

## Pauci-Immune necrotising glomerulonephritis associated with ANCA in two siblings

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### ■ ABSTRACT

Pauci-immune necrotising glomerulonephritis with extracapillary proliferation is a common renal histological manifestation of systemic vasculitis. Although its aetiopathogenesis is not well known, it is possible that environmental factors may have a bearing on genetically predisposed subjects, since there are many familial cases of systemic vasculitis. The frequent association between systemic vasculitis and ANCAs suggests autoimmune mechanisms play a part in its pathogenesis. We report two cases of necrotising extracapillary proliferative glomerulonephritis in two siblings sharing the same environment. We do not know if the first case had ANCAs, meaning the role of the autoimmune mechanism is not clear (diagnosis was made in 1988 when it was not possible to measure ANCAs in this hospital). Since the second case had the same kind of illness associated to positive ANCAs and autoimmune hypothyroidism, we presume that both siblings presented the same pathogenesis.

These two cases of familial vasculitis appear to support the hypothesis that environmental, genetic and autoimmune factors influence the pathogenesis of systemic vasculitis.

#### Key-Words:

ANCA; familial systemic vasculitis; necrotising glomerulonephritis.

### ■ INTRODUCTION

Pauci-immune necrotising glomerulonephritis (PING) with extracapillary proliferation is the renal anatomopathological expression of systemic vasculitis. This disease typically affects small to medium-size blood vessels and is commonly associated with the presence of antineutrophil cytoplasmic antibodies (ANCAs)<sup>1</sup>. The pathogenesis of systemic vasculitis is unknown, although it involves genetic and environmental factors<sup>2,3</sup>. The literature describes different associations of familial vasculitis<sup>4,5</sup>. We report the presence of necrotising glomerulonephritis in two siblings.

### ■ CASE 1

A 63 year-old male shepherd from a rural environment. In August 1988 he presented at our hospital with poor general health, asthenia, anorexia, and nausea, a metallic taste in his mouth, weight loss and general leg pain. His medical history was marked by hoacusia from childhood, attributed to measles.

On physical examination, patient's BP was 170/90 mmHg, with pale skin and mucosas. Cardiac auscultation showed 80 bpm and regular rhythm with holosystolic murmur. Lung auscultation was normal. His abdomen was tender to palpation in the epigastric area and he had an enlarged liver, two fingers wide. Lower extremities showed oedema up

to the knee. Neurological examination revealed sensory-motor disturbance in the distal two-thirds of both lower limbs.

Blood analysis on admission: Creatinine 28 mg/dl, Na 140 mEq/L, K 9.7 mEq/l, pH 7.14, pCO<sub>2</sub> 20.7 mmHg, bicarbonate 7 mEq/l, haemoglobin 9.2 g/dl, haematocrit 28%, leucocytes 15800.

Chest X-ray revealed bi-basal bronchiectasis.

Ultrasound scan showed kidneys were 11 cm in size, with no dilation. Abdominal ultrasound revealed a mass in the right liver lobe; further tests diagnosed a hydatid cyst.

A kidney biopsy was performed through lumbotomy. Histological examination revealed necrotising vasculitis of medium-sized arteries with extracapillary proliferative glomerulonephritis, which affected over 90% of the glomeruli, with 70% of them presenting total sclerosis.

The patient was oligoanuric at admission making haemodialysis necessary. Electromyogram showed moderate motor and sensory demyelinating axonal neuropathy.

Vasculitis was treated with steroids (prednisone 1mg/kg/day) and oral cyclophosphamide (100mg/day). The patient's general condition and neuropathy improved with this treatment. Kidney function did not recover, so patient was enrolled in chronic haemodialysis. In 1991 he was admitted with respiratory disease. The first determination of ANCA was made in 1995, with negative results. In 2003 the patient died due to progressive deterioration in his general health.

## ■ CASE 2

A 72 year-old male farmer from a rural environment. He presented at our hospital in April 2004 with poor general health, cough, expectoration, asthenia and anorexia. On reviewing his family history, it was found he was a sibling of Case 1.

His parents had died of old age; he had two siblings with type 2 diabetes mellitus, one of whom had a history of lung tuberculosis.

Physical examination showed markedly pale skin and mucosas. Cardiac auscultation showed 120 bpm and a regular rhythm with a panfocal systolic murmur. Lung auscultation revealed left basal crepitus. There was foveal oedema of the lower limbs. The rest of the examination was normal.

Blood analysis was as follows. Creatinine, 1.8 mg/dl, Na 139 mEq/L, K 4.4 mEq/L, haemoglobin 9.6 g/dl, haematocrit 28.3%, leucocytes 10070. Albumin 2.6 g/dl, total proteins 5.8 g/dl, ferritin 539 ng/ml. Serology for virus B, C and HIV was negative.

Urinary sediment: micro-haematuria, leucocyturia and hyaline-granular cylinders. Proteinuria was 1.72 g/day.

Immune assays were positive for ANCA with pattern p-ANCA (Anti MPO positive titration 442 U/ml with ELISA method, Anti-PR<sub>3</sub> negative), Anti-MBG negative, ANA positive, Reactive C protein 10.6 mg/dl. Other immunology tests were normal.

Determination of thyroid hormones was as follows. TSH 14.75 µIU/mL (RV: 0.4-5), free T<sub>4</sub> 8.88 pmol/L (RV:11-23) and anti-thyroid antibodies 115 IU/mL (RV: 0-50).

X-ray on admission revealed an increase in patchy density. Chest CAT scan showed bilateral basal bronchiectasis, pleural leaks and parenchymatous condensation. Bronchoscopy was normal and a trans-bronchial biopsy showed unspecified mild chronic inflammation without granuloma.

An ultra-sound guided kidney biopsy was performed, with the following results: 13 glomeruli were seen, one completely necrotised. Crescent formations were seen in two other glomeruli. In addition, several focal and segmented necrotising lesions were identified in several glomeruli. There was interstitial patchy lymphocytic infiltrate. Immunofluorescence was negative.

Steroid treatment was begun (6-methyl-prednisolone bolus IV 1g/day for three days, followed by oral steroids in tapered doses) and a monthly 1g IV bolus of cyclophosphamide was administered for 6 months followed by maintenance treatment with mycophenolate mofetil, 500 mg/12h. With this treatment the patient improved clinically and the ANCA's were negative in three months.

The last check-up in January 2007 showed an asymptomatic patient, with stable kidney function; serum creatinine 1.7 mg/dl, CrC 40 ml/min and proteinuria 1.19 g/day.

## ■ DISCUSSION

Pauci-immune necrotising glomerulonephritis with extracapillary proliferation is the renal anatomopathological expression of systemic vasculitis. These diseases are characterised by inflammation of small to medium-sized blood vessels. They include Wegener's granulomatosis (WG), microscopic polyangiitis (PAM), Churg-Strauss syndrome or vasculitis limited to the kidney<sup>1</sup>.

Its aetiopathogenesis is unknown. It has been suggested that genetic factors may contribute to its genesis, since it can affect several members of the same family<sup>2</sup>. The literature describes familial cases of WG<sup>4,6</sup>, PAM<sup>7</sup> and vasculitis affecting large vessels<sup>8</sup>, with different presentations in different family members. In WG, the most frequent familial link seen is between siblings<sup>4,9</sup>, although mother-daughter<sup>10</sup> and father-daughter<sup>11</sup> cases have also been described. Some cases of PAM have been seen affecting identical HLA siblings<sup>12</sup> as well as father-son cases<sup>7</sup>. We reported two cases of necrotising glomerulonephritis as a renal manifestation of systemic vasculitis in two siblings, with the disease starting in the second after the first had died. The presence of the same disease in two siblings adds further support to the theory of a genetic component in the aetiopathogenesis of vasculitis.

That is why some researchers have tried to find an association between vasculitis and HLA genes<sup>2</sup>. In our cases, as the disease appeared in the second sibling after the first had already died, we do not have the HLA run from the first patient to compare with. Recent studies have found a positive association with DR1 HLA, especially in patients with WG, and negative associations with DR3 HLA, especially in Churg-Strauss granulomatosis and polyarteritis nodosa<sup>2,13</sup>. Our patient presented haplotype A1, B8 B35 Cw4 Cw7 DR3 and DR5 DQ2.

Due to possible genetic participation in the pathogenesis of vasculitis, it would be interesting to carry

out genetic testing in patients affected with vasculitis, since the disease can appear in other family members at a later date, as in the two cases we report. This could help improve our knowledge of these diseases.

It has also been suggested that environmental factors in genetically-predisposed individuals could contribute to the development of these diseases<sup>3</sup>. Some studies hint at an increase in the incidence of WG in the north of Europe<sup>14</sup>, whereas PAM is more common in the south of Europe<sup>15</sup>. However, another Swedish study found a ratio of PAM (79%) versus WG (21%) in patients admitted to a Nephrology Unit<sup>16</sup>. In our cases, the siblings came from a rural environment, so there is a possibility that both patients may have been subject to the influence of the same environmental factor.

The strong association of ANCAs with small-vessel vasculitis suggests these antibodies may play a role in the pathogenesis of the disease<sup>17</sup>, although cases of vasculitis without the presence of ANCAs have been described<sup>18</sup>. In ANCA-positive vasculitis, these antibodies activate neutrophils through different mechanisms, causing neutrophil and endothelial cell apoptosis and necrosis<sup>17</sup>. In ANCA-negative vasculitis the presence of neutrophils in the lesions occurs independently of ANCAs, and can be due to other unidentified antibodies or T cell-dependent mechanisms<sup>19</sup>.

Davies *et al*<sup>20</sup> described in 1982 the presence of cytoplasm-specific antibodies in IgG-class neutrophils in eight Australian patients with necrotising segmented glomerulonephritis. In 1985, ANCAs were reported for the first time in patients with WG and other small-vessel vasculitis<sup>21</sup>.

Advances in the knowledge of ANCAs have allowed us to distinguish between C-ANCA (which react against proteinase 3), frequently associated to WG, and P-ANCA (which react against myeloperoxidase), and which are present especially in patients with PAM<sup>18,22</sup>.

The positivity and pattern of ANCAs, in addition to helping diagnose and determine the type of vasculitis, are very useful as serologic markers of activity. In 1988, when our Case 1 presented, we were not yet able to determine ANCAs in our hospital, so the diagnosis was established based on kidney biopsy.

The first ANCA determination performed on Case 1 was in 1995, and it was negative (but the patient had already received treatment).

In Case 2, in addition to elevated P-ANCAs, auto-immune subclinical hypothyroidism was detected, which was positive to antithyropoxidase antibodies, suggesting the participation of an autoimmune mechanism in the aetiopathogeny of vasculitis.

Although we do not know whether ANCAs would have been detected or not in Case 1, the similarity between the symptoms in both siblings, including acute kidney failure with pauci-immune necrotising glomerulonephritis seen in renal histology and lung bronchiectasis, the positive ANCAs in Case 2 make it reasonable to suggest that the first patient might also have been positive for ANCAs.

In conclusion, with the description of two cases of necrotising glomerulonephritis in two siblings from the same environment, antibodies in one of them would support the hypothesis of the influence of environmental factors in genetically predisposed individuals and its association with autoimmune mechanisms in the aetiopathogeny of vasculitis. In order to clarify the possible relationship of HLA genes with vasculitis, it would be interesting to know the HLA run of affected patients, given the possibility of a later diagnosis in other members of the family, as in the two cases presented here.

**Conflict of interest statement.** None declared.

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