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CASE REPORT

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Monoclonal gammopathy of clinical significance in a young patient treated with melphalan-thalidomide-prednisone

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Key Clinical Message

We report an observation of a young patient presenting with severe type 1 cryoglobulinemic vasculitis revealing a monoclonal gammopathy of clinical significant. Treatment with Melphalan-Thalidomide Prednisone improved the symptoms. Early diagnosis would prevent serious tissue damage.

Abstract

Monoclonal gammopathy encompass diverse clinical forms. Only the cancerous form, multiple myeloma (MM), is treated based on specific diagnostic criteria. A new clinical entity, monoclonal gammopathy of clinical significance (MGCS), warrants special attention due to its need for specific treatment. It involves patients with signs of potentially severe organ involvement that do not meet MM criteria. We present the case of a 34-year-old Malagasy woman with severe type I cryoglobulinemic vasculitis associated with noncancerous monoclonal gammopathy, showing a favorable outcome after treatment with Thalidomide. Symptoms included toe necrosis, a severe ulcer on the left calf evolving for 3 months, and stocking-like dysesthesias. Investigations revealed monoclonal gammopathy at 30.1 g/L, proteinuria at 1 g/24 h, medullary plasma cell at 6%, and circulating cryoglobulin of Ig kappa type. CRAB criteria (anemia, hypercalcemia, renal insufficiency, and osteolysis) were absent. Treatment with Thalidomide, combined with corticosteroids and local care for 4 months, resulted in ulcer healing, disappearance of dysesthesias, and persistent normalization of gammaglobulin. Our case underscores the importance of specific treatment for MGCS.

KEYWORDS

cryoglobulinemia, melphalan-thalidomide-prednisone, MGCS, toe necrosis

1 | INTRODUCTION

Monoclonal gammopathy encompass all pathologies resulting from the hypersecretion of gammaglobulin due to medullary proliferation of plasma cells. They predominantly affect individuals over 50 years old, with occurrences in individuals under 40 years old being less than 2%.[1] The immediate therapeutic indication concerns the cancerous form known as multiple myeloma (MM), defined by the presence of one or more of the following criteria: (1) target organ lesions, including hypercalcemia, renal insufficiency, anemia, lytic bone lesions (CRAB), (2) medullary plasma cell clone greater than 60%, serum-free light chain (FLC) ratio ≥ 100, (3) more than one focal lesion found on MRI. These criteria must be associated with a medullary plasma cell rate greater than 10% or bone or extra-medullary plasma cell proven by biopsy.[2] In the asymptomatic form known as monoclonal gammopathy of undetermined significance (MGUS), regular monitoring is recommended. Currently, potentially severe organic manifestations that do not meet the diagnostic criteria for MM are described.[3–5] These clinical forms, referred to as monoclonal gammopathy of clinical significance, warrant specific and urgent management.[6] We report a case of a 34-year-old female patient presenting with clinically significant monoclonal gammopathy with toe necrosis due to type 1 cryoglobulinemic vasculitis, showing favorable evolution after treatment with melphalan-thalidomide-prednisone.

2 | CASE HISTORY

The patient was a 34-year-old woman with no notable medical history, particularly no history of infectious episodes or medication use. She was admitted in early May 2023 for toe necrosis. Three months before her admission, she had developed necrosis of the second and third toes bilaterally. Progressive extension of the necrosis was noted, affecting other toes and the dorsum of the foot. The necrosis was associated with a stocking-like paresthesia (triggered by cold and relieved by warming). There was no fever and her general condition was well-maintained.

Clinical examination at admission revealed stable hemodynamic status and afebrile condition. Dermatologically, bilateral necrotic lesions of the feet were observed (Figure 1) along with livedo on the legs and a deep ulcer on the left leg (singular, suspended, irregularly bordered, slightly infiltrated with a dirty fibrino-necrotic base, digging, and with minimal budding on the right leg) (Figure 2). The face, trunk, and upper limbs were spared. Cardiovascular examination showed present and symmetrical pulses in the lower limbs, with no cardiac murmurs.

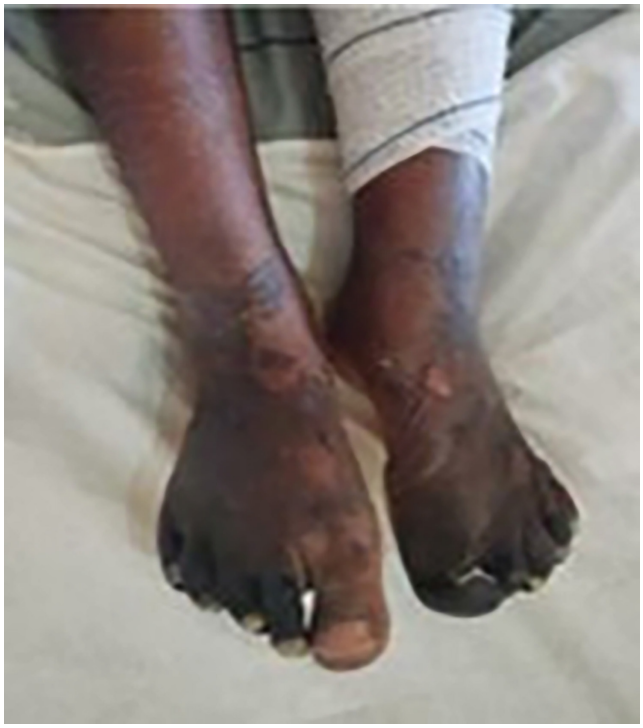

FIGURE 1 Bilateral necrotic lesion of the feet and gangrene of the toes at the time of diagnosis. The photograph was taken at the Rheumatology Department, CHU Befelatanana Antananarivo, Madagascar.

There was no splenomegaly or superficial lymphadenopathy. Neurological examination of the lower limbs revealed no motor deficit, and thermoalgesic and epicritic sensitivity were normal, with present osteotendinous reflexes. The rest of the examination was unremarkable.

3 | METHODS: DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS AND TREATMENT

In fact, the main clinical symptoms, such as progressive necrosis of the toes with livedo and paresthesia of the feet, partially reversible after rewarming, suggest two diagnostic hypotheses: lower limb ischemia due to embolism or small-to-medium caliber vasculitis. Arterial angioscan of the lower limbs and Cardiac Doppler ultrasonography were normal, ruling out the diagnosis of lower limb ischemia due to embolism.

Laboratory tests revealed monoclonal gammopathy at 30.1 g/L, non-dystrophic medullary plasma cells at 6%, and circulating monoclonal cryoglobulin of type IgG kappa. Initial and follow-up laboratory results are summarized in Table 1.

Standard X-rays of the bones (spine, pelvis, skull) show no geodes or osteolysis. Cardiac Doppler ultrasonography

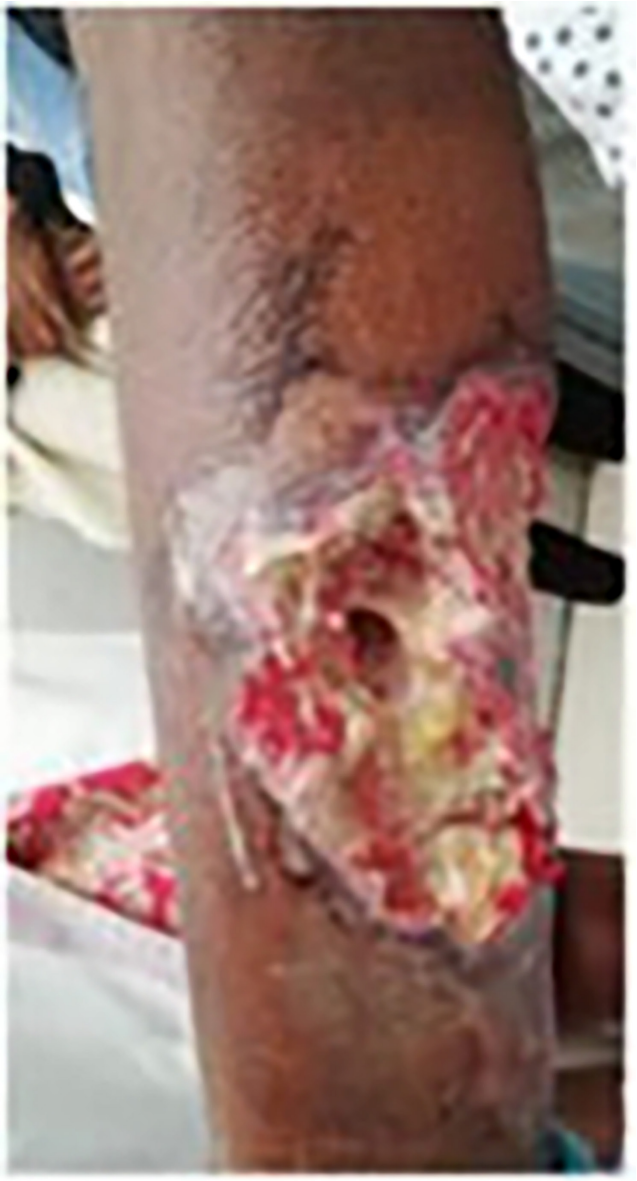

FIGURE 2 Deep ulcer of the left leg with irregular border, slightly infiltrated with a dirty fibrino-necrotic background at the time of diagnosis. The photograph was taken at the Rheumatology Department, CHU Befelatanana Antananarivo, Madagascar.

was normal. Skin biopsy histology shows fibrinoid necrotic vessels surrounded by inflammatory cells.

The diagnosis of clinically significant monoclonal gammopathy with toe necrosis due to type 1 cryoglobulinemic vasculitis was established in the presence of monoclonal gammopathy that did not meet the CRAB criteria (hypercalcemia, renal insufficiency, anemia, bone lesions), bone marrow plasmacytosis of less than 10% and circulating monoclonal cryoglobulin of the Ig G kappa type.

The end of May 2023, the patient received a bolus of Methylprednisolone at 500 mg/day for 3 days, followed by a bolus of cyclophosphamide at 1 g/day. The lack of clinical improvement after 1 month of this treatment, along with the extension of foot necrosis, prompted the initiation of specific chemotherapy targeting the B clone on July 1, 2023. This involved the MTP protocol, combining Melphalan at 9 mg/m^2 for 4 days, Thalidomide at 100 mg/day was continued for 45 days, and Prednisolone at 60 mg/m^2 for 4 days. The medical treatment was complemented by bilateral transmetatarsal amputation after 20 days of chemotherapy.

4 | CONCLUSION AND RESULTS: OUTCOME AND FOLLOW-UP

The patient's condition showed the disappearance of stocking-like paresthesia. There was also a favorable evolution of wounds, with nearly complete healing of the left foot amputation stump (Figure 3), complete healing of the right stump, and nearly complete healing of the ulcer on the left leg (Figure 4). There was no recurrence of symptoms at 3 months posttreatment. Biologically, gamma globulin levels continued to normalize at one and three months posttreatment. Proteinuria decreased by 0.35 g/24 h. Cryoglobulin monitoring was not performed due to lack of funds. The patient is currently on corticosteroid therapy alone at 10 mg/day.

5 | DISCUSSION

Clinical presentations of monoclonal gammopathy are heterogeneous, ranging from asymptomatic forms to cancerous diseases. MGUS, defined by a monoclonal immunoglobulin level less than 3 g/dL, a medullary plasma cell rate less than 10%, and the absence of target organ involvement known as CRAB criteria, is considered a precancerous form. The overall prevalence of MGUS is 2.4%, with a median age at diagnosis of 70 years.[2] In individuals under 40 years old, the prevalence is less than 0.3%.[1] The annual risk of progression to MM varies from 0.5% to 1%.[1,7] Currently, potentially severe organic manifestations, such as in the case of our patient, not meeting the diagnostic criteria for MM are described.[3–5] These syndromes, termed MGCS, can affect the kidneys, peripheral nerves, skin, eyes, or other systemic syndromes not confined to one organ.[6] The prevalence of these syndromes, likely underestimated due to diagnostic challenges, is 4% in patients over 40 years old.[8] Mechanisms leading to tissue damage are numerous: (1) deposition of part or all of the monoclonal Ig in the form of aggregates of amorphous, crystalline, macrotubular, or fibrillar forms, (2) activation of autoantibodies against tissue antigen, formation of immune complexes, and complement activation, (3) activation of the B

TABLE 1 The initial and follow-up biological examinations are summarized in the table below.

Biomarker	At diagnosis	M1 of chemotherapy	M3 of chemotherapy
Hemoglobin level	12 g/dL	11.8 g/dL	13.2 g/dL
Erythrocyte sedimentation rate	120 mm		
C-reactive protein (CRP)	201 mg/L	16 mg/L	1 mg/L
Gammaglobulin level	30.1 g/L	11.89 g/L	9.8 g/L
Immunofixation of proteins	IgG Kappa type		
Plasma cell percentage	6% without particularity		
Creatinine level	39 µmol/L	45 µmol/L	29 µmol/L
24-h proteinuria	1 g	0.35 g	
Corrected calcium level	2.30 mmol/L	2.40 mmol/L	2.36 mmol/L
Circulating cryoglobulin	Monoclonal cryoglobulin (IgG Kappa type)		
Hepatitis B and C serologies	Negative		
Antinuclear antibodies	Negative		

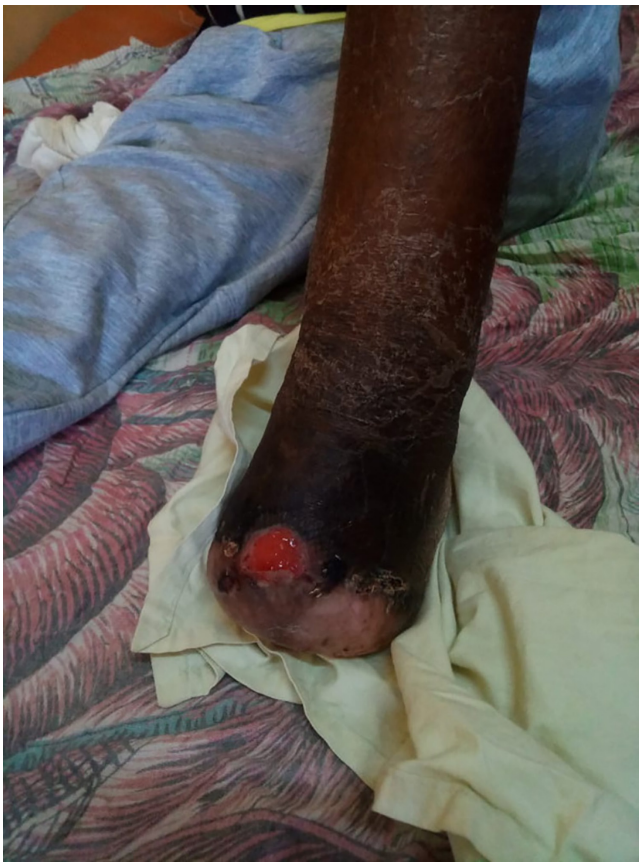

FIGURE 3 Almost complete healing of the amputation stump of the left foot after 3 months postchemotherapy. The photograph was taken at the Rheumatology Department, CHU Befelatanana Antananarivo, Madagascar.

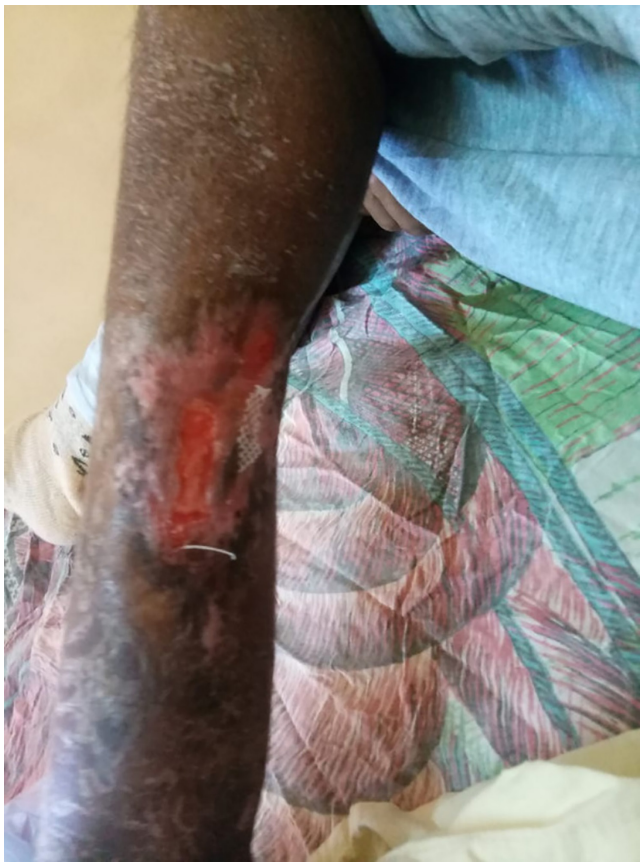

FIGURE 4 Almost complete healing of the left leg ulcer 3 months after chemotherapy. The photograph was taken at the Rheumatology Department, CHU Befelatanana Antananarivo, Madagascar.

clone with absorption of biologically active substances and secretion of cytokines, (4) unknown mechanism.[6] Type I cryoglobulinemia is one of the manifestations of MGCS, with a prevalence of around 40%.[3,5] In 50% of cases, circulating cryoglobulin remains asymptomatic. Common symptoms include cutaneous signs such as livedo reticularis, purpura, Raynaud's phenomenon, acrosyndrome, and even ulcerations of the extremities.

Rheumatologic signs may manifest as arthromyalgia, proteinuria, and weakness. These ulcerations indicate occlusion of small and medium-caliber vessels.[8] Benjamin Terrier et al. had described that 78% of patients presented severe manifestations of vasculitis defined by the presence of extensive skin ulcers and/or necrosis, mononeuropathy multiplex, sensory-motor, and/or glomerulonephritis.[9] Our patient had severe necrosis of the extremities, necessitating bilateral transmetatarsal amputation, severe ulceration of the left leg, glomerular proteinuria, and probable sensory neuropathy of the lower limbs.

Treatment for MGCS focuses on addressing the proliferative B clone that poses a risk, and relies on organic lesions.[6] The selection of therapy for type 1 cryoglobulinemic vasculitis is contingent upon the hematopathy underlying the condition, the severity of symptoms, and whether the clone producing monoclonal immunoglobulin is plasmacytic or lymphoplasmacytic in nature.[9,10] Corticosteroid therapy at a dose of 60 mg/day as monotherapy or in combination with an alkylating agent such as cyclophosphamide is recommended as initial treatment, but failure or relapse is common. Symptomatic treatment, such as warming the extremities, is always recommended.[10] If this fails, the same specific treatment as for MM is required.[11] Proteasome inhibitors, especially bortezomib, or immunomodulatory drugs such as thalidomide and lenalidomide have shown efficacy.[5,12] Our patient initially received a 3-day course of methylprednisolone followed by oral corticosteroid therapy at a dose of 1 mg/kg/day equivalent prednisone and cyclophosphamide, but without significant efficacy. The use of clone B-specific chemotherapy, as per the melphalan-thalidomide-prednisone protocol, along with foot amputation and local care, resulted in almost complete healing of the left leg and stump, and complete healing of the right stump. Biologically, there was a persistent normalization of gammaglobulin levels at 1 and 3 months posttreatment. Proteinuria decreased to 0.35 g/24 h. Cryoglobulin control was not performed due to financial constraints.

6 | CONCLUSION

We have reported a case of a young patient with severe type 1 cryoglobulinemic vasculitis associated with monoclonal gammopathy, which showed favorable evolution after treatment with melphalan-thalidomide-prednisone. Her condition falls within the spectrum of MGCS. These symptoms deserve attention from all clinicians as they require specific and urgent management. Early diagnosis can prevent severe tissue damage.

AUTHOR CONTRIBUTIONS

Oliva Henintsoa Rakotonirainy: Conceptualization; formal analysis; writing – original draft; writing – review and editing. **Lalao Nomenjanahary Rakotonirina:** Writing – original draft; writing – review and editing. **Stevy Desana:** Writing – original draft; writing – review and editing. **Lauréat Brunda Manahandray:** Supervision; validation. **Rajo Païdia Radinasoa:** Validation; visualization. **Tahinasoa Randriamampianina:** Resources. **Fahafahantsoa Rapelanoro Rabenja:** Resources; supervision.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors thank the patient who provided written consent for this report. The article omits any personal information that might identify the patient. The names and dates on the chest CT scan have been redacted. The authors have included only the information necessary for scientific understanding.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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