Case report

The transition of renal histopathology after immunosuppressive therapy in a woman with renal limited ANCA-associated vasculitis: a case report and literature review

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Received on July 27, 2015; accepted in revised form on October 26, 2015.

Clin Exp Rheumatol 2016; 34 (Suppl. 97): S115-S120.

Key words: antineutrophil cytoplasmic autoantibody, pauci-immune, necrotising vasculitis, glomerular crescent, renal histology

Competing interests: none declared.

ABSTRACT

Objective. *The kidneys are frequently involved in antineutrophil cytoplasmic autoantibody (ANCA) associated small-vessel vasculitis (AASVV). The pathological hallmark of ANCA-associated glomerulonephritis (AAGN) is a pauci-immune necrotising crescentic glomerulonephritis. The histopathology of AAGN may change during the course of the disease as a consequence of immunosuppressive therapy. Herein, we report the pathological evolution of a case of AAGN.*

Methods. *We report a female presented with renal-limited AASVV, hypocomplementaemia and nephrotic syndrome. The first renal biopsy revealed "crescentic" changes at presentation, but after treatment with immunosuppressive treatment, a second renal biopsy four years later showed "mixed" changes of AAGN and immune complex deposition mimicking a mesangial proliferative glomerulonephritis. A literature review was undertaken in order to understand these transformations and factors which determine the pathological transitions.*

Results. *AAGN is commonly described as a pauci-immune necrotising crescentic glomerulonephritis, but immune complex depositions have been frequently identified under electronic microscopy and is associated with greater levels of proteinuria. Acute lesions such as fibrinoid necrosis or glomerular crescent may completely disappear or reduce significantly after immunosuppressive therapy, but chronic changes may increase over time.*

Conclusion. *Based on our review and the illustration of this case, the initial histopathology of an AAGN and its active fibrinoid necrosis and cellular glomerular crescent may disappear or resolve after immunosuppressive therapy with resulting non-distinctive feature. Understanding the transition may facilitate the clinical diagnosis and provide further insight into this disease.*

Introduction

Antineutrophil cytoplasmic autoantibody (ANCA) associated small-vessel vasculitis (AASVV) is an autoimmune disease characterised by small-vessel inflammation and necrosis in presence of auto-antibodies targeting at proteinase 3 (PR3) or myeloperoxidase (MPO) (1). AASVV can virtually affect any organ in the body. When the kidneys are involved, it usually results in an ANCA-associated glomerulonephritis (AAGN). In AASVV, depending on the different cohorts studied, renal involvement is reported to have an incidence of about 70–100% (2, 3, 4, 5). Noticeably, the incidence rate of AAGN is mobile and may increase during the course of AASVV, with only 18% at first presentation, but could increase to 77% thereafter in garnulomatosis with polyangiitis, for instance (3). In AASVV, the presence of renal involvement is associated with greater patient morbidity and mortality (4, 5). AAGN typically manifests as a rapidly progressive glomerulonephritis (RPGN) characterised by pauci-immune necrotising GN with crescent formation (6). The European Vasculitis Studying Group (EUVAS) has developed a histopathological classification for AAGN to describe the different pattern and to predict renal survival. There are four histology classes: focal, crescentic, mixed, and sclerotic, with the ascending order of pathological hierarchy and descending likelihood of renal survival during the course of disease (7). The use of high-dose steroids and cyclophosphamide has significantly improved the prognosis and

kidney survival of AASVV (8). Serial histopathological studies revealed that resolution of acute lesions (particularly crescent and fibrinoid necrosis) and preservation of normal glomeruli are the basis of favourable renal outcome (7, 9, 10). Here, we have reported a case of a 37-year-old female with serum MPO-ANCA positive renal-limited vasculitis, and compare her clinical manifestation and renal histopathology before and after immunosuppressive treatment followed by a review of literature.

Case report

History and physical examination

A 37-year-old female first presented on June 17, 2010 with 2-month history of facial and bilateral lower-leg oedema. She was previously healthy and denied any ear, nose, throat or respiratory symptoms. There was no past history of any skin rash, photosensitivity, alopecia, arthralgia, fever, weight loss or other institutional symptoms. There was no reduction of her urinary volume. On examination, her blood pressure was 130/68 mmHg supine. There was moderate facial and bilateral lower leg oedema. The physical examination of her ear, ear, throat, lungs, heart, abdomen, central and peripheral nervous system were all normal.

Investigations

After admission, the blood routine test showed a haemoglobin level of 79g/L (120–150g/L), white blood cells(WBC) 4830/mm^3 (47.9% neutrophils), normal platelet count. Urinalysis revealed 3+ protein, 3+ blood; urine microscopy showed red blood cells (RBC) 3860/ul (0-15/ul), WBC 69 (0–17/ul), hyaline casts 18 /LP (0–1/low-power field). The serum creatinine level was 162 umol/L[eGFR(EPI)=34.6 min–1.73m^2]; the serum albumin level, 21.7g/L, liver functional tests were normal. The 24-hour urinary protein was 7290 mg. Serum C3 level was 0.35 g/L (0.8–1.5g/L), C4 level was 0.06 g/ L (0.1–0.4g/L), serum immunoglobulins (Ig) G, A and M were within normal range. The perinuclear ANCA [p-ANCA] was positive by indirect immunofluorescence (IIF) test. The titer of MPO-ANCA (ELISA) was 187RU/L (0–30RU/L). The anti-nuclear antibody and anti-double-strand DNA antibody were negative. The extractable nuclear antibodies, anticardiolipin antibody and rheumatoid factor were negative. Her chest x-ray was normal.

She underwent her first renal biopsy 12 days after admission. The light microscopy (LM) showed 22 glomeruli. 7 of the 22 glomeruli contained large-cellular crescents, 4 with large cellular-fibrotic crescents, 3 global sclerotic glomeruli, 1 segmental sclerotic glomerulus, 4 glomeruli with segmental fibrinoid necrosis in the glomerular tuft, the other 7 glomeruli were with moderate to severe mesangial cellular and extracellular matrix proliferation (Table I). IF microscopy revealed granular deposition of 2+ IgM and 2+ C3 in the glomerular tufts and mesangial area, IgG, IgA, C4 and C1q were negative (Table II). There were moderate interstitial mononuclear cell infiltrate (30%) with mild interstitial fibrosis (10–20%) and tubular atrophy (10–20%) with no tubular necrosis (Table III). Electronic microscopy (EM) contained 4 glomeruli which showed a medium to moderate mesangial cellular proliferation and segmental endothelial proliferation. Electron-dense depositions were seen sporadically distributed in the mesangial, subepithelial and subendothelial areas. There was diffuse podocytic process effacement. The final diagnosis was a renal limited AAGN and nephrotic syndrome with feature of a pauci-immune crescentic glomerulonephritis with tuft necrosis and moderate mesangial proliferation and mild to moderate interstitial lesion.

Table I. Glomerular lesions in the first and second biopsies.

Histological parameter	First biopsy [glomerulus (%)]	Second biopsy [glomerulus (%)]
Crescentic glomeruli	11 (50)	0 (0)
Cellular crescent	11 (50)	0 (0)
Segmental sclerosis	1 (4.5)	4 (13.8)
Global sclerosis	3 (13.6)	12 (41.4)
Mesangial proliferative glomeruli	7 (31.8)	17 (58.6)
Glomeruli affected	22 (100)	29 (100)

Table II. Immunofluorescence in the first and second biopsies.

Immunofluorescence[a]	First biopsy	Second biopsy
IgA	—	±
IgG	—	2+
IgM	2+	1+
C1q	—	1-2+
C3	2+	1+

[a]On a scale of 0 to 4+.

Table III. Tubular interstitial lesions in the first and second biopsies.

Histological parameter	First biopsy (% of total area)	Second biopsy (% of total area)
Infiltrates	30	30-40
Fibrosis	10-20	20
Tubular atrophy	10-20	10-20
Tubular necrosis	0	0

Treatment and disease evolution

The patient was given 500 mg pulse intravenous (*i.v.*) methylprednisolone(MP) over three consecutive days followed by a pulse of 600 mg(10 mg/kg of body weight) *i.v.* cyclophosphamide (CYC) and started on oral prednisone at 60 mg/day and valsartan. The same *i.v.* regimen was repeated 2 weeks later. Thereafter, she continued to receive *i.v.* CYC 500 mg(8.3mg/kg of body weight) fortnightly until she reached a cumulative dose of 7,200 mg at 9 month when she complained of irregular period and the CYC was stopped.

She refused to take trimethoprim/sulphamethoxazole throughout the course for fear of anaphylaxis and its potential risk of inducing crystalline-related kidney injury, especially during aciduria. The prednisolone was tapered slowly after 2 months until a maintenance dose of 10 mg/day prednisone was given at month 7. Her serum P-ANCA became negative, C3, C4 and serum albumin were normalised after 3 months. The serum creatinine fell to 72–86 umol/L within 4 months. The 24hr urine protein reduced to 1500-2200 mg in 6 months and remained so for a long period. 31 months later, in January 2013, when she was taking 10 mg prednisolone and 160 mg valsartan, her serum P-ANCA became positive again without increase in proteinuria, mycophenolate mofetil (MMF) 500 mg twice daily was added. On June 2014, four year after disease onset, her serum creatinine was 73 umol/L but her 24-hour urinary protein reached 2408 mg, MPO-ANCA titer was 173 RU/L (ELISA), PRO-ANCA 14.5 RU/L (0-130 RU/L). In the following 5 months, her 24-hour urinary protein had further increased to 6220mg, serum creatinine increased from 85 to 102 umol/L, serum C3 level has reduced from 0.81 to 0.61g/L (0.8–1.5g/L), serum C4 was 0.1g/L (0.1–0.4g/L). Consequently, she underwent a second renal biopsy.

Renal histology in the second biopsy

The LM revealed a total of 29 glomeruli. Table I showed some of the histological characteristic. 12 glomeruli were globally sclerotic (41.4%), 4 glomeruli with segmental sclerosis (13.8%). No cellular or fibrotic crescents were seen. The non-sclerosed glomeruli showed diffuse (58.6%) mesangial cellular and extracellular matrix proliferation with irregular thickening of basement membrane. There was no subepithelial or subendothelial eosinophilic substance deposition. IF showed granular deposition of 2+ IgG, 1+ IgM, 1+ C3, 1-2+ C1q and ± IgA in the mesangial, paramesangial area and capillary tufts (Table II). The blood vessels were normal. In the interstitial area, there were multifocal infiltration by lymphocytes (30-40%), focal tubular atrophy (10-20%) but no periglomerular fibrosis (Table III). 2 glomeruli were seen under EM. Minor electron-dense deposits were seen to be distributed sporadically in the mesangial, paramesangial and subepithelial area. There was diffuse podocytic process effacement. Granular degeneration was seen in the endothelial and tubular epithelial cells. The pathology of the second renal biopsy was compatible with a mesangial proliferative glomerulonephritis.

Management after second biopsy and response

The patient was given 500 mg pulse *i.v.* MP over three consecutive days and 600mg(around 10mg/kg of body weight) pulse *i.v.* CYC. The prednisolone dose was increased to 60 mg/day and then began to taper after 2 months by 5 mg every two weeks. A further. 600 mg pulse *i.v.* CYC was given every fortnight until a dose of 5,800 mg was reached. 3 months after treatment, her serum C3 has normalised (0.95g/L). Her 24-hour urine protein fell to 750 mg and serum creatinine fell to 75-89 umol/L at month 5. At month 7, she suffered from one episode of moderate acute bronchopneumonia and was cured with ten-day oral amoxicillin and clavulanate potassium tablets. At month 8, her MPO-ANCA titer was 46.1RU/L (0–30 RU/L). Concerned about the cumulative side effects of cyclophosphamide, and in light of early signs of primary drug-induced immune suppression, one single dose of 600 mg rituximab was introduced (roughly equal to 375 mg/m^2/body surface area) as a maintenance therapy in addition to 5 mg prednisolone. The regimen was well tolerated and her blood CD19+ cell (a standard surrogate for B cell in practice) was found to be fully depleted in month 10 without adverse event, and the 5 mg prednisolone was discontinued then. In reference of literature experience (11), a repeat course of 600 mg rituximab is planned after four months of initial dose in order to prevent B cell repopulation and disease progression.

Discussion

AASVV is a systemic disease that can affect ear, nose, throat, the lungs, the kidneys, the heart, the digestive system, the nervous system, the eyes, the skin and rarely other organs (12). Generally, it is divided into three clinicopathological entities: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), eosinophilic GPA (formerly known as Churg-Strauss syndrome). Renal limited AASVV refers to kidney involvement only without extra-renal manifestations. It is reported to occur more frequently in the presence of MPO-ANCA (13), such as in our case. Clinically, patients with AAGN often present as RPGN, but syndromes of acute nephritis or asymptomatic haematuria and proteinuria may also occur (14). Often the proteinuria is of sub-nephrotic range, between 2–3 g/day, but some patients might have as little as 0–0.5g/day, or as much as 7.35–20g/day (14, 15).

Renal biopsy is the gold standard to make a diagnosis of AAGN (14, 16) and to evaluate disease activity and to facilitate treatment decision (9, 17). Once the treatment decision is made, it is normal practice to use serum creatinine and urine protein level and autoantibody as indicators of response and disease activity. Repeat biopsies are mainly performed at the indications of disease relapse or unexplained serum creatinine increase to provide practical information (18).

AAGN is characterised histologically by fibrinoid necrosis of capillary loops, extracapillary proliferation with crescent formation, periglomerular and interstitial inflammatory cellular infiltrates. However, glomerular fibrinoid necrosis and crescent formation may not always exist concomitantly in a given biopsy specimen, they may appear distinctly in different phases of this disease (19). It is also accepted that these histological changes are not pathognomonic of AAGN, unless the ANCA is positive and there is a paucity of immune deposits in glomerulus. In 1990, Falk and Jennette (21) were first to define "pauci-immune deposit" as ≤2+ (on a 0 to 4+ scale) intensity for any Ig by IF, and an absence of deposition by EM. The predominant Ig deposition is IgM, whereas C3 is the main

complement factor. The weak deposition of Igs or complement components in the glomeruli was considered to be the result of passive trapping in the areas of injury (20), rather than caused by the vasculitis *per se*. Pauci-immune necrotising crescentic glomerulonephritis is widely regarded as a pathological "hallmark" of AAGN and which distinguishes itself from immune complex-mediated or anti-glomerular basement membrane antibody-mediated RPGN. Later on, however, other researchers once used <2+ intensity on a 0 to 3+ semi-quantitative scale (21, 22), or even ≤1+ on a 0 to 4+ scale (23) of immunostaining to define "pauci-immune deposit". But corresponding EM criteria of "pauci-immune deposit" were not identical, from total absence (23) to no more than 1 electron-dense deposit limited to mesangial fields and/or along glomerular basement membrane(either subendothelial, intramenbranous or subepithelial) (21, 22).

A number of subsequent studies reported that 2.2%(2 out of 93) (20) to 13.6% (8 out of 59) (24) of AAGN patients showed a >2+ (on a 0 to 4+ scale) Ig and/or complement deposition by IF. Using EM, a higher percentage (54%) of glomerular IC deposits has been found in ANCA-associated crescentic glomerulonephritis in a study (24). More IC deposition has seen observed where there is an overlap between an AAGN and an IC-related glomerular disease in the same patient such as IgA nephropathy, membranous nephropathy, or post-infectious glomerulonephritis (25-27). It is noteworthy that increased glomerular immune deposits are associated with a greater level of proteinuria and an unfavourable renal outcome (22). It is proposed that IC localisation could synergise with or potentiate the effect of ANCA to induce more intense inflammation, consequently more severe glomerular damage (24).

The role of complements in the pathogenesis of AASVV and AAGN has been demonstrated in animal model (28). It is now known that complement activation via alternative pathway play an important role in the development of AAGN in human (15). Hypocomplementaemia (defined as <0.9g/L) has been found in 20% (6 out of 30) of patients with AASVV in one series (21), and the intensity of complement activation is found positively associated with the severity of the renal pathology and correlated negatively with renal and patient survival. In another study, Yu and colleagues reported that amongst 74 Chinese patients with AAV and kidney involvement (proteinuria, haematuria or renal dysfunction), 23 (31%) of them had immune complex deposition (identified by the presence of electron-dense deposit under EM) in the compartment of glomerulus. And 15 (52.2%) of these 23 patients had low serum complement C3 levels(defined as ≤0.8g/L) (23). But the overall percentage of hypocomplementaemia among the patient group was not documented. The relative higher proportion of hypocomplementaemia is thought to be associated with local immune complex deposition and subsequent complement activation in the subgroup. Our case showed that the serum C3 level decreased during disease flare and returned to normal after partial remission was attained.

In 2010, EUVAS developed a histopathological classification for AAGN that includes four classes: focal, crescentic, mixed, and sclerotic, with the ascending order of pathological severity and descending sequence of renal survival after one to five years of observation (7). "Focal" subtype refers to ≥50% of normal glomeruli in the specimen; "crescentic" indicates ≥50% of the glomeruli have crescent formation; "sclerotic" means ≥50% of the glomeruli are globally sclerosed; "mixed" type is defined if <50% of glomeruli are normal, crescentic, or sclerosed. A number of validated studies indicated that "focal" class is associated with the best preservation of renal function; "crescentic" class has a favourable chance of renal recovery; whereas "mixed" and "sclerosed" classes are associated with an intermediate or high risk of progression to end-stage renal disease (ESRD) (7). Subsequent validation studies generally confirmed the predictive value for renal outcome of the classification system (29). However, slightly conflicting results are noted regarding crescentic and mixed classes, in which the renal outcome of patients with a crescentic class is worse or similar to that of patients with mixed class renal biopsies. The discrepancy is considered to be partially attributable to interobserver variability in the evaluation and classification of cellular, fibrocellular or fibrous crescents (30).

Since the 1970s, the use of glucocorticoid and cyclophosphamide has improved the prognosis of AASVV considerably (31, 32). The mainstay of treatment including the induction and maintenance therapies have been optimised after some major randomised controlled trials (16). AASVV is managed by stage- and activity-driven regimens, which aims to control disease activity and prevent progression. The induction therapy typically includes oral or *i.v.* pulse prednisolone in combination with oral or pulse cyclophosphamide (16). Steroid is usually tapered within 3–6 months after remission is achieved. After 3–6 months, to reduce toxicity, CYC is usually replaced with low dose azathioprine (AZA, 2 mg/kg/day), or methotrexate (20–25 mg/kg/week), or leflunomide (20–30 mg/day), or MMF (2000 mg/day), in conjunction with low dose prednisolone (usually 10mg or less/day) (16). The IMPROVE trial showed that MMF was less effective in comparison with AZA as a maintenance drug (33). The application of MMF, which is generally more costly than AZA, in our case did not curb or stop the recurrence or progression of renal disease, may remind caution of selection of agents in this setting. B-cell depleting agent, such as rituximab, has established as an effective treatment. The use of rituximab and glucocorticoid in combination have been shown to be comparable to glucocorticoid and CYC as induction therapy (34, 35) and to glucocorticoid and AZA as maintenance therapy (36, 37). Plasma exchange has a beneficial effect on renal survival, but it bears no significant effect on overall survival (38).

Here, we have reported a female with positive MPO-ANCA, low complements, kidney dysfunction and nephrotic syndrome and her subsequent course. Her initial renal biopsy was consistent with a pauci-immune crescentic glo-

merulonephritis and in the absence of any extra-renal involvement, the diagnosis of renal-limited AASVV was made. According to EUVAS classification, the first kidney biopsy and renal histopathology was a "crescentic" type as 50% (11/22) of the glomeruli contained cellular crescents (7). She responded well to initial therapy of steroid and CYC therapy.

The histopathology of the second biopsy four years later revealed no necrotising GN or crescents, but there was a greater proportion of chronic glomerular lesions: with 41.4% (12/29) of global sclerosis, 13.8% (4/29) segmental sclerosis. Only 20.7% (6/29) of the glomeruli were "normal"(without vasculitis lesions, capsular adhesion, or focal sclerosis) (7). IF microscopy revealed deposition of Ig and complement components in the mesangial, paramesangial area and glomerular capillary with an intensity less or equal to 2+(0 to 4 scale). By EUVAS criteria, the second biopsy was consistent with the "mixed" class of AAGN. The Igs and complement deposition in the glomeruli might have been trapped in the inflamed glomeruli during the disease course. The increased mesangial cellular and matrix proliferation might have resulted from stimulation of immune-complex and inflammation.

At first glance, the histopathology of second renal biopsy was consistent with a mesangial proliferative glomerulonephritis and global and segmental glomerulosclerosis but the same has been described in treated AASVV. Hauer *et al*. (39) reported the findings of repeat renal biopsies of 31 patients with treated AASVV, whereby the percentage of glomerular fibrinoid necrosis decreased from 22% to 8%, extracapillary proliferation decreased from 57% to 30%; but the proportion of sclerosed glomeruli increased from 12% to 39%. In another cohort whereby 14 patients of AASVV underwent a second renal biopsy after an average of 41.2±26.6 months, the chronicity scores increased significantly after given immunosuppressive therapy (20). In 2005, Neumann *et al*. reported a case series of 67 patients of AASVV, 24 of these patients underwent follow-up renal biopsies because of renal relapses or rising serum creatinine. The chronicity index in the follow-up biopsy increased significantly as a result of glomerular and tubular fibrosis. Interestingly, after immunosuppressive therapy, in the subgroup with rising serum (8 patients), there were no crescents or fibroid necrosis seen in the repeat biopsies, but slight intracapillary and mild mesangial cellular proliferation (40). Similar observations were noted in the protocol renal biopsies (regardless of relapse or stable AASVV) undertaken by Hruskova *et al*. (18). After a time interval of 11–28 months, the acute lesions including capillary necrosis and glomerular crescent were shown to reduce significantly whereas chronic changes increased in the second biopsies following immunosuppressive treatment.

The literature so far suggests that in AAGN, active lesions of fibroid necrosis or glomerular crescent may completely disappear or otherwise reduced significantly after immunosuppressive therapy, but replaced by chronic changes such as glomerular sclerosis, or interstitial fibrosis during the course of the disease (18, 20, 39-41). In our patient, her biopsy transformed from a "crescentic" type to a "mixed" pathological type after 4.5 years. The presence of chronic lesions such as glomerular sclerosis, mesangial matrix expansion, and tubular atrophy correlated positively with the amount of urinary protein excretion (40). Adequate maintenance immunosuppressive treatment is needed to prevent disease flare and to preserve functioning nephrons in any patient. The use of rituximab therapy in refractory and relapsing AASVV (11, 36, 37) is established. Whether rituximab may serve as a more superior maintenance therapy remains to be elucidated.

Conclusion

We have reported a case of a female patient with renal limited AAGN and positive MPO-ANCA, hypocomplementaemia, renal impairment and nephrotic syndrome. First renal biopsy showed features of "crescentic" type AAGN. After steroid and CYC treatment, the proteinuria fell significantly but rose again four years later, associated with elevated MPO-ANCA titer, hypocomplementaemia, nephrotic range proteinuria and impaired renal function once again. Repeat renal biopsy did not demonstrate any glomerular fibrinoid necrosis or crescent, but an increased proportion of sclerosis in glomerular and interstitial region, and IC deposition in the glomeruli, accompanied by increased mesangial proliferation that mimic mesangial proliferative glomerulonephritis. Upon literature review, these changes may follow the use of immunosuppressive treatment, and have been observed in AAGN during the chronic disease course.

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