A case of lupus vasculopathy presenting favorable renal outcome

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Abstract

Noninflammatory necrotizing vasculopathy, also referred to as lupus vasculopathy, is not infrequently observed in the pathology of lupus nephritis. It affects vessels causing them to become severely narrowed and occluded by a mechanism involving immune complexes. We experienced a 51-year-old woman with lupus nephritis class IV + V, which was accompanied by lupus vasculopathy. Renal biopsy and light microscopy showed eosinophilic hyaline-like material in the afferent and/or efferent arterioles, which narrowed the lumen, and which were positive for IgG by immunofluorescent analysis. Electron microscopy indicated that amorphous material and endothelial detachment occluded the arterioles. These findings were consistent with those of lupus vasculopathy. We treated the patient with steroids and cyclophosphamide. By the day of discharge, her levels of creatinine and proteinuria had undergone partial remission. Although lupus vasculopathy was implied as a lesion with unfavorable renal prognosis, some recent reports suggest its true renal prognosis is not unfavorable necessarily. Nevertheless, lupus vasculopathy is an important finding in diagnosis in contradiction to other vascular lesions in systemic lupus erythematosus. In addition, a standard therapy has also not been established. Therefore, it is important to accumulate cases of lupus vasculopathy to determine its prognosis and develop standard treatments.

Keywords Lupus vasculopathy · Noninflammatory necrotizing vasculopathy · Lupus nephritis

Introduction

Lupus nephritis (LN) presents with morphologic changes in the glomerulus, tubulointerstitium and vessels. Intrarenal vascular lesion was first described by Klemperer in 1941 [1], although it was overshadowed by glomerular lesions, which are a well-established prognostic lesion. However, lupus vascular lesions are also important, and have been identified in 53.4% of biopsy-proven LN patients in Mexico [2], 27.7% in Italy [3] and 81.8% in China [4]. These reports suggest it has a poor renal prognosis [2–5]. Lupus vasculopathy, one of lupus vascular lesions, is a complication in systemic lupus erythematosus (SLE). Because its characteristics are still unclear [2, 5], the accumulation of case reports is important. Here, we report our experiences of a case of lupus vasculopathy with LN class IV + V occurring in a middle-age woman, as well as a literature review.

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Case report

A 51-year-old woman was transferred to our hospital with a suspicion of SLE, and who presented with 1-month history of a febrile state with edematous lower limbs accompanied by pancytopenia, hypoalbuminemia, urinary abnormalities, and positivity for anti-nuclear antibody and anti-dsDNA antibody in a previous hospital.

On admission to our hospital, physical examination showed a blood pressure of 158/96 mmHg, body temperature of 37.6 °C, facial and lower limb edema, anemic conjunctiva palpebrarum and coarse crackles by chest auscultation. Laboratory tests showed white blood cells of 3,800/ μ L, red blood cells of 319×10^4 / μ L (hemoglobin: 8.9 g/dL), platelets of 8.6×10^4 / μ L, serum albumin of 2.80 g/dL, urea nitrogen of 22.0 mg/dL, creatinine (Cre) of 1.29 mg/dL, estimated glomerular filtration of 46 mL/min/1.73 m², and urinalysis showed urinary protein (U-Pro) of 17.2 g/g Cre and urinary red blood cells (RBCs) of 5–9/F. In addition, immunological tests revealed elevated anti-nuclear antibody of 1: 2,560 (homogenous type) and anti-dsDNA antibody of 399 IU/L, but anti-phospholipid antibodies including anti-cardiolipin antibody (aCL-IgG), anti-cardiolipin- β_2 -glycoprotein-1 antibody (a β_2 GP-1), and lupus anticoagulant (LA) were negative findings (others are shown in Table 1). Computed tomography showed right axillary and supraclavicular lymphadenopathies, and thoracoabdominal fluid. These findings provided a definitive diagnosis of SLE according to the 1982 American College of Rheumatology (ACR) criteria revised in 1997 [6, 7] (renal disorder, hematologic disorder, immunologic disorder, and anti-nuclear antibody positivity). Then, a renal biopsy was performed.

Table 1 Urinalysis and blood tests of this case

RBCs	5–9/F	TP	5.61 g/dL
UP/Ucr	17.2 g/gCr	Alb	2.8 g/dL
		BUN	22 mg/dL
WBC	3800/ μ L	Cre	1.29 mg/dL
Neut.	79.3%	eGFR	46 mL/min/1.73 m ²
Lymph.	14.6%	C3	35 mg/dL
Mono.	5%	C4	4 mg/dL
Eosin.	0.8%	CH50	14 U/mL
Baso.	0.3%	ANA	2560 folds
RBC	319×10^4 / μ L	ds-DNA	399 IU/L
Hb	8.9 g/dL	aCL-IgG	8 U/mL
Ht	26.3%	a β_2 GPI	1.2 U/mL
Plt	8.6×10^4 / μ L	LA	1.09

RBCs red blood cells, UP/Ucr the ratio of the urinary protein/urinary creatinine, ANA anti-nuclear antibody, ds-DNA anti-dsDNA antibody, aCL-IgG anti-cardiolipin antibody, a β_2 GP-1 anti-cardiolipin- β_2 -glycoprotein 1 antibody, LA lupus anticoagulant

In the light microscopy, forty-three glomeruli were observed. Most glomeruli showed segmental-to-global endocapillary proliferation with subendothelial deposits and duplication of glomerular basement membrane, as well as some cellular-to-fibrocellular crescents and tuft necrosis (Fig. 1a, b), although glomerular fibrin thrombi were not seen. An immunofluorescent (IF) study using a frozen specimen showed fine-to-coarse granular and band-like (ring-shaped) deposition of IgG along the capillary wall (Fig. 1c), as well as C3 and C1q. An electron microscopic (EM) study revealed diffuse subepithelial, subendothelial, mesangial, and intramembranous electron-dense deposits including organized finger print deposits and tubuloreticular material in endothelial cells (Fig. 1d–f). Moreover, luminal deposits of eosinophilic hyaline-like material were frequently present in vascular poles, afferent arterioles, and interlobular arteries, which had a narrowed lumen. There were such five legions in the biopsy specimen. These deposits lacked features of fibrinoid necrosis or cellular infiltration (Fig. 2a), and were positive for IgG by IF using a paraffin-embedded specimen (Fig. 2b). Hyaline-like material (periodic acid–Schiff (PAS) and fuchsin positive) was frequently present in the afferent arteriole at the vascular pole and the consecutive interlobular artery (Fig. 2c, d). In summary, these findings were consistent with lupus vasculopathy on the basis of lupus nephritis class IV + V [modified National Institutes of Health (NIH) activity index: 10, modified NIH chronicity index: 4] [8, 9]. The process of differential diagnosis is discussed below.

Figure 3 shows the clinical time course. Steroid pulse therapy (methylprednisolone 1000 mg, 3 days), followed by oral prednisolone (60 mg/day) was started from the day of admission, and then intravenous cyclophosphamide (IV CYC 500 mg every 2 weeks) was added from hospital day 18. An angiotensin II receptor blocker and diuretics were administered to control blood pressure and volume overload. Although cyclophosphamide was discontinued after two administrations because of cytopenia and hepatic disorder, serum creatinine was improved to 0.77 mg/dL and U-pro was 2.3 g/g Cre by the day of hospital discharge.

Discussion

We report a woman who suffered from lupus nephritis class IV + V accompanied by lupus vasculopathy. She presented with acute-to-subacute progressive renal failure with nephrotic syndrome and hypertension. Her renal function and hypertension were improved by glucocorticoid plus cyclophosphamide (CYC) therapy and antihypertensive drugs including a Ca blocker and angiotensin II receptor blocker, while proteinuria was decreased but sustained at the time of discharge.

Fig. 1 Histopathology of the kidney biopsy. **a** Light microscopy (PAS stain, 200×). Mesangial and endocapillary proliferation, duplication of glomerular basement membrane and/or “wire loop” lesions. **b** Light microscopy (200×). Cellular crescent and wire loop lesions. **c** Immunofluorescent study (200×) using frozen specimen. Coarse granular and ring-shaped (band-like) staining along GBM and mesan-

gial deposits of IgG was noted. **d–f** Electron microscopy (**d** 6000×, **e** 12000×, **f** 30000×). Subendothelial (white arrow) and subepithelial (black arrow) electron-dense deposits are frequently seen. Some deposits revealed parallel arrays (finger print). These findings were consistent with those of lupus nephritis class IV + V

As shown in Table 2, intrarenal vascular lesions in LN are classified as follows: (I) uncomplicated vascular immune complex deposits, (II) thrombotic microangiopathy (TMA), (III) true renal vasculitis, (IV) Anti-phospholipid syndrome (APS), and (V) lupus vasculopathy, which we encountered. Lupus vasculopathy is a relatively uncommon disease and accounts for only 9.5% of all vascular complications in SLE in Italy [1], 5.4% in Mexico [2], and 3.8% in China [4]. Lupus vasculopathy is seen in the skeletal muscle in addition to the kidney [10]. Appel described its pathogenesis as follows: initial endothelial cell damage associated with immune deposition is followed by plasma protein insudate in vessel walls and subsequent intravascular coagulation [3].

Table 3 summarizes recent case reports of lupus vasculopathy or a case series in the past 8 years. These data suggest that lupus vasculopathy is frequently accompanied by hypertension, as seen in the present case. Regarding renal prognosis, we reviewed three cohort studies. In 1991, Banfi et al. reported that lupus vasculopathy had lower renal survival at 5 years than SLE patients without renal

vascular lesions ($68.1 \pm 10.2\%$ vs $89.6 \pm 2.7\%$) [5], while both Wu et al. in 2013 and Mejia-Vilet et al. in 2017 did not address the poor renal outcome of lupus vasculopathy [2, 4], although vascular lesions were closely correlated with clinical disease activity and renal outcome [2]. In addition, recent case reports by Chu et al. and Kaul et al. showed that 60% and 78% of patients with lupus vasculopathy reached complete or partial remission, respectively [11, 13]. Lupus vasculopathy was reported to cause hypertension which perhaps exacerbates the vascular change, and rapid progression to renal failure. However, considering our favorable renal prognosis mentioned above and review of recent studies, the renal prognosis of lupus vasculopathy might be more favorable than previously expected by Banfi et al. in 1991, on the basis of development of treatment strategy and modern immunosuppressant. Therefore, the importance of identifying lupus vasculopathy is related to select appropriate treatment, rather than to predict renal prognosis.

Despite the importance, it is difficult to differentiate lupus vasculopathy from TMA [3] and APS, because their

Fig. 2 Histopathology of the kidney biopsy. **a** Light microscopy (HE stain, 200×). Intraluminal deposits of eosinophilic hyaline-like material without severe inflammatory cell infiltrate was noted at the vascular pole. **b** Immunofluorescent study using serial paraffin-embedded section (200×). Strong staining of IgG was detected in the material (at the same lesion of the intraluminal deposits). **c, d** Light microscopy (**c** PAS stain, **d** Masson's trichrome stain, 10×). Hyaline-like material was frequently noticed in the afferent arteriole at the vascular pole (white arrow) and in the consecutive interlobular artery (black arrow). These intraluminal materials were both PAS and fuchsin positive

Fig. 3 Clinical course during hospitalization. Renal function, the level of urine proteinuria, and therapeutic interventions are demonstrated. *IV CYC* intravenous cyclophosphamide pulse, *MP Pulse*

methylprednisolone pulse, *UP/UCr* urinary protein per urinary creatinine. The dosage of MP pulse is 1 g/day for 3 days and we used 500 mg/body for IV CYC each time

Table 2 Classification of vascular lesions. The table was adapted from the previous studies of Appel [3], Wu [4], and Sinico [17] with partial modification and summarization

Pathological/clinical classification	Location/distribution	Immuno-globulin deposits	Characters by light microscopy
Uncomplicated vascular immune complex deposits	Arterioles, capillaries, small arteries	+	The extraglomerular arteries and arterioles are usually normal There is no thrombosis, necrosis, and inflammatory infiltration of the vessel walls
Thrombotic microangiopathy	Arterioles, capillaries, small arteries	–	The affected vessels are narrowed or total occluded by intraluminal fibrin and platelet thrombi The endothelial swelling, denudation, fragmented and hemolyzed erythrocytes are also accompanied
True renal vasculitis	Arterioles, capillaries, small arteries	–	Inflammatory cells, neutrophils and mononuclear leukocytes, infiltrate the arterial walls In the acute phase, severe fibrinoid necrosis are seen frequently in the intima
Lupus vasculopathy	Arterioles, capillaries, small arteries	+	Eosinophilic and fuchsinophilic material is seen in the lumen and intima of vessels The endothelium is swollen and denuded The elastic membrane of interlobular arteries is disrupted, but there is no inflammatory infiltration
Anti-phospholipid syndrome	Arterioles, capillaries, small arteries, renal vein	–	Thrombosis of large renal vessels and microthrombi of glomerular capillaries are seen The endothelial cells are damaged by binding the anti-phospholipid antibodies

Table 3 The resent case reports of Lupus Vasculopathy in past 8 years and the present case

Author	Year	Total patient	Pathology	Management	Symptom	Prognosis
Chu [13]	2014	9	Class III (1) Class IV (8)	PE (1)	HT(5)	CR (4)
				MP (2)		PR (3)
				P (9)		TF (2)
				CYC (6)		
				AZA (1) MMF (1) LEF (1)		
Varalaxmi [12]	2015	1	Class III (1)	MP (1) P (1) CYC (1)	N/A	N/A
Kaul [11]	2017	5	Class III/IV (1) N/A (4)	HD (2)	HT (4)	CR (2)
				PE (2)		PR (1)
				MP (5)		TF (2)
				CYC (1) MMF (1)		
Mejia-Vilet [2]	2017	6	Class III/IV (3) Class V (1) Class III/IV, V(2)	CYC (5)	N/A	N/A
				MMF (1)		
Present case	2017	1	Class IV/V (1)	MP (1) CYC (1)	HT (1)	CR (1)

AZA azathioprine, CR complete remission, CYC cyclophosphamide, LEF leflunomide, MMF mycophenolate mofetil, MP methylprednisolone impulse, P oral prednisolone, PE plasma exchange, PR partial remission, TF treatment failure

lesions present with a similar morphologic pattern in vessels. A light microscopic study of both lupus vasculopathy and TMA using Hematoxylin and Eosin (HE) and Masson's trichrome stained sections showed intraluminal eosinophilic and fuchsinophilic material, respectively, as well as the narrowing or occlusion of the lumen with endothelial swelling and denudation [3]. This suggests that TMA is likely to be distributed in glomerular capillaries but not in lupus vasculopathy [3]. Regarding pathophysiology, immunostaining is very useful to distinguish between each disease subtype. Lupus vasculopathy contains immune complex including IgG and coagulation products [3]. In contrast, TMA in SLE contains thrombi induced by the activated classical pathway of complement [14], and is unrelated to immune complex [3]. Therefore, positive staining for IgG in vessel material suggests lupus vasculopathy but not TMA [3]. In the present case, because the frozen specimen lacked vascular lesions, immunofluorescent staining of the paraffin-embedded specimen was performed. This method is recommended as a salvage technique in cases of non-availability of appropriate lesions in frozen specimens [15, 16], and moreover, we propose that it can clarify the distribution pattern of vascular deposition in specimens, allowing comparison with an equivalent section stained with PAS or another stain. APS also shows similar intraluminal material by thrombosis at all levels of the renal vasculature including not only renal artery, but also renal vein [17] and vascular endothelial damage without evidence of active immune deposits [3]. Furthermore, APS intimately connected with SLE as aCLs (anti-cardiolipin antibodies) [18] was found in 72% of the patients with SLE and symptomatic APS was occurred in 22% of the patients with SLE [19]. However, in the present case, APS could be excluded by the absence of anti-phospholipid antibodies, negative clinical features of thrombotic events such as arteriovenous thrombosis and recurrent miscarriage, and the prominent IgG deposition in the luminal materials, which was not compatible with those of APS [3]. Taken together, immunostainings are greatly helpful to differentiate lupus vasculopathy from those resembling vascular lesions.

Because of the scarcity of available data regarding lupus vasculopathy, its adequate therapy has not been fully established. A study in China [20] comparing mycophenolate mofetil (MMF) and CYC in class IV with lupus vasculopathy reported that complete and partial remission in MMF was superior to CYC with less adverse events; however, a recent trend in lupus vasculopathy therapy (Table 3) suggests that various therapy options are chosen based on a case-by-case basis, indicating standard therapies have not been established. In the present case, the patient received aggressive immune suppressive therapy mainly consisting of corticosteroids and additional CYC based on the guidelines of the American College of Rheumatology [21]. We emphasize that the current

case responded well to the combination therapy, followed by an improvement in kidney function and attenuation of proteinuria, although lupus vasculopathy was frequently seen in various vessels. The clinical course implied that lupus vasculopathy itself might be a reversible lesion and could be improved if adequate therapy is performed.

In summary, we experienced lupus vasculopathy with diffuse proliferative LN. Although recent studies imply that lupus vasculopathy is no longer unfavorable vascular lesions, it is still important lesion for selecting appropriate therapy. Regarding its diagnosis, the distribution pattern of vascular lesions by light microscopy and positive IgG immunofluorescent staining using a paraffin-embedded specimen were helpful.

The current therapeutic guidelines for LN are predominantly based on glomerular lesions [21], while we are concerned that vascular lesions including lupus vasculopathy are not specifically mentioned. However, to describe it adequately, we must first clarify whether its prognosis is poor and establish a standard therapy for LN with lupus vascular lesions (e.g. confirming whether MMF is more useful compared with CYC for cases of lupus vasculopathy). Therefore, the accumulation of more case studies is required.

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Finding None.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Human and animal rights This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the article.

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