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FENÓMENO DE RAYNAUD COM ISQUÉMIA ACRAL – UM CASO DE CRIOGLOBULINÉMIA ESSENCIAL

Casos Clínicos

Doenças Autoimunes e vasculites

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RESUMO

Crioglobulinas são imunoglobulinas que precipitam a baixas temperaturas e redissolvem após reaquecimento, potencialmente causando uma forma rara de vasculite - CryoVas. A Infecção pelo vírus da Hepatite C é a principal causa de CryoVas, mas muitas outras etiologias têm sido identificadas. Ocasionalmente não se identifica qualquer causa etiológica e a crioglobulinémia é designada como essencial. Descrevemos um caso de apresentação invulgar de crioglobulinémia tipo II, sob a forma de fenómeno de Raynaud com isquémia acral. Apesar de nenhuma etiologia ter sido identificada o tratamento sintomático permitiu a cura das úlceras digitais. Os autores têm como objectivo destacar a forma de CryoVas não associada ao vírus de Hepatite C. À medida que vão surgindo novas opções terapêuticas para o vírus C, a CryoVas tornar-se-á um distúrbio ainda mais raro, dificultando o diagnóstico.

Palavras Chave :
Crioglobulinémia essencial; Fenómeno de Raynaud; Isquémia acral.

ARTIGO

Introduction

Cryoglobulins are immunoglobulins that precipitate at low temperatures and redissolve after rewarming[1–8]. *Brout et al* classification, based on the clonality of the immunoglobulins, presents a good correlation between clinical manifestations and associated etiologies[5,6]. Type I are pure monoclonal immunoglobulins, usually IgG or IgM and are essentially associated with B-cell-proliferative disorders. Type II consists of polyclonal IgG with monoclonal IgM. Type III cryoglobulins are a mixture of polyclonal IgG and IgM[1,2,4–7]. Types II and III are generally referred to as mixed cryoglobulinemias and present rheumatoid factor activity. They develop secondarily to infections (most importantly hepatitis C virus – HCV), autoimmune or neoplastic disorders[1–6,8]. Table 1 presents some of the clinical conditions/agents that may be associated with cryoglobulinemia. When no etiology is identified the cryoglobulinemia is designated as essential[2,4,5,7].

Cryoglobulins can cause tissue damage either by hyperviscosity or by vascular inflammation mediated by immune complex depositions and complement fixation[1,4,5]. Type I cryoglobulinemia patients tend to present clinical manifestations related to complications of hyperviscosity whereas types II and III patients usually display manifestations caused by small-medium vessel vasculitis - Cryoglobulinemia vasculitis (CryoVas)[1,4–7].

It is believed that 2% to 50% of the patients develop symptoms[5].Furthermore, clinical expression is extremely variable as CryoVas can involve a variety of tissues (skin, kidneys, joints, lungs, peripheral nerve system or gut) with symptoms that can range from mild (arthralgia) to fulminant life-threatening (widespread vasculitis)[1,2,6,8]. Meltzer triad – purpura, arthralgia and fatigue - is present in 25% to 80%[1,5,6]. The skin is the most frequently damaged organ (55% to 100% of the patients) with palpable purpura of the lower extremities as the most frequent sign[1,2,5,6]. Raynaud's phenomenon (RF) and acrocyanosis can occur and evolve to digital ulceration / acral ischaemia[1,2,5,6,8].

Case Description

A 63-year-old female was referred to an Internal Medicine consultation for possible autoimmune disease. She had a 3-month history of extremally painful digital ulcers, beginning in winter, complicating a RF that started 2 years before. Previous Vascular Surgery consultation had ruled out thromboangiitis obliterans (Buerger's disease) after extensive study. There was no clinical improvement with smoking cessation. RF was biphasic and symmetrical to both hands and feet. The patient also referred involuntary weight loss and fatigue. She reported no other symptoms.

The patient had a past medical history of hypertension and depression under treatment with losartan 50 mg q.b., clomipramine 25 mg q.b., and aspirin 100 mg q.b..

Physical examination revealed severe ulceration of the distal phalanx of the second right finger with bone exposure (figure 1) and small punctate necrosis of the distal phalanx of the third right and left fingers (figure 2 – left finger). None of the ulcerations were infected but all were extremely painful. The remaining clinical observation was unremarkable.

Laboratory results showed a rheumatoid factor of 27 UI/mL (reference range < 20 UI/mL) and the presence of cryoglobulins compatible with cryoglobulinemia type II: 0.9 mg/dL of polyclonal IgG and 4.5 mg/dL of monoclonal IgM. Nailfold capillaroscopy revealed giant capillaries, capillary hemorrhages, and mild disorganization of the capillary architecture (figure 3).

Complete blood cell count, serum biochemistry (including complement C3 and C4), urinalysis and thyroid hormonal studies were normal. Clinical relevant serologies were negative namely HCV, hepatitis B virus (HBV), human immunodeficiency virus 1 and 2 (HIV 1 and 2) and Interferon Gamma Release Assay (IGRA). Serologic tests for autoantibodies were negative including anti-Ro/SSA and anti-La/SSB antibodies (anti-Sjögren's syndrome related antigen A and B), ANA (anti-nuclear antibody), ANCA (anti-neutrophil cytoplasmic antibodies), APS (antiphospholipid syndrome antibodies) and ACPA (anti-citrullinated protein antibodies). No suspicious lesions were identified in computed tomography of the neck, chest, abdomen and pelvis as well as in the PET-scan (positron emission tomography). Bone marrow biopsy revealed no abnormalities.

No life-threatening organ damage and no associated etiology was found. Essential type II cryoglobulinemia was assumed and symptomatic treatment was directed to the RF and pain relief. Amlodipine 10 mg, pentoxifylline 400 mg, naproxen 250 mg where started, as well as cold temperature avoidance, use of gloves and skin hydration. After 2 months, the small digital ulcers had healed and the largest one cured after 6 months (figures 4 and 5) with no recurrence after 1 year. Serologies were repeated and remained negative.

Discussion

HCV is the predominant cause of CryoVas, accounting for roughly 80% of the cases[1–4,6,7,9]. This identification allowed a better understanding of the disorder[1,10]. However, as the association was only identified in 1991[11], most previous studies report results of heterogeneous populations (with or without HCV)[2,6,7]and most recent studies derive from HCV-positive populations. Thus, data on presentation, therapeutic management and prognosis of non-HCV CryoVas patients is limited[3,4]. Initiated in 2010, the French CryoVas survey (a national retrospective study) has brought some new insight on non-HCV CryoVas[2,3,7].

Essential cryoglobulinemia (EC), as was the case of our patient, accounts for nearly 10% of all patients (up to 25% in non-HCV populations)[4,5]. Mostly, therapeutic management of CryoVas takes into consideration the underlying disease, the predominant etiopathogenic mechanism (vasculitis vs hyperviscosity) and the severity of the disease[1,2,4,9,10]. In EC, the absence of etiology and population-orientated studies implies that the best therapeutic management has yet to be defined and treatment usually just involves symptomatic relief[2]. Mild-to-moderate CryoVas treatment may include resting, cold temperature avoidance, nonsteroidal anti-inflammatory drugs, colchicine and disulone (dapsone and ferrous oxalate)[2,4,8]. Severe CryoVas can be treated with a combination of corticosteroids, immunosuppressants (rituximab, cyclophosphamide, azathioprine or mycophenolate mofetil) or therapeutic plasma exchange[2,4,5,8]. Considering that our patient did not present any severe organ damage, conservative treatment directed to RF was our option.

CryoVas presents significant morbidity and mortality[10]. Prognosis relates to vital organ damage, underlying disease and comorbidities[2,4,5,7,8]. Generally patients have a worse 10-year survival rate than general population with 15% developing life-threatening complications, although roughly half of the patients never develop vital organ involvement[5,8].

CryoVas is already considered a rare disorder despite the absence of adequate epidemiological studies[1,5,8]. With the development of new therapeutic options for HCV, prevalence of the disorder will eventually decline even further. This case report highlights the importance of awareness of non-HCV CryoVas and the management of these patients.

Acknowledgements

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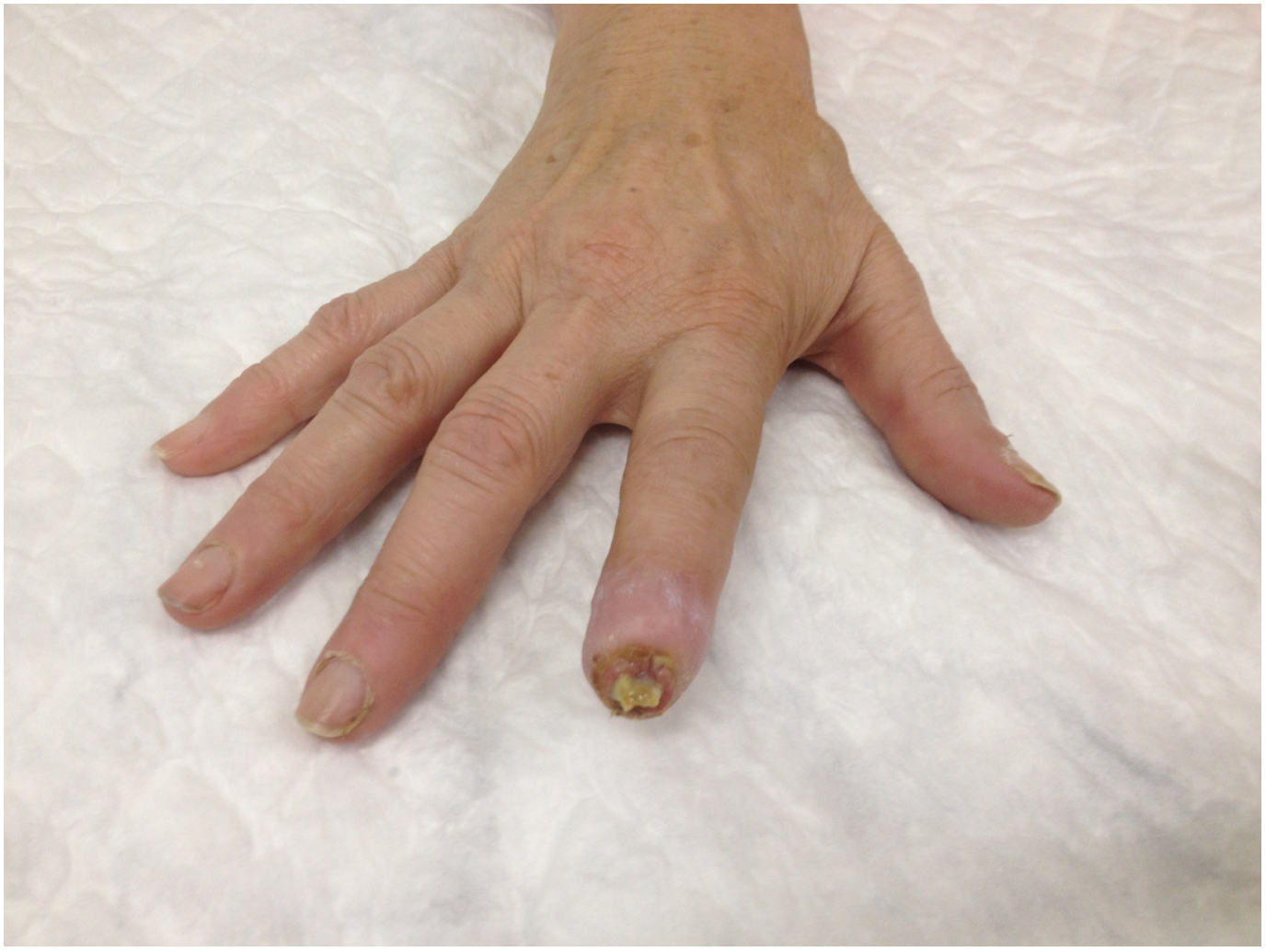
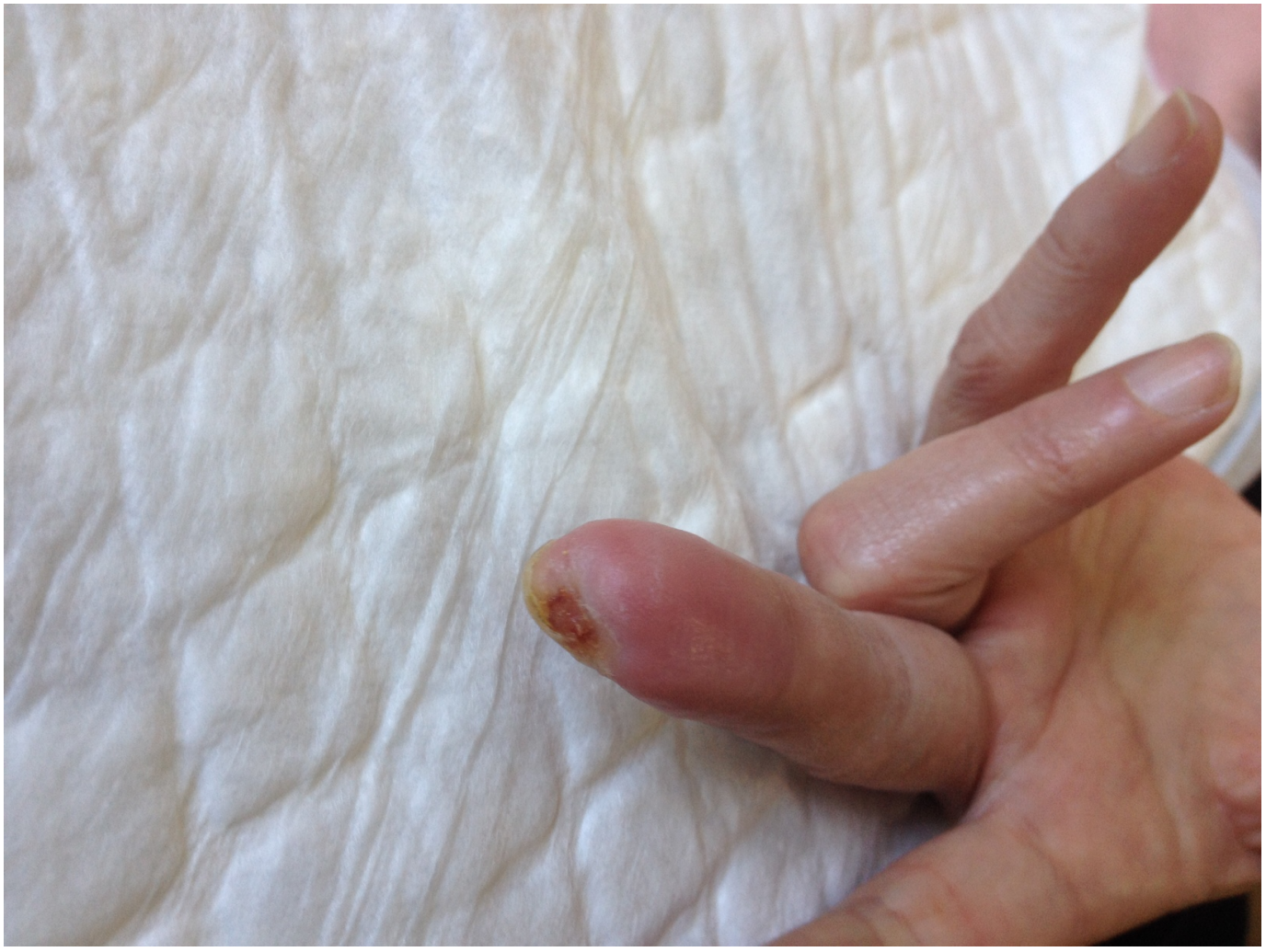
Figura I



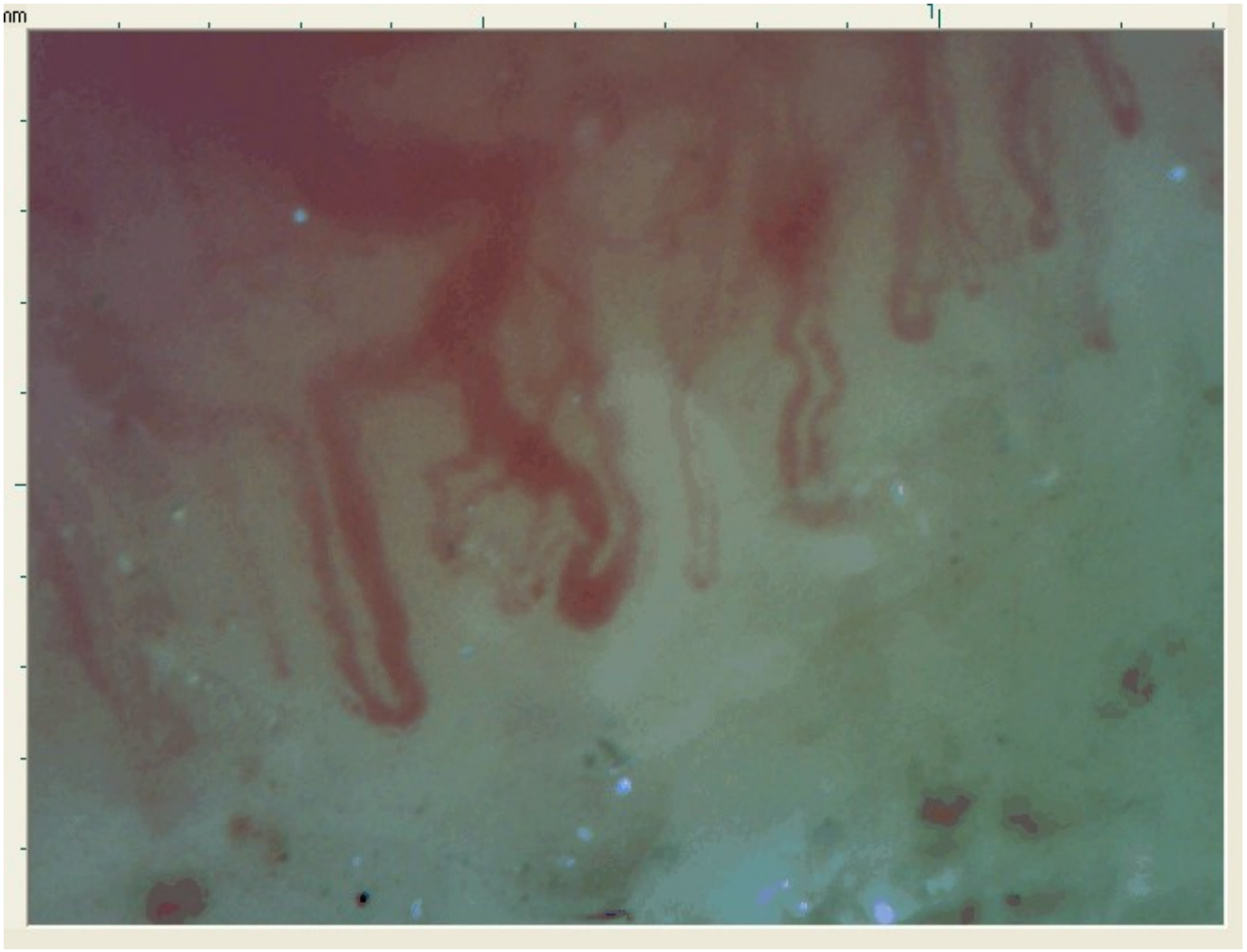
Digital ulceration

Figura II



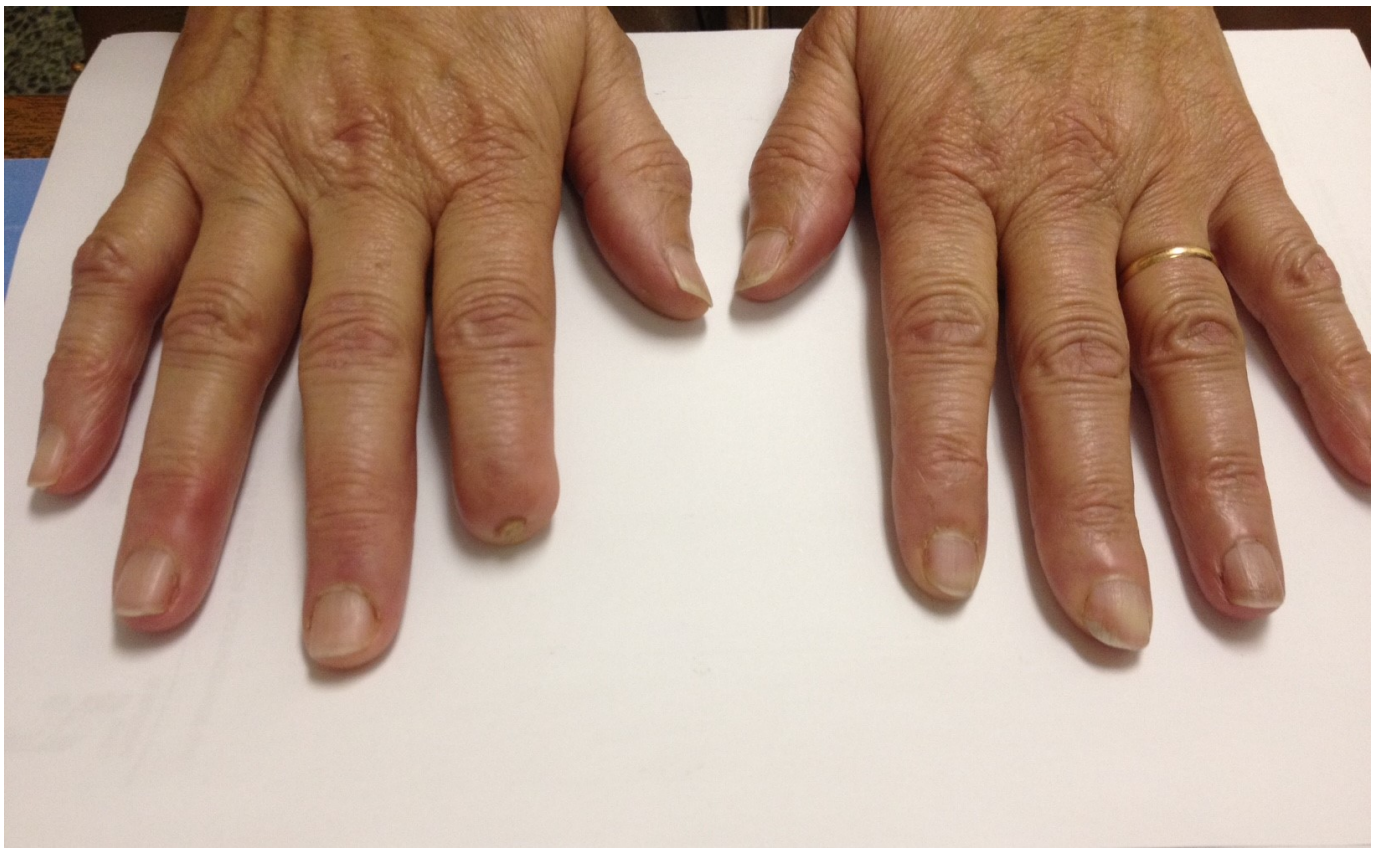
Small punctate necrosis

Figura III



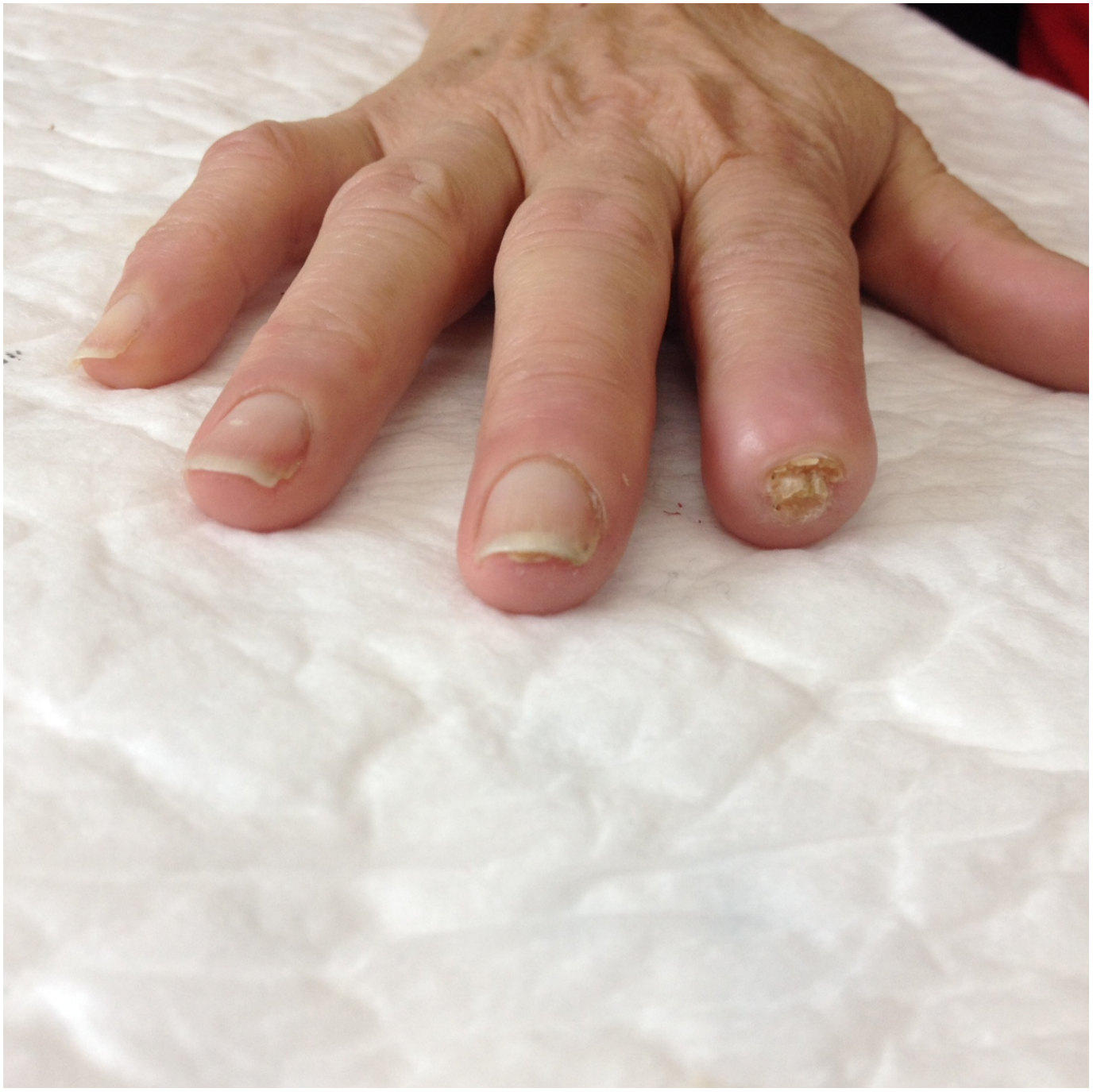
Nailfold capillaroscopy

Figura IV



Evolution

Figura V



Evolution

Figura VI

Table 1 - Clinical conditions/agents that may be associated with cryoglobulinemia

Clinical conditions/agents that may be associated with cryoglobulinemia	
Infections	**Viral:** Hepatitis C virus; Hepatitis B virus; Hepatitis A virus; HIV - human immunodeficiency virus; Cytomegalovirus; Parvovirus B-19; Chikungunya virus; Epstein-Barr virus; Hantavirus. **Bacterial**: *Treponema pallidum*; *Streptococcus* spp; *Brucella* spp; *Coxiella* spp; *Borrelia* spp; *Klebsiella* spp; *Leishmania* spp; *Chlamydia* spp; *Mycobacterium tuberculosis*; *Mycobacterium leprae* - Lepromatous leprosy; Subacute bacterial endocarditis. **Fungal**: Coccidioidomycosis. **Parasitic**: *Toxoplasma gondii*; *Leishmania donovani*; *Entamoeba sp.*; *Echinococcus sp.*; *Plasmodium* sp.; *Schistosoma sp.*; *Trypanosoma sp.*
Autoimmune diseases	Sjögren's syndrome; Systemic lupus erythematosus; Rheumatoid arthritis; Systemic sclerosis; Primary antiphospholipid syndrome; Inflammatory myopathies - Dermatomyositis-polymyositis; Adult-onset Still's disease; Polyarteritis nodosa; Giant-cell arteritis; Takayasu's arteritis; ANCA-associated vasculitis; Autoimmune hepatitis; Autoimmune thyroiditis; Inflammatory bowel disease; Pemphigus vulgaris; Primary biliary colangitis.
Cancer	B-cell lymphoma; Multiple mieloma; Hodgkin's lymphoma; Non-Hodgkin's lymphoma; Chronic lymphocytic leukaemia; Chronic myeloid leukaemia; Myelodysplasia; Waldenstrom's macroglobulinemia; Hepatocellular carcinoma; Papillary thyroid cancer; Lung adenocarcinoma; Renal cell carcinoma; Nasopharyngeal carcinoma.
Non-neoplastic haematologic diseases	Henoch-Schönlein disease; Thrombocytopenic thrombotic purpura; Cold agglutinin disease; Castleman disease.
Other causes	Sarcoidosis; Endomyocardial fibrosis; Idiopathic pulmonary fibrosis; Alcoholic cirrosis; Co-trimoxazole*; Interferon alpha*; Cocaine*; Intravenous radiographic contrast*; Influenza vaccination; Hepatitis B vaccination; Intravesical BCG; Moyamoya disease; Chilblains.

Table 1 – List of conditions that may be associated to cryoglobulinemia(5,6); * - Associated with cryoglobulinemic exacerbation.

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