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CASE REPORT

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Tubulointerstitial immune complex nephritis in a patient with systemic lupus erythematosus: role of peritubular capillaritis with immune complex deposits in the pathogenesis of the tubulointerstitial nephritis

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Abstract
Class IV-G (A/C) diffuse lupus nephritis and tubulointerstitial (TI) nephritis in a 31-year old woman was studied by light, immunofluorescence (IF), and electron microscopy (EM), to determine the pathogenesis of the TI lesions. The light microscopic findings showed peritubular capillaritis in the interstitium, with ruptures in the capillary structure, lysis of the surrounding tubular basement membrane (TBM), extravasated red blood cells (RBCs), the infiltration of neutrophils and mononuclear cells, and edema. The IF study revealed IgG, IgA, IgM, C1q, C3, and C4 depositions along the TBM, on the capillary walls, and in the interstitium proper. The EM study disclosed the deposition of immune complexes in the TBM, the capillary wall, and the interstitium proper. Based on these findings, the TI nephritis in this patient was considered to be due to peritubular capillaritis secondary to the immune complex depositions in the capillary wall of the interstitium.

Key words Tubulointerstitial nephritis · Systemic lupus erythematosus · Peritubular capillaritis · Immune complex · Sjögren syndrome

Introduction

Primary tubulointerstitial (TI) nephritis with systemic lupus erythematosus (SLE) has been well described in the literature.[1–8] The pathogenetic mechanism of primary TI nephritis in SLE has mainly been ascribed to either immune complex deposition in the tubular basement membrane (TBM) or in the peritubular capillary wall, or to cell-mediated immunity.[1–10] However, when analyzing the described cases very carefully regarding their pathologies and pathogeneses, we found that only a few reports had accurately investigated these points by means of light, immunofluoresence, and electron microscopy, as well as by serum immunologic examinations.[1–3,5–8] In these reports, an unresolved question has yet to be answered; namely, whether or not immune complexes deposited in the TBM or capillary wall in the interstitium actually induce TI nephritis. Furthermore, if these deposits actually induce TI nephritis in these patients, then what is the mechanism of such disease induction? We experienced a patient with TI nephritis with SLE in whom the TI nephritis was presumed to have been induced by peritubular capillaritis caused by immune complex deposition in the peritubular capillary wall. We, herein, present this case; we also review similar cases in the literature,[1–3,5–7] and discuss the pathogenetic mechanism of the TI nephritis in our patient.

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Case report

A 31-year old woman was admitted to our hospital for further evaluation and treatment of systemic lupus erythematosus (SLE). Her illness had started at the age of 26, when she developed postdelivery hypothyroidism. Two years later, during her second pregnancy, she demonstrated toxemia of pregnancy associated with positive proteinuria and antinuclear antibody (ANA). The patient had been treated by her local physician under the diagnosis of Hashimoto's thyroiditis. Since that time, she had suffered from occasional high fever, arthralgia, and swollen fingers.

Laboratory examinations on admission to another hospital had shown positive findings for proteinuria; ANA, 10240x; anti-double-stranded DNA antibody (anti-ds DNA Ab), 400 IU/ml; anti-Smith antibody (anti-Sm Ab), >500; hypergammaglobulinemia (4.7 g/dl); and low complement activity (CH50, 16 U/ml). Based on these clinical features

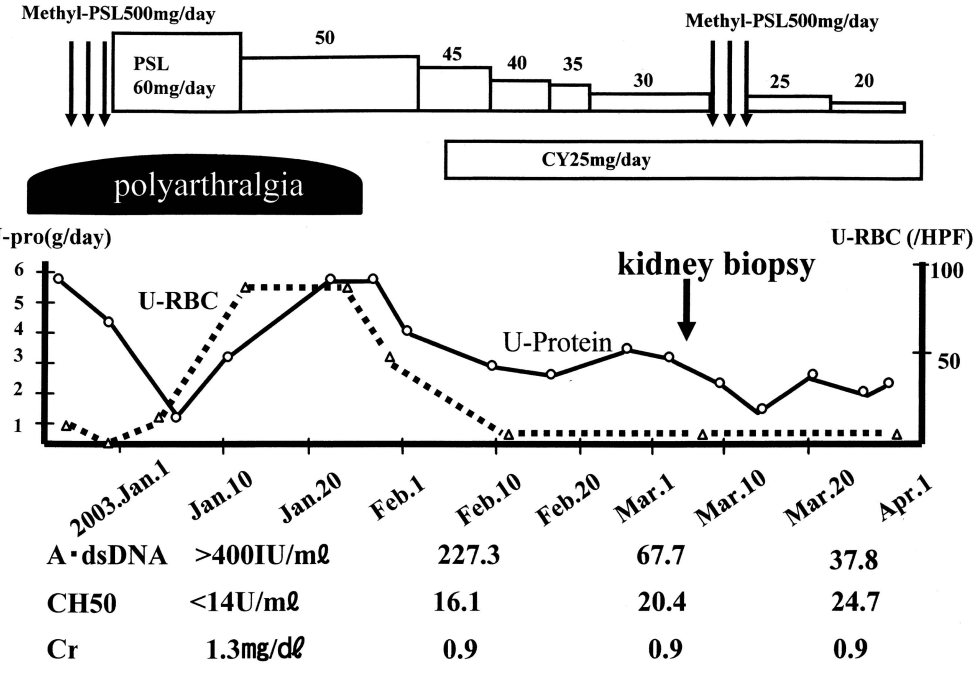

Fig. 1. Clinical course. *PSL*, prednisolone; *Cr*, serum creatinine; *U-pro*, urinary protein; *U-RBC (/HPF)*, urinary red blood cells (/high-power field); *Cy*, cyclophosphamide; *A-dsDNA*, anti-double-stranded DNA antibody; *CH50*, complement activity

and laboratory data, she was suspected to have SLE and was transferred to our hospital.

Physical examination on admission showed facial and leg edema and positive Raynaud phenomenon in the fingers. The laboratory data were as follows: urinalysis revealed a positive finding for proteinuria (4.3 g/day), as well as red blood cells (RBCs) and RBC casts in the sediment. The hematology findings were as follows: hemoglobin, 12.5 g/dl; white blood cells (WBCs), 8900/μl; and platelets, 21.3 × 104/μl. Blood chemistry showed: total protein, 9.1 g/dl, gamma globulin, 6.5 g/dl; blood urea nitrogen (BUN), 18.6 g/dl; serum creatinine (Cr), 1.3 mg/dl; and total cholesterol, 180 mg/dl. Immunological tests demonstrated ANA, 5120x; anti-ds DNA Ab, >400 IU/ml; anti-SS (Sjögren syndrome) –A Ab, 217.3 (<30); anti-SS-B Ab, 34.3 (<25); anti-Sm Ab, 151.3 (<30); anti-cardiolipin Ab (anti-CL Ab) IgG, 26 U/ml (<10 U/ml); anti-β2 glycoprotein-I (anti-β 2GPI) Ab, 3.8 U/ml (<3.5 U/ml); anti-ribonucleoprotein (RNP) Ab, 185 (<22); anti-thyroglobulin Ab, 75.3 U/ml (<0.3 U/ml); anti-thyroid peroxidase Ab (anti-TPO Ab), 4.2 U/ml (<0.3 U/ml); immune complex (IC) by C1q assay, 14.5 μg/ml (<4.0 μg/ml), rheumatoid factor, 108 IU/ml; CH50, <14 IU/ml, negative myeloperoxidase (MPO)-antineutrophil cytoplasmic autoantibodies (ANCA) and proteinase (PR)3-ANCA; negative Ab to tubular basement membrane (TBM), negative Ab to hepatitis B and C viruses, and negative cryoglobulin test. An ophthalmologic examination demonstrated positive findings for keratoconjunctivitis sicca, based on the findings of the Schirmer test, the Rose-Bengal test, and the fluororescence test. According to these findings, the patient was confirmed to have SLE and Sjögren syndrome. She initially received intravenous methylprednisolone semi-pulse therapy (M-PSL 500 mg) for 3 consecutive days; this was followed by oral PSL 60 mg per day (Fig. 1). The treatment improved her clinical symptoms and laboratory data; namely, the edema and arthralgia both disappeared, while the ANA and anti-ds DNA Ab decreased to 1280× and 67.7 IU/ml, respectively. However, the proteinuria remained at about 3.0 g per day.

Because of the persistent marked proteinuria, a renal biopsy was performed to identify the most appropriate further therapy after the initial 3-month treatment.

The renal biopsy specimen contained 15 glomeruli, and, by light microscopy, they revealed histological features of diffuse lupus nephritis (Fig. 2a,b); there were 12 mesangiocapillary and endocapillary proliferative glomeruli, 2 partially crescentic glomeruli, and 1 sclerotic glomerulus. These pathological findings indicated a diagnosis of class IV-G (A/C) diffuse lupus nephritis, according to the International Society of Nephrology/Renal Pathology Society (INS/RPS) 2003 classification. In addition, diffuse TI nephritis, associated with an infiltration of polymorphoneutrophils and mononuclear cells, extravasated RBCs, and edema, was observed around the peritubular capillaries and arterioles throughout the entire specimen (Figs. 2a and 3). On light microscopy, observation of the peritubular capillaries at high magnification demonstrated ruptures in the capillary structure, indicated by the existence of extravasated RBCs and the lysis of the surrounding TBM (Fig. 3b). Some of the infiltrated cells were positive for naphthol-AS-D-chloroacetate-esterase staining (Fig. 3c), and thus were identified as polymorphoneutrophils. However, none of these cells were attached to the TBM. Furthermore, four areas infiltrated densely by mononuclear cells were also demonstrated adjacent to the sclerotic and partially sclerotic glomeruli as well as the postcapillary venules. An immunofluorescence study disclosed granular deposits of IgG, IgA, IgM, C1q, C3, and C4 along the capillary loop, as well as in the mesangium. In addition, granular deposits were also observed along the TBM, on the capillary and

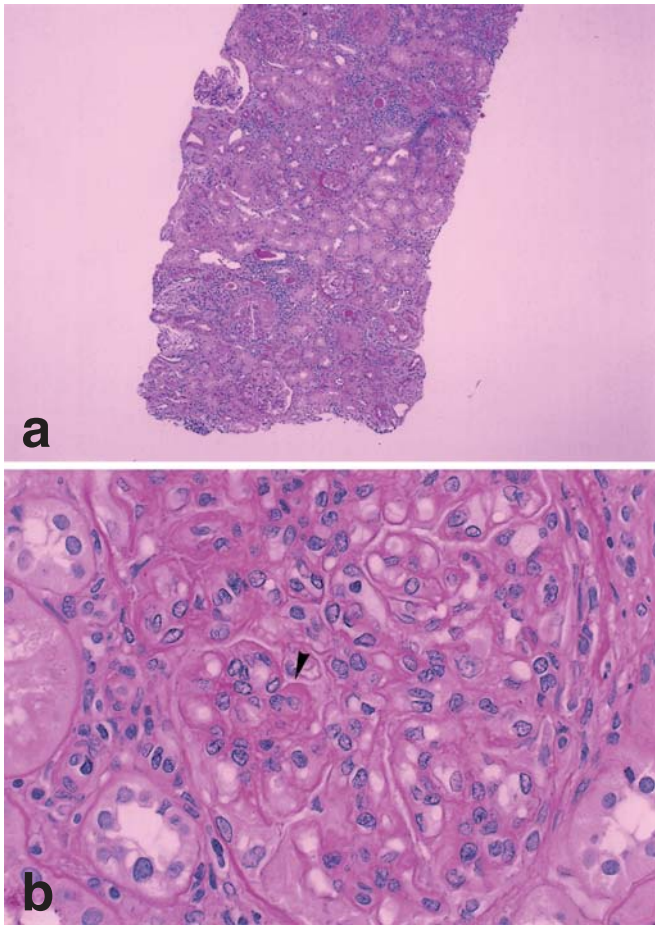

Fig. 2. **a** The renal specimen shows diffuse tubulointerstitial (TI) nephritis with diffusely infiltrated areas of inflammatory cells among the tubules, as well as areas densely infiltrated by mononuclear cells adjacent to damaged glomeruli and postcapillary venules. **b** A glomerulus shows mesangiocapillary proliferation with a few subendothelial deposits (*arrowhead*). **a** PAS, ×40; **b** PAS, ×400

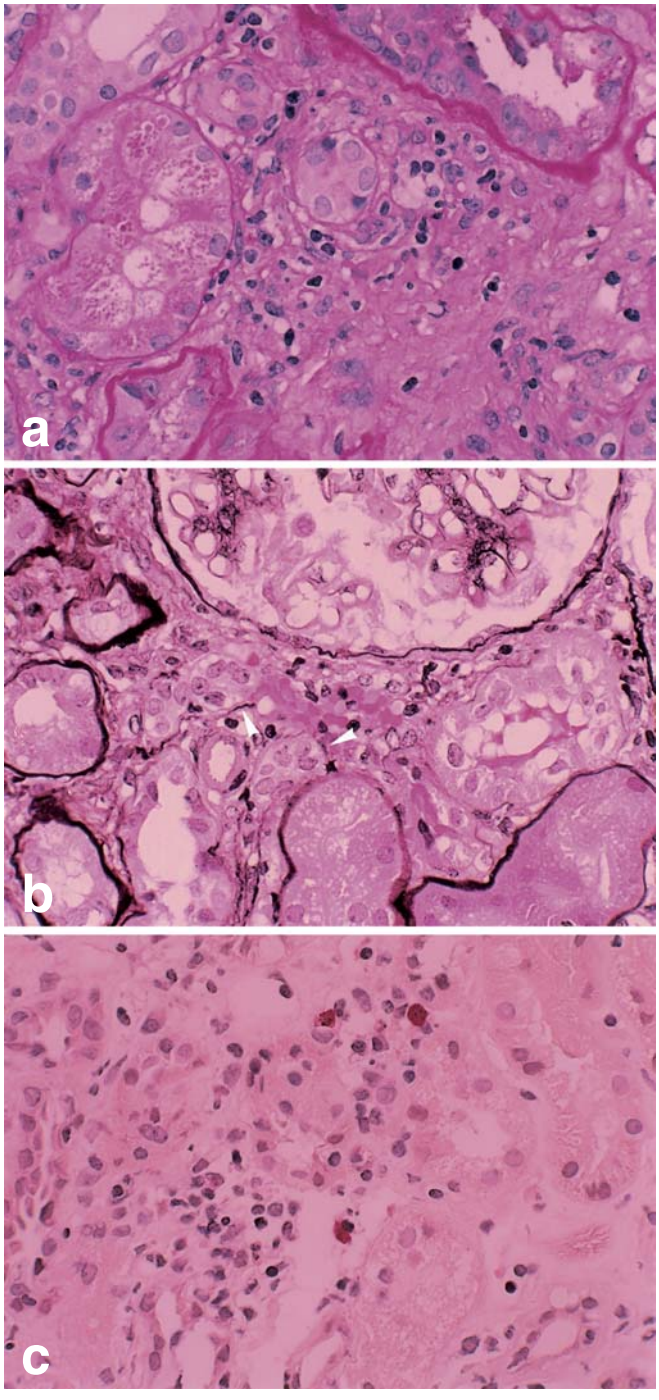

Fig. 3. **a** Interstitium reveals TI nephritis with infiltration of inflammatory cells and edema. **b** Extravasated RBCs are demonstrated in the interstitium, associated with the remnants of lytic tubular basement membrane (*arrowheads*). **c** Neutrophil infiltration identified by positivity for esterase staining. **a** PAS, ×400; **b** PAM, ×600; **c** Naphthol-AS-D-chloroacetate esterase, ×400

arteriole walls, in the interstitium proper, and in the cytoplasm of tubular epithelial cells (Fig. 4). An electron microscopic study showed electron-dense deposits of various sizes in the subepithelial, intramembranous, and mesangial areas of the glomeruli. In the interstitium, electron-dense deposits were also observed in the TBM, capillary wall (Fig. 5), and arteriole wall, and in the interstitium proper. These interstitial findings led to a diagnosis of TI nephritis due to peritubular capillaritis[11] secondary to immune complex deposition in the vascular wall, because peritubular capillaritis was diagnosed based on the ruptures in the capillary structure, the presence of extravasated RBCs, the lysis of the surrounding TBM, and the existence of inflammatory cells consisting of neutrophils and mononuclear cells.

Discussion

We have described here a female patient with SLE and Sjögren syndrome, with associated diffuse proliferative glomerulonephritis and TI nephritis. The pathological appearance of diffuse proliferative glomerulonephritis was compatible with the diagnosis of lupus nephritis, because the glomeruli showed mesangiocapillary and endocapillary proliferation with occasional subendothelial deposits, as well as positive staining for IgG, IgA, IgM, C1q, C3, and C4

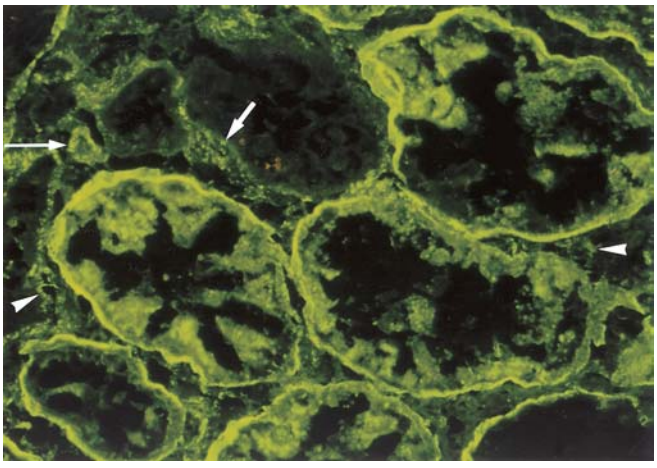

Fig. 4. Immunofluorescence (IF) study shows IgG deposits along the tubular basement membrane (TBM), on the capillary walls (*arrowheads*), in the interstitium proper (*short arrow*), and in the cytoplasm of tubular epithelial cells. *Long arrow* indicates positive finding in an arteriole wall. Anti-IgG antibody (Ab), ×400

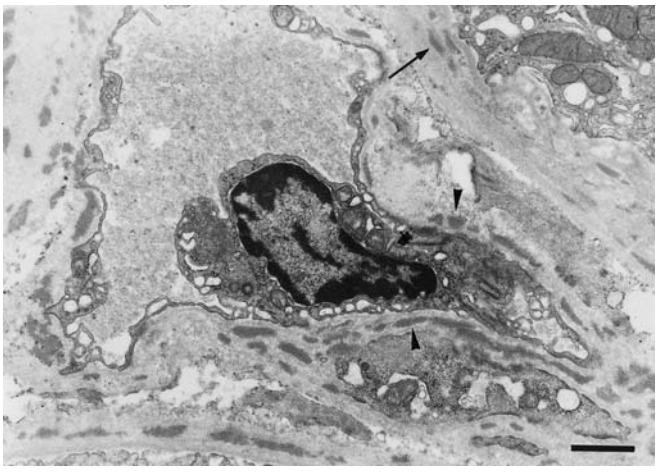

Fig. 5. Electron microscopy (EM) study discloses electron-dense deposits in the capillary wall (*arrowheads*) and TBM (*arrow*). ×8000; *bar* indicates 1 μm in length

along the glomerular capillary loops and mesangial areas. In addition, electron-dense deposits were observed in the subepithelial, intramembranous, and mesangial areas. Primary Sjögren syndrome itself has not been previously described as presenting these pathological features.[12–14] Indeed, to date only five cases of primary Sjögren syndrome have demonstrated membranoproliferative glomerulonephritis, and, in these cases, IgM and C_3, but not IgG and C_1q, were revealed in the glomeruli, as far as we could ascertain in a literature search.[12–14] Therefore, it appears that the glomerulonephritis in the present patient was due to SLE, and not to Sjögren syndrome. The TI nephritis in the present case was characterized by the infiltrations of two different types of inflammatory cells, manifested by diffusely infiltrated lesions or densely infiltrated ones. The densely infiltrated lesions were only observed around the sclerotic or partially sclerotic glomeruli and in the postcapillary venules. These lesions were presumed to be due to damaged glomeruli or postcapillary venulitis, as is seen in common glomerulonephritis, because these infiltrating cells were identified as a mixture of T and B cells by staining with monoclonal antibodies[15] (data not shown). The diffusely infiltrated lesions seemed to be specific for our case, and were characterized by ruptures in the capillary structure, the presence of RBCs, the lysis of the surrounding TBM, and the existence of inflammatory cells consisting of neutrophils and mononuclear cells. In addition, immune deposits of IgG, IgA, IgM, C1q, C3, and C4 were observed along the TBM, in the capillary and arteriole walls, and in the interstitium proper. Therefore, the pathological diagnosis of peritubular capillaritis in the interstitium was made, based on the demonstration of the above-described pathological findings. The peritubular capillaritis was presumed to have been induced by the deposition of the immune complexes that had been demonstrated in the capillary and arteriole walls, and was assumed to have arisen from SLE, as has been shown in experimental acute serum sickness.[16,17] TI nephritis caused by Sjögren syndrome was excluded because the TI nephritis in primary Sjögren syndrome is usually induced by two different pathogenetic mechanisms, neither of which was shown in our patient. In one, major TI nephritis tends to be caused by cell-mediated immunity to tubular epithelial cells associated with T-cell infiltration around the tubular epithelial cells.[18] The other types of TI nephritis are due to vasculitides which are almost always associated with cryoglobulinemia, macroglobulinemia, hepatitis B virus surface (HBs) antigen positivity, or hepatitis C virus (HCV) antibody positivity.[19,20] The present patient did not show positive findings for mononuclear cells attached to the tubular epithelial cells, or any of the above-mentioned positive data. Furthermore, these TI nephritides have not generally demonstrated interstitial immunofluorescence positivity (except for two cases; in one there were local TBM deposits of IgG and C3,[19] and in the other, the positivity arose from the presence of plasma cells[21]). These immunofluorescence findings are quite different from those in the present case. Therefore, it can be concluded that the TI nephritis in the present patient did not result from primary Sjögren syndrome.

TI nephritis caused by other factors is generally thought to be induced by various primary or secondary events, according to previous reports in the literature.[22] The TI nephritis in the present patient was not related to infection, drug-induction, toxins, metabolic disorders, or to hereditary or hematologic disorders; factors reported to be causes of primary TI nephritis. Because the onset of her illness was not associated with an infection, the intake of drugs or Chinese herbs, or any of the other above-mentioned causes, her TI nephritis was presumed to have been induced by immune-mediated primary TI nephritis or secondary TI nephritis associated with vascular disease, or to have been induced by the activation of tubular epithelial cells stimulated by either inflammatory cytokines or other factors that leaked out from the glomerular lesions (glomerulonephri-

Table 1. Findings of tubulointerstitial nephritis with interstitial immune complex deposition in systemic lupus erythematosus. Cases studied with light, immunofluorescence, and electron microscopic analyses are presented

Authors	Year published	No. of cases	Pathological findings		
			LM	IF	EM
Klassen et al.[1]*	1972	3	MNC infiltration	Granular Ig and C along TBM	Deposits in TBM
Andres and McCluskey[2]	1975	?	MNC and PMN infiltration	Granular Ig and C along TBM, in capillary, and in interstitium	Deposits in TBM, capillary BM, and interstitium
Brentjens et al.[3]	1975	31	MNC, PMN, and plasma cell infiltration	Granular Ig and C along TBM, in capillary, and in interstitium	Deposits in TBM, capillary wall, and interstitium
Makker[5]	1980	1	MNC infiltration	Linear Ig and C along TBM; granular Ig and C in capillary wall	No deposits
Schwartz et al.[6]	1982	20	Leukocyte infiltration	Granular Ig and C3 along TBM and in capillary wall	Deposits in TBM and capillary wall
Park et al.[7]	1986	31	MNC and plasma cell infiltration	Granular Ig and C3 along TBM, in capillary wall, and in interstitium	Deposits in TBM, capillary wall, and interstitium
Present patient	2005	1	MNC and PMN infiltration	Granular Ig and C along TBM, in capillary wall, and in interstitium	Deposits in TBM, capillary wall, and interstitium

A patient with Anti-TBM mediated TIN[8] was excluded

tis). Vascular disease in secondary TI nephritis is commonly used to define the TI lesions induced by the inflammatory process of arteritis, which is associated with the infiltration of inflammatory cells around the inflamed vessels. Therefore, the present case was not considered to be the so-called TI nephritis that is due to vascular disease in secondary TI nephritis, because the primary lesion was not associated with arteritis, but was rather, associated with capillaritis. TI nephritis induced by the activation of tubular epithelial cells is not commonly associated with the infiltration of neutrophils and ruptures in the capillary structure in the early phase of the illness, or with immunofluorescence positivity for the TBM, capillary wall, and interstitium proper.[23] Therefore, the present case was not considered to be a case of TI nephritis associated with glomerular lesions produced by vascular disease. Based on the above evidence, the TI nephritis in the present patient was diagnosed to have been induced by peritubular capillaritis, caused by the deposition of immune complexes in the capillary wall of the interstitium, and it was not regarded as arising from other causes, such as anti-TBM antibody or ANCA.

Cases of TI nephritis associated with SLE, studied by light, immunofluorescence, and electron microscopy and demonstrating positive immunofluorescence findings in the interstitium, have been described in the literature,[1–3,5–8] but such cases were only shown to have an infiltration of mononuclear cells, plasma cells, or polymorphoneutrophils in the interstitium, and depositions of immunoglobulins and complements on the TBM, capillary and arteriole walls, and in the interstitium proper (Table 1). Electron-dense deposits in the TBM, capillary and arteriole walls, and interstitium proper have also been demonstrated. However, such depositions of immune complexes were not reported to have resulted in a pathogenesis of peritubular capillaritis thereby inducing TI nephritis, in these patients. Although, we finally concluded that the TI nephritis observed in the present patient was caused by peritubular capillaritis in the interstitium, induced by the deposition of immune complexes. Since peritubular capillaritis has never been described to play a role in the pathogenetic mechanism of TI nephritis in lupus nephritis, we therefore described this pathogenetic process in the present patient.

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