CASE REPORT

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Idiopathic hypocomplementaemic interstitial nephritis treated with mycophenolic acid

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ABSTRACT

Interstitial nephritis with immune-complex deposits in the tubular basement membrane with minimal or no glomerular involvement is rare. In reported cases, hypocomplementaemia is consistently found.

Experience treating idiopathic hypocomplementaemic tubulointerstitial nephritis is limited to eleven reported cases. Most of them were treated with prednisone and only three received other immunosuppressants (cyclophosphamide in two).

We describe a case of idiopathic hypocomplementaemic tubulointerstitial nephritis, successfully treated with prednisone and mycophenolic acid.

Key-Words:
Hypocomplementaemic immune-complex interstitial nephritis; mycophenolic acid; prednisone.

INTRODUCTION

Eleven cases of idiopathic hypocomplementaemic tubulointerstitial nephritis have been reported so far. All these cases were primarily characterised by tubulointerstitial immunological damage, other conditions causing deposits in the tubular basement membrane (TBM) having been excluded[1-10].

Early and prolonged treatment with immunosuppressant drugs has been suggested, as this condition seems to have a potentially progressive nature. However, variable responses to therapy have been described in the literature[1,3,4,10].

Mycophenolate mofetil has been reported as a useful therapeutic option for steroid-resistant acute tubulointerstitial nephritis and may be considered potential first-line therapy in selected populations[1].

Our patient is the first with a diagnosis of idiopathic hypocomplementaemic tubulointerstitial nephritis to be treated with a combination of prednisone and mycophenolic acid.

CASE REPORT

A 74-year-old man was admitted to our hospital with progressive impairment of renal function. He had a history of coronary artery stenting for acute coronary syndrome ten years previously, diet-controlled diabetes mellitus for five years, benign prostate hyperplasia and sleep apnoea disorder treated with CPAP. His medications included fluvastatin, aspirin, diltiazem, finasteride and nitroglycerin patches. He had not taken over-the-counter medications, NSAIDs, herbal remedies, and reported no infections or antibiotic use in the previous six months. He had no history of joint pains or fever.

On admission, he was well hydrated and, apart from bradycardia (45bpm), physical examination was unremarkable. His blood pressure was 105/67mmHg. He had no skin lesions. Ophthalmologic examination was performed, ruling out uveitis, choroiditis or infection. Schirmer´s test was negative.

Initial laboratory testing revealed serum creatinine 5.05 mg/dl, and urea 145 mg/dl,. Serum potassium, sodium, calcium, phosphorus, CPK, LDH and albumin were normal. Thyroid hormone levels were normal. Haemoglobin was 9.3g/dl, platelets 229,000 mm3, leucocytes 7500; neutrophils 5.3; lymphocytes 1.52; monocytes 0.38; eosinophils 0.2; basophils 0.1. Cryoglobulins and autoantibody screening (ANCA, anti GBM, ANA, anti-DNA anti Ro, anti La, RNP, RF) were negative. IgA, IgM, and IgG were in the normal range and there was no monoclonal paraprotein. Complement C3 and C4 levels were reduced: C3 63.2mg/dl, (N=75-135mg/dl) and C4 11.90mg/dl (N=14-60mg/dl). Hepatitis B surface antigen, Hepatitis C serum antibody and HIV ELISA were all negative. Cancer markers were negative. Urinalysis showed no leucocytes, erythrocytes or nitrites. Urine glucose was 1.5g/l; pH 7; proteins 0.3g/l. Urine culture was negative.

Chest X-ray was unremarkable and ultrasound showed kidneys of normal size, with normally echogenic cortex and no hydronephrosis.

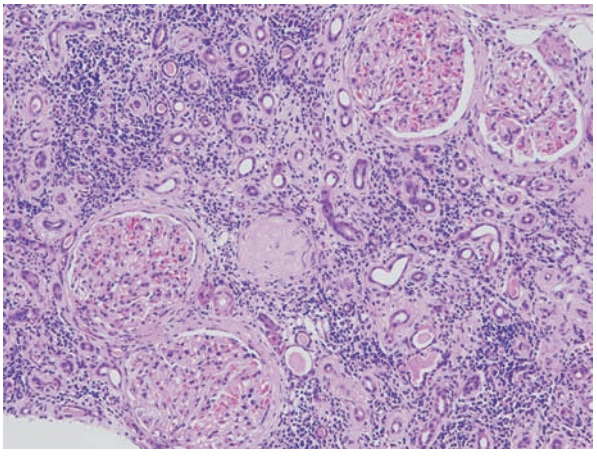

Figure 1

Interstitial nephritis with severe tubular atrophy and interstitial fibrosis with chronic inflammatory cells. There is slight periglomerular fibrosis without affecting the glomeruli. Hematoxylin/Eosin stains (Magnification 10×).

A renal biopsy was performed. 20 glomeruli were obtained, all apparently normal on light microscopy and immunofluorescence. There was a diffuse interstitial nephritis with mainly small and mature lymphocytes and plasma cells. No eosinophils were found either in the cortex or the medulla. Tubules were atrophic and thickened (Figs. 1,2). Immuofluorescence microscopy showed IgG and C3 in a granular pattern in the tubular basement membrane.

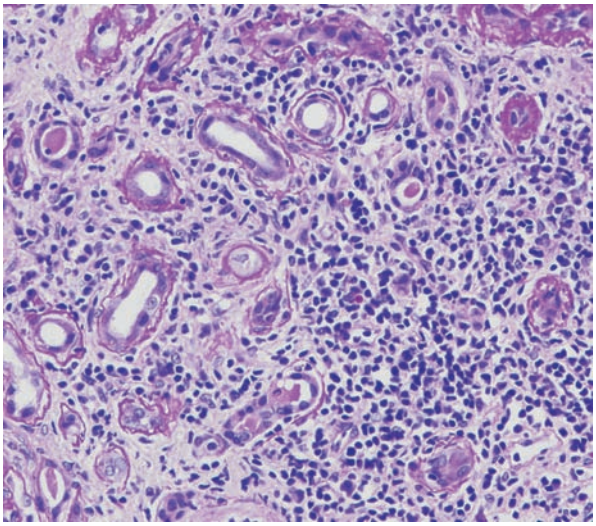

Figure 2

Interstitial infiltrate consisting of lymphocyte and plasma cells. Hematoxilin/Eosin stains (Magnification 60×).

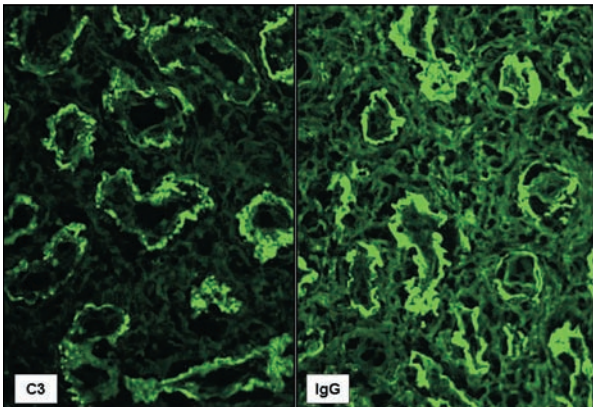

Figure 3

Tubular basement membranes staining for anti-IgG and C3 with a granular pattern.

Table I

Serum creatinine, proteinuria and complement follow-up. Steroids were introduced at 19/06/2009 and mycophenolic acid at 28/06/2009. Kidney biopsy was performed at 24/06/2009.

		08-11-2006	22-05-2008	16-03-2009	22-04-2009	18-06-2009	21-06-2009	24-06-2009	01-09-2009
Serum Creatinine	**mg/dl**	1.4	1.3	3.1	3.7	5.05	4.31	3.64	1.6
Urine Protein	**g/l**	NEG	NEG	–	0.3	–	–	–	–
	g/24h	–	–	–	–	1.87	2.87	1.79	0.75
C3	**mg/dl**	–	–	–	–	–	63.2	–	71.5
C4	**mg/dl**	–	–	–	–	–	11.9	–	16

Stains for IgM, IgA, C1q and C4, fibrinogen, and kappa and lambda chains were negative (Fig. 3)

A diagnosis of acute immune-complex mediated tubulointerstitial nephritis was made. Prednisone 1mg/kg/day had been started empirically 5 days before the renal biopsy, with some improvement in renal function, but hyperglycaemia developed so the dose was reduced to 0.5 mg/kg/day and then tapered to zero in fifteen days. Mycophenolic acid (180mg/12h) was added. Follow-up biochemical data are shown in Table I.

DISCUSSION

Tubulointerstitial nephritis (TIN) with immune-complex deposits in the tubular basement membrane and minimal or no glomerular involvement is infrequently reported[1,3,4,10]. The patient we present here had renal failure, hypocomplementaemia and proteinuria (always below 3 g/day). He did not have an active urinalysis, eosinophilia, or renal tubular acidosis. Skin lesions were absent. There was no evidence of environmental exposure to arsenic, cadmium, mercury, gold or herbal medicines. No new drugs had been started during the year before presentation. Tubulointerstitial immunological damage was the main feature, with deposits of C3 and IgG in the TBM in a granular and diffuse pattern.

Linear or granular TBM deposits may be found in systemic lupus erythematosus, Goodpasture's syndrome, Sjögren's syndrome, and membranous glomerulopathy, and also rarely, with a linear pattern, in drug-induced nephropathy secondary to methicillin and phenytoin[1-3]. They have also been described in urticarial vasculitis syndrome, adenovirus infection, renal allograft rejection or mixed cryoglobulinaemia, all of which were excluded in our patient[4,8]. Many of these diseases have predominantly glomerular involvement, which was absent in our patient. Autoimmune disorders such as systemic lupus erythematosus and Sjögren's syndrome, which may cause isolated TBM deposits, were also ruled out (there were no symptoms or signs of systemic lupus erythematosus, and antinuclear antibody, anti DNA, anti Ro and anti La were negative). Although aspirin and diltiazem can cause allergic TIN, no drug has been reported to cause immune-complex mediated TIN. Our patient also had hypocomplementaemia which has not been reported in drug-induced interstitial nephritis to our knowledge[3,9]. After excluding these possible causes, a diagnosis of idiopathic hypocomplementaemic tubulointerstitial nephritis was made.

In kidney biopsies of cases of idiopathic immune-complex TIN, TBM deposits always show a granular and predominantly diffuse staining for IgG, with variable staining for IgM (4 cases), C3 (6 cases), C1q (7 cases). Lambda and kappa chains were found in 9 of the eleven reported cases, but not in our case[1,3,4,10]. In one case, hypocomplementaemia was reported to precede the full manifestation of acute renal failure[4]. Our patient, and one previous case[1], showed normalisation of the complement level as renal function improved. Hypocomplementaemia might therefore be a marker of clinical activity.

The heterogeneous nature of the reported cases calls into question the possibility of a shared aetiology, but TIN with immune deposits seems to occur more frequently in older men with underlying immunologic disorders including sclerosing cholangitis (two cases), marginal B cell lymphoma (one case), leucocytoclastic vasculitis (one case), adult onset of diabetes mellitus (four cases, five including ours),

and coronary artery disease (five cases, six including ours)[1,3,4,10].

All cases were treated with immunosuppressant drugs including at least prednisone. One patient was treated with 1mg/kg/day for 8 weeks which was then tapered over 6 months without relapse. Another case was also effectively treated with 60 mg/day but relapsed after discontinuation. No other references have been found describing doses used[1,3,4,10]. Prolonged therapy has been suggested, with a median of 8.5 months (3-20 months) in the cases reported. In three cases, additional immunosuppressant agents were added: in two, this was cyclophosphamide. One patient had a marginal B cell lymphoma, and another developed thrombotic thrombocytopenic purpura requiring plasmapheresis. The third patient had cirrhosis and a monoclonal interstitial infiltrate and underwent liver transplantation several weeks after the biopsy, and was thereafter maintained on tacrolimus, mycophenolate mofetil and prednisone. The variability of treatment response may be related to differences in the severity of the cases and the presence of irreversible lesions[1].

Mycophenolate mofetil has been reported as a useful therapeutic option for steroid-resistant AIN and may be considered as potential first-line therapy in selected patients[13]. In our case, we initially tried prednisone at 1 mg/kg/day. Renal function slowly improved but hyperglycaemia developed. We therefore decided to taper the dose of prednisone rapidly to zero, and add mycophenolic acid. A satisfactory overall response and a better glycaemic profile were obtained.

In summary, the combination of prednisone and mycophenolic acid appears to be a useful therapeutic option for hypocomplementaemic tubulointerstitial nephritis in patients with diabetes. Prolonged immunosuppression has been suggested for this condition and we believe that the addition of mycophenolic acid may improve the risk-benefit profile in selected patients. It might also be useful in steroid-resistant patients, although further studies are needed to investigate this approach.

Conflict of interest statement. None declared.

References

1. Vaseemuddin M, Schwartz MM, Dunea G, Kraus MA. Idiopathic hypocomplementemic immune complex-mediated tubulointerstitial nephritis. Nat Clin Pract 2007;3:50-58
2. Lehman DL, Wilson CB, Dixon FJ. Extraglomerular immunoglobulin deposits in human nephritis. Am J Med 1975;58:765-786
3. Khambham N, Markowitz GS, Tanji N, Mansukhani MM, Orazi A, D'Agatti V. Idiophatic hypocomplementemic interstitial nephritis with extensive tubulointerstitial deposits. Am J Kidney Dis 2001;37:388-399
4. Tokumoto M, Fukuda K, Shinokazi M, *et al.* Acute interstitial nephritis with immune complex deposition and MHC class II antigen presentation along the tubular basement membrane. Nephrol Dial Transplant 1999;14:2210-2215
5. Winner RL, Cohen A, Sawhney A, Garman J. Sjögren's syndrome with immuno-complex tubulointerstitial renal disease. Clin Immunol Immunopathol 1977;8:494-505
6. Najima Y., Terai C, Takano K, Takehara k, Yamada A, Takaku F. Tubulointerstitial immune complex nephritis in a patient with cutaneus vasculitis. Clin Nephrol 1986;25:48-51
7. Yuhawa Y, Awi N, Fukatsu A, *et al.* Acute renal failure and degenerative tubular lesions associated with in situ formation of adenovirus immune complex in a patient with allogenic bone marrow trasplantation. Trasplantation 1993;55:67-72
8. Andres GA, Acciniri J, Hsu KO, *et al.* Human renal trasplant: III Immunopathologic studies. Lab Invest 1970;22:588-604
9. Abadin J, Duran JA, Pérez de León JA. Probable Diltiazem-Induced Acute Interstitial Nephritis. Ann Pharmacother 1998;32:656-658
10. Hyun J, Galen MA. Acute interstitial nephritis –a case characterized by increased IgG,IgM and IgE concentrations, eosinophilia and IgE depositions in renal tubules. Arch Intern Med 1981;141:679-681
11. Preddie DC, Markowitz GS, Radhakrishnan J, *et al.* Mycophenolate mofetil for the treatment of Interstitial Nephritis. Clin J Am Soc Nephrol 2006;1:718-722

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