Bilateral ocular disease as the initial presentation of malignant lymphoma

ROBERT WEISENTHAL, WILLIAM C FRAYER, CHARLES W NICHOLS,
AND RALPH C EAGLE

From the ¹Department of Ophthalmology, University of Pennsylvania, and the Scheie Eye Institute, Philadelphia, PA, USA

SUMMARY Malignant lymphocytic lymphoma rarely involves the eye. In two patients we found ocular signs and symptoms as the initial presentation of systemic disease. In the first patient periorbital swelling and ptosis of one year's duration ultimately proved to be the result of malignant lymphoma. After resolution of swelling and ptosis with chemotherapy, the patient returned with diffuse iris involvement and uveitis with a hypopyon. In the second patient an acute change of refractive error proved to be the result of a lymphomatous deposit in the choroid. In both instances common symptoms were the initial manifestations of a diffuse malignant disease.

Although malignant lymphocytic lymphoma involves the orbit in 2-3% of cases, intraocular lesions are very uncommon. In any event infiltration of ocular or orbital tissues is usually a late manifestation of the disease. We describe here two patients with ocular and adnexal involvement by malignant lymphocytic lymphoma in whom these ocular signs were the first indication of systemic disease. For this reason the ophthalmologist must be aware of the varied presentations of malignant lymphoma in the eye and orbit.

Case reports

CASE 1

A 60-year-old white woman first noted swelling round her right eye in September 1982. The painless periorbital swelling persisted and became bilateral. In January 1983 an ophthalmologist treated her with topical steroids and antibiotics, but there was no improvement. In the same month she was admitted to the hospital for further medical evaluation. At that time she denied any history of fevers, muscle aches, pain, or rashes. Her past medical history was remarkable only for arthritis and for a radical mastectomy in 1982 for breast carcinoma without subsequent radiotherapy or chemotherapy.

A general physical examination showed an en-

larged right submandibular lymph node, but she showed no cervical or supraclavicular adenopathy or hepatosplenomegaly. Her visual acuity was 20/40 OD, 20/70 OS. She had bilateral periorbital swelling with secondary ptosis. The palpebral conjunctiva was puffy and reddened, with redundant folds. The results of ocular examination were within normal limits.

A CT scan of the head showed a density in the right maxillary antrum without evidence of bony destruction. Although no note was made of any orbital lesions, a subsequent review of the CT scan revealed a subtle diffuse infiltration of the orbit. Exploration of the sinus was performed through a Caldwell-Luc incision, and a large cyst was removed from the maxillary sinus. Biopsy of the palpable submandibular lymph node was done at the same time. Microscopic study of the antral cyst revealed only the non-specific inflammation of the sinus mucosa. The lymph node changes were interpreted as fibrotic reactive hyperplasia. It was believed that a tumour, cardiovascular disease, and vasculitis had been ruled out, and that the periorbital swelling was non-specific, possibly secondary to Graves' disease or amyloid, although all thyroid tests were normal. She was discharged on hydroxyzine hydrochloride tablets, and was to be followed up by her ophthalmologist.

The periorbital swelling persisted and progressed, so that she soon noticed proptosis and diplopia. On 19 September 1983 the patient came to the Scheie

Correspondence to William C Frayer, MD, Scheie Eye Institute, 51 North 39th Street, Philadelphia, PA 19104, USA.

Fig. 1 Appearance of patient 1 at the time of her initial visit. Note ptosis and periorbital swelling.

Eye Institute. Ophthalmic examination revealed visual acuity to be 20/80 OU with symmetrical periorbital soft tissue swelling, exophthalmos, and restricted extraocular movements (Fig. 1). Abnormal tissue densities were palpable beneath the skin of the lids bilaterally. Fundus examination revealed choroidal folds (Fig. 2). Ultrasound examination showed low reflective, regularly structured, multilobulated lesions involving orbital soft tissues, lid, extraocular muscles, and lacrimal glands. A general medical examination showed nothing abnormal. The patient had no lymphadenopathy or enlargement of liver or spleen. CT scan at this time showed extensive infiltration of both orbits by soft tissue masses of various sizes (Fig. 3). A biopsy of the nodular tissue by anterior orbitotomy revealed a fibrous, salmon coloured tissue which on histological section was composed of poorly differentiated lymphoblasts (Fig. 4). Further staging by oncologists demonstrated splenic enlargement on abdominal CT scan and bone marrow involvement consistent with poorly differen-

Fig. 2 Fundus photograph of the left eye showing chorioretinal folds secondary to infiltration of lymphomatous lesions.

Fig. 3 Axial view of the orbit shows diffuse infiltration of lymphoma throughout the orbit.

tiated lymphocytic lymphoma. As the patient denied fever, night sweats, or weight loss, she was staged IV A. Chemotherapy was begun on 30 September with cyclophosphamide 750 mg/m² by mouth, doxorubicin hydrochloride 50 mg/m², vincristine 1.5 mg/m², and prednisone 100 mg. The cyclophosphamide, doxorubicin, and vincristine were given on day 1. Prednisone was given on five consecutive days following initiation of therapy. This regimen was repeated approximately every three weeks. By 12 October the patient showed dramatic improvement, with resolution of periorbital swelling and diplopia (Fig. 5). Subsequently she was given six additional treatments over five months, with continued improvement in her condition.

In January 1985 the patient first noted sharp pain, redness, and intermittent blurred vision in her left eye. She had received her last chemotherapeutic treatment in October 1983 and had been asymptomatic since that time. On examination at the initial visit in January 1985 her visual acuity was 6/12 OU. She showed no signs of exophthalmos, decreased extraocular movements, or periorbital swelling. On slit-lamp examination there was corneal epithelial oedema, 2+ anterior chamber cells, and flare with a few fine keratitic precipitates in her left eye. Her intraocular pressures were 11 mmHg in OD and 34

Fig. 4 Cells of malignant lymphoid infiltrate have large vesicular, cleaved or reniform nuclei and prominent nucleoli. *H and E, $\times 400$.*

mmHg in OS, with open angles in both eyes. Her fundus examination was normal. She was started on prednisolone sodium phosphate solution in the left eye four times a day.

On repeat examination a week later she no longer noted the pain and redness. Her physical signs had resolved, and the steroids were gradually tapered. Over the next several months she had two episodes of uveitis which responded to steroids and cycloplegia. In June 1985 the uveitis again returned, but this time it did not respond to treatment. The oncologist who had been following her up found recurrent lymphoma of the abdomen and chest. By 17 July 1985 her vision had dropped to 20/80, with a large hypopyon and 4+ cell and flare with dramatic nodular iris infiltrates (Fig. 6). The patient was put on chemotherapy with N-methylfermanide, but without improvement of her uveitis or systemic lymphoma. Treatment with 2400 rads of radiation therapy did not help. Another

biopsy was done in the hope of obtaining a more accurate diagnosis for treatment. Histological sections of a subcutaneous nodule in the right leg showed a diffuse, undifferentiated (non-Burkitt) cell type by the Rappaport classification. Since that time the patient's vision has dropped to light perception OS and remains 6/6 OD. The uveitis persists despite several additional treatments with chemotherapy.

Fig 5 After two treatments with chemotherapy the patient shows resolution of her periorbital swelling and ptosis.

Fig. 6 Slit-lamp photograph showing an anterior uveitis and hypopyon, with a diffuse iris infiltration.

CASE 2

A 55-year-old white male first noted blurred vision in his left eye which improved when he removed his myopic correction. He was seen by an ophthalmologist, who noted a serous detachment of the left macula overlying a solid, pale white choroidal mass which accounted for the change in his refraction. In addition the physician noted an elevated, amelanotic lesion over the vortex vein in the superotemporal periphery of the same eye. Although the patient had no other systemic symptoms, it was decided to send him for a further examination to rule out metastatic disease.

On 16 April 1984 the patient was admitted to the Hospital of the University of Pennsylvania for investigation of oesophageal lesions seen on radiography of the upper gastrointestinal tract. At that time he was referred to the Ophthalmology Service. He noted no change in his symptoms. We found his visual acuity was 6/6 OU with a refractive error of $-4.00 +0.75 \times 180$ OD and $+1.00$ sphere OS. In the left eye the previously noted macular and peripheral lesions were unchanged. However, during the examination we noted for the first time, a 3 mm elevated pale white choroidal lesion overlying the vortex vein in the right eye. The remainder of the ocular examination was normal. On fluorescein angiogram the three lesions hyperfluoresced early and stained late (as shown in Fig. 7). There was some leakage from the foveal lesion in the left eye. The angiogram was interpreted as compatible with metastatic disease.

Biopsy of the oesophageal lesions by endoscopy revealed a mixed lymphocytic lymphoma with small

and large cells. Further examination ultimately revealed diffuse involvement of the oesophagus, bone marrow, and submental, cervical, and retroperitoneal lymph nodes, so the disease was staged as grade 4. Chemotherapy was initiated with vincristine, cyclophosphamide, and dexamethasone.

By 10 May 1984 the refractive error in the left eye had reverted to its pre-existing state, with resolution of the serous detachment. The two peripheral lesions noted in the superotemporal quadrants in both eyes had also regressed, leaving only a scattered pigment epithelial reaction over the previous areas of involvement. Similarly, the oesophageal and lymph node lesions cleared after seven courses of chemotherapy.

Discussion

This report concerns two patients with diffuse lymphocytic lymphoma whose initial symptoms led them to consult an ophthalmologist. The first patient presented with chronic periorbital swelling and ptosis (which had been increasing) for one year. Subsequently the patient returned with diffuse iris infiltration and uveitis which initially responded to steroids, and then progressed despite radiation therapy and several courses of chemotherapy. In the second patient a change in refraction secondary to lymphomatous choroidal deposits brought him to an ophthalmologist, who initiated the examination that led to the diagnosis of a malignant lymphocytic lymphoma. Neither patient noted night sweats, fever, weight loss, or any other systemic manifestations of the disease.

Orbital infiltrates are not uncommon in malignant lymphoma, occurring in 2–4% of patients, but it is usually a late complication and may be difficult to diagnose.^{1–3} The conjunctiva is the most frequent tissue involved followed by the lid, orbit, and lacrimal gland. Most lesions occur unilaterally, involving right and left sides equally frequently. Periorbital swelling is the commonest presenting symptom followed by proptosis, ptosis, pain, and poor or blurred vision. Abnormal tissue can be palpated in over 90% of orbital metastases. Most lesions are present for 8 to 10 months prior to diagnosis.⁴

In contrast, intraocular involvement in lymphoma is uncommon, except in cases of reticulum cell sarcoma or large cell histiocytic lymphoma. Reticulum cell sarcoma usually presents as a chronic uveitis which is not responsive to steroids in a patient in the sixth or seventh decade of life.^{5–7} Reticulum cell sarcoma may also present with choroidal or retinal lesions.^{6,7} Multiple pigment epithelial detachments are considered characteristic of this disease.⁸ The uveitis responds to radiation therapy.⁹

Intraocular infiltration is especially rare in patients

Fig. 7 Fluorescein angiogram of the left eye showing early hyperfluorescence of superotemporal lesion.

with lymphocytic lymphoma. A literature review reveals only isolated case reports. One patient with lymphoblastic lymphoma was noted to have a perivenous retinal infiltrate, associated with haemorrhages, venous congestion, and cotton-wool patches.¹⁰ There are two reports of choroidal infiltration in lymphocytic lymphoma. Hartshorne described a 3-year-old child with lymphosarcoma of the choroid.¹¹ Chambers and Mosher reported on a 47-year-old Caucasian man with generalised lymphoblastic lymphoma without clinical signs of intraocular involvement. Necropsy revealed microscopic infiltration of the choroid in the posterior pole.¹²

In the first patient the intraocular involvement was seen late in the course of the disease and initially responded well to topical steroids. Subsequently the uveitis recurred and did not respond to steroids, chemotherapy, or radiation therapy. In the second patient the choroidal lesions responded well to systemic chemotherapy.

In summary, these patients illustrate the need for complete examination in the face of non-specific or negative findings, so that a correct diagnosis can be made. The ophthalmologist must be aware that potentially malignant lesions may present solely with common ocular symptoms and may be the harbingers of systemic disease.

This study was supported by unrestricted grants from the Frank and Elizabeth Whited Teaching and Research Fund and by Research to Prevent Blindness, Inc.

References

- 1 McGavie JS. Lymphomatoid diseases involving the eye and its adnexa. *Arch Ophthalmol* 1943; **30**: 179-89.
- 2 Rosenberg SA, Diamond HD, Jaslowitz B, Craver LF. Lymphosarcoma: a review of 1269 cases. *Medicine* 1961; **40**: 31-76.
- 3 Yanoff M, and Scheie HG. Malignant lymphoma of the orbit: difficulties in diagnosis. *Surv Ophthalmol* 1967; **12**: 134-40.
- 4 Knowles DM, Jakobiec FA. Orbital lymphoid neoplasms: a clinicopathologic study of 60 patients. *Cancer* 1980; **46**: 576-89.
- 5 Cooper EL, Riker JL. Malignant lymphoma of the uveal tract. *Am J Ophthalmol* 1951; **34**: 1153-8.
- 6 Simon JW, Friedman AH. Ocular reticulum cell sarcoma. *Br J Ophthalmol* 1980; **64**: 793-9.
- 7 Vogel MH, Font RL, Zimmerman LF, Levine RA. Reticulum cell sarcoma of the retina and uvea. *Am J Ophthalmol* 1968; **66**: 205-15.
- 8 Gass JDM, Sever RJ, Grizzard WS, *et al.* Multifocal pigment epithelial detachment by reticulum cell sarcoma. *Retina* 1984; **4**: 135-43.
- 9 Margolis L, Fraser R, Lichter A, Char DH. The role of radiation therapy in management of ocular reticulum cell sarcoma. *Cancer* 1980; **45**: 688-92.
- 10 Lewis RA, Clark RB. Infiltrative retinopathy in systemic lymphoma. *Am J Ophthalmol* 1975; **79**: 48-52.
- 11 Hartshorne I. Lymphosarcoma of the orbit probably arising in the choroid. *Am J Ophthalmol* 1922; **5**: 604-8.
- 12 Chambers JD, Mosher ML. Intraocular involvement in systemic lymphoma. *Surv Ophthalmol* 1966; **11**: 562-4.

Accepted for publication 10 February 1987.