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Raynaud's Phenomenon as a Manifestation of Vasculitis C – ANCA: Case Report and Literature Review

Ana Livia Domínguez Rodríguez*[1], Perla Karina Hernández de Lira[1], Andrea Carolina Torres Ruiz[2], Elizabeth Torres Ruiz[1]

[1] Mexican Social Security Institute – General Hospital of Zone No. 33. Department of Internal Medicine. Monterrey, Nuevo León, México

[2] Mexican Social Security Institute – General Hospital of Zone No. 50. Department of Surgery. San Luis Potosí, San Luis Potosí, México

ABSTRACT

Raynaud's phenomenon is a vasospastic condition affecting capillaries in the distal region of the extremities. It is divided into primary and secondary and 80-90% of patients are associated with primary or idiopathic disease, while 10-20% are secondary, with multiple etiologies including connective tissue, vascular, hematologic, and endocrinopathic diseases.

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) correspond to a group of necrotizing vasculitides of medium (0.2 to 2.0 mm in diameter) and small blood vessels (arterioles, capillaries, postcapillary venules). Clinically, it is characterized by multisystem involvement, with upper and lower respiratory tract and renal damage standing out for their frequency. The least frequent manifestations are cutaneous, with digital ischemia and gangrene occurring in less than 1% of cases.

The diagnosis is based on a detailed clinical history and physical examination in addition to complementary studies including a complete metabolic panel, muscle enzymes, viral panel, thyroid profile and a rheumatologic panel to assess secondary causes of Raynaud's phenomenon.

Calcium antagonists are considered the first-line treatment in both etiologies, and phosphodiesterase-5 inhibitors are another alternative.

This article presents a case of a patient with Raynaud's phenomenon as an initial clinical manifestation and later presentation of C-ANCA vasculitis.

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INTRODUCTION

Raynaud's phenomenon is a vasospastic condition that affects the capillaries in the distal region of the extremities. It is described as a triad consisting of pallor, cyanosis, and reactive hyperemia. Symptoms are exacerbated by exposure to cold temperatures or emotional stress and can be divided into primary or secondary. 80-90% of individuals correspond to primary or idiopathic, while 10-20% to secondary which is associated with multiple etiologies including connective tissue, vascular, hematological and endocrinopathies diseases (1).

Vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA) corresponds to a group of necrotizing vasculitis that affects small and medium caliber vessels. Granulomatosis with Polyangiitis (GPA), previously known as Wegener's Granulomatosis, is a type of vasculitis usually associated with the presence of C-ANCA. The clinical manifestations can be multisystemic, with those mainly affected being the upper and lower respiratory tract and kidney disease. A less frequent manifestation is digital ischemia and even more so when it is associated with gangrene with a prevalence reported in less than 1% of cases (2).

CASE REPORT

We present the case of a 46-year-old female patient with no medical history relevant to the current condition.

Her condition began 3 weeks prior to our evaluation when she presented a change to violaceous discoloration of the extremity predominantly affecting the second phalanx of the left hand as well as the first and third phalanx of the right hand, accompanied by burning pain and presenting exacerbation of the symptoms with a drop in temperature to levels lower than 10ºC. After 8 days, her symptoms worsened, progressing to necrosis in the affected regions, and adding violet color to the acral region of both lower extremities, as well as burning pain, which is why he attended our hospital (Figure 1).

She was received with vital signs within normal parameters, on physical examination: necrosis in the distal region of the phalanx of the 3rd finger of the left hand, as well as in the distal region of the 1st, 2nd and 3rd phalanx of the right hand, in the lower extremities, necrosis was noted. bilateral toes and back of both feet to both ankles.

During your initial evaluation, the following laboratory tests were performed:

Hemoglobin 10.3 g/dL, leukocytes 13,330 k/uL, platelets 303 k/uL, ESR 32 mm/h, CRP 20.7 mg/dl, general urine examination, without alterations, hepatitis B, C and human immunodeficiency virus negative. Within the rheumatological profile, rheumatoid factor was reported 140.8 IU/ml, anti-proteinase 3 antibodies 527,700 UR/mL and a negative result for antinuclear antibodies, anti-La/SSB, anti-Ro/SSA, anti-Smith, anti-DNA, anti-myeloperoxidase and anti-cardiolipin G and M, complement C3 and C4 within normal parameters.

Given the single elevation of anti-proteinase 3 antibodies, the diagnosis of ANCA vasculitis was reached, so it was decided to begin management with methylprednisolone and Cyclophosphamide in a single dose of 750 mg intravenously, subsequently Rituximab 1 gram. Regarding the treatment of Raynaud's phenomenon, acetylsalicylic acid was added as well as calcium antagonists and Sildenafil.

However, despite the initiation of medical management in the presence of distal gangrene, surgical debridement was performed on the lower extremities; As for her upper extremities, she was not a candidate for eschar removal. She was discharged with Prednisone 40 mg orally every 24 hours, Sildenafil 12.5 mg every 238 hours, acetylsalicylic acid, and oral analgesics.

After a month of follow-up, the patient reported poor adherence to treatment; however, she did not present progression of necrosis or Raynaud's phenomenon in the rest of the phalanges.

Figure A. Distal cyanosis in the second and third fingers of the left hand. B. Cyanosis, ischemia and distal gangrene in the right hand.

C. Cyanosis and distal necrosis of both lower limbs.

DISCUSSION

Raynaud's phenomenon is caused by a constriction of blood capillaries that causes changes in skin color, edema and paresthesia. It generally affects distal areas of the extremities, but other sites such as the nose, ears and nipples can be affected. It can be divided into primary or secondary, with primary being that which is related to a benign course. On the other hand, secondary or Raynaud's syndrome can even progress to dry gangrene. Among the secondary causes, we can find connective tissue diseases, occlusive arterial diseases, trauma, drugs, hematological causes, among others (Table 1) (3, 19).

Regarding its pathogenesis, there are various factors that are involved, including vascular, intravascular and neural. However, its pathophysiology is not yet fully understood (4).

The diagnosis is based on a thorough clinical history and physical examination considering secondary causes, especially in patients over 30 years of age in the case of unilateral symptoms with a progressive course. Within the laboratory tests, it is important to consider a complete metabolic panel, muscle enzymes, rheumatoid factor, viral panel, thyroid profile, and a rheumatological panel that includes antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, antiphospholipid antibodies, anti-SSA, anti - SSB, anti Smith, among others (4 - 7).

Among other diagnostic tools is nailfold capillaroscopy, which gives us a unique and non – invasive view of the structure of microcirculation (6). Its main usefulness lies in

the distinction between primary and secondary Raynaud's phenomenon, as well as in the diagnosis of systemic sclerosis and related diseases (8).

Calcium antagonists are part of the first line treatment for both primary and secondary uncomplicated Raynaud's phenomenon. They should be started at the lowest dose and titrated over the following weeks to tolerance (9). Phosphodiesterase-5 inhibitors are another alternative. Its benefit has been reported by reducing the frequency and duration of attacks. Among them, sildenafil is recommended for acute symptoms, while tadalafil has shown efficacy together with calcium antagonists (10).

Our patient presented Raynaud's phenomenon secondary to GPA with necrotizing vascular inflammation associated with the presence of antineutrophil cytoplasmic antibodies (C-ANCA) and perinuclear antineutrophil cytoplasmic antibodies (P-ANCA), which are directed toward proteinase-3, present into neutrophil granules and toward myeloperoxidase, respectively (1).

The main pathological features include systemic necrotizing vasculitis, inflammation and necrotizing glomerulonephritis. Vasculitis, then, will be responsible for vascular occlusion and, therefore, tissue ischemia (11). glomerulonephritis. Vasculitis, then, will be responsible for vascular occlusion and, therefore, tissue ischemia (11).

Table 1. Secondary causes of Raynaud's phenomenon [3].

Reumatological: - Scleroderma - Systemic lupus erythematosus - Rheumatoid arthritis - Necrotizing vasculitis - Dermatomyositis and polymyositis - Sjögren's syndrome	Drugs and toxins - Ergotic derivatives - Bromocriptine - Vinblastine - Bleomycin - Cocaine, amphetamines - Exogenous estrogens
Arterial occlusive disease: - Atherosclerosis - Thromboembolism - Buerguer's disease	Endocrinological: - Hypothyroidism - Pheochromocytoma
Neurological - Carpal tunnel syndrome - Complex regional pain syndrome - Poliomyelitis	Blood dyscrasias - Hyperviscosity syndrome - Cryoglobulinemia - Cold agglutinin disease
Trauma	Miscellaneous - Fibromyalgia - Pulmonary hypertension - Low body mass index
Myeloproliferative diseases	

Current clinical practice guidelines suggest that ANCA be performed only to establish the diagnosis of ANCA associated vasculitis, since they are present in all patients with severe disease, and in up to 80% of patients with limited disease (12).

The clinical manifestations of GPA are varied, making this disease a diagnostic challenge. Respiratory and renal manifestations are classic, but their presence can vary, presenting sinusitis in 58% of cases and glomerulonephritis in 51%. On the other hand, skin involvement is less frequent, and is reported in only 20% of cases (1,20). Purpura is the most common skin finding; among others, the presence of ulcers, vesicles, papules, subcutaneous nodules (14). Presentation with digital ischemia and gangrene, as in the case of the patient, is reported even in less than 1% (13).

There are no diagnostic criteria for GPA and the diagnosis is made based on the clinical manifestations of systemic disease, positive serology for ANCA supported by histological evidence of necrotizing vasculitis (11). In ANCA vasculitis, the presence of positive serology may, in the appropriate clinical setting, exclude the need for biopsy (15). In this case, there was the difficulty of not having histopathological evidence; however, by having the clinical and biochemical criteria, the diagnosis could be correctly established. Despite this, histological confirmation is recommended when available.

As for treatment, it consists of two phases: an induction phase lasting 3 to 6 months, and a second maintenance phase for 12 to 24 months to consolidate remission and avoid relapses (16). In the induction phase, glucocorticoids take on special importance; however, there is no consensus on their dosage. It is possible to combine them with immunosuppressive or immunomodulatory drugs such as cyclophosphamide or rituximab, being this regimen the standard in severe disease (17). Without treatment, GPA progresses rapidly with a 2-year survival rate of 10%. Therefore, appropriate medical treatment has dramatically increased their long-term survival (18).

CONCLUSION

Granulomatosis with polyangiitis, previously called Wegener's granulomatosis, is a medium-vessel vasculitis that is characterized by the involvement of multiple systems, the most common being kidney and respiratory tract involvement. Skin involvement has a lower rate of appearance, however within it and its multiple manifestations, we have Raynaud's phenomenon as a rare manifestation, present in less than 1% of cases. However, it is also associated with other diseases or as a primary phenomenon. Therefore, it is important to know the treatment of both Raynaud's phenomenon and the etiology to which it is associated. This article focused on both the manifestations, diagnosis and timely treatment of Raynaud's phenomenon, as well as granulomatosis with polyangiitis, since it has been seen that in these patients' timely treatment substantially increases their survival.

CONFLICT OF INTERESTS

The authors have declared no conflicts of interest.

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