ISSN 2664-3987 (Print) & ISSN 2664-6722 (Online)
South Asian Research Journal of Medical Sciences
Abbreviated Key Title: South Asian Res J Med Sci

| Volume-6 | Issue-5 | Sep-Oct -2024 | **DOI: https://doi.org/10.36346/sarjms.2024.v06i05.007**

Case Report

Refractory Undifferentiated Vasculitis: A Case Report

Madrid-Morales Mariana[1*], Ortiz-Valdés Carolina Paola[1], Pérez-Campos Laura Areli[2], Montaño-Sosa Julia Magaly[3]

[1]Department of Internal Medicine, Hospital Regional de Alta Especialidad "Bicentenario de la Independencia", Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, México
[2]Department of Dermatology, Hospital General "Adolfo López Mateos", Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, México
[3]Department of Internal Medicine, Hospital General "Adolfo López Mateos", Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, México

***Corresponding Author:** Madrid-Morales Mariana
Department of Internal Medicine, Hospital Regional de Alta Especialidad "Bicentenario de la Independencia", Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, México

Article History
Received: 11.09.2024
Accepted: 16.10.2024
Published: 18.10.2024

Abstract: The ANCA-Associated Vasculitis is a group of rare diseases that affect blood vessels and are related to the presence of specific antibodies called antineutrophil cytoplasmic antibodies (ANCA). While respiratory and kidney involvement are the most common in ANCA-associated vasculitis and thus are part of the classification criteria, it is important to remember that vasculitis are diseases with the potential to cause multi-organ damage. We present this case to emphasize that a sequential approach is necessary for decision-making regarding treatment to prevent complications and improve quality of life, especially when they are refractory to first-line treatment.

Keywords: ANCA Associated Vasculitis, mononeuritis multiplex, cutaneous manifestations, small-vessel vasculitis.

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of diseases characterized by systemic symptoms and severe inflammation of small vessels. The three subtypes of AAV are eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA), and granulomatosis with polyangiitis (GPA). Serologic classification of AAV into proteinase 3–ANCA disease and myeloperoxidase-ANCA disease correlates with a number of disease characteristics. AAV has a predilection for the kidney, with >75% of patients having renal involvement [1, 2].

The cause and pathogenesis of AAV are multifactorial, with contributions from genetic factors, environmental exposures, infections, characteristics of the innate and adaptive immune system, and the intensity and duration of the injury. Acute vascular inflammation is induced when resting neutrophils, which have ANCA autoantigens sequestered in cytoplasmic granules, are exposed to priming factors such as cytokines induced by infections or philogogenic factors released by complement activation, causing the release of ANCA antigens on the surface of neutrophils and in the surrounding microenvironment. ANCA binds to these antigens, activating neutrophils through Fcγ receptor engagement and F(ab')2 binding on the neutrophil surface. ANCA-activated neutrophils release factors that activate the alternative complement pathway, generating C5a, a chemoattractant for neutrophils; C5a also primes the incoming neutrophils for activation by ANCA. Activated neutrophils adhere to and penetrate vessel walls, releasing toxic oxygen radicals and destructive enzymes that cause apoptosis and necrosis of both the neutrophils and the adjacent vessel wall cells and matrix[2].

The clinical spectrum of the disease is very broad and can present with involvement of various organs. Clinical characteristics of GPA and MPA are similar due to their propensity to affect tiny vessels. The nonspecific symptoms of

multisystem disease, such as fever, malaise, anorexia, and weight loss, are frequently seen in patients with EGPA. The second most frequent symptom, mononeuritis multiplex, affects as many as 72% of patients. Up to 61% of patients have allergic rhinitis and sinusitis, which are frequently seen early in the course of the illness [3, 4]. Here, ischemic occlusion of the vasa nervosum-that is, blockage of the tiny blood arteries supplying the nerves-is the cause of the neuropathy. Due to their increased vulnerability to ischemic injury, large myelinated sensory and motor fibers are usually impacted [5]. Neurological manifestations can also be present in the form of mononeuritis multiplex, sensory neuropathy, cranial nerve dysfunction, sensorineural hearing loss, and space-occupying lesions GPA presents with characteristic involvement of the ear, nose, throat, lungs, and kidneys, such as recurrent rhinosinusitis, earache, cough, hemoptysis, dyspnea, hematuria, and proteinuria, with or without renal dysfunction. The nervous system can be involved in forms like mononeuritis multiplex, sensory neuropathy, cranial nerve abnormalities, sensorineural hearing loss, and central nervous system mass lesions. Involvement of the peripheral nervous system is seen in up to 15% of patients with GPA and typically occurs after a prolonged course of sinusitis, lung manifestations, or renal involvement. Rarely, it can be the presenting manifestation. Very few cases of GPA presenting with mononeuritis multiplex have been reported [3].

CASE PRESENTATION

A 33-year-old Mexican woman with no history of chronic diseases, with current diagnosis of ANCA-associated small vessel vasculitis with severe cutaneous vasculitis of the distal pelvic limbs and mononeuritis multiplex. Symptoms began a year ago with neuropathic pain in both pelvic limbs without improvement with analgesia and progression limiting ambulation, adding to hand paresthesias 4 months after the onset of pain.

Later on, 5 months ago she developed erythematous lesions on her feet, legs, and thighs, which became confluent on the dorsum and base of the toes, predominantly on the right side, progressing to a painful erythematous-violaceous plaque. She later developed violet discoloration on the pulp of the right first toe, at the base of the right third, fourth, and fifth toes, distal coldness, and delayed distal capillary refill.

Clinically: Neurological manifestations: in glove hypoesthesia of thoracic limbs and long boot hypoesthesia in pelvic limbs. Without pulmonary, renal, nasal, cartilaginous or hearing involvement.

Abnormal nerve conduction velocities: presence of moderate to severe mononeuritis multiplex characterized by axonal degeneration and conduction block in some nerves.

Immunological studies: C-ANCA (+; 221.84), ANA (+; 2.3) ESR 49 mm/hr. Extended protocol: P-ANCA, anti double-stranded DNA, anti Smith, complement levels, anticardiolipins, eosinophil count, viral panel: Negative

Renal ultrasound without alterations, without proteinuria (19 mg in 24-hour collection), without hematuria.

Chest x-ray without lesions suggestive of nodules, cavitations, fibrosis or interstitial disease. She was evaluated by vascular surgery, who ruled out large vessel involvement, suggesting probable small vessel vasculitis.

Treatment was started with 3 pulses of methylprednisolone, and continued with a dose of glucocorticoid 1 mg/kg body weight, 1 g IV of cyclophosphamide, mycophenolate mofetil 1 g daily and maximum vasodilator treatment: amlodipine, cilostazol, nitroglycerin patch, atorvastatin, acetylsalicylic acid, with very slight improvement.

After receiving treatment, the patient still complained of localized pain in her right foot. Right foot with a purplish color change on the pad of the first toe and on the dorsum of the foot at the base of the 3rd, 4th and 5th toes, without active edge, some non-active satellite erythematous lesions. Distal temperature slightly decreased. Right pedal pulse present decreased.

Next line of treatment is started despite not being possible to classify it, probable undifferentiated vasculitis, with little response to the immunosuppressive treatment used, with risk of progression to necrosis and affection of the toes 1, 3, 4 and 5.

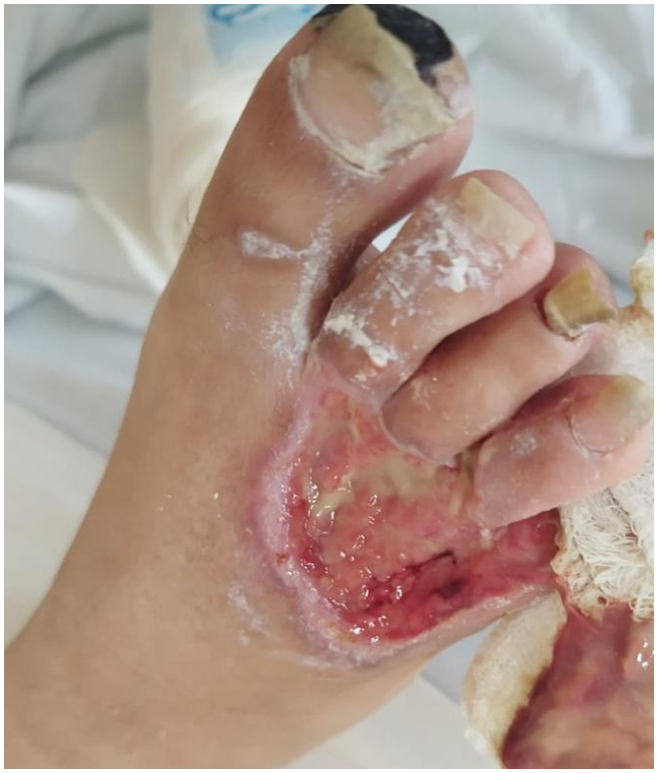

Figure 1: Follow-up at 4 months of ulcer on the dorsum of the right foot, persisting with sites of necrosis in the first toe but with a significant response in toes 3 and 4

The patient was assessed by the internal medicine and rheumatology service and by consensus it was decided to start Rituximab 1 g IV in weeks 0 and 2, every 6 months. Obtaining remission of symptoms, with follow-up of the wound and stoma clinic on an outpatient basis to optimize ulcer closure on the back of the right foot. With a notable improvement in quality of life since she was able to return to her work activities with minimal limitations.

DISCUSSION

The case report that is being presented began with symptoms a year before it was assessed by the Internal Medicine department. Meanwhile, the patient suffered from neuropathic-type pain of varying intensity, according to the evolution, which began to modify and reached the point of impacting the patient's quality of life.

She had the opportunity to go to the emergency department on several occasions as well as to private doctors to receive care. In which case she never had a complete remission of the symptoms since they associated the pain with a postural etiology or as a result of poor spinal hygiene since the patient worked as administrative staff in an office. But at no time did it have a follow-up or study protocol, despite undergoing different treatments based on NSAIDs and non-steroidal anti-inflammatory drugs. It was not until the patient developed purpuric lesions distally in the lower limbs where the need to initiate a study protocol was recognized in the event of suspicion of a disease of autoimmune origin and was referred to the Internal Medicine department.

Antineutrophil cytoplasmic antibody-associated vasculitis is a group of diseases characterized by systemic symptoms and severe inflammation of small vessels. The first step to reach this diagnosis is clinical suspicion and considering its evolution as well as extension studies, which are not only serum tests, in this case to corroborate the damage clinically suspected at the level of the peripheral nervous system it was necessary to perform the test of nerve conduction velocities. The protocol we conducted also included renal ultrasound, quantification of creatinine clearance and determination of proteinuria in 24-hour urine collection, chest X-rays, thoracic abdominal and pelvic computed axial tomography and the assessment of the otorhinolaryngology, vascular surgery and neurology department [6, 7, 10]. It is needed to rule out alternate diagnoses which could mimic vasculitis prior to applying the classification criteria, such as systemic lupus erythematosus, systemic infections, hematologic malignancies or paraneoplastic diseases [8-10].

According to the latest review and update of the ACR/EULAR Classification Criteria for Vasculitis, the patient only meets mononeuritis multiplex within the clinical Criteria and cANCA positiveness in the laboratory and biopsy criteria. In the effort to classify it, she does not sum up the score of six or more points within the seven items needed to classify it as an eosinophilic granulomatosis with polyangiitis. In order to classify it as a microscopic polyangiitis the

patient is ruled out due to not meeting the clinical criteria of nasal bloody discharge, ulcers, crusting, congestion or blockage, or nasal septal defect / perforation. And for granulomatosis with polyangiitis the patient does not meet any clinical criteria (nasal, cartilaginous or hearing involvement), within the laboratory, imaging and biopsy she only meets five points for being cANCA positive summing up the score of five or more points within the ten items needed to classify it as a granulomatosis with polyangiitis, but it does not correlate the clinical manifestations of the patient since she does not show any pulmonar or renal involvement within the extended protocol we conducted [6].

Based on the positivity of ANCA and the clinical signs of small vessel vasculitis, it is important to classify it into one of the three known variants to define the most adequate treatment due to the suboptimal response to the first line treatment the patient presented. The use of rituximab is approved in the management of this kind of vasculitis specially when the remission induction is not reached or if it is being refractory to the high dose glucocorticoid use as well as cyclophosphamide and mycophenolate mofetil in optimal doses [7-10].

CONCLUSIONS

Vasculitis associated with ANCA can cause multi organ damage; at a neurological level, mononeuritis multiplex is the most common form of damage and it manifested itself in this case at least a year before rheumatological disease was suspected. Clinical suspicion is imperative to provide an adequate approach and early treatment, since although it does not meet classification criteria, not providing treatment causes complications and deteriorates quality of life.

Although respiratory and renal system conditions are the most common in ANCA-associated vasculitis and are therefore part of the classification criteria; It is important to remember that vasculitis is a disease with the capacity to cause multi-organ damage. We present this case to be reminded of the importance of the sequential approach, not only for making decisions regarding treatment, but to reach a timely diagnosis in order to prevent complications and improve the quality of life of our patients.

ACKNOWLEDGEMENTS

We are grateful to the Department of Internal Medicine Hospital Regional de Alta Especialidad "Bicentenario de la Independencia", Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado and to the multidisciplinary team who was involved in the management and follow-up of this case.

REFERENCES

1. Geetha, D., & Jefferson, J. A. (2020). ANCA-Associated Vasculitis: Core Curriculum 2020. *American journal of kidney diseases: the official journal of the National Kidney Foundation*, *75*(1), 124–137.
2. Xiao, H., Hu, P., Falk, R., & Jennette, J. (2015). Overview of the pathogenesis of ANCA-associated vasculitis. *Kidney Diseases*, *1*(4), 205–215.
3. Ahlawat, M., Shivnitwar, S., Kanitkar, S., Borle, A., Ande, S., & Reddy, A. (2024). Antineutrophil Cytoplasmic Antibodies Associated Vasculitis Presenting As Neuropathy. *Cureus*, *16*(3), e57046.
4. Patel, A., Patel, U. M., & Sojitra, V. (2023). Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (AAV) Masquerading As Mononeuritis Multiplex: A Case Report. *Cureus*, *15*(5), e38651.
5. Suppiah, R., Hadden, R. D., Batra, R., Arden, N. K., Collins, M. P., Guillevin, L., Jayne, D. R., Luqmani, R. A., & European Vasculitis Study Group (2011). Peripheral neuropathy in ANCA-associated vasculitis: outcomes from the European Vasculitis Study Group trials. *Rheumatology (Oxford, England)*, *50*(12), 2214–2222.
6. Robson, J. C., Grayson, P. C., Ponte, C., Suppiah, R., Craven, A., Judge, A., Khalid, S., Hutchings, A., Watts, R. A., Merkel, P. A., Luqmani, R. A., & DCVAS Investigators (2022). 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. *Annals of the rheumatic diseases*, *81*(3), 315–320.
7. Chung, S. A., Langford, C. A., Maz, M., Abril, A., Gorelik, M., Guyatt, G., ... & Mustafa, R. A. (2021). 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of antineutrophil cytoplasmic antibody–associated vasculitis. *Arthritis & Rheumatology*, *73*(8), 1366-1383.
8. Arzoun, H., Srinivasan, M., Thangaraj, S. R., Thomas, S. S., Yarema, A., Lee, B., & Mohammed, L. (2022). Recent advancements in the management of anti-neutrophil cytoplasmic antibody-associated vasculitis: a systematic review. *Cureus*, *14*(2), e21814.
9. Ross, C., Makhzoum, J. P., & Pagnoux, C. (2022). Updates in ANCA-associated vasculitis. *European Journal of Rheumatology*, *9*(3), 153–166.
10. 10 Floege, J., Jayne, D. R., Sanders, J. F., Tesar, V., & Rovin, B. H. (2024). KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis. *Kidney International*, *105*(3), S71–S116.