Unusual clinical and histopathological findings in ocular sarcoidosis

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SUMMARY A 37-year-old Caucasian woman presented with a blind left eye and a granulomatous panuveitis in the right eye. There was a subretinal neovascular membrane with haemorrhage beneath the macula and widespread subretinal lesions that were interpreted as choroidal granulomas in the right eye. A chest x-ray that showed diffuse pulmonary fibrosis without hilar lymphadenopathy was the only contributory clinical finding. Systemic and subconjunctival steroids and photocoagulation to the right macula brought about temporary remission. The painful left eye was enucleated. Histopathological examination revealed diffuse, noncaseating granulomas in the iris and ciliary body, retina, choroid, optic nerve, sclera and scleral emissaria, and inferior oblique muscle. A preretal membrane was studied by electron microscopy. It was composed of a collagenous matrix containing fibroblasts and fibrous astrocytes. Some vessels, surrounded by a multilaminar basement membrane, revealed many features of normal retinal vasculature. Others were lined by markedly attenuated endothelial cells with occasional ‘open’ junctions and fenestrations.

The various clinical and histopathological findings of ocular sarcoidosis have been described by many authors. The case presented here is particularly unusual, however, and merits separate description. Clinically, widespread granulomatous involvement of the choroid of one eye was evident together with the singular finding, for this disease, of a subretinal neovascular membrane. Granulomas of ocular and adnexal structures were demonstrated histopathologically in the fellow eye, as well as an intravitreal neovascular membrane extending from the optic nerve head. This was studied by electron microscopy. It is to our knowledge the first such membrane from a case of ocular inflammatory disease to be so examined. The results of this investigation demonstrate anatomical features that may account for some of the abnormal physiological behavior of vitreoretinal neovascularisation.

Patient and methods

A 37-year-old white woman was referred for evaluation and treatment of uveitis in the right eye. The left eye had been totally blind for many years. Over the past several months the right eye had occasionally become red and painful. There was photophobia and a gradual decrease in visual acuity. Systemic evaluation was entirely negative except for a history of sarcoidosis.

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Fig. 1 Posterior pole of the right eye, showing a macular subretinal haemorrhage and a ‘corkscrew’ segment of the inferior temporal vein.
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of ‘asthma’. Ophthalmic examination revealed vision of 20/200 OD, and no light perception OS. Aqueous ray and cells were present in the anterior chamber of both eyes, and there were ‘mutton fat’ keratic precipitates in the right eye. Conjunctival and iris nodules were absent. The lens of the right eye was clear. A dense cataract and posterior synechiae were present in the left eye. The intraocular pressure was 28 mmHg OD, and 7 mmHg OS.

Ophthalmoscopic examination of the right eye showed pink nodules overlying the optic disc and the retina just below the disc. A subretinal haemorrhage was present in the macula. The inferotemporal vein was irregularly dilated and tortuous, with a corkscrew segment and reduplication suggesting an old occlusion (Fig. 1). Multiple large, soft, white subretinal lesions were scattered throughout the fundus. In view of the overall clinical picture these were thought to represent choroidal granulomas. Fluorescein angiography showed a subretinal neovascular membrane just nasal to the fovea (Fig. 2, A-D). There was late leakage of fluorescein from the nodules on the optic disc (Fig. 2D).

Areas of choroidal hyperfluorescence corresponded to the white subretinal lesions seen clinically. The clinical impression was that the patient had a granulomatous uveitis of unknown aetiology.

Physical examination was entirely negative except for psoriasis and diffuse pulmonary wheezing. A chest x-ray showed diffuse pulmonary fibrosis in the absence of hilar lymphadenopathy. Intermediate strength PPD (purified protein derivative), histoplasmin, blastomycin, and coccidioidin skin tests were negative. A serological test for syphilis was
nonreactive. Complete blood count, serum protein electrophoresis, serum calcium, and latex fixation tests were negative.

The patient was treated with 60 mg oral prednisone daily. Argon laser photocoagulation was applied to the subretinal neovascular membrane in the right macula. over the next few months her vision improved to 20/40, but the steroids were discontinued because of the development of a cushingoid appearance. The left eye became painful and was enucleated. After the oral prednisone was stopped there was an exacerbation of the uveitis in the right eye, which was treated by subconjunctival steroids. At her most recent visit to the clinic the patient's visual acuity was recorded as 20/80. Serological tests performed at this time revealed that both lysozyme and angiotensin converting enzyme levels were at the upper limits of normal, with lysozyme levels of 13-7 μg/ml (normal 7-14 μg/ml) and angiotensin converting enzyme levels of 123 U (normal 4-125 U). (SI conversion: μg/ml=mg/l.)

The eye was fixed for 24 hours in a 1:1 solution of formaldehyde-glutaraldehyde (Yanoff's modification of Karnovsky's fixative). It was then sectioned. The portion used for light microscopic examination was rinsed in water for several hours and processed as usual. The neovascular membrane was removed and postfixied with 1% osmium tetroxide. The specimen
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was then dehydrated in graded alcohols and embedded in Epon; sections 1 μm thick stained with toluidine blue were prepared and appropriate areas were thin-sectioned, stained with uranyl acetate and lead citrate, and examined with a Philips 301 transmission electron microscope.

Results

The globe was of normal size and did not transmit light. The cornea was clear and measured 11×10 mm. Whitish material filled the anterior chamber. The iris was bound to the lens by posterior synechiae. The retina was totally detached. Gelatinous, partially haemorrhagic exudate filled the subretinal space. The choroid was irregularly thickened. A whitish mass lay over the optic disc. Numerous delicate membranous strands extended from it into the vitreous cavity.

On light microscopic examination small aggregates of polymorphonuclear cells and lymphocytes were occasionally adherent to the corneal epithelium. A proteinaceous exudate was present in the anterior chamber. There were delicate peripheral anterior synechiae and artifactually torn posterior synechiae.

A cortical cataract was present. The root of the iris contained noncaseating epithelioid granulomas. Similar granulomas were present in the vitreous, some of them adherent to the nonpigmented ciliary epithelium. Numerous noncaseating granulomas were present in the retina (Fig. 3). Rarely the granulomas showed central necrosis. There was secondary retinal detachment. The subretinal space was filled with proteinaceous exudate intermixed with blood. The choroid contained many discrete granulomas that did not involve the overlying retinal pigment epithelium. The optic nerve head was diffusely infiltrated with granulomas. A vascular membrane extended from the optic disc into the vitreous cavity. The sclera, scleral emissaria, and the inferior oblique muscle (Fig. 4) also contained epithelioid granulomas. Special stains for fungi and acid-fast bacteria were negative, and light microscopic examination with polarised light failed to reveal any foreign body.

Electron microscopic examination was carried out on the neovascular membrane extending from the optic nerve head. The stroma was composed of a collagenous matrix. Two types of stromal cells could
be distinguished. Both were elongated, with oval nuclei and long attenuated cytoplasmic processes. One type of cell had distinct cytoplasmic fibrils measuring 5 nm in diameter (Fig. 5). Occasionally an extracellular basal lamina was noted. These cells might represent fibrous astrocytes. The second type of cell had no unique cytoplasmic organelles or extracellular secretions (Fig. 6). We therefore consider these cells to be fibroblasts.

Many blood vessels were embedded in this stroma. A cross-section of one, a capillary, is shown in Fig. 7. Endothelial cells of normal appearance are joined by tight junctions, and lip-like processes extend into the capillary lumen on either side of the junction. The endothelial cells and pericytes are each surrounded by a multilaminar basement membrane. All the vessels embedded in this preretinal membrane show this feature. The finding, however, of such a multilaminar basement membrane within and around the wall of capillaries of the retinal or choroidal circulation is unusual. Other unusual features include abnormal junctions between vascular endothelial cells. For example, the endothelial junction shown in Fig. 8 does not appear to have any membrane fusion or other specialisation. Though this section was cut slightly obliquely, it is apparent that the junction is not 'tight' and seems to represent an 'open' junction through which luminal contents could extravasate into the extravascular tissues. Similarly, the venular endothelial cell shown in Fig. 9 is markedly attenuated, and displays a fenestration (arrow), which may also be a site of egress for intravascular contents.

Discussion

Although sarcoidosis is a multisystem disease, whose diagnosis can usually be made without much difficulty,
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Fig. 6 Fibroblasts lacking characteristic cytoplasmic organelles represent the second type of cell located in the collagenous matrix of the neovascular membrane. (× 5090).

there are occasionally cases in which many of the characteristic features are missing. The diagnosis in the present case is almost surely sarcoidosis. The ocular specimen showed noncaseating epithelioid granulomas in which no organisms or foreign body could be demonstrated. A variety of skin tests for tuberculosis and mycotic infections were nonreactive, and the chest x-ray showed diffuse pulmonary fibrosis. While hilar lymphadenopathy is considered a characteristic chest x-ray finding in sarcoidosis, it need not always be present, and in longstanding cases parenchymal fibrosis may be the only radiographic abnormality. Recently determinations of serum levels of angiotensin convertase and lysozyme activity have been introduced as adjunctive tests for sarcoidosis. Although levels of these enzymes are usually raised in the sera of sarcoidosis patients, a recent study by Katz and associates shows that raised lysozyme activity may also be present in patients with other granulomatous diseases, so that this enzyme is not a specific indicator of sarcoidosis. However, they found raised angiotensin convertase activity only in their sarcoidosis patients and not in patients with other granulomatous disease. Moreover, only in sarcoidosis were levels at the upper limits of normal found, so that such high normal values must be considered strongly suggestive. Our patient had serum angiotensin and lysozyme levels at the upper limits of normal, even after treatment with systemic steroids and at a time when she was free of symptoms. This finding, therefore, strongly supports the diagnosis of sarcoidosis.

The fundus lesions seen ophthalmoscopically had several features that are well recognised in ocular sarcoidosis but others that are uncommon. Granulomatous masses extending from the optic nerve head have often been described. Subretinal granulomas have also been reported previously. Henkind stated that subretinal neovascularisation was known in ocular sarcoidosis, but he gave no references and presented no cases of his own. Recently Gragoudas and Regan described 2 additional cases of subretinal neovascularisation in presumed sarcoidosis. In any event subretinal neovascularisation appears to be an extremely rare finding in this disease. The tortuous, reduplicated,
inferotemporal vein in the right eye suggests a previous venous occlusion, but the cause of this event is not apparent. No vasculitis was evident clinically in the right eye, nor was it apparent on microscopic examination of the left eye.

Histopathologically the extensive involvement of intraocular structures is unusual. Orbital involvement with sarcoid granulomas is rare, and we are unaware of previous descriptions of involvement of scleral emissaria or of extraocular muscle by sarcoid granulomas. Discrete choroidal granulomas are also infrequent. Gass and Olson have suggested that, when choroidal granulomas are suspected on the basis of clinical observation (as in our patient’s right eye) ‘these often turn out to be located external to the retinal pigment epithelium, but internal to the Bruch membrane.’

Finally, our electron microscopic examination of the neovascular membrane extending from the optic nerve head showed one aspect of the variable composition of these structures. Some authors have reported a primarily fibroblastic component of stromal cells, while others have indicated that the stromal cells were largely fibrous astrocytes. Clarkson and associates reviewed 168 cases of preretinal membranes and described several different types, of which the purely glial membrane (in which the cellular component of the stroma consists of fibrous astrocytes) was 3 times commoner than the others. Other types of membranes included the predominantly fibroblastic, a membrane formed of cortical vitreous; the fibroinflammatory, and the combination membrane composed of both glial and fibroblastic elements. Our case appears to represent the last type.

The blood vessels that are embedded in this membrane, although newly formed, appear surprisingly normal by electron microscopy. Kenyon and Michels and Pederson and associates have reported similar observations. However, the presence in our specimen of occasional ‘open’ junctions and of attenuated and fenestrated endothelial cells suggests anatomical correlates with the leakiness to fluorescein dye and to plasma that is observed clinically. Similar findings have been reported in neovascular pro-
liferations in human diabetic retinopathy12 26–28 and in animals with experimental retinal neovascularisation produced by hyperoxia shortly after birth.29

References

Fig. 9 Portion of venule embedded in the preretinal membrane. Marked attenuation of endothelial cells and focal fenestration, shown by the arrow. (×2414).