Progressive subretinal fibrosis and uveitis

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SUMMARY Three patients with intraocular inflammation and unusual progressive subretinal lesions are described. This entity is characterised by a chronic vitreous inflammation in association with whitish ‘fibrotic’-like subretinal lesions which progressively enlarge and coalesce. The patients all developed cystoid macular oedema. The differential diagnosis of this entity is discussed. These patients appear to have a unique and previously undescribed inflammatory disorder. The macular oedema responded to corticosteroid therapy in only one patient, and no therapy appeared to alter the course of the disease. Unlike many other patients with posterior uveitis these did not respond to the retinal S-antigen.

Many inflammatory disorders of the posterior segment of the eye have been described. These include disorders with a known aetiology such as toxoplastic retinochoroiditis and disorders such as sympathetic ophthalmia in which the aetiology has not been established. In general a specific aetiological cause is rarely found in inflammatory disorders of the retinal pigmented epithelium (RPE) or choroid. The most important criterion in the diagnosis and classification of inflammations of the retinal pigment epithelium and choroid has been the ophthalmoscopic appearance and natural history, since in most cases the aetiology is unknown. This article describes three patients in whom a progressive subretinal fibrosis occurs in association with uveitis. The clinical course and differential diagnosis are discussed.

Methods

Three patients were examined at the National Eye Institute (NEI) after being referred with a diagnosis of uveitis or retinitis of unknown origin. Ocular examination included best corrected visual acuity, slit-lamp examination, and dilated fundus examination including either Hruby lens or contact lens examination of the posterior pole. Fluorescein angiography was performed with a Zeiss fluorescein fundus camera following injection of 5 ml of 10% sodium fluorescein. Electroretinography was done in all three patients. The patients were dark adapted for 30 minutes after dilatation. With a Ganzfeld ERG sphere dark-adapted responses followed by light-adapted responses were recorded as described in detail elsewhere.¹ An electro-oculogram was obtained in two of the three patients with a period of 15 minutes being used for recording dark responses followed by a 15-minute period for recording light responses. The peak to trough ratio was then calculated. Lymphocyte culturing in order to evaluate the in-vitro response to the retinal S-antigen was performed as previously described.²

Case reports

CASE 1
A 28-year-old white woman was seen at the NEI in 1978 for progressive visual loss. She had a history of allergic responses, was allergic to penicillin, and prone to develop nasal polyps. She had had recurrent iritis and episcleritis in both eyes since she was 17, though her vision remained good. She had episodes of episcleritis and iritis every two years from 1968 to 1975 when they then became more frequent. In March 1977 she developed blurred vision in the left eye without pain or redness. The vision decreased to 20/50. A diagnosis of posterior uveitis with several small subretinal infiltrates was made, and she was treated with periocular steroid injections and oral steroids without significant
improvement. Her vision decreased to counting fingers (CF) at 10 feet (3 m) because of submacular inflammation. In early 1978 vision in the right eye decreased to 20/40 accompanied by redness, pain, and photophobia. She was seen at that time by two of us (L.M.P., D.L.K.). There was a low grade iritis OD and a low grade vitritis OS. Several non-pigmented lesions approximately 1/3 disc diameter in size were seen at the level of the retinal pigment epithelium (RPE) in the right eye. A fluorescein angiogram done at this time showed blockage of background choroidal fluorescence with less staining of some lesions but no leakage of dye in the right eye (Fig. 1). The left macula had what appeared to be a subretinal fibrotic lesion (Fig. 2).

Laboratory studies were non-contributory except for the following tests: The histoplasmin skin test was markedly positive, and serological determinations showed a histoplasmin titre of 1:8, *Histoplasma capsulatum* yeast titre of 1:32, and

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**Fig. 1A** Right eye of patient 1, July 1978.

**Fig. 1B** Fluorescein angiogram early phase, showing multiple areas of blockage of choroidal fluorescence and other areas of hyperfluorescence.

**Fig. 1C** Fluorescein angiogram late phase, showing late staining of some lesions without leakage.

**Fig. 2** Left eye of patient 1, July 1978.
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blastomycosis titre of 1:16. VDRL was negative as was a purified protein derivative (PPD) skin test. Toxoplasma titre was 1:4. Hilar adenopathy on the right side was noted on chest x ray. A mediastinal biopsy performed at the Johns Hopkins Hospital showed no evidence of sarcoid granulomas but revealed histoplasma organisms on tissue section. Cultures were not performed on the biopsied tissue. In June and July 1978 the patient received intravenously a total of 920 mg of amphotericin B with concomitant steroid therapy, which led to a slight improvement in the vision of the left eye to 20/80. The histoplasmin skin test remained positive with 3 cm induration. The amphotericin B was discontinued because of renal toxicity.

When first seen at the NEI in July 1978 the patient’s visual acuity was 20/20 in the right eye and 20/200 in the left eye. There was a stromal scar in the right cornea which was the residue of a past inflammatory episode. The anterior chambers were calm and the lenses were clear. There were trace cells in the vitreous of the right eye and 1+ cells in the left eye. There was mild cystoid macular oedema in the left eye. The optic discs were normal. Many paramacular non-pigmented subretinal discoid lesions were noted in both eyes (Fig. 1A), and whitish subretinal alterations were present in the left macula (Fig. 2). She was maintained on 20 mg prednisone daily.

The patient returned in December 1978. Vision was 20/40 in the right eye and 20/200 in the left eye. New areas of subretinal lesions were seen in the right eye and they appeared to be ‘fibrotic’ (Fig. 3). The fluorescein angiogram now showed leakage of dye. She had been on 30–40 mg of prednisone for the past several months without significant change in her vision. The anterior chamber and vitreous were now quiet in both eyes, but the erythrocyte sedimentation rate was 43. The histoplasmin skin test was less positive at 11 mm. The patient returned in March 1979. Vision in the right eye was 20/200 and in the left eye 20/300. A culture of the patient’s lympho-

Fig. 3A  Right eye of patient 1, December 1978.

Fig. 3B  Fluorescein angiogram early phase, showing multiple areas of hyperfluorescence and areas of blockage of choroidal fluorescence.

Fig. 3C  Fluorescein angiogram late phase, showing leakage from subretinal lesions.
cytes was taken and there was no response to the retinal S-antigen or to crude retinal or choroidal extracts. The ERG revealed markedly reduced rod responses (left more than right) with diminished cone responses in both eyes. An EOG revealed a peak to trough ratio of 111% in both eyes with normal being greater than 190%. Her systemic corticosteroids were slowly tapered at this point.

In the summer and autumn of 1979 the patient experienced recurrent bouts of scleritis in the left eye and developed limbal phlyctenules. This episode was treated with topical prednisolone and gentamicin, while a biopsy of the episclera revealed non-specific inflammatory changes. Although the patient’s PPD skin test was negative she was placed on a trial of isoniazid and rifampicin because of the phlyctenular keratitis.

The patient’s subretinal lesions gradually progressed and in July 1980 the vision was 20/100 in the right eye and counting fingers at 1 foot (30 cm) in the left eye. The isoniazid and rifampicin were stopped. She had continued to have recurrent episcleritis and Indocin (indomethacin as capsules) 25 mg by mouth three times daily was used with moderate effect.

She was last seen in October 1982. Vision was 20/200 in the right eye and counting fingers at 1 foot (30 cm) in the left eye. There were trace cells and flare in the anterior chamber of the right eye and trace cells in the left with 1+ cells in the vitreous of the right eye and 1-2+ cells in the vitreous of the left eye. There was bilateral cystoid macular oedema. The subretinal lesions were basically unchanged in both eyes compared with them in 1980.

case 2

A 16-year-old black woman was first seen at the NIH in 1974. At that time her visual acuity was 20/200 in the right eye and 20/20 in the left eye. There was no active intraocular inflammation. Multiple old chorioretinal scars in the right eye were noted, but the colour and pigmentation were not recorded. The toxoplasma titre was 1:4. Histoplasmin and PPD skin tests were negative, as was the VDRL. There was no active disease and the patient was not treated.

She returned in May 1982 complaining of blurred vision in the left eye. Visual acuity was 20/200 in the right eye and 20/30 in the left eye. Both anterior segments were normal, but there were trace cells in the vitreous of the left eye. Multiple whitish irregular subretinal fibrotic lesions were present in both eyes with a small amount of surrounding pigmentation (Fig. 4) accompanied by cystoid macular oedema. The patient received 2 mg of Decadron (dexamethasone sodium phosphate) subconjunctivally with improvement of the vision to 20/20 in one week. A chest x ray was negative. An EOG was done and the peak over trough ratio was 150% in the right eye (subnormal) and 208% in the left eye (normal).

An ERG showed decreases in both rod and cone functions of both eyes, which were worse in the right eye. There was no response in lymphocyte culture to the S-antigen.

The patient returned in August 1982 again complaining of blurred vision in the left eye. Vision was

Fig. 4A  Right macula of patient 2, showing subretinal lesions.

Fig. 4B  Left eye of patient 2 inferior to optic disc, showing subretinal lesions.
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20/40 in the left eye. The anterior chamber was quiet, but there were trace to 1+ cells in the vitreous of both eyes. Cystoid macular oedema was again present in both maculae (Fig. 5) and the subretinal lesions were unchanged. There were no subretinal lesions in the macula of the left eye. The patient was treated with 40 mg of prednisone orally daily for one week, and vision returned to 20/20 with resolution of the cystoid macular oedema. The patient was tapered on alternate-day prednisone over a two-month period. When last examined in February 1983 her vision was 20/200 in the right eye and 20/20 in the left eye.

CASE 3
A 12-year-old black girl was seen by her ophthalmologist in March 1976. Her vision was 20/20 in the right eye and 20/30 in the left eye. There was a white peripapillary scar in the left eye nasally. She was seen again in June 1978, at which time the vision in the left eye had fallen to 20/70. There were 1-2+ cells in the anterior chamber and vitreous of the left eye. The peripapillary lesion had extended along the superior and inferior temporal arcades. A new white lesion was noted superior to the left temporal
arcades. She was put on oral prednisone for one month without improvement in vision. This was stopped in July 1978. In September 1978 she had 1+ cell and flare in both anterior chambers and 1-2+ cells in the vitreous of both eyes. She was placed on 100 mg of prednisone daily as well as topical steroids and atropine.

She was first examined at the NIH in October 1978. Vision was 20/20 in the right eye and 20/100 in the left. The corneas were clear. There was trace flare in the anterior chambers of both eyes. The vitreous contained 1-2+ cells in both eyes. The white subretinal opacities were seen in both eyes, in the left more than the right (Fig. 6). There was little pigmented reaction. There were also several small areas of perivascular infiltrate in the right retina.

The patient had negative titres to histoplasmosis, toxoplasmosis, candida, and blastomycosis. Toxoplasmosis titre was 1:4. A PPD skin test was negative, as was a VDRL. The chest x ray was negative. An ERG revealed a marked depression of response by both rods and cones in the left eye. The patient’s lymphocytes did not react to the S-antigen in culture. The patient was kept on high doses of oral steroids for a month without significant improvement and was then lost to follow-up.

Discussion

The differential diagnosis of subretinal inflammatory lesions is quite large and includes entities in which the aetiological agent is known or suspected. However, many entities involving the retinal pigment epithelium and choroid have unknown aetiological agents and are diagnosed simply on their ophthalmoscopic appearance. We believe that these three patients have a similar entity that is unique both in its appearance and its clinical course and which has not been previously described.

The differential diagnosis of a patient such as the ones presented here might include sarcoidosis, the presumed ocular histoplasmosis syndrome, tuberculosis, syphilis, birdshot retinochoroidopathy, toxoplasmosis, and possibly other fungal infectious causes. One might also consider an unusual form of acute posterior multifocal placoid pigment epitheliopathy (APMPPE) or geographical choroiditis.

We believe that the vitreous inflammation found in all three patients and the anterior segment inflammation which was present in two of the three patients in association with the unusual and progressive subretinal lesions allows one to exclude most of these entities.

Sarcoidosis is difficult to rule out in any differential diagnosis. Only the first patient had an abnormal chest x ray, and a mediastinal biopsy failed to show histologically identifiable alterations consistent with sarcoidosis. This patient was not anergic. The retinal and vitreal findings would be unusual for sarcoid in that there were no aggregates of cells in the vitreous, and retinal perivascular lesions were seen in only one eye. All the remaining fundus findings were located subretinally.

Two of the three patients had negative histoplasmosis titres. It is unlikely in the first case that this was either presumed or disseminated ocular histoplasmosis, though the skin test was markedly positive. Anterior segment and vitreous inflammation does not occur in the presumed ocular histoplasmosis syndrome (POHS). In disseminated histoplasmosis with ocular involvement patients are systemically ill and have local invasion of the histoplasmosis organism. Lastly, the subretinal proliferative response is unusual in POHS unless there is a subretinal neovascular membrane. This was not demonstrated by fluorescein angiography in any of the patients presented here. We cannot rule out the possibility that patient 1 had an ocular allergic response to histoplasmosis elsewhere in her body.

Tests for tuberculosis and syphilis were negative in all three patients, and fungal titres were negative in cases 2 and 3. It would be unusual for a fungal infection to progress as slowly as the lesions in the first patient did, particularly when the patient was taking high dose corticosteroids. Secondly, a therapeutic trial with amphotericin B was only questionably beneficial, and the patient is still healthy five years after the onset of the posterior pole disease.

Birdshot retinochoroidopathy is a recently described entity. Most of these patients are HLA-A29 positive and respond to the retinal S-antigen. None of the three patients in this report responded to this antigen, which is an antigen of the outer segments of the photoreceptors. A positive response has been seen in lymphocyte culture in many other forms of posterior uveitis.

The toxoplasmosis titres were less than 1:4 in all patients. The subretinal location of the lesions and the non-atrophic nature of the affected overlying retina would seem sufficient to rule out ocular toxoplasmosis.

The appearance of these three patients and their clinical course are not consistent with geographical choroiditis because of the lack of choroidal atrophy. The lesions as well do not have the appearance of those seen in APMPPE, and the prolonged clinical course and poor visual outcome is against this diagnosis as well.

Therefore we believe that the entity described in this paper constitutes a unique ocular inflammatory
response consisting of intraocular inflammation in combination with a subretinal proliferation of tissue leading to retinal dysfunction and cystoid macular oedema. Although the inflammatory response is primarily subretinal, and frequently does not initially involve the macula, the result of the inflammatory response is great enough to produce cystoid macular oedema. All three patients had a markedly decreased ERG, implying diffuse retinal involvement. These patients' failure to respond to the S-antigen and the striking fibroticlike picture distinguishes it from other types of posterior uveitis.

We have termed this entity progressive subretinal fibrosis with uveitis because the subretinal lesions have an appearance similar to subretinal fibrosis seen in other retinal diseases such as complications of retinal detachment. This does not imply an aetiological entity but is an attempt to define a type of ocular response to inflammation. Some similarity of this entity to a recently described disciform maculopathy can be noted. However, the lesions in our patients occur both in the macula and elsewhere, and no subretinal neovascularisation was noted.

There does not at present appear to be any treatment capable of arresting the subretinal process. The process is multifocal and located posteriorly, so that it is unlikely that laser or cryotherapy would be of use. Corticosteroids appear to be able transiently to reduce the macular oedema but do not seem to affect the overall course. It is important to note that only in case 2 did the macular oedema respond to steroids and that the subretinal lesions were not located beneath the macula in this eye. Once there has been fibrosis beneath the macula it is reasonable to assume that irreversible structural alterations occur. However, it is possible that the process may spontaneously cease to progress as seen by the lack of progression or further loss of vision in case 1.

As our understanding of intraocular inflammation improves we hope to be able to classify these entities on immunological or other criteria. The fact that these patients do not respond to the S-antigen and do not fall into any of the known aetiological categories implies that there is much to learn concerning the pathogenesis of ocular inflammatory disease.

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References

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