British Journal of Ophthalmology 1993; 77: 184–187

Anterior visual system involvement in non-Hodgkin's lymphoma

A G Zaman, E M Graham, M D Sanders

Medical Eye Unit, St Thomas's Hospital, London SE1 7EH
A G Zaman
E M Graham
M D Sanders

Department of Neuro-Ophthalmology, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1 3BG
E M Graham
M D Sanders

Correspondence to:
Mr A Zaman, Department of Immunology, Rayne Institute, St Thomas's Hospital, London SE1 7EH.

Accepted for publication
3 November 1992

Abstract

Non-Hodgkin's lymphoma may have ocular involvement but optic nerve and chiasmal disease is unusual. Determining the cause of the neuropathy in this group of patients presents major difficulties despite modern neuroimaging and immunocytochemistry. Two patients with NHL are presented; one had an anterior chiasmal syndrome and the other bilateral optic nerve involvement. The first patient was thought to have lymphomatous infiltration and the second a concomitant infection (progressive multifocal leucoencephalopathy). Toxic effects of therapy were considered but finally rejected. The importance of modern neuroimaging and the role of optic nerve biopsy are discussed.

(*Br J Ophthalmol* 1993; 77: 184–187)

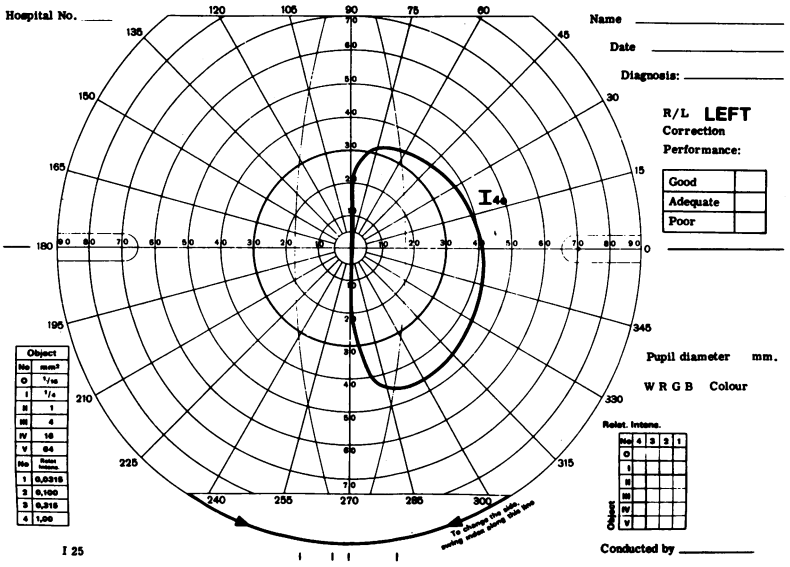

Figure 1 Patient 1. Goldmann visual field of left eye demonstrating temporal loss.

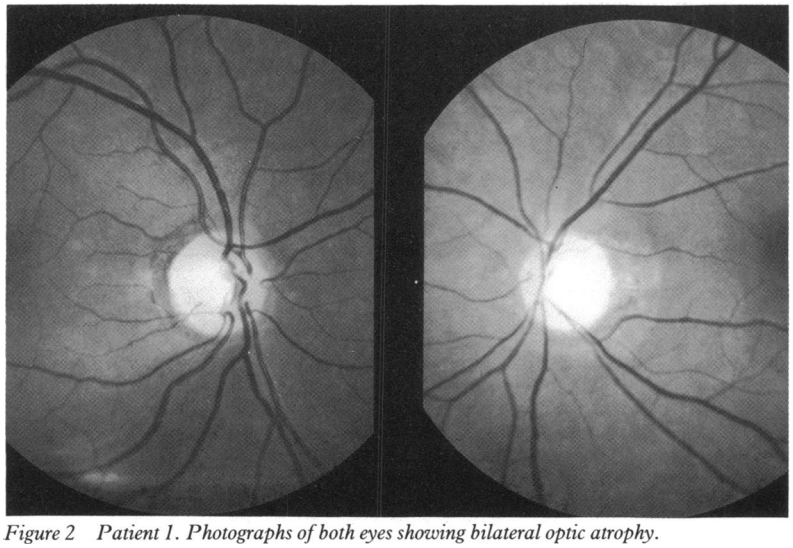

Figure 2 Patient 1. Photographs of both eyes showing bilateral optic atrophy.

Visual loss in non-Hodgkin's lymphoma (NHL) may be due to disease of the uveal tract, or of the visual pathways from retina to cerebral cortex. The incidence of CNS involvement is increasing because of longer survival associated with more effective treatment and thus the ophthalmologist has an increasing chance of being involved with these patients. Optic neuropathy in NHL is extremely rare. There are few well documented series and many anecdotal cases with a paucity of histological examinations. Optic nerve involvement has been associated with lymphomatous infiltration,[1] infections,[2 3] neurotoxic drugs,[4] radionecrosis,[5] and paraneoplasia.[6 7]

The management of such patients requires prompt investigation to exclude treatable causes such as infiltration, drug toxicity, and certain infections. However establishing the diagnosis may prove difficult, as tissue biopsy of optic nerve is often unavailable.

We present two cases of NHL and visual loss which demonstrate the value of accurate visual field assessment and modern neuroimaging.

Case reports

CASE 1

A 42-year-old woman presented in 1988 with a fever of unknown origin. A lymph node biopsy from the left axilla revealed centroblastic non-Hodgkin's lymphoma and a staging computed tomographic (CT) scan showed splenomegaly and enlarged lymph nodes in the axillae and para-aortic region. At the time she had weakness in both arms and legs with impaired power and areflexia in both lower limbs. A CT scan of the brain, lumbar puncture, and bone marrow examination were normal.

Despite improvement with vincristine, doxorubicin hydrochloride, prednisolone, and etoposide, multiple cranial nerve palsies and right sided myoclonic jerks developed after 6 months. A CT scan showed a non-enhancing, ill defined low density lesion in the left temporal lobe but no brain stem mass and a lumbar puncture was normal. A diagnosis of cerebral lymphoma was made and whole brain irradiation was begun (400 cGy over 4 weeks). Intrathecal methotrexate and cytosine arabinoside were also instituted and there was a marked improvement in her clinical condition. However 6 months after radiotherapy she noted loss of vision in her right eye followed by temporal loss in her left eye. These signs suggested an anterior chiasmal lesion.

However, a CT scan of the orbits and brain showed only the temporal lobe lesion and a further lumbar puncture was normal. It was felt that as the initial course of radiotherapy may

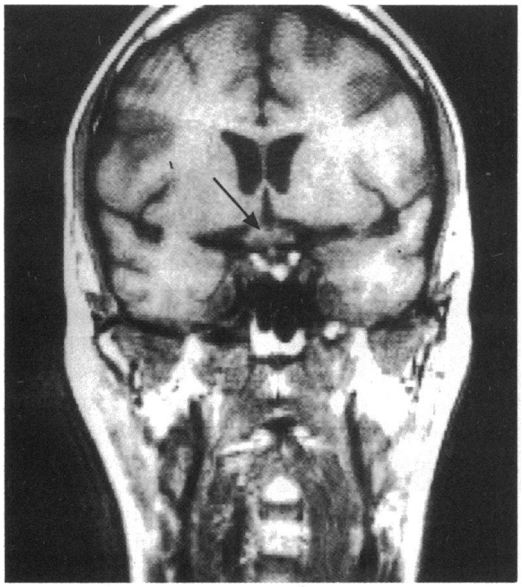

Figure 3 Patient 1. MRI scan. T1 weighted coronal section demonstrating thickened optic chiasm (arrow).

have left the optic nerves untreated, the visual loss could be due to lymphomatous infiltration and both optic nerves were irradiated (a total of 2400 cGy over 2 weeks). However there was no improvement in vision and the patient was referred to St Thomas's Hospital.

On examination there was no evidence of systemic relapse. The visual acuity in the left eye was 6/12 and she could identify 14 of the 17 Ishihara plates. The visual acuity in the right eye was perception of light and there was a right relative afferent defect. The field (Fig 1) showed temporal loss in her left eye and the optic discs were pale (Fig 2). Haematological and biochemical tests were normal and the CSF showed a white cell count of 4×10^6/l with normal cytology. There were no red cells and the protein level was 0·6 g/l. In contrast to earlier CT scans, a magnetic resonance imaging (MRI) scan of the brain and orbits now revealed thickening of the optic chiasm (Fig 3) and a diagnosis of lymphomatous infiltration was made.

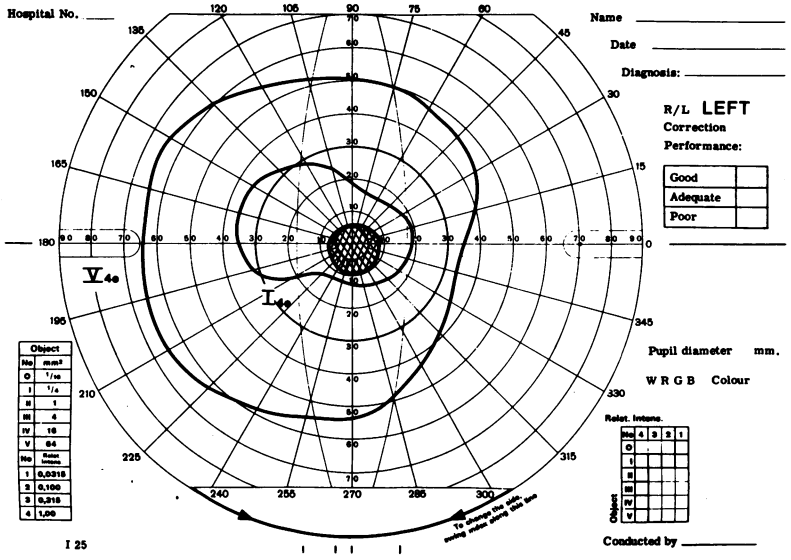

Fig 4A

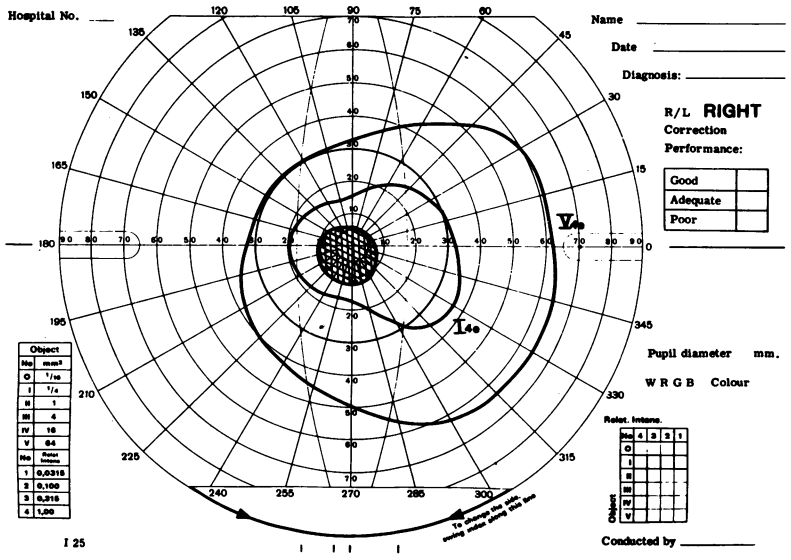

Fig 4B

Figure 4 Patient 2. Goldmann visual fields showing central scotomas with loss of peripheral isoptres in both eyes. (A) Left eye. (B) Right eye.

CASE 2

A 36-year-old woman presented in 1985 with painless lymphadenopathy affecting the axillae and both sides of the neck. A lymph node biopsy revealed nodular poorly differentiated NHL and a staging CT scan demonstrated enlarged para-aortic nodes and splenomegaly. Neurological examination was normal as was the bone marrow. She was treated intermittently for periods of 3–4 months with vincristine, chlorambucil, and prednisolone with no change in the disease.

Three years later she noticed progressive bilateral deterioration of vision without other symptoms. On examination the visual acuity was 6/12 in each eye and she could not identify any of the Ishihara plates. Visual fields showed constriction with central scotomas (Fig 4A and 4B) and the optic discs were pale (Fig 5). Neurological examination was normal as was a CT scan of the orbits and brain. A lumbar puncture was also normal and treatment with vincristine, chlorambucil, and prednisolone was continued.

Nine months later she developed dysarthria and right sided myoclonic jerks. An MRI scan now showed an abnormality lateral to the body of the left ventricle and a further lumbar puncture was normal. Despite whole brain irradiation (3000 cGy over 3 weeks) she continued to deteriorate rapidly with confusion, ataxia, motor weakness, and multiple cranial nerve palsies. Her vision deteriorated to perception of light in both eyes. Haematological and biochemical tests were normal as was a lumbar puncture. Viral titres to JC, BK, and herpes simplex virus were negative and an electroencephalogram showed diffuse abnormalities. A CT scan showed extensive bilateral low density lesions of the white matter and dilated ventricles (Fig 6) leading to a diagnosis of progressive multifocal leucoencephalopathy (PML). The patient died 6 days later and consent for a postmortem examination was denied.

Comment

Two patients with NHL and visual loss are

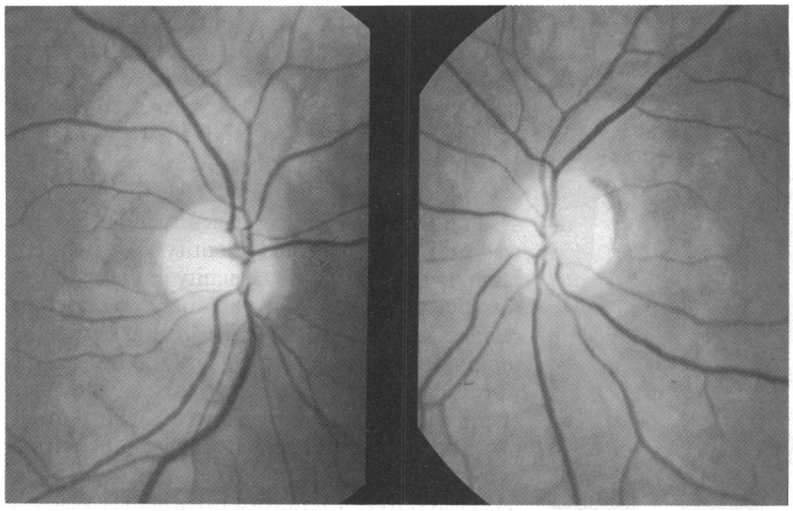

Figure 5 Patient 2. Photographs of both eyes showing bilateral optic atrophy.

presented; in one patient there was a bilateral optic neuropathy and in the other an anterior chiasmal syndrome. In the first case the involvement of multiple sites in the CNS with improvement following radiotherapy supported the diagnosis of lymphomatous infiltration, as did the appearance of the optic chiasm on MRI scanning. Radionecrosis was considered but the low dose of radiation and appearance of the optic chiasm were not consistent with the diagnosis.

In the second case the signs of bilateral optic neuropathy together with the characteristic CT findings suggested PML as the diagnosis. Infiltration was considered unlikely because of the rarity of cerebral metastasis in this type of lymphoma and also because of the failure to respond to radiotherapy. The low dose of vincristine and the absence of a peripheral neuropathy argued against drug toxicity.

CNS involvement in NHL is uncommon but ultimately occurs in about 10% of cases.[8] Of these 5% will develop optic nerve infiltration[9] and although this usually occurs in established CNS disease it may be a presenting symptom of the lymphoma,[10] or a manifestation of recurrence in patients in clinical remission.[11 12] Both unilateral and bilateral cases have been reported[12] and optic discs may be swollen but progress to atrophy. CT scans may be normal and modern MRI imaging is much more sensitive in detecting CNS disease. Infiltrative neuropathy may respond to radiotherapy[13] and it is essential to keep a high index of suspicion despite apparently normal investigations. Delay may lead to irreversible visual loss.

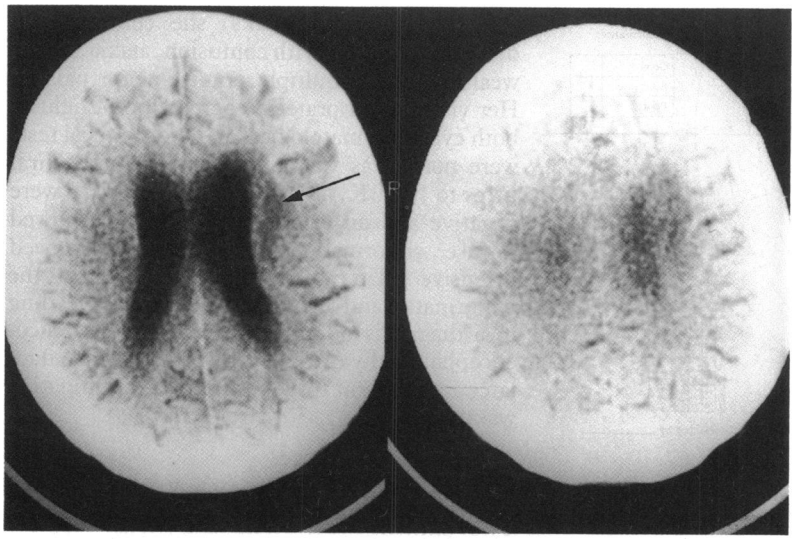

Figure 6 Patient 2. Axial CT scan, demonstrating dilated ventricles and multiple white matter abnormalities of varying sizes with one large lesion (see arrow).

Radionecrosis of the optic nerves is uncommon[14 15] and rarely occurs with low doses of radiation (a total of 5000 cGy with daily fractions less than 200 cGy is considered safe).[16] Severe visual loss is the rule, often sudden in onset with the other eye becoming involved a few weeks later. The neuropathy occurs from 4 months to years after treatment with a peak at 18 months. CT scans are either normal or show white matter changes adjacent to the anterior visual pathways. The recent use of MRI with gadolinium DTPA enhancement is more specific and sensitive leading to increasing recognition of this condition.[17]

PML is a rare disease of the CNS caused by infection with a polyoma virus, usually JC virus, in the presence of immunosuppression.[2] Visual symptoms are common, the majority being due to homonymous hemianopia. In a series of 74 histologically confirmed cases 37·8% had visual defects at presentation; 23% had a homonymous hemianopia, 2·7% cortical blindness, 2·7% diplopia, and 8·7% visual blurring. Optic neuropathy is very rare and only one patient in the above series had optic atrophy. Henson[18] mentions optic neuritis in PML but gives no further details, and there is one case report of optic neuropathy progressing to homonymous hemianopia in a patient with a clinicoradiological diagnosis of PML.[2] To date there has been no report of histology from optic nerves in such patients.

Optic neuropathy has been attributed to vincristine[19 20 21] which both our patients received but there was no evidence that this drug produced the neuropathy per se, although in combination with the other mechanisms it may have had a contributary effect.

Early diagnosis is essential in management of these cases if vision is to be preserved. However, as our two patients demonstrate this can be extremely difficult despite extensive investigations. The advent of sophisticated neuroimaging has enhanced the diagnostic yield of patients with visual loss in NHL. Both lymphomatous infiltration and PML have characteristic radiological appearances and radionecrosis can now be accurately diagnosed by MRI with gadolinium DTPA enhancement. Thus in the absence of clinical clues a radiological diagnosis may provide therapeutic guidelines.

Occasionally a clinicoradiological diagnosis may not be sufficient and in these cases it may be worth considering biopsy of optic nerve and sheath when vision is extinguished. This procedure is simple with a medial approach and has proved invaluable in our own experience with late onset optic nerve gliomas.

The authors thank Mrs Deborah Embleton for secretarial help and Mr Richard Dewhirst for the illustrations.

1 Kline LB, Garcia JH. Lymphomatous optic neuropathy. *Arch Ophthalmol* 1984; **102**: 1655–7.
2 Walker DL. Progressive multifocal leucoencephalopathy. In: Koetsier, ed. *Handbook of clinical neurology*. 1985; **3**: 503–24.

3 Ofner S, Baker RS. Visual loss in cryptococcal meningitis. *J Clin Neuro Ophthalmol* 1987; 7: 45–8.
4 Imperia PS, Lazarus HM, Lass JL. Ocular complications of systemic chemotherapy. *Surv Ophthalmol* 1989; **34**: 209–230.
5 Schatz NJ, Lichtenstein S, Corbett JJ. Delayed radiation necrosis of the optic nerves and chiasm. In: Glaser JS, Smith JL, eds. *Neuro-ophthalmology*. Symposium of the University of Miami and the Boscom Palmer Eye Institute, St Louis: Mosby, 1975; **8**: 131–9.
6 Pilay N, Gilbert JJ, Ebers GC, Brown JJ. Internuclear ophthalmoplegia and optic neuritis. Paraneoplastic effects of bronchial carcinoma. *Neurology*, 1984; **34**: 788–91.
7 Sebag M, Michaud J. Paraneoplastic optic neuritis and encephalomyelitis. *Arch Neurol* 1988; **45**: 353–6.
8 Lester EP, Ultman JE. Lymphoma. In: Williams WJ, Beutlar E, Erslev AJ, Lichtman MA, eds. *Hematology*. New York: McGraw Hill, 1990: 1067–89.
9 Mackintosh FR, Colby TV, Podolsky WJ, Burke JS, Hoppe RT, Rosenfelt FP, *et al*. Central nervous system involvement in non-Hodgkin's lymphoma. An analysis of 105 cases. *Cancer* 1982; **49**: 586–95.
10 Kansu T, Orr LS, Savino PJ, Schatz NJ, Corbett JJ. Optic neuropathy as initial manifestation of lymphoreticular diseases: a report a five cases. In: Smith JL, ed. *Neuro-ophthalmology focus*. 1980; 125–36.
11 Kay MC. Optic neuropathy secondary to lymphoma. *J Clin Neuro Ophthalmol* 1986; 6: 31–4.
12 Lanska DJ, Lanska MJ, Tomsak RL. Unilateral optic neuropathy in non-Hodgkin's lymphoma. *Neurology* 1987; **37**: 1563–4.
13 Holte H, Saeter G, Dahl IMS, Abrahamsen AF. Progressive loss of vision in patients with high grade non-Hodgkin's lymphoma. *Cancer* 1987; **60**: 2521–3.
14 Pasquier F, Leys D, Dubois F, Fallas P, Lessoin F, Petit H. Chiasm and optic nerve necrosis following radiation therapy. *Neuro-Ophthalmology* 1989; **9**: 331–6.
15 Martins AN, Johnston JS, Henry JM, Stoffel TJ, Di Chiro G. Delayed radionecrosis of the brain. *J Neurosurg* 1977; **47**: 336–45.
16 Kline LB, Kim JY, Ceballus R. Radiation optic neuropathy. *Ophthalmology* 1985; **92**: 1118–23.
17 Zimmerman CF, Schatz NJ, Glaser JS. Magnetic resonance imaging of radiation optic neuropathy. *Am J Ophthalmol* 1990; **110**: 389–94.
18 Henson RA, Urich HI. *Cancer and the nervous system*. Oxford: Blackwell, 1982: 522–3.
19 Sanderson PA, Kwabara T, Cogan DC. Optic neuropathy presumably caused by vincristine. *Am J Ophthalmol* 1978; **81**: 146–50.
20 Shurin SB, Rekate KL, Annable W. Optic atrophy induced by vincristine. *Paediatrics* 1982; **70**: 288–91.
21 Sandler SG, Tobin W, Henderson ES. Vincristine induced neuropathy. *Neurology* 1969; **19**: 367–74.

(*Br J Ophthalmol* 1993; 77: 187–189)

Necrotic orbital melanoma arising de novo

Jerry A Shields, Carol L Shields, Ralph C Eagle Jr, Patrick De Potter, Glen L Oliver

Abstract

A 76-year-old man with compressive optic neuropathy secondary to a retrobulbar mass was managed by orbitotomy and removal of the mass. The lesion proved histopathologically to be an unusual orbital melanoma with massive central necrosis. There was no histopathological evidence of congenital melanocytosis. Dermatological and systemic evaluation before and after orbital surgery revealed no evidence of primary melanoma elsewhere. The patient developed hepatic metastasis 2 years after excision of the orbital tumour. It appears that the melanoma was a primary orbital tumour and not a metastatic melanoma from an occult primary lesion.

(*Br J Ophthalmol* 1993; 77: 187–189)

Wills Eye Hospital, Thomas Jefferson University, Philadelphia

Ocular Oncology Service
J Shields
C Shields
P De Potter

Department of Pathology
R C Eagle

Lehigh Valley Hospital, Allentown, PA, USA
G L Oliver

Correspondence to:
Jerry A Shields, MD, Director, Ocular Oncology Service, Wills Eye Hospital, 900 Walnut Street, Philadelphia, PA 19107, USA.

Accepted for publication 8 December 1992

Orbital malignant melanoma most often occurs from direct orbital extension of uveal, conjunctival, or eyelid melanoma.[1–4] Less often, orbital melanoma can occur as a metastasis from a previously diagnosed non-ocular melanoma. Primary orbital melanoma tends to occur in patients with predisposing melanocytic lesions such as congenital orbital melanocytosis or cellular blue naevus.[1–18] Primary orbital melanoma arising de novo without such pre-existing conditions is exceedingly rare. We report an unusual case of orbital melanoma that apparently developed as a primary orbital lesion in a patient who had no clinical or histopathological evidence of congenital orbital melanocytosis or cellular blue naevus. The lesion presented as a circumscribed orbital mass with extensive central necrosis.

Case report

A 76-year-old white male, who had no previous ocular problems except for mild amblyopia of the left eye, developed blurred vision in the right eye associated with epibulbar redness. An orbital computed tomography (CT) detected a retrobulbar mass. The initial clinical diagnosis was orbital inflammatory pseudotumour. After a 14 day course of oral corticosteroids failed to relieve his symptoms, the patient was referred to the ocular oncology service on 10 December 1990 for further evaluation and management.

The patient had a history of medically controlled hypertension, three previous myocardial infarctions, a prostatectomy for benign prostatic hypertrophy, and an inguinal herniorrhaphy. Two histopathologically confirmed seborrhoeic keratoses had been recently excised from his right scapular area. There was no history of ocular or cutaneous melanoma.

Our evaluation revealed best corrected visual acuities of 6/12 in the right eye and 6/21 in the amblyopic left eye. Intraocular pressures were normal. There was mild oedema of the right upper and lower eyelids and no proptosis. Ocular motility and colour plates were normal. Fundus examination of the right eye showed an elevated, hyperaemic optic disc and several juxtapapillary flame shaped haemorrhages. The left eye was normal except for decreased visual acuity due to amblyopia.

B-scan ultrasonography showed a rounded retrobulbar mass with acoustic hollowness and good sound transmission. CT revealed a 1·5 cm round, well circumscribed, intraconal mass abutting the globe and the optic nerve superotemporally (Fig 1).