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CASE REPORT

Reversible posterior leukoencephalopathy syndrome: a possible manifestation of Wegener's granulomatosis-mediated endothelial injury

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Abstract We present the case of a 15-year-old girl who had Wegener's granulomatosis with severe intestinal involvement. During the clinical course, she developed generalized seizures and was diagnosed with reversible posterior leukoencephalopathy syndrome (RPLS). Plasma exchange combined with steroid pulse therapy was initiated and showed marked improvement. This is one of the few cases of RPLS without severe hypertension or renal failure, suggesting that RPLS is likely to be a manifestation of Wegener's granulomatosis-mediated endothelial injury.

Keywords Reversible posterior leukoencephalopathy syndrome (RPLS) · Vasculitis · Wegener's granulomatosis

Introduction

Reversible posterior leukoencephalopathy syndrome (RPLS) is a clinicoradiological disorder characterized by headache, seizures, altered mental status and visual disturbances associated with reversible changes as seen on magnetic resonance imaging (MRI) of the brain [1]. Since the first report by Hinchey et al. [1], RPLS has been associated with various conditions, including hypertension, renal insufficiency, pre-eclampsia and the use of immunosuppressive drugs such as cyclosporine A [2], tacrolimus [3] and azathioprine [4]. To our knowledge, 32 cases of RPLS complicated with various connective tissue diseases have been reported in the literature [1, 2, 5–19]. Of these 32 cases, 17 were associated with systemic lupus erythematosus and only two were associated with Wegener's granulomatosis [6, 9]. Here, we report a case of Wegener's granulomatosis complicated by RPLS and discuss the pathogenesis of RPLS in this case.

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Case report

A 15-year-old girl was transferred to our hospital because of high fever, abdominal pain, melena, and bloody sputum. She had been in good health until 1 month previously, when she developed a high fever and swelling in the lower limbs. She visited her family physician and was diagnosed with cellulitis. She was hospitalized and treated with antibiotic therapy, without noticeable effects. Thereafter, she developed melena, abdominal pain, and purpura in the lower limbs. Laboratory studies revealed a serum creatinine of 0.55 mg/dl and blood urea nitrogen of 18.7 mg/dl. Urinalyses showed (±) for proteinuria and (2+) for ocuult blood. Gastrointestinal endoscopy revealed extensive ulcers and mucosal loss in the duodenum. She was diagnosed with Henöch–Schönlein purpura and treated with intravenous prednisolone therapy at 80 mg daily with little effect; the dose of prednisolone was rapidly tapered to 5 mg daily over 3 weeks. Because her symptoms worsened and hemoptysis appeared, a 3-day course of methylprednisolone pulse therapy (1,000 mg daily) was used. She was thus transferred to our hospital for further evaluation and treatment.

At the time of admission, her blood pressure was 114/90 mmHg and pulse rate was 64 beats per minute. There were small palpable nodules on her forehead and multiple purpura were observed on her lower limbs. Opthalmologically, she had no visual blurring or conjuctival injection. Although she had repeated epistaxis, saddle nose deformity and nasal discharge were not observed. There was no evidence of otorrhea, stomatitis, or pharyngitis. There was generalized muscular rigidity of the abdomen along with marked tenderness, and bowel sounds were weak. Rectal examination revealed fresh bleeding.

Laboratory results showed leukocytosis, normochromic normocytic anemia, slightly elevated transaminases, hypoalbuminemia normal renal function and a mild increase in C-reactive protein (CRP) levels. A high titer of proteinase 3 antineutrophil cytoplasmic antibody (PR-3 ANCA) was detected. Repeated urinalyses showed (±) for proteinuria and (2+) for occult blood (Table 1).

Chest X-ray showed bilateral infiltrative shadow and a thick-walled cavity in the left lower lobe. Computed tomography (CT) scan revealed the ground glass opacity in both lung fields and a cavity at S10 of the left lung. These findings suggested alveolar hemorrhage and granulomatous inflammation due to pulmonary vasculitis. Gastrointestinal endoscopy repeated at our hospital revealed extensive ulcers and mucosal loss of the duodenum (Fig. 1a). Endoscopy of the colon showed scattered ulcers and mucosal loss in the terminal ileum along with the lesions seen on gastrointestinal endoscopy. Microscopic examination of the duodenum revealed nonspecific inflammation with granulation and necrosis. Although histopathological confirmation was not obtained, we diagnosed her as having Wegener's granulomatosis with intestinal involvement based on a high titer of PR-3 ANCA and pulmonary vasculitis.

The patient was treated with a 3-day course of methylprednisolone pulse therapy (at a local hospital) followed by intravenous prednisolone therapy at 60 mg daily and intravenous cyclophosphamide 400 mg weekly. After this treatment, melena, hemoptysis, and the nodular lesion on the forehead disappeared, PR-3 ANCA titer gradually decreased, and follow-up CT scan revealed improvement of the ground glass opacity. However, the high fever and severe abdominal pain persisted and her CRP level rose. Complications associated with intestinal infection were suspected, and antibiotic therapy was administered. Prednisolone therapy was gradually tapered. On day 32, although fever persisted, PR-3 ANCA titer decreased to 164 U/ml (Fig. 2).

On day 34, she suddenly complained of a severe headache and nausea followed by a generalized convulsion. Her blood pressure was 126/60 mmHg. CT scan revealed bilateral low-density areas in the occipital and posterior

Table 1 Laboratory data on admission

Blood cell count	
White blood cell	35,680 per μl
Neutrophil	92.3%
Lymphoid cell	5.6%
Monocyte	2.0%
Eosinophil	0.0%
Basophil	0.1%
Red blood cell	302×10^4 per μl
Hemoglobin	9.1 g/dl
Hematocrit	26.5%
MCV	87.7 fl
MCH	30.1 pg
MCHC	34.3 g/dl
Platelet	27.2×10^4 per μl
Blood chemistry	
AST	21 IU/l
ALT	46 IU/l
ALP	337 IU/l
LDH	317 IU/l
ChE	62 IU/l
CK	16 IU/l
γ-GTP	144 IU/l
Total bilirubin	0.8 mg/dl
Total protein	4.6 g/dl
Albumin	41.5% (2.0 g/dl)
α1-Globulin	9.2%
α2-Globulin	12.4%
β-Globulin	12.3%
γ-Globulin	24.6%
Urea nitrogen	23.7 mg/dl
Creatinine	0.47 mg/dl
Sodium	130 mEq/l
Potassium	4.6 mEq/l
Chloride	95 mEq/l
Glucose	362 mg/dl
Total cholesterol	111 mg/dl
HDL-cholesterol	28 mg/dl
Triglyceride	82 mg/dl
Serological test	
CRP	3.17 mg/dl
Immunoglobulin G	1,051 mg/dl
Immunoglobulin A	167 mg/dl
Immunoglobulin M	185 mg/dl
C3	91.8 mg/dl
C4	11.8 mg/dl
CH50	32.1 U/ml
RF	901 IU/ml
ANA	40×
Proteinase 3 ANCA	411.0 U/ml
Myeloperoxidase ANCA	1.3 U/ml

Table 1 continued

Urinalysis	
pH	7.5
Specific gravity	1.012
Protein	(±)
Occult blood	(2+)
Glucose	(2+)

MCV mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase, *ChE* choline esterase, *γ-GTP* γ-glutamyl transpeptidase, *ALP* alkaline phosphatase, *CRP* C-reactive protein, *RF* rheumatoid factor, *ANA* anti-nuclear antibody, *ANCA* antineutrophil cytoplasmic antibody

parietal lobes. T2-weighted MRI showed bilateral high-intensity areas in the white matter of the occipital, parietal, and frontal lobes (Fig. 3a). These findings suggested the onset of RPLS. Examination of cerebrospinal fluid showed no abnormalities. Anticonvulsant and anesthetic therapy were administered under intubation to control convulsions. Because her average blood pressure before the onset of RPLS was 126/80 mmHg and renal function was normal (creatinine 0.27 mg/dl), we considered the cause of RPLS to be Wegener's granulomatosis-mediated endothelial injury. Two courses of methylprednisolone pulse therapy combined with plasma exchange were performed to control vasculitis. Cyclophosphamide therapy was not withdrawn. After the pulse therapy, her blood pressure rose (maximum 160/80 mmHg), but was well controlled by intravenous antihypertensive medication. Follow-up MRI 13 days after the first studies revealed almost complete resolution of abnormal lesions (Fig. 3b), which confirmed the diagnosis of RPLS. Her consciousness and mental status gradually recovered and no sequelae were observed. Her PR3-ANCA level gradually decreased and reached 15.3 U/ml on day 87 (Fig. 2). Follow-up gastrointestinal endoscopy done on day 79 revealed almost complete regeneration of the duodenum membrane (Fig. 1b). She was discharged on day 102 with no neurological manifestations while receiving 17.5 mg of

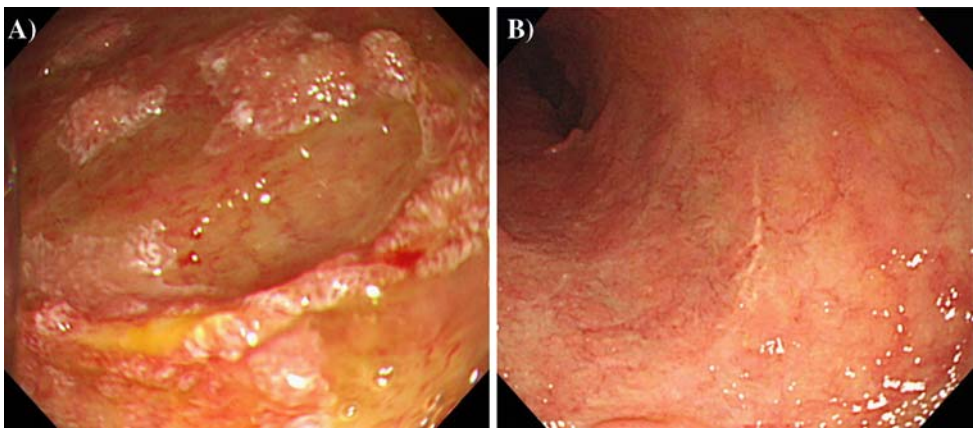

Fig. 1 **a** Gastrointestinal endoscopy (on the first day) revealed extensive ulcers and mucosal loss of the duodenum. **b** Follow-up examination (on day 79) showed almost complete regeneration of the duodenum membrane

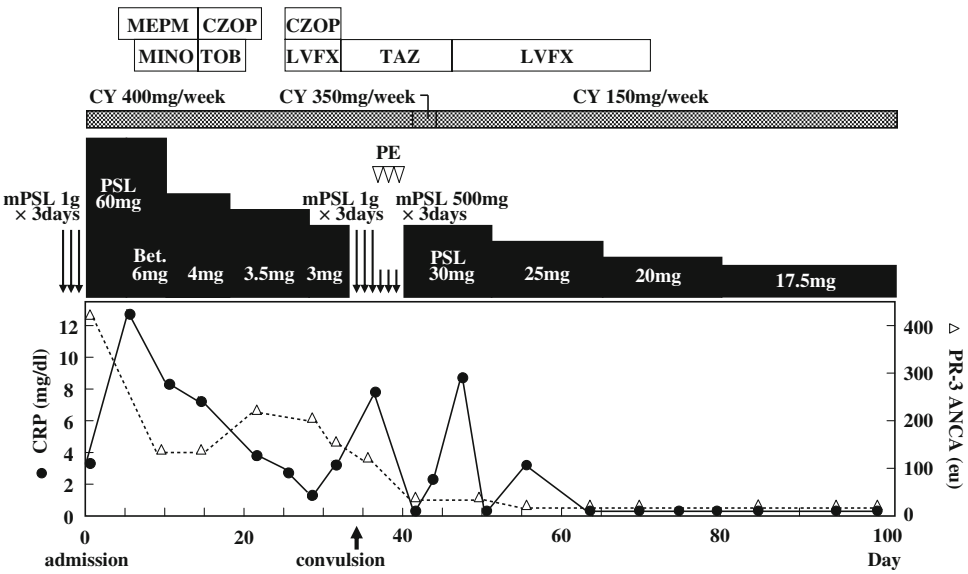

Fig. 2 Clinical course after admission. *PSL* prednisolone, *Bet.* betamethazone, *mPSL* methylprednisolone, *CY* cyclophosphamide, *PE* plasma exchange, *MEPM* meropenem, *CZOP* cefozopran, *MINO* minocycline, *TOB* tobramycin, *LVFX* levofloxacin, *TAZ* tazobactam, *PR-3 ANCA* proteinase 3 myeloperoxidase antinutrophil cytoplasmic antibody

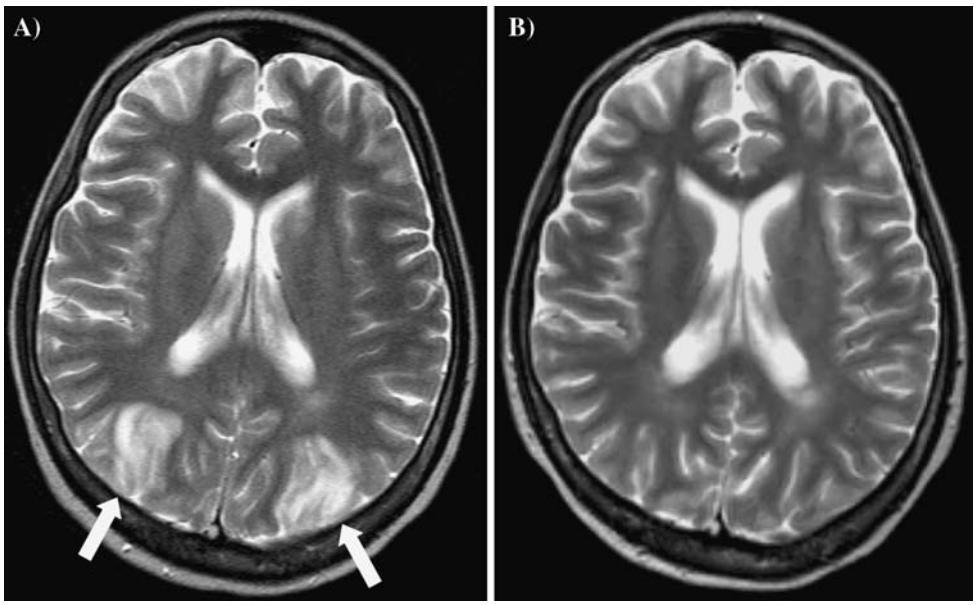

Fig. 3 **a** Brain T2-weighted magnetic resonance imaging (on day 34) revealed bilateral high-intensity areas in the *white* matter (*arrows*) of the occipital, parietal and frontal lobes. **b** Follow-up MRI 13 days after the first studies revealed almost complete resolution of the abnormal lesions

prednisolone therapy daily, and 200 mg of cyclophosphamide therapy weekly.

Discussion

The pathogenesis of RPLS is not completely understood, but it is believed that the most fundamental mechanism of RPLS is vasogenic edema caused by cerebral endothelial injury [1]. This endothelial injury is frequently attributed to severe hypertension, renal failure and cytotoxic medications [1–4, 12].

In the case of rheumatologic disease, the etiology of RPLS is more complicated. Table 2 [5, 7–9, 14–16] shows the clinical characteristics of 18 cases in which sufficient data regarding the preceding medications, blood pressure, serum creatinine level and therapy are described. Most of the previously reported cases of RPLS associated with rheumatologic disease, including both reported cases of Wegener's granulomatosis, had severe hypertension or renal failure. Furthermore, because almost all rheumatologic patients required immunosuppressive therapy, especially during the active phase of the primary disease, RPLS has rarely been regarded as a direct result of disease activity.

In the present case, we considered several mechanisms for the development of RPLS. First, RPLS may be a direct result of Wegener's granulomatosis-mediated vascular injury. In vitro evidence suggests that PR-3 ANCA causes direct injury to the endothelium by activating neutrophils [20]. Endothelial damage may increase vascular permeability, which can break the blood–brain barrier, resulting in leakage of plasma into the brain parenchyma [1, 15]. Our case is one of the few cases without hypertension or renal failure, suggesting that RPLS can be a manifestation of the disease activity.

Second, RPLS may be a complication of treatment for Wegener's granulomatosis. In cases of rheumatologic disease, it has been reported that risk factors for the development of RPLS include recent treatment with cyclophosphamide therapy [15]. However, cyclophosphamide therapy has usually been used for patients who have other risk factors such as hypertension and/or renal failure [6, 14]. Moreover, in cases of RPLS seen in the oncology literature, high-dose cyclophosphamide therapy has been used in combination with other chemotherapy agents [21]. Thus, it is doubtful that the use of cyclophosphamide therapy is a risk factor for the development of RPLS.

The use of high-dose corticosteroid therapy has also been reported to be a risk factor for the development of RPLS [6]. Corticosteroid therapy has been shown to inhibit endothelial prostacyclin production and increase thromboxan A2 production, leading to platelet aggregation and a decrease in blood flow to the organs [22]. The decreased renal cortical blood flow activates the renin-angiotensin system, which precipitates endothelial dysfunction and results in rapid elevation of blood pressure. Consequently, the use of corticosteroid therapy may trigger the development of RPLS. However, in the present case, the average blood pressure before and soon after the onset of RPLS was 126/80 mmHg. Although we cannot deny that the slight increase of blood pressure for her age had some influence on vascular permeability, it is not reasonable to regard this as the only cause of RPLS.

On the basis of the ideas mentioned above, we concluded that RPLS was a manifestation of Wegener's granulomatosis-mediated vascular injury rather than a

Table 2 Clinical characteristics of 18 cases of RPLS with connective tissue disease

Year	First author	Age/sex	Underlying disease	Preceding medications	Blood pressure (mmHg)	Creatinine (mg/dl)	Therapy for RPLS
1997	Arai	57/M	Classical PN	mPSL pulse/CY	200/140	1.8	PSL
2001	Primavera	23/M	WG	mPSL pulse/CY	220/150	3.6	CY withdrawn
		22/F	SLE	mPSL/CY	200/130	4.4	CY withdrawn
		22/F	SLE	CY/AZA	170/110	9.5	HD/CY withdrawn
		30/F	SLE	PSL	210/125	6.2	HD/CY withdrawn
2002	Kawano	73/F	MPA	mPSL pulse	200/116	0.97	mPSL pulse
		77/F	MPA	mPSL pulse	186/123	3.08	
2004	Ohta	14/F	WG	PSL/CY	180/92	7.8	
2006	Magnano	37/M	SLE	PSL	210/100	3.7	
		24/F	SLE	CY/PSL	156/94	5.2	CY withdrawn
		32/F	SLE	CY/PSL	175/97	1.8	CY withdrawn
		30/F	SLE	CY/PSL	158/110	3.1	CY withdrawn
		40/F	SLE	PSL	180/100	3	
2006	Min	22/F	SLE	CY/PSL	200/110	2.5 (HD)	PE/mPSL pulse/CY withdrawn
2006	Kur	29/F	SLE	CS/PSL	206/135	1.5	CS withdrawn/midazolam
		23/F	SLE	PSL	140/90	1.1	CY/mPSL pulse
		23/F	SLE	PSL/MM	194/126	1.7	PE/CY/mPSL pulse
	Present case	15/F	WG	PSL/mPSL/CY	126/60	0.27	mPSL pulse/PE

PN polyarteritis nodosa, *WG* Wegener's granulomatosis, *SLE* systemic lupus erythematosus, *MPA* microscopic polyangitis nodosa, *mPSL* methylprednisolone, *CY* cyclophosphamide, *AZA* azathioprine, *PSL* prednisolone, *CS* cyclosporine, *MM* mycophenelate mofetil, *HD* hemodialysis, *PE* plasma exchange

complication of medications. Because cyclophosphamide is the key drug to control the activity of Wegener's granulomatosis and was the most frequently used therapy for RPLS with rheumatologic disease in the reported cases, we decided to continue cyclophosphamide therapy. High-dose corticosteroid therapy is also said to be useful for the treatment of RPLS because corticosteroid therapy alters the brain vascular permeability [23]. Therefore, we decided to administer methylprednisolone pulse therapy to reduce vascular permeability and control disease activity. It has been reported that plasma exchange is useful for the treatment of ANCA-related vasculitis because it can quickly remove the ANCA [24]. Thus, we initiated a 3-day course of plasma exchange combined with pulse therapy, which resulted in rapid reduction of PR-3 ANCA titer. Although her blood pressure rose after the pulse therapy, it was well controlled with using antihypertensive medication. The therapeutic regimen used resulted in an excellent patient outcome in this case.

Intestinal involvement associated with Wegener's granulomatosis is uncommon, and only scattered cases of intestinal involvement have been reported [25–29]. Autopsy studies of patients with Wegener's granulomatosis showed intestinal involvement in 24% of cases, although none of these patients had symptoms associated with gastrointestinal involvement [30]. A large prospective study of 158 patients with Wegener's granulomatosis reported no intestinal involvement throughout the course of disease [31]. The relationship between the onset of RPLS and severe intestinal involvement is uncertain. However, it has been reported that intestinal involvement in Wegener's granulomatosis occurs in active phase of the disease [26], suggesting that intestinal involvement may be a marker of severity of endothelial injury, which may be one reason for the development of RPLS in the present case.

In summary, we encountered a patient who developed RPLS following therapy for Wegener's granulomatosis with severe intestinal involvement. This is one of the few cases of RPLS without severe hypertension or renal failure, suggesting that RPLS is likely to be a manifestation of Wegener's granulomatosis-mediated endothelial injury.

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