Ocular reticulum cell sarcoma

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SUMMARY Although rare, ocular reticulum cell sarcoma presents a recognisable clinical pattern, as confirmed by 3 new cases. Typical patients, in their sixth and seventh decades, initially complain of gradual visual loss. Examination reveals 'uveitis' with prominent vitreous debris and/or chorio-retinal infiltrative lesions. Topical steroid and mydriatic therapy is ineffective. Reticulum cell sarcoma in the central nervous or other systems may precede or accompany the ophthalmic presentation. In an increasing number of cases tissue diagnosis and effective therapy have followed vitreous aspiration.

Reticulum cell sarcoma or, as reclassified by Rappaport,¹ histiocytic lymphoma, is a malignancy composed of large cells resembling histiocytes. Its origin, which may be single or multicentric, is usually within the reticuloendothelial system—chiefly lymph nodes—or in the central nervous system (CNS), where it is often referred to as microglioma. Precise definition of the cell of origin, its immunological markers, the relationship between the disease and other non-Hodgkin's lymphomas, and its aetiology have all eluded researchers.² However, dramatic progress has been attained recently in treatment. Chemotherapeutic remissions 'tantamount to cure' have been achieved in 41% of patients with the most advanced stages of disease.² Localised involvement is treated with radiation, either alone or in conjunction with chemotherapy, with even greater success.³

Ocular involvement in reticulum cell sarcoma is rare, with only 25 histologically proved cases in the world literature. Until recently examination of enucleated specimens was required for diagnosis. More frequent reports during the past 10 years have demonstrated a recognisable ophthalmic presentation, typically as a refractory uveitis in middle-aged patients. Vitrectomy has provided a relatively noninvasive, and in many cases the only available, source for tissue diagnosis.⁴ As outlined below, treatment of affected eyes, which were previously doomed, has resulted in rewarding local cures.

In this article we describe the clinical and pathological findings in 3 new cases of reticulum cell

sarcoma involving the eye. The literature is reviewed with particular reference to defining further the early ophthalmic manifestations of the disease.

Case reports

CASE 1

A 66-year-old white man was seen in April 1979 because of gradual visual loss in both eyes, left more than right, during the previous 6 weeks. Past medical history included gout, controlled by diet, acute myocardial infarction in 1976, and diabetes mellitus treated with diet and oral hypoglycaemic drugs. Examination was essentially negative. Ophthalmic examination showed corrected visual acuities of 6/140 right eye and 6/60 left eye. Corrected near acuities were J2 right eye, and J10 left eye. Applanation tensions were 16 and 18 mmHg respectively. Ocular motility was full and the lids were normal. The anterior segments were unremarkable with the exception of trace cell and flare bilaterally. There was 1+ nuclear sclerosis of both lenses. Pupils were equal and reactive. In the right eye the vitreous contained 2+ cells with a posterior vitreous detachment and additional cells collected on the posterior vitreous face. In the left eye there were approximately 3+ vitreous cells with more confluent precipitates on the detached posterior vitreous face. The discs were normal, but throughout the fundus there were many focal yellow-white subretinal lesions with surrounding retinal haemorrhages (Fig. 1).

The patient was admitted to the hospital. A and B scan ultrasonography performed in both eyes showed the posterior vitreous detachments with a membrane-like formation extending from the region of the disc to the vitreous base (Fig. 2). Fluorescein

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Fig. 1 Case 1. Clinical photograph, left eye, showing retinal and subretinal infiltrates and retinal haemorrhages. Moderate vitreous haze precludes clear view.

Fig. 2 Case 1. B scan ultrasound, left eye, showing detachment and thickening of posterior vitreous face (V).

Fig. 3 Case 1. Fluorescein angiogram, right eye, showing subpigment epithelial infiltrates and leakage.

Fig. 4 Case 1. Photomicrograph of vitreous aspirate, left eye, demonstrating characteristic cells of reticulum cell sarcoma (arrows). (Giemsa, $\times 980$).

angiography showed the presence of subpigment epithelial infiltrates with diffuse leakage in later shots (Fig. 3). Physical examination and routine laboratory studies were within normal limits except for a mildly raised blood sugar. Titres for toxoplasmosis, candida, and cytomegalovirus were negative. A vitreous aspiration was performed in the left eye with the Ocutome. The material collected was cytocentrifuged, spread on slides, stained, and examined.

Cytological examination revealed many large cells with ill-defined cell borders and large pale oval-shaped nuclei. Many nuclei were multilobulated, and some contained a distinct basophilic nucleolus. Moderate pleomorphism was present, with occasional finger-like projections of the nuclei (Fig. 4). A diagnosis of reticulum cell sarcoma of the vitreous was made. Neurological examination and computerised tomography revealed no evidence of CNS disease. The patient was put on 80 mg of prednisone daily by mouth. Over the ensuing 2 weeks there was a gradual improvement in vision to the level of 6/7 right eye and 6/8 left eye. The patient has been maintained on prednisone, 40 mg daily, and the vision has remained stable. The vitreous infiltration has cleared, and there is a marked clearing of the subretinal pigment epithelial infiltrates. In these areas there have been some pigment epithelial migration and proliferation.

CASE 2

A 77-year-old white female was first seen in November 1976 with a history of blurred vision in the left

Fig. 5 Case 2. Clinical photograph, left eye, showing subretinal infiltrates and vitreous haze.

eye of 2 weeks' duration. An ophthalmic examination showed corrected visual acuities of 6/21 right eye and 6/120 left eye. Ocular motility was normal. Intraocular pressures were 18 mmHg bilaterally. Slit-lamp examination revealed normal anterior segments with mild nuclear sclerosis bilaterally. The vitreous contained a moderate cellular infiltration, and in the right fundus there was a small exudate just outside the inferotemporal arcade. These deposits were at the level of the retinal pigment epithelium. In the left fundus, adjacent to the superior temporal retinal vessels and just superior to the macula, was a white fluffy lesion of approximately 3 to 4 disc diameters which also had the appearance of an infiltrate at the level of the retinal pigment epithelium. There were scattered haemorrhages at the superior edge of this lesion and marked macular oedema (Fig. 5). General physical examination, complete blood count, urine analysis, and results of liver chemical tests were within normal limits. A chest x-ray was negative, as were serological tests for toxoplasmosis, cytomegalovirus, and candida.

The patient was put on 40 mg of prednisone for 10 days, by which time visual acuity in the left eye had improved to 6/60. There were some pigmentary changes of the retinal pigment epithelium in the region of the inflammatory focus in the left eye. Approximately 2 weeks later the patient became confused and complained of increased blurring of vision. Examination of the left eye revealed a studing of the retina with pale yellow-white exudates obscuring overlying retinal detail. Fluorescein

angiography of the left eye suggested lesions at the level of the retinal pigment epithelium.

The patient was continued on corticosteroids, but by January 1977 the lesions had progressed. In the left eye the vitreous was markedly hazy, and vision had dropped to light perception. The patient was admitted to the hospital. A general medical examination was again entirely negative. Computerised tomography revealed a large mass in the region of the splenium of the corpus callosum. It could not be determined whether the lesion was metastatic or lymphomatous in origin. During the course of the examination the patient became increasingly disorientated and died on the tenth day in hospital. The eyes were enucleated post mortem.

Gross and microscopic examination of the right eye gave normal results. Gross examination of the left eye revealed a large amount of opaque material with haemorrhages in the vitreous. A zone encompassed by the superior temporal and inferior temporal vessels contained marked retinal thickening and opacification. There were several haemorrhages in the surrounding area. Microscopic examination revealed a normal cornea and anterior chamber. The iris and ciliary body contained a light infiltrate of inflammatory cells, chiefly lymphocytes. There was early posterior migration of the lens epithelium. Within the vitreous body, which was detached, were a moderate amount of degenerating blood and necrotic cells, some of which were identified as histiocytes. There was a massive chorioretinal lesion corresponding to the abnormality noted posteriorly on gross examination. Throughout this area the retinal pigment epithelium and Bruch's membrane had been destroyed and the retina had degenerated. Scattered infiltrates in the subretinal pigment epithelial zone contained abnormal histiocytes (Fig. 6). Many had pale nuclei with coarse clumped chromatin. There were abundant mitotic figures, and many nuclei were multilobulated. In the overlying retina were large amounts of extravasated blood and severe cystoid degeneration. A preretinal glial membrane was present. The choroid contained patchy prominent collections of lymphocytes and histiocytes, many of which were abnormal. There were no viral inclusion bodies, and no micro-organisms could be identified with fungal and bacterial stains. Cross-sections of the optic nerve showed degenerative changes of the nerve fibres. Necropsy confirmed the presence of reticulum cell sarcoma involving the central nervous system.

CASE 3

A 68-year-old woman was seen approximately 2 years after uneventful cataract extraction. At that time she complained of progressive loss of vision

in both eyes. Ophthalmic examination revealed finger counting vision right eye and 6/120 left eye. Intraocular pressures were 16 mmHg in each eye. Ocular motility was full. The anterior segments were normal except for the presence of bilateral peripheral iridectomies and evidence of previous cataract extraction. A general medical examination and routine laboratory data were within normal limits. The patient underwent vitrectomy, first right

eye and then left eye, with approximately 4 to 5 months between the operations. The material collected was not studied for cytology but was cultured for fungi and bacteria. These cultures were negative. Postoperatively the patient's vision was 6/9 in each eye. During the course of the next 9 months she became progressively disorientated and obtunded. She was admitted to hospital in a coma and died without a definitive diagnosis. A general necropsy was refused, but the family granted permission for examination of the eyes.

Gross examination revealed 2 similar eyes. Lenses were absent, and there were peripheral iridectomies. Opening the eyes revealed a layering of thick white material on the pars plana for 360° in each eye (Fig. 7). The material had the consistency of sour cream. The central vitreous was clear and liquified. The optic nerve and retina posteriorly in each eye were unremarkable. Histopathological examination was similar bilaterally. Anterior segments were normal. Lying on the surface of the pars plana was a diffuse vitreal infiltration with abnormal histiocytes (Fig. 8). The tumour cells contained oval nuclei with prominent nucleoli and a thick rim of dark blue cytoplasm. The cells were highly pleomorphic, and there were abundant mitotic figures. A diagnosis of reticulum cell sarcoma was made.

Discussion

By all accounts intraocular reticulum cell sarcoma is unusual. Allen and Straatsma,⁵ in their review of 76 patients with leukaemia and allied disorders, discovered no ocular involvement among 10 cases of malignant lymphoma. In 2 separate reviews a total of 88 patients with orbital lymphomas included only 4 with intraocular disease.^{6,7}

Cooper and Riker⁸ presented the first case of ocular reticulum cell sarcoma; 47 additional cases have been reported to date. Of these, approximately half are considered primary—that is, the disease was either limited to the eye or appeared extraocularly long after an ophthalmic presentation. Two patients who came to necropsy with no history of specific therapy were found to have only eye involvement, providing strong evidence for an ocular origin of the disorder. Secondary cases, presumably including some with multicentric origins, are those with associated CNS or systemic presentations. Although the lymph node and visceral form is by far the more common, eye involvement is more frequent in the CNS form. Neault *et al.*⁹ found an associated 'uveitis' in 7 of 17 patients who underwent craniotomy for CNS reticulum cell sarcoma. Our 3 cases are all primary; 2 eventually had CNS

Fig. 6 Case 2. Photomicrograph, left eye, showing abnormal reticulum cells in subpigment epithelial space. (Haematoxylin and eosin, $\times 400$).

Fig. 7 Case 3. Opened globe viewed posteriorly showing layering of white material on pars plana.

Fig. 8 Case 4. Photomicrograph of area shown in Fig. 7, showing characteristic tumour cells on pars plana. (Haematoxylin and eosin, $\times 420$).

manifestations without clinical evidence of systemic disease.

Patients have been typically in their sixth and seventh decades at the time of presentation. The first report was of a 27-year-old man, and 1 patient was 81. These are exceptions, however, and the mean age is 64. There is no discernible sex predilection among reported cases despite a male: female ratio of 2:1 in cerebral reticulum cell sarcoma.¹⁰ Three patients are identified as blacks, roughly in proportion to the general population.

Ophthalmic consultation was sought in most cases because of decreased visual acuity. One patient initially described floaters, and a second complained of photopsia.¹¹ The principal finding, almost without exception, was debris which appeared inflammatory—variable in location and extent, but generally refractory to topical steroid therapy. Both eyes were involved in roughly 50% of cases, though asymmetry is typical.¹⁰ One patient¹² presented with a hypopyon; more typically, anterior segment reaction resembled a mild, nongranulomatous iritis, with or without keratic precipitates.

It was in the posterior segment that the disorder presented most characteristic findings. In slightly more than half of cases, fundus lesions resembling retinal or subretinal infiltrates were noted. Involved retina is described as white and thickened, with surrounding haemorrhage.⁴ Some observers have depicted the lesions as patchy, yellow-white to greenish-grey in colour, with fluffy outlines that rapidly become confluent.¹³ Encroachment of the lesions on optic nerve or macula rapidly diminished visual acuity. Vitreous involvement typically accom-

panied fundus lesions but occasionally was seen alone. It has been variously described as inflammatory cells, debris, or veils—often dense enough to obscure underlying retinal detail.⁴

Secondary glaucoma accompanied intraocular reticulum cell sarcoma in approximately half the cases.¹² In 4 of 17 cases¹⁴ the mechanism was rubeosis iridis and neovascular angle closure. Increased intraocular pressure has more typically been related to cellular debris and synechial closure in the anterior chamber angle. Glaucoma was not seen in our 3 cases. In other respects, however, they confirm the typical clinical presentation: patients in their 60s and 70s whose decreased acuity was ascribed to 'uveitis' wherein vitreous debris and/or chorioretinal infiltrative lesions were prominent features. In all 3 cases topical steroid and mydriatic therapy was ineffective. The diagnosis is even more suggested when there is evidence of CNS or systemic reticulum cell sarcoma.

The pathological data in our cases likewise typify the ocular involvement in this disease. Interestingly, the inflammatory component on histological examination is as prominent as in the clinical setting. In at least 1 case¹⁵ a patient with bilateral posterior uveitis was found at necropsy to have neoplastic changes confined to the choroid and retina of one eye. Choroidal lesions and vitreous debris noted before death in the fellow eye represented infiltrations of chronic inflammatory cells.

The tumour cells are indistinguishable from those of reticulum cell sarcoma elsewhere or microglioma in the CNS. They are large and pleomorphic, with scant cytoplasm and prominent nuclear membranes.

Nuclei are round or oval, occasionally multiple, and with frequent mitoses, clumped chromatin, and prominent nucleoli. Immunoperoxidase staining has been used to demonstrate a B cell origin, though post-mortem changes may interfere with results,¹⁰ and the cell or origin remains in doubt.¹⁴ Reticulum cells are present in normal choroid, and microglia are normal retinal constituents.⁴

On microscopic examination retinal involvement is most commonly seen. In retina as in brain tissue the cells follow a perivascular distribution, often surrounded by fine reticulum fibres which stain with silver and give the tumour its name. In the uveal tract cells tend to infiltrate more diffusely, forming dense placoid masses.¹³ An unusual characteristic of the tumour is its capacity to break through Bruch's membrane, forming discrete masses beneath the retinal pigment epithelium.¹² Exudative retinal detachment and vitreous haemorrhage have followed; papilloedema has occurred with infiltration of the optic disc.¹⁶

Retinal and uveal lesions may occur separately or together. Vitreous debris may accompany either or, as in our case 3, may occur alone.^{11 14 16} Several authors have traced a trend for CNS disease to coexist with retinal involvement, whereas 'pure' uveal infiltration occurs more frequently with systemic disease.

Other entities may produce similar white retinal lesions and must be distinguished from reticulum cell sarcoma. Retinal metastases are exceedingly rare and are generally found in the terminal stages of widespread disease. Leukaemic infiltrates and retinitis secondary to bacterial or fungal sepsis are more common but can be readily diagnosed with bone marrow or blood studies. Similarly, toxoplasmosis and cytomegalovirus infection can be differentiated with high, or ideally rising, serum titres. Cotton-wool spots are generally seen in association with systemic hypertension or collagen vascular disease, have more sharply defined borders, and are unaccompanied by other signs of inflammation.

Tissue diagnosis is a prerequisite for the initiation of therapy in reticulum cell sarcoma. Systemic disease is diagnosed by biopsy of involved lymph nodes, bone marrow, spleen, or other viscera; in the CNS examination of the cerebrospinal fluid has circumvented the necessity for craniotomy in some cases. Ocular involvement has usually been diagnosed post mortem, though in 7 cases diagnoses were made after enucleation of blind, painful eyes. In 1 case diagnosis followed biopsy of a subcutaneous lid lesion.¹² Most notable are the 3 cases previously reported,^{4 11} to which we add our case 1, in which diagnosis came from examination of vitrectomy specimens from visually intact eyes. In

each case vitrectomy improved visual acuity, if only transiently.

Radiation therapy has proved especially efficacious in affected eyes. So far 8 cases have been reported in which eyes were irradiated with appropriate shielding. In 6 treatment resulted in shrinkage of chorioretinal lesions, clearing of vitreous debris, and permanent improvement in visual acuity. Chemotherapy has produced somewhat less impressive results in cases of eye involvement, though treatment regimens have varied.^{12 17} A mass in the ciliary body responded dramatically to procarbazine, lomustine and vincristine in the only case in which therapy approximated to that now recommended.^{2 14}

Barr *et al.* noted¹² that of 14 patients with primary intraocular reticulum cell sarcoma 9 eventually developed CNS or systemic involvement. Since approximately half of all cases with eye findings present with eye symptoms, it is to be hoped that early diagnosis with vitrectomy may make possible earlier institution of specific systemic therapy in the future.

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