Combined malignant lymphoma of the eye and CNS (reticulum-cell sarcoma)

Report of three cases

EDWARD J. ROCKWOOD, M.D., Z. NICHOLAS ZAKOV, M.D., AND JANET W. BAY, M.D.
Departments of Ophthalmology and Neurosurgery, The Cleveland Clinic Foundation, Cleveland, Ohio

Three cases of histopathologically proven combined ocular and central nervous system (CNS) malignant lymphoma (reticulum-cell sarcoma) are presented. A review of the literature revealed 33 cases described with this syndrome. Symptoms and signs of both CNS and ocular disease are discussed. The results of computerized tomography and angiography are also reviewed. The diagnosis has been made by craniotomy, cerebrospinal fluid cytological examination, and by pars plana vitrectomy. The latter two procedures should probably be attempted prior to considering craniotomy. Reticulum-cell sarcoma of the eye and CNS possibly has a multicentric origin.

KEY WORDS • reticulum-cell sarcoma • ocular lymphoma • uveitis • vitreitis • central nervous system lymphoma • pars plana vitrectomy • microglioma

Much has been written on central nervous system (CNS) lymphomatosis (reticulum-cell sarcoma), either as a primary disease or, less commonly, as a manifestation of disseminated systemic lymphoma. Ocular reticulum-cell sarcoma has been reported to exist alone or in association with CNS reticulum-cell sarcoma. To our knowledge, 58 cases of ocular reticulum-cell sarcoma have been reported in the English literature: of these, 33 had an associated CNS reticulum-cell sarcoma.1-5,8-19,21,22 This paper presents three new cases of combined ocular and CNS reticulum-cell sarcoma and reviews the other 33 cases in the literature.

Case Reports

Case 1

This 57-year-old woman presented to our Ophthalmology Department in March, 1979, with a diagnosis of bilateral uveitis of 1 year's duration that had been treated with topical, subconjunctival, and oral steroids. At that time, her visual acuity was 20/50 in both eyes, and examination revealed bilateral cataracts and uveitis. By October, 1979, vision had worsened to 20/60 in the right eye and 20/200 in the left. There were keratic precipitates on the corneal endothelium as well as a vitreitis rated as 2+ in the right eye and 3+ to 4+ in the left. Routine blood work, tests for venereal disease (VDRL), antinuclear antibody, purified protein derivative, fungal serology, rheumatoid factor, and Toxoplasma titer, as well as chest and skull radiographs were all normal. Vision improved to 20/40 in the right eye and 20/60 in the left eye on oral steroids.

In October, 1980, the patient was admitted for evaluation of forgetfulness, drowsiness, personality change, decreased coordination, and slurred speech of about 4 months' duration. Neurological examination demonstrated a left ptosis, right upper extremity weakness, bilateral Babinski responses, and an ataxic gait. Computerized tomography (CT) demonstrated multiple enhancing left hemispheric lesions (Fig. 1 left). One week later, she underwent a left frontal craniotomy with biopsy that revealed a malignant lymphoma of the reticular cell type (Fig. 1 right). Postoperatively she received a course totaling 4600 rads of whole-brain irradiation.

She was readmitted in February, 1981, because of the development of a right lower extremity paresis. A CT scan of the head and a myelogram were both normal; however, the cerebrospinal fluid (CSF) demonstrated malignant lymphoma cells. The family refused to allow chemotherapy, and the patient died in April, 1981. Permission for autopsy was not obtained.
Case 2

This 64-year-old man was first examined in the Ophthalmology Department in September, 1981, complaining of seeing “milky clouds” in each eye since July, 1980. He had been treated for this condition with topical ocular steroids. Visual acuity was 20/40 in the right eye and 20/20 in the left. Ocular examination demonstrated a normal anterior chamber in both eyes except for keratic precipitates; there were 3+ to 4+ vitreous cells in each eye with normal-appearing fundi. Extensive laboratory and radiological evaluation, including a CT scan of the head, was normal.

In December, 1981, the patient complained of left axillary pain of 1 month’s duration, and admitted to left upper extremity paresthesias as well as weakness for approximately 1 year. Neurological evaluation revealed bilateral pyramidal tract signs, worse on the left, that were attributed to cervical myelopathy secondary to demonstrable cervical spondylosis. No therapy was administered.

In April, 1982, he complained of facial paresthesias, and was found to have a small 4- to 5-mm pontine lesion consistent with an infarct on a high-resolution sector scan of the posterior fossa. Analysis of CSF, including cytology, was normal. By July, he was noted to have slower mentation and bilateral spasticity, greater in the upper extremities. A third CT scan of the

---

**Fig. 1.** Case 1. *Left:* Computerized tomography (CT) scan of the head demonstrating two anterior left hemispheric lesions. *Right:* Photomicrograph of CT-guided needle biopsy of the brain tumor demonstrating tumor cells, predominantly in a perivascular location. H & E, × 240.

**Fig. 2.** Computerized tomography scans in Case 2. *Left:* Scan before radiation therapy demonstrating a small enhancing lesion (arrow) in the left cerebral hemisphere above the lateral ventricle. *Right:* Postirradiation scan demonstrating resolution of the previous enhancing lesion.

**Fig. 3.** Case 2. Vitreous cytology demonstrating a lymphoma cell with a large nucleus, scant cytoplasm, and multiple nuclei.
Reticulum cell sarcoma of eye and CNS

FIG. 4. Case 3. Photographs of the right optic disc and fundus. Left: The pretreatment photograph is blurred because of the vitreal haze. There are also choroidal and retinal pigment epithelial changes. Right: Postvitrectomy postirradiation photograph showing partial clearing of the vitreal haze. The retinal pigment disturbance is more evidence here than in left.

head showed a small area of enhancement in the left hemisphere above the ventricle and atrophy not noted in the previous CT scan (Fig. 2 left). Lumbar puncture was performed and the CSF cytology demonstrated “an occasional atypical reactive cell.” Bone-marrow biopsy and CT scan of the abdomen were normal. Electroencephalography demonstrated diffuse slowing.

In July, 1982, the patient underwent a lensectomy and pars plana vitrectomy in the right eye. Vitreous pathology was consistent with a small cell neoplasm (Fig. 3). He received 4500 rads of whole-brain and 3200 rads of right ocular irradiation over a 5-week period.

After irradiation, the patient’s vision and mental status improved; however, he continued to complain of bilateral upper extremity weakness. A CT scan demonstrated resolution of the left hemispheric lesion (Fig. 2 right). Pantopaque myelography was normal, and electromyography suggested a motor neuropathy. In view of his progressive myelopathy, radiation therapy was administered to the spinal cord in March, 1983. The patient died the following month, apparently from sepsis secondary to a neurogenic bladder. Autopsy failed to demonstrate any tumor in the brain, spinal cord, or systemically. Tumor cells were present in the vitreous of the non-irradiated left eye, but not of the irradiated right eye.

Case 3

This 69-year-old woman presented to our Neurology Department in April, 1983, for evaluation of disorientation. She had been treated for a uveitis since 1979, and subsequently became disoriented and began to complain of decreased vision in August, 1981. A CT scan of the head reportedly demonstrated a lesion of the corpus callosum. Cerebral angiography was normal. She was diagnosed as having had a cerebral hemorrhage. No therapy was administered, and a repeat CT scan in July, 1982, was reported to be normal.

On examination in April, 1983, the patient was noted to be disoriented and to have a marked diminution of immediate recall. She was also found to have mild right upper extremity weakness, astereognosis, and a right-left disorientation. Ocular examination demonstrated a bilateral uveitis with a mild anterior chamber reaction and multiple vitreous cells. Visual acuity was 20/60 in both eyes. There were areas of retinal pigment epithelium dropout in both eyes (Fig. 4 left).

A CT scan of the head demonstrated a right cerebellar hemispheric lesion (Fig. 5); a CT scan of the abdomen, an ultrasonogram of the liver, and a bone marrow biopsy were unremarkable. Analysis of CSF demonstrated 2 white blood cells/µl with a differential of 90% lymphocytes and 10% monocytes. Occasional “plasmacytoid” cells were noted. A diagnostic vitrectomy demonstrated cells consistent with reticulum-cell sarcoma. Whole-brain and binocular irradiation was administered, and the patient has since had significant improvement in mental status and some vitreal clearing (Fig. 4 right).

Discussion

Of 36 cases of combined CNS and ocular reticulum-cell sarcoma, including the three cases presented here, 19 were found in men and 17 in women. The average age of onset of either ocular or CNS symptomatology in the 36 cases was 57.7 years, with an age range from 38 to 77 years.
Ocular preceded CNS symptoms in 28 (77.8%) of the 36 cases, and CNS preceded ocular symptoms in seven cases (19.4%). The time from onset of ocular symptoms to development of CNS symptomatology ranged from less than 1 month to 10 years in one case. When CNS disease presented first, the time differential ranged from 5 months to 489 years. One case was reported to have a simultaneous onset. Twenty-seven (81.8%) of 33 cases had binocular involvement; however, many of these cases began in one eye or had an asymmetric degree of ocular disease. Char, et al., reported an 80% incidence of binocular involvement in their review of 50 cases of ocular reticulum-cell sarcoma.

Initial ocular symptoms most often included complaints of decreased vision, cloudy vision, blurred vision, or floaters. Visual acuity ranged from 20/20 to no light perception. Pain was either absent or not a prominent complaint in many cases. Clinically, ocular reticulum-cell sarcoma presented as a uveitis with the posterior segment (vitreous, choroid, and retina) being more involved than the anterior segment. Anterior segment findings included keratic precipitates on the corneal endothelium, anterior chamber inflammatory reaction ("cells" and "flare"), and conjunctival injection. Posterior segment findings invariably included a vitreitis, clinically recognized as cellular infiltrates, and debris in the vitreous. Vitreous debris ranged from a mild haze to dense vitreous veils with significant reduction of visual acuity. The CNS symptoms and signs, whether as the initial presentation or subsequent to ocular disease, included both localizing and non-localizing neurological deficits.

The retina and choroid were normal in some cases, and in others a retinitis, a chorioiditis, or both were present. Klingele and Hogan and Sullivan and Dallow suggested that retinal lesions are associated with CNS reticulum-cell sarcoma, while choroidal lesions are associated with systemic lymphomatous disease; however, CNS reticulum-cell sarcoma has been found with choroidal, retinal, or combined (chorioretinal) disease. Choroidal tumors can induce secondary overlying retinal changes that might be misinterpreted as tumor involvement. Raju and Green discussed the histopathological findings of an enucleated eye in which retinal changes, including necrosis, was found over a choroidal tumor infiltrate. Neovascular glaucoma and retinal detachment have also been reported in patients with ocular reticulum-cell sarcoma.

Table 1 lists the method of diagnosis in the 36 cases reviewed here. Enucleation for tissue diagnosis was generally performed only in blind and painful eyes, often with neovascular glaucoma. One patient diagnosed as having reticulum-cell sarcoma from tissue obtained by enucleation had earlier undergone a craniotomy with no tissue diagnosis obtained. Another case reported by Wagoner, et al., had a diagnosis of oligodendroglioma after craniotomy; however, reexamination of this tissue after a subsequent vitrectomy demonstrated reticulum-cell sarcoma of the brain as well as the eye.

Laboratory studies including blood cell counts, biochemical profiles, VDRL, Toxoplasma titers, and histoplasmosis titers were often performed as part of an uveitis work-up, and were usually negative; however, one case had a monoclonal gammopathy. The results of CT scans of the head, described in 10 cases, were positive in all. Our Case 2 had an initial normal CT scan despite CNS symptomatology. Our Case 3 had a changing pattern of abnormalities seen on CT scan: the second CT scan was normal, whereas the first and third scans were positive. Carotid angiography was discussed in eight cases and reported as positive in five. Normal angiography in the documented presence of tumor could suggest the histopathology of cerebral reticulum-cell sarcoma. Usually a perivascular diffuse infiltration of tumor cells rather than a frank vascular or avascular mass is found in such cases. The CSF studies were described in 14 cases, the results of which are listed in Table 2. Less specific abnormalities included increased CSF protein and lymphocytosis. Metastatic work-
Reticulum cell sarcoma of eye and CNS

TABLE 2

<table>
<thead>
<tr>
<th>Cytological Findings</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>6*</td>
</tr>
<tr>
<td>negative</td>
<td>5</td>
</tr>
<tr>
<td>atypical cells</td>
<td>1</td>
</tr>
<tr>
<td>increased lymphocytes</td>
<td>2</td>
</tr>
<tr>
<td>total cases</td>
<td>14</td>
</tr>
</tbody>
</table>

* One case was interpreted as metastatic carcinomab.

ups documented systemic lymphomatous disease in four cases. None of our three patients had evidence of systemic involvement.

Reticulum-cell sarcoma can involve one or both eyes. Both the anterior (iris, ciliary body) and posterior uvea (choroid) have been found on histopathological examination to have malignant infiltration. In retinal or choroidal involvement, areas of inflammatory cell infiltration with lymphocytes and plasma cells as well as direct tumor involvement are seen. Kennerdell, et al., reported a case of cerebral reticulum-cell sarcoma confirmed at autopsy that initially presented as binocular uveitis. Histopathological examination of the eyes demonstrated a non-malignant heavy infiltrate of mononuclear cells. No tumor was found. This case could either be a coincidental uveitis, a case of "premalignant" manifestation of ocular reticulum-cell sarcoma, or a case in which significant pathology was not appreciated. The sites of CNS involvement varied. Many cases appeared to be unilateral, but three patients were documented at autopsy as having multiple sites of CNS involvement.

Current thinking on the origin of CNS and ocular reticulum-cell sarcoma focuses on a theory of multicentric origin. This hypothesis is supported by Case 3 reported by Barr, et al., where binocular involvement was documented at autopsy; however, the CNS and the rest of the body were completely free of tumor. Metastasis of reticulum-cell sarcoma from one eye to another without systemic spread would seem unlikely. Neault, et al., observed that metastasis from the eye to one or more regions of the brain without systemic spread would also be unlikely. Of the three patients documented histopathologically as having multifocal CNS disease, only one was found to have systemic lymphoma. That CNS involvement was not a manifestation of contiguous spread from the eye through the optic nerve is documented by a number of cases where no tumor was found in the optic nerve despite its presence in both brain and ocular tissues. In fact, in a number of cases in which disc edema was seen clinically, no tumor was found. Presumably, disc swelling was secondary to increased intracranial pressure.

The actual origin of ocular involvement is unknown. Some investigators have implicated the retina, recognizing that embryologically it is an extension of the CNS. However, some eyes demonstrate choroidal and uveal involvement but no retinal tumor. Of particular interest are those cases like our Case 2 in which a vitreitis was seen clinically, but the retina and choroid both appeared normal. Finally, it is notable that in some cases with bilateral vitreitis, retinal infiltrates were seen clinically in only one eye. These cases suggest that tumor might also arise in the iris or ciliary body or may even be clinically undetectable in some ocular tissues, particularly in those cases of isolated vitreitis.

Kaplan, et al., presented a case of ocular reticulum-cell sarcoma in a patient with chronic lymphocytic leukemia, in whom cell surface marker studies on a vitreous aspirate demonstrated the presence of transformed B cells. They pointed out that cases of morphologically diagnosed reticulum-cell sarcoma which have undergone histochemical studies have cells of lymphoid, not histiocytic origin.

Currently, whole-brain irradiation is recommended for cerebral reticulum-cell sarcoma, and ocular irradiation for ocular disease. Considering the high incidence of bilateral disease in ocular reticulum-cell sarcoma, we recommend binocular radiation for patients with clinical evidence of binocular disease even when there is minimal or asymptomatic involvement of one eye. Due to the retrospective nature of this study, we cannot recommend prophylactic whole-brain irradiation. However, any patient with documented ocular reticulum-cell sarcoma should have an extensive neuroradiological evaluation even if no symptoms are present. Negative studies in patients with ocular reticulum-cell sarcoma and unexplained neurological symptoms should be repeated, and such patients require very close follow-up review.

Conclusions

Ocular and CNS reticulum-cell sarcoma is a multicentric malignancy within these tissues and occasionally is systemic. Recent histochemical studies have suggested that many of these cases may actually be of T or B cell origin and not histiocytic.

The diagnosis of reticulum-cell sarcoma should be suspected in patients in their fifth to seventh decade of life who have a history of chronic unilateral or bilateral uveitis, more prominently a vitreitis (with or without retinal and choroidal disease) that has been refractory to corticosteroid therapy. Particularly when focal or diffuse CNS symptoms and signs develop in these patients, an effort must be made to rule out reticulum-cell sarcoma. Computerized tomography is the most sensitive neuroradiological investigation; CSF cytology may be diagnostic, but the examiner should be alert to nonspecific clues such as increased protein content, increased lymphocyte counts, or a finding of atypical cells.

Definitive diagnosis can be made by brain biopsy at the time of craniotomy, with CT needle guidance, or from tissue obtained by enucleation of a blind painful.
eye. However, success with diagnostic vitrectomy or vitreal aspiration suggests that this procedure should be performed first in an attempt to make the diagnosis and thus avoid cranial surgery in cases where vitreitis is seen clinically. Patients with ocular reticulum-cell sarcoma should probably have binocular irradiation and also whole-brain irradiation if CNS disease is strongly suspected.

References

Manuscript received November 3, 1983. Accepted in final form February 7, 1984. Address reprint requests to: Janet W. Bay, M.D., Section of Neuro-Oncology, The Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44106.