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Bilal Saeed
163.bilal@gmail.com

Samah Abu Omar

Robert Jones

Christopher James Haas

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CASE REPORT

Light Chain Myeloma Precipitating Cryoglobulinemic Vasculitis

Bilal Saeed [a,*], Samah A. Omar [a], Robert Jones [c], Christopher J. Haas [a,b]

[a] Medstar Health Internal Medicine Residency Program, Baltimore, MD, USA
[b] Assistant Professor of Medicine, Georgetown University Medical Center, Washington, DC, USA
[c] Department of Pathology, MedStar Franklin Square Medical Center, USA

Abstract

Multiple Myeloma (MM) is characterized by monoclonal immunoglobulin production leading to widespread skeletal destruction and renal dysfunction. Light chain multiple myeloma (LCMM) affects 15% of individuals with MM and has an overall poor prognosis. Cutaneous manifestations are uncommon and it is rarely complicated by Type I Cryoglobulinemia (CG). Here we present an atypical case of κ-predominant LCMM complicated by Type I CG in an 80-year-old man who presented with a progressive non-blanching necrotic rash and ulcers involving his face, distal extremities, and oropharynx of two months duration prior to his admission at our facility. On admission to our facility, workup showed an overabundance of κ-light chains, elevated free κ/λ ratio, cryoglobulins, and an acute kidney injury. Marrow biopsy demonstrated 60% plasma cells with κ-light chain predominance. Cutaneous manifestations such as acral cyanosis and distal gangrene in LCMM indicate late stages of the disease, and such findings should raise suspicion for additional comorbid pathologies, including cryoglobulinemia, which could help direct earlier initiation of treatment.

Keywords: Light chain multiple myeloma, Cryoglobulinemia, Type I Cryoglobulinemia, κ-Light chain myeloma

1. Introduction

Multiple myeloma (MM) is characterized by the dysregulated proliferation of clonal plasma cells that cause widespread skeletal destruction, metabolic abnormalities, and renal dysfunction. These clonal cells produce monoclonal immunoglobulins (M-protein) that may be an intact immunoglobulin or, rarely, heavy and light chains individually. The latter, designated as light chain multiple myeloma (LCMM), constitutes approximately 15% of patients with MM and carries a poorer prognosis than other subtypes.[1,2] Such cases are readily detected by serum free light chain analysis and urine protein electrophoresis with immunofixation and often lack expression of immunoglobulin heavy chains. The cytogenetic abnormalities in MM involve translocation errors of the immunoglobulin heavy chain locus and its juxtaposition to an oncogene during immunoglobulin class switching (i.e., IgM to IgG or IgA), ultimately resulting in overexpression of various cell cycle genes (cyclin D1, D3) which allow the cells to escape apoptosis and clonally expand.[3]

Commonly reported clinical features include hypercalcemia, renal failure, anemia, and bone lesions, colloquially known as "CRAB" symptoms. In patients with LCMM, common symptoms at disease presentation were bone pain, weakness, and renal failure,[1] yet cutaneous manifestations - vesiculobullous lesions, digital ischemia, Raynaud's phenomenon, acrocyanosis, purpura, and leukocytoclastic vasculitis[4] - are uncommon.

In MM, monoclonal immunoglobulins may behave as cryoglobulins, precipitating from plasma. These cold-induced precipitates lead to a thrombotic process within small vessels leading to skin necrosis. The Brouet criteria classify cryoglobulinemia into three subgroups based on their immunoglobulin composition.[5] Type I cryoglobulinemia typically contains a monoclonal immunoglobulin in the setting of protein secreting gammopathies such as MGUS, MM, and

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* Corresponding author.
E-mail address: 163.bilal@gmail.com (B. Saeed).

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Waldenström Macroglobulinemia. Type II and III cryoglobulinemia contain a mixture of monoclonal IgM with rheumatoid factor activity and polyclonal immunoglobulins, commonly IgG, that are strongly associated with autoimmune conditions, such as Systemic Lupus Erythematosus, or persistent viral infections (i.e., HCV).[6] Literature has been limited with scarce reports noting an association between MM and more specifically, LCMM, with cryoglobulinemia.[5,7] To our knowledge, there are four case reports that have demonstrated an association between κ-light chain myeloma with Type I cryoglobulinemia.[8-11]

2. Case description

An 80-year-old man developed a progressive non-blanching, purpuric, and necrotic rash involving his face, extensor surfaces, and distal extremities approximately two months prior to his admission at our hospital. He noted usual health until two months prior at which time an erythematous rash that spread from his bilateral distal lower extremities cranially to involve his toes, ankles, knees, elbows, and hands. He noted no adjunctive fevers, chills, or additional systemic symptoms at that time, and no new medications, exposures, recent travel, or substance use. Within a week of his rash, he began experiencing sinus pressure and congestion and was treated for sinusitis with three separate courses of amoxicillin/clavulanate, Doxycycline, and Augmentin over the next six weeks. He was being followed by his otolaryngologist for refractory sinusitis during this time for which he was diagnosed with nasal polyposis and was offered surgery, however he refused. During these six weeks his rash continued to evolve into a non-confluent, painful, purpuric, and necrotic rash involving his lower extremities with eventual involvement of his ears, lips, and oral mucosa with ulceration leading to poor oral intake. At the end of his second course of Augmentin he followed up with his otolaryngologist who noted his necrotic lesions and ultimately sent him to the emergency department at an outside facility.

While hospitalized at the outside facility the patient remained hemodynamically stable. Laboratory diagnostics were notable for a low C4, low immunoglobulins, and a monoclonal κ-light chain restricted paraproteinemia. Additional testing for viral hepatitis, Human Immunodeficiency Virus, COVID-19, and cryoglobulins were all negative (Table 1). He underwent skin biopsy of the distal right thigh which demonstrated thrombotic

Table 1. Laboratory Diagnostics on sequential hospitalizations.

	Prior hospital	Reference Range	Our Hospital	Reference Range
BUN	21 mg/dl	(8-29)	47 mg/dl	(9-23)
Creatinine	2.9 mg/dl	(0.5−1.2)	1.94 mg/dl	(0.6−1.1)
C-Reactive Protein	21.18 mg/dl (<0.5)	(<0.5)	N/A	N/A
SARS CoV −2	Not detected	N/A	Not detected	N/A
HCV	Non-reactive	N/A	Not detected	N/A
HIV	Non-reactive	N/A	Not detected	N/A
IgM	26 mg/dl	(48−298)	30 mg/dl	(40−230)
IgG	462 mg/dl (622)	(622)	634 mg/dl	(700−1600)
C3	11.4 mg/dl (15−46)	(15−46)	104 mg/dl	(90−180)
C4	105.9 mg/dl	(76−100)	18.4 mg/dl	(10−40)
ANA Screen	Negative	N/A	Negative	N/A
ANCA Screen	Negative	N/A	Negative	N/A
Rheumatoid Factor	Negative	N/A	<10 IU/ml	<10 IU/ml
CCP Antibody	<16	(<20)	–	–
Scl-70	<1.0	(<1.0)	–	–
SSA	<1.0	(<1.0)	1	1−40
SSB	<1.0			
DsDNA	Negative	N/A	Negative	N/A
Cryoglobulins	Negative	N/A	Positive	N/A
UPEP	κ light chain without a corresponding heavy chain (32% of total protein)	N/A	Free kappa light chain	N/A
SPEP	κ-monoclonal protein without a corresponding heavy chain comprising 1.23% of the total protein	N/A	Free kappa light chain	N/A
Free κ	–	–	5229 mg/L	(3.30−19.4)
Free λ	–	–	8.34 mg/L	(5.71−23.4)
Free κ/λ Ratio	–	–	627	0.26−1.25

vasculopathy and was discharged with a presumptive diagnosis of COVID-19 induced vasculopathy, despite the negative serology. A few days after his discharge, he was seen in the dermatology clinic for which he was initiated on Apixaban and Prednisone 60 mg daily. He failed to show improvement and within one week of his dermatology appointment, he presented to our facility due to the increasing lethargy, persistent necrotic rash, oral ulceration and decreased oral intake. No neurological symptoms (i.e., altered mentation, visual disturbance, nystagmus) were noted on an outpatient basis.

On presentation, he was afebrile, mildly tachycardic (98–105 bpm), and hypertensive (140–160 mmHg), with a preserved oxygen saturation (93–97%) on room air. Physical examination was remarkable for a multifocal, purpuric, non-blanching violaceous rash localized to the bilateral external ears, knees, and elbows as well as open, non-healing dry wounds of the ankles. The oropharynx and bilateral calcanei demonstrated superimposed necrosis with shallow ulceration upon the background rash (Fig. 1). Laboratory diagnostics were notable for a normocytic, normochromic anemia, with no adjunctive abnormalities in his white blood cell or platelet counts. A metabolic panel, including serum creatinine and calcium, were unremarkable and urinalysis demonstrated mild proteinuria without hemoglobinuria. Inflammatory markers including C-reactive protein and erythrocyte sedimentation rate were elevated. Rheumatological markers were negative. Infectious workup including Hepatitis Panel, HIV, respiratory viral panel, and COVID-19 were negative. Repeat C3 and C4 were normal. Serum and urine electrophoresis demonstrated a peak in the gamma globulin region. Serum free light chains revealed an overabundance of κ-light chains with a κ/λ ratio of 627. Cryoglobulins were found to be positive. Flow cytometry revealed a small population of monoclonal plasma cells (0.02% of the leukocytes) suspicious for a plasma cell dyscrasia. The laboratory diagnostics and reference ranges are listed in Table 1. Bone marrow biopsy confirmed the diagnosis of MM with plasma cells comprising at least 60% cellularity with κ-light chain predominance (Fig. 2).

Oncology was consulted and recommended initiation of dexamethasone with plans for outpatient treatment with Cyclophosphamide, Bortezomib, and Dexamethasone (CYBORD). Unfortunately, prior to initiation of his chemotherapy, he was readmitted to an outside facility for Methicillin Sensitive Staphylococcus bacteremia. He was transferred to a tertiary academic center for chemotherapy where he completed three cycles of CYBORD therapy. Repeat serum and urine protein immunofixation demonstrated the presence of a free κ-light chain monoclonal protein and a persistently elevated κ/λ ratio of 382.4. Whole-body PET/CT demonstrated multiple FDG-avid osseous lesions in the thoracic and lumbar spine, left pelvis, and left hip favoring metastasis (Fig. 3). A repeat bone marrow biopsy was performed and demonstrated κ-restricted plasma cells. His course was complicated by hypoxemic respiratory failure due to hospital-acquired pneumonia and an apical pneumothorax and he was transitioned to comfort care.

3. Discussion

Cutaneous manifestations of multiple myeloma occur infrequently and are rare in the absence of pre-existing 'CRAB' symptoms, oftentimes only occurring late in the disease.[12,13] Histopathologically, direct infiltration of plasma cells has been observed, yet a number of cases also demonstrated small vessel occlusion due to cryoglobulin deposition.[12] Our patient's rapid and progressive acral necrosis were explained by the presence of type I cryoglobulins secondary to a κ-LCMM.

Type I cryoglobulinemia may cause cutaneous lesions including digital ischemia and cutaneous

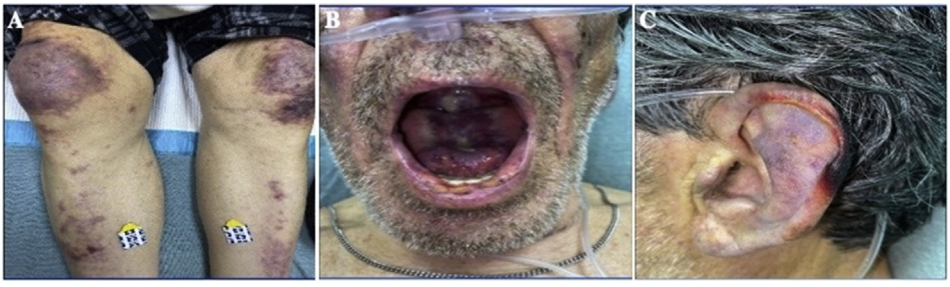

Fig. 1. Skin findings on bedside physical examination. Panel A demonstrates a violaceous, non-blanching, purpuric rash involving the bilateral knees and extensor surfaces of the lower extremities. Panel B demonstrates erosive oral ulcerations upon a background of petechiae and purpura. Panel C demonstrates evidence of a necrotic appearing lesion of the left pinnae.

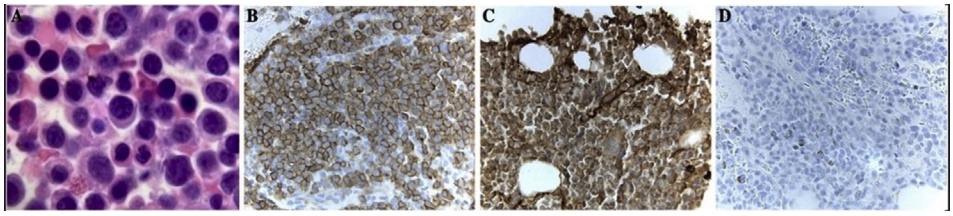

Fig. 2. Immunohistochemical staining of bone marrow biopsy. Panel A demonstrates a Hematoxylin and Eosin (H&E) stain highlighting the effacement of normal hematopoietic marrow elements by sheets of plasma cells, characterized by abundant pink cytoplasm, eccentric nuclei, perinuclear clearing and clock-face chromatin. Panel B demonstrates diffuse immunohistochemical staining for CD138, a surface plasma cell marker. Panel C demonstrates abundant κ -positivity in the plasma cells, Panel D displays plasma cells which are negative for λ by immunohistochemistry.

necrosis, which without treatment may progress to gangrene in more than half of cases.[14] The lower extremities, as in our patient, are commonly involved, though multiple sites may be affected.[15,16] Cryoglobulin insolubility and aggregation have been hypothesized to depend upon a myriad of interacting protein-related (concentration, ionic bond strength, and amino acid composition) as well as environment-related factors (temperature and pH).[17] Specific amino acid sequences of the IgG cryoglobulins undergo a structural change and auto-aggregate at the level of the quaternary structure of the protein due to a combination of weak non-ionic and hydrophobic interactions culminating in its precipitation.[18] The cryocrit, a measure of centrifuged volume of the precipitate as a percentage of the original serum volume at 4 °C is a prominent laboratory hallmark of cryoglobulinemia, with a cryocrit close to zero considered normal. A cryocrit of 0.5–1% or a direct cryoglobulin concentration over 50mcg/ml is considered diagnostic for cryoglobulinemia.[19,20]

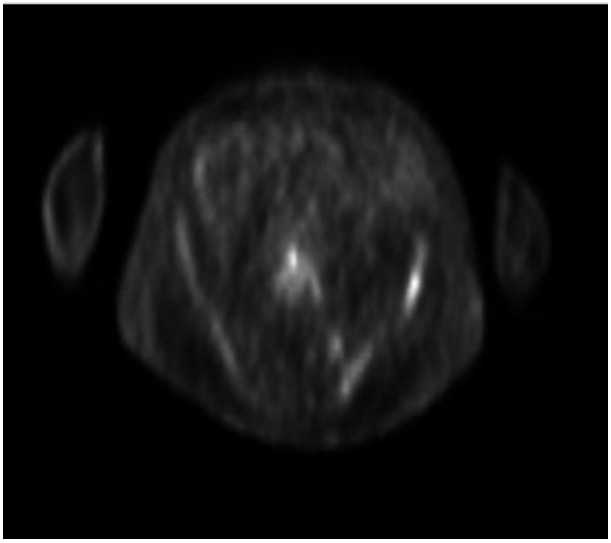

Fig. 3. PET/CT demonstrating foci of increased metabolic activity corresponding to lytic lesions in left iliac crest (SUV) = 5.7.

Intriguingly, Type I cryoglobulinemia may have a cryocrit of nearly 50% or involve the entire serum of the affected patient.[19] Ninomiya et al. demonstrated a cryocrit of 20% in a case of Type I cryoglobulinemia with underlying IgG λ and IgA κ monoclonal gammopathy, ultimately leading to small vessel occlusion.[21] In a review of 64 MM cases with cutaneous manifestations, IgG MM was the most frequently associated subtype, with superimposed cryoglobulinemia associated with a progression of erythematous macules to skin necrosis of the head, neck and oral mucosa, similar to our case. Additionally, they reported a higher association of IgG κ and IgA λ MM with Type I cryoglobulinemia.[22]

The case presented here, however, is atypical in that our patient demonstrated Type I cryoglobulinemia in the context of a κ-LCMM without adjunctive heavy chain involvement.[4] The incidence of Type I cryoglobulinemia and LCMM is rare, limited to six case reports, with four that highlighted predominant hyperviscosity symptoms - headache, confusion, diplopia, and sudden-onset hearing loss - without cutaneous involvement.[8-11] Two recently published cases demonstrated findings of skin ulcerations at the extremities in the setting of relapsed cryoglobulinemic vasculitis due to underlying monoclonal IgG Lambda and represent a heavy chain component.[23,24] As such our case report is an addition to the aforementioned rare cases highlighting cutaneous lesions as a presenting complaint with involvement of κ light chain. The pathogenesis of Type I cryoglobulinemia, including its molecular formation and aggregation, in the presence of predominant κ-chain myeloma, has yet to be elucidated. Bachrach et al. proposed that large quantities of light chains intrinsically enhance their ability to form protein-cell matrices and increase intracellular adhesion.[8] Dasanu et al. and Carter et al. theorized that the high serum viscosity of LCMM is due to the presence of a large or highly polymerized molecule, leading to an unusual degree of aggregation of the κ-light chains.[9,10] Although

both cases reported that their patients presented with Raynaud's complicated by hyperviscosity, neither of the reported cases of κ-LCMM demonstrated mucocutaneous necrosis and ulceration.

Hyperviscosity often manifests as an acute neurologic change - confusion, dementia, stroke or coma - and requires prompt intervention with plasmapheresis. Measurement of serum viscosity aids in its diagnosis with a value of at least 4 cP (normal $\leq$1.5 cP).[25] It is known to occur frequently in Waldenstrom's Macroglobulinemia where there is formation of large polymerized IgM macromolecules.[10] The incidence of hyperviscosity syndrome with pure κ-light chain myeloma has been limited to the sporadic case reports mentioned previously, with its pathophysiology linked to the ability of the κ-light chains to form dimers and tetramers leading to macromolecular aggregation.[10,11] Our patient's encephalopathy was felt to be multifactorial—acute hypoxemia, sepsis, and/or antibiotic-associated (cefepime). Unfortunately, plasma viscosity testing was not performed during his hospitalizations, thus precluding a diagnosis of this phenomenon.

The incidence of renal failure is significantly higher in LCMM versus classic MM,[1,26] and is commonly due to crystalline precipitation of monoclonal free light chains within distal tubules.[27] On the other hand, renal failure may also occur as a result of thrombotic disease, especially with Type I cryoglobulinemia, however, this is limited to a single case series of 7 patients.[28] Renal biopsy was not pursued in our patient, thus the etiopathogenesis of our patient's renal insufficiency remains speculative. However, both crystalline deposition of the free light chains in the distal tubules and formation of glomerular capillary thrombi from cryoglobulinemia remain possible etiologies.

Management of Type I cryoglobulinemia depends upon the treatment of the underlying malignancy, symptoms associated with vascular thrombosis, and other complications such as renal failure and hyperviscosity syndrome. High dose chemotherapy followed by autologous hematopoietic cell transplant (HCT) is considered standard of care for eligible patients with newly diagnosed MM. At this time, however, there is no defined eligibility criteria for autologous HCT in the US and eligibility varies across institutions. Multiple combinations of induction chemotherapy exist, and treatment decisions depend on availability, tolerability of side effects, renal function, and molecular studies (i.e., karyotype). Briefly, Bortezomib, lenalidomide, dexamethasone is the preferred chemotherapy due to a superior progression-free and overall survival.[29] Treatment with Bortezomib has shown statistically significant improved outcomes than non-Bortezomib treatment groups as demonstrated by Zhang et al.[30] Plasmapheresis is a reasonable option in patients with complications,[28] however, there are no randomized trials have demonstrated a mortality benefit. Although our patient may have benefitted from plasmapheresis symptomatically, his rapidly progressive skin necrosis, renal failure and significantly elevated serum free light chains with a high tumor burden all contributed to an overall poor prognosis, even prior to receiving high dose chemotherapy.

4. Conclusion

This case is a reminder of the atypical presentation of LCMM where cutaneous manifestations including acral cyanosis and distal gangrene can appear without preexisting 'CRAB' symptoms. It also identifies the rare association of pure κ-light chain myelomas with Type I cryoglobulinemia as compared to other monoclonal subtypes such as IgG and IgM. Although LCMM without cryoglobulinemia is known to have an overall poor prognosis, outcomes with early therapeutic intervention are not known. Therefore, swift recognition of cold-aggravated, purpuric and necrotic lesions of the distal extremities should raise providers' index of suspicion for the presence of cryoglobulins along with an underlying malignant process which could potentially direct earlier initiation of treatment resulting in favorable outcomes.

Conflict of interest

No potential conflict of interest was reported by the author(s).

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