Clinical Case Report

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A multiple myeloma that progressed as type I cryoglobulinemia with skin ulcers and foot necrosis

A case report

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Abstract

Rationale: Type I cryoglobulinemia is a rare and life-threatening condition. It occurs mainly in B-cell lymphoproliferative disorder. In almost half of the patients, type I cryoglobulinemia is characterized by severe cutaneous involvement.

Patient concerns: A 71-year-old man comes to our observation because of the onset of persistence of paresthesia and painful acrocyanosis in the fingers and toes. IgG-k multiple myeloma treated with chemotherapy and radiation therapy on the left iliac wing characterized his clinical history. At the evaluation of response after the first-line therapy, the patient achieved a very good partial response. At the time of progression, the same myelomatous disease has taken a typical behavior of cryoglobulinemia.

Diagnoses: Type I multiple myeloma-associated cryoglobulinemia was diagnosed.

Interventions: The patient underwent to an immediate composite therapeutic approach based on prostanoid infusion, plasmapheresis along with second-line chemotherapy.

Outcomes: Despite the rapid biochemical response, the ischemia of the feet worsened. Moreover, a bacterial infection overlapped. The surgical amputation of both feet was necessary. Allowing MM cytoreduction continuation the patient's clinical condition became stabilized.

Lessons: Though rare, type I cryoglobulinemia can be associated with plasma cell dyscrasias. Any delay in diagnosis and the start of therapy can cause worsening of organ damage and endanger the patient's life. Therapeutic strategies in these cases should be directed to the underlying diseases.

Abbreviations: CRAB = calcium elevated, renal failure, anemia, bone lesions, ISS = International Staging System, MC = monoclonal component, MM = multiple myeloma, MRI = magnetic resonance imaging, STEMI = ST elevation myocardial infarction, VGPR = very good partial response.

Keywords: integrated therapeutic approach, monoclonal component, multiple myeloma, skin ulcers, type I cryoglobulinemia

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1. Introduction

Multiple myeloma (MM) is a plasma cell tumor that localizes to and expands in the bone marrow, and produces a monoclonal immunoglobulin, namely monoclonal component (MC).[1] The MC exhibits various features and biological activities, and can cause a plethora of disorders such as hyperviscosity syndrome, renal failure, amyloidosis, and autoimmune disease.[1] In rare cases, the MC can behave as a cryoglobulin, generally of type I.[2]

Type I cryoglobulin is a single monoclonal circulating immunoglobulin that precipitates with cold temperature and dissolves with rewarming. It is always linked to a B-cell lymphoproliferative disorder.[3] Type I cryoglobulin is found in 10% to 15% of patients with cryoglobulinemia[4,5] and is considered a life-threatening disorder because of the severity of cutaneous and renal involvement, and the underlying hemopathy.[6,7] Signs and symptoms are generally associated with vascular occlusion by the cryoprecipitate, although small-vessel vasculitis features may also be seen (e.g., purpura, glomerulonephritis, and neuropathy).[8] Skin involvement is characterized by the presence of symptoms linked to cold exposure, such as acrocyanosis and Raynaud's phenomenon, livedo, urticaria, cold-induced necrotic purpura of the extremities, painful necrotic ulcers, or gangrene of the extremities.[8]

In this report, we describe a case with atypical progression of MM in which the MC became a type I cryoglobulin. This behavior, that was not present at diagnosis, could be attributed to clonal selection of plasma cells with the emergence of a subclone producing this type of monoclonal protein. In this case, the diagnosis of MM progression was difficult to distinguish from the coexistence of 2 different diseases.

2. Case report

The informed consent was obtained from the patient for publication of this case report and accompanying images.

A 71-year-old caucasian male patient comes to our observation in November 2017 because of the onset of persistent paresthesias and painful acrocyanosis in the fingers and toes. His clinical history was characterized by paroxysmal atrial fibrillation, previous ST elevation myocardial infarction (STEMI) treated with aortocoronary bypass. In April 2015, due to pain in the left hip, he underwent magnetic resonance imaging (MRI), with evidence of osteolytic bone lesion within the left iliac crest. Serum electrophoresis showed a MC, typed as IgG-k. The bone marrow biopsy showed a bone marrow infiltration >90% of plasmocytic elements (CD138, MUM1-IRF4 and kappa chains positive). MC was 15.5% (1.19 g/dL). Free light chains ratio was 12.64. IgG-k Symptomatic International Staging System (ISS) stage I MM was diagnosed and the patient underwent therapy with bortezomib-melphalan-prednisone (V-MP). From July to August 2015, he receives radiation therapy on the left iliac wing (20 Gy total dose). The revaluation of the disease carried out at the end of the treatment showed a very good partial response (VGPR) and zoledronic acid treatment was started.

In September 2017, the patient experienced chest discomfort and dyspnea, along with pulmonary rales and peripheral edema. The echocardiographic examination, showing biatrial dilation and a pulmonary scintigraphy was performed, highlighting perfusion defects with segmental extension at the right lung apical segment, likely to be attributed to an embolic process. A venous and arterial eco-color Doppler examination of the lower limbs was also performed, ruling out thrombosis. The patient was admitted as an inpatient and low molecular weight heparin (LMWH) 1 mg/kg bid was started.

In October 2017 finger paresthesia appeared, bilaterally. Over time this neurologic symptoms worsened, involving the feet as well. Because of persistence of paresthesias, painful acrocyanosis in the fingers and toes (Fig. 1A–C), massive thrombosis of feet vessels (Fig. 1D), and ulcerative lesions of the ankles (Fig. 1E–G) he was admitted to an Internal Medicine Unit. Blood tests were normal: hemoglobin (Hb) 134 g/L, platelets 152,000/μL, and leucocytes 6250/μL. Leucocyte differential count, calcium, and lactate dehydrogenase (LDH) serum level were normal. β 2-Microglobulin was 4.3 mg/L; albumin was 36 g/L; k/λ free light chain ratio was 16.42. No Bence Jones proteinuria was detected. Bone marrow plasma cell infiltration was 54%. The MC was 1.59 g/dL at serum electrophoresis (Fig. 2A) typing as IgG-k (Fig. 2B). Circulating cryoprecipitate was found along with rheumatoid factor and hepatitis C virus (HCV) negative tests. The electrophoresis performed after removal of cryoprecipitate showed the reduction of two-thirds of the MC (Fig. 2C), and the cryoprecipitate was typed as IgG-k with immunofixation (Fig. 2D). To confirm the cryoprecipitate behavior of the MC the immunotyping (Fig. 2E) and electrofocusing (Fig. 2F) tests were performed.

The progressive increase of the same isotype of MC (IgG-k) with the same electrophoretic mobility of the first diagnosis as well as the progressive increase in the infiltration of the bone marrow by plasma cells characterized by the same initial phenotype suggest that at the time of progression the same myelomatous disease has taken a typical behavior of cryoglobulinemia. From these observations type I MM-associated cryoglobulinemia was diagnosed and the patient underwent to an immediate composite therapeutic approach based on prostanoid infusion, plasmapheresis along with cytoreduction with bendamustine-prednisone (BP). Despite rapid biochemical response (MC 0.33 g/dL), the ischemia of the feet worsened. Moreover, a bacterial infection overlapped, and the surgical amputation of both feet was necessary. After the first cycle of chemotherapy, both feet were amputees without delay in the continuation of the therapeutic process.

In June 2018, after 8 cycles of chemotherapy, the patient obtained a partial response of multiple myeloma with the disappearance of cryoglobulin. A quarterly follow-up was started. The patient underwent the application of the foot prostheses with the recovery of autonomous walking.

3. Discussion

Type I cryoglobulinemia is considered a rare and life-threatening condition characterized by severe cutaneous involvement (necrosis and ulcers) in almost half the patients with this disorder. It causes high serum cryoglobulin levels and a lower frequency of glomerulonephritis than other types of cryoglobulinemia.[3,9] In lymphoproliferative disorders (i.e., monoclonal gammopathies and B-cell lymphomas), type I cryoglobulinemia is rarely evidenced but can be responsible for severe organ damage.[2] In type I cryoglobulinemia, a predominant role for hyperviscosity in the pathogenesis of vasculitis cutaneous manifestations has been proposed, with minor relevance of immune complex-induced vasculopathy.[10] However, in our patient, as in the majority of reported cases of organ damage due to monoclonal gammopathy-associated type I cryoglobulinemia,[2,3,8,9] no classical manifestations of hyperviscosity syndrome were found.

In our patient, the first evidence of MM was neither accompanied by signs and/or symptoms of hyperviscosity, nor were vasculitic manifestations present. After the first-line therapy, our patient was healthy. As MM progressed, despite no signs of MM-related organ damage (i.e., elevated calcium, renal failure, anemia, bone lesions—CRAB),[11] characteristic signs of small-vessel vasculitis and small-vessel occlusion could be observed. In fact, the development of pulmonary perfusion defects without evidence of venous and/or arterial thrombosis, nor cardiac arrhythmias or other anomalies, could be signs of pulmonary capillaritis.[12] One month after MM progressed, the patient complained of paresthesia and, at a later time, of painful acrocyanosis in the fingers and toes. Rapidly, diffuse progressive vascular occlusion-related damage at both superior and inferior extremities appeared and the patient came to our attention. These symptoms were accompanied by the presence of a cryoprecipitate that was shown to contain the MC of MM.

The change in behavior of the disease during its natural history in this patient can be explained by the selection of a clone producing the cryoglobulin at progression. In fact, intraclonal heterogeneity is now considered an important feature of MM biology, represented by a composite mixture of clones without a linear evolution.[13–15] The clonal evolution theory, based on Darwinian behavioral characteristics of cancer stem cells, implies the importance of genomic instability, the role of epigenetics, and the impact of the cancer microenvironment on clonal selection.[13,14] Following initiation, myeloma plasma cells become

Figure 1. (A–C) Ischemic lesions of the fingers (panel A and B) and toes (panel C). (D) Extensive vascular thrombosis of the foot. (E–G) Ulcerative lesions of the ankles.

heterogeneous, evolving from normal plasma cells to the final stage of the transformation process, plasma cell leukemia or extramedullary myeloma.[13] MM cells present with significant genomic instability that plays a major role in MM clonal heterogeneity and the evolution of this disease.[16] During the evolution process, a pivotal role is played by the microenvironment which is able to guide clonal evolution and heterogeneity in MM.[17–20] Finally, selective pressure from treatment(s) may have caused the disappearance of the original dominant clone in this patient, with the appearance of a new dominant clone producing the cryoglobulin.[21]

In type I cryoglobulinemia, treatment is reserved for symptomatic disease and is directed against the underlying disorder. Only aggressive and prompt treatment can induce a rapid response of hematologic disease and reduce the organ damage caused by cryoglobulin.[22–24] In our patient, despite the prompt start of an integrated therapeutic approach with prostanoid infusion,[25] plasmapheresis,[23,26]

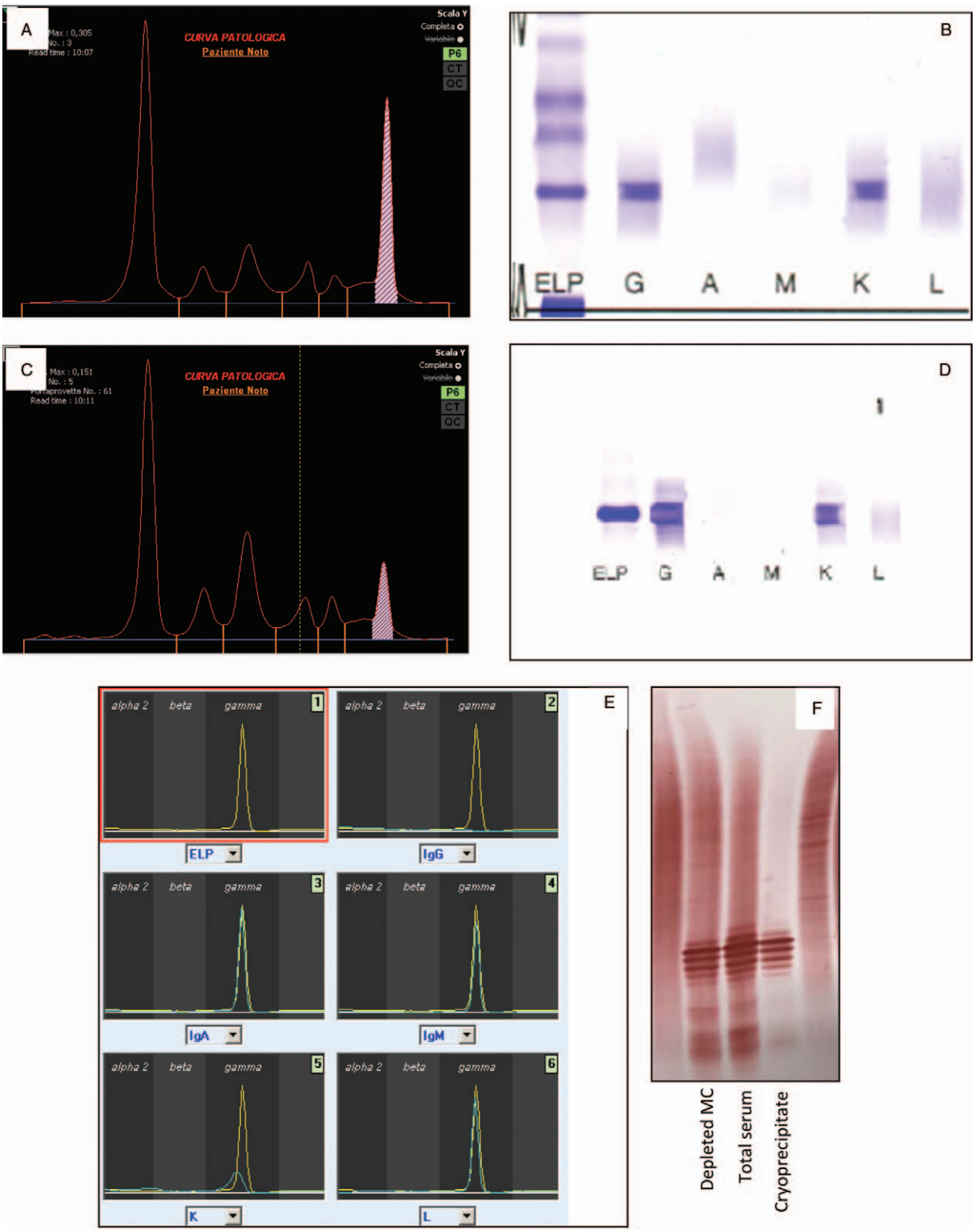

Figure 2. (A) Serum electrophoresis and (B) immunofixation of the serum proteins. (C) Electrophoresis of the serum proteins carried out after removal of the cryoprecipitate. (D) Immunofixation of the cryoprecipitate. (E) Immunotyping of the cryoprecipitate. (F) Electrofocusing of the serum total protein, cryoprecipitate, and supernatant after cryoprecipitate removal.

and chemotherapy,[2,27] vascular damage was advanced and irreversible. Therefore, the patient was subjected to amputation of both feet because of necrosis. The ulcers and necrotic purpura of hands and ankles have slowly healed, while the paresthesias and painful acrocyanosis have progressively resolved in parallel to the reduction of the cryocrit percentage and cryoglobulinemia.

In conclusion, though rare, type I cryoglobulinemia can be associated with plasma cell dyscrasias. Thus, cryoglobulin testing should be done in all patients presenting with cold-aggravated,

purpuric, necrotic lesions. Any delay in diagnosis and the start of therapy can cause worsening of organ damage and endanger the patient's life. Therapeutic strategies in these cases should be directed to the underlying diseases; this is particularly important in hematological disorders.

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References

[1] Kumar SK, Rajkumar V, Kyle RA, et al. Multiple myeloma. Nat Rev Dis Primers 2017;3:17046.
[2] Payet J, Livartowski J, Kavian N, et al. Type I cryoglobulinemia in multiple myeloma, a rare entity: analysis of clinical and biological characteristics of seven cases and review of the literature. Leuk Lymphoma 2013;54:767–77.
[3] Terrier B, Karras A, Kahn JE, et al. The spectrum of type I cryoglobulinemia vasculitis: new insights based on 64 cases. Medicine (Baltimore) 2013;92:61–8.
[4] Brouet JC, Clauvel JP, Danon F, et al. Biologic and clinical significance of cryoglobulins. A report of 86 cases. Am J Med 1974;57:775–88.
[5] Morra E, Cryoglobulinemia . ASH Education Book. Hematol Am Soc Hematol Educ Program 2005;2005:368–72.
[6] Monti G, Galli M, Invernizzi F, et al. Cryoglobulinaemias: a multi-centre study of the early clinical and laboratory manifestations of primary and secondary disease. GISC. Italian Group for the Study of Cryoglobulinaemias. QJM 1995;88:115–26.
[7] Trejo O, Ramos-Casals M, Garcia-Carrasco M, et al. Cryoglobulinemia: study of etiologic factors and clinical and immunologic features in 443 patients from a single center. Medicine (Baltimore) 2001;80:252–62.
[8] Harel S, Mohr M, Jahn I, et al. Clinico-biological characteristics and treatment of type I monoclonal cryoglobulinaemia: a study of 64 cases. Br J Haematol 2015;168:671–8.
[9] Cacoub P, Comarmond C, Domont F, et al. Cryoglobulinemia vasculitis. Am J Med 2015;128:950–5.
[10] Caimi G, Carlisi M, Urso C, et al. Clinical disorders responsible for plasma hyperviscosity and skin complications. Eur J Intern Med 2017;42:24–8.
[11] Rajkumar SV. Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol 2016;91:719–34.
[12] Jara LJ, Vera-Lastra O, Calleja MC. Pulmonary-renal vasculitic disorders: differential diagnosis and management. Curr Rheumatol Rep 2003;5:107–15.
[13] Greaves M, Maley CC. Clonal evolution in cancer. Nature 2012;481: 306–13.
[14] Burrell RA, McGranahan N, Bartek J, et al. The causes and consequences of genetic heterogeneity in cancer evolution. Nature 2013;501:338–45.
[15] Morgan GJ, Walker BA, Davies FE. The genetic architecture of multiple myeloma. Nat Rev Cancer 2012;12:335–48.
[16] Baylin SB, Jones PA. A decade of exploring the cancer epigenome—biological and translational implications. Nat Rev Cancer 2011;11:726–34.
[17] Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. Nat Med 2013;19:1423–37.
[18] Hideshima T, Mitsiades C, Tonon G, et al. Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets. Nat Rev Cancer 2007;7:585–98.
[19] Camussi G, Deregibus MC, Tetta C. Tumor-derived microvesicles and the cancer microenvironment. Curr Mol Med 2013;13:58–67.
[20] Yang C, Robbins PD. The roles of tumor-derived exosomes in cancer pathogenesis. Clin Devel Immunol 2011;2011:842849.
[21] Keats JJ, Chesi M, Egan JB, et al. Clonal competition with alternating dominance in multiple myeloma. Blood 2012;120:1067–76.
[22] Muchtar E, Magen H, Gertz MA. How I treat cryoglobulinemia. Blood 2017;129:289–98.
[23] Moussi-Frances J, Sallée M, et al. Apheresis to treat systemic vasculitis. Joint Bone Spine 2018;85:177–83.
[24] Treon SP. How I treat Waldenström macroglobulinemia. Blood 2015;126:721–32.
[25] Kawakami T, Kawasaki K, Mizoguchi M, et al. Therapeutic effect of lipoprostaglandin E1 on livedoid vasculitis associated with essential cryoglobulinaemia. Br J Dermatol 2007;157:1051–3.
[26] Kalayoglu-Besisik S. The use of emergency apheresis in the management of plasma cell disorders. Transfus Apher Sci 2018;57:35–9.
[27] Cook G, Zweegman S, Mateos MV, et al. A question of class: treatment options for patients with relapsed and/or refractory multiple myeloma. Crit Rev Oncol Hematol 2018;121:74–89.