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Goodpasture´s syndrome with neurologic involvement and negative ANCA

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Nefrologia 2010;30(5):584-7
doi:10.3265/Nefrologia.pre2010.Mar.10237

ABSTRACT

Goodpasture´s syndrome is a rare autoimmune disorder characterized by rapidly progressive glomerulonephritis (RPGN) and alveolar hemorrhage in the presence of anti-glomerular basement membrane (anti-GBM) antibodies. Central nervous system involvement is highly unusual in the absence of anti-neutrophil cytoplasmic antibodies. We report the case of a 20-year-old man with RPGN accompanied by bloody sputum, tonic-clonic seizure and high titers of anti-GBM antibody. After treatment with immunosuppressants and plasmapheresis, the patient showed reduced anti-GBM antibody titers and improved neurologic and respiratory symptoms, but renal failure persisted, requiring hemodialysis. Twenty months later, with the disease in remission, he underwent deceased-donor renal transplantation.

Key words: Acute renal failure. Goodpasture syndrome. Cerebral vasculitis. Anti-glomerular basement membrane disease

Síndrome de Goodpasture asociado con vasculitis cerebral ANCA negativa

RESUMEN

El síndrome de Goodpasture (SGP) es una rara entidad de base inmunológica, caracterizada por la asociación de una glomerulonefritis rápidamente progresiva (GNRP) y hemorragia alveolar en presencia de anticuerpos antimembrana basal. La afectación del sistema nervioso central (SNC) en el SGP es extremadamente infrecuente en ausencia de ANCA. Presentamos el caso de un paciente de 20 años que comenzó con una GNRP acompañada de esputos hemoptoicos y dos episodios de crisis convulsivas tónico-clónicas generalizadas, en presencia de elevados títulos de anticuerpos antimembrana basal glomerular (Ac-anti-MBG). Tras tratamiento inmunosupresor asociado con plasmaféresis, el paciente presentó descenso de los títulos de Ac-anti-MBG, así como mejoría de los síntomas neurológicos y respiratorios, aunque sin recuperación de la función renal, permaneciendo en programa de hemodiálisis. Veinte meses más tarde, con la enfermedad en remisión, el paciente recibió un trasplante renal de cadáver.

Palabras clave: *Fracaso renal agudo. Síndrome de Goodpasture. Vasculitis cerebral. Enfermedad por anticuerpos antimembrana basal*

INTRODUCTION

Anti-glomerular basement membrane antibody disease is an immunological disorder characterized by the presence of circulating antibodies that act directly against an intrinsic antigen of the glomerular basement membrane, provoking a rapidly progressive glomerulonephritis (RPGN).

Goodpasture's syndrome (GS) has generally been used as a synonym for anti-glomerular basement membrane antibody (anti-GBM antibodies) disease, which is characterized by the association of RPGN and alveolar hemorrhage in the presence of anti-GBM antibodies. Central nervous system (CNS) involvement is highly unusual in the absence of anti-neutrophil cytoplasmic antibodies (ANCA), with only four cases reported in the literature [1-4].

We report the case of a 20-year-old man with RPGN, bloody sputum and tonic-clonic seizure in the presence of circulating anti-GBM antibodies.

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CLINICAL CASE

A 20-year-old man, smoker and former cocaine and cannabis user, who was admitted to hospital for macroscopic hematuria and acute oliguric renal failure. Twelve days before, he had presented with asthenia, anorexia, fever, vomiting and dysuria; for which he visited a general practitioner and an urinary tract infection was diagnosed and ciprofloxacin was prescribed. Four days later, the patient presented fever (38ºC), macroscopic hematuria and decrease urine output.

On admission, physical examination revealed: blood pressure (BP) 140/90 mmHg, temperature 37ºC, cutaneous and mucous paleness and reduced bilateral lower-lobe ventilation. Upon admission, AORF was observed, requiring hemodialysis within the first 24 hours. Forty eight hours later he presented bloody sputum, followed by two episodes of generalized tonic-clonic seizures.

Blood tests at admission showed: hematocrit 25.5%, Hb:8.9g/L, leucocytes 16700/mm^3, platelets 344000/mm^3 erythrocyte sedimentation rate: 96mm/h, creatinine 11.8mg/dl, BUN 80mg/dl, glucose 97mg/dl, albumin 4.5gr/dl, sodium 134mEq/L and potassium 4.2mEq/L. Proteinogram, immunoglobulin and κ/λ light chains were normal. Liver function tests showed no alterations. Hepatotrope virus and HIV serology were negative. Blood and urine toxins, including cocaine and cannabis metabolites, were not detected. Antinuclear antibodies, ANCA, antiphospholipid antibodies and complement levels were normal. However, anti-GBM antibodies were positive (72.5 U. Normal range <10U).

Twenty four-hour urine test showed proteinuria of 850 mg/day. Severe hematuria was observed in urinary sediment.

Chest X-ray showed bilateral alveolar-interstitial infiltrate indicative of alveolar hemorrhage. Renal ultrasound showed normal-sized kidneys, with increased cortical echogenicity. Electroencephalography, brain magnetic resonance imagen (MRI) and Willis polygon angio-MRI were normal.

Four days after admission, percutaneous renal biopsy showed 100% crescentic glomerulonephritis with glomerular tuft collapse and isolated fibrinoid necrosis, moderate inflammatory infiltrate, incipient interstitial fibrosis and tubular atrophy (Figure 1). Immunofluorescence showed linear IgG deposition around the glomerular basal membrane.

GPS was diagnosed, associated to probable CNS vasculitis with negative ANCA. The patient received 3 pulses of 500 mg 6-methylprednisolone during three consecutive days. After that, oral cyclophosphamide was initiated (1.5mg/Kg/day) and 15 sessions of plasmapheresis were administered. In addition, the patient received treatment with valproic acid. Respiratory and neurological symptoms disappeared with the prescribed treatment, but renal function did not recover and the patient remained on dialysis.

Twenty five days after admission, the patient was discharged with negative titers of anti-GBM antibody allowing immunosuppression tapering. Cyclophosphamide was stopped 3 months after admission, but the patient remained on low-dose steroids (2.5 mg/day) and on hemodialysis schedule (Figure 2).

Subsequent evolution

Six months after discharge, after non-compliance for antihipertensive treatment, the patient was re-admitted for a hypertensive emergency (blood pressure 220/120mmHg) with right temporal intraparenchymal hematoma, requiring surgical drainage. At this point serial measurements of anti-GBM antibodies titers were negative. Depite the severity of this clinical condition, the patient was discharged without neurological sequels.

Twenty months later, the patient underwent deceased-donor kidney transplantation and received immunosuppressive therapy with, tacrolimus, mycophenolate mofetil and prednisone. Post-transplant evolution to date has been excellent, with no evidence of relapse of underlying disease (Table 1).

DISCUSSION

GPS is a rare autoimmune disorder characterized by a triad of RPGN, circulating anti-GBM antibodies and alveolar hemorrhage. Although genetic factors have been associated

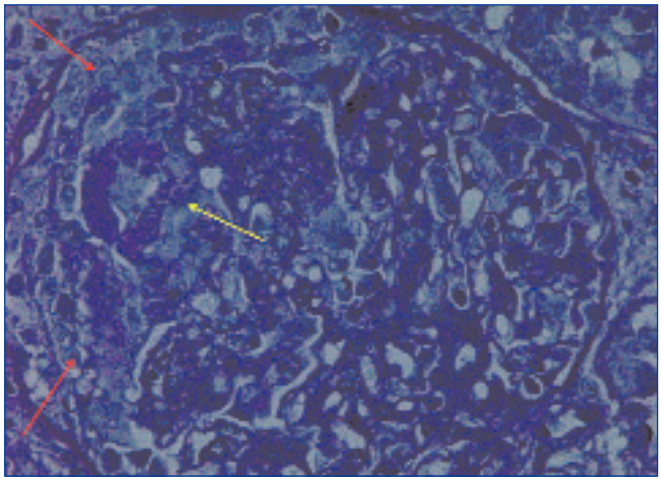

Figure 1. Extracapillary crescentic glomerulonephritis (red arrows) with fibrinoid necrosis areas (PAS stain, 400 x 400).

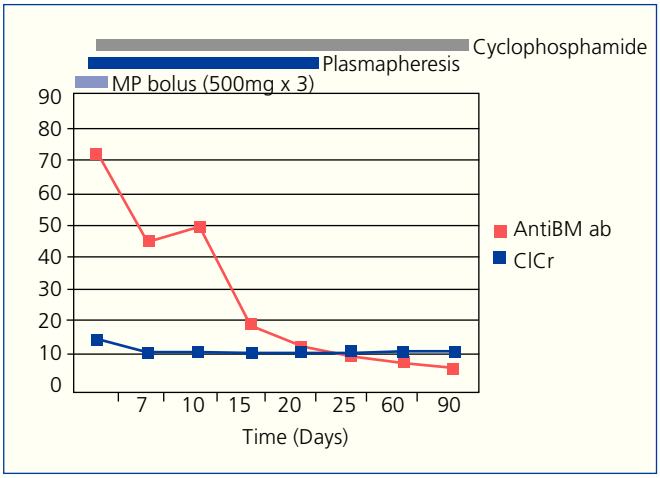

Figure 2. Evolution of Anti-GBM antibodies and renal function following the initiation of treatment with steroids, oral cyclophosphamide, and plasmapheresis.

with increased susceptibility for developing this syndrome, other factors such as environmental exposure (including viral infection, exposure to volatile hydrocarbons and smoking) may trigger the disease in predisposed individuals, particularly those with underlying lung damage.[5] Additionally, cocaine use has also been related with anti-GBM disease.[6] Our patient had a history of smoking and cocaine use, which may have triggered the onset of GPS.

Between 10 and 30% of anti-GBM disease is associated with ANCA, and most cases show low levels of antimyeloperoxidase antibodies (MPO). This subgroup of patients probably present a variant of associated vasculitis.[7] Although the cause of ANCA in this disease is unclear, some authors suggest that the mechanism responsible is polyclonal immune activation.[8]

GPS is characterized by the presence of antibodies against the alpha 3 chain of type IV collagen epitope (α-3 (IV) NCI) labelled Goodpasture antigen.[9] Although widely distributed, this antigen is mainly expressed in the glomerular and alveolar basement membranes; it is less frequently found in tubular basement membranes, cochlea, retina and choroid plexus.

Cerebral involvement in GPS is extremely rare in the absence of ANCA, with only four cases reported.[1-4] All of them presented recurrent seizures, related to cerebral vasculitis, with or without pulmonary hemorrhage. Rydel et al,[1] first described a case of ANCA negative cerebral vasculitis associated with GPS, with vasculitic infiltrate found in meningeal biopsy. Although meningeal and cerebral biopsy constitute the gold standard procedures for the diagnosis of cerebral vasculitis, their use is usually reserved for doubtful cases because of their aggressive nature of the procedure. In fact, the diagnosis of ANCA negative cerebral vasculitis associated with GPS has mostly been based on the clinical picture and diagnostic image findings.[2-4] Our patient initially presented RPGN requiring dialysis from the beginning, followed by alveolar hemorrhage and seizures, with high titers of anti-GBM antibody. ANCA measurements were repeatedly negative and we ruled out other possible triggers of the seizures (metabolic disorder, severe hypertension, drug withdrawal etc.). Although brain MRI was normal in our patient, we cannot rule out that small vassel vasculitis lesions could have contributed to cerebral damage because up to 35% of cases of cerebral vasculitis present normal MRI findings.[10] Cerebral angiography was not performed due to the neurological symptoms resolved with the treatment described above.

After completion of the treatment, respiratory symptoms also improved, but renal function did not recover. Levy et al. reported that advanced renal failure estimate by plasma creatinine levels (>5.7mg/dl), the need for early dialysis and >50% crescentic renal biopsy findings were factors of poor prognosis for the recovery of kidney function.[11] Kidney transplantation is indicated in GPS, but the risk of relapse has prompted delaying transplantation at least six months, making sure that

Table 1. Data on tle patients evolutions from the onset of GPS.

	Start of GPS		HD	Kidney Transplant		24 months after the Kidney Transplant
	Admission	Discharge		Admission	Discharge	
Haemoglobin (g/L)	8.9	9.9	12.2	13.6	14.6	13.1
Haematocrit (%)	25	28.4	37.2	40.7	42.9	37.8
Platelets (mm3)	344,000	120,000	234,000	204,000	362,000	226,000
ESR (mm/h)	96	2	5	3	8	4
Creatinine (mg/dL)	11.8	7.2	9.6	6	1.2	1.3
SBP (mmHg)	140	130	150	128	125	120
DBP (mmHg)	90	90	98	80	80	70
ANCA	Negative	Negative	Negative	Negative	-	Negative

anti-GBM antibody titers are undetectable. This is a promising strategy in most cases, as in our patient, who received an deceased donor kidney transplant 20 months later, presenting a good clinical outcome and no signs of recurrence of the disease.

In summary, GPS with neurological involvement is extremely rare, especially with negative ANCA. Normal brain MRI findings do not rule out small-vessel cerebral vasculitis, so GPS requires early diagnosis and aggressive treatment to improve prognosis.

Acknowledgements

The authors would like to thank Dr. Eduardo Salido for his renal pathologic assessment and review of this manuscript.

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Received: 9 Feb. 2010 | Accepted for publication: 30 Mar. 2010