

# Update in the study of Granulomatosis with polyangiitis (Wegener's granulomatosis)

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## Actualización en el estudio de Granulomatosis con poliangeítis (Granulomatosis de Wegener)

**Resumen:** La granulomatosis con poliangeítis (GPA) es una vasculitis sistémica de pequeño vaso, que afecta más frecuentemente el tracto respiratorio y el riñón. Sus criterios diagnósticos se basan en la clínica, exámenes de laboratorio, imágenes e histología. El 90% son ANCA (anticuerpos anticitoplasma de neutrófilos) positivos. La histología muestra inflamación granulomatosa, necrosis y vasculitis. Los exámenes de imagen son de vital importancia en su estudio inicial y seguimiento, correspondiendo principalmente a técnicas tomográficas. La tomografía Computada (TC) es el método de elección para la evaluación de vía aérea superior y pulmón, con alta sensibilidad en afectación de cavidades nasal/paranasales, árbol bronquial y pulmón. La Resonancia Magnética está indicada en compromiso del sistema nervioso central y corazón. El PET/CT presenta alta sensibilidad en enfermedad tóraco-abdominal, es de utilidad en detectar lesiones no visibles con otras técnicas, y en control de tratamiento. El compromiso renal, de alta ocurrencia en GPA, presenta escasa traducción en las imágenes y es frecuentemente indetectable con imágenes, aunque el PET/CT puede ser positivo en casos de glomerulonefritis acentuada. La radiología simple no debe ser utilizada en el estudio de GPA dado su bajo rendimiento diagnóstico. El tratamiento se basa en terapia corticoidea e inmunosupresora. Las recaídas son frecuentes, por lo que estos pacientes requieren seguimiento a largo plazo.

**Palabras clave:** Granulomatosis con poliangeítis, Granulomatosis de Wegener, vasculitis, Positron emission tomography, Tomografía computada.

**Abstract:** Granulomatosis with polyangiitis (GPA) is a systemic type of vasculitis that affects small vessels, most commonly involving the respiratory tract and kidneys. Diagnosis is based on clinical criteria, laboratory tests, imaging and histology. Ninety percent are ANCA (anti-neutrophilic cytoplasmic antibodies) positive. Histology demonstrates granulomatous inflammation, necrosis and vasculitis. Imaging studies are vital for the initial work-up and follow-up. Computed Tomography (CT) is the method of choice for evaluation of the upper airway and lungs, because of its high sensitivity detecting anomalies of paranasal sinuses, bronchial tree and lungs. Magnetic Resonance is indicated for evaluation of the central nervous system and heart. PET/CT has high sensitivity for thoracic and abdominal disease, is useful at detecting lesions not seen with other imaging techniques, and for follow-up. Renal involvement, very frequent on GPA, is usually undetectable at imaging, but may be seen at PET/CT in cases of marked glomerulonephritis. Plain X-rays should not be used for evaluation of GPA because of their low diagnostic performance. Treatment is based on corticosteroid and immunosuppressive therapy. Relapses are frequent, so these patients require long-term follow-up.

**Key words:** Computed tomography, Granulomatosis with polyangiitis, Positron emission tomography, Wegener's granulomatosis, vasculitis.

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## Introduction

Vasculitis is a group of diseases characterized by inflammation of the walls of blood vessels. According to the 2012 Chapel Hill consensus, which classifies them according to the type of vessel that is predominantly affected, small vessel vasculitis involves small intraparenchymal arteries, arterioles, capillaries and venules, being able to also affect medium-sized vessels. This group includes vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA), whose major exponents are microscopic polyangiitis, granulomatosis with polyangiitis (GPA) (ex Wegener), eosinophilic granulomatosis with polyangiitis (EGPA) (Churg Strauss) and those limited to a specific organ<sup>(1)</sup>.

GPA is a systemic ANCA-associated granulomatous vasculitis whose lesions mainly affect the respiratory tract and kidneys<sup>(2)</sup>. It can occur at any age with a peak at 65-74 years of age. Its annual incidence is 5-10/million with a prevalence of 24-157 cases per million, being similar between both sexes<sup>(3,4)</sup>. In the etiopathogenesis, infectious, environmental or pharmacological triggers would be involved that, in genetically predisposed individuals, generate an inflammatory response and production of ANCA against proteinase-3 (PR3) and myeloperoxidase (MPO) in 80% and 10% of the patients respectively, developing necrotizing granulomatous inflammation<sup>(4)</sup>.

## Clinical manifestations

The disease can present with non-specific constitutional symptoms: malaise, myalgia, arthralgia, anorexia, weight loss. It affects different organs, airways and renal involvement being the most frequent. The involvement of the upper airway is the most common and characteristic (70-100% at the time of diagnosis), mainly at the nasal and sinus levels, and may manifest with nasal discharge, epistaxis, nasal ulcers, perforation of the nasal septum, granulomatous lesions or destruction of facial cartilage with deformation of the nasal bridge, sinus or paranasal inflammation. It can also present chronic otitis media, glottic or subglottic stenosis. In the lower airway it can manifest with cough, dyspnea, bronchial obstruction, and at the pulmonary level, present in 50-90% of patients, you can find nodules, cavitations, infiltrates, pleuritis or pleural effusion and alveolar capillaritis hemorrhage. 40-100% of the patients may have renal involvement, characterized by segmental necrotizing glomerulonephritis with formation of pauci-immune growth (absence of immunoglobulin deposits or complement on the immunofluorescence) manifesting with hematuria, proteinuria and renal failure. There may also be skin (leukocytoclastic vasculitis, purpura, infarcts, ulcers, nodules), mucocutaneous (ulcers, oral granulomas), musculoskeletal (myalgias, arthralgias, arthritis), ocular (scleritis, episcleritis, uveitis, retinal alterations, retinal thrombosis, orbital masses granulomatosis, blindness)

and urogenital (prostatitis, orchitis, epididymitis, pseudotumors, stenosis, ulcerations) involvement. At the nervous system level, it can have central and peripheral manifestations, including stroke, brain masses, seizures, meningitis, cranial nerve palsy, sensory or motor neuropathy, multiple mononeuritis. Less frequent are cardiovascular manifestations (pericarditis, cardiomyopathy, ischemic or valvular heart disease) and gastrointestinal manifestations (mesenteric vasculitis, ulcers, perforations)<sup>(2,4)</sup>. In general, two types of GPA presentation can be distinguished: localized or limited, with involvement limited to the upper airway, and the systemic or diffuse form, with renal, pulmonary involvement and constitutional symptoms<sup>(2)</sup>.

## Diagnostic criteria

For the diagnosis it is necessary to consider the clinical manifestations that suggest the presence of vasculitis, ANCA determination and histopathological evidence of the compromised organ<sup>(4)</sup>. In 1990, the ACR (American College of Rheumatology) defined 4 criteria, of which there must be at least 2 to define GPA: 1) sinus involvement, 2) alterations in pulmonary radiology, 3) alteration of urinary sediment (hematuria, hematic cylinders), 4) histology with the presence of perivascular granulomas, with a sensitivity and specificity of 88% and 92%<sup>(2)</sup>.

Although the determination of ANCA supports the diagnosis of GPA, in 10% of patients it is not detectable. The determination of variations in ANCA titers in the evolution of the disease has not been shown to be useful in predicting relapse, but the presence of persistently high titers could be a predictor<sup>(2)</sup>. The differentiation between MPO-ANCA and PR3-ANCA could predict the response to different types of immunosuppressants<sup>(5)</sup>.

## Histology

The histological manifestations of GPA are varied, but in general terms, it is made up of three elements. Inflammation, necrosis and vasculitis<sup>(6,7)</sup>.

Inflammation is characterized as a process that includes elements of chronic inflammation such as lymphocytes, plasma cells and histiocytes, some of which form a poorly defined granulomatous reaction associated with multinucleated giant cells (Figure 1). It is accompanied by acute inflammation made up of neutrophils, microabscesses and numerous eosinophils. In the periphery, the lesion usually identifies old hemorrhage and foci of bronchiolitis obliterans - organizing pneumonia.

The necrosis is usually of a geographical and fundus type (cellular detritus), giving it a basophilic appearance. Unlike other processes, this necrosis does not necessarily have a relationship with the granulomatous reaction.

Vasculitic phenomena usually predominate in arterioles and venules and may contain the same inflammatory elements previously described (Figure 1). Its presence is not specific, nor is it indispensable to make the diagnosis.

### Imaging Role

GPA is a vasculitis that can affect multiple organs and systems, however, it shows a clear predilection for the respiratory system, in 92% of patients, and the kidneys, in 80% of the cases<sup>(8)</sup>. For its imaging study, tomographic techniques are mainly used: Computed tomography (CT), PET/CT (Positron Emission Tomography / Computed tomography), and Magnetic Resonance (MRI)<sup>(8)</sup>. The imaging examinations are of vital importance in the study of GPA and constitute an important pillar in the diagnostic criteria. A summary of its indications is shown in table 1.

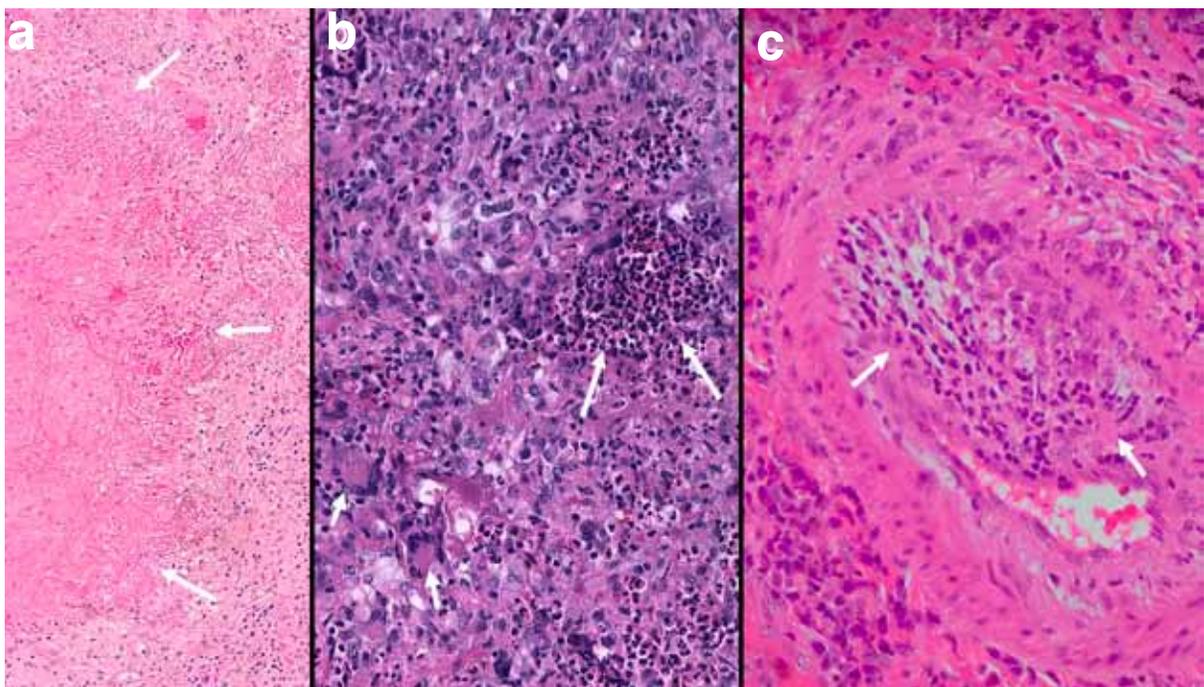
CT is the technique of choice for the characterization of manifestations in GPA, due to its high spatial resolution, wide availability and lower cost. It presents high diagnostic performance in paranasal cavities pathology, and is the test with the best cost-effectiveness in the assessment of the thorax, especially the lung, tracheobronchial tree, mediastinum and vascular structures.

MRI is most useful in cardiac, encephalic and ocular manifestations that, although unusual in GPA, require an early diagnosis and an accurate characterization<sup>(8,9)</sup>.

It must be considered that the small vessels affected by the vasculitis process will not be visible with this or any other tomographic imaging technique, since their small size exceeds the spatial resolution of the CT and MRI. What these tests usually detect are the associated inflammatory or necrotic phenomena, which manage to constitute a macroscopic lesion in an organ or tissue.

PET/CT is also not capable of detecting small vessel vasculitis per se, although being a functional study, it can investigate inflammation in a macroscopically normal tissue, as long as it is of sufficient size to be detected. For this reason, PET/CT can contribute to an early diagnosis, with positivity in cases with normal CT, and findings that even precede the laboratory alterations<sup>(10)</sup>. In addition, it can differentiate inflammatory granulomatous tissue, which usually shows high uptake of marked glucose, necrotic or fibrotic tissue, which does not capture F18-FDG. For this reason, PET/CT is useful in the control of treatment and follow-up, since it allows evaluation of the activity of the disease, and the detection of early relapses<sup>(11)</sup>. Several studies have shown a correlation between the uptake intensity of F18-FDG and disease activity measured with clinical indices such as the Birmingham score<sup>(11)</sup>.

The role of ultrasound is reserved primarily for the evaluation of extra pulmonary vascular and thoracic involvement. In particular, ultrasound is able to detect and characterize cardiac involvement, evaluating atrial masses and septal or aortic wall thickenings,



**Figure 1:** a) Area of geographic necrosis (arrows). b) mixed inflammatory process (chronic and acute) with microabscesses in the center (long arrows) and two multinucleated giant cells inside a granuloma with ill-defined edges (short arrows). c) arteriolar vasculitis with infiltration of the intima by lymphocytes, plasma cells and histiocytes (arrows).

**Table 1.** Frequency of clinical-imaging involvement and diagnostic technique of choice.

Laboratory	Frequency	Diagnostic technique
• ANCA +	90%	ELISA
ANCA PR3	80%	
ANCA MPO	10%	
Constitutional symptoms	30-80%	Clinical examination
<b>Upper airway</b>		
• Paranasal cavities	100%	CT
• Nasal cavity	100%	CT
• Middle ear / mastoid	30-50%	CT
• Subglottic thickening	30-50%	CT
<b>Lower airway</b>		
• Mass / lung nodule	70-90%	CT or PET/CT
• Cavitated pulmonary nodule	50%	CT or PET/CT
• Condensation / frosted glass	25%	CT
• Trachea thickening	16-50%	CT
• Bronchiectasis	10-20%	CT
• Pleural effusion	25%	CT
• Diffuse alveolar hemorrhage	10%	CT
<b>Renal</b>		
• Necrotizing glomerulonephritis	40-100%	Urine Test
<b>Other organs</b>		
• Articular	50-70%	MRI or soft tissue ultrasound
• Skin and mucous membranes	14-50%	Clinical examination
• Eye, optic nerve	30-60%	MRI
• Central and peripheral nervous system	10-54%	MRI
• Pericardium	3-15%	CT or PET/CT
• Myocardium	Rare	MRI or PET/CT
• Gastrointestinal	4-24%	CT
• LV involvement (Aorta and its branches)	Rare	CT angiography, PET/CT
• Urogenital	Rare	UroCT or MRI

LV: Large vessels, CT: Computed Tomography, MRI: Magnetic Resonance, PET/CT: Positron Emission Tomography / Computed Tomography.

rare but possible to find in GPA, being useful also in objectifying the regression of anomalies<sup>(9)</sup>.

There is consensus that simple radiography should not be used for the evaluation of the manifestations of systemic vasculitis, since they do not contribute in assessing its extension or evolution<sup>(12)</sup>.

**Usual Manifestations**

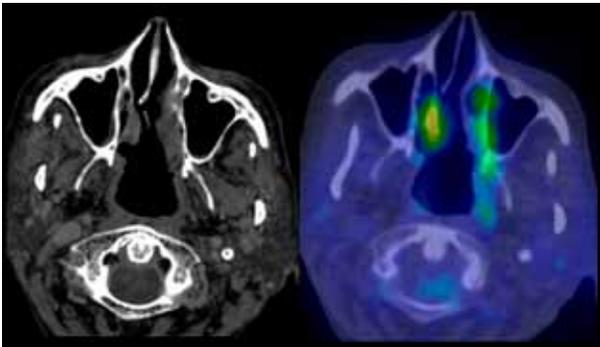
**Upper respiratory tract**

Sinus involvement is one of the most frequent, and is easily detectable with CT. The characteristic findings are pansinus mucosal thickening and the existence of soft-tissue nodules that enhance with contrast medium<sup>(8)</sup>. In some cases you can see osteo-cartilaginous alterations, the most common perforation

of the nasal septum, lamina papyracea, and walls of the nasal cavity. MRI is less sensitive than CT in detecting bone destruction<sup>(13)</sup>. PET/CT is also highly sensitive in sinus involvement, with high mucosal, cartilaginous and bone uptake in early stages, even with normal CT<sup>(14)</sup> (Figure 2).

Otitis and mastoiditis are also frequent, visible in images such as invasion of middle ear and mastoid cells by material with soft tissue density.

Subglottic stenosis is a frequent manifestation, in up to 50% of the patients<sup>(15)</sup>, most of the time asymptomatic, becoming symptomatic in advanced cases with stenosis of more than 80% of the lumen<sup>(15)</sup>. It can occur at the time of diagnosis or later in patients with GPA under treatment, as an early sign of relapse<sup>(16)</sup>.



**Figure 2:** Axial section of paranasal cavities shows PET/CT (right) with marked uptake of F18-FDG in bone structures of maxillary sinus and left pterygoids, and right inferior turbinate, with normal CT (left).

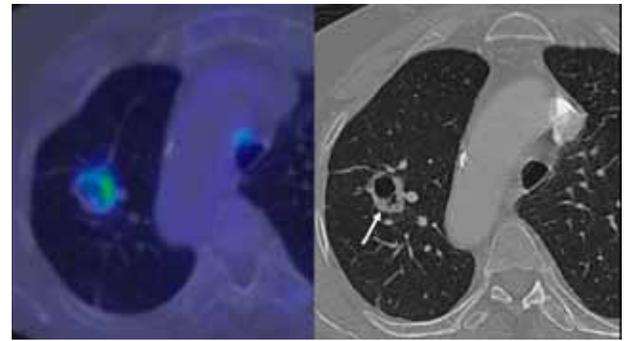
Tracheal involvement occurs in 16-50% of cases, typically in patients with multisystem disease<sup>(8,13)</sup>. The circumferential involvement including the posterior tracheal membrane is its distinctive characteristic, allowing differential diagnosis with the relapsing polychondritis and osteochondroplastic tracheobronchopathy, which only affect the cartilaginous portion, respecting the membranous membrane<sup>(8)</sup>. In a series of 51 patients with GPA studied with CT, Daum et al<sup>(17)</sup> reported ulcerative tracheo-bronchitis in 60%, subglottic stenosis in 17%, and tracheal or bronchial stenosis in 13%.

PET/CT shows high sensitivity in the detection of thoracic involvement in active GPA, higher than that observed in other ANCA positive vasculitis, with 100% sensitivity in respiratory and vascular thoracic involvement, although with low sensitivity in eye lesions, skin or central/peripheral nervous system<sup>(11)</sup>. MRI usually does not add extra information to that provided by CT and PET/CT in the upper respiratory tract<sup>(11)</sup>.

### Lung

Lung involvement in GPA has been extensively described using CT, and this exam is usually sufficient to demonstrate and characterize it. Pulmonary nodules and masses are the most frequent radiological finding in GPA, present in 70-90% of patients<sup>(8,18)</sup>. They may present peripheral or peribronchovascular distribution, usually bilateral, and tend to cavitate especially those lesions larger than 2 cm<sup>(18)</sup> (Figure 3). Consolidation areas and ground-glass opacities can be seen in 25% of cases<sup>(18)</sup>.

Mediastinal adenopathies are rare as an isolated finding, and are only visible in concomitance with pulmonary lesions<sup>(14)</sup>. In cases of mediastinal adenopathy associated with tracheal thickening and normal lung, other diagnoses should be considered such as sarcoidosis, infectious tracheitis, lymphoma or bronchogenic cancer<sup>(8)</sup>.



**Figure 3:** Cavitated pulmonary nodule in LSI visible on CT (left), with F18-FDG uptake in PET/CT (right).

### Kidney

Renal involvement corresponds to the most frequent clinical manifestation in our environment<sup>(19)</sup>. 80-90% of patients with GPA present clinical or morphological evidence of renal involvement<sup>(13,20)</sup>. The conventional tomographic imaging studies (CT, MRI) are usually negative on the affected kidney, except when it presents as a nodule or renal mass. PET/CT is probably the most sensitive imaging method in the detection of non-mass involvement, due to its functional and not purely anatomical nature<sup>(11)</sup>, showing diffuse or patchy hyper-uptake of F18-FDG in the renal cortex in cases of accentuated glomerulonephritis (Figure 4). Recently, Fu et al reported a case of incidental detection of bilateral renal involvement in a patient with GPA with normal ultrasound and CT<sup>(21)</sup>.

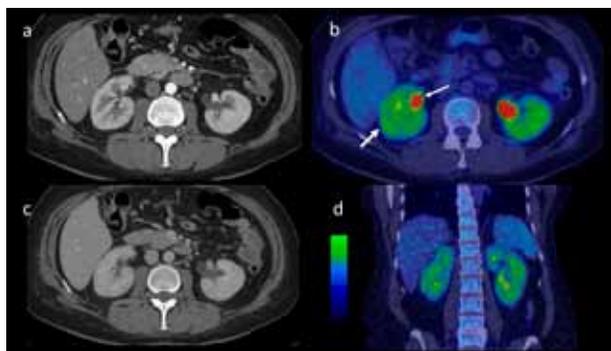
### Unusual manifestations

#### Orbital

Although it is not widely known, it can appear in up to 60% of patients with GPA and even as an initial manifestation<sup>(22)</sup>. It clarifies ischemic phenomena and necrosis, in addition to granulomatous inflammation. Orbital and periorbital inflammatory infiltration with proptosis, usually unilateral, is the most frequent form of presentation. Less frequently, it compromises the optic nerve sheath and periorbital fibrosis, findings that can be characterized with MRI. The involvement of lacrimal glands is infrequent in GPA and allows differential diagnosis with sarcoidosis or lymphoproliferative diseases<sup>(23)</sup>. The presence of tissue with bilateral soft tissue density and symmetric medial inferior in the intraconal fat, in the presence of an "empty nasal fossa" is highly specific for GPA<sup>(24,25)</sup>.

#### Temporal bone

Otic manifestations occur in up to 40% of patients and are produced by direct extension from the sinonasal involvement, causing serous otitis media



**Figure 4:** CT in arterial (a) and porto-venous (c) phase without renal alterations. PET/CT with intense diffuse uptake in the renal parenchyma (b, d), greater to the liver and spleen (thick arrow). Renal pelvis showing normal excretion of F18-FDG by the urine (thin arrow).

with or without mastoid involvement. Subsequently, granulomatous inflammation can lead to bone destruction, simulating coalescent otomastoiditis, findings that can be demonstrated with CT<sup>(23)</sup>. There are also cases of otitis that present with facial paralysis, which can progress to sensorineural hearing loss, requiring bone evaluation of the temporal bone using CT, and of the affected cranial nerves by MRI<sup>(26)</sup>.

### Central Nervous System

They are rare as initial presentation in GPA, being more frequent in advanced stages of the disease<sup>(27)</sup>. The most frequent is vascular involvement, which can be associated with ischemic events (infarction or transient ischemic attack), hemorrhage or venous thrombosis. In contrast-enhanced MRI, although less frequent, pituitary involvement can be observed, characterized by increased volume and loss of normal T1 hyperintensity of the posterior pituitary gland, thickening and enhancement of the hypophyseal stalk with hypothalamic extension and secondary compression of the optic chiasm<sup>(23,28)</sup>. Meningeal involvement (pachymeningitis), with linear thickening (focal or symmetrical) and dural enhancement, is also infrequent<sup>(23,29,30)</sup>. At the base of the skull, also by sinonasal or orbital extension, it may present with neuropathies due to dysfunction of mainly olfactory and optic cranial nerves. The latter condition should be suspected with the concomitant presence of typical intracranial lesions, and it is well characterized with MRI showing thickening and T2 hyperintensity of the II pair<sup>(23)</sup>.

### Large vessels

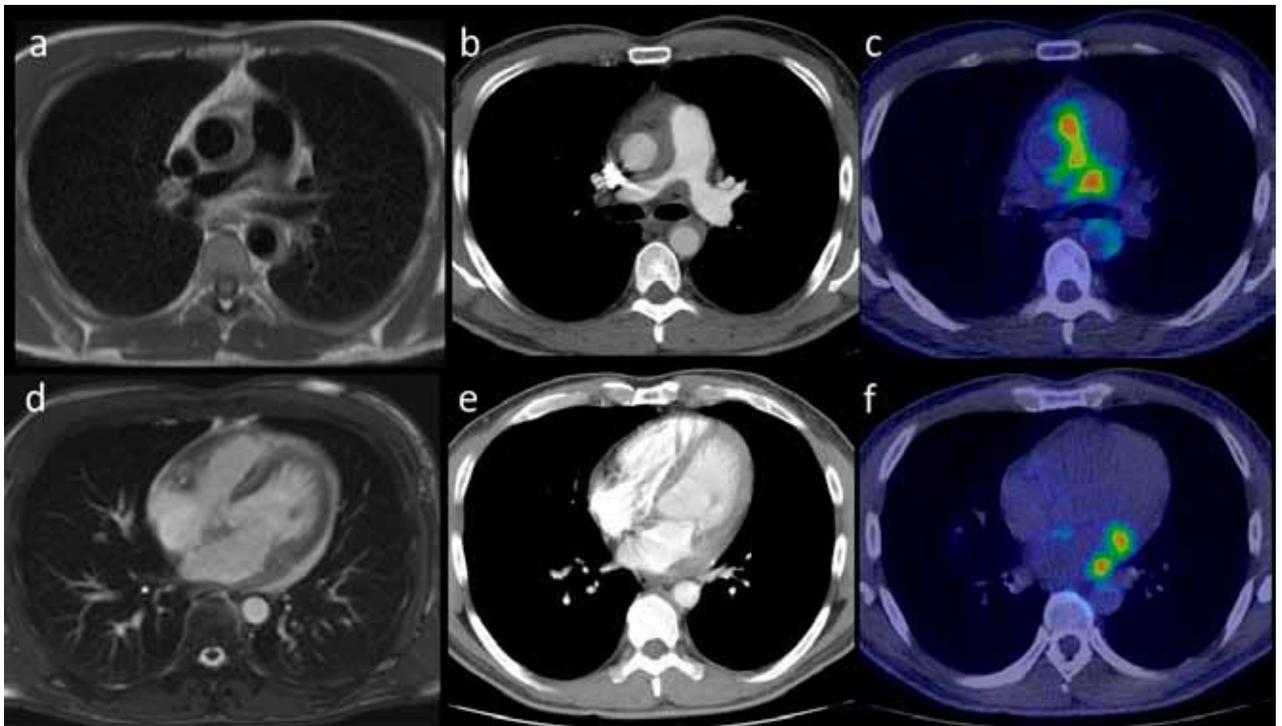
Aortitis and periaortitis in GPA have been described, the latter being the most frequent. It would be produced by a small vessel involvement of the vasa vasorum<sup>(31)</sup> and/or by extension of the granulomatous involvement of the arterial wall towards the perivas-

cular tissues (Figure 5). Aortitis/periaortitis can be well characterized with contrast-enhanced CT or MRI, both with excellent precision, so the preference of one method over another will depend on its availability as well as other factors such as contraindications to the respective contrast media, presence of artifacts or considerations regarding radiation. They will show diffuse thickening of the arterial wall with edema and delayed enhancement<sup>(32)</sup> (Figure 6). The role of both techniques in determining the degree of activity in large vessel vasculitis remains uncertain<sup>(33)</sup>. In a review of 23 cases, thoracic aortic involvement was 23%, subclavian artery 17% and internal carotid artery 17%<sup>(30)</sup>. The findings of aneurysms<sup>(30)</sup> or vascular stenosis, the latter described mainly in large vessel vasculitis<sup>(29)</sup>, were also less frequent. A retrospective analysis of 21 patients with GPA studied with PET/CT, showed high uptake of 18F-FDG in the aorta at values similar to those found in patients with large vessel vasculitis, so this exam would not allow differentiation between these two entities<sup>(34)</sup>. There are recent publications that assign an added value to the morphological and hemodynamic ultrasonographic evaluation of vasculitis and perivascular inflammation, adding prognostic factors for atheromatosis, important to detect and treat in these patients<sup>(35)</sup>.

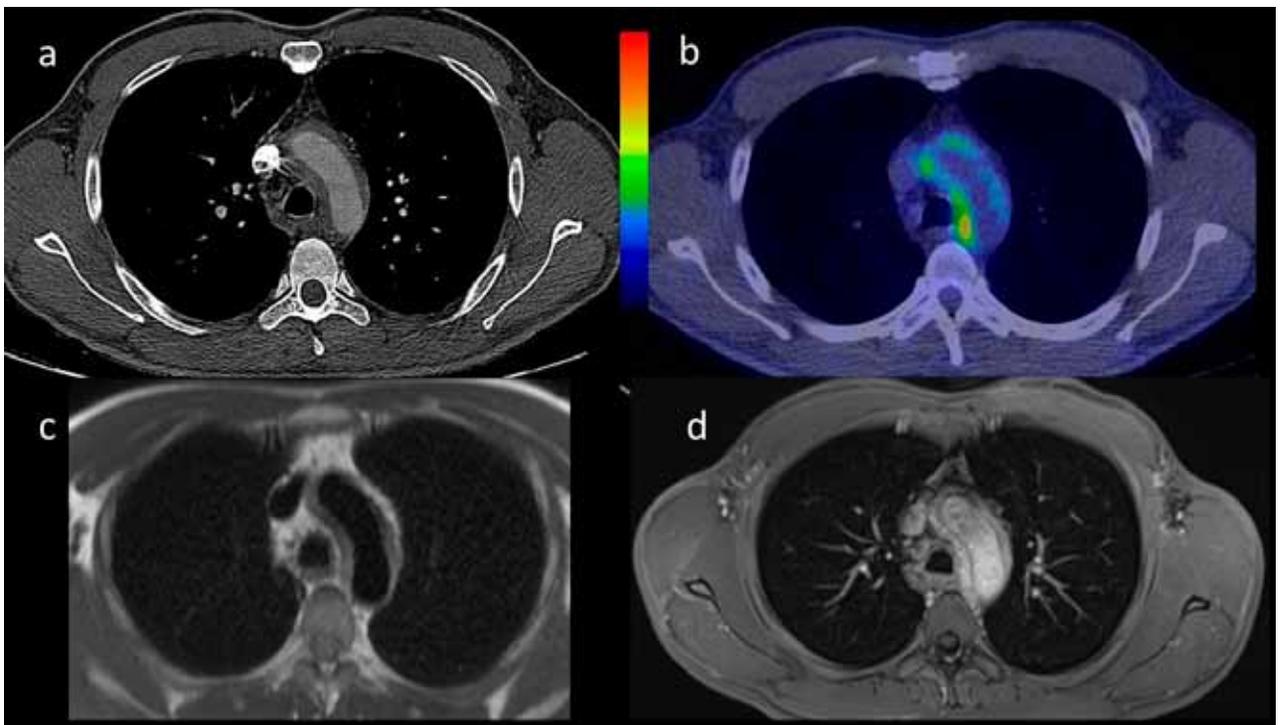
The abdominal aorta constitutes the most frequently affected segment (52%), above the number of cases with involvement of the thoracic or subclavian segment<sup>(30)</sup>. In these patients, who also have abdominal pain, GPA can also cause retroperitoneal fibrosis concomitant to periaortitis<sup>(31)</sup>.

### Heart

It occurs between 3.3% and 15% of patients with GPA<sup>(13,36)</sup>, and although potentially fatal if not treated in a timely manner, it is not associated with a worse prognosis<sup>(36)</sup>. It is frequently underdiagnosed as it is often subclinical<sup>(37)</sup>. Several studies suggest that an initial approach with transthoracic echocardiography followed by evaluation with contrasted cardiac MRI are the most sensitive tools for detecting anomalies in patients with GPA, and they also seem to be reliable methods for follow-up and monitoring therapy in these patients<sup>(37,38)</sup>. A French study retrospectively analyzed cardiac involvement in 31 patients with confirmed GPA<sup>(37)</sup>. They concluded that 61% of the patients had at least one cardiac anomaly attributable to GPA, which was also correlated with the time elapsed since the diagnosis (more than 18 months) and that clinically symptomatic patients had more extensive lesions. The main findings in MRI include granulomatous myocarditis (with ventricular hypokinesia and delayed subepicardial enhancement with gadolinium), left ventricular dysfunction (EF <45) and pericarditis<sup>(37)</sup>. Other alterations described include coronary arteritis and incidental mitral valve involvement<sup>(9)</sup>. PET-CT



**Figure 5:** a) Axial HASTE sequence showing periaortic thickening and around the right pulmonary artery, which determines decrease in its caliber. Same slice in contrasted CT (b) and PET/CT (c). d) Axial SSFP sequence "white-blood" slice that shows solid tissue that compromises both auriculoventricular grooves surrounding the coronary arteries. PET/CT with hyper-uptake foci in these same locations (f). The lesions are not evident on the contrasted CT (e).



**Figure 6:** Contrast CT with periaortic thickening (a), which on PET/CT shows intense irregular hyper-uptake of F18-FDG (b). c) Axial HASTE sequence slice with periaortic thickening at the level of the arch. d) Axial T1 sequence with fat saturation showing late impregnation of the periaortic solid tissue.

has also shown high positivity in cardiac lesions with excellent correlation with the alterations evident on MRI. Its usefulness in post-treatment control has also been suggested in some series<sup>(11)</sup>.

### Gastrointestinal tract

Although the involvement at this level is unknown, it should be considered as it can affect both the small intestine and the colon, with serious complications that may require urgent surgical management. It is described that it affects between 10% and 24% of patients during the first two years of diagnosis, although histological confirmation is achieved in few cases, mostly in autopsies. It should be suspected in cases suggestive of inflammatory bowel disease, with symptoms such as abdominal pain and gastrointestinal bleeding. These symptoms explain the macroscopic findings detected by endoscopy, such as ulcerations, intestinal parietal necrosis and perforation<sup>(39)</sup>.

### Other systems

The involvement in salivary glands, skin lesions and some articular manifestations, frequent during episodes of active disease, is also described<sup>(11)</sup>. PET/CT can help detect some of these alterations, at the articular level<sup>(14)</sup> or in salivary glands<sup>(11)</sup>.

### Treatment

Treatment consists of two phases: a first induction phase, from 3 to 6 months, whose objective is to achieve remission, and a second maintenance phase, of 12-24 months, to consolidate the remission and avoid relapses<sup>(2)</sup>. For the induction in the systemic form of the disease, corticosteroids are recommended in high doses associated with another immunosuppressant, cyclophosphamide or rituximab; some cases may require plasmapheresis. For localized forms without involvement of vital organs, the use of corticosteroids associated with methotrexate or mycophenolate mofetil is recommended. In the maintenance phase, the combination of low doses of oral corticosteroids with azathioprine or methotrexate is recommended and, in some cases, mycophenolate mofetil and leflunomide may be considered. The use of rituximab has also been shown to maintain remission of the disease with a lower percentage of relapses. The routine use of cotrimoxazole is recommended to prevent relapse and *Pneumocystis jirovecii* infections<sup>(2,3,40)</sup>.

The authors declare there are no conflicts of interest.

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