

Histopathological changes in the eyes in systemic lupus erythematosus: An electron microscope and immunohistochemical study

T.C. Nag and S. Wadhwa

Department of Anatomy, All India Institute of Medical Sciences, New Delhi, India

Summary. This paper reports the histopathological findings in the eyes of a 26-year-old female patient diagnosed with systemic lupus erythematosus (SLE) with peripheral neuropathy. The patient had no significant ocular problems. She died of pneumonia after two years of suffering. The eyeballs were procured at autopsy and the retina, choroid and optic nerve processed for light and electron microscopy, and immunohistochemistry for immunoglobulin G (IgG), glial fibrillary acidic protein (GFAP), calbindin and parvalbumin. Histologically, there was haemorrhaging in the retinal nerve fibre layer. Ultrastructurally, the axons of this layer were swollen, and contained an unusual accumulation of microtubules and smooth endoplasmic reticulum. There were degenerative changes in the pericytes and smooth muscle cells of blood vessels. The capillary lumen was partially obliterated, and contained IgG, which was also detected throughout the choroid and wall of choroidal arterioles. The latter and Bruch's membrane showed fibrin deposits. The optic nerve showed infiltrated mononuclear cells near the degenerated axons, these axons lacked immunoreactivity to calbindin and parvalbumin. Compared to the control, the connective tissue sheaths of the central retinal vessels possessed a vast number of proliferated fibroblast cells, and trichrome staining showed transmural vessel scarring. Dense GFAP immunoreactivity was observed surrounding the vessel wall. These pathological changes are due to impaired blood circulation caused by haemorrhaging and vasculitis, and vessel occlusion by fibrin. The nature of the changes observed tends to indicate that a regular, thorough ophthalmic examination should be conducted even in the absence of significant ocular symptoms in SLE.

Key words: Eye, Vasculitis, Immunoglobulin G, Fibrin, Calcium-binding proteins

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by abnormal deposition of circulatory immune complexes in blood vessel walls. The deposition causes inflammation through activation of the complement system, resulting in tissue damage and disease manifestations (Gauthier and Emlen, 1997). The disease affects mainly the joints, skin, kidneys and cardiopulmonary system. However, other organs like the liver, spleen, brain and eyes may be involved as well. In the latter, the chief clinical manifestations are cotton-wool exudates, retinal oedema and haemorrhaging, vasculitis of the retinal small vessels and optic neuropathy (Gold et al., 1972; Diddie et al., 1977; Jabs, 1994; Jabs et al., 1986, 1988; Spalton, 1990; Teoh et al., 2001). Occlusive retinal vasculitis, resulting in ischemia, may also develop, though it is less common (Jabs et al., 1986; Read et al., 2000).

Reports on the ocular histopathological changes in SLE are rather limited. Maumenee (1940) noted the frequent occurrence of mononuclear inflammatory cells in the choroid in untreated patients with SLE. Clifton and Greer (1955) reported 'cytoid bodies' in the retina of patients with SLE, which are characterized by hypertrophy or ganglioform degeneration of the nerve fibres. In one acute case of SLE, Graham et al. (1985) found fibrinous necrosis of the choroidal vessels that showed a typical vasculitis, whereas the retinal vessels showed a deposition of amorphous material in the absence of vasculitis. Immune-complex deposition has been found in the basement membrane of the pigment epithelium of the ciliary process and the pars plana of the choroid (Aronson et al., 1979), and in the blood vessels of the conjunctiva, choroid, retina and ciliary body (Karpik et al., 1985).

In this paper, we describe histopathological changes in the retina, choroid and optic nerve of a patient with SLE at autopsy, as examined by light microscopy and transmission electron microscopy (TEM). Immunohistochemistry was performed to localise immunoglobulin G (IgG), and to see the pattern of changes in calbindin and

parvalbumin (Ca²⁺ buffers that serve as markers of neuronal activity), and glial fibrillary acidic protein (GFAP) expression in the retina and optic nerve.

Materials and methods

Case report

A 26-year-old woman was admitted in September 1999 to the Department of Medicine, All India Institute of Medical Sciences, New Delhi, with complications of fever, symmetrical arthralgia and polyarthritis that developed five months before. During her stay, the patient was diagnosed as having SLE with a high anti-nuclear antibody titre, and accompanied by early peripheral neuropathy with lower limb involvement. There were no systemic diseases. She was discharged after a week with a treatment regimen of hydroxychloroquine (400 mg a day for 3 months). Prednisone (35 mg a day) was started after two months, and continued with a tapering dose. The ophthalmologists did not detect any significant ocular symptoms other than having her convergence insufficiency. Her vision was 6/6 on both eyes.

On December 10th, 2001, the patient had sudden breathing difficulty due to pneumonia and mumps and was admitted again. Supportive management with ventilation and intravenous fluid continued. The eyeballs were protruding, the pupils dilated and fixed, and did not react to light. Doll's eye movement was absent. The fundus status could not be examined due to hazy media. It was learned that the patient had visual problems that started three weeks before, in the form of repeated, sudden visual loss that lasted for about one minute on every attack. She did not seek at that time a clinical check-up. Her condition worsened gradually and she died on December 11th, 2001. An autopsy was performed 45 minutes postmortem and the eyeballs were available for the study.

Tissue preparation

The eyeballs were donated to the National Eye Bank, Dr. Rajendra Prasad Centre of Ophthalmology, AIIMS and procured by us. Ethical clearance to use them in research was obtained. The right eye and the intraorbital part of the optic nerve were fixed in 4% paraformaldehyde (PF, pH 7.4), and the left eye was fixed in Karnovsky's fixative (used in TEM).

Light microscopy

In the right eye, small haemorrhagic lesions were noted on the temporal retina, close to the optic disc. This part of the retina was cut and processed for paraffin histology. The sections (7 µm thick) were stained with haematoxylin and eosin (H&E). The samples of retina-choroid (midperipheral) and optic nerve were cut into 16-20 µm thick frozen sections and mounted on gelatin-

coated slides. They were stained with H&E, Mason's trichrome stain (Bancroft and Gamble, 2002), and for calbindin and parvalbumin immunohistochemistry.

TEM

The macula, and the periphery of the retina with adherent choroid (6-16 mm away from the fovea) were cut and sub-divided. The samples were postfixed in 1% OsO₄, dehydrated and embedded in araldite CY 212. Sections were stained with uranyl acetate and lead citrate and observed under a Morgagni 268D (Fei Company, The Netherlands) transmission electron microscope. A part of the peripheral retina and optic disc from the right eyeball was also examined, after fixing in 2.5% glutaraldehyde and processing in the same way as already outlined.

Immunohistochemistry

Sections were quenched of endogenous peroxidase activity in 0.3% hydrogen peroxide, washed and incubated in monoclonal anti-calbindin (dilution: 1:5000), anti-parvalbumin (1:5000) and anti-GFAP antibodies (1:200) (Sigma Chemicals Co., St. Louis, USA) for 48 h at 4 °C. After washes, sections were again incubated in biotinylated anti-mouse IgG (1:200; Vector Laboratories, California, USA) for 6 h at 4 °C and washed. The antigen-antibody binding sites were visualized by the avidin-biotin immunoperoxidase method, using 0.06% diaminobenzidine tetrahydrochloride as the chromogen. The slides were dehydrated and coverslipped with DPX. For immune-complex labelling, sections were incubated in anti-human IgG conjugated to FITC (γ-chain-specific, 1:200; Sigma Chemicals Co., catalogue number 6380), washed, mounted in Vecta-shield and observed under a fluorescence microscope using an FITC filter set.

As control, the eyes of a 19-year-old female, who died of asthma (postmortem delay in fixation: 1h), were used in all methods with light and electron microscopy and immunohistochemistry, as stated above.

Results

Light microscopy

Histologically, there was evidence of haemorrhagic lesions in the temporal retinal nerve fibre layer (Fig. 1A). The large blood vessels of this layer were compressed and packed with erythrocytes. Wandering cells, presumably blood-borne macrophages, were present in the vicinity of the damaged vessels and inner retina (Fig. 1B). There was an apparent loss of neurones from the inner nuclear layer in areas with lesions (Fig. 1B). In the choroid, infiltration of leucocytes was observed surrounding the large vessels (Fig. 2). Most of the vessels appeared highly compressed. There was no sign of depigmentation of the retinal pigment epithelium

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(Fig. 2). In the optic nerve, infiltrated mononuclear cells were present near the degenerative axons (Fig. 3). A vast number of fibroblast cells surrounded the thick connective tissue (collagenous) sheaths of the central retinal vessels. Also, fibroblast cell proliferation was evident in an area of optic nerve fascicles close to the collagenous sheaths (Fig. 4). With Mason's trichrome method, a deep staining of the collagenous sheaths was found to surround the vessels (not shown). This staining

was not observed in the control optic nerve sections. Also, the choroidal and retinal vessels did not stain conspicuously with the trichrome method. Immunoreactivity to calbindin and parvalbumin was present in all axonal fascicles of the control optic nerve (Fig. 5A, calbindin), but was absent in many degenerated axonal fascicles of the diseased optic nerve (Fig. 5B). Also, clearly, calbindin and parvalbumin expression was increased in the axonal fascicles that

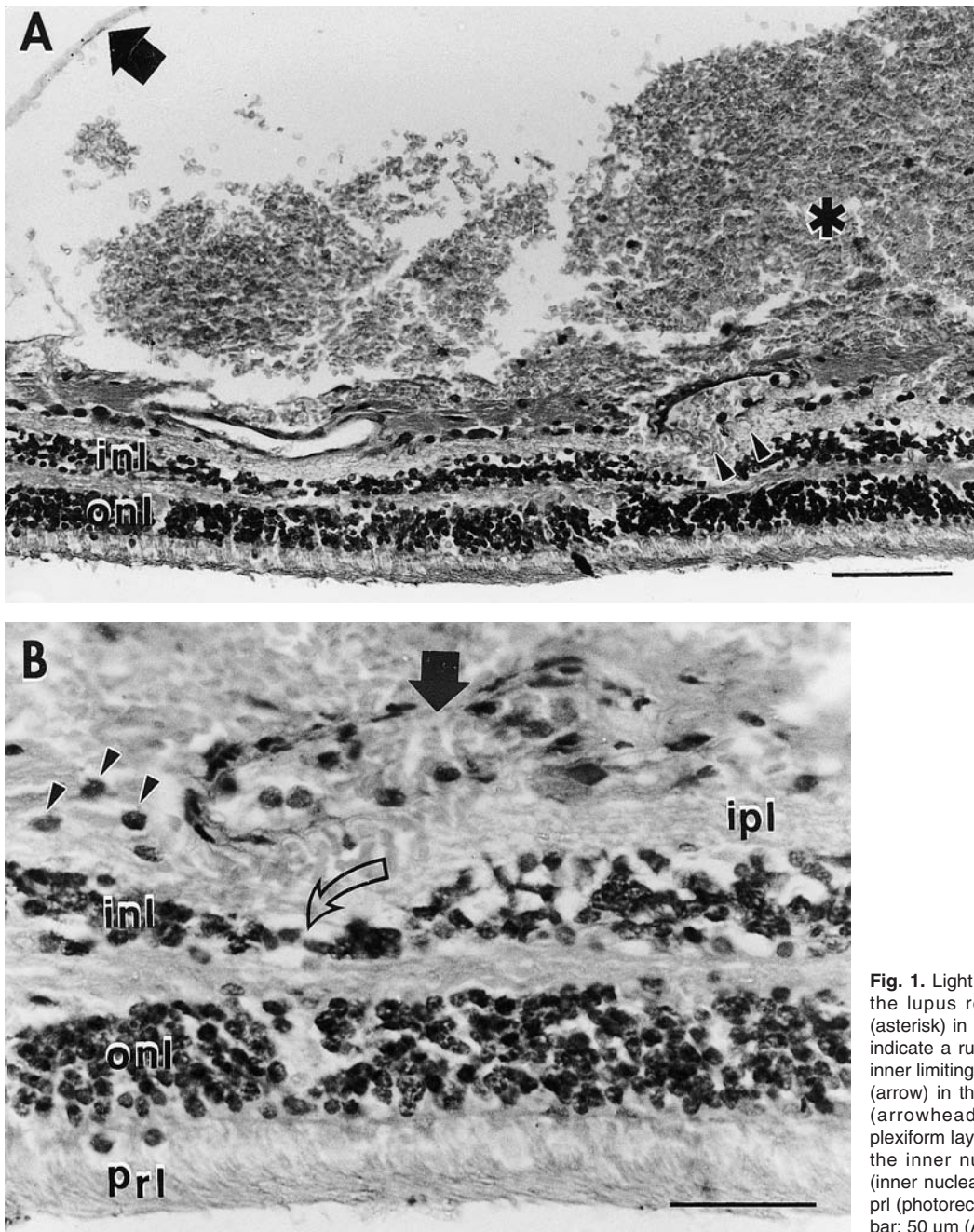


Fig. 1. Light micrographs showing changes in the lupus retina. **A.** Haemorrhagic lesion (asterisk) in nerve fibre layer. The arrowheads indicate a ruptured vessel lying in situ. Arrow, inner limiting membrane. **B.** A damaged vessel (arrow) in the lesioned area. Wandering cells (arrowheads) are present near the inner plexiform layer (ipl). Neuronal loss is evident in the inner nuclear layer (curved arrow). Inl (inner nuclear layer); onl (outer nuclear layer); prl (photoreceptor layer) (indicated in B). Scale bar: 50 μ m (A) and 25 μ m (B).

retained them. No significant changes in immunoreactivity to calbindin and parvalbumin were noted in the retina (not shown). The wall of the central retinal vessels in the optic nerve showed an increased immunoreactivity for GFAP (Fig. 6A), compared to that in the control optic nerve vessels (Fig. 6B). A significant GFAP immunolabelling was not seen in the retinal vessels. In the choroid, anti-IgG labelling was found throughout the entire choroid and deposited in the wall of the choroidal arterioles (Fig. 7A), and lumen of retinal vessels (Fig. 7B). The control sections did not show any labelling in the blood vessels (not shown).

TEM

Retina

In the nerve fibre layer, many axons were degenerative, containing a large number of vesicles and tubules of the smooth endoplasmic reticulum in their axoplasm. These axons contained an increased number of microtubules (Fig. 8A), compared to that in the control axons (Fig. 8B). Many ganglion cell axon terminals showed a large number of accumulated cystic mitochondria, forming the so-called cytoid bodies (Fig.

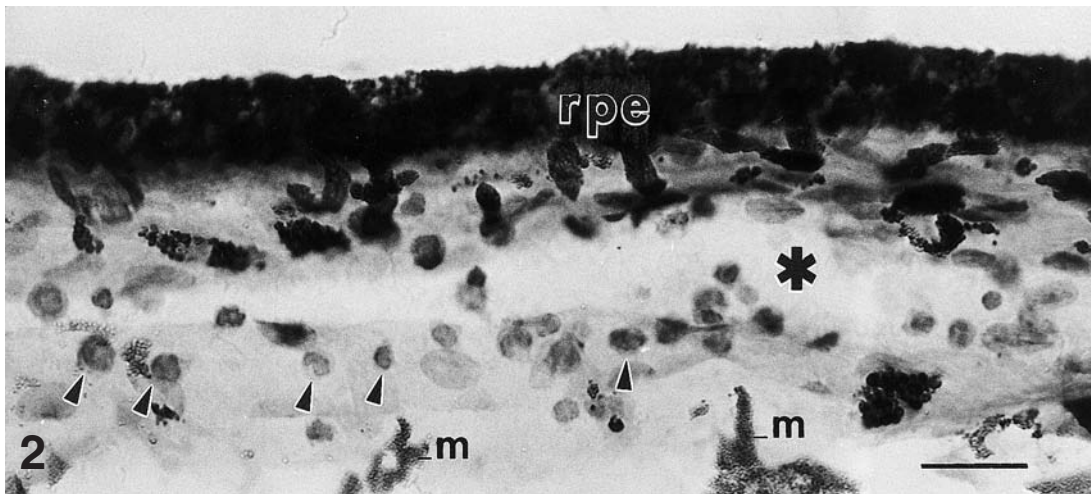


Fig. 2. Light micrograph of a part of choroid, showing infiltrated leucocytes (arrowheads) in the wall of a blood vessel. Its lumen (asterisk), which is highly compressed, also contains a number of leucocytes. rpe (retinal pigment epithelium); m (melanocytes of choroid). Scale bar: 20µm.

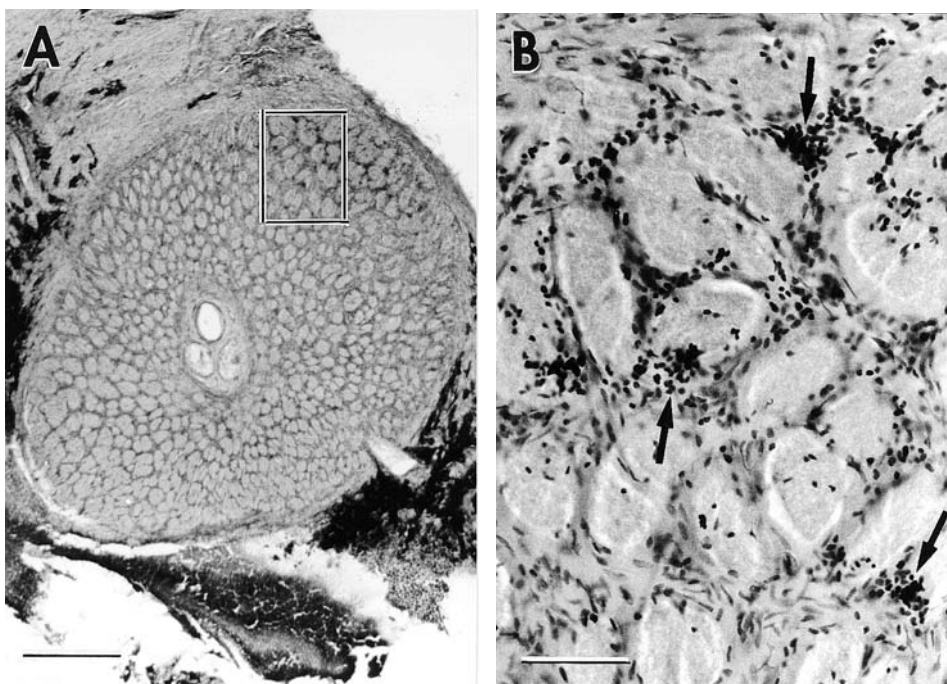


Fig. 3. Light micrograph shows infiltrated cells (arrows) in lupus optic nerve (A, B). The boxed area in A is enlarged to show the cells in B. Scale bars: 500 µm (A) and 80 µm (B).

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8C). The cells in the ganglion cell layer were degenerative and possessed swollen mitochondria with cristae disorganisation. As observed by light microscopy, wandering macrophage-like cells were detected electron microscopically in the inner retinal layers. The wall of

the large blood vessels was oedematous, and the pericytes, as well as smooth muscle cells, were markedly degenerative, the latter containing many secondary lysosomes and multivesicular bodies in their cytoplasm (Fig. 8D). The capillary lumen was obliterated, and the

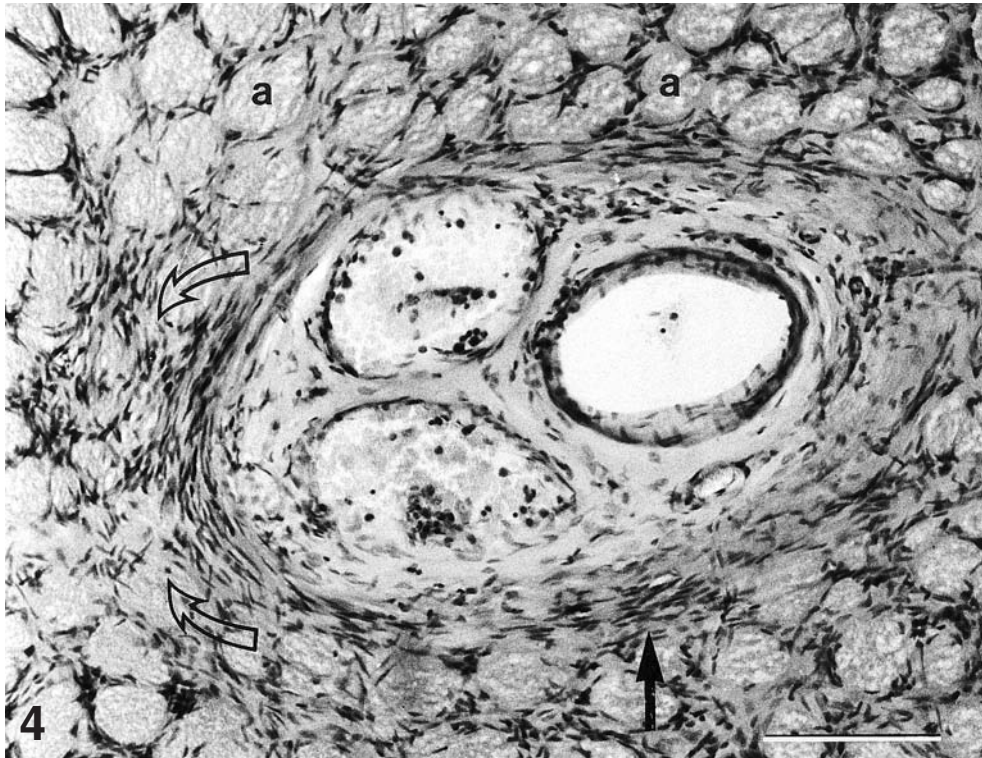


Fig. 4. Light micrograph shows a vast number of fibroblast cells (arrow) surrounding the thick connective tissue (collagenous) sheaths of central retinal vessels in lupus optic nerve. Also, fibroblast cell proliferation is evident in an area of optic nerve fascicles (shown between the curved arrows) close to the collagenous sheaths. a (axonal fascicles). Scale bar: 100 μ m.

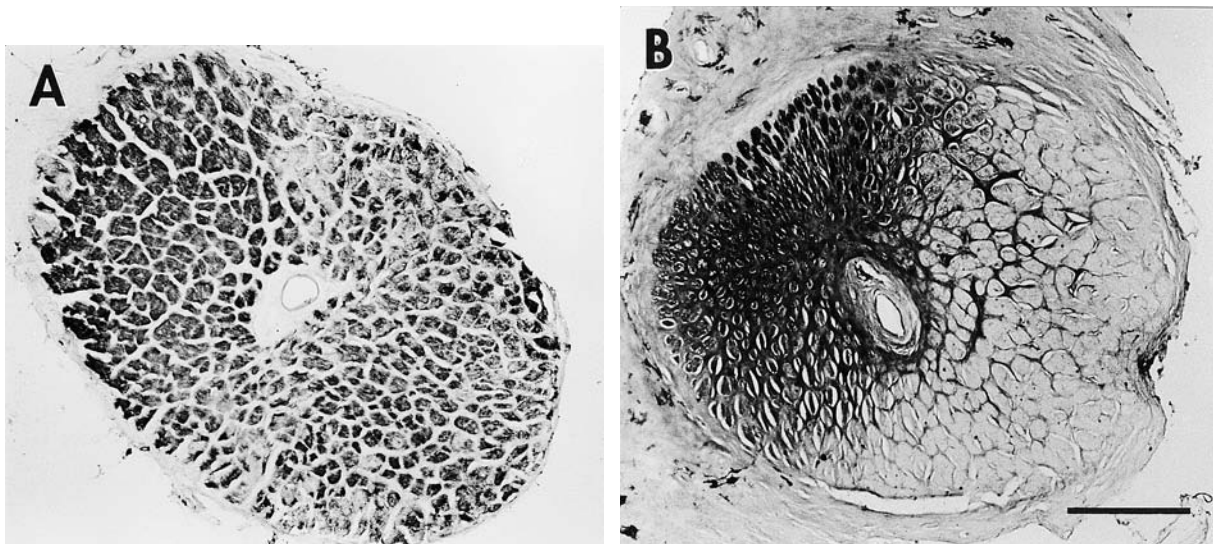


Fig. 5. Calbindin immunoreactivity in control and lupus optic nerves. In control (A), it is present in all axonal fascicles; in lupus nerve, it is lost from one half of the nerve (asterisk), the other half retains it (B). Scale bar: 500 μ m (shown in B, common to both figures).

pericyte cytoplasm degenerative. No infoldings were observed at the basal part of the retinal pigment epithelium (RPE, Fig. 9). The RPE was necrotic and contained hypertrophic mitochondria. The photoreceptors appeared unaffected.

Choroid

In both eyes, there was fibrin deposition in Bruch's membrane (BM; Fig. 9). Fibrin was also present in lumen in the choriocapillaris, and outer to the endothelial basal lamina in choroidal arterioles (Fig. 10A,B). The endothelium of the choroidal arterioles showed occurrence of large tubulo-reticular inclusions (Fig. 10A). Such inclusions were also found in the retinal capillary endothelial cells.

At the optic disc, there were axonal swelling and

astroglial hyperplasia (Fig. 11A). Fibrin partially filled the lumen of the large vessels (Fig. 11B). The control eyes did not show any of the degenerative changes, as mentioned above.

Discussion

Histologically, there is evidence of ocular involvement in this case of SLE, though at presentation and during the course of treatment there were no significant ocular symptoms. We have described here the ocular histopathological findings into this case of SLE at autopsy. There were subtle changes at the level of histopathology, fine structure and certain immunohistochemical markers in both eyes of the deceased, the severity of those changes was most marked in the optic nerve, followed by the retina and

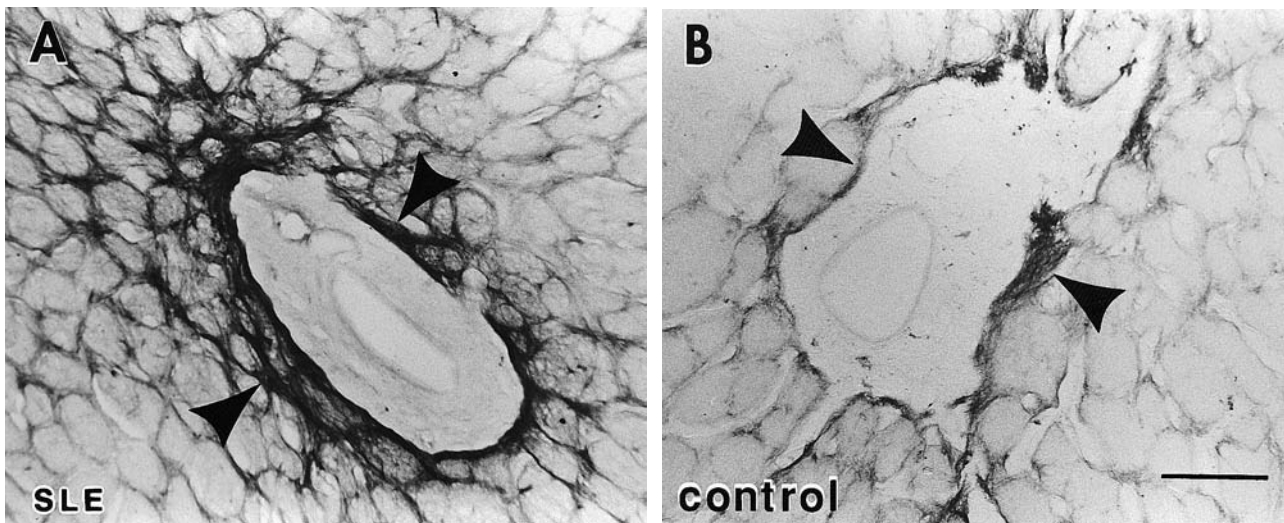


Fig. 6. GFAP immunoreactivity in the wall of central retinal vessels in lupus (SLE, **A**) and control optic nerve (**B**). In the former, there is an apparent increase at the level of immunoreactivity (arrowheads), compared to control. Scale bar: 100 μ m (shown in **B**, common to both figures).

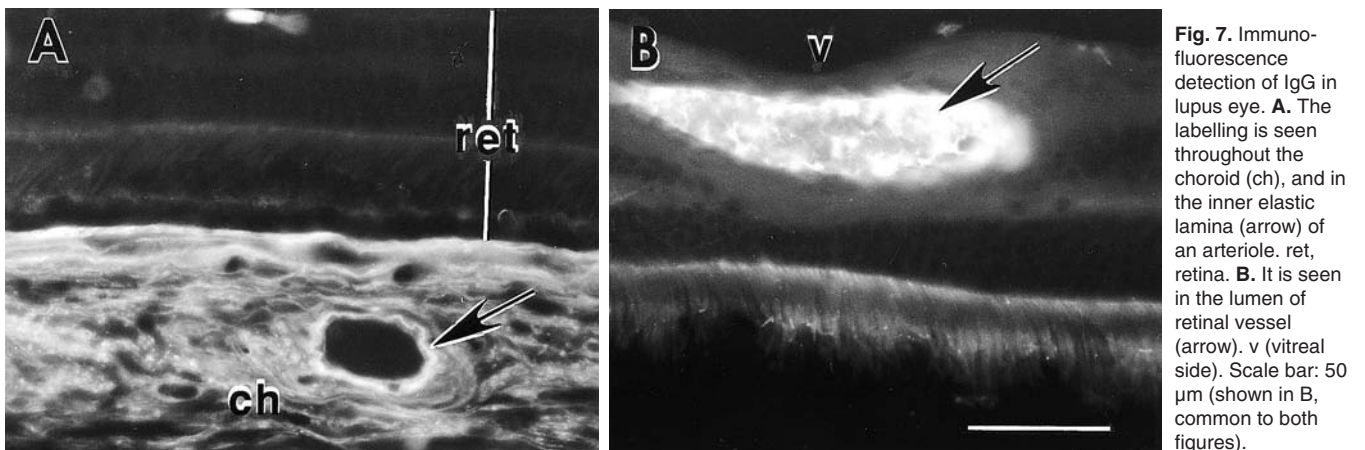


Fig. 7. Immunofluorescence detection of IgG in lupus eye. **A.** The labelling is seen throughout the choroid (ch), and in the inner elastic lamina (arrow) of an arteriole. ret, retina. **B.** It is seen in the lumen of retinal vessel (arrow). v (vitreal side). Scale bar: 50 μ m (shown in **B**, common to both figures).

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choroid. In the retina, the changes were more prominent towards the periphery than in the macula. The possible aetiological factors responsible thereof could be the haemorrhaging and vasculitis. The peripheral retina is

supplied with blood by the distal arterioles of the retinal circulatory bed. It is likely that a decreased blood flow through the large vessels, caused by vasculitis, and fibrin depositions (in the optic disc vessels), has produced its

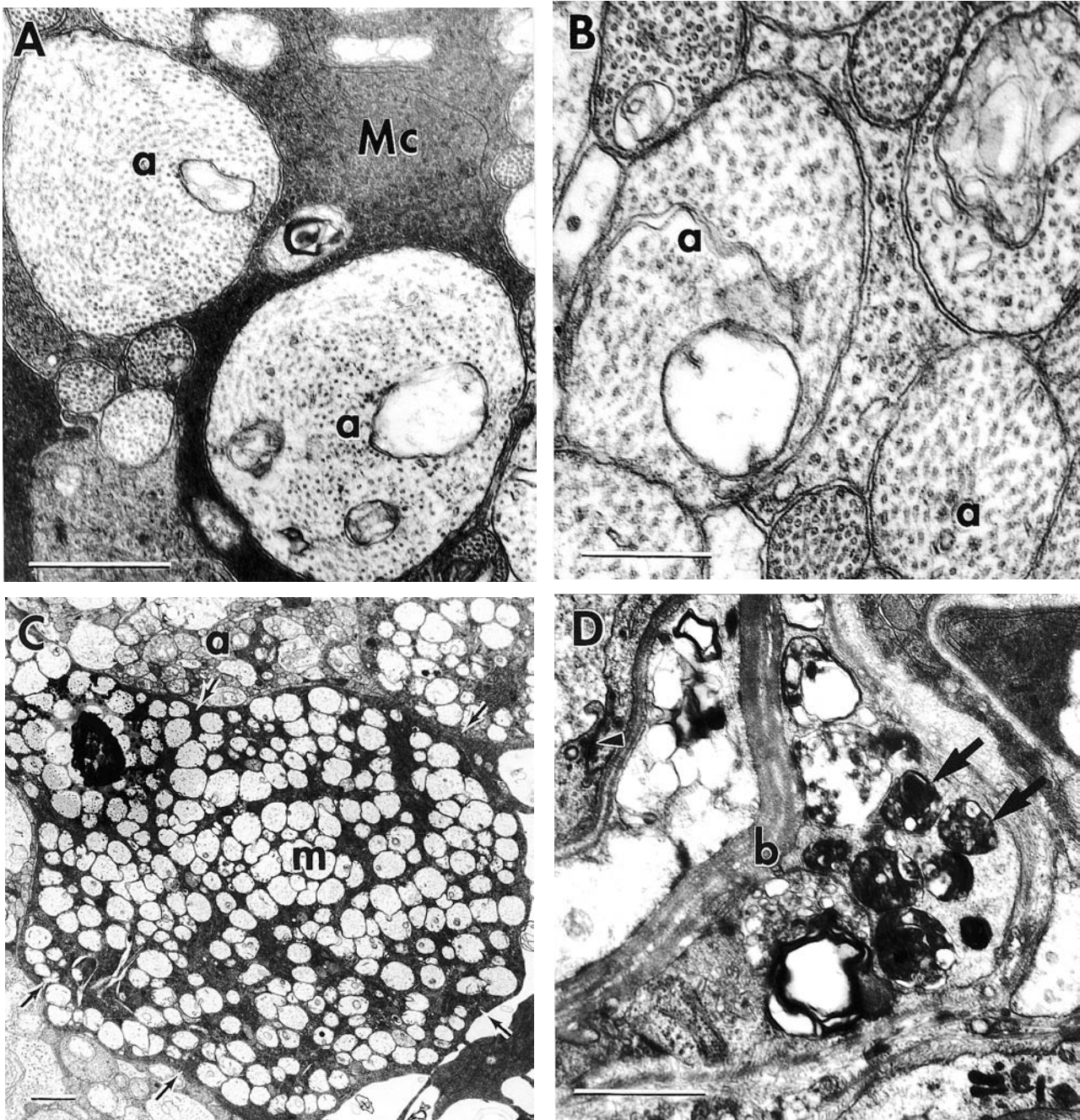


Fig. 8. Transmission electron micrographs showing changes in the lupus retina (A, C, D). A. Two large ganglion cell axons (a) show an increased number of microtubules, as compared to axons (a) of control retina (B). Mc, Müller cell cytoplasm (in A). C. A cytooid body, whose contour area is indicated by arrows, shows numerous cystic mitochondria (m). a (axons). D. Degenerative changes of a retinal arteriole (of nerve fibre layer), showing accumulation of secondary lysosomes and multivesicular bodies (arrows) in smooth muscle layer cytoplasm. b: basal lamina of muscle cells; arrowhead: endothelial cell junction. Scale bars: 1 μ m (A, C, D) and 0.5 μ m (B).

greatest effect in the peripheral retina.

The occurrence of fibrin deposition in BM was a notable finding. Fibrin appeared as electron-dense, irregularly oriented strands in association with the two collagenous layers of BM. The deposition presumably resulted from extravasation of plasma fibrinogen and its coagulation *in situ*. However, the mechanism by which this happened is not clear. Fibrin deposition may be a part of an immunological reaction to SLE, as has been reported for other antibody-mediated lesions and in many vasculitides (Harris et al., 1982).

Our immunofluorescence data revealed that there is

deposition of IgG in vasculature throughout the entire choroid. This is in line with the two previous reports (Aronson et al., 1979; Karpik et al., 1985). The demonstration of fibrin (by electron microscopy) and IgG (by immunofluorescence labelling) in the choroidal vessels in our study is interesting, and this probably reflects different states of inflammatory reactions. Fibrin deposition is a consequence of increased vascular permeability that triggers immune-complex deposition within vessel walls. The deposited immune-complexes trigger local inflammatory reactions, and later, are rapidly removed by phagocytosis (Wolff et al., 1978).

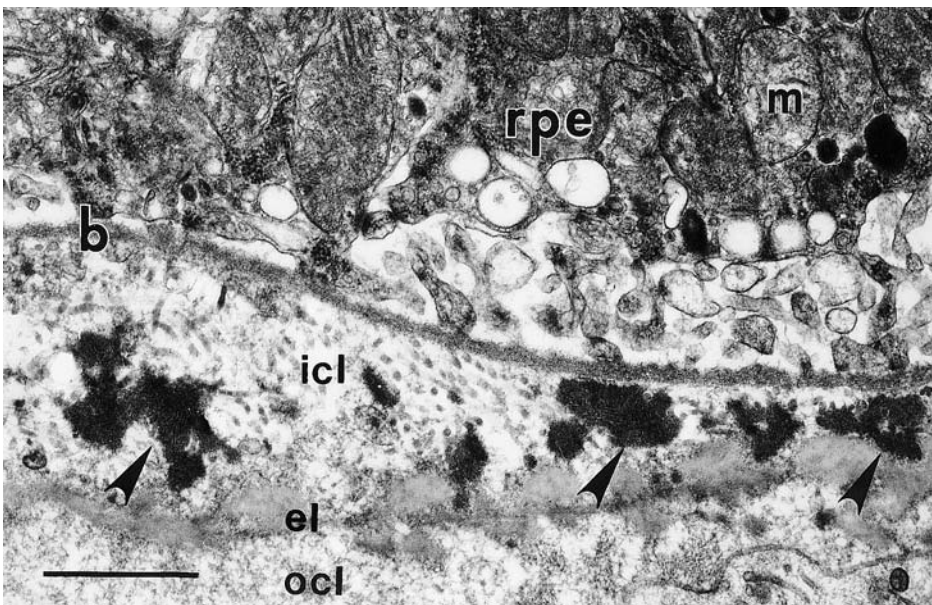


Fig. 9. Fibrin (arrows) in the inner collagenous layer (icl) of BM. The retinal pigment epithelium (rpe) is without basal infoldings and shows hypertrophic mitochondria (m). b: basal lamina of rpe; el and ocl: respectively elastic and outer collagenous layers of BM. Scale bar: 1µm.

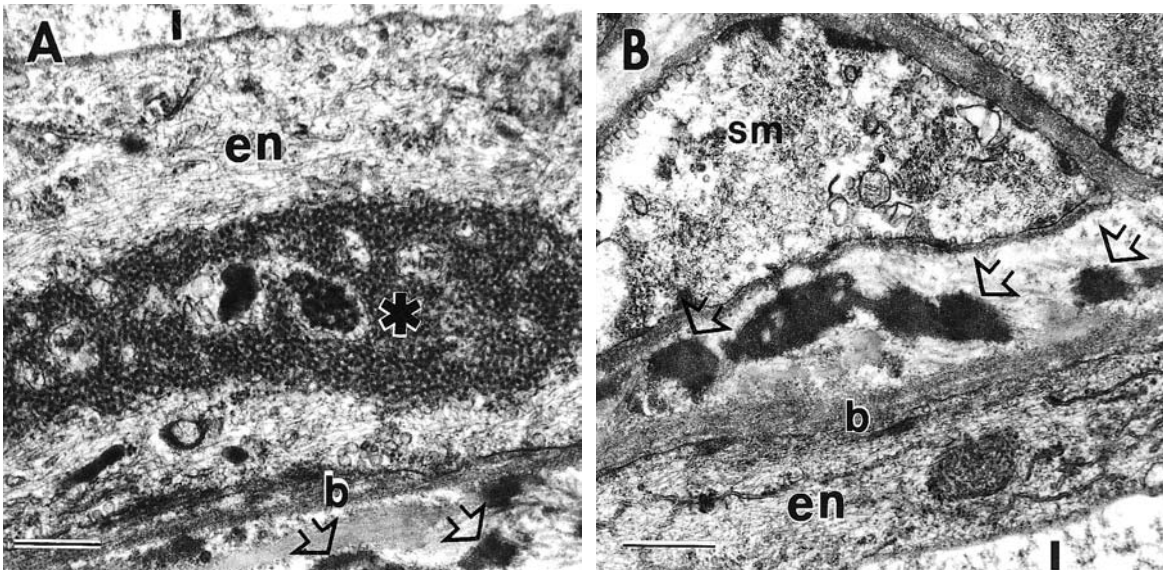


Fig. 10. Endothelium (en) of choroidal vessels, showing a large tubuloreticular inclusion (A, asterisk), and fibrin outer to the endothelial basal lamina (A, B; arrows). b: basal lamina of endothelium; l: lumen of vessels. Scale bars: 1µm.

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We found degenerative changes in the overlying RPE, especially in the form of necrosis, loss of basal infoldings and mitochondrial hypertrophy. These changes are most likely related to the effects of choroidal vascular changes (e.g., hypoperfusion) mediated by fibrin and immune-complex deposition. Pigment epithelial degeneration is reported in some patients of SLE (Sawa et al., 2002). Though photoreceptors were spared, it may be that they undergo degeneration in advanced state of SLE, and this has been reported in a mouse model of SLE (Nakamura et al., 1998).

The significance of the occurrence of tubuloreticular inclusions in the endothelium of choroidal and retinal vessels is not known; they have been reported to occur in SLE, especially involving kidney (cited in Bancroft and Gamble, 2002, Fig. 32.3). These endothelial cell inclusions, thus appear to be an electron microscopic diagnostic feature for SLE.

The physiological significance of differences in GFAP immunoreactivity in the wall of central retinal vessels of diseased and control optic nerve needs elaboration. Compared to the control, in the diseased optic nerve, there was an apparent, increased expression of GFAP in the glial endfeet and processes that surrounded the injured vessels. Also, astroglial hyperplasia and increased synthesis of glial intermediate filaments were observed by electron microscopy in the diseased optic nerve head. These features, along with the observed huge population of fibroblast cells and a dense trichrome staining of the collagenous sheaths surrounding the central retinal vessels in the diseased optic nerve are perhaps an indication of a healed

vasculitis, mediated by prednisone therapy.

An important finding of this study was the degeneration of retinal axons in the nerve fibre layer (cytoid bodies; Clifton and Greer, 1955; Wolter, 1959) and optic nerve. The occurrence of numerous microtubules and smooth endoplasmic reticulum in the axons (at the interface between normal and injured portion) reflects organelle accumulation, which was perhaps caused by the blockade of rapid axonal transport (McLeod et al., 1977; Radius and Anderson, 1981). Earlier, Shakib and Ashton (1966) reported organelle accumulation in terminal axon swellings within areas of focal retinal ischaemia, after carotid artery embolisation in pigs. The ultrastructural features reported by the authors, and those seen in hypertensive retinopathy (e.g., cytoid bodies and fibrin, Garner et al., 1975) and in cotton-wool spots (Ashton and Harry, 1963; McLeod et al., 1977) are similar to our findings in the diseased retina. We link the observed axonal degeneration with haemorrhaging and vasculitis, which led to impaired circulation in the optic nerve and inner retina. The fate of the degenerated axons is not known. Macrophage infiltration was noted in the retina as well as the optic nerve, which was likely due to the need to scavenge dead axons. The bilateral optic neuropathy was likely due to fibrin deposition and ischemia of the vessels supplying the optic nerve. We have shown that in the degenerated optic nerve axons, there was loss of calbindin and parvalbumin immunoreactivity. Both are reported, however, to occur in the normal, human optic nerve axons (Nag and Wadhwa, 1996, 1999), to regulate their excitability. These proteins disappear most

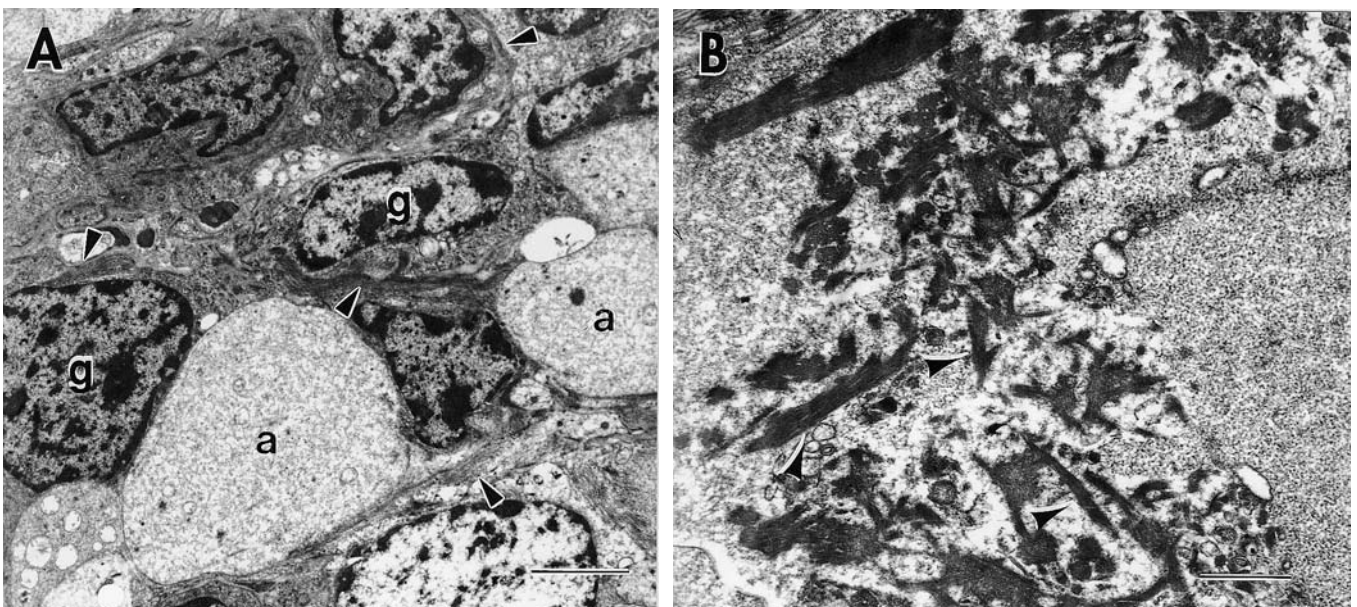


Fig. 11. **A.** Astroglial hyperplasia at the optic disc. The arrowheads indicate glial filaments. The axons (a) are swollen. g: glial nucleus. **B.** Fibrin (arrowheads) in the lumen of a vessel. Scale bars: 1 μ m.

probably as a consequence of degenerative changes in the lupus optic nerve or defects in axoplasmic transport.

The nature of histopathological changes noted in the eyes of the deceased prompt us to advise that periodic, thorough ophthalmic examinations should be conducted even in the absence of significant ocular symptoms in SLE, so that necessary treatment and preventive measures, as and when warranted, can be planned for.

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