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CASE REPORT

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Mononeuritis multiplex, protein-losing gastroenteropathy, and choroidopathy seen together in a case of systemic lupus erythematosus

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Abstract A 43-year-old woman with systemic lupus erythematosus (SLE) had an episode of mononeuritis multiplex prior to developing protein-losing gastroenteropathy. Four years later, she had another episode of mononeuritis multiplex, followed by choroidopathy. These manifestations are uncommon in SLE, but may be attributed to vasculitis. The laboratory findings indicated that the elevation of D-dimer and thrombin–antithrombin complex levels seen in this case might be useful in evaluating vascular lesions in SLE.

Key words Choroidopathy · Mononeuritis multiplex · Protein – losing gastroenteropathy · Systemic lupus erythematosus (SLE) · Vasculitis

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic disease characterized by a great variety of autoantibodies and immune complexes. While mononeuritis multiplex is one of the neurological signs commonly associated with SLE, the clinical manifestations of protein-losing gastroenteropathy and choroidopathy are uncommon in this illness.[1–3] Here we present a case of SLE with mononeuritis multiplex, protein-losing gastroenteropathy, and choroidopathy.

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Case report

A 31-year-old woman was referred to our hospital in May 1984 after developing erythematous macules on her hand, foot, and face. Laboratory studies showed leukopenia, high titers of ANA, and anti-dsDNA antibody, and low complement activity (CH50). SLE was diagnosed, and she was treated with 20 mg/day prednisolone (PSL), which was gradually reduced to 5 mg/day.

On March 19, 1996 (age 45), she had a sudden onset of numbness and weakness in her left leg (Fig. 1a). On examination, she was found to be hypotensive (94/48 mmHg), and she had slight pyrexia (37.5°C). There were no abnormal findings in the chest or abdomen. Neurological examination revealed a weakness of the left anterior tibial and left gastrocnemius muscles, loss of sensation in the left foot and leg, and diminished left ankle jerk. Motor nerve conduction velocities (MCV) of the right and left peroneal nerves were 52.3 m/s and 87.5 m/s, respectively, indicating axonal degeneration of the left peroneal nerve at the level of the fibular head, and of the left tibial nerve at the level of the ankle.

Two weeks later, the patient had an episode of melena. Laboratory examination revealed lymphocytopenia, hypoproteinemia, elevation of serum amyloid protein A (SAA) and C-reactive protein (CRP), low complement activity, and a high titer of anti-DNA antibodies (Table 1). Activated partial thromboplastin time (APTT) was within the normal range, and both anticardiolipin antibody and the rapid plasma reagin test were negative. The levels of D-dimer and thrombin–antithrombin (TAT) complex were elevated. Angiography of the left lower leg showed narrowing of the popliteal artery from its origin (figure not shown), and the disappearance of the lateral plantaris arch (Fig. 2a). The branches of the mesenteric arteries were also narrowed or interrupted (Fig. 2b–d). A scintigram using ^{99m}Tc-diethyltriaminepentaacetic acid (DTPA) labeled with human serum albumin (HSA) revealed loss of protein from the colon (Fig. 3). The leaked ^{99m}Tc–DTPA–HSA had collected around the right common iliac artery, indicating that the lesion was limited, not diffuse. Unfortunately, fiberoptic

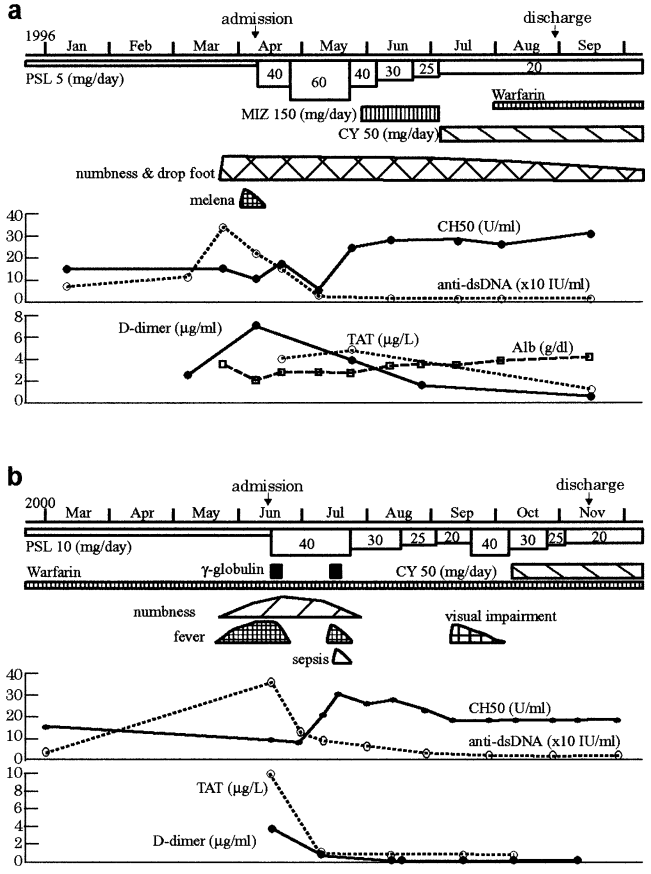

Fig. 1. The clinical course of the patient. *PSL*, prednisolone; *CY*, cyclophosphamide; *SAA*, serum amyloid protein A; *TAT*, thrombin – antithrombin complex; *Alb*, albumin. **a** 1996; **b** 2000

colonoscopy could not be completed because of the pain involved. Combination therapy of PSL (60 mg/day), cyclophosphamide (CY) (50 mg/day), and warfarin improved the patient's clinical condition. The dose of PSL was successfully tapered to 10 mg/day, and CY was able to be stopped after 1 year.

In May 2000 (age 49), the patient had another episode of fever, numbness, and weakness in her left leg, as shown in Fig. 1b. Laboratory data were similar to those found in 1996, with the exception of a slightly prolonged APTT due to warfarin. A ^{99m}Tc–DTPA–HSA scintigram was conducted and found to be normal. The neurological symptoms in her left leg were eliminated by increasing the PSL dose to 40 mg/day. In August, she complained of dry eye. Schirmer's test and rose bengal staining indicated keratoconjunctivitis sicca, but corrected vision was normal (1.5 bilaterally). On September 12, the patient complained of diminished vision in her left eye. The corrected vision on the left had decreased to 0.2. Funduscopy revealed an area of serous retinal detachment, and a fluorescein angiogram showed fluorescein leakage (Fig. 4a). Indocyanine green angiography (ICG) showed an area of choroidal vascular hyperfluorescence (Fig. 4b). The effusions spread over the fundus, including the macula lutea. No significant abnormality was found in the right eye. Administration of an increased dose of PSL (40 mg/day) resolved the left-sided serous retinal detachment and restored the vision to 1.0. CY (50 mg/day) was then added to the treatment regimen and the patient was discharged on November 11.

Discussion

This case had unique clinical features, including numbness, melena, protein-losing gastroenteropathy, and choroidopathy. Angiography revealed multiple lesions of arteries resembling those seen in polyarteritis nodosa (PN), where inflammatory cells may infiltrate all layers of the vessel wall and perivascular areas (necrotizing vasculitis). The presence of p-antineutrophil cyloplasmic autoantibodies (p-ANCA) was suggestive of a PN-like systemic vasculitis, although p-ANCA is also positive in 31% of patients with SLE.[4] The neurological findings and MCV were consistent with those seen in mononeuritis multiplex. The neurological findings also corresponded well to the site of the vascular lesions in the patient's left leg, indicating that these lesions were responsible for the numbness and weakness occurring there. Similarly, the rapid resolution of melena with corticosteroid therapy suggests that this symptom was due to ischemic colitis associated with necrotizing vasculitis. Conversely, protein-losing gastroenteropathy remained even after resolution of the melena. Although we could not obtain intestinal biopsy specimens, a number of studies have demonstrated that histological findings in SLE with protein-losing gastroenteropathy were either normal, or showed edema, infiltration of mononuclear cells, or lymphangiectasia, but that necrotizing vasculitis was rare.[2,5,6] In some cases associated with autoimmune diseases, deposits of immunoglobulin and/or complement have been shown in the intestinal vessels.[7] Elevated serum levels of SAA, as seen in this case, could suggest amyloidosis as a cause of the protein-losing gastroenteropathy.[8,9] However, this possibility is unlikely here, as amyloid-associated gastroenteropathy is usually resistant to immunosuppressive therapies, whereas steroid therapy was effective in the present case.[10,11] A diagnosis of amyloidosis was made even less likely by the observation that SAA levels were within the normal range during the inactive phase of the SLE.

Another unusual manifestation in this case is choroidopathy, which is an uncommon feature of SLE.[3] The choroid consists mainly of a dense capillary plexus, and its internal surface is firmly attached to the retina. Since the venous pressure of the choroid is higher than the intraocular pressure, damage of this capillary plexus resulted in leakage from the capillary, causing a serous retinal detachment. Choroidopathy is seen in a variety of diseases, e.g., infection, hypertension, diabetes mellitus, malignancy, and immunologic diseases, including SLE and sarcoidosis.[12–18] SLE was the only one of the above-mentioned conditions suggested in our patient. She was also diagnosed with Sjögren's syndrome in 2000, and while it is possible that this syndrome was responsible for her choroidopathy, no reports of choroidopathy associated with Sjögren's syndrome

Table 1. Laboratory findings on admission

Admission	April 10, 1996	June 14, 2000	Admission	April 10, 1996	June 14, 2000
Urinalysis			CK (IU/l)	20	37
Protein	1+	1+	BUN (mg/dl)	7	8
Sugar	–	–	Cr (mg/dl)	0.3	0.6
Occult blood	–	–	UA (mg/dl)	2.9	3.3
			Na (mEq/l)	136	137
WBC (/μl)	6500	3500	K (mEq/l)	2.9	3.5
Seg. (%)	71	43	Cl (mEq/l)	102	101
Stab. (%)	16	48			
Eosi. (%)	2	0	ESR (mm/h)	115	56
Baso. (%)	0	0	SAA (μg/ml)	27.9	82.2
Ly. (%)	6	4	CRP (mg/dl)	1.9	1.0
Mono. (%)	1	2			
RBC ($\times 10^4$/μl)	424	399	IgG (mg/dl)	2346	1899
Hb (g/dl)	11.0	10.6	IgA (mg/dl)	390	245
Ht (%)	34.4	32.9	IgM (mg/dl)	380	430
PLT ($\times 10^4$/μl)	23.9	7.2	C3 (mg/dl)	38	36
			C4 (mg/dl)	4	7
APTT (s)	29.6	44.7	CH50 (U/ml)	10.1	10.4
Fib (mg/dl)	402.7	358	ANA	1280	640
FDP (mg/ml)	21.2	20.1	RA	(−)	ND
D-dimer (<0.5 mg/ml)	7.2	3.9	Anti-dsDNA (<12 IU/ml)	209.5	>400
TAT (<2.5 mg/l)	3.9	10.2	Anti-ssDNA (<25 AU/ml)	554.6	685
TM (<4.0 FU/ml)	8.7	2.8	Anti-cardiolipin (<10 U/ml)	ND	6.6
			Anti-Sm (<5 U/ml)	ND	6.9
T-Bil (mg/dl)	0.4	0.5	Anti-SS-A (<7 U/ml)	ND	21.3
AST (IU/l)	30	39	Anti-SS-B (<10 U/ml)	ND	8.5
ALT (IU/l)	22	25	C-ANCA (<3.5 U/ml)	ND	1.1
LDH (IU/l)	441	842	P-ANCA (<9 U/ml)	ND	10.1
ALP (IU/l)	182	135	Coombs	–	ND
γGTP (IU/l)	30	22	Cryoglobulin	–	ND
ChE (IU/l)	76	98	RPR	–	–
TP (g/dl)	6.1	6.3	HBs Ag	–	ND
Alb (g/dl)	2.4	3.0	HCV Ab	–	ND

WBC, white blood cells; RBC, red blood cells; PLT, platelets; APTT, activated partial thromboplastin time; Fib, fibrinogen; FDP, fibrin degradation product; TAT, thrombin–antithrombin complex; TM, thrombomodulin; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl-transpeptidase; ChE, cholinesterase; TP, total protein; Alb, albumin; CK, creatine kinase; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; ESR, erythrocyte sedimentation rate; SAA, serum amyloid protein A; CRP, C-reactive protein; Ig, immunoglobulin; CH50, 50% hemolytic complement activity; ANA, antinuclear antibodies; RA, rheumatoid arthritis test; ANCA, antineutrophil cytoplasmic antibodies; RPR, rapid plasma reagin test; HBs Ag, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody; ND, not determined

could be found in the literature except for a case of ischemic choroidopathy.[19] Systemic vascular diseases, including lupus nephritis, CNS lupus, and systemic vasculitis, are important predisposing factors in lupus choroidopathy.[18] Histopathological studies in lupus choroidopathy have demonstrated an infiltration of mononuclear cells and immunoglobulin deposition in the vascular layer of choroid capillaries.[20,21]

We administered prednisolone and cyclophosphamide in this case because the combination therapy has been shown to be effective in patients with lupus choroidopathy and systemic vascular disease.[22,23] This therapy successfully resulted in recovered vision, and also stopped protein loss from the intestines, indicating that the immune mechanism might be responsible for the patient's choroidopathy and protein-losing gastroenteropathy, as well as her mononeuritis multiplex.

As far as we know, this is the first presentation to show the coexistence of choroidopathy, protein-losing gastroenteropathy, and mononeuritis multiplex. We should therefore consider other disease states which could cause a similar clinical picture, such as retinal and choroidal ischemic syndrome, digestive tract and renal small vessel hyalinosis, and intracerebral and phenotypic abnormalities. These might constitute a new family syndrome.[24] However, our patient did not have any cerebral or renal lesions, and there was no suggestion of these in her family history. It is therefore reasonable to conclude that both the choroidopathy and the protein-losing gastroenteropathy could be attributed to a single mechanism in which the deposition of immunoglobulin, complement, and immune complex play a role in vessel hyperpermeability.

Finally, we should like to address the possibility of covert vasculitis in SLE. A diagnosis of protein-losing gastroenteropathy or choroidopathy is straightforward when a ^{99m}Tc–DTPA–HSA scintigram, or a fluorescein angiography and ICG angiogram are used.[18,25] However, some cases of protein-losing gastroenteropathy may subside with the treatment of other symptoms without ever having been symptomatic. Also, choroidopathy may be often missed because the patients are not likely to have symptoms unless the lesion involves the macula lutea. Furthermore, funduscopy might not reveal significant changes in the retina even

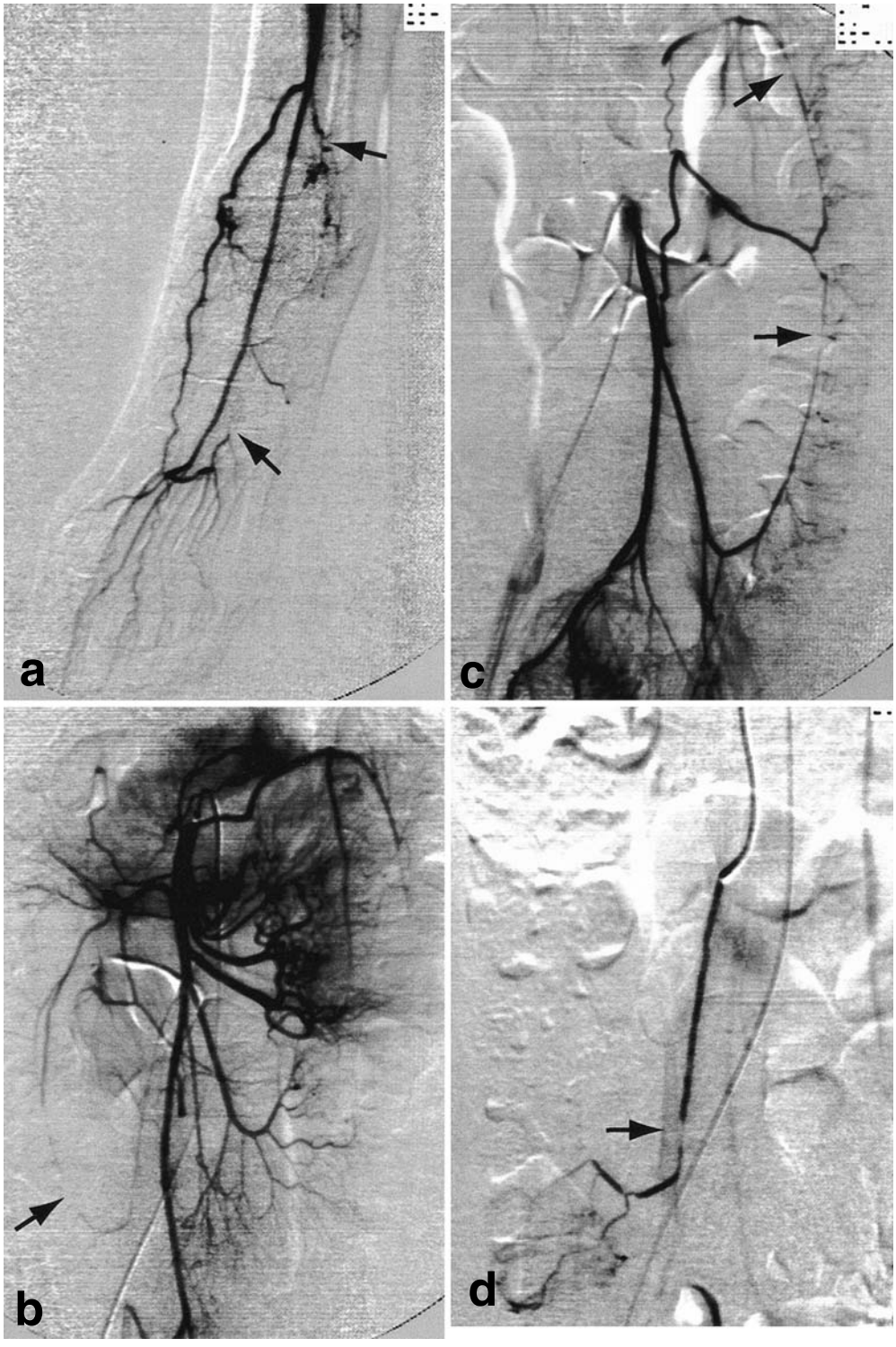

Fig. 2. Angiography of **a** the left femoral artery, **b** the superior mesenteric artery, **c** the inferior mesenteric artery, and **d** the ileo colic artery. *Arrows* indicate typical lesions of the arteries

when choroidopathy is present. It is therefore necessary to consider these covert vasculitides even when no overt vasculitis exists. We noted that the levels of D-dimer or TAT complex (the parameters for hypercoagulation or fibrinolysis activation) were elevated during the episodes of vasculitides. These levels were well correlated with the patient's disease activity, and were negatively correlated with serum albumin levels (see Fig. 1a). It is possible that levels of D-dimer and TAT complex are useful in evaluating the damage to vascular endothelium, including covert vasculitides, in patients with active SLE.

In conclusion, we have described the case of a patient with SLE who showed choroidopathy, protein-losing gastroenteropathy, and mononeuritis multiplex. This may be

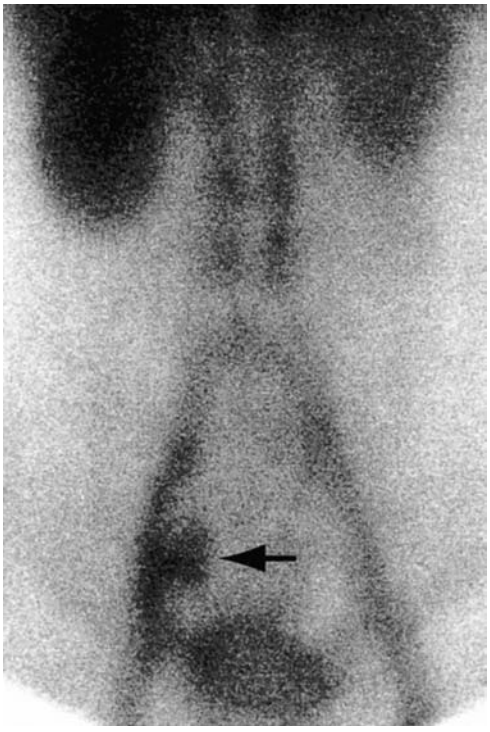

Fig. 3. ^{99m}Tc-diethyltriaminepentaacetic acid (DTPA) scintigram-labeled human serum albumin (HSA). The *arrow* indicates a site where leakage occurred

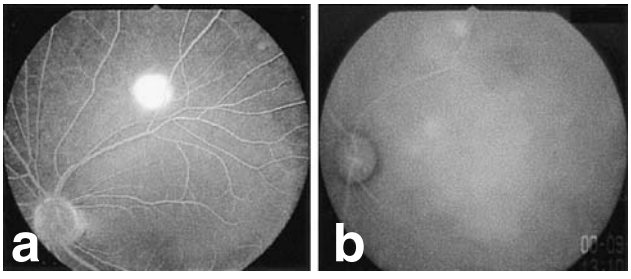

Fig. 4. Left eye. **a** Fluorescein angiography showing an area of fluorescein leakage. **b** Indocyanine green angiogram, late phase, showing an area of subretinal leakage with pooling corresponding to the area of serous retinal detachment and serous elevation

the first report to show the coexistence of these manifestations in a case of SLE.

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