Cryoglobulinemic Vasculitis Stemming from Delayed Recognition of Rheumatoid Arthritis

Vasculite Crioglobulinémica como Apresentação Inicial de Artrite Reumatoide

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Resumo:

A vasculite crioglobulinémica (VC) é uma doença mediada por imunocomplexos com envolvimento multiorgânico e uma apresentação clínica heterogénea. A VC tem sido documentada em doentes com artrite reumatoide (AR), mas a sua incidência é atualmente rara devido ao diagnóstico precoce e à instituição de terapêutica adequada para a AR, incluindo fármacos biológicos modificadores da doença.

Reportamos o caso de uma doente do sexo feminino de 61 anos que apresentava um quadro de 5 dias de evolução de lesões maculares violáceas em ambos os membros inferiores, hipostesia do membro inferior esquerdo e incapacidade para a marcha. Referia também uma história de 17 anos de evolução de poliartralgia aditiva simétrica crónica das articulações metacarpofalângicas, acompanhada de sinovite e deformidades dessas articulações.

Analiticamente, apresentava anemia normocítica, elevação dos parâmetros inflamatórios, fator reumatoide e anticorpo antipeptídeo citrulinado, diminuição do componente 4 do complemento e crioglobulinas elevadas com padrão de crioglobulinemia mista tipo III. A biópsia cutânea revelou vasculite necrotizante cutânea / venulite neutrofílica. Foram iniciados corticoterapia sistémica e rituximab com subsequente melhoria clínica e analítica.

Este caso de AR seropositiva de longa data previamente não tratada, que se apresentou com VC, demonstra que, embora a VC seja uma complicação rara da AR, pode ser a sua apresentação inicial. Um elevado índice de suspeição clínica é a chave para o diagnóstico precoce e o tratamento imediato é crucial para minimizar a morbilidade e mortalidade.

Palavras-chave: Artrite Reumatoide; Crioglobulinemia; Doenças do Sistema Nervoso Periférico; Vasculite Leucocitoclástica Cutânea; Vasculite Sistémica.

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Abstract:

Cryoglobulinemic vasculitis (CV) is an immunocomplex-mediated condition with multi-organ involvement and a heterogeneous clinical presentation. CV has been documented in patients with rheumatoid arthritis (RA) but its incidence is nowadays rare due to the early diagnosis and proper therapeutic management of RA, including the emergence of biologic disease-modifying antirheumatic drug therapy.

We report a case of a 61-year-old woman who presented with a 5-day history of violaceous macular lesions on both lower limbs, decreased left lower limb sensitivity and inability to walk. She also reported a 17-year history of chronic symmetrical additive polyarthralgia of metacarpophalangeal joints, which was accompanied by synovitis and deformities of these joints.

Blood analysis showed normocytic anemia, elevated acute phase reactants, elevated rheumatoid factor and anti-cyclic citrullinated peptide antibody, reduced complement component 4 and elevated cryoglobulins with type III mixed cryoglobulinemia pattern. Skin biopsy revealed cutaneous necrotizing vasculitis / neutrophilic venulitis. Systemic corticosteroid therapy and rituximab were started with clinical and analytical improvement.

This long-standing untreated case of seropositive RA presenting with CV demonstrates that, despite being a rare complication of RA, CV can be its initial presentation. A high index of clinical suspicion is the key to an early diagnosis, and prompt treatment institution is crucial to minimize morbidity and mortality.

Keywords: Arthritis, Rheumatoid; Cryoglobulinemia; Peripheral Nervous System Diseases; Systemic Vasculitis; Vasculitis, Leukocytoclastic, Cutaneous.

Learning Points

1. Cryoglobulinemic vasculitis is an immunocomplex-mediated condition with multi-organ involvement and a nonspecific and heterogeneous clinical presentation, making it a real diagnostic challenge.

2. A high index of clinical suspicion is key to making the diagnosis, especially in an adult who presents with arthralgia, purpura, peripheral neuropathy, renal disease, in the setting of chronic viral hepatitis, monoclonal gammopathy, or any connective tissue disease. A careful laboratory and histopathologic assessment help in achieving an accurate diagnosis.
3. Prompt recognition of this often underestimated but potentially serious and life-threatening condition is crucial so that appropriate and aggressive immunosuppressive treatment can be timely instituted, reducing associated morbidity and mortality, and securing a better prognosis.

Introduction

Cryoglobulinemic vasculitis (CV) is an immunocomplex--mediated condition with multi-organ involvement and a nonspecific and heterogeneous clinical presentation. Chronic stimulation of the immune system induced by lymphoproliferative disorders, chronic infections or autoimmune diseases results in increased concentrations of immunoglobulins that can combine into cryoglobulins.[1] In particular, mixed type III cryoglobulinemia is distinguished by the existence of circulating immune complexes composed of polyclonal IgG and IgM.[1] Although the most frequently associated autoimmune disease is Sjögren syndrome, CV has been documented in up to 10% of patients with systemic lupus erythematosus or rheumatoid arthritis (RA).[1]

Case Report

We report a case of a 61-year-old woman with hypertension, dyslipidemia, smoking habits, and carotid atherosclerotic disease who presented to the emergency department with a 5-day history of violaceous macular lesions, initially small and localized only on the thighs, progressing in number and extending to the legs bilaterally, associated with decreased sensitivity of the left leg and inability to walk. She also reported a 17-year history of chronic symmetrical additive polyarthralgia of metacarpophalangeal joints and wrists, with chronic consumption of non-steroidal anti-inflammatory drugs, requiring a dose increase in the last 2 months due to pain exacerbation.

Upon examination, the patient presented large, erythematous-violaceous macules, painful to touch, localized on both legs, with a posterior predominance (Fig. 1); hypoesthesia of the lateral surface of the distal left leg with impaired dorsiflexion of the left foot and a non-palpable left dorsalis pedis artery; active bilateral synovitis of the 2nd and 3rd metacarpophalangeal joints; positive bilateral squeeze test; deformities of the metacarpophalangeal joints with fixed finger flexion and inability to extension; and apparent rheumatoid nodules on both elbows.

The initial laboratory investigation revealed normocytic anemia and significantly elevated inflammatory biomarkers, namely leukocytosis and significantly elevated C-reactive protein, erythrocyte sedimentation rate and ferritin (Table 1).

A bilateral hand radiograph was performed and revealed symmetric joint space narrowing, marginal erosions,

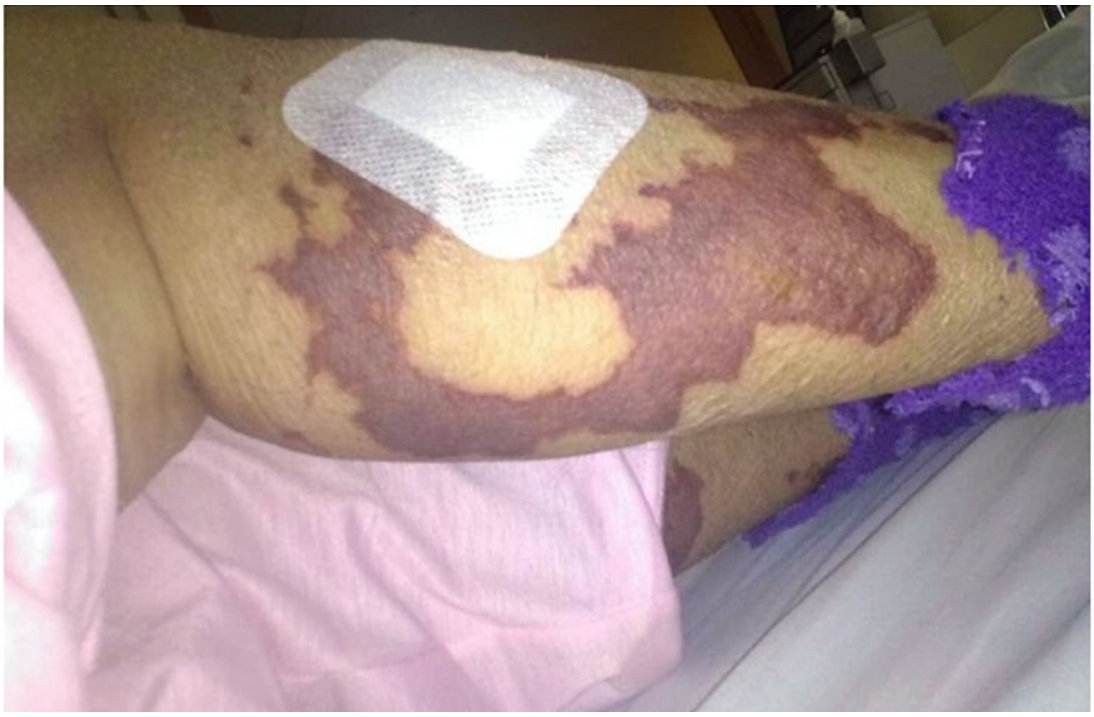

Figure 1: Clinical presentation: large, erythematous-violaceous macules, localized on the posterior surface of both legs.

Tabela 1: Initial laboratory investigation.

Laboratory tests	Patient Values	Referenge range
Hemoglobin	8.9 g/dL	12-15 g/dL
Mean corpuscular volume	84 fL	80-100 fL
White blood cells	14.91 x 10^3/µL	4.0-11.0 x 103/µL
Neutrophils	12.04 x 10^3/µL	2.0-7.50 x 103/µL
Lymphocytes	1.70 x 10^3/µL	1.40-4.0 x 103/µL
Monocytes	0.75 x 10^3/µL	0.20-0.80 x 103/µL
Eosinophils	0.38 x 10^3/µL	0.04-0.40 x 103/µL
Basophils	0.04 x 10^3/µL	0.02-0.10 x 103/µL
Platelets	320 x 10^3/µL	150-400 x 103/µL
Alanine transaminase	9 U/L	10-30 U/L
Aspartate transaminase	28 U/L	10-36 U/L
Alkaline phosphatase	110 U/L	32-104 U/L
γ-Glutamyl transpeptidase	45 U/L	6-39 U/L
Total bilirubin	0.62 mg/dL	0.2-1.0 mg/dL
Lactate dehydrogenase	131 U/L	135-214 U/L
Serum creatinine	0.4 mg/dL	0.5-0.9 mg/dL
Blood urea nitrogen	29 mg/dL	10-50 mg/dL
Sodium	139 mmol/L	135-145 mmol/L
Potassium	3.5 mmol/L	3.5-5.0 mmol/L
Creatinine kinase	17 U/L	24-173 U/L
C-reactive protein	221 mg/L	0-5 mg/L
Erythrocyte sedimentation rate	>100 mm/h	0-20 mm/h
Ferritin	1004 ng/mL	2.20-178 ng/mL
Urinalysis and urinary sediment	No significant alterations (with no leukocytes or erythrocytes)	

periarticular osteopenia, and soft tissue swelling in the carpal, proximal and intermediate interphalangeal joints (Fig. 2).

Further diagnostic testing revealed significantly elevated rheumatoid factor and anti-cyclic citrullinated peptide antibody (anti-CCP), elevated antinuclear antibody (ANA), slightly reduced complement component 4 (C4) and increased cryoglobulins with polyclonal characteristics. A comprehensive infectious and autoimmune workup yielded negative results, including the search for viral hepatitis, Sjögren syndrome, systemic lupus erythematosus and anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (Table 2).

A skin biopsy was performed and revealed: epidermis with atrophy, slight melanic hyperpigmentation of the basal layer, hydroptic degeneration of the basal layer, and orthokeratotic hyperkeratosis; the fibrous dermis, with polymorphous inflammatory infiltrate with neutrophils and numerous nuclear debris; presence of vasculitis lesions with fibrinoid necrosis of the vessel wall (leukocytoclastic vasculitis), intravascular thrombi, and erythrocyte extravasation; the polymorphous infiltrate and vasculitis lesions extend to the subcutaneous fatty tissue with septal panniculitis lesions; conclusion: Cutaneous necrotizing vasculitis / neutrophilic venulitis.

An electromyogram was also conducted, and the result was compatible with moderately isolated left fibular sensory-motor neuropathy.

Considering the clinical presentation and the analytical results, the diagnosis of cryoglobulinemic vasculitis was established, secondary to the previously undiagnosed long-evolution seropositive erosive rheumatoid arthritis.

Systemic corticosteroid therapy (prednisolone 1 mg/kg) and rituximab (four weekly infusions of 375 mg/m^2) were started with clinical and analytical improvement. At the follow-up appointment, one-month post-therapy initiation,

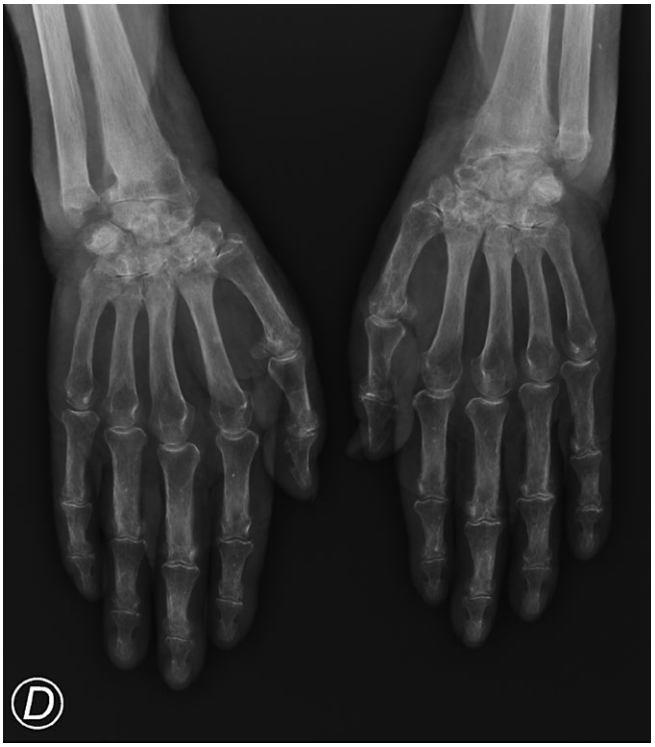

Figure 2: Bilateral hand radiograph shows extensive and symmetric findings of uniform joint space narrowing, marginal erosions, periarticular osteopenia, and soft tissue swelling involving the radio-carpal, carpal, and proximal and intermediate interphalangeal joints, without signs of bone production. There are subchondral cysts in the distal radius as well as erosion of its ulnar aspect. Slight ulnar deviation of the metacarpophalangeal joints is also present. There is relative sparing of the trapeziometacarpal and distal interphalangeal joints.

the patient reported remission of the initial skin lesions and progressive scarring, improvement of joint-related symptoms, and reduction of the inflammatory markers (with normal hemogram, erythrocyte sedimentation rate 27 mm/h, C-reactive protein 2.31 mg/L). Subsequently, disease-modifying antirheumatic drugs were started, initially with methotrexate but posteriorly modified to baricitinib (2 mg once daily) due to cytocholestasis and recurrence of joint complaints. There has been a sustained global improvement.

Discussion

CV has heterogeneous and non-specific clinical manifestations, such as fever, fatigue, myalgia, arthralgia, and weight loss. Recurrent palpable purpura is the most prevalent manifestation and consists of erythematous macules and purpuric papules of the lower extremities but may present as extensive coalescent necrotic ulcerated lesions.[2] Peripheral neuropathy occurs in 20% of CV patients and is characterized by lower extremity slowly progressive asymmetric paresthesias, followed by motor impairment, presenting as foot drop.[2] Our patient presented both cutaneous and neurological manifestations of CV as the initial disease presentation.

While CV diagnosis requires observation of serum cryoglobulins, its absence does not rule out the disease, and serial evaluation is recommended, since false-negative results may occur due to inaccurate sample collection, inconsistent laboratory procedures, and variable serum cryoglobulin concentrations.[3] The often-found reduced serum C4 concentration is related to its consumption by cryoglobulin-containing immune complexes and may be a marker of disease activity, whereas C3 levels are usually minimally impacted.[3] Given CV is associated with a systemic inflammatory response, acute phase reactants such as the erythrocyte sedimentation rate and C--reactive protein are usually elevated. A cutaneous biopsy usually reveals leukocytoclastic vasculitis, which constitutes the hallmark histopathological feature and the gold standard for diagnosing CV.[3] Our patient presented both analytical and histopathological findings compatible with the CV diagnosis.

CV has been documented in patients with RA but its incidence is nowadays rare due to the early diagnosis and proper therapeutic management of RA, including the emergence of biologic disease-modifying antirheumatic drug therapy. CV usually manifests in patients with long-standing (generally exceeding 10 years in duration) seropositive and joint-erosive RA, frequently accompanied by rheumatoid nodules.[4] The average interval between the diagnosis of RA and the onset of CV is 10 to 14 years, and it is uncommon for this complication to manifest within the first 5 years following the RA diagnosis.[4] Our patient had chronic untreated severe rheumatoid arthritis, which ultimately predisposed to CV emergence. A timely diagnosis and appropriate treatment of RA might have averted the onset of this complication and its associated morbidity.

In CV, prognosis strongly depends on concomitant pathologies, response to treatment, and severity of organ damage.[5] Careful monitoring of life-threatening complications (namely renal, pulmonary, gastrointestinal and central nervous system involvement) should be carried out in these patients.[5] Sepsis and uncontrolled vasculitis activity are the leading causes of short-term death.[5] In our patient's case, the prognosis hinges on the RA treatment response and on cutaneous and neurological-induced morbidity. In fact, CV's cutaneous involvement can result in gangrene requiring surgical limb amputation, and the neuropathy may cause chronic debilitating pain or permanent function loss, with subsequent quality of life deterioration.[5]

Prompt immunosuppression is paramount to prevent end--organ damage by inhibiting immune complex formation.[6] Rituximab is currently the treatment of choice in combination with high-dose glucocorticoids for moderate manifestations of CV, showing an effective immunologic response that translates to sustained clinical remission.[6] In cases of severe, life-threatening or organ-threatening disease manifestations, other therapeutic options should be considered, such as cyclophosphamide combined with high-dose corticosteroids, or, as second-line therapies, plasmapheresis or mycophenolate mofetil.[6]

Table 2: Subsequent laboratory investigation.

Laboratory tests	Patient Values	Referenge range
Anti-human immunodeficiency virus antibody	Non detectable	12-15 g/dL
Anti-hepatitis C virus antibody	Non detectable	80-100 fL
Hepatitis B virus surface antigen	Non detectable	4.0-11.0 x 103/µL
Anti-Hepatitis B virus surface antibody	Detectable	
Anti-Hepatitis B virus core antibody	Non detectable	
Blood culture	Negative	
Serum protein electrophoresis	Hypergammaglobulinemia policlonal	0.04-0.40 x 103/µL
Antinuclear antibody	1/640, mottled pattern	<1/160
Anti-double strand DNA (dsDNA) antibody	0.6 UI/mL	<15 UI/mL
Anti-Smith antibody	0.4 U/mL	<10 U/mL
Anti-Sjögren syndrome related antigen A antibody (Anti-SSA/anti-Ro)	0.5 U/mL	<10 U/mL
Anti-Sjögren syndrome related antigen B antibody (Anti-SSB/anti-La)	0.6 U/mL	<10 U/mL
Rheumatoid factor	666.9 UI/mL	<14 UI/mL
Total bilirubin	0.62 mg/dL	0.2-1.0 mg/dL
Anti-CCP (Cyclic Citrullinated Peptide) antibody	>250 U/mL	<10 U/mL
Complement component 4 (C4)	8.2 mg/dL	11-42 mg/dL
Complement component 3 (C3)	127 mg/dL	81-167 mg/dL
Total complement activity (CH50)	32 U/mL	23-60 U/mL
Cryoglobulins (quantification)	25 mcg/mL	<15 mcg/mL
Cryoglobulins (characterization)	IgA, IgG and IgM with polyclonal characteristics	24-173 U/L
Immunoglobulin A (IgA)	285.1 mg/dL	114-457 mg/dL
Immunoglobulin G (IgG)	1414 mg/dL	793-1590 mg/dL
Immunoglobulin M (IgM)	88 mg/dL	29-226 mg/dL
Myeloperoxidase anti-neutrophil cytoplasmic antibodies (MPO-ANCA)	5.6 UQ	<20 UQ
Anti-proteinase-3 anti-neutrophil cytoplasmic antibodies (PR3-ANCA)	2.3 UQ	<20 UQ

In conclusion, the presented case aims to underscore that CV is a rare complication of chronic RA, but it can occur if a timely and accurate diagnosis of RA is not established and an appropriate treatment is not initiated. It also emphasizes that a high index of clinical suspicion is the key to an accurate diagnosis and that prompt treatment is crucial to minimize morbidity and mortality. ■

Declaração de Contribuição

ACM - Pesquisa bibliográfica, avaliação do paciente e redação do artigo.
IV, TF: Revisão crítica do manuscrito.
TFS: Descrição e interpretação de achados radiográficos, revisão crítica do manuscrito
Todos os autores aprovaram a versão final a ser publicada.

Contributorship Statement

ACM - Literature search, patient assessment and writing the article.
IV, TF: Critical revision of the manuscript.
TFS: Description and interpretation of radiographic findings, critical revision of the manuscript
All authors approved the final version to be published.

Responsabilidades Éticas

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