Lessons to be learned from patients with vasculitis

J. Montoliu*, M. L. Amoedo, M. J. Panadés and J. Ramos

Nephrology and Pathology Services, Hospital Universitari Arnau de Vilanova and Department of Medicine, Universitat de Lleida, Lleida, Catalonia, Spain

Introduction

The classification of vasculitis has traditionally been a conflicting subject. Several classifications gained wide acceptance [1], and recently, a consensus was reached at the Chapel Hill Conference [2] and the classification derived from it is generally regarded as appropriate for clinical and histological purposes. However, exceptions to the rule do exist, and some patients with vasculitis have atypical or overlapping features. In this paper we describe three such patients. Our goal is to remind clinical nephrologists of the wide range of manifestations that vasculitic patients can have.

Case 1

A 70-year-old man was admitted to the hospital with a 2-week history of bilateral temporal headache and fever. The patient also complained of shoulder, hip, and ankle pain. There was no history of visual loss. Both temporal arteries were palpable and tender and the rest of the physical examination was unremarkable. Laboratory studies revealed: haemoglobin 11 g/dl, white blood cell count 12 000/mm³ (12 × 10⁹/l), with normal differential count, platelets 434 000/mm³, erythrocyte sedimentation rate (ESR) 113 mm/h, serum creatinine 159.2 µmol/l and serum protein concentration 69 g/l. Liver function tests, serum immunoglobulins and serum complement levels (C3 and C4) were normal. Antinuclear antibodies, rheumatoid factor, serum cryoglobulins, and hepatitis B surface antigen were negative. Sera were tested by indirect immunofluorescence on ethanol-fixed neutrophils for antineutrophil cytoplasmic antibodies (ANCA) and for antibodies against myeloperoxidase and proteinase 3 by enzyme-linked immunosorbent assay (ELISA) and both were negative. Urine showed a protein content of 980 g/24 h and 8 red cells per high-power field. A biopsy of the right temporal artery (Figure 1) showed changes consistent with temporal arteritis. A percutaneous renal biopsy was performed. On light-microscopy 10 glomeruli were available for observation. Four of them had a segmental necrotizing lesion with cellular proliferation and circumferential crescents (Figure 2). There was also an interstitial mononuclear infiltrate. There were no lesions of vasculitis in the...
renal vessels. Immunofluorescence was negative for IgG, IgA, IgM, C3, and C4. Fibrinogen was present in the crescent. No electron-microscopic study was performed.

After the temporal artery biopsy the patient was treated with prednisone (1 mg/kg/day), which induced complete resolution of his symptoms in 48 h. His renal function improved, with a decrease in serum creatinine to 106 μmol/l after a single cyclophosphamide dose. Protein disappeared from the urine and the urinalysis became normal. The erythrocyte sedimentation rate decreased gradually to 18 mm/h 2 months after beginning therapy and the patient is currently doing well on low-dose prednisone.

Comment on case 1

Temporal arteritis is classified as a large- vessel vasculitis [2]. It usually occurs in patients older than 50 years and is often associated with polymyalgia rheumatica. Renal manifestations are unusual and rarely mentioned in large series [2–6]. The association between necrotizing glomerulonephritis with extracapillary proliferation and temporal arteritis is extremely rare, although some cases have been reported [7–10]. To demonstrate this association it is necessary to be certain that the disease we are dealing with is actually temporal arteritis and not involvement of the temporal artery by another vasculitic process such as microscopic polyangiitis. Temporal arteritis has a predilection for the external carotid system, but single or multiple large and medium-sized arteries anywhere in the body can be affected, including the renal arteries, as has been demonstrated in autopsy studies [2]. However, patients with temporal artritis only rarely have clinical evidence of renal disease. Well-documented cases of glomerular involvement are even more unusual [7–11]. There are two reported cases of nephrotic syndrome, one of them caused by membranous nephropathy [12]. The existence of necrotizing glomerulonephritis with extracapillary proliferation suggests small-vessel vasculitis and implies some degree of overlap with simultaneous involvement of vessels of small and large size.

The key question is to differentiate whether we are confronted with temporal arteritis or another type of vasculitis with involvement of the temporal artery. In other words, some patients with arteritis of the temporal artery do not have the classical ‘temporal arteritis’ [13]. A diagnosis of temporal arteritis is based on the clinical picture, laboratory data that include absence of ANCA in serum [14], and consistent histopathological features such as lymphocytic and histiocytic inflammation of the vessel wall with or without giant cells or disruption of the elastic lamina [4,5,13]. In our case the temporal artery biopsy showed no fibrinoid necrosis or small-vessel vasculitis suggestive of necrotizing vasculitis, and there was a mononuclear infiltrate. The clinical and histopathological features fulfilled the criteria of the American College of Rheumatology for the diagnosis of temporal arteritis [5].

The absence of ANCA is another recognized characteristic of temporal arteritis [14–16], in contrast with their presence in other types of vasculitis. In our case, ANCA were negative, and moreover antigen specificity was sought after by determination of antibodies against proteinase 3 or myeloperoxidase, with negative results. These data also support a diagnosis of temporal arteritis. The response of our patient to therapy was excellent, as usually occurs in temporal arteritis.

Therefore we believe that this patient had temporal arteritis from the clinical and histological points of view. He also had simultaneous involvement of small-size vessels with necrotizing glomerulonephritis and extracapillary proliferation. Although we cannot establish accurately the pathogenic mechanism which links both processes, it seems that there are patients with temporal arteritis that present with features overlapping those of small-vessel vasculitis. We would like to remind clinical nephrologists that in cases of temporal arteritis and renal disease, renal biopsy may provide useful diagnostic information and serve as a guide for therapy. Further experience is needed to determine if this association is commoner than previously thought.

Case 2

An 80-year-old woman with a history of mild hypertension was admitted to the Hospital for investigation of renal failure. In July 1995 she was known to have a serum creatinine of 88.4 μmol/l. In September 1995 she had symptoms of cystitis and received norfloxacin 500 mg b.i.d. for 1 week. Two days after discontinuation of treatment her serum creatinine was found to be 274 μmol/l and she was admitted to the Hospital. Physical examination disclosed pallor and a blood pressure of 185/85 mmHg, but was otherwise unremarkable. There was no skin rash or purpura. Examination of the ear, nose, and throat was normal. Laboratory studies revealed haemoglobin 10.8 g/dl, white blood cell count 8100/mm³, with normal differential and no eosinophilia. The urine contained 0.8 g protein/24 h, 5–10 red blood cells and 20–25 white blood cells per high-power field. Eosinophils were identified in the urine sediment after Wright’s staining. Ultrasonography showed normal-sized kidneys and no hydronephrosis. A chest X-ray was normal. Antinuclear antibodies and serum complement levels (C3 and C4) were negative and within normal limits respectively. However, serum ANCA were found to be positive with a cytoplasmic pattern (c-ANCA). Serum antiproteinase levels were 108 (normal values 0–10 μ/ml). The patient’s serum creatinine peaked at 539 μmol/l 2 months after norfloxacin had been discontinued and serum antiproteinase values ranged from 100 to 125 μ/ml. A percutaneous renal biopsy was then performed. On light-microscopy 20 glomeruli were available for observation. All of them had a normal appearance (Figure 3). No necrosis or extracapillary proliferation were seen. Similarly, the renal vessels present in the biopsy specimen were essentially normal.
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nephritis associated with c-ANCA and in the absence
of vasculitic lesions was made. The patient was treated
with methylprednisolone 1 g i.v. for 3 consecutive days
followed by prednisone 1 mg/kg/day for 1 month.
Steroids were then tapered off and discontinued after
2 months. Cyclophosphamide 800 mg i.v. was also
given from the start of treatment and repeated at
monthly intervals for 8 months. With that treatment,
serum creatinine decreased initially to 292 μmol/l but
later on increased again progressively, and is now
486 μmol/l. Despite cyclophosphamide administration,
serum antiproteinase 3 levels have remained consist-
ently above 100, ranging from 105 to 132 u/ml.

Comment on case 2

Renal vasculitis associated with ciprofloxacin has been
reported in two patients [17]. Both of them had
interstitial nephritis with acute renal failure. In one of
them coexisted necrotizing glomerulitis and in the other
necrotizing arteritis with normal glomeruli. Serum
ANCA were negative in the first patient and positive
with a perinuclear pattern in the second. In both
patients, renal function improved after discontinuation
of the antibiotic and institution of immunosuppressivestudy was performed. A diagnosis of acute interstitial
without fibrinoid necrosis, disruption of the vessel wall
or perivascular inflammation. (Figure 4). A diffuse
interstitial infiltrate was present, made up of mono-
nuclear and plasma cells. Abundant eosinophils were
present in the infiltrate (Figure 5). No granulomas
were seen. Immunofluorescence was negative for IgG,
IgA, IgM, C3, and fibrinogen. No electron-microscopic
study was performed. A diagnosis of acute interstitial

Fig. 3. Case 2. Normal-appearing glomerulus. (PAS × 400).

Fig. 4. Case 2. Renal vessels showing no necrosis or perivascular
inflammation (PAS × 400).

Fig. 5. Case 2. Interstitial inflammatory infiltrate made up of mono-
nuclear and plasma cells. Eosinophils can also be seen. (H&E × 400).

On the other hand, ciprofloxacin can induce acute
interstitial nephritis unrelated to vasculitis and with
negative ANCA [21,22]. In our patient, we propose
that acute interstitial nephritis was the only manifesta-
tion of norfloxacin-induced and c-ANCA-associated
vasculitis. However, the persistence of high levels of
antiproteinase 3 antibodies in spite of discontinuation
of the antibiotic and intensive cyclophosphamide treat-
ment remains to be clarified, and it is also possible
that the persistence of ANCA is unrelated to the
antibiotic. The origin of interstitial nephritis as the
only manifestation of vasculitis has been attributed to
peritubular capillaritis resulting exclusively in inter-
stitial inflammation and sparing larger vessels and
glomeruli [23]. In a similar way, in Wegener’s granulo-
matisis severe necrotizing capillaritis of the vasa recta
of the papilla may occur and lead to papillary
necrosis. [24].

Case 3

A 67-year-old woman sought medical advice in March
1996 because of fatigue. A physician found anaemia
(haemoglobin 8.1 g/l), a serum creatinine of
115 μmol/l, and a normal urine sediment with no
proteinuria. No specific treatment was given. Six weeks
later she was admitted to the hospital with increasing
fatigue, breathlessness, and declining urine output.
There was no history of haemoptysis. On admission
blood pressure was 165/95 mmHg, heart rate 110/min, respiratory rate 18/min, and she was afebrile. The skin was pale but there were no skin lesions. There was jugular venous distension at 45°. Examination of the chest revealed a grade 2/6 holosystolic murmur and bibasilar rales. The abdomen and the neurological examination were negative. The rest of the physical examination was non-contributory.

Laboratory studies showed haemoglobin 7 g/dl, white blood cell count 10 600/mm³ with normal differential, platelet count 516 000/mm³, serum creatinine 787 µmol/l, serum sodium 138 mmol/l, serum potassium 5.4 mmol/l. Arterial blood gases were as follows: ph 7.38, pCO₂ 3.6 kPa (to convert to traditional units multiply by 7.50), pO₂ 10.9 kPa (to convert to traditional units multiply by 7.50) and bicarbonate 26 mmol/l. The urine contained 8–10 red blood cells per high-power field and 151 mg of protein per 24 h. Creatinine clearance was 4 ml/min. An ECG showed normal sinus rhythm at a rate of 110/min a right bundle branch block and peaked T waves. The chest X ray disclosed cardiomegaly, cephalization of blood flow, Kerley B lines and small bilateral pleural effusions. Sera was obtained for further laboratory studies and haemodialysis immediately instituted via a subclavian catheter. Ultrasonography showed normal sized kidneys with no hydronephrosis Hepatitis B surface antigen, antibodies to hepatitis C virus, antinuclear antibodies and serum cyoglobulins were negative, and serum complement components were within the normal range. However, ANCA were positive in serum, with a perinuclear pattern (p-ANCA) and an antimeylperoxidase titre of 24 u/ml (normal <10). At the same time antilysosomal basement antibodies (determined by ELISA) were consistently positive in serum at high titres (222 u/ml and 217 u/ml in 2 consecutive days). Methylprednisolone 1 g i.v. for 3 consecutive days and a single 800-mg cyclophosphamide i.v. dose were administered, and a percutaneous renal biopsy performed. On light-microscopy there was extensive extra-capillary proliferation in 90% of glomeruli, the crescents were very cellular, contained mitoses, and were accompanied by zones of necrotizing glomerulitis in most glomeruli (Figure 6). In addition, many small and medium-sized vessels showed marked fibrinoid necrosis and perivascular inflammation (Figure 7). Moreover, granulomas composed of epithelioid and giant cells and areas of necrosis were found throughout the renal parenchyma, sometimes surrounding necrotic vessels or glomeruli with crescents and necrotizing glomerulitis (Figure 8). Most unfortunately, no immunofluorescence study could be done for technical reasons. Twice-weekly plasmapheresis was added to the therapeutic regime for 1 month, and prednisone given at a dose of 1.5 mg/kg/day. With that, serum ANCA became negative after 2 months and anti-GBM antibodies have progressively declined (115, 7, 10, 17 and 19 u/ml at 1, 2, 3, 4, and 5 months of follow-up respectively) The patient has been followed now for 5 months. She has not recovered renal function and has entered a chronic haemodialysis programme, where she is clinically stable and has never had any episode of haemoptysis. After resolution of the initial pulmonary oedema, no pulmonary lesions have appeared in serial chest X rays and CT scans. Detailed evaluation by an ENT consultant has failed to show any
abnormality in the upper respiratory airways, ear, nose, or sinuses. During this time the patient has been receiving monthly cyclophosphamide doses. Serum ANCA remained negative at the most recent follow up.

Comment on case 3

This patient can be diagnosed as suffering from anti-glomerular basement disease on the basis of high titre circulating anti-GBM antibodies that were consistently present early in the course of the disease. Circulating anti-GBM antibodies are the gold standard for the diagnosis of anti-GBM disease, because of their high sensitivity and specificity. A linear pattern in the immunofluorescence study of the renal biopsy would also have been helpful, but unfortunately could not be done in this case. Despite this, we believe the diagnosis of anti-GBM disease can be made with a more than reasonable degree of certainty. In this case ANCA coincided with anti-GBM antibodies. It has recently been shown that ANCA are present in approximately 20–30% of patients with anti-GBM disease [25–30]. These patients tend to be considerably older than those with anti-GBM disease alone [26] and ANCA show antigen specificity against myeloperoxidase, as in our case, in 75% of patients. Other clinical features that have been claimed for this group of patients with the ‘double antibody syndrome’ include the possibility of late recovery of renal function [26,30] and a worse prognosis for those with higher anti-GBM antibody titres than for those with relatively higher ANCA levels [30]. However, the clinical significance of this association is still not completely understood at the moment. The pathogenetic mechanism leading to this ‘double antibody syndrome’ is purely speculative, but it has been suggested that these patients have vasculitis that damages the kidney, which releases basement membrane and then secondary anti-GBM antibodies are formed [30].

Another interesting feature in this case was the abundant presence of granulomas in the kidney, surrounding vessels and glomeruli. This initially suggested Wegener’s granulomatosis, but no evidence whatsoever of pulmonary or upper airway involvement ever developed throughout this patient’s clinical course, and therefore we believe this diagnosis cannot be made. Moreover, granulomatous vasculitis can exist in microscopic polyangiitis, involving vessels or glomeruli [24,31]. Thus granulomas are seen not only in Wegener’s granulomatosis but also in other forms of vasculitis affecting the kidney, including microscopic polyangiitis. Multinucleated giant cells have also been reported in antiglomerular basement membrane disease [32] and have been suggested to be of the of the macrophage–monocyte lineage because of their CD68 positivity. Immunostaining in the case reported by Ito and co-workers [32] showed intense staining of interleukin-6(IL-6) in all kidney sites involving multinucleated cells, crescents, tubules and infiltrating cells, suggesting that the kidney itself might be the source of the systemically elevated levels of IL-6.

References


