

VANCA-associated vasculitis: a likely overlap with lupus?

Vasculite associada ao ANCA e lúpus: subtipo ou sobreposição?

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ABSTRACT

ANCA-associated vasculitides are defined as necrotizing vasculitis with infiltration of neutrophils and monocytes in the vessel walls and characterized by the absence of immunoglobulin deposition (pauci-immune). They may be confused with Systemic Lupus Erythematosus (SLE) or may be superimposed on this disease. In this case report, the possible concomitance of an ANCA-associated vasculitis (granulomatosis with polyangiitis or GPA and microscopic polyangiitis or PAM) with SLE is shown. The patient opened the picture with cutaneous manifestations, arthralgias and arthritis, in addition to respiratory symptoms. She had renal dysfunction requiring hemodialysis, with a renal biopsy compatible with GPA, pauci-immune glomerulonephritis type, and alveolar hemorrhage. Furthermore, she was positive for the anti-dsDNA antibody suggesting the diagnostic possibility of SLE. The presented ANCA had an ANCA-p pattern, while the one expected in GPA would be ANCA-c. For this reason, microscopic polyangiitis (MPA) can also be considered as a possible diagnosis, given the similarities of manifestations. As for the overlap with SLE, its concomitance with GPA is known in the literature. Therefore, the probable final diagnosis of the condition presented was ANCA-p vasculitis with overlapping SLE.

Keywords: Vasculitis; ANCA; Systemic lupus erythematosus (SLE); Microscopic polyangiitis; Granulomatosis with polyangiitis.

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Supporting sources:

There were no supporting sources.

Ethics Committee:

Opinion number - 6.129.250.

Conflict of interests:

The authors declare they have no conflicts of interest.

Received on: July 5th, 2023

Approved on: January 27th, 2024

Publication Date: 06 July 2024.

DOI: 10.5935/2238-3182.2024e34403-en

RESUMO

As vasculites associadas ao ANCA são definidas como vasculites necrosantes com infiltração de neutrófilos e monócitos na parede dos vasos e que se caracterizam por ausência de deposição de imunoglobulinas (pauci-imune). Podem ser confundidas com Lúpus Eritematoso Sistêmico (LES) ou podem estar sobrepostas a essa doença. Neste relato de caso, mostra-se a possível concomitância de uma vasculite ANCA associada (granulomatose com poliangéite ou GPA e poliangéite microscópica ou PAM) com LES. A paciente abriu o quadro com manifestações cutâneas, artralgias e artrites, além de sintomas respiratórios. Apresentou disfunção renal com necessidade de hemodiálise, com biópsia renal compatível com GPA, do tipo glomerulonefrite pauci-imune, e hemorragia alveolar. Além disso, tinha positividade para o anticorpo anti-dsDNA sugerindo a possibilidade diagnóstica de LES. O ANCA apresentado possuía padrão do tipo ANCA-p, enquanto o esperado em GPA seria o de ANCA-c. Por esse motivo, pode-se, também, considerar a poliangéite microscópica (PAM) como possível diagnóstico, visto as semelhanças das manifestações. Quanto à sobreposição com LES, a sua concomitância com GPA é conhecida na literatura. Portanto, o diagnóstico final provável do quadro apresentado foi o de uma vasculite ANCA-p com sobreposição de LES.

Palavras-chave: Vasculite; ANCA; Lupus eritematoso sistêmico (LES); Poliangiite microscópica; Granulomatose com poliangéite.

INTRODUCTION

ANCA-associated vasculitis predominantly affects small vessels in any organ or tissue, the most affected being the upper and lower respiratory tract and kidneys. Symptoms such as fever, malaise, anorexia, weight loss, myalgia, arthralgia and migratory polyarthropathy can persist for weeks to months until the diagnosis is confirmed. Therefore, hypothetically, obstacles are expected in the differential diagnosis of infections, neoplasms or connective tissue diseases¹.

This disease is chronic, with destructive characteristics that can cause, for example, perforation of the nasal septum, leading to a saddle nose appearance, and kidney dysfunction. Up to 80% of patients develop glomerulonephritis or some other severe manifestation of the disease². These are defined as being necrotizing vasculitis with infiltration of neutrophils and monocytes and which are immunologically characterized by the absence of immunoglobulin deposition on vessel walls (pauci-immune). ANCA is decisive for the diagnosis, since it is an anti-neutrophil cytoplasmic antibody that reacts to polymorphonuclear neutrophil granule proteins, directly involved in the pathogenic mechanisms of the disease².

The disease can present different subtypes such as Granulomatosis with Polyangiitis (GPA), Microscopic

Polyangiitis (PAM), Eosinophilic Granulomatosis with Polyangiitis (EGPA) and Vasculitis limited to the kidney, all with low incidence in the world population. GPA has a prevalence of 2.5 to 10 cases per million people/year and predominates in populations of European descent; PAM has a prevalence of 0.5 to 24 cases per million person-years, being more common in Asian countries (China and Japan) and twice as high in white populations².

As already mentioned, the disease can be confused with connective tissue diseases, mainly Systemic Lupus Erythematosus (SLE), causing diagnostic difficulties. There are also rare cases described in which the two diseases overlap³.

In this case description, a possible association of an ANCA-associated vasculitis (GPA or PAM) with Systemic Lupus Erythematosus (SLE) is shown.

This paper is a case report of a patient at the Rheumatology service at Hospital Evangélico Mackenzie. The methodology used was a review of the patient's medical records reported between April and May 2023, using medical evolutions, laboratory and imaging tests, prescriptions and biopsies. The objective of this report is the clinical discussion and the exchange of knowledge about the diagnosis and therapy used, aiming to improve the approach and outcomes for patients in this situation. As possible risks, there is the breach of medical confidentiality, which will be avoided

by maintaining the patient's anonymity throughout the description. Free and informed consent terms were applied.

CASE REPORT

We present the case of a 37-year-old white female patient, from Curitiba, Brazil, who is a supermarket employee. Three months before initial care at a tertiary hospital, she had painful ulcerated lesions on her inner thighs. She associated the appearance with prolonged (more than 3 years) and almost daily use of naproxen for arthralgias and myalgias. She was treated with antibiotics for 7 days and oral corticosteroids. She showed partial improvement, but similar lesions appeared on her forearm and were treated, at the time, as herpes zoster with an antiviral. This caused adverse events with swelling of the tongue.

Two months after the appointment, she started presenting diffuse abdominal pain, alternating constipation with diarrhea, a lack of appetite and weight loss of 12 kg. In addition, she had a productive cough, night chills, a flu-like illness, and dyspnea. For this reason, she used antibiotics for 15 days, which was interrupted due to diarrhea. 4 days after the appointment, she developed intense epigastric pain radiating to the entire abdomen, constipation - resolved with a laxative - nausea, vomiting, dysuria.

In her past history, she had a history of arterial hypertension and chronic arthralgia in the metacarpophalangeal joints, wrists, elbows, shoulders. She used enalapril 10mg every 12 hours. From a gynecological point of view, she was G1C1A0 and had a previous history of eclampsia. She denied smoking

and alcoholism. Her mother had rheumatoid arthritis and fibromyalgia.

On physical examination upon admission, the patient was pale, with mild abdominal pain on palpation of the upper floor, mild hepatomegaly, lower limb edema 1+/4+ without pitting, purpuric lesions on the lower limbs, metacarpophalangeal and proximal interphalangeal arthritis. Table 1 shows the laboratory tests at admission.

Serologies for sexually transmitted diseases and hepatitis were negative, in addition to several negative blood and urine cultures. Other laboratory test findings were unchanged and/or irrelevant.

A sinus radiograph showed thickening of the mucous lining of the maxillary sinuses. Cranial tomography (Figure 1) showed thickening of the lining mucosa with retention cysts/polyps in the maxillary sinuses.

Chest tomography showed multiple nodular images with soft tissue density, some associated with discrete ground glass sparse in the lungs, more numerous in the lower lobes, measuring up to 5 mm in mean axial diameter (solid nodules? inflammatory granulomas?). There was lymph node enlargement measuring 12 mm in the shortest axial axis in the pre-vascular chain. The echocardiogram showed preserved ejection fraction (67%), left ventricle with mild concentric hypertrophy, grade I diastolic dysfunction, mild aortic, mitral and tricuspid regurgitation and mild pulmonary hypertension.

A renal biopsy was performed which demonstrated 2 globally sclerotic glomeruli and 3 glomeruli with fibrous crescents. In addition, enlargement due to edema of the

Table 1. Admission laboratory examinations.

Hemoglobin (VN=11.5-14.9g/dl)	
Reticulocytes (VN=0.5-1.5%)	8.6 g/dL
Leukocytes (VN=4.000-10.000 cel/mm ³)	0.78%
Lymphocytes (VN=900-2.900 cel/ μ L)	3200 cel/ μ L
Creatinine (VN=0.6-1.1 mg/dL)	896 cel/ μ L
Urea (VN=10-45 mg/dL)	3.87 mg/dL
ESR (VN=0-25 mm)	111mg/dL
24 hour proteinuria (VN= <0.2g)	100 mm
Immune profile	0.75 g
Rheumatoid factor	
Antinuclear factor	Negative
ANCA p	1/640 - Dense fine dotted nuclear
Anti dsDNA	>1/80
Anti-Sm	1/40
Direct coombs	Negative
Cryoglobulins	Positive
C3 (VN=87-200 mg/dL)	Negative
C4 (VN=19-52 mg/dL)	95 mg/dL
C4 (VN=19-52 mg/dL)	16 mg/dL



Figure 1. Cranial tomography showing mucosal thickening, retention cysts and polyps in the maxillary sinuses.

tubulointerstitial space with a discreet granulomonuclear infiltrate with plasmocytes was observed (Figure 2), in addition to fibrosis (30-40%) with proportional tubular atrophy. The immunofluorescence reaction reveals

pauci-reactivity, highlighting traces/trapping of marking for C3 and Kappa in loops (Figure 3). The other studies carried out, which included IgA, C3, Fibrinogen, C1q, IgM and Lambda, were negative. Therefore, it was concluded that it was a focal crescentic glomerulonephritis, in the sclerosing phase, probably a type III pauci-immune form, possibly corresponding to ANCA-associated vasculitis such as Microscopic Polyangiitis or Granulomatosis with Polyangiitis (Wegener's granulomatosis).

During hospitalization, the patient presented hemoptysis, suggestive of alveolar hemorrhage, requiring orotracheal intubation and 24 days in intensive care. In addition, she required hemodialysis due to progressive worsening of her renal function, and this procedure was maintained in the clinic after discharge.

The patient received pulse therapy with methylprednisolone 1g/day for 3 days, followed by oral prednisone 80mg/day, in addition to monthly intravenous cyclophosphamide (960mg/pulse or 15mg/kg with dose adjustment for renal dysfunction) during hospitalization, with improvement. She was discharged to the rheumatology clinic, where she continued treatment with prednisone 80mg/day (1mg/kg/day) and pulses of cyclophosphamide. In addition, she used prophylactic trimethoprim-sulfamethoxazole (400/80mg/day) and calcium and vitamin

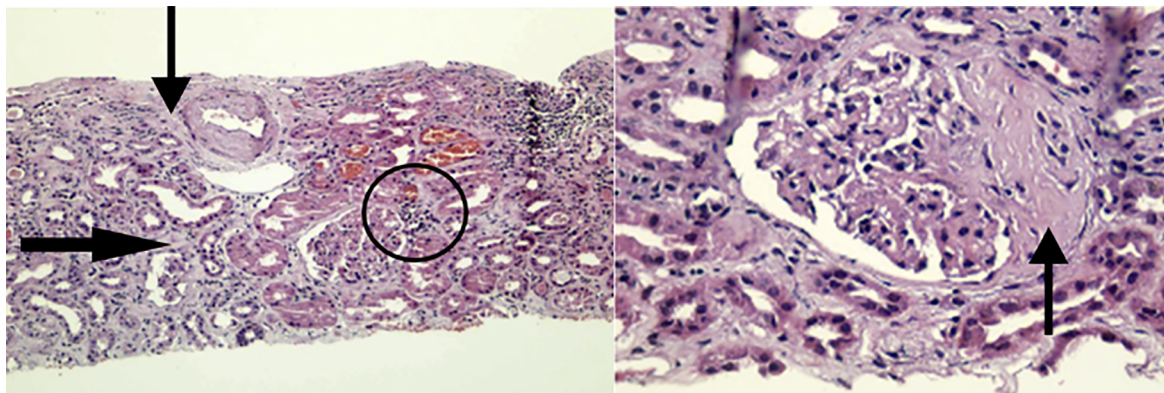


Figure 2. Histological findings of renal biopsy showing globally sclerotic glomeruli with fibrous crescents in addition to edema of the interstitial tubule spaces with plasma cell infiltrate.

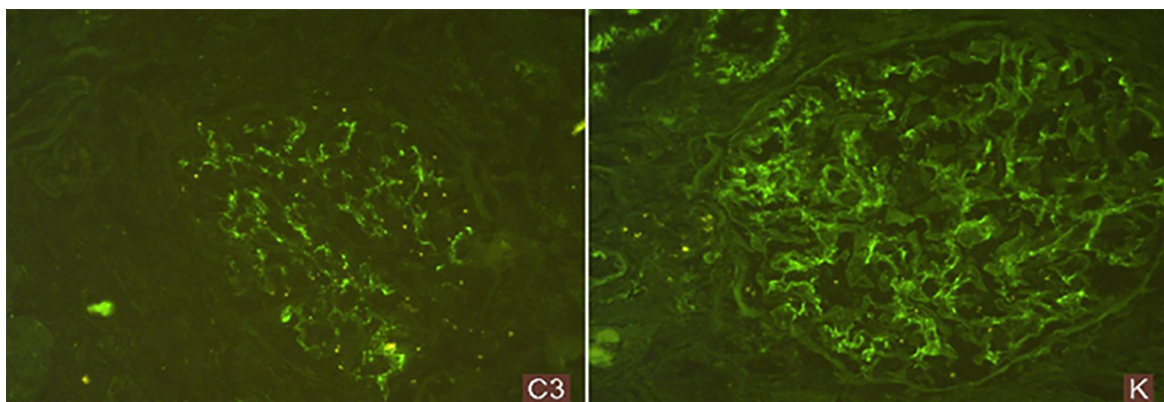


Figure 3. Kidney biopsy with immunofluorescence findings for plasma cell C3 and with immunofluorescence findings for K chain.

D replacement due to the use of corticosteroids and the risk of osteopenia.

DISCUSSION

The patient described presented a classic clinical picture of GPA, with involvement of the upper and lower airways, pauci-immune glomerulonephritis and positive ANCA.

The most common otorhinolaryngological manifestations in patients with GPA are mainly bone and cartilaginous destruction, nasal crusts, sinusitis, otitis media, ear pain, otorrhea, persistent rhinorrhea, purulent/bloody nasal discharge, oral and/or nasal ulcers and polychondritis, in addition to conductive and/or sensorineural hearing loss². The patient in question presented involvement of the maxillary sinuses with mucosal thickening, cysts and polyps, demonstrated in tomography.

The airways may be affected by hoarseness, cough, dyspnea, stridor, wheezing, hemoptysis or pleuritic pain, tracheal or subglottic stenosis, pulmonary consolidation and/or pleural effusion, interstitial lung disease, pulmonary fibrosis and pulmonary arterial hypertension. One may encounter radiographic findings such as nodules, irregular or diffuse opacities, and fleeting pulmonary infiltrates, as well as hilar adenopathy². In the case described, the presence of nodular lesions was observed and later — during hospitalization — a picture compatible with alveolar hemorrhage.

Renal involvement in GPA may be the initial manifestation of the disease in 18% of cases, appearing later in 77 to 85% of cases. It usually occurs within the first two years of disease onset with a typical presentation of rapidly progressive glomerulonephritis. In addition, it can cause intermittent asymptomatic hematuria and creatinine worsening over days/weeks, with a rapid increase in creatinine with hematuria, hypertension and edema^{1,2}. Subnephrotic proteinuria may also be present. If it is less than 1g/24h, it suggests fibrous glomeruli or tubular fibrosis. If it is greater than 3g/24h, it suggests later disease with previous necrotizing glomerulonephritis or other concomitant glomerular diseases (such as membranous nephropathy) or an atypical histological pattern with immune complex deposition¹. In the case in question, renal failure requiring renal replacement therapy and biopsy compatible with GPA or MAP, of the pauci-immune glomerulonephritis type, was observed.

Furthermore, cutaneous involvement of GPA can be found in the form of cutaneous vasculitis in 30 to 50% of cases. This presents itself as lower extremity purpura, urticaria, livedo reticularis, nodules, erythema nodosum, pyoderma gangrenosum, and Sweet's syndrome (acute febrile neutrophilic dermatosis)^{4,5}. The patient described here presented a picture compatible with vasculitis in the lower limbs and forearm, which were the initial clinical manifestations of the disease.

However, some points deserve consideration regarding the diagnosis of GPA. One of them is that the ANCA presented

had an ANCA-p-type immunofluorescence pattern, while the one expected in GPA would be that of ANCA-c. The ANCA survey is a test that should be performed in any suspected vasculitis. Indirect immunofluorescence (IIF) is the most sensitive form of detection. Enzyme immunoassays (ELISA) for proteinase 3 (PR3) and myeloperoxidase (MPO) are more specific. In 82 to 94% of patients with GPA or MAP, ANCA is positive, with a positive predictive value (PPV) of 90%. GPA is associated with PR3-ANCA and c-ANCA, while PAM is mainly associated with MPO-ANCA and p-ANCA. p-ANCA is much more prevalent than c-ANCA when it comes to MAP and the opposite is true for GPA. However, about 10% of patients with GPA or MAP are ANCA negative, which does not exclude the diagnosis. Furthermore, ANCA status may change over time⁶.

Thus, we can also consider the possibility of microscopic polyangiitis (MPA) as a possible diagnosis, given the similarities of the manifestations presented. This is characterized by a varied and nonspecific clinic⁷. Hematuria, hemoptysis, purpura, peripheral neuropathy, abdominal pain, gastrointestinal bleeding, sinusitis, fever, weight loss, myalgias and arthralgias are frequent manifestations of PAM. Alveolar hemorrhage occurs in up to 30% of cases and is accompanied by renal manifestations in 97% of cases. As in the case reported, arthralgias and myalgias may precede the onset of renal and pulmonary involvement by years. In addition, it is characterized as the main cause of the “lung-kidney” syndrome and should be considered in patients with hemoptysis with renal dysfunction¹.

In histopathology, the glomerular lesion presented is identical in MAP, GPA and Churg-Strauss Syndrome (CSS), making diagnostic differentiation difficult. In imaging exams, by definition, MAP does not cause granulomatous inflammation (lung nodules or cavities and destructive bone lesions in the upper respiratory tract), so its presence in small vessels should be indicative of GPA⁷.

As for overlap with SLE, false-positive p-ANCA can occur in lupus patients who are ANA positive (and vice versa) since the immunofluorescence patterns are very similar. This could have happened in the situation described. However, this does not explain the presence of the anti dsDNA antibody, which is considered one of the most specific for SLE⁸.

The anti-dsDNA antibody is useful for the diagnosis and follow-up of SLE, especially in patients with lupus nephritis. The comparison between chemiluminescence, using the indirect immunofluorescence test as a reference, demonstrates that for the diagnosis of SLE, when this antibody is investigated by the first method, it presents 100% sensitivity and 82% specificity⁸. In the patient in question, this antibody was positive, positive ANA in high titers (1/640) with characteristic of a dense fine punctuated nucleus, complement consumption, anemia and lymphopenia. As for the clinical manifestations of SLE, the patient had arthralgias, skin lesions suggestive of vasculitis and renal dysfunction requiring hemodialysis. Therefore,

it is observed that the patient also presented a condition suggestive of SLE according to the EULAR/ACR 2019 diagnostic criteria, covering more than 10 points and at least one clinical criterion^{7,9}.

Some points regarding the interpretation of the presented autoantibodies deserve observation: the first is that the immunofluorescence pattern of the dense fine speckled type, as presented in this case, is commonly found in healthy individuals¹⁰, although it has been described in a small percentage of patients with SLE¹¹. The second is that the ANCA p antibody can be found in lupus nephritis (in up to 70%), showing a positive association with disease activity and aggressiveness⁴. It is positive when the disease is active, however its association with remission is unknown. It is associated with endocapillary hypercellularity, necrosis, formation of crescents, interstitial inflammation, tubular atrophy and interstitial fibrosis^{4,6,12} — findings compatible with those presented in the clinical case. The third observation is that, in ANCA-associated vasculitis, it has been described that ANA may be present in up to 50% of cases and anti-dsDNA in up to 20%¹³. Therefore, although the anti-dsDNA positivity presents a strong indication of the possibility of lupus, its finding should not be exclusively related to this diagnosis.

Although the diagnosis of SLE is not established by the result of renal biopsy, some histopathological findings support this hypothesis. The presentation of membranous glomerulonephritis superimposed with diffuse proliferative glomerulonephritis, with a full house immunofluorescence pattern, makes the diagnosis of lupus nephritis probable. The full-house pattern is characterized by the presence of IgG, IgM, IgA, C3 and C1q deposits and occurs in 71% of lupus nephritis, with a specificity of 90%. The association of ANCA-associated vasculitis and full-house nephropathy was described in only 3% of cases^{5,6}. In the case presented here, the immunofluorescence showed only positivity for C3 and Kappa chains, without characteristics compatible with lupus nephritis. The literature shows a description of 8 cases of overlap between SLE and ANCA vasculitis with glomerulonephritis that demonstrated the existence of pauci-immune glomerulonephritis in 5 of these, while class 4 lupus glomerulonephritis was found in another 2 and class 2 in 1 patient¹⁴. Therefore, it is observed that the renal damage seen in cases of overlap can be similar to either of the two seen in these diseases.

The treatment protocol for any patient with ANCA-associated vasculitis with active disease should include systemic glucocorticoids, associated immunosuppressive and/or biological therapy¹⁵. The initial dose of prednisone is 0.5 to 1 mg/kg/day and there is no evidence of the superiority of intravenous therapy, except when there is involvement of vital organs. In this case, one should opt for intravenous pulse therapy with methylprednisolone 15 mg/kg/day or 0.5 to 1.0 g/day for one to three days at the beginning of treatment¹⁵. The introduction of cyclophosphamide changed the natural history of the disease, improving treatment response and survival. In addition, rituximab is a therapeutic

option for inducing disease remission¹⁴. These drugs also work in cases of lupus glomerulonephritis. Milder or limited forms of ANCA-associated vasculitis can be treated with methotrexate⁸. Plasmapheresis is indicated in patients with rapidly progressive glomerulonephritis and serum creatinine >5.8 mg/dL, as it improves renal survival when associated with glucocorticoids and cyclophosphamide. However, there is still no evidence of the efficiency of this form of treatment for alveolar hemorrhage¹⁵.

CONCLUSION

The present case demonstrates the difficulty in the differential diagnosis between GPA and SLE and illustrates the possibility of overlap between these two entities, which is believed to be the final diagnosis of the patient described. Although the treatment of the two entities is very similar, every effort should be made to reach a definitive diagnosis, as the future course and prognosis of the disease may differ.

AUTHORS' CONTRIBUTIONS

We describe contributions to the papers using the taxonomy (CRediT) provided above: Conceptualization, Investigation, Methodology, Visualization & Writing – review & editing; Project administration, Supervision & Writing – original draft; Validation & Software; Resources & Funding acquisition; Data curation & Formal Analysis: Manfredini GB, Skare TL.

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