Severe granulomatous polyangiitis refractory to conventional treatment

Laura María García-Henao, Edgar Eduardo Castro-Osorio,
Diego Alfonso Sánchez-Rodríguez • Manizales (Colombia)
Diana Marcela Hoyos-Llanos • Bogotá, D.C. (Colombia)

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Abstract

A 40-year-old female patient with a diagnosis of granulomatous polyangiitis c-ANCA positive vasculitis and severe destructive involvement of the nose and sensorimotor polyneuropathy of the lower limbs received three pulses of cyclophosphamide, high-dose steroids, rituximab, azathioprine and methotrexate. She was refractory to treatment, forcing the clinicians to look for differential diagnoses and make decisions based on the clinical picture. She was ultimately treated with plasmapheresis (07/24/2022), with this being the first case described using this treatment despite not having kidney progression or severe diffuse pulmonary hemorrhage. **(Acta Med Colomb 2023; 48. DOI: https://doi.org/10.36104/amc.2023.2836).**

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Dra. Laura María García-Henao: Médica General. SES Hospital Universitario de Caldas; Dr. Edgar Eduardo Castro-Osorio: Especialista en Medicina Interna y Geriatría. SES Hospital Universitario de Caldas, Universidad de Manizales;
Dr. Diego Alfonso Sánchez-Rodríguez: Especialista en Medicina Interna e Infectología, SES Hospital Universitario de Caldas, Universidad de Caldas. Manizales (Colombia).
Dra. Diana Marcela Hoyos-Llanos: Especialista en Medicina Interna, servicio de trasplantes. Fundación Santa Fe de Bogotá. Bogotá, D.C. (Colombia).
Correspondencia: Dra. Laura María García Henao. Manizales (Colombia).
E-Mail: lauragarciah20@gmail.com
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Introduction

Granulomatosis with polyangiitis (GPA) is a type of vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) (1). It usually affects both the upper and lower respiratory tracts, with a 90% prevalence (2, 3) and kidneys with 78% (3, 4). The 10-year survival rate is estimated to be 40% when the kidneys are involved and 60-70% when they are not (5). The current standard treatment is a combination of glucocorticoids and cyclophosphamide, which has increased survival and produced remission in more than 90% of patients, especially patients who have not developed significant kidney damage (5).

We present a case of GPA without kidney involvement in which, despite early diagnosis and treatment in line with the scientific literature, severe tissue necrosis developed which was refractory to medical treatment.

Clinical case

This was a previously healthy 40-year-old female patient from Chinchiná, Caldas, Colombia, with no significant family history including a lack of autoimmunity disorders. Her clinical picture began in December 2020, with constant serosanguinous nasal discharge and headache since November 2021, symmetrical ascending lower limb dysesthesia associated with recurrent mouth sores and occasional skin rashes with worsening nasal lesions. She did not have Raynaud's phenomenon, dry symptoms, arthritis, alopecia, contact with toxins, use of recreational drugs, silica, hydrocarbon pesticides, piercings, nasal surgeries, recurrent respiratory infections or travel to areas with a high risk of leishmaniasis.

In October 2021, antineutrophil cytoplasmic antibodies (c-ANCAs and p-ANCAs) were negative. An initial nasal biopsy reported inflammatory changes with no other abnormalities; another biopsy in December 2021 reported acute inflammation with fibrin deposits, abundant polymorphonuclear infiltrate with a few areas with small vessel proliferation, and lymphocytic, plasmacytic and histiocytic inflammatory infiltrate, with no vasculitis or granulomas. The patient's polyneuropathy symptoms progressed, and her nasal discharge worsened, with concomitant scabbing. She therefore underwent electromyography and nerve conduction testing which confirmed sensory-motor polyneuropathy of all four extremities, as well as magnetic resonance imaging (MRI) of the paranasal sinuses which showed a perforated nasal septum (Figure 1).

In light of the signs and symptoms suggestive of GPA, despite having negative c-ANCA titers, and considering the risk/benefit ratio, treatment was begun in February 2022 with methotrexate, 15 mg per week, along with folic acid, with no improvement. New p-ANCA levels were negative, c-ANCA levels were positive at 1:20, and proteinase 3 was negative. Since there was no response to methotrexate, intravenous cyclophosphamide pulses at 750 mg per month were ordered, with daily trimethoprim 160 mg/sulfamethoxazole 800 mg prophylaxis. After three pulses, with no response, she had

progressive necrotizing tissue destruction with complete loss of her nasal septum and columella. She continued to be hospitalized for multidisciplinary treatment.

Laboratory tests ruled out *Mycobacterium tuberculosis*, nontuberculous mycobacteria, Histoplasma, Cryptococcus, paracoccidioidomycosis, *Straphylococcus areus and Leishmania* infections. New biopsies were taken, with a dermatopathology report of ulceration, areas of discharge, dense and diffuse infiltrates, and histiocyte clusters corresponding to granulomas, as well as microangiopathy, fibrinoid necrosis and arteriolar destruction (Figure 2), confirming the diagnosis of granulomatosis with polyangiitis, consistent with the previous clinical presumption.

Rituximab 375 mg/m^2 weekly was ordered for four weeks (500 mg per week). As side effects of this medication her blood pressure rose, she developed cystitis, headache and worsening nasal pain, and vaginal and nasal candidiasis, which improved with medical treatment, and after four weeks she continued treatment with methotrexate. Her nasal discharge and polyneuropathy decreased for only one week, followed by progressive necrosis of the nasal tissue.

In view of her nonresponse to treatment, five sessions of plasmapheresis were ordered, which were well tolerated and slowed the progression of tissue destruction. She was prescribed outpatient treatment with mycophenolate 500 mg every 8 hours, pentoxifylline 400 mg every 12 hours, prednisolone 5 mg/day and, for pain management, tapentadol 50 mg every 12 hours and pregabalin 25 mg in the morning and 150 mg at night.

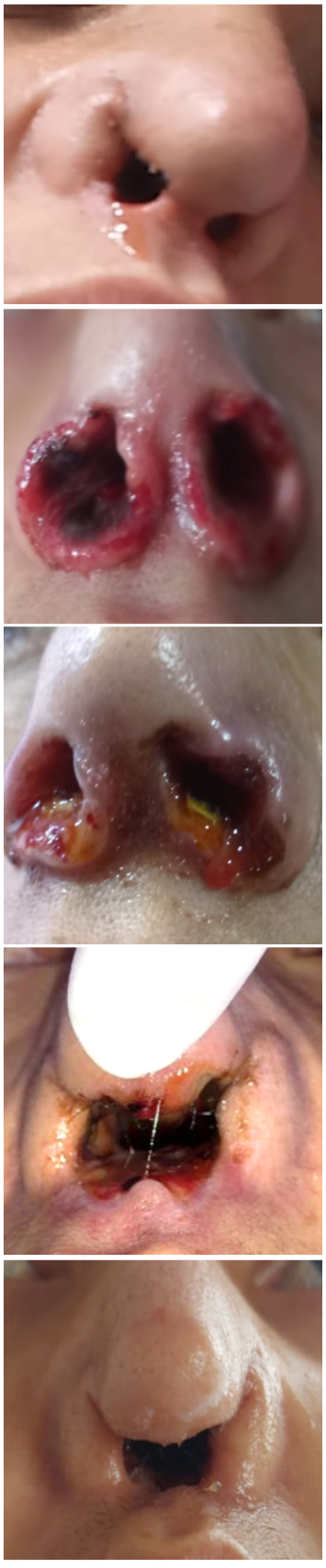
This treatment slowed the progression of the condition, without achieving remission. As of this writing, the patient continues to have a smaller amount of serosanguinous nasal secretion and polyneuropathy symptoms in her lower limbs with 4/5 strength, currently.

Discussion

As will be discussed further on, GPA has clinical, paraclinical and pathological diagnostic criteria. Since these were not met in the initial stages of this case, empirical treatment was necessary, considering the patient's greatest benefit. However, an effective response to treatment was not obtained despite the use of all the treatment lines described to date for this disease.,

This disease has a prevalence of 24-152:1,000,000 (2), and belongs to the ANCA-associated vasculitis group, affecting small to medium-size vessels. These antibodies are positive in approximately 70-80% of patients, and PR3, specifically, in only 10% (4). It occurs in all races and ages (6), with a greater prevalence between the ages of 45 and 60 (5). Its reported risk factors include genetics, exposure to silica, hydrocarbons, smoke, pesticides and infectious agents, mainly *Staphylococcus aureus*, which has also been reported to cause increased activity and more relapses (5).

Cytoplasmic (c)-ANCAs have been reported to be highly specific for active GPA, with titers directly related to disease activity, and a high rate of false negative ANCAs (30%) (5).



Onset of sero-sanguinous discharge, December 2020.

November 2021: progressive worsening of inflammation and discharge.

February 2022: increased discharge. Methotrexate was started at 15 mg per week followed by cyclophosphamide pulses.

March 2022: complete destruction of the nasal septum and columella (three pulses of cyclophosphamide had been administered.

July 2022: after rituximab administration and plasmapheresis.

Figure 1. *Photographic follow-up of nasal lesion progression.*

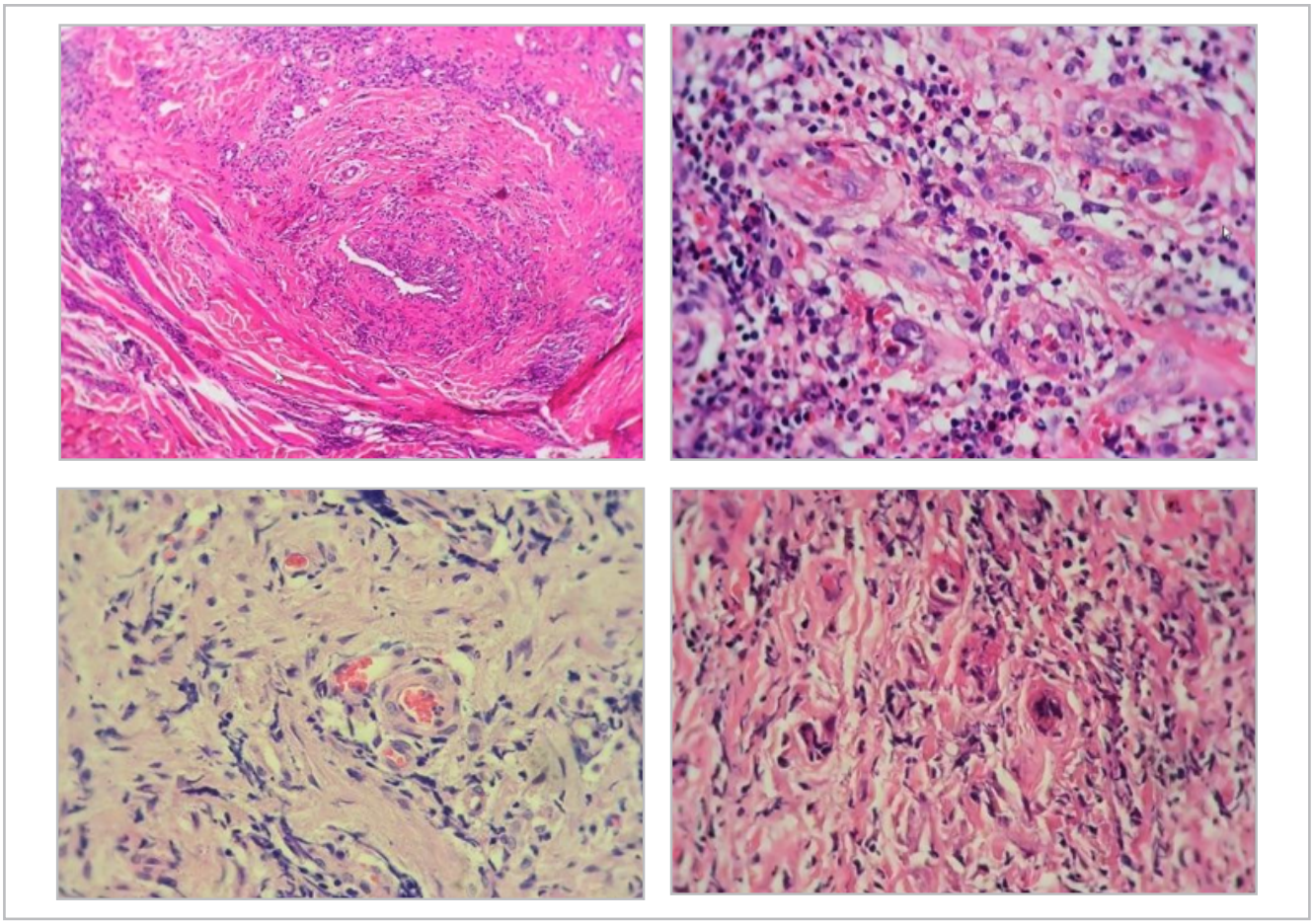


Figure 2. *Ulceration, areas of discharge, dense and diffuse infiltrates, with histiocyte clusters corresponding to granulomas, along with microangiopathy, fibrinoid necrosis and arteriolar destruction.*

The patient in this clinical case had late positive c-ANCAs at low titers, with initially negative tests.

Histologically, most samples have nonspecific findings (5). The classic triad of vasculitis, necrosis and granulomatous inflammation may be found in up to 16% of cases; vasculitis and granulomas are found together in up to 21-23%, and vasculitis and necrosis features may be found (7). In this clinical case, the patient's last biopsy finally showed the classic triad of the disease.

As occurred with this patient, classic ENT symptoms may be the initial clinical manifestation in 70-100% of cases (5). The nasal cavity and paranasal sinuses are the most commonly affected sites (85-100%), while ear disease is found in approximately 35% (4). The most common characteristics of nasal disease were scabbing, bloody discharge, and nasal obstruction, with septal perforation in 24% of the cases (5) and acute pain, fever and mucopurulent discharge in 10% of the patients. The most affected area was the maxillary sinus. Atypical disease presentations including neurological, cardiovascular, cutaneous, gastrointestinal, muscular, joint and eye involvement have been reported (5). This patient showed peripheral nervous system abnormalities through her polyneuropathy signs and symptoms.

The diagnosis is based on the American College of Rheumatology and EULAR criteria (6), based on 10 clinical, imaging, pathological and laboratory criteria, with the diagnosis confirmed by a score equal to or greater than five points. In this particular clinical case, the patient had an initial score of three, which complicated her diagnosis and treatment, but as the disease progressed, she later obtained a score of 10, confirming the diagnosis.

Timely identification of GPA is important for its prognosis, because immunosuppression regimens can induce rapid remission and reduce the disease's morbidity and mortality in the long term (8, 9), which did not occur in this clinical case.

The differential diagnosis is extensive, including other vasculitides, other autoimmune disorders, infections, tumors, and drug toxicity (10). The vasculitides include Churg-Strauss syndrome which, in its initial stage, may present with necrotizing respiratory tract lesions, before progressing at an unpredictable rate to a generalized phase characterized by systemic vasculitis symptoms; it is differentiated by evidence of eosinophilia both on biopsy as well as in peripheral blood (11).

The differential diagnosis of infectious diseases is remarkable for leishmaniasis, as 10% of patients have a nasal mucosal lesion that may spread to the oral mucosa, larynx and nose;

this diagnosis can be ruled out if there is no epidemiological link, and with a biopsy (12,13). Paracoccidioidomycosis brasilensis may cause destructive nasal lesions; however, they are caused by extension of upper lip lesions and may also affect the gastrointestinal system and be coupled with lymphadenopathy (14,15). On the other hand, tuberculosis (TB) may be the hardest to differentiate from GPA, since it shares clinical signs and symptoms, histopathological findings like granulomas and vasculitis, and laboratory markers like elevated ANCA in 10-40% of patients (16), 52.4% of whom may have elevated p-ANCA and 38.1% elevated c-ANCA (17). Clinically, it can be differentiated because TB may also have erythema, urticaria and blisters; the biopsy shows immune complex deposits, and auto-reactive B and T lymphocytes; and, in the laboratory, the lack of positive cultures help to rule out this diagnosis (18).

Several phases of treatment have been described, with the goal of the first phase being to induce remission (9, 19). Treatment with methotrexate and folic or folinic acid is recommended in the early stages. For severe disease, cyclophosphamide (intravenous or oral) and prednisolone may be given (20), if there is adequate clinical stability, keeping in mind cyclophosphamide's own side effects like infections, bone marrow suppression, cystitis and toxicity (8). Rituximab is effective as an immunosuppressant, and therefore may be used as an alternative to cyclophosphamide (8, 9, 19), although with a similar efficacy (1). It should be noted that the patient received all of the treatments in this first phase, with no response.

The second phase, known as the maintenance phase (avoiding new exacerbations of the disease), consists of administering low-dose glucocorticoids and azathioprine, leflunomide or methotrexate, which should be continued for at least 18 months (20). Only in the event of rapidly progressive kidney failure or severe diffuse pulmonary hemorrhage is plasmapheresis recommended. However, its efficacy has not been well studied (5, 9). Due to the refractory nature of the disease in this clinical case, plasmapheresis was required as an alternative measure, which produced a better clinical response, without complete disease remission.

This case is remarkable for the diagnostic difficulties due to initially negative c-ANCA titers coupled with nonspecific biopsies, with a refractory response to the standard treatment described in the scientific literature, forcing the clinicians to look for differential diagnoses and make decisions based on clinical criteria, due to the severity and progression of the clinical condition.

Conclusion

Granulomatosis polyangiitis may be difficult to diagnose due to a lack of laboratory, imaging and pathological findings in the initial stages, requiring a multidisciplinary team for prompt diagnosis and specific timely treatment to avoid progression and complications. We believe that studies are needed to look for more effective treatments to halt the clinical course, since in cases like the one we have presented, it may be refractory to treatment.

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