Upper airway changes and rapid progressive glomerulonephritis in an old woman

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ABSTRACT

Granulomatosis with polyangiitis, microscopic polyangiitis, allergic granulomatous angiitis, and idiopathic pauci-immune glomerulonephritis are ANCA-associated vasculitides that, and affect arterioles, capillaries, and venules, and more commonly involving the air ways and kidneys. Granulomatosis with polyangiits (Wegener’s granulomatosis) is described in a 76-year-old woman presenting with chronic sinonasal disorder, and early onset,new onset andrecent rapidly progressive glomerulonephritis. ConclusiveDefinitive diagnosis was achieved by clinical and laboratory data, and renal biopsy findings. Imaging studies of the thorax and functional respiratory evaluations showed no abnormalities. A sSuccessful therapeutic approach included corticosteroids, cyclophosphamide and antibiotics. Early diagnosis and prompt treatment can yielpropitiate better outcomes, even among old individualspeople. Diagnostic pit-falls may be lessened by the enhancing theof suspicion index about rare diseases.

Key words. Granulomatosis with polyangiitis, rapidly progressive glomerulonephritis, sinonasal involvement, small-vessel vasculitis, Wegener’s granulomatosis.

RESUMO

Alterações de vias aéreas superiores e glomerulonefrite rapidamente progressiva em idosa

Granulomatose com poliangetê, poliangetê microscópica, angetê granulomatosa alérgica e glomerulonefrite pauci-immune são vasculites associadas a anticorpo anticitoaxila de neutrófilos, que afetam arteríolos, capilares e vênulas, mais comumente envolvendo as vias aéreas e os rins. Um caso de granulomatose com poliangetê (granulomatose de Wegener) é descrito em uma mulher de 76 anos etários, com doença crônica nasal e nos seios da face, com glomerulonefrite rapidamente progressiva de início recente. O diagnóstico definitivo foi estabelecido com dados clínicos, resultados de exames laboratoriais e dados de análise de amostra de biópsia renal. Os exames de imagem do tórax e as avaliações funcionais pulmonares não mostraram alterações. A abordagem terapêutica de sucesso incluiu corticosteroides, ciclofosfamida e antibióticos. O diagnóstico precoce e o tratamento imediato podem propiciar melhores resultados, mesmo entre indivíduos idosos. As dificuldades de diagnóstico podem ser reduzidas pelo aumento do índice de suspeita sobre doenças raras.

Palavras-chave. Granulomatose com poliangetê;
**INTRODUCTION**

Wegener’s granulomatosis or granulomatosis with polyangiitis (GPA), was first described in 1939 by Friedrich Wegener in a 36-year-old woman.¹ This rare condition is characterized by necrotizing lesions in small and medium arteries, necrotizing granulomatous inflammation of respiratory tract, and necrotizing glomerulonephritis; or exclusive respiratory involvement.¹⁻¹⁰ GPA more often affects white people of both sexes, between 50 and 70 years of age.⁷ Despite familial predisposition, linked to HLA-B8 and HLA-DR2, and the main association with antineutrophil cytoplasmic antibodies (cANCA), the etiopathogenesis of GPA is unclear.¹⁻¹⁰ Additionally to ANCA, the alternative pathway of the complement system, neutrophils, endothelial cells, T-cells, microbial factors, and drugs can play some role in the pathogenic mechanisms.⁶ The course is indolent or rapidly progressive, with rhinorrhea, purulent coryza and epistaxis, nasal and oral ulcerations, otolaryngologic and tracheal changes, glomerulonephritis, and systemic involvement.¹⁻¹⁰ The level of renal function is related to mortality in older people.⁵ Concomitant involvement of the kidneys and of upper respiratory tract by GPA is reported in an old woman successfully controlled with corticosteroids, cyclophosphamide and antibiotics.

**CASE REPORT**

In July 2013, a 76-year-old hypertensive woman treated with losartan, presented with high fever, purulent coryza, and epistaxis. She had a previous history of chronic sinusitis, allegedly controlled by bilateral turbinectomy. She was unsuccessfully treated with azithromycin during 5 days, followed by levofloxacin for 10 days. With symptoms lasting over a month, her chest x-ray was normal, and imaging study of paranasal sinuses showed bilateral abnormalities (figure 1). She was admitted to another hospital and underwent treatment with ceftriaxone and clindamycin, without clinical improvement. Furthermore, a course of caspofungin was also administered without success, and the

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*Figure 1. A: Normal aspect of the chest radiography; B to F (Computed tomography): image of material with soft tissue attenuation partially obliterating the ethmoidal cells and the right maxillary sinus; edematous mucosa in the left maxillary sinus, and in the frontal and esphenoidal sinuses, as well as in the left ethmoidal cells; and left deviation of nasal septum.*
patient was transferred to our hospital on the first week of September. Rhinoscopy and video nasal endoscopy showed septal deviation to the left, in addition to mucosal edema and hyperemia involving the right middle meatus, the uncinate process and the ethmoidal crest. A right maxillary antrotomy was performed and a large volume of pus was drained. The secretion was sent for microbial cultures, and the results were negative. Because of persistent high fever, empirical treatment with piperacillin and tazobactam was used during 8 days, changed for meropenem and fluconazole for 9 days, and further to vancomycin during 5 days; no clinical improvement was achieved. A control video nasal endoscopy was performed, and samples of the secretion were sent to new cultures including the search for fungi, but all the results were negative for microorganisms. The chest radiography was unremarkable; and computed tomographic images showed partial obliteration of the ethmoidal cells and maxillary sinus at the right, mucosal edema at the entire nasal cavity, and left deviation of the nasal septum (figure 1). Laboratory tests on admission revealed anemia, neutrophilic leukocytosis, elevated C-reactive protein, high erythrocyte sedimentation rate, microalbuminuria and glomerular hematuria. The clinical and imaging evaluations of the pleural and pulmonary fields were unremarkable and blood and urine cultures were negative. She evolved with proteinuria up to 455 mg/24 hours, elevated serum creatinine, and creatinine clearance of 58 mL/min/1.73 m². There was a gradual worsening of renal function and elevation of blood pressure. Even after discontinuation of vancomycin, serum creatinine levels raised up to 3.3 mg/dL. Because of the suspicion of glomerulonephritis in the setting of a chronic disease of upper airways, complementary tests were done to evaluate the diagnostic hypothesis of a rapidly progressive glomerulonephritis (RPGN) associated with GPA. To prevent further deterioration of renal function, even before the result of ANCA determination, on September 23rd she underwent pulse therapy with methylprednisolone 1g daily for 3 days. Serum pANCA was positive with a 1:20 titer, and anti-MPO-ANCA and PR3-ANCA were negative; C3 and C4 complement levels were normal; serum ANA, rheumatoid factor, anti-CCP, cryoglobulin, anti-HIV-1 and HIV-2, anti-HCV and HBsAg, were all negative. Histopathology studies of renal biopsy samples revealed glomeruli with hyper-cellularity, segmental areas of capillary retractions and sclerosis, debris and synechiae, and surrounded by fibro cellular crescents (figure 2). Except for the ANCA profile, these findings were consistent with the typical characteristics of GPA. Oral prednisone 1mg/kg was used during 8 days, and a rapid improvement of fever and of rhinorrhea was observed. The patient received prophylactic albendazole, and losartan was changed for amlodipine 10 mg/day. Because of the patient’s age, induction treatment with cyclophosphamide was carried out with half a dose, accordingly to European Vasculitis Study Group (EUVAS). Currently, she is asymptomatic, using prednisone 70 mg/day, cyclophosphamide 75 mg/day, and alendronate 70 mg weekly. Additionally, she has received anti-influenza and anti pneumococcal vaccines.

**DISCUSSION**

This 76-year-old white woman with a previous history of chronic sinusitis and bilateral turbinectomy...
was admitted because of severe symptoms of rhinosinusitis uncontrolled by antibiotic therapy. GPA more often affects white people aged between 50 and 70 years, with no sex differences. Upper airway manifestations can be the initial features in up to 92% of the patients, and relapses are frequently observed in the course of disease, as was observed in this case study. The findings more frequently reported in patients with GPA are nasal crusting, chronic sinusitis, nasal obstruction, variable rhinorrhea, epistaxis, hyposmia/anosmia, and epiphora. Middle ear and mastoid changes, vertigo, hearing loss and facial nerve palsy occur as well. Potential causative factors of GPA include fibrinoid necrosis of blood vessels, epithelial granulomas, chronic inflammation, and prior surgical intervention on the sinonasal region. Typical histopathology data include palisading epithelioid granulomas and vascular lesions. The patient herein described was previously submitted to a bilateral turbinectomy; however, the respective histopathological study did not disclose any specific chronic inflammation. False-negative results are not infrequent in studies of head and neck biopsy specimens. The involvement of the Kiesselbach plexus, which supplies blood to the anterior septum, can propitiate the occurrence of perforation, mimicking the lesions caused by cocaine inhalation.

Diagnostic pitfalls increase by non-specific signs and symptoms, local trauma or cocaine use. Nasal endoscopy shows characteristics of the lesions and enables biopsy procedures, and computed tomography study is necessary to confirm the head and neck involvement of GPA. The patient had concurrent manifestations of RPGN associated with data of renal biopsy, which reinforced the diagnostic hypothesis of GPA. Of note, the pANCA positive profile with a 1:20 titer, and negative anti-MPO-ANCA and PR3-ANCA, were not the classical of GPA. The main differential diagnosis of GPA are microscopic polyangiitis (MPA), polyarteritis nodosa, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), idiopathic pauci-immune necrotizing crescentic glomerulonephritis (NCGN), cocaine-induced lesions, rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, and T-cell lymphoma.

Watts et al. studied 111 patients with GPA and 58 patients with MPA, and found respective annual incidences of 11.3/million and 5.9/million; the periodicity for GPA was of 7.6 years. On a clinical standpoint, the differential diagnosis between GPA and MPA may be challenging because of their similarities; moreover, there is a strong relationship between cANCA/PR3-positive vasculitis and GPA, and of pANCA/MPO-positive vasculitis with MPA. Typical GPA is a necrotizing vasculitis with presence of granulomas and involvement of the upper respiratory tract; in MPA, the main involvement is on the lower respiratory tract. The patient herein reported did not have pulmonary disturbances during the course of disease, and the histopathology studies of the renal biopsy revealed crescentic glomerulonephritis with segmentary extracapillary proliferation, that are also described in NCGN. Although NCGN may be associated with systemic small vessel vasculitis (human neutrophil elastase-ANCA-positive), MPO-ANCA and PR3-ANCA are the serological markers of this condition; in addition, glomerular lesions develop without concomitant upper airway involvement. Despite the initial concerns about differential hypotheses, the following criteria established the diagnosis of GPA - purulent rhinorrhea and epistaxis, hematuria, proteinuria, rapidly progressive renal failure, hypertension, in addition to approximately 4 weeks of high fever, and histological data of necrotizing crescentic glomerulonephritis without immune deposits. GPA is a pauci-immune vasculitis, in which no immunoglobulins or complement are detected, and the etiopathogenic mechanism is associated with activation of neutrophils by ANCA.

In GPA, cANCA/PR3-positive may be found in up to 90% of cases, but it was not seen in this patient, a phenomenon which cannot be explained on the basis of previously used medications. ANCAs are strongly associated with manifestations and outcomes of PGA; however, Holle et al. did not detect ANCA-positive results in 54% of patients with persistent localized GPA. This finding is indicative of disorders associated with cellular immune effector mechanisms. Moreover, in patients in which the diagnosis of vasculitis is being considered and which have atypical ANCAs detected by indirect immunofluorescence, the diagnosis of ANCA associated systemic vasculitis should not be excluded even if specific reactivities to MPO and PR3 antigens.
are found negative.\textsuperscript{11} This entity was successfully controlled by corticosteroids, cyclophosphamide and antibiotics,\textsuperscript{8} and the patient is currently undergoing a long term regimen of immunosuppression. The vast majority (up to 96\%) of patients with GPA improve with immunosuppressive therapy, but maintenance medication should be utilized to prevent the usual recurrent exacerbations.\textsuperscript{2} Ideal management include internists, nephrologists, otolaryngologists, and rheumatologists.\textsuperscript{2}

CONCLUSION

The clinical diagnosis of GPA is often challenging because of nonspecific features, in special the sinonasal disturbances, which are very frequent among individuals from diverse age groups. Early diagnosis and prompt adequate management of GPA propitiates better outcomes. Therefore, this entity should be hypothesized in the setting of chronic sinonasal disturbances, and respective investigation of renal or systemic associated involvement must be performed. The authors believe that case studies can enhance the suspicion index about this rare entity.

REFERENCES