

# TYPE I MONOCLONAL CRYOGLOBULINEMIA IgG KAPPA WITH SECONDARY VASCULITIS AS ONSET MANIFESTATION OF MULTIPLE MYELOMA

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## Abstract

A 49-year-old patient initially admitted to the Rheumatology Clinic for arthralgias, swelling in the fists, knees and ankles, at a bilateral level, with RM>1h, dot-like necrotic lesions on the back side of his fingers and toes, extensive hemorrhagic lesions on the backside of his hands and feet, and, from a biological point of view, intense inflammatory syndrome and increased IgG are detected, so the patient was transferred to the Fundeni Hematology Clinic on the presumption of a monoclonal gammopathy diagnosis. The tests performed revealed IgG kappa monoclonal cryoglobulinemia and multiple myeloma stage IIIA. The skin biopsy confirmed the clinical suspicion of cryoglobulinemia vasculitis. The patient received bortezomib-based induction therapy with the multiple myeloma achieving complete remission and disappearance of rheumatoid syndrome/vasculitis. Subsequently, remission was consolidated with an autologous bone marrow transplant.

Rheumatoid syndrome and cryoglobulinemia vasculitis are rare onset manifestation in multiple myeloma. The association of multiple myeloma with symptomatic monoclonal cryoglobulinemia is an indication of chemotherapy and autologous bone marrow transplant, even in multiple myeloma stage I or II.

**Keywords:** rheumatoid syndrome, monoclonal cryoglobulinemia vasculitis, multiple myeloma, bortezomib, autologous bone marrow transplant

## INTRODUCTION

Cryoglobulins are abnormal serum immunoglobulins that precipitate at temperatures below 37°C, and dissolve when reheated to 37°C. Type I cryoglobulins (approximately 10-15% of all cryoglobulinemia cases) are monoclonal immunoglobulins, usually of IgM type, associated with some chronic lymphoproliferative diseases-lymphoma, Waldenstrom disease, chronic lymphocytic leukemia. The association between monoclonal gammopathy of unknown significance or multiple myeloma and type I cryoglobulinemia is rare and usually a type of IgG immunoglobulin is involved (1). Monoclonal cryoglobulinemia is frequently symptomatic, and sometimes diagnosis is lost for technical reasons related to inadequate blood sampling or inadequate handling

of blood samples taken from the patient. Clinical symptoms are determined by organic lesions through intratissular deposits, usually in the skin (vasculitis), nerves (neuropathy) or kidneys (glomerulopathies). It is not seldom that the presence of these cryoglobulins modifies the lab tests – e.g. false cytopenia in the blood count or disorder in coagulation tests.

In this article we are reporting a case of multiple myeloma who presented with rheumatoid syndrome and a monoclonal cryoglobulinemic vasculitis IgG kappa.

## CASE PRESENTATION

A 49-year-old patient, with a known history of high-blood pressure, sinus bradycardia, and ischemic heart disease, without significant medical his-

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tory for the current condition, came in to the Rheumatology Clinic “Sf. Maria” with painful swelling of the carpi, bilateral metacarpophalangeal II-III, knees and ankles at a bilateral level, but also with necrotic dot-like lesions on the backside of his fingers and toes. Biologically, an intense inflammatory syndrome is identified: Erythrocyte sedimentation rate (ESR) = 105 mm/h, C reactive protein (CRP) = 46.85 mg/l, normocytic normochromic anemia (Hb= 10.4 g/dl), complement levels (C3, C4) normal, rheumatoid factor (RF) and anti-CPP antibodies negative. The muscle-skeleton echogram reveals synovitis in the fists and knees, bilaterally. During hospitalization, the patient was treated with injectable corticosteroid, followed by the resolution of arthralgias and swelling, and decrease of CRP to 10.2 mg/l. The pa-

tient is discharged with a diagnosis of rheumatoid arthritis – in observation, on cortisone treatment, and he was asked to come back for reevaluation in 6 weeks. He is readmitted for reevaluation with erythematohemorrhagic, necrotic lesions on the back side of his hands and legs, bilaterally and on the calcaneus extending toward the Achilles tendon and minimally painful swelling left metacarpophalangeal joint III. Laboratory tests: ESR=109 mm/h, CRP=3.46 mg/l, normocytic normochromic anemia: (Hb=9.6 g/dl), C3, C4 within normal ranges, RF and anti-CPP antibodies negative, proteinuria/24 h absent. The muscle-skeleton echogram shows paratendonitis of IIIrd finger, left hand, and edema of subcutaneous tissue on the dorsal side of left hand; synovitis was absent. Dermatological examination: acral ery-

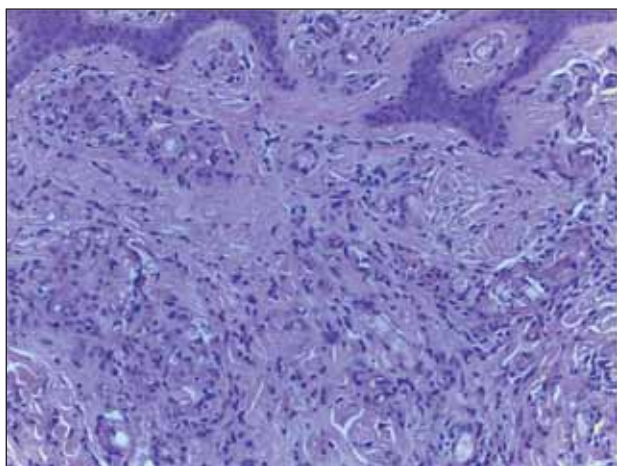


**FIGURE 1 a-e.** Vascular ulceronecrotic lesions in the stage of crustification on the soles, back sides of hands and both knees on approximately 5% of the body area

themato-bullous-papular exanthema suggestive of connective tissue disease, a cutaneous biopsy is performed. Further investigations are carried out: antibodies – antinuclear (ANA), anti dsDNA, anti Ro, cANCA, pANCA, circulating immune complexes – all yielding negative results.

The patient is discharged with treatment on methylprednisolone 1 mg/kg, but is readmitted after a week in worse clinical condition with worsening and extension of cutaneous lesions – hemorrhagic lesions, bullous-, ulceronecrotic, on the back side of his hands and legs, on the lateral side of his leg and calcaneus, bilaterally, observing the palm and the sole, but also on the left knee and right thigh.

Laboratory tests: ESR=99 mm/h, CRP=2.51 mg/dl. Electrophoresis of serum proteins with a spike in gamma-globulin zone and the level of immunoglobulins: IgG=6111 mg/dl, IgM=25 mg/dl, IgA=28 mg/dl, suggests a monoclonal gammopathy. The skin biopsy showed acanthosis and papillomatosis, fibrin deposits in the dermis, and large amount of polymorphous inflammatory infiltrate with a perivascular distribution, but also in the wall of the dermal vessels – pathological findings suggesting a diagnosis of vasculitis (Fig 2).



**FIGURE 2.** Skin biopsy: inflammatory change in the wall of the dermal vessels (HE staining, x20)

With the high suspicion of multiple myeloma, the patient was transferred to the Fundeni Hematology Clinic.

Upon admission, the patient exhibits vascular ulcero-necrotic lesions in the stage of crustification on the soles, back sides of hands and both knees on approximately 5% of the body area (Fig. 1a-1e), without clinical signs of peripheral neuropathy, no bone pains.

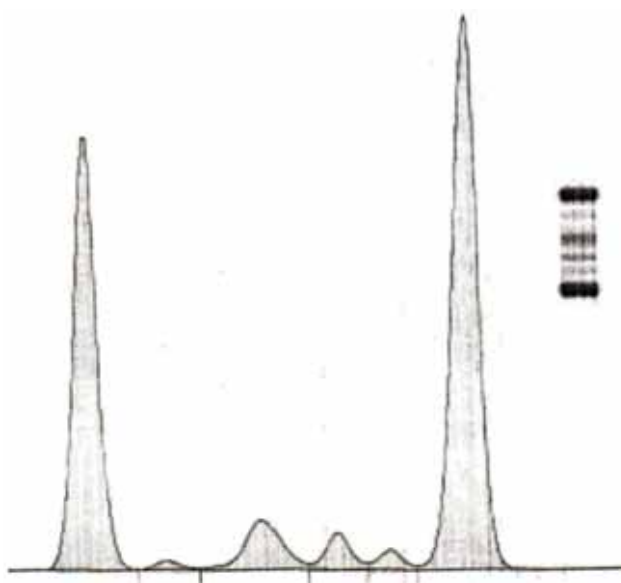
Hematological evaluation:

Blood cell counts: Hb=11.7g/dl, Hct=34.4%, WBC= 13.390/mmc, PLT = 224.000/mmc. (S=84%, Ba 1%; Lf=8%, Mo=8%), erythrocytes in rouleaux;

Beta 2 microglobulin = 2.54 g/L (N 0.7-1.8); Serum viscosity = 1.5 cp; LDH 193 U/L (N 135-225); Ca=8.05 mg /dl; creatinine=1 mg/dl, uric acid=6.2 mg/dl.

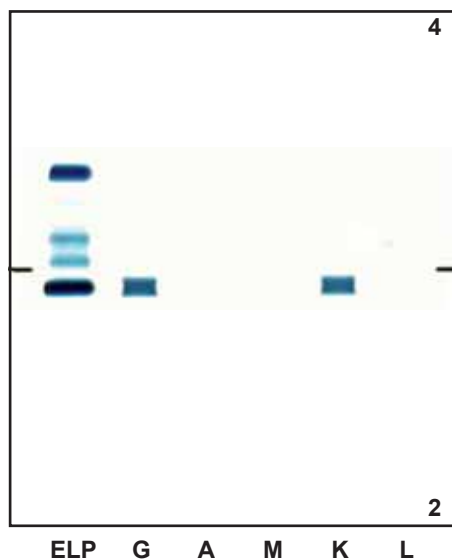
Serum protein electrophoresis: Total proteins: 11.9 g/dl; Albumin=36.6%; alpha 1=0.8%; alpha 2= 6.5%; Beta 1=3.3%; Beta 2=1.7%; gamma = 51.1%.

A spike in gamma-globulin zone = 6.08 g/dl (Fig. 3)



**FIGURE 3.** At diagnosis, monoclonal IgG M – spike 6,08 g/dl

IgG=12.500 mg/dL (Normal 700-1600 mg/dL); IgA=35.4 mg/dL (70-400 mg/dL); IgM=37.2 mg/dL (40-230 mg/dL).



**FIGURE 4.** Immunofixation of cryoglobulins: positive for Ig G Kappa

Serum free light chain kappa = 524 mg/l (N 3.3-19.4); Serum free light chain lambda=1.05 mg/l (N 5.71-26.3); Ratio free light chain kappa/lambda=499.04 (N 0.26-1.65).

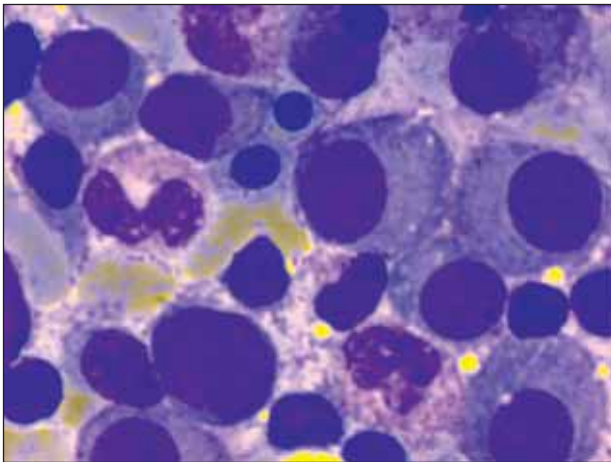
Cryoglobulins present in deposit.

Immunofixation of cryoglobulins (isolated in deposit and washed at 4°C): positive for Ig G Kappa (Fig. 4).

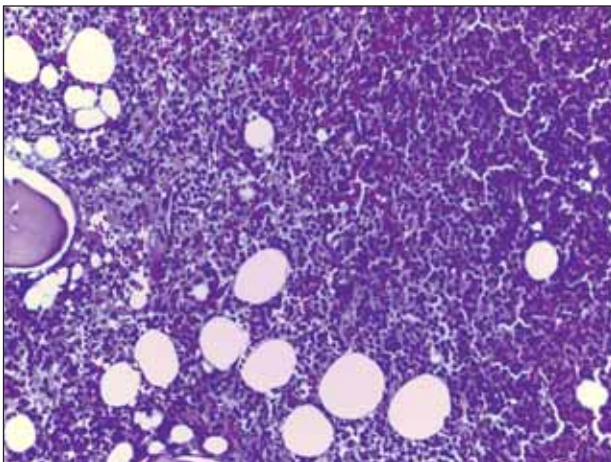
Viral markers: Ag HBs negative, Ac VHC negative, HIV negative.

The cytology of marrow aspirate (Fig. 5) and the pathological examination of bone marrow biopsy (Fig. 6) revealed a hypercellular bone marrow with 67-80% diffuse myeloma cells infiltrate; small areas with reduced normal hematopoiesis. The immunohistochemistry (IHC) stains sustains the clonality of marrow plasma cells infiltrate with kappa light chain restriction, kappa/lambda rapport >20/1 (Fig. 7a and 7b).

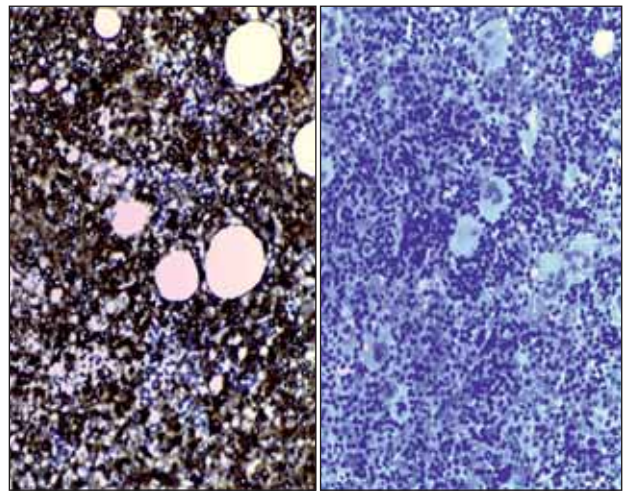
Skeleton radiography reveals no osteolysis lesions, but the thorax CT exam reveals diffuse bone



**FIGURE 5.** Bone marrow aspirate – atypical plasma cells infiltrate (MGG staining, ob x100 oil immersion)



**FIGURE 6.** Bone marrow biopsy – hypercellular marrow with diffuse atypical plasma cells infiltrate (Hematoxylin & Eosin staining, obx40)



**FIGURE 7a-7b.** Bone marrow biopsy – plasma cells infiltrate present kappa light chain restriction (IHC staining for kappa light chain – 7a, and lambda light chain – 7b, ob x40)

demineralization with multiple osteolytic lesions, of the order of millimeters, on thoracic spinal column and vertebral arches and an old fracture on the pathological bone, rib II right side.

The investigations performed established a diagnosis of multiple myeloma IgG kappa associated with type I cryoglobulinemia and secondary vasculitis.

It is then decided to initiate chemotherapy as per protocol CyBorD: Velcade 1.3 mg/mp iv (D1, 4, 8, 11) + Cyclophosphamide 300 mg/mp iv (D 1, 8, 15, 22) + Dexamethazone 32 mg iv D 1-4, 9-12 (first 2 cycles); D1-4 (cycle 3-8) and biphosphonates (Zoledronic Acid 4 mg/month iv). A prophylactic treatment is established for viral infection for zoster herpes: Acyclovir 800 mg/day.

The response evaluation after 3 cycles revealed the disappearance of more than 90% of the cutaneous elements (Fig. 8), a reduction of the monoclonal component by 78% (Good Partial Response – PR)



**FIGURE 8.** The disappearance of cutaneous elements more than 90% after 3 cycles of chemotherapy

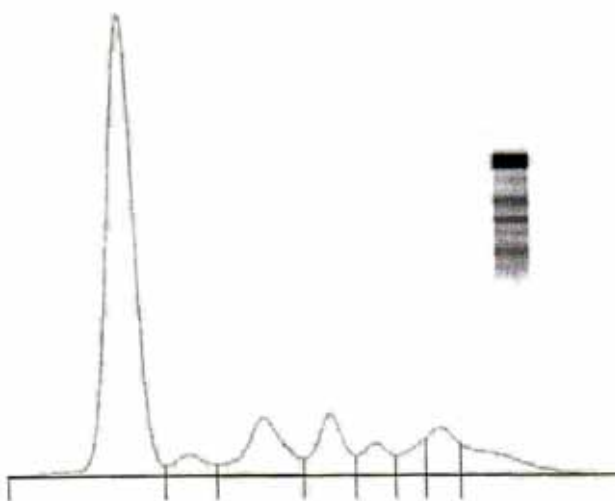
and the decrease of the marrow infiltrate to <5% plasmocytes.

**TABLE 1.** Evolution of monoclonal protein

	Diagnosis	Interm. Balance	PreTransplant
IgG (mg/dl)	12.500	2.910	963
FreeKappa (mg/l)	524	3.23	3.59
CM (g/dl)	6.08	1.3	0.24
Immunofixation of serum proteins IgG K	+	+	+
Serum cryoglobulins	+	-	-

The patient was presented to the Bone Marrow Transplant Committee for autologous stem cells transplantation. Two more cycles CyBorD were applied, followed by a mobilization of hematopoietic stem cells (HSC) with Cyclophosphamide 3.000 mg/m<sup>2</sup> with uroprotection, and then giving G-CSF 10 microgr/kg/day from Day 5 of the cure until leukocytic nadir; stem cells were collected in the amount of 5.76x10<sup>6</sup> CD34/Kgc, enough HSC for two grafts.

Chemotherapy was continued to 8 cycles CyBorD, and the pre-transplant evaluation revealed a very good partial response VGPR (the decrease of monoclonal component by >90%) (Fig. 9).



**FIGURE 9.** Pre-transplant monoclonal IgG M-spike 0,24 g/dl (reduced by more than 90%)

The chemotherapy of CyBorD type was followed by a conditioning cure with Melphalan 200 mg/m<sup>2</sup> and the graft administration after 48 hours (no. of cell stems 2.88x10<sup>6</sup> CD34/Kgc), with the patient out of aplasia in day 11, with more than 1000 leucocytes. The remaining cryopreserved cells (HSC 2.88x10<sup>6</sup> CD34/Kgc) for the second autologous transplant to be carried out after the first relapse of the disease.

Subsequently, the patient will be monitored once every 3 months (blood cell counts, kidney function, blood viscosity, b2m, LDH, serum protein electrophoresis, Ig dosage, monitoring of serum free light chains assays), medullogram and/or imagistic evidence (Skeletal radiography, Magnetic Resonance Imaging), if the patient is clinically symptomatic. The treatment with bisphosphonates will continue monthly for a period of 24 months.

## DISCUSSION

Cryoglobulinemia represents a clinical condition determined by the presence in the serum of a pathological immunoglobulin with the property of precipitating itself in deposits at temperatures below 37°C and then of re-dissolving at 37°C. As a matter of fact, the method of identification of cryoglobulins relies on the same property – the appearance of deposits in suspension or a deposit after keeping the sample in the refrigerator (0-4°C). If cryoglobulinemia is suspected, the assay and serum separation procedures must be performed very carefully. The sampling procedure will be carried out at warm temperatures (in a warm collection tube), the transfer to the laboratory at 37°C, and the centrifugation in a centrifuge preheated to 37°C. If no meet these simple conditions, the cryoglobulins will precipitate in a clot, and it will no longer be possible to identify them after centrifugation. The characterization of cryoglobulins will be achieved by immunofixation of the isolated deposits washed at 4°C. In our experience, the method of light serum free chains is of great help, as well.

Depending on the chemical composition of these deposits, three types of cryoglobulins can be found: Type I – monoclonal cryoglobulin; Type II (mixed) Ig monoclonal (IgM, IgG or IgA) and Ig polyclonal (usually IgG); Type III (mixed) Ig polyclonal (2).

The case presented herein is classified as a multiple myeloma stage III due to the high values of monoclonal Ig (Ig G above 7g/dl) and the bone disease, which means indication for starting the therapy, bortezomib-based standard therapy followed by autologous bone marrow transplantation for consolidation.

It is worth mentioning that in the case of patients considered eligible for marrow transplant (aged under 70, without co-morbidities) we must avoid induction chemotherapy with alkylating agents since they harm the hematopoietic stem cells.

## CONCLUSION

Rheumatoid syndrome and cryoglobulinemic vasculitis are rare onset manifestations of multiple myeloma. The association of multiple myeloma with symptomatic monoclonal cryoglobulinemia represent a clear indication for starting chemotherapy and a bone marrow transplantation even in multiple myeloma stage I or II.

Acknowledgement: part of this study (implementation of Free Light Chain assay) was funded by the National Research Project CEEX 74/2006.

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