

Ten-year experience with primary ocular 'reticulum cell sarcoma' (large cell non-Hodgkin's lymphoma)*

MARC J SIEGEL,¹ JACK DALTON,² ALAN H FRIEDMAN,¹
JAMES STRAUCHEN,^{3,4} AND CAROLYN WATSON³

From the Departments of ¹Ophthalmology, ²Radiation Therapy, ³Pathology, and ⁴Neoplastic Diseases, Mount Sinai School of Medicine, New York, New York 10029, USA

SUMMARY Fourteen patients with intraocular 'reticulum cell sarcoma' (non-Hodgkin's large cell lymphoma) ranging in age from 27 to 77 are presented. All patients had evidence of vitritis with 50% showing intraretinal and/or subretinal lesions and 21% having anterior uveitis. Five of the patients developed central nervous system lesions and subsequently died. Primary radiation therapy to the eyes and CNS appears to prevent spread of the disease and improve longevity. Chemotherapy improved survival in one patient with CNS spread of disease.

Reticulum cell sarcoma (RCS) is a rare non-Hodgkin's large cell lymphoma which can masquerade as chronic uveitis. This disease occurs in two broad forms, with one variety primarily involving the systemic lymph nodes, visceral organs, and uveal tract and another primarily affecting the retina, vitreous, and central nervous system (CNS). In the Rappaport classification the disease was relabelled as a histiocytic lymphoma.¹ More recently surface marker studies² have shown these cells to be of lymphoid and not histiocytic origin.

Over 100 cases³⁻¹⁰ of ocular RCS have been described in the literature. Typically, the patients have been in their sixth or seventh decade when either a unilateral or bilateral painless decrease in visual acuity occurred. No sexual or racial predilection has been noted. Invariably, ocular findings include vitreous cells and debris (Fig. 1). The retina and choroid (Fig. 2), the conjunctiva, and the optic nerve may be infiltrated by tumour. Less commonly an anterior chamber reaction or an exudative retinal detachment may be presenting sign (Fig. 3). Systemic spread is common, with the CNS being affected first (Fig. 4). It is not clear if this spread of tumour represents true metastatic disease or whether it reflects a multicentric origin of the lymphoma. Diagnosis is achieved by means of vitreous aspiration and

examination of a slide prepared from the cytopspin or Millipore filter of the specimen (Fig. 5).

Over the last 10 years we have had the opportunity to treat 14 patients with RCS, with a follow-up time of up to seven years. A profile of these patients, their clinical findings, and treatment is presented (Table 1).



Fig. 1 Vitritis and subretinal lesions in patient with active disease.

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Correspondence to Alan H Friedman, MD Department of Ophthalmology, Box 1183, Mount Sinai School of Medicine, One Gustave L Levy Place, New York, NY 10029, USA

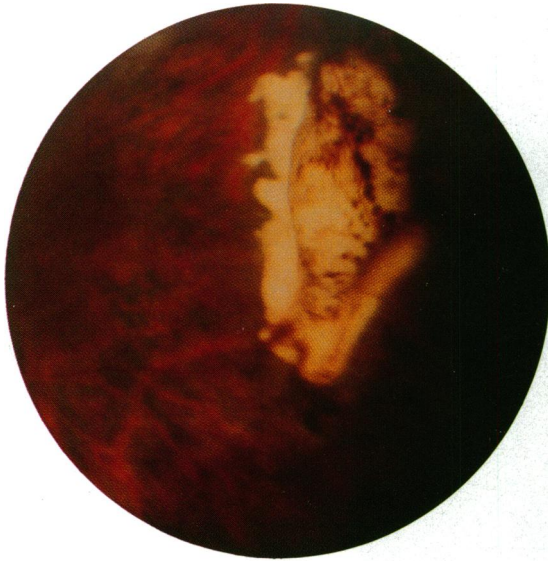


Fig. 2 Large subretinal nodule seen at initial presentation.

Results

The age at presentation ranged from 27 to 77 years, mean 65. Nine out of 14 or 64% of the patients were women, with no black patients in our series. Disease was bilateral in 71% of the patients. There was vitritis in 100% of the patients and retinal/subretinal lesions in 50%. Three of the fourteen patients had an



Fig. 3 Extensive vitritis and exudative detachment as presenting sign.

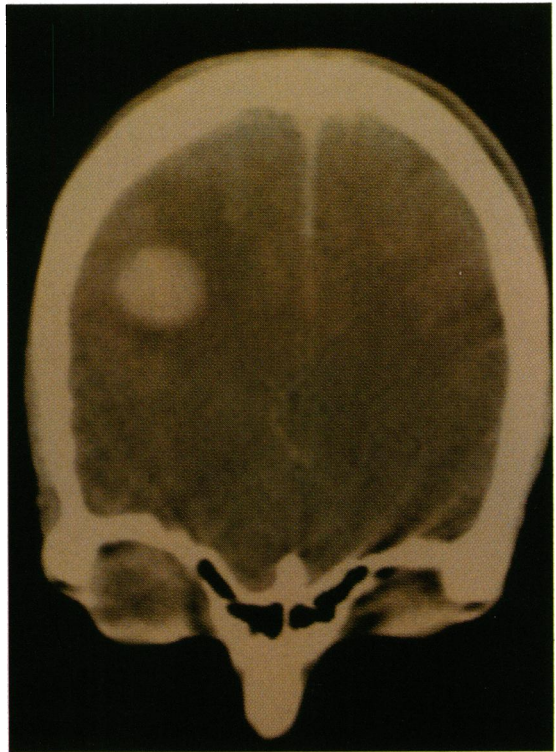


Fig. 4 Typical CNS lesion from metastatic RCS.

anterior uveitis as well, with one being moderately intense.

Initial investigations included a complete systemic evaluation with head CT scan, lumbar puncture for examination of cerebrospinal fluid, and bone marrow aspiration. Central nervous system involvement was present at the time of initial diagnosis in two cases and subsequently developed in four additional patients. All patients with CNS lesions except one died about six months after the presence of these lesions was confirmed.

The diagnosis of RCS was confirmed in 11 patients by means of a vitreous aspiration. This was performed with a 19 gauge needle introduced via the pars plana with 0.5 ml of fluid aspirated. One patient refused any diagnostic or therapeutic manoeuvres and two patients were not suspected of harbouring RCS until the time of necropsy. Nine patients who were diagnosed by vitreous aspiration underwent radiation therapy. Of the two patients who received radiation only to the orbits and not the brain one subsequently developed CNS lesions. One patient who received CNS and orbital radiation had an ocular recurrence after one year and systemic recurrence 18 months after initial diagnosis (Fig. 4) but was without evidence of CNS spread. In an additional

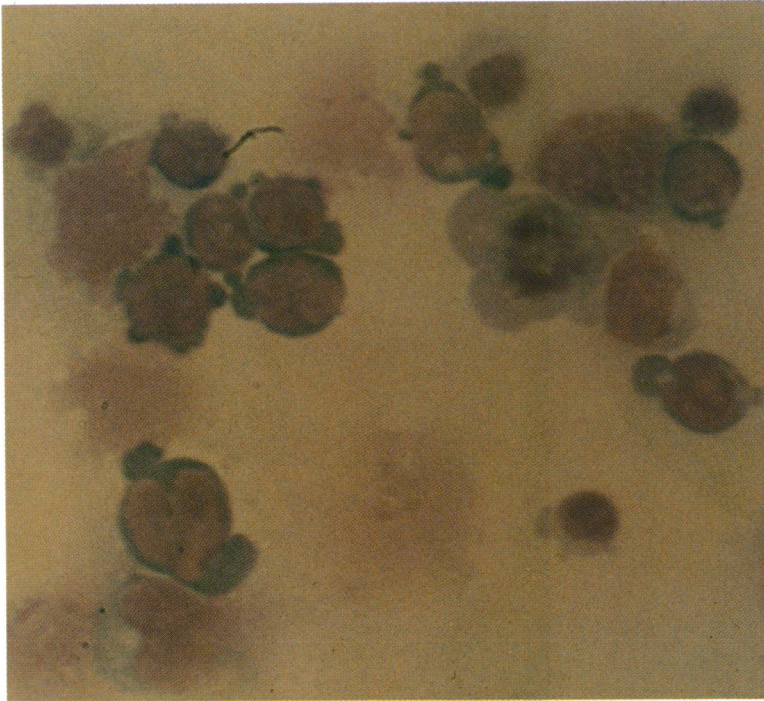


Fig 5 High-power view of vitreous cytospin showing the large atypical cells seen in large cell lymphoma. Giemsa, $\times 1200$.

patient an ocular recurrence and a new brain lesion appeared one and one-half years after ocular and CNS radiation.

In patients who received primary radiation therapy, chemotherapy was reserved for recurrent CNS disease and was effective in one case in causing regression of tumour and preventing death. Two patients received intravenous cytosine arabinoside (Ara-C) as primary therapy for localised ocular disease. At three months follow-up there was no evidence of metastatic disease and partial improvement in ocular findings, though visual acuity remained unchanged.

Our chemotherapy protocol was to give Ara-C 2000–3000 mg/m² intravenously over a period of one hour. Treatment was repeated every 12 hours for three doses in the hospital and then as single doses repeated at weekly intervals as an outpatient. Toxicity was minimal, consisting of nausea, vomiting, and myelosuppression. No patients showed signs of CNS or cerebellar toxicity.

Discussion

Our findings confirm many of those noted in smaller series of cases of RCS. Although the mean age of 65 in our series is similar to that in previous reports, one patient was 27 at initial diagnosis. Interestingly, the

first patient described with RCS was also 27¹¹ and so emphasises that, though very unusual, this condition should be thought of in younger patients as well as the elderly.

The most frequent finding in this series was an unexplained posterior and occasionally anterior uveitis. While negative blood studies, chest x-ray, and a thorough retinal examination can help to exclude some causes of uveitis, a vitreous aspiration is required for definitive diagnosis. This procedure was performed in all of our patients who consented and in whom the diagnosis was suspected. When present, a characteristic fundus picture of multicentric subretinal pigment epithelial lesions^{12,13} can help suggest the diagnosis of RCS and was present in half our cases.

Tissue typing is useful in systemic lymphomas both for prognosis and in guiding therapy. Determining whether our cases of RCS were of B-cell or T-cell origin was very difficult given the small volume of vitreous aspirate obtained in individual cases. Only one patient could be typed and this patient had a T-cell lymphoma. Other workers have noted a predominance of B-cell lymphomas,¹⁴ but all involve a small number of cases. Whether this information will become useful in future in planning treatment of RCS remains to be determined. It is possible that a pars plana vitrectomy would facilitate typing by providing

Table 1 Data summary of patients with reticulum cell sarcoma seen over the last 10 years

Age/sex	Initial visual acuity		Ocular findings at presentation	CNS lesions at presentation	Radiation treatment	Chemotherapy	Recurrence	Outcome	Length of follow-up
	OD	OS							
55/F	20/20	20/25	Vitreous cells, OS	Yes	40 grey (4000 rad) brain and OS	Cytosan, adriamycin, prednisone, vincristine (used after recurrence)	CNS lesions	Died 1½ yr	
60/F	20/30	20/25	Vitreous cells OU	None	40 grey brain and OU	None	None	Visual acuity unchanged, no metastases	6 mon
27/F	20/15	20/50	Vitreous cells, OU; focal area of RPE atrophy OS	None	40 grey brain and OU	IV Ara-C after recurrence	CNS after 1½ years	20/20 OU, metastases improved with Ara-C	18 mon
66/F	20/50	20/40	Vitreous cells and posterior vitreous detachment OU	None	40 grey brain and OU	None	None	20/30 OU	9 mon
55/F	20/70	20/20	Anterior uveitis OU; Koeppe nodule OD; retinal masses/infiltrates OD; vitreous cells OU	None	4000 rad brain and OU	None	None	20/20 OU; required low dose oral prednisone for mild persistent uveitis. Repeat vitreous tap normal 1 year ago	3½ yr
70/M	20/200	20/200	Vitreous cells OU	None	40 grey OU	Methotrexate, adriamycin, prednisone (used after recurrence)	CNS lesions in 6 months	Lost to follow-up, visual acuity 20/70 OD and 20/400 OS, CNS lesions still present and patient gravely ill	2 yr
64/F	20/70	20/200	Vitreous cells OU, cystoid macular oedema and retinal exudates OS	None	20 grey OU	None	None	20/20 OD, 20/70 OS, no metastases or large bowel involvement	7½ yr
70/M	20/70,	Finger counting	Vitreous cells OU, retinal exudates OS	None	40 grey brain and OU	None	Ocular, and large bowel involvement, 1 year. No CNS lesion	20/80 OD, 20/100 OS, terminally ill	1½ yr
61/M*	20/30	20/30	Vitreous cells OU	None	Refused	Refused		Died 6 months with CNS disease	
68/M	20/30,	Finger counting	Coarse vitritis OD, retinal exudates OS	None	40 grey brain and eyes	None	None	20/30 OD and 20/50 OS	1 yr
66/M*	20/400	20/40	Trace anterior uveitis OU, subretinal lesions OS, vitreous cells OU	None	None	40 mg prednisone p.o. qD		Died after 6 mon Diagnosed post mortem	
77/F*	20/30	20/200	Vitreous cells OU, retinal exudates OS	None	None	40 mg prednisone orally as required		Died after 6 mon Diagnosed post mortem	
66/M	20/20	20/50	Vitreous cells OS	None	None	IV Ara-C	None	Acuity unchanged	3 mon
62/F	20/30	20/100	Trace anterior uveitis OS. 4+ vitreous cells OS	None	None	IV Ara-C	None	Acuity unchanged	3 mon

*Cases previously reported.⁴

a larger quantity of cells than is obtained by vitreous aspiration.

The rapid demise of all patients who developed central nervous system lesions speaks for the need to prevent spread of this rapidly fatal disease. Radiation therapy causes effective amelioration of ocular symptoms and was usually given in a dosage of 40 grey

(4000 rad). Although largely empirical, whole brain radiation of 40 grey was also given in the hope of preventing CNS spread of disease. Within the limitations of our follow-up only one patient who was free of CNS lesions at presentation and received prophylactic whole brain radiation subsequently developed CNS metastasis. One additional patient developed

systemic but not CNS spread of disease. This contrasts with a 75% incidence¹⁵ of CNS involvement reported in other series. Our radiation protocol is similar to that used in other centres.¹⁶

The use of chemotherapy for RCS is less clear. The experience of Char *et al.*¹⁷ with three patients given combination chemotherapy, including intrathecal treatment, was favourable. Baumann *et al.*¹⁸ successfully treated one patient with intravenous high-dose cytosine arabinoside (Ara-C) who suffered recurrence after radiation therapy. Evidence suggests that Ara-C reaches therapeutic levels in the CSF and vitreous after intravenous therapy.¹⁸ Our experience with three patients given high-dose intravenous Ara-C has been encouraging. Our one patient with the best response had received radiation therapy primarily. A prospective trial to evaluate the role of systemic high-dose Ara-C in combination with ocular and CNS irradiation as primary therapy needs to be undertaken.

In summary, a high degree of suspicion is needed in patients in whom a chronic posterior uveitis of obscure aetiology persists. Chronic uveitis is unusual in people over 60, and the differential diagnosis includes sarcoidosis, syphilis, tuberculosis, toxoplasmosis, Whipple's disease, cytomegalovirus infection, metastatic disease, and amyloid disease. The presence of multifocal subretinal lesions is even more suggestive of RCS. If the diagnosis of RCS is entertained, diagnosis can easily be confirmed by means of a vitreous aspiration. It should be remembered that young patients may occasionally be affected with this disease as well. It seems reasonable that such patients with idiopathic posterior uveitis with or without characteristic fundus lesions should undergo diagnostic vitreous aspiration.

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