

Cerebral and Retinal Vascular Changes in Systemic Lupus Erythematosus

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Abstract: A 16-year-old white boy with acute systemic lupus erythematosus (SLE) who presented with chorea and florid retinopathy died in renal failure three months after diagnosis. Pathological studies revealed two types of lesion in both the cerebral and ocular vessels. Some meningeal and choroidal vessels showed a typical vasculitis with fibrinoid necrosis, whereas other meningeal and retinal vessels were occluded by amorphous hyaline material in the absence of vasculitis. [Key words: choroidal vessels, retinal vessels, systemic lupus erythematosus.] *Ophthalmology* 92:444-448, 1985

Patients with systemic lupus erythematosus (SLE) may develop retinal or cerebral symptoms. Fortunately the severity of these complications has been reduced in recent years due to earlier diagnosis and better treatment. We describe the clinical and post mortem findings in a young patient with acute, severe SLE who presented with neurological symptoms and developed a florid retinopathy.

CASE REPORT

Case 1. A 16-year-old bank clerk presented in October 1979 with a six-week history of colicky abdominal pain, diarrhea and weight loss. His parents and friends had noticed that he had become increasingly withdrawn during this time. There was no relevant family or past history and he had never travelled abroad. He was not taking any drugs.

Examination showed a thin young man who was febrile (39.7° C) with purpura on his left shoulder and a left subconjunctival hemorrhage. The pulse was rapid, the blood pressure was 80/55 mmHg and there was a cardiac mid-systolic murmur. The abdomen was doughy but there were no masses or localized areas of tenderness. Rectal examination was normal. Examination of the central nervous system revealed continuous choreiform movements which particularly affected the upper limbs. Tests of higher mental function were performed slowly but correctly with good cooperation. There were no

other focal neurological signs. Visual acuity was 6/5 in the right eye and 6/6 in the left with a supero-nasal field defect. There was no inflammation in the anterior chamber or vitreous cavity of either eye. The right optic disc and retinal vessels were normal, but there was a cotton wool spot temporal to the optic disc (Fig 1) and a deep retinal hemorrhage was seen in the infero-temporal quadrant. The left optic disc was normal, but the infero-temporal retinal artery was occluded with associated extensive retinal cloudy swelling. The affected arterioles were filled with segments of dark brown material and were blocked completely beyond the occlusion (Fig 2).

Relevant investigations were Hb 8.4 g/dl, white count 11,600/cmm and ESR 83 mm/Hour. Urine microscopy revealed hematuria and proteinuria. The urea was 12.6 mmol/l and serum creatinine 180 µmol/l.

Immunological investigations showed low C4 (0.09 gm/l), raised circulating immune complexes: C1q 2.52 mg IgG/l (1.1 ± 0.1) and PEG 40.0 mg Ig/dl. Anti-nuclear factor (diffuse IgG) was positive 1:40 and mitochondrial antibodies type V positive 1:80. DNA antibodies were present 95 u/ml. Both hepatitis B antigen and rheumatoid factor were absent. An echocardiogram showed a cardiomyopathy. The cerebrospinal fluid was normal. The protein was 20 gm/litre, oligoclonal bands were absent and the white count was less than 1 cell/cmm.

A renal biopsy confirmed the presence of acute arteritis involving small arteries and arterioles, and causing extensive infarction of the kidney. Crescents were present associated with fibrinous exudation in Bowman's capsule. Severe tubular damage had occurred and many tubules contained red cell casts.

The clinical diagnosis of systemic lupus erythematosus was confirmed by the raised DNA binding titer, the presence of type V mitochondrial antibodies and the findings at the renal biopsy.

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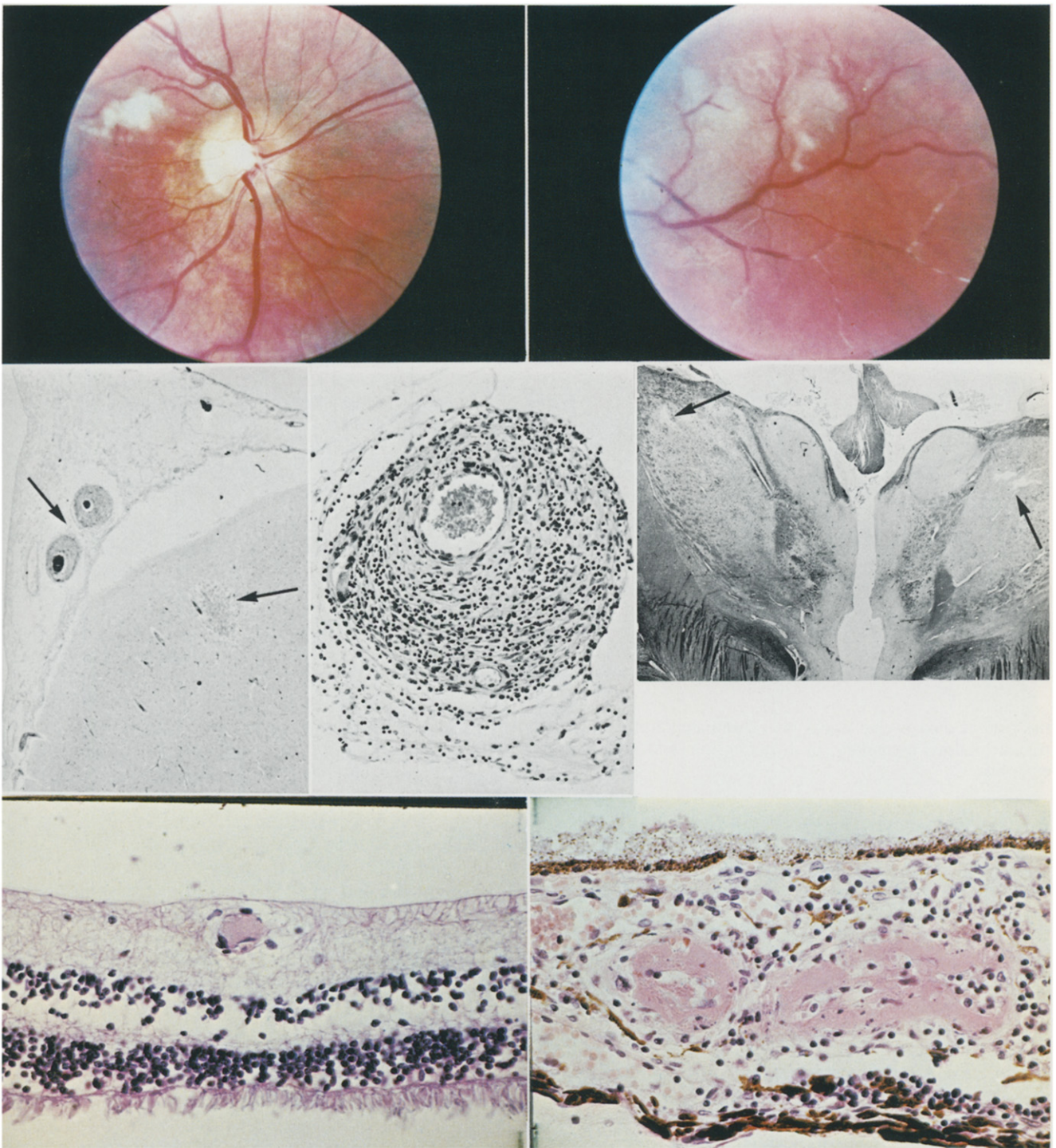


Fig 1. *Top left*, right eye showing large cotton-wool spot. **Fig 2.** *Top right*, infero-temporal quadrant of left eye. Proximally the artery contains dark red material (?) stagnation thrombus and distally it contains white material. The surrounding retina shows cloudy swelling. **Fig 3.** *Second row left*, cerebral meninges. Two arteries showing arteritis with infarct in cerebral cortex (arrows) (hematoxylin Van Gieson, $\times 33$). **Fig 4.** *Second row center*, arteritis of meningeal vessel (hematoxylin-eosin, $\times 330$). **Fig 5.** *Second row right*, a small infarct is demonstrated in each thalamus (arrows) (luxol fast blue, $\times 4$). **Fig 6.** *Bottom left*, a terminal arteriole in the retina is occluded by amorphous hyaline material, but there is no sign of vasculitis. (The detachment of the retina is a postmortem artifact) (hematoxylin-eosin, $\times 430$). **Fig 7.** *Bottom right*, occluded arterioles in the choroid showing vasculitis and fibrinoid necrosis (hematoxylin-eosin, $\times 430$).

Treatment was started with prednisolone and azathioprine but renal function and mental state continued to deteriorate. A course of 8 plasmaphereses produced temporary improve-

ment. However, further renal and myocardial deterioration occurred leading to pulmonary edema requiring dialysis.

Dialysis was followed by severe circulatory problems and

Table 1. Retinal Arteriolar Occlusions in Systemic Lupus Erythematosus

Study	Patient No.	Sex	Age (years)	Cardiac Lesion	Response of Retinopathy to Steroids	Postmortem Findings
Cordes & Aiken (1947)	1	F	30	Mitral and aortic valve disease	No treatment	Thrombi in retinal arterioles but no inflammation. Mitral and aortic valvulitis. Emboli to brain stem
Hammami & Streiff (1966)	2	M	12	Libman-Sacks endocarditis	Improved	Not performed
Pfaffenbach & Hollenhorst (1973)	3	F	21	None	Blocked arterioles opened	Not performed
Gold et al (1977)	4	M	52	Pericarditis	Not reported	Not performed
	5	F	30	None	Not reported	Not performed
	6	F	39	None	Blocked arteriole opened sheathing resolved	Not performed
Coppeto and Lessell (1977)	7	F	32	Systolic ejection murmur	Not reported	Not performed
Graham et al (1985)	8	M	16	Mid-systolic murmur endocarditis	No improvement	Blocked retinal arterioles but no inflammation. Vasculitis in choroid and brain. Fresh vegetations on mitral valve and foramen ovale.

the patient died twelve weeks after admission from left ventricular failure secondary to hypertension and pulmonary embolism.

POSTMORTEM FINDINGS

Petechial hemorrhages were prominent over the emaciated body. No abnormality was found in the pancreas, thyroid, endocrine system or lymph glands. Both lungs were congested with areas of consolidation due to extensive bronchopneumonia. Both kidneys were enlarged. Histological examination revealed a diffuse proliferative glomerulonephritis associated with vasculitis, infarcts and abscesses.

The heart showed left and right ventricular hypertrophy. Chronic inflammatory cells were present in the myocardium and beneath the pericardium. Small areas of infarction were found at the apex of the right ventricle. Fresh vegetations were deposited on the mitral valve and foramen ovale. A subphrenic abscess was present.

Brain. External examination of the brain was unremarkable. Small recent infarcts were found in the grey and white matter of the frontal, parietal and temporal lobes, and the cerebellar folia. These infarcts were recent and cellular with abundant microglia and leucocytes. Some small meningeal arteries showed active arteritis, with infiltration of all coats, and rarely thrombosis (Fig 3). The inflammation was most marked in the small meningeal arteries of the frontal and parietal lobes. Other small arteries were occluded by amorphous hyaline material without any arteritis.

Examination of the central grey matter revealed two very small infarcts in each thalamus at the level of the mammillary bodies (Fig 4). The caudate nucleus, putamen, globus pallidus and substantia nigra were normal.

Eyes. Macroscopic examination of the eyes was unremarkable. Microscopically, the cornea, iris, ciliary body and sclera were all normal. Examination of the retina of the left eye revealed the occasional vessel occluded with hyaline thrombus. Such vessels, however, were not noticeably inflamed since the walls were not thickened, necrotic or infiltrated with white cells (Fig 5). A deep hemorrhage was present and a small focus of nerve-fiber swelling and cytooid body formation was found. The retina of the right eye showed some post mortem autolysis but little else. There was marked inflammation in the post-equatorial choroid of both eyes in the form of diffuse lymphocytic infiltration. Many of the choroidal arterioles were occluded in association with extensive vasculitis and fibrinoid necrosis (Fig 6). The retinal pigment epithelium was essentially normal and subretinal exudates were not observed.

DISCUSSION

Systemic lupus erythematosus is a multi-system disease characterized by small vessel occlusion in different organs. The most common clinical features are polyarthritides, skin rashes, fever and neuropsychiatric disorders. Immunological abnormalities are frequent, particularly

the presence of anti-nuclear antibodies, especially anti DNA antibodies and type V mitochondrial antibodies.¹

The pathogenesis of the neurological complications of SLE is multifactorial. Both cerebrovascular disease and immunological mechanisms contribute to the clinical picture.² A good correlation between clinical features and localization of the vascular defect is often observed: in patients with seizures and cranial nerve palsies, microinfarcts are frequently found in the cerebral cortex and brain stem respectively. The predominant neuropathological findings are destructive and proliferative changes in the arterioles and capillaries with microinfarcts and occasional foci of inflammatory cells. However, a true vasculitis of cerebral vessels is uncommon. The presence of endocarditis with cerebral lesions is rare so these lesions probably do not have an embolic aetiology.^{3,4} Assessment of cerebral blood flow and metabolism with oxygen 15 brain scans is frequently abnormal in patients with cerebral SLE.⁵

Cammarata examined three patients with SLE and chorea.⁶ Fibrinoid necrosis, perivascular lymphocytes and 'encephalomalacia' were observed but no localized changes were found in the basal ganglia. Although selective atrophy of the caudate nucleus is described as a characteristic feature of Huntington's chorea, there are often no detectable changes in Sydenham's chorea.

This close correlation between clinical signs and pathological changes is not always evident, particularly in patients with psychiatric disease or myelopathy. In these patients, immunological mechanisms may play an important role.

Examination of the cerebrospinal fluid is abnormal in about half the patients with neurological disease; the protein content is raised, a lymphocyte pleocytosis occurs, and complement C4 and Ig levels may be reduced. Immunoglobulin and complement deposits are found in the choroid plexus of patients with cerebral SLE,⁷ and more frequently antineuronal IgG and lymphocytotoxic IgM antibodies have been demonstrated in the sera of patients with neurological disease.

A retinopathy in a patient with SLE was first reported by Bergmeister in 1929.⁸ He described the retinal lesions in a patient three weeks after an acute exacerbation of the skin lesions. The right optic disc was hyperaemic, irregular white patches surrounded some retinal veins; cotton-wool spots were present throughout the fundus of the left eye with small white dots in the macular region.

The cotton wool spot has frequently been reported and is the hallmark of the classic retinopathy of SLE.^{9,10} The patients are often normotensive and blood cultures are negative. Arteriolar dilatation may be present in contrast to cotton wool spots associated with diabetic or hypertensive retinopathy when arteriolar constriction is the rule.

Occlusion of large retinal arteries is also well documented in SLE. The pathogenesis of the vascular occlusion is uncertain. The obstruction of the vessels may be due to local disease of the artery wall, embolism, or rheological factors producing thrombosis in situ.

There are five reports documenting seven patients

with retinal arteriolar occlusion in SLE similar to that seen in our patient¹¹⁻¹⁵ (Table 1). In three patients there was no clinical evidence of cardiac abnormality and post mortem examinations were not performed. The remaining four patients were documented as having pericarditis, systolic ejection murmur, Libman Sachs endocarditis and mitral and aortic valve disease respectively. Post mortem examination of the first patient mentioned revealed fresh vegetations on the diseased mitral and aortic valves and emboli in the brain stem.

In three patients both the vascular sheathing and the flow in the affected vessels improved shortly after treatment with systemic steroids was commenced. This may suggest an inflammatory element to the aetiology of the occlusion despite the paucity of vasculitic change in the retinal arterioles at post mortem. On the other hand, the time scale is not accurately reported and it is well known that the retinal appearance returns to normal a few weeks after arteriolar occlusion of non-inflammatory aetiology.

Rheological factors predisposing to thrombosis in situ may be haematological or immunological. Hyperviscosity was not recorded in any of these patients. In contrast, anaemia and thrombocytopaenia were common findings. Case 7, reported by Coppeto and Lessell¹⁵ had a hypergammaglobulinaemia at the time of the occlusion, but there is no mention of high plasma proteins, or raised circulating immune complexes in the other patients. Our patient had raised globulins in addition to high levels of circulating immune complexes.

There is no evidence that local disease of the wall of the retinal vessel is a contributory factor. All histopathological studies of the retina have demonstrated thrombosed arterioles with thickened intima but active vasculitis or foci of inflammatory cells have not been reported. However, examination of the choroid frequently shows round cell infiltration which may be accompanied by vasculitis or subretinal fluid and serous detachment of retina.^{11,16,17}

Accini and Dixon¹⁸ studied the pathogenesis of "non-inflammatory" vascular disease in mice with lupus-like disease and concluded that these lesions were caused by local deposition of antigen antibody complexes. They suggested that the absence of a vasculitis might be caused either by depletion of certain mediators of inflammation in a chronic disorder, or the amount of complex in proportion to the amount of antigen.

The ability of the complex to permeate the vessel wall may also be relevant. An intense inflammatory reaction is perhaps found in the choroid in these patients because choroidal vessels are permeable and leucocytes can readily be attracted to the sites of intramural complex. The retinal vessels have tight endothelial junctions which will prevent passage of either immune complexes or leucocytes from the retinal arterioles to the retina.

Our patient presented with chorea, developed severe renal failure and died three months later. On admission he had severe acute SLE, with high sedimentation rate, low C4, high levels of circulating immune complexes and autoantibodies. Post mortem showed fresh vegetations deposited on the mitral valve and foramen ovale,

a vasculitis in the kidney, the brain and the choroid but "non-inflammatory" vascular disease in the retina. The retinal arteriolar occlusion could have been caused either by an embolus from his diseased heart valve or local antigen antibody complex formation itself blocking the vessel lumen.

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