

Tubulointerstitial Nephritis Cases With IgM-Positive Plasma Cells



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INTRODUCTION

Tubulointerstitial nephritis (TIN) is an inflammatory disorder in renal tubules and interstitium without involvement of glomerular lesions. Causes of TIN are diverse and include drug reactions, Sjögren syndrome, sarcoidosis, tubulointerstitial nephritis and uveitis (TINU) syndrome, and IgG4-related kidney disease, although the causes remain unknown in many cases, which are diagnosed as idiopathic TIN.¹ Pathologically, infiltrations of various inflammatory cells, including lymphocytes, plasma cells, and macrophages, are observed in renal interstitium in TIN patients.² Although infiltration of IgG-positive plasma cells is a common finding in TIN patients, Takahashi *et al.* recently reported TIN cases with IgM-positive plasma cell accumulation within the interstitium.³ The cases have characteristic findings of high serum IgM levels, high prevalences of distal renal tubular acidosis (d-RTA), Fanconi syndrome, positive anti-mitochondrial antibodies (AMA), and primary biliary cholangitis (PBC). These cases were termed “IgM-positive plasma cell–tubulointerstitial nephritis” (IgMPC-TIN).³ IgMPC-TIN may be the cause of some of the idiopathic TIN cases with unknown etiology. Although intermediate-dose glucocorticoid therapy is highly effective in most cases of IgMPC-TIN,³ the long-term prognosis of IgMPC-TIN is still uncertain. Here, we describe 2 cases of IgMPC-TIN in patients who were sensitive to initial glucocorticoid therapy but relapsed after early tapering of glucocorticoid.

CASE PRESENTATION

Case 1

A 54-year-old Asian woman without significant past medical history was referred to our department because of renal dysfunction. Physical examination findings were normal. Laboratory examination revealed elevated levels of serum creatinine (s-Cr, 1.2 mg/dl), serum IgM (s-IgM, 716.6 mg/dl; normal range, 50–269 mg/dl) with normal levels of IgG and IgA, and hepatobiliary enzymes (alanine transaminase, 25 IU/l; normal range, 7–23 IU/l; γ -glutamyltransferase, 39 IU/l; normal range, 9–32 IU/l). Urinalysis showed mild proteinuria (0.5 g/gCr), renal glycosuria, and elevated level of urinary β_2 -microglobulin (u- β_2 MG, 65,010 μ g/gCr and 32.7 μ g/ml; normal range, 0–0.29 μ g/ml) without hematuria. The patient had no symptoms of dry mouth or dry eye, and anti-Sjögren syndrome (SS)-A and anti-SS-B antibodies were negative, denying the possibility of Sjögren syndrome. Further analysis revealed normal anion gap metabolic acidosis (standard bicarbonate, 20.9 mmol/l; normal range, 22–26 mmol/l) with urinary pH persistently >5.5, which suggested d-RTA.⁴ Her first renal biopsy findings revealed severe infiltrations of inflammatory cells, including lymphocytes and plasma cells in the tubules and interstitium with moderate interstitial fibrosis, tubular atrophy, and tubulitis without glomerular abnormality (Supplementary Figure S1; inflammatory cell infiltration, 40%; tubular atrophy and interstitial fibrosis,

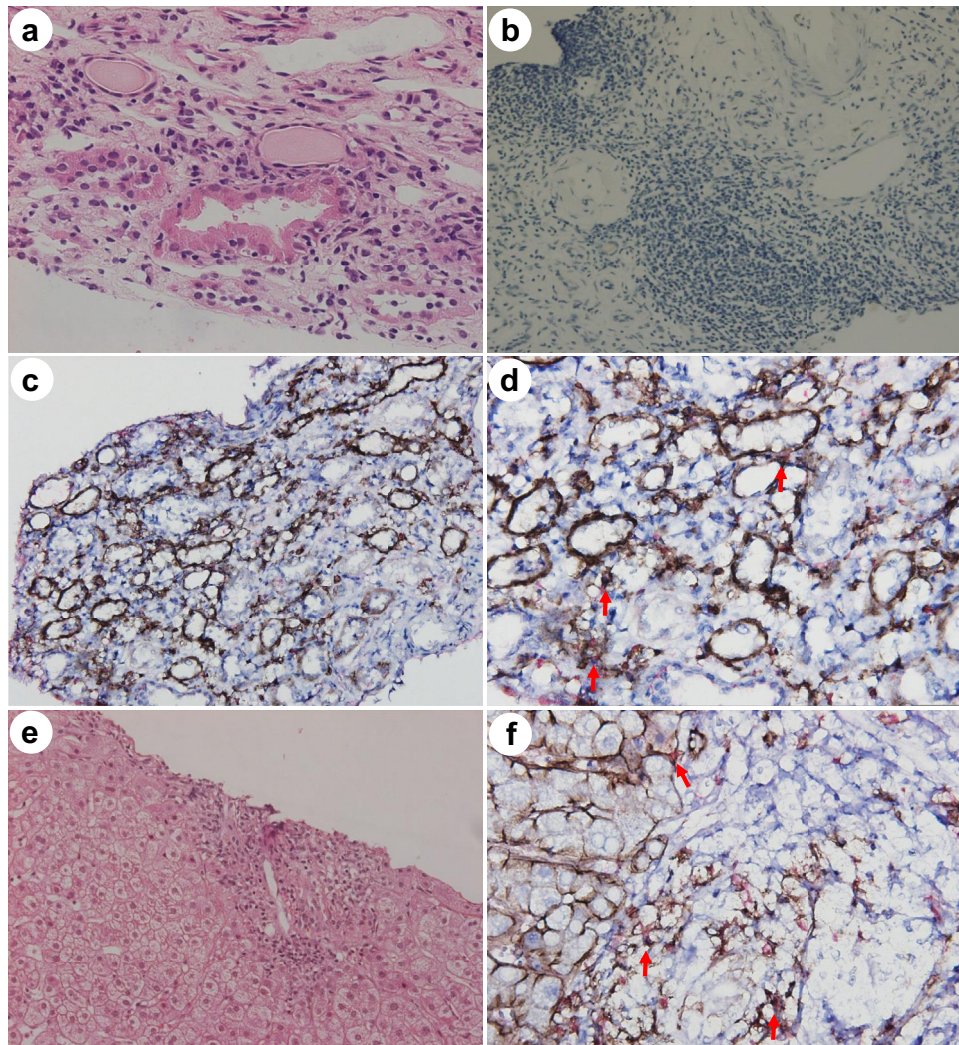


Figure 1. The second renal biopsy and liver biopsy findings in case 1. (a) Light microscopy image with periodic acid–Schiff stain, showing massive inflammatory cell infiltration in renal tubulointerstitium. Original magnification $\times 400$. (b) Image of staining of IgG4, showing no infiltration by IgG4-positive plasma cells. Original magnification $\times 100$. (c) Image of dual staining of CD138 (brown) and IgM (pink), showing the extent of IgM-CD138 dual-positive plasma cell infiltration. Original magnification $\times 100$. (d) Image of dual staining of CD138 (brown) and IgM (pink), showing massive infiltration by IgM-CD138 dual-positive plasma cells in renal interstitium. Red arrows show representative IgM-CD138 dual-positive cells. Original magnification $\times 400$. (e) Light microscopy image with hematoxylin and eosin stain, showing nonsuppurative destructive cholangitis in the liver. Original magnification $\times 200$. (f) Image of dual staining of CD138 (brown) and IgM (pink), showing massive infiltration by IgM-CD138 dual-positive plasma cells in liver. Red arrows show representative IgM-CD138 dual-positive cells. Original magnification $\times 400$.

20%; tubulitis, mild). Immunofluorescence staining was negative for immunoglobulins and complements. The patient was originally diagnosed with idiopathic tubulointerstitial nephritis (TIN) with a possibility of drug-induced TIN because she had sometimes taken hyaluronic acid tablets, although the result of the drug-induced lymphocyte stimulation test for hyaluronic acid was negative. She was treated with prednisolone (40 mg/d); her glycosuria improved, and both u- β_2 MG and s-Cr levels gradually decreased (Supplementary Figure S2). Because of side effects from prednisolone (fatigue and malaise), prednisolone was tapered quickly and stopped after 3 months.

Seven months after the discontinuation of prednisolone, glycosuria reappeared, and the levels of s-Cr, s-IgM, and u- β_2 MG gradually increased (Supplementary Figure S2). Laboratory examination revealed mild proteinuria (0.69 g/gCr), normal anion gap metabolic acidosis, hypokalemia (3.8 mEq/l), hypophosphatemia (3.1 mg/dl), hyperphosphaturia (percent tubular reabsorption of phosphate, 50.4%), and pan-aminoaciduria, typical of Fanconi syndrome.⁵ Her second renal biopsy was performed. Similar to the first biopsy result, there were severe inflammatory cell infiltration of the tubules and interstitium (Figure 1a–c; inflammatory cell infiltration, 60% including about 20% of plasma cells and 80% of lymphocytes; tubular atrophy and interstitial

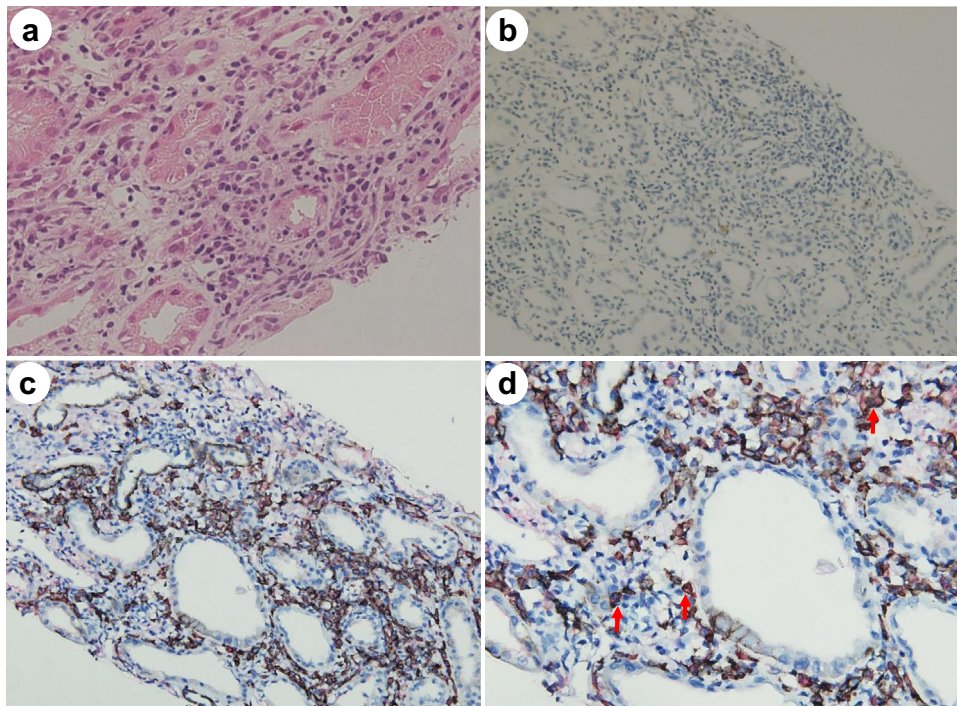


Figure 2. The second renal biopsy and liver biopsy findings in case 2. (a) Light microscopy image with periodic acid–Schiff stain, showing massive inflammatory cell infiltration in renal tubulointerstitium. Original magnification $\times 400$. (b) Image of staining of IgG4, showing no infiltration by IgG4-positive plasma cells. Original magnification $\times 100$. (c) Image of dual staining of CD138 (brown) and IgM (pink), showing the extent of IgM-CD138 dual-positive plasma cell infiltration. Original magnification $\times 100$. (d) Image of dual staining of IgM (pink) and CD138 (brown), showing massive infiltration by IgM-CD138 dual-positive plasma cells in renal interstitium. Red arrows show representative IgM-CD138 dual-positive cells. Original magnification $\times 400$.

fibrosis, 60%; tubulitis, severe; IgG4, negative). At this time, we conducted dual staining of IgM and CD138, a specific marker of plasma cells.⁶ There were IgM-CD138 double-positive cells in the tubulointerstitium (21 infiltrating IgM-CD138 dual-positive plasma cells per high-power field; [Figure 1d](#)), and we therefore rendered a diagnosis of IgMPC-TIN. Because of the patient's high levels of hepatobiliary enzymes, we suspected PBC, and further analysis was conducted. Anti-mitochondrial M2 antibody was positive, and liver biopsy was conducted, which satisfied the PBC criteria ([Figure 1e](#)). Dual staining of IgM and CD138 in the liver tissue also revealed infiltrations of IgM-CD138 dual-positive plasma cells ([Figure 1f](#)), suggesting the common pathophysiological conditions between the kidney and liver. She was treated with prednisolone (45 mg/d) and ursodeoxycholic acid. Her glycosuria resolved, and both u- β_2 MG and s-IgM levels decreased ([Supplementary Figure S2](#)).

Case2

A 57-year-old Asian woman without significant past medical history was referred to our department because of impaired renal function and proteinuria (0.7 g/gCr). Her s-Cr levels had increased from 1.2 mg/dl to 1.95 mg/dl over 1 year. Her physical examination findings were

normal. Laboratory examination revealed a high level of s-IgM (516.6 mg/dl), a slight increase in hepatobiliary enzymes (alkaline phosphatase, 353 IU/l; γ -glutamyl-transferase, 46 IU/l), and a high level of u- β_2 MG (81,701 μ g/gCr) without hematuria. The patient had no symptoms of dry mouth or dry eye, and anti-SS-A and anti-SS-B antibodies were negative, denying the possibility of Sjögren syndrome. Renal biopsy findings revealed severe infiltration of the tubules and interstitium by lymphocytes and plasma cells with moderate interstitial fibrosis and tubular atrophy ([Figure 2a–c](#); inflammatory cell infiltration, 70% including about 30% of plasma cells and 70% of lymphocytes; tubular atrophy and interstitial fibrosis, 50%; tubulitis, moderate; IgG4, negative). No glomerular abnormality was observed. Immunofluorescence staining was negative for immunoglobulins and complements. She had sometimes taken loxoprofen, acetaminophen, and zolpidem. Thus, we conducted a drug-induced lymphocyte stimulation test for these medications, and the acetaminophen test result was positive. Hence, she was diagnosed drug-induced TIN by acetaminophen. She was then treated with prednisolone (50 mg/d) and stopped taking acetaminophen. Her glycosuria disappeared immediately, and both u- β_2 MG and s-Cr levels gradually decreased ([Supplementary Figure S3](#)). Prednisolone treatment was tapered to 3 mg/d within 6 months.

Three months after the prednisolone tapering to 3 mg/d, glycosuria reappeared, and levels of s-Cr, s-IgM, and u- β_2 MG increased (Supplementary Figure S3). IgM-CD138 dual staining in tissue from the original kidney biopsy was performed. There were IgM-CD138 double-positive cells in the tubulointerstitium (Figure 2d; 84 infiltrating IgM-CD138 dual-positive plasma cells per high-power field), which led to the diagnosis of IgMPC-TIN. Prednisolone dose increased (20 mg/d), and the levels of s-Cr, s-IgM, and u- β_2 MG were decreased (Supplementary Figure S3).

DISCUSSION

This is the first report of IgMPC-TIN cases that relapsed after prednisolone treatment. Our 2 cases had been initially diagnosed with idiopathic or drug-induced TIN at the first examination and were subsequently diagnosed with IgMPC-TIN with a second analysis after the relapse of TIN. Because IgMPC-TIN may be associated with involvement of other organs, including the liver and salivary glands, appropriate diagnosis of IgMPC-TIN is important for proper treatment and monitoring. In addition, it is reported that ursodeoxycholic acid may reduce s-IgM levels in PBC^{7,8}; thus it may be a useful option for reducing infiltration by IgM-CD138-positive plasma cells in IgMPC-TIN cases, thereby preventing the possible relapse of TIN. In addition to the high levels of s-IgM, prominent plasma cell infiltration in renal tubulointerstitial areas is another important characteristic of IgMPC-TIN. Although prominent plasma cell infiltration is known to be observed in other causes of TIN, including IgG4-related kidney disease, Sjögren syndrome,^{S1} and some drug-induced TIN, we also need to consider IgMPC-TIN as one of the differential diagnoses in cases of plasma cell infiltrations in TIN cases. Taken together, nephrologists need to be aware of IgMPC-TIN cases and might need to re-examine the past cases of TIN, especially when the patients had high s-IgM levels and/or prominent plasma cell infiltration.

For the diagnosis of IgMPC-TIN, the infiltration of IgM-positive plasma cells in the tubulointerstitium by IgM-CD138 dual staining is required.³ Mizoguchi *et al.* recently reported cases of the concurrence of PBC and TIN with positive IgM staining in renal tissue. They summarized 16 cases, indicating the possibility of IgMPC-TIN.⁹ However, they did not perform IgM-CD138 dual staining, and therefore were unable to indicate IgM-positive plasma cell infiltration and make the diagnosis of IgMPC-TIN. Interestingly, it is difficult to observe IgM deposition in tubulointerstitium by conventional immunofluorescence staining; instead, this requires immunohistochemical staining of

Table 1. Pre- and post-treatment laboratory values

Laboratory data	Pretreatment	Post-treatment	P value
s-Cr (mg/dl)	1.42 ± 0.45	1.31 ± 0.40	0.062 ^a
eGFR (ml/min per 1.73 m ²)	35.4 ± 10.9	38.1 ± 13.8	0.225 ^a
U-P (g/gCr)	1.51 ± 1.76	0.58 ± 0.56	<0.001 ^a
s-IgM (mg/dl)	837 ± 385	401 ± 259	<0.001 ^a
u- β_2 MG(μ g/l)	48,922 ± 29,880	26,801 ± 29,994	0.004 ^a
Glucosuria +/-	16/1	8/8	0.007 ^b

eGFR, estimated glomerular filtration rate; s-Cr, serum creatinine; s-IgM, serum IgM; U-P, urinary protein; U- β_2 MG, urinary β_2 -microglobulin.

^aStatistical calculations using Wilcoxon signed rank test were performed using JMP version 14.0 (SAS Institute, Cary, NC).

^bStatistical calculations using Fisher exact test were performed using JMP version 14.0 (SAS Institute).

Data of the first treatment and the second treatment after the recurrence in our cases are included.

formalin-fixed, paraffin-embedded renal biopsy specimens after antigen retrieval. It had been reported that some of the IgMPC-TIN cases are slightly positive for IgM on the tubular basement membrane by immunofluorescence staining, but this is often too slight to be recognized. It is possible that the enzyme treatment after heat treatment, which is needed for IgM-CD138 dual staining, makes it easier to react to the antibodies by unmasking IgM epitopes.^{S2}

In our first case, the liver specimen, in addition to the kidney, had infiltrating IgM-CD138 dual-positive plasma cells, suggesting that IgMPC-TIN might not be only a kidney disease but a systemic disease similar to IgG4-related kidney disease. This hypothesis might explain why IgMPC-TIN patients have several specific symptoms, including PBC, d-RTA, Fanconi syndrome, and Sjögren syndrome. In fact, there are a number of reported cases with co-occurrence of TIN and Sjögren syndrome and/or PBC. However, it is unknown whether all these reported cases might fulfill IgMPC-TIN criteria because of the lack of IgM-CD138 dual staining. Further accumulations of IgMPC-TIN cases and systemic analyses are required to define the clinical features and to establish the diagnostic criteria.

According to the previous report, patients with IgMPC-TIN are more likely to be sensitive to glucocorticoid.³ However, data on long-term prognosis are still lacking. Despite the initial sensitivity to glucocorticoid in our cases, there were relapses after rapid tapering of glucocorticoid in both cases, indicating that IgMPC-TIN cases might be relapsed. Although further

Table 2. Teaching points

1. TIN with IgM-positive plasma cells may be the cause of some of the idiopathic TIN cases with unknown etiology.
2. Although IgM-PC-TIN cases are steroid sensitive in most cases, we need to be aware of possible relapse even after remission with initial glucocorticoid therapy.
3. Monitoring levels of u- β_2 MG, s-IgM, s-Cr, and glycosuria may facilitate detection of relapse.

TIN, tubulointerstitial nephritis.

analysis is required to determine whether we need to taper the glucocorticoid more slowly, continue glucocorticoid treatment in the maintenance dosage, or add another immunosuppressant to the treatment in IgMPC-TIN cases, careful monitoring seems necessary even after the remission. Which parameters can be good markers under the treatment? We compared pre- and post-treatment values of the 13 patients in the original report³ and our 2 patients (Supplementary Table S1 and Table 1). Levels of urinary protein, s-IgM, and u- β 2MG in the post-treatment group were significantly lower compared to those in the pretreatment group, and glycosuria significantly improved after the treatment. On the other hand, s-Cr and estimated glomerular filtration rate were not significantly improved (Table 1). In our cases, high levels of s-Cr, s-IgM, and u- β 2MG as well as the glycosuria had been improved after the initial treatment, and these parameters worsened again at the relapse. Taken together, we conclude that levels of s-IgM, u- β 2MG, and s-Cr as well as glycosuria can be useful markers in the treatment of IgMPC-TIN cases.

In conclusion, we have presented 2 cases of IgMPC-TIN that were sensitive to the initial glucocorticoid treatment but that relapsed after tapering of glucocorticoid. Although most cases of IgMPC-TIN are sensitive to glucocorticoid, some of them may relapse. Therefore, we propose to monitor levels of s-IgM, u- β 2MG and s-Cr as well as glycosuria in the treatment to find or to avoid the recurrence of IgMPC-TIN (Table 2).

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. The first renal biopsy finding in case 1. (A) Light microscopy image of kidney with periodic acid–Schiff

stain, showing intact glomeruli. (B) Light microscopy image of kidney with periodic acid–Schiff stain, showing massive inflammatory infiltration in tubulointerstitium.

Figure S2. Clinical course in case 1.

Figure S3. Clinical course in case 2.

Table S1. Clinical and immunohistologic data of IgMPC-TIN at the time of renal biopsy.

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