Abstract
The authors present a case of Wegener’s granulomatosis that had as first symptom scleritis, uveitis and proptosis. Because of rapidly progressive glomerulonephritis, the patient was admitted three months later. On the 12th day, third of cyclosphamamide therapy, the patient died in respiratory distress. Autopsy disclosed focal and segmental necrotizing glomerulonephritis with crescent formation, and medium and small vessels necrotizing vasculitis in the lung, liver, and spleen. Necrotizing granulomas, massive alveolar hemorrhage, capillaritis, and extensive fibrosis in the lung was also observed.

Ocular, lung and kidney involvement in the limited and diffuse forms of Wegener’s granulomatosis are discussed. A statement on ANCA’s value in the diagnosis and follow-up of Wegener’s patients is also made.

Key words: ANCA, proptosis, rapidly progressive glomerulonephritis, scleritis, vasculitis Wegener granulomatosis.

Introduction
Wegener’s granulomatosis (WG) was initially described by Klinger in 1931 and subsequently characterized by Wegener in 1936 and 1939.¹ The diagnostic criteria established by Godman and Churg² included: 1 - necrotizing granulomatous lesions in the respiratory system; 2 – generalized necrotizing vasculitis, involving either arteries or veins, almost always affecting the lungs, and disseminated to a greater or lesser extent in the other organs; 3 – glomerulitis characterized by necrosis and thrombosis of the glomerular capillaries, capsular adhesion and evolution to granulomatous lesion.

The characterization of Wegener’s granulomatosis as a distinct clinical-pathological entity, currently with defined diagnostic criteria,³ for classification, was partly due to the definition of other necrotizing angiitis. Many of them, previously designated periarteritis nodosa (PAN), were recognized as distinct entities. However, all appear to belong to a spectrum whose limits are angiitis, on one side, and granulomatosis, on the other.⁴ ⁵

The initial and most frequent clinical presentation of WG includes a relatively long history of rhinorrhea, epistaxis, nasal obstruction, pain and sinusitis. Serous otitis and decreased uni- or bilateral auditory acuity are also common. Although symptoms of the upper respiratory system are predominant, and apparently occur in isolation, in the majority of cases, pulmonary involvement is detected at an early stage of evolution of the disease. This can occur asymptptomatically, with fixed infiltrates, nodules and cavities or any combination of the three, visible in the thoracic teleradiography, or symptomatically, with the patient complaining of cough, haemoptysis or pleuritic type pain.¹ ⁶ ⁸ Asymptomatic renal involvement can occur in the initial phases of the disease, manifesting essentially through microhaematuria and cylindruria, yet it tends to evolve to rapidly progressive glomerulonephritis, one of the main determinants of the prognosis.¹ ⁶ ⁸ Limited forms of WG have also been described. These are mostly characterized by disease of the upper and/or lower airways, or less frequently, by the involvement of one of these plus another organ, such as the eyes, but never the kidneys.¹ ⁹ Although these limited forms have a better prognosis and a more indolent course, they may, at any time, evolve to the generalized form. Whether the WG is limited or generalized, practically any organ or system may be involved during the evolution of the disease, determining greater or lesser morbidity. An entity that is difficult to distinguish from WG is microscopic polyarteritis (MP),¹⁰ which is characterized clinically and histopathologically by necrotizing vasculitis of the small vessels, associated with focal and segmental necrotizing glomerulonephritis.¹⁰ As in WG, in MP it is also possible to find anti-neutrophil cytoplasmic antibodies with a cytoplasmic pattern (cANCA).¹¹ Savage et al¹² make a distinction between MP from
WG, essentially by the absence of pulmonary involvement in the former. However, they acknowledge that distinguishing between the two entities can be very difficult. Hence it makes sense to ask whether, in fact, these two entities are not just different expressions of the same pathological phenomenon.

We can conclude that although WG has a more or less typical pattern, there is considerable variability in its forms of presentation and evolution, which can lead to diagnostic, prognostic and therapeutic problems. For this reason, we present a clinical case representing WG, and making some considerations on certain characteristics of the case in question.

**Clinical case**

Male patient, 45 years of age. Healthy until July 1993, when he began to suffer lacrimation, photophobia and progressively worsening conjunctival hyperemia that was resistant to topical treatments (cycloptropic drugs and corticosteroids). He reported no other accompanying symptoms. Ocular pain, proptosis (more accentuated on the left side) and exophthalmia emerged progressively over the next three months. At this time, the patient underwent cranoencephalic and orbital computed axial tomography scan, which revealed a “mass” with inflammatory characteristics, involving the temporal and posterior walls of the left orbit, and a less accentuated, more diffuse inflammatory process in the right orbit (Fig. 1). He reported having carried out routine analyses, which did not show any alterations. Notably, around the middle of October 1993, he showed hemoglobin (Hb) of 16.3 g/dl, hematocrit (Htc) of 46%, leukocytes (Leuc.) of 9100/mm3 (60% of PMN), erythrocyte sedimentation rate after the 1st hour of 2 mm, urea of 44 mg/dl, creatinine of 1.0 mg/dl and urine II without alterations.

The patient developed purulent otorrhoea in October 1993, but reported no otalgia, decreased auditory acuity or fever. At that time, he had a radiography of the paranasal sinuses (three positions), which did not reveal any alterations. Despite the therapy (fusidic acid PO; deflazacort, 24 mg/day PO and astemizole, 2 mg/day), the patient continued to have otorrhoea until admission to hospital. In November 1993, there was accentuated worsening of the ocular complaints with the appearance of fever, intense myalgias and abdominal and lumbar pain. During the past four months there has been weight loss of around 5 kg. At this point he came to the ER of our hospital and was admitted.

The patient was suffering greatly, feverish and with reasonable general state. His blood pressure was 110/65 mmHg, with a radial pulse of 100 ppm, rhythmic, regular and ample. The aspects of the objective exam that merited special emphasis were conjunctival hyperemia and bilateral venous congestion, bilateral exophthalmia, more accentuated on the left side, and proptosis on the left side. Bilateral purulent otorrhoea. Painful tongue with depapillation over its entire surface. Cardiopulmonary observation showed accentuated tachycardia and vesicular murmur without adventitious noises. The abdomen was diffusely painful, with palpation of an uncharacteristic hepatomegaly around 2 cm below the ribcage, on the medioclavicular line. Bilateral renal Murphy’s sign. Painful palpation of the muscular masses of the limbs and slight malleolar edema. Neurological exam and exam of the osteoarticular system did not present alterations.

There was no relevant personal history, in particular, patient reported no complaints suggestive of sinusopathy and rhinitis.

The ophthalmic exam showed conserved visual acuity (10/10); exophthalmia of 22 mm on the right and 23 mm on the left; proptosis of the left eye (LE) without alterations in ocular movements; conjunctival and ciliary hyperemia, with engorgement of the
conjunctival vessels, more accentuated in the LE; thinning of the peripheral cornea with perilimbal keratic infiltrates, more accentuated in the LE; ocular globes very painful to touch; reduced intraocular pressures; ocular fundi with engorgement and venous tortuosity, more evident in the LE; and concentric retraction of the peripheral visual field in the LE. Ocular echography did not show any significant alterations. Concluding, it was a case of bilateral scleritis with anterior uveitis, more accentuated in the LE.

Complete blood count showed Hb of 12.8 g/dL with Htc of 37.9%; leukocytosis of 14200 with 80% of PMN and ESR of 95 mm were highlighted. The coagulation parameters were within the reference value range. Biochemical analyses showed fibrinogen of 739 mg; urea of 10.3 mmol/l; creatinine of 216 mmol/l; creatine phosphokinase (CPK) of 11 U/L; serum immunogram without alterations; and C-reactive protein (CRP) of 35.4 mg (normal < 3). Urine II showed urine density of 1020, proteinuria of 1.5 g/l, leukocyturia, pyuria, erythrocyturia and cylindruria.

The electrocardiogram did not show any alterations, and the thoracic radiography showed slight accentuation of the reticule in the lower third of the right lung field. The abdominal echography showed slight homogenous hepatosplenomegaly, adenomegaly in the peripancreatic area and kidneys without alterations, namely good corticomedullary differentiation and normal dimensions (+ 11 cm of bipolar diameter). The echography also revealed a small bilateral pleural effusion of the posterior sac, which were not visible in the thoracic teleradiography.

On the 5th day of hospitalization there was worsening of the symptoms and signs, which motivated hospitalization, with progressive deterioration of renal function (urea of 22.9 mmol/L and creatinine of 651 mmol/L) and severe metabolic acidosis (pH of 7.21); leukocytosis and high VS were maintained, with 24-hour hypoalbuminaemia and proteinuria of 0.35 g with diuresis of 300 ml in the 24 hours. Hydric balances were positive, with variations from 500 to 1000 cc/day. At this point the patient was placed on broad-spectrum antibioticotherapy (cefuroxime and netilmicin) and methylprednisolone pulse (1g/day during 3 days), which were followed by cyclophosphamide (2 mg/Kg/day, i.v.), as well as support therapies.

At this point the medical team opted to perform renal biopsy (RB), which revealed focal and segmental necrotizing glomerulonephritis, with extracapillary proliferation and crescent formation (Fig. 2); the investigation of immunoglobulin and complement deposits in the glomerular lesions was negative; they also observed chronic interstitial nephritis, of preferential periglomerular location. The vessels involved in the biopsy showed no alterations.

On the 10th day of hospitalization (3rd day of cyclophosphamide), there was improvement of the scleritis/uveitis and glossitis, and absence of otorrhea. However, the patient began to develop a cough, with purulent and hemoptoic expectoration. He remained febrile and presented edema of the lower limbs, up to the root of the thigh, and sacral. In the lung auscultation, stasis rales were heard in the lower third of both hemithoraces, and diffuse crepitating rales. Diuresis was 200 ml/day. The patient maintained leukocytosis and progressive deterioration of renal function (creatinine of 950 mmol/l). He had slight anemia, normocytic and normochromic (Hb of 10.2 g/dL), and CPR was 35.8 mg. It was only on the 11th day that he had his first haemodialysis session. He was febrile (39°C), polypnoea, with anasarca and anuria. He had purulent expectoration and abundant haemoptysis. On the 12th day (5th day of cyclophosphamide), there was worsening of the respiratory state, with signs of respiratory difficulty and severe hypoxemia, which improved considerably with oxy-
gen therapy. Lung auscultation revealed crepitating and subcrepitant rales and the expiratory time was prolonged. Thoracic teleradiography (Fig. 3) showed diffuse and heterogeneous hypodensity throughout both lung fields, with ‘fluffy’ appearance, bilateral hilar ingurgitation and cardiomegaly. Creatinine was 1008 mmol/L. The patient suffered respiratory failure in the dialysis room, and failed to react to resuscitation procedures.

The hemocultures and urocultures were sterile. The antinuclear and anti-DNA antibodies were negative. The anti-neutrophil antibodies with nuclear pattern (pANCA), whose result was only known after the death of the patient, were negative and those with cytoplasmic pattern (cANCA) were positive, with a titer of 1/38 (immunofluorescence technique).

Macroscopic exam of the necropsy revealed thrombosis of the left femoral vein and periprostatic plexuses; embolism of the main branches of the right pulmonary artery; diffuse interstitial pulmonary fibrosis; pulmonary congestion and edema; fibrinous pericarditis; liver stasis; splenomegaly with infarct areas; and pale, tumescent kidneys.

Microscopic exam of kidney fragments had aspects coinciding with those observed in the biopsy: focal and segmental necrotizing glomerulonephritis, crescentic, with obliteration of Bowman’s space and destruction of the capsule, which associated with the periglomerular lymphohistiocitary inflammatory infiltrate, produced the characteristic glomerular “granulomatous” appearance; some glomeruli were also observed, with thrombosis of the capillaries and others with total sclerosis; the vessels did not have vasculitis lesions. The lung was another organ affected, with several types of lesion: extensive focal points of intra-alveolar hemorrhage, focal destruction of the alveolar septa with inflammatory infiltrate by partly necrotized neutrophil granulocytes, (capillaritis) (Fig. 4a); and vasculitis lesions that affected the small and medium-caliber veins and arteries (Fig. 4b), some with extensive necrosis of the wall, necrotizing granulomas in which focal points of necrosis were observed, with cellular debris and neutrophils, surrounded by histiocytary cells arranged in a palisade formation, sometimes with multinucleated giant cells (Fig. 4c); extensive areas of necrosis of the parenchyma; interstitial fibrosis with inflammatory infiltrate comprised of neutrophil granulocytes, lymphocytes and histiocytes. In the spleen, numerous veins were identified with transmural inflammatory infiltrate and fibrinoid necrosis of the wall (Fig. 5), some with thrombosis; extensive areas of hemorrhage and necrosis of the parenchyma were also observed. The liver, although with preserved architecture and without parenchymatous alterations, also presented vasculitis lesions.

**Discussion**

The existence of scleritis, uveitis, microscopic hematuria, proteinuria, pyuria and cylindruria, all of which are suggestive of glomerulonephritis, associated with fever, myalgias, high ESR, leukocytosis and very high CPR, may be manifestations of vasculitis, particularly polyarteritis nodosa (PAN). The negativity of the antinuclear antibodies and rheumatoid factor, as well as the absence of relevant events in the previous history, also support this diagnosis. The existence of exophthalmia, proptosis and otorrhoea do not support this diagnosis, rather, these alterations are strongly suggestive of another entity, namely WG. Moreover, the inexistence of arterial hypertension, in this clinical context does not support a diagnosis of PAN, but is in favor of WG.

Ocular involvement in WG can take two forms: focal and contiguous. The focal disease can manifest as conjunctivitis, episcleritis, scleritis, corneo-scle-
rotic ulcerations, uveitis, retinal vasculitis and optic neuropathy. It is believed that these alterations are essentially due to vasculitis of the anterior or posterior ciliary arteries, vessels of the retina, or vessels of the optic nerve. Granulomatous inflammatory infiltration of the vessels and of the ocular tissue itself was also demonstrated. The contiguous disease manifests as inflammation of the orbit, either by direct propagation of disease of the paranasal septa (PNS), or by obstruction of the nasolacrimal duct.

On the other hand, ocular involvement, as an initial manifestation of WG, is infrequent, varying in the largest series between 15% and 16%, for conjunctivitis, uveitis and scleritis and between 2% and 7% for proptosis. However, during the evolution of the disease, over 50% of patients will have some form of ocular involvement, proptosis, within the adequate clinical context, being highly suggestive of a diagnosis of WG.

The existence of scleritis, uveitis, proptosis, otorrhoea and acute glomerulonephritis there make the diagnosis of WG probable. On the other hand, the inexistence of a history of recurrent sinusitis, rhinitis or nasal symptoms, epistaxis, cough, haemoptysis, dyspnoea and alterations in thoracic teleradiography (fixed infiltrates, nodular lesions and cavities), the most frequent symptoms of WG, make this diagnosis less likely.

In terms of therapeutic decision, the precise diagnosis of the clinical entity in question was not particularly important. The severity and speed of evolution of the renal disease called for aggressive therapeutics to preserve renal function, not to mention preserving the patient’s life. Corticosteroids in high doses, and cyclophosphamide, would be indicated in any of the situations. On the other hand, this line of therapy does not exclude the early start of haemodialysis, which in this case, for reasons unknown to us, was only begun very late. However, in prognostic terms it was important to have a diagnosis. Of the organs involved in the initial phase of hospitalization (eyes and kidney), we opted to perform renal biopsy (RB), as this could provide us with more prognostic information.

The renal lesion most frequently found in Wegener’s granulomatosis is focal and segmental necrotizing glomerulonephritis, with extra-capillary proliferation and crescent formation, associated with greater morbidity (chronic renal insufficiency) and mortality. This entity can be observed in a wide
range of situations. However, the absence of immunoglobulin and complement deposits in the lesions reduces the spectrum to a small number of diseases, such as WG, PAN, MP, Churg-Strauss syndrome and “idiopathic” glomerulonephritis, and given the clinical context, the latter two could be excluded. Granulomatous and vasculitis lesions, which are so characteristic in the other organs, are rarely observed in the kidneys. Hence, in a series of 158 patients, in which 144 renal biopsies were performed, vasculitis was only found, which not related to the glomerular vessels, in 8% of the RBs, with vasculitis and granulomatous lesions in 3%, whereby the RB, alone rarely serves as a guideline for the diagnosis.

In the same series, diagnosis was carried out on more than 90% of the open pulmonary biopsies, and in 16-23% of biopsies of the upper airways, whereas vasculitis was only found in 7% of bronchoscopic biopsies. Due to the small quantity of biopsy material, the biopsy of small organs, like the eye, exhibit low sensitivity.

If there were doubts about the diagnosis up to this stage, we would be in the presence of microscopic polyarteritis, as there was no clinical evidence of pulmonary involvement, the appearance of purulent and hemoptoic expectoration and haemoptysis with fast evolution to a syndrome of respiratory difficulty, and respective pathological anatomical findings, make the final diagnosis of WG clear.

In the lung, the association of necrotizing granulomas and necrotizing vasculitis is characteristic of WG, although not pathognomonic. It is, however, necessary to exclude other granulomatous angiitis like Churg-Strauss syndrome, bronchocentric granulomatosis, lymphomatoid granulomatosis, and necrotizing sarcoid granulomatosis, whose clinical characteristics and particular morphological aspects distinguish them from WG. Another type of lesion that occurs in this entity is capillaritis, which is responsible for intralveolar hemorrhage. The most frequent causes of massive pulmonary hemorrhage are: Goodpasture syndrome, collagen diseases, particularly systemic erythematosus lupus (SLE), idiopathic pulmonary hamosiderosis, and toxics. The absence of capillaritis in Goodpasture syndrome and idiopathic pulmonary hemosiderosis, the presence of immunocomplexes in the lesions, the absence of granulomas, the characteristics of renal involvement, and the data from the clinic and analytical exams enable a differential diagnosis to be made between these entities and WG. Fibrinoid necrosis in the pulmonary vessels seldom occurs, yet it is the one that occurs most frequently in the visceral vessels, as observed in this case in the spleen. Splenic and renal involvement were thus practically identical to what was observed in PAN, yet this entity does not affect the lungs and in rare cases in which there is pulmonary lesion, only the arteries are involved and there are no granulomas.

The positivity of anti-neutrophil cytoplasmic antibodies (ANCA) was a new argument in favor of the WG hypothesis, albeit only known after the patient’s death.

ANCAs were initially described in 1982, in the
blood serum of patients with necrotizing glomerulonephritis and systemic vasculitis. Subsequently, they were described in patients with various forms of vasculitis including WG, PAN and idiopathic crescentic glomerulonephritis. Two patterns of ANCA were identified using a neutrophil immunofluorescence technique: a cytoplasmic pattern (cANCA) and a perinuclear pattern (pANCA). cANCA is specifically related to a protein called PR3 (proteinase 3), which is present in leucocytes and monocytes, with proteolytic enzymatic activity. cANCA appears to present a high specificity for WG and PM, its sensitivity depending on the extent and activity of the disease. Its titers do not have prognostic value, yet they appear to be good markers of the activity of the disease. pANCA have specificity for myeloperoxidase, and their perinuclear location appears to be due to an artifact of the fixation technique. pANCA are described for numerous pathologies, for example idiopathic glomerulonephritis, PAN and other types of vasculitis, connectivitis (LES and rheumatoid arthritis), inflammatory bowel disease, primary biliary cirrhosis, etc. For this reason they have low specificity as a diagnostic aid, although with high sensitivity.

In conclusion, WG is a rare granulomatous necrotizing vasculitis, whose peak of incidence is in the 5th decade of life, having no gender preference, and of unknown etiology. It characteristically and classically involves the upper and lower airways and the kidneys, however, it can involve any organ or system, and its initial manifestations are polymorphic. Even rare manifestations of a rare disease, as they are so suggestive, oblige us to think about the diagnosis. As the natural evolution of the disease is extremely aggressive and of frequently fatal evolution, the case presented here being paradigmatic of this situation, diagnosis and start of adequate therapy are urgent requirements, as these will allow long survival periods in remission and often with low morbidity of a disease until only a few years ago, was invariably fatal.

References

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