via* BH3-only protein Noxa that inhibits MCL-1 which can confer venetoclax resistance at increased levels [6]. The combination of daratumumab, venetoclax, bortezomib, and dexamethasone was used in a case of treatment-refractory pPCL who failed several lines of treatment, including ASCT [5,6]. Furthermore, the combination of low dose venetoclax, daratunumab, and dexamethasone was used to successfully treat a patient with "double hit" pPCL relapse [4]. The advantageous combination of low-dose venetoclax, daratunumab, and dexamethasone permits its use in older and frail patients with kidney dysfunction that otherwise would not be candidates for first-line treatment. Finally, disease activity/remission should be closely followed. Complete remission is achieved when light chain serum concentration normalizes, the bone marrow plasma cell proportion is <5%, and the peripheral smear reveals no plasma cells.

Cryoglobulinemia in hematologic malignancies

There are three types of cryoglobulinemia. Types 2 and 3 require the presence of Rheumatoid Factor (RF) that causes precipitation of polyclonal IgG resulting in activation of complement, vasculitis, and tissue damage. Type 2 and 3 cryoglobulinemia are caused by hepatitis C virus (less commonly by other viruses) and connective tissue disorders, respectively [8]. Type 1 cryoglobulinemia is commonly secondary to lymphoproliferative disorders and the spectrum of monoclonal gammopathies. For example, Monoclonal Gammopathy of Uncertain Significance (MGUS) was found in around 38% of the cases, lymphoblastic lymphomas around 20%, multiple myeloma/smoldering myeloma in 20% of the cases and

other lymphomas in 4% of the cases [9]. Type 1 cryoglobulinemia results from the precipitation of monoclonal immunoglobulins and thrombosis of small and medium size vessels, resulting in sluggish blood flow and tissue damage, especially in acral regions due to lower temperature. These monoclonal immunoglobulins are most commonly IgG or IgM, which are manufactured by neoplastic cells. In type 1 cryoglobulinemia, the clinical manifestation will depend on the cryoglobulin concentration and temperature, the higher the concentration the more it will precipitate at warmer temperature [10]. In fact, our patient had an excessive amount of cryoglobulin, and he presented with severe skin involvement in summer.

Presentation and diagnosis of cryoglobulinemia in hematologic malignancies

The most common clinical manifestations involve skin with purpura seen in 69% of the cases, acrocyanosis in 30%, skin necrosis in 28%, and skin ulcers in 27%, predominantly located in the acral regions (coolest) such as the distal limbs, ear, and tip of the nose. Patients also may present with neuropathy (motor, sensory, or mixed) in 40% of the cases and renal involvement in around 30% [11]. Other manifestations include constitutional symptoms such as asthenia, weight loss, lack of appetite, arthritis, arthralgias, upper respiratory infections, or can be asymptomatic [9]. Furthermore, cryoglobulinemia can present as MM relapse. Our patient's laboratory data had almost all common signs seen in type one cryoglobulinemia that is worth reviewing, Table 1. He had normocytic anemia with low reticulocyte response with bone marrow infiltration. His differential count revealed plasma cells and leukoerythroblastosis that raised suspicion for leukemia. His acute kidney injury was suspected to be secondary to volume depletion from reduced oral intake from constitutional symptoms, cast nephropathy from elevated serum and urine levels of light chains, and intraluminal glomerular thrombosis from his cryoglobulinemia. A complete renal workup ruled out obstruction and glomerulonephritis as the relevant differentials. Moreover, he had elevated ESR and Rouleaux formation, both classical of MM and caused by immunoglobulin mediated red blood cell agglutination. Furthermore, he had low C4 levels and normal C3 levels, characteristic of type 1 cryoglobulinemia. This patient's rheumatoid factor was negative, ruling out type 2 and 3 cryoglobulinemia. His CT showed evidence of lytic lesions and no lymphadenopathy, suggesting a plasma cell dyscrasia rather than a lymphoproliferative disorder.

Although a rash classic of cryoglobulinemia may quickly aid the clinician towards the right diagnostic path, sometimes the unsuspected diagnosis is made during the workup for another organ manifestation (e.g., neuropathy). When the diagnosis is suspected, the clinician's task is to confirm the elevated cryoglobulin level, define the type of cryoglobulinemia, shorten the list of differential diagnoses, and finally find the etiology of cryoglobulinemia. Tissue samples may be required. Extensive necrotizing retiform purpura typically mandates urgent skin biopsy that will reveal thrombotic vasculopathy with no or little vasculitis in type 1 cryoglobulinemia. Bone marrow biopsy will be necessary if there is laboratory evidence of MG or unexplained cytopenia. Bone marrow tissue will provide information regarding the type of cancer, degree of bone marrow infiltration, and cytogenetics, the latter necessary for prognostic purposes. When the kidneys are the predominant organ involved, the diagnosis will be made with a kidney biopsy [12].

Management of type 1 cryoglobulinemia in plasma cell leukemia

The cornerstone of type 1 cryoglobulinemia management lies in treating the underlying plasma cell dyscrasia. However, severe organ dysfunction should raise consideration for disease temporization with plasma exchange. In one case series, plasma exchange was used in patients with type 1 cryoglobulinemia presenting with or having a MM relapse with complete or good response in 90% [8]. In 2 patients, plasmapheresis was delayed; resulting in progressive renal failure requiring dialysis and the other one requiring skin surgery, with rapid disease stabilization after plasmapheresis was started. Thus, plasma exchange is effective at stabilizing and improving severe organ dysfunction to allow the chemotherapy effects to take in.

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