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Original article

The correlation between antiphospholipid syndrome and cryoglobulinemia: case series of 4 patients and review of the literature



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ABSTRACT

Background: Cryoglobulinemia is an immune-complex-mediated small vessel vasculitis that classically involves the skin, kidneys and peripheral nerves. Antiphospholipid syndrome (APS) is an autoimmune hypercoagulable disorder which causes blood vessel thrombosis. It can present as a multi-organ microthrombotic disorder which is called catastrophic APS.

Objective: In this case series we aim to describe the diagnostic and management challenges that arise when these two severe disorders simultaneously present in the same patient.

Methods: We describe four patients who were admitted to our hospital due to multi-organ life threatening damage mediated by cryoglobulinemic vasculitis with concurrent APS.

Results: Clinical manifestations included leg ulcers, livedo reticularis, renal failure, and peripheral neuropathy. Suggested etiologies for the combined syndromes were hepatitis C, systemic lupus erythematosus and myeloproliferative disease rectal maltoma. All of our patients were treated with anticoagulation, high-dose corticosteroids, rituximab, intravenous gammaglobulins and plasma exchange.

Conclusion: The rare association of severe or catastrophic APS with cryoglobulinemia in patients should be considered by physicians who treat patients with multi-organ ischemia or necrosis.

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Correlação entre a síndrome antifosfolípídica e a crioglobulinemia: série de quatro casos e revisão da literatura

R E S U M O

Palavras-chave:

Crioglobulinemia
Síndrome antifosfolípídica
Vasculite

Introdução: A crioglobulinemia é uma vasculite de pequenos vasos mediada por imunocomplexos que normalmente envolvem a pele, os rins e os nervos periféricos. A síndrome antifosfolípídica (SAF) é um transtorno da hipercoagulabilidade autoimune que provoca trombose dos vasos sanguíneos. Pode se manifestar como um distúrbio microtrombótico que afeta múltiplos órgãos, denominado SAF catastrófica.

Objetivo: Esta série de casos objetiva descrever os desafios de diagnóstico e tratamento que surgem quando esses dois graves transtornos estão presentes simultaneamente no mesmo paciente.

Métodos: Foram descritos quatro pacientes internados em nosso hospital em decorrência de danos graves a múltiplos órgãos mediados pela vasculite crioglobulinêmica com SAF concomitante.

Resultados: As manifestações clínicas incluíram úlceras de perna, livedo reticular, insuficiência renal e neuropatia periférica. As etiologias sugeridas para a combinação de síndromes foram a hepatite C, o lúpus eritematoso sistêmico e a doença mieloproliferativa retal associada a linfoma de zona marginal tipo células B. Todos os pacientes foram tratados com anticoagulantes, altas doses de corticosteroides, rituximabe, gamaglobulinas intravenosas e troca de plasma.

Conclusão: A rara associação entre a SAF grave ou catastrófica e a crioglobulinemia deve ser considerada por médicos que atendem pacientes com isquemia ou necrose de múltiplos órgãos.

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Introduction

Cryoglobulins (CG) are immune complexes comprised of immunoglobulins (IGs), either poly- or monoclonal, that binds other IGs that are deposited in small blood vessels and glomeruli upon exposure to cold temperatures. The prevalence of clinically significant cryoglobulinemia has been estimated at approximately 1 in 100,000.¹⁻⁴ The presence of the CG-containing immune complexes often results in small to medium vessel vasculitis.⁵⁻⁷ The Brouet classification of cryoglobulinemia is based on the composition of the CGs:⁸ Type I – isolated monoclonal IGs; Type II – Mixed CGs – immune complexes formed by monoclonal IGs, this is the most common type and associated with HCV and HIV; Type III – Mixed CGs – immune complexes formed by polyclonal IGs.

Although most of the patients with cryoglobulinemia remain asymptomatic, the disease may involve mainly the skin, kidneys and peripheral nervous system. Type I cryoglobulinemia manifestations are usually due to hyperviscosity and/or thrombosis, including Raynaud's phenomenon, digital ischemia and gangrene, livedo reticularis, purpura and neurologic symptoms. In contrast, type II and III cryoglobulinemia causes arthralgia, fatigue, myalgia, palpable purpura, peripheral neuropathy as well as membranoproliferative glomerulonephritis.⁹⁻¹¹ Antiphospholipid syndrome (APS) is an autoimmune hypercoagulable disorder characterized by arterial and/or venous thrombosis, pregnancy morbidity including recurrent fetal loss and eclampsia in the presence of elevated levels of anti-cardiolipin (ACL) (≥ 40 U

and/or β_2 glycoprotein I IgG and/or IgM antibody (>99th percentile) and/or lupus anticoagulant (LAC).

Antiphospholipid antibodies (aPL). According to the laboratory revised criteria the anti-cardiolipin (ACL) IgG, IgM antibody and/or anti- β_2 glycoprotein I (β_2 GPI) IgG, IgM (according to our laboratory kit, above >20 U) and/or positive test for lupus anticoagulant (LAC) tested positive on 2 consecutive occasions at least 12 weeks apart.¹²⁻¹⁵ An association between cryoglobulinemia and APS has been previously reported (Table 1).¹⁶⁻²⁰ In this study, we describe four patients who presented with manifestations of both cryoglobulinemic vasculitis²¹ and APS.

Case presentation

Case 1

A 51-year-old female was presented with diabetes mellitus type 2 and hypertension. In 1997 she suffered from sudden loss of vision in right eye. In 2001 she developed livedo reticularis of both lower extremities. Laboratory tests revealed urine stick test protein level of 500 mg/dL, CRP level was 54.85 mg/dL (upper normal range – 0.5 mg/dL), and positive aPL serology (2 tests taken 12 weeks apart – values are listed in Table 2).

Also, positive ANA titer (1:160), positive cryofibrinogen IgG and IgM kappa, and IgM cryoglobulins type 1 (215 mg/L, reference range 0-60 mg/L) were revealed. Kidney biopsy demonstrated evidence of membranoproliferative glomerulonephritis. The patient was treated with 1 g methylprednisolone followed by a 6-month period of tapering down

Table 1 – Laboratory characteristics of our patients case series.

Patient num.	Age	Sex	Etiology	ACL antibody ^{a,b}	Anti-β2GPI antibody ^{a,b}	LAC ^{a,c}	ANA	Anti-DsDNA	RF	Cryoglobulins mono-clonal/polyclonal/mixed
1	51	F	Idiopathic	+	+	-	+	-	NS	IgM kappa monoclonal
				IgM = 153 U, 109 U IgG = 98 U, 115 U	IgM = 100 U, 73 U IgG = 81 U, 49 U					
2	66	M	Multiple myeloma	-	+	-	+	-	-	IgG kappa monoclonal
					IgG = 78 U, 122 U					
3	40	M	HCV and SLE	+	+	+	+	+	-	Mixed
				IgM = 132 U, 49 U	IgM = 67 U, 50 U					
4	65	F	MALT lymphoma	+	+	+	+	-	+	Mixed
				IgG = 91 U, 73 U	IgG = 56 U, 62 U					

ACL, anticardiolipin; anti β2GPI, anti-β2 glycoprotein I; LAC, lupus anti coagulant; ANA, anti nuclear antibody; anti DsDNA, anti double strand DNA; RF, rheumatic factor; HCV, hepatitis C virus

^a 2 values for 2 tests taken 12 weeks apart.

^b ACL and anti-β2GPI IgG, IgM antibody assayed by ELISA according to manufacturer's guidelines.

^c Lupus anti coagulant tested with RVVT, Positive values above 1.5 ratio.

Table 2 – Summary of case studies and series of clinical and laboratory characteristic in patient with antiphospholipid syndrome and cryoglobulinemia.

Study	Study design	Co morbidity	Clinical presentation	Treatment	Cryoglobulins mono-clonal/polyclonal/mixed	aPL antibodies (ACL, β2GPI), LAC
Yancey et al. (1990)	Case study – 1 patient – 35-years-old female	SLE	Livedo reticularis, renal failure, arthralgia, 2 miscarriages	NS	Serum cryoglobulins were positive (values NS)	ACL IgG – 200GPLU/mL (normal < 5.5 GPLU/mL)
Asherson et al. (1992)	Case series – 2 patients	Hereditary complement factor 2 syndrome, Sjögren's syndrome	Livedo reticularis	NS	Serum cryoglobulins were positive (values NS)	Patients 1 ACL IgG 14.4 units (n ≤ 5 units). Patients 1 ACL IgG 10.2 units (n ≤ 5 units)
Hanly and Smith (2000)	Case series – 5 patients – 4/5 females mean age – 53.2 ± 2.9 y	NS 3 of them had SLE	Venous thrombosis – 2 patients. Arterial thrombosis – 1 patients. Thrombocytopenia – 2 patients	NS	All patients, one patient had IgM kappa – type 1, the remain patients had mixed type III (values NS).	All patients had positive LAC. And 4/5 had positive IgG ACL (values NS).
Andrejevic et al. (2003)	Case study – 1 patient – 69-years-old female	NHL	Leg ulcers	Aspirin, heparin, prednisone	Mixed type II Cryocit@ 12%	ACL IgG – 92 GPLU/mL (normal < 5.5 GPLU/mL)
Chang et al. (2006)	Case study – 1 patient – 14-year-old boy	Partial DiGeorge syndrome and recent streptococcal infection	Pulmonary embolus, proliferative glomerulonephritis	Warfarin, prednisone, and mycophenolate mofetil	Mixed type III Cryocit@ 10%	LAC was borderline positive; ACL IgM – 17 PLU (normal < 10); Anti-β2GPI IgM – 36 U/mL (normal < 10 U/mL)

NHL, non-Hodgkin's lymphoma; ACL, anticardiolipin; Anti β2GPI, anti-β2 glycoprotein; LAC, lupus anti-coagulant; NS, non-stated; Cryocit@, percentage of packed cryoglobulins referred to total serum after centrifugation at 4 °C.

to 60 mg prednisone. 3 years later, the patient was admitted to the hospital with purpura, ulcers in her lower extremities and splinter hemorrhages of the nails.

She showed evidence of nephrotic syndrome with urine protein of 5 g/24 h and acute renal failure (serum creatinine level was 2.8 mg/dL). Skin biopsy demonstrated a thrombotic event without evidence of vasculitis. Urine was positive for Bence-Jones protein. CGs and Cryofibrinogen were positive (315 mg/L, reference range 0–60 mg/L, and 3 g/L; upper normal range – 0.5 g/L, respectively). Hepatitis B and C were both negative. Bone marrow biopsy showed no evidence of myeloma or other lymphoproliferative disease.

The patient was treated with 60 mg prednisone and warfarin (dose adjusted according to INR goal of 2–3) with improvement of cutaneous findings and partial normalization of creatinine level (1.7 mg/dL). Urine protein was 2.3 g/24 h.

Two years later she presented with dyspnea, hemoptysis, anemia, lower extremities purpura and elevated creatinine level. Chest CT revealed diffuse alveolar hemorrhage. The treatment with warfarin was then discontinued. Creatinine level was 4.62 mg/dL with urine protein of 7.125 g/24 h and RBC casts were observed on microscopic examination of urine. Cryofibrinogen IgG kappa was positive (2 g/L, upper normal range 0.5 g/L). CGs were negative (32 mg/L, reference range 0–60 mg/L) and aPL were positive. Treatment was initiated with dialysis, hydrocortisone (100 mg × 3 d), 2 courses of rituximab (1 g) infusions and plasmapheresis. The patient died in the intensive care unit 2 weeks after being admitted to the hospital due to sepsis.

Case 2

A 66-year-old male with diabetes mellitus type 2. In 2003 he presented with lower extremity ulcers (mainly in toes). He was treated with prednisone (60 mg × 1 d) with tapering down for 3 months and IV iloprost (prostacyclin PGI₂ analog). Serology for Hepatitis B was positive (HBs and HBe were positive) and anti-viral treatment with Lamivudine (nucleoside analog reverse transcriptase inhibitor) was initiated (300 mg × 1 d). Under this treatment the patient's ulcers improved.

Three years later he presented with ischemic ulcers in a number of toes and purpura in both lower extremities. Skin biopsy revealed fresh bleeding in dermis with mononuclear infiltrate around blood vessels. One blood vessel was surrounded by polymorphonuclear infiltrate and in some vessels thrombi were evident. Monoclonal CGs IgG light chain kappa type 1 was found (152 mg/L, reference range 0–60 mg/L). C3 and C4 levels were normal. Bone marrow biopsy revealed 7–8% plasma cells positive for IgG kappa. Most of the plasma cells were monoclonal for IgA. The patient was treated for type 1 cryoglobulinemia with monoclonal gammopathy with plasmapheresis and IV cyclophosphamide for 6 months.

Six years after the initial presentation he developed left hemiparesis. Laboratory tests were positive twice, 12 weeks apart, for aPL serology (Table 2) and ANA titer was 1:160. The patient was diagnosed with APS and treated with warfarin.

One year later, he presented with right 3rd finger necrosis and palpable purpura on left lower limb. He was treated with a sympathetic block, hydrocortisone (100 mg × 3 d),

plasmapheresis, IV iloprost and warfarin. Bone marrow biopsy demonstrated positivity for CD138 with plasma cells secreting lambda and kappa light chains.

In 2011 a bone marrow biopsy showed 15% plasma cells positive for IgG kappa light chain secretion (multiple myeloma-clonal plasma cells >10% on bone marrow biopsy). The patient was positive for CGs (343 mg/L, reference range 0–60 mg/L). Therefore, the patient was diagnosed with multiple myeloma and began treatment with melphalan, prednisone and bortezomib.

Case 3

A 40-year-old male known to be a hepatitis C (HCV) carrier was diagnosed with systemic lupus erythematosus (SLE) in 1999. The disease presentation included malar rash, leucopenia, thrombocytopenia, photosensitivity, arthritis and alopecia. Laboratory: analysis showed that ANA and dsDNA were positive (ANA of 1:160, dsDNA of 25%, normal range 0–20%). The patient was treated with hydroxychloroquine and prednisone (in varying dosages). Five years later he presented with right foot gangrene which necessitated below knee amputation and CVA with right hemiparesis. CT scan revealed left parietal infarct. In laboratory testing, there was positivity for aPL (2 tests taken 12 weeks apart – values are listed in Table 2) and mixed cryoglobulinemia (type 2) – 511 mg/L (reference range 0–60 mg/L). He was treated with warfarin, hydroxychloroquine (200 mg × 2 d) and prednisone (60 mg) with three months tapering down.

Case 4

A 65-year-old female who had been suffering from intermittent purpura for nearly 30 years and in the last few years began complaining of numbness of the lower limb. EMG studies revealed severe axonopathy. CT of the spine showed only spondylolisthesis in L5-S1. Laboratory was positive for mixed cryoglobulinemia – CGs level of 215 mg/L (reference range 0–60 mg/L) and ANA titer of 1:160. C3 and C4 levels were very low and serology's for hepatitis C and B were negative. aPL serology was positive (2 tests taken 12 weeks apart – Table 2). The patient underwent an abdominal CT which revealed an inflamed terminal ileum.

Colonoscopic examination showed macroscopic appearance of proctitis and the biopsy was compatible with mucosa-associated lymphoid tissue (MALT) lymphoma. Treatment with rituximab, cyclophosphamide and prednisone was initiated. A week later, the patient was re-admitted to the hospital due to livedo reticularis, purpura, lower extremities ulcers and confusion. Head CT showed no infarcts. Laboratory tests revealed microangiopathic anemia (schistocytes on blood smear) and thrombocytopenia of 70 K/ μ L (normal range 150,000–450,000 K/ μ L).

Treatment with hydrocortisone (100 mg × 3 d) and anticoagulation with IV heparin was initiated. Under this treatment, the confusion improved partially, but the leg ulcers progressed to anaerobic infection and then sepsis, eventually leading to above knee amputation of his left leg.

Discussion

In the case series presented here we describe four patients with cryoglobulinemic vasculitis present concurrently with clinical features of APS. All our patients suffered from recalcitrant leg ulcers and skin necrosis, resulting in amputations in 2 out of the 4 patients.

In a case-series of 200 consecutive patients with APS (either primary APS or APS secondary to SLE), skin ulcers and/or necrosis was reported in only 2% of the patients,²² whereas it occurs in 10% of patients with cryoglobulinemia.²³ In our series, all four patients suffered from skin ulcers and necrosis, most probably secondary to the synergistic effect of cryoglobulin and thrombosis-mediated cutaneous ischemia as result of small and medium-sized blood vessel occlusion.

Our case-series is in accordance with three case-series of patients with both cryoglobulinemia and APS.¹⁶⁻¹⁸ This suggests that the concurrent presentation of overlapping clinical features due to cryoglobulinemia and APS should be assessed in patients with severe ischemic cutaneous lesions. The etiology of cryoglobulinemia and APS in the Hanly and Smith¹⁶ and Yancey et al.¹⁷ series was mostly due to SLE. In our case series, two patients (2, 4) suffered from lymphoproliferative disease, one patient was diagnosed with primary APS and one had HCV and SLE.

Like patients 2 and 4 in our series who had lymphoproliferative disease, Andrejevic et al.,¹⁸ described patients with non-Hodgkins lymphoma, monoclonal cryoglobulinemia and ACL antibodies with vasculitis. They concluded that patients with lymphoid malignancies and ACL antibodies in their cryoprecipitate may be at risk for developing clinical manifestations of APS.

Chang et al.¹⁹ also described a patient with DiGeorge syndrome who developed mixed cryoglobulinemia, APS and systemic vasculitis after a streptococcal infection.

Asherson et al.,²⁰ described two sibling with hereditary complement factor 2 deficiencies. They both presented with cutaneous vasculitis, cryoglobulinemia and ACL antibodies. After removal of the cryoprecipitate from the serum sample of the two patients the serum antibodies of ACL fell. This implicates the incorporation of ACL antibodies within cryoprecipitates.

The formation of β_2 glycoprotein I and anti- β_2 glycoprotein I antibody immune-complexes has been documented.²⁴

However, Bardin et al.²⁵ described 55 patients with APS who were positive for both cryoglobulinemia and IgM phosphatidylethanolamine antibodies (aPE). Determination of IgM aPE levels was made before and after removal of cryoprecipitate from the serum. Of the 55 patients, 52 (95%) showed no significant difference of IgM aPE levels before and after cryoprecipitation. They concluded that in most cases cryoprecipitation does not interfere with IgM aPE level. Thus, IgM aPE does not appear to be involved in the formation of the cryoprecipitate.

Our study is not without limitations; it includes only a small number of patients, with different types of cryoglobulins, different isotypes of antiphospholipid antibodies, as well as different co-morbidities. In spite of this heterogeneity, all four patients had hard to treat ischemic cutaneous ulcers and

this is the most important manifestation related to the presentation of the two syndromes presented together.

We recommend ruling out the presence of APS in patients with cryoglobulinemic vasculitis recalcitrant to the standard therapy and vice versa.

Conflicts of interests

The authors declare no conflicts of interest.

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