Interesting Case

Head or tail?

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Introduction

Vasculitis is an inflammation of the blood vessel walls of any type and in any organ. It is currently classified on the basis of the predominant vessel affected (large, medium, small). Both large- and small-vessel vasculitis may involve medium-sized arteries, but only small-vessel vasculitis will affect vessels smaller than arterioles [1].

Vasculitis must be recognized early for treatment to be successful. Left untreated, acute vasculitis can cause major long-term morbidity, such as end-stage renal failure, and death from major organ failure. However, tracing the vasculitis to a specific entity may be difficult because signs and symptoms are variable and protean and a variety of vasculitides may share the same histological findings.

Some vasculitides may be categorized by the presence of specific antibodies. Myeloperoxidase-antineutrophilic cytoplasmic antibody (MPO-ANCA) is highly specific for small-vessel vasculitis. When systemic disease is present, its sensitivity is ~90%, and its specificity even higher. However, over-reliance on ANCA may be hazardous, and histology is warranted for final diagnosis and for determination of disease activity.

Giant cell arteritis (GCA) is a granulomatous inflammation of large- and medium-sized arteries. New-onset headache, symptoms beginning at age 50 or older, erythrocyte sedimentation rate (ESR) over 50 mm/h, temporal artery tenderness and evidence of arteritis on temporal biopsy are the main diagnostic criteria [2]; the presence of any three or more criteria has a sensitivity of 93.5% and a specificity of 91.2%. Although GCA is recognized as a systemic illness, renal involvement is very uncommon. There are reports of normal renal function with occasional haematuria, red cell casts and minimal proteinuria [3]. Even more rare is an overlap or association of classic GCA and another form of systemic vasculitis.

We describe a patient with biopsy-proven GCA and ANCA-associated microscopic polyangiitis (MPA). The presence of linear glomerular basement membrane (GBM) deposits and serum anti-GBM antibodies during the course of MPA is noteworthy.

Case

A 54-year-old male was hospitalized because of fever up to 38°C of 1 month’s duration accompanied by night sweats, headache, loss of appetite with a 10 kg weight loss, and generalized weakness.

The patient immigrated from Russia at the age of 14 years. He had been a heavy smoker (60 packs/year) until 2 years previously. He did not drink alcohol or use illicit drugs. Two years before presentation he had undergone omentopexy for a perforated duodenal ulcer.

On physical examination, the patient appeared cachectic but in general good health. Weight was 58 kg, height 182 cm; blood pressure and pulse were normal. The neck was supple, and there was no tenderness over the sinuses or temporal arteries. Heart sounds and lung examination were normal. The liver was palpable 2 cm below the costal margin, and the tip of the spleen was palpable. No eruption or splinter haemorrhages were noted. Neurological and ophthalmologic examinations revealed no abnormalities.

Laboratory data showed an increased ESR (110 mm/h), leukocytosis (11 200 μl) with normal differential count, mild normocytic normochromic anaemia (haemoglobin 10.7 g/dl) and thrombocytosis (525 000 μl). Liver enzymes, kidney function tests and urinalysis were within normal limits.

An infectious disease or neoplastic disorder was suspected on the basis of the clinical presentation.

Blood culture and acid-fast staining of sputum, urine and gastric lavage were negative. Serology for human immunodeficiency virus, cytomegalovirus and Brucella was negative. Chest X-ray, abdominal ultrasound
and computed tomography were non-contributory. Computed tomography and magnetic resonance imaging of the head and cerebrospinal fluid examination were normal.

During the next 3 weeks, the fever persisted, accompanied by severe headache, and the patient lost another 3 kg. Serum haemoglobin dropped to 7.5 g/dl, and albumin level decreased from 3.1 to 2.1 g/dl. Serum immunoelectrophoresis showed polyclonal hyperglobulinaemia. Serum creatinine levels remained normal (0.9 mg/dl). Urinalysis showed 3–4 red blood cells (10 000 ml), 1–2 granular casts per high-power field and proteinuria on dipstick +2. Daily protein excretion was 0.5 g, and electrophoresis showed non-selective proteinuria. Temporal artery biopsy revealed no abnormality. Serum levels of ANA, anti-dsDNA, C3 and C4 were normal. Test for ANCA was positive with a perinuclear pattern of staining (P-ANCA). Anti-MPO titre (tested by ELISA using a kit manufactured by Euro-Diagnostica, Malmö, Sweden) was 176 EU (normal 0–20 EU). Anti-PR3 titre was normal (tested with a kit manufactured by the same company). Anti-GBM with specificity for the NC1 domain of the alpha-3 chain of type IV collagen was within the normal range (tested by ELISA using a kit manufactured by BL-Diagnostica GmbH, Mainz, Germany).

The clinical presentation of fever, headache and anaemia was suggestive of GCA, and the severe weight loss and relatively young age, although unusual, was still consistent with this diagnosis. However, a positive MPO-ANCA is very unusual in GCA, but it is characteristic of ANCA-associated vasculitis [4]. Headache due to the temporal and cranial arteritis has been reported in various vasculitides, but its combination with the kidney involvement is uncommon.

A contralateral temporal artery biopsy showed changes typical of GCA (Figure 1). Treatment with prednisone 1 mg/kg/day was initiated. The fever and headache disappeared promptly, and the patient reported feeling better. However, during the next week, serum creatinine increased to 2.5 mg/dl, and urinalysis revealed an active nephritic sediment with numerous dysmorphic red blood cells (50 000/ml), red blood cells and granular casts. Kidney biopsy showed crescentic glomerulonephritis (Figure 2) in 11 out of 14 glomeruli. Immunofluorescence showed faint linear deposits of IgG and IgM along the GBM. No electron-dense deposits were observed on electron microscopy. The renal pathology was consistent with acute vasculitic (pauci-immune) glomerulonephritis, MPA type. On repeated testing, anti-GBM was 138 IU/ml (normal range 0–20 IU/ml).

Treatment with pulse methylprednisone 1 g/day for 3 days and intravenous cyclophosphamide 900 mg in a single dose was initiated, followed by prednisone 60 mg/day and oral cyclophosphamide 100 mg/day, 1 month later. During the next 2 months, the creatinine level rose to 4 mg/dl, and then decreased and stabilized at 1.7 mg/dl. Urinalysis showed mild improvement in the sediment: no casts, 5–7 red blood cells per high-power field (15 000/ml) and proteinuria q1. Levels of MPO-ANCA and anti-GBM gradually returned to normal.

One year later, cyclophosphamide treatment was interrupted. The patient remained in good health, the creatinine level remained unchanged, and the nephritic sediment disappeared.

Discussion

We describe an unusual case of MPA with kidney involvement preceded by biopsy-proven GCA.

GCA is a granulomatous inflammation of large- and medium-sized arteries. Because of the focal segmental nature of the inflammatory process, ~35–40% of all positive biopsies do not show giant cells. Only a minority of patients with GCA have renal involvement manifested as minimal proteinuria, occasional haematuria and red cell casts. Renal pathological study usually reveals no gross glomerular or larger vessel disease [3]. Vascular involvement of the kidney has

Fig. 1. Temporal artery showing intimal thickening and fragmentation of internal elastic layer accompanied by lymphohistiocytic infiltrate and a single multinucleated giant cell (arrow) (haematoxylin and eosin, ×40).

Fig. 2. Renal biopsy showing crescentic glomerulonephritis with necrotizing changes and interstitial inflammation. No vasculitis is observed in the blood vessels (haematoxylin and eosin, ×200).
been reported in some cases in GCA—usually necropsy studies—with giant-cell infiltrates and arteritis of the renal arteries. Some of the affected patients developed renal failure and some were asymptomatic [4]. Other pathological findings were focal segmental necrotizing glomerulonephritis with crescents and membranous glomerulonephritis [4,5].

The overlap of classic GCA and another form of systemic vasculitis is rare, with no more than 40 documented cases to date. The most common form of vasculitis coexisting with GCA is MPA, followed by Wegener’s granulomatosis and Churg–Strauss syndrome.

The clinical picture of rapid-progressive glomerulonephritis, the pathological picture of crescentic glomerulonephritis, and the high titre of MPO-ANCA are diagnostic for MPA. Our literature review yielded only two reports of an association of MPA with GCA. O’Neill et al. [6] described a case of classic GCA and crescentic glomerulonephritis and vasculitis of small renal arteries and arterioles. However, they provided no data on the clinical course of the patient. Canton et al. [7] described a case similar to ours of biopsy-proven temporal arteritis which improved with steroid therapy but subsequently developed renal failure. Kidney biopsy showed crescentic glomerulonephritis and small-vessel vasculitis. Treatment with pulse steroids and cyclophosphamides led to normalization of renal function.

Remarkable in our case was the linear deposition of IgG and IgM along the GBM and the appearance of specific anti-GBM antibodies in the plasma. Approximately 8% of patients with ANCA-associated nephritis also have anti-GBM antibodies, and ~30% of patients with anti-GBM antibodies also have ANCA [8]. The relationship between these two antibodies is unclear. There may be primary production of both antibodies. Alternatively, an ANCA-vasculitis could be the primary disease, with renal damage leading to secondary anti-GBM formation.

The linear GBM deposits in the kidney in conjunction with the positive anti-GBM antibodies in the plasma in a patient with crescentic glomerulonephritis raised the possibility of Goodpasture’s syndrome. However, linear GBM deposits are not specific for Goodpasture’s syndrome and have been reported in association with rapid progressive glomerulonephritis of other causes as well, as with other conditions affecting the kidneys. In our patient the prominent constitutional symptoms (fever and weight loss), and the favourable renal response to immunosuppressive therapy only, are characteristic of systemic vasculitis. The clinical presentation and the temporal sequence of antibody appearance (initial negative serum level of anti-GBM antibodies which thereafter become positive) are consistent with ANCA-associated microscopic polyangiitis with coexistence (secondary formation) of anti-GBM antibodies.

To the best of our knowledge, this is the first reported case of an association between GCA and MPA with double positivity for MPO-ANCA and anti-GBM antibodies.

This case is a good reminder of the substantial overlap that exists in the clinical presentation of vasculitis. The term ‘polyangiitis overlap syndrome’ has been proposed, but this is not a unique entity. A thorough investigation of these cases is the key for getting as close as possible to a specific diagnosis and for guiding therapy.

Conflict of interest statement. None declared.

References


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