LETTERS TO
THE EDITOR

Familial uveal melanoma: report on three sibling cases

EDITOR,—Uveal melanoma is the most common primary malignant intraocular tumour in adults, representing 70% of all malignant ocular tumours.1

They appear sporadically in the absence of clear predisposing genetic factors. However, the family history of some patients suggests that there could be a genetic basis.2 Some cases of family uveal melanoma have been described in the literature, and they point to a dominant autosomal hereditary transmission.1

The family uveal melanoma accounts for only 0.6% of patients with uveal melanoma. Considering the low incidence of uveal melanoma in the general population, the possibility of developing uveal melanoma in a family context is very low. Since the first description by Silcock in 1892 of the case of a mother and her two daughters affected with this illness, only 51 families had been reported until 1996.1

Unidentified mutations on the germinal line might be involved in its pathogenesis.1 There are several reports of simultaneous occurrence of uveal melanoma and breast cancer. Some of them are related to one of the genes already known as predisposing to breast and ovary cancer, the "BRCA2."1

Even though there is no demonstration of an implicated gene, many studies suggest that the occurrence of family uveal melanoma is not just a coincidence.1

Three clinical cases of histopathologically proved intraocular malignant melanoma involving first generation members of the same family (siblings) are analysed, and their evolution is reported.

CASE REPORTS

Case 1
A 40 years old male patient, with a history of ocular trauma 2 years earlier, presented with a loss of vision in the right eye, being admitted to hospital in March 2000. The earlier examination showed an ulcerated tumour in the right eye that protruded over the lower eyelid, round in shape, 1 cm diameter, pigmented and painful. He underwent a computed tomography (CT) scan of the orbit with general deterioration and evidence of liver dysfunction, the primary ocular tumour could not be given and a palliative symptomatic treatment was undertaken.

Case 2
A 39 years old healthy female patient suffered a sudden loss of vision in November 1994 and a left eye retinal detachment was found at the ocular examination. The orbital ultrasound suggested a typical choroidal melanoma on the left eye. The orbital CT scan showed an intraocular tumour on the nasal side of the posterior pole of the left eye, in contact with the retina, with 10 mm thickness and probable episceral infiltration. Her left eye was enucleated on January 1995. Histopathological findings were that of a mixed cell malignant uveal melanoma, with predominance of epithelioid type, with significant scleral invasion.

In November 1997 a right breast nodule was found, measuring 2 cm in diameter. The mammography showed the right breast lump compatible with a primary breast tumour and the biopsy was positive for malignancy. It was finally resected in December 1997. The histopathological report confirmed a breast metastasis of a malignant uveal melanoma with auxillary ganglion metastases.

Systemic treatment with polichemotherapy was started in February 1998, based on cisplatin, dacarbazine, and tamoxifen, five series were completed by July 1998. In August 1998 the patient suffered a right coxofemoral pain irradiated to the ipsilateral knee. Pelvic x-rays showed multiple lytic lesions in the pelvis. Bone scintigraphy (September 1998) noted hyperactive areas in the anterior arc of the third rib, pelvic bones, iliac wing, and superior third of the right femoral bone.

She was evaluated because of the risk of a local bone fracture and a surgical fixation was then implemented. Histopathological bone biopsy (November 1998) confirmed bone metastases of a melanocytic tumour, in accordance with the primary ocular melanoma. She died in December 1998 with a progressive disease.

Case 3
A 38 years old female patient, who was operated on her left breast (modiﬁed radical mastectomy) in September 1998 because of a 30 × 33 mm ductal infiltrating carcinoma (DIC), with local extension to the skin carcinoma, histological grade II, 0/6 negative axillary nodes. She then received polichemotherapy with four cycles of doxorubicin and cyclophosphamide (AC) followed by radiotherapy, completing the treatment with tamoxifen because of high positive oestrogen receptors.

In March 2000 she suffered a trauma in her right eye. An ocular ultrasound scan showed a retinal detachment and a tumoral image resembling a choroidal metastasis. The ocular computed tomography scan showed no other alterations than the apparently ocular metastatic involvement. Liver function and enzymes were normal.

Because of the family history of ocular melanoma, enucleation of the right eye was performed in June 2000 (despite the ocular ultrasound and the CT scan oriented to a metastatic breast tumour). The histopathological report showed a mixed cell malignant uveal melanoma with predominance of epithelioid variant.

The patient is now being treated for a second breast tumour (at the remnant of the right breast).

COMMENT
The family presented includes not only three individuals affected with this unusual pathology but they are also three siblings belonging to the same generation, which is even more unusual.

All the cases corresponded to mixed uveal melanomas; in one of these cases (case 3) the patient also had a malignant breast tumour which was diagnosed 2 years before the ocular tumour; in this same case, even though the clinical findings and the imaging tests were suspicious of a choroidal metastasis, the history of two ocular melanomas in her siblings led to the enucleation of the eye, with the subsequent diagnosis of ocular melanoma; the patient is still alive but is being treated for a new breast lump.

Case 2 shows another peculiarity; the patient had been enucleated in January 1995 because of a mixed choroidal melanoma; almost 3 years later she was operated because of a probable primary breast tumour, and the mastectomy specimen showed a breast and axillary compromise of the formerly enucleated ocular melanoma. Nine months later, bone metastases of the primary choroidal melanoma were diagnosed and histologically confirmed. The patient died a few months later.

The first case (case 1) was another unusual one: at the diagnosis, the patient had an externalised ocular melanoma with extrascleral invasion allowing a preoperative diagnosis through a biopsy, even though this procedure is difficult to achieve in most of the ocular melanomas. In this patient an orbital exenteration was done owing to its extension beyond the eye itself. The histopathological report was that of a mixed melanoma (with epithelioid component). Seven months later the patient developed progressive liver metastasis with general deterioration, while under palliative care.

Figure 1  Genealogical family tree. UM = uveal melanoma, LC = lung cancer, BC = breast cancer, Dg = diagnostic age, De = death age, Dg/De = diagnostic and death age, y = years, I = first generation, II = second generation, III third generation.

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Once again this case denotes the aggressiveness of this tumour in this family.

The genealogical family tree (Fig 1) shows that the siblings' parents developed malignant tumours: the father was diagnosed with lung cancer at the age of 59 dying a few months later and the mother had breast cancer diagnosed at the age of 49 dying at the age of 57. Also a maternal aunt was diagnosed with lung cancer at the age of 38 and died 2 years later, while another maternal aunt is still alive with breast cancer diagnosed when she was 43. The paternal family history was irrelevant with no malignancies in any of the first or second generation members.

The family tree shows, in the same generation as the affected patients, five more siblings, all of them aged less than 40 years who are currently healthy but may eventually be affected with ocular melanoma or another malignancy; are there any kind of preventive measures we can take for these patients?

Anecdotal reports of cases of ocular melanoma occurring in families with inherited susceptibility to breast cancer owing to brca2 germ line mutations have been previously reported. Although germ line brca2 mutations may account for a small proportion of all ocular melanoma cases, there may be additional loci contributing to family aggregation of uveal melanoma and to the family association between ocular melanoma and breast cancer. Based on the limited data available, an autosomal dominant mode of inheritance with incomplete penetrance has been postulated to explain the family involvement in uveal melanoma.

In order to determine some genetic alteration that could account for this family uveal melanoma, blood samples were recently taken from different members of the family (apart from the affected patients still alive).

The family predisposition to uveal melanoma can be a component of a wider predisposition syndrome to cancer, which could explain the high number of tumours affecting these families, with multiple organs involved and the appearance at younger ages than those observed in the general population.

Because of no previous evidence of family members with uveal melanoma in the genealogical tree (Fig 1), either an environmental factor that remains undisclosed might be suspected or a new mutation may have arisen. Either way careful monitoring of the remaining siblings would be of great interest.

### CASE REPORTS

**Case 1**
A 68 year old female patient presented to the cornea department of the eye clinic, University of Athens, in January 1997. She was being treated for primary open angle glaucoma with latanoprost drops once daily for the past 3 months. Visual acuity in the right eye was 20/40 and in the left 20/20. The intraocular pressure of the left eye was 16 mm Hg. Examination with a slit lamp demonstrated a dendritic ulcer in the right eye (Fig 1). Immunofluorescence studies of the cornea epithelium from the ulcer demonstrated the presence of herpes simplex virus. Latanoprost treatment was discontinued and the patient was placed on antiviral treatment. Two weeks later the keratitis had resolved.

**Case 2**
A 65 year old female presented to the cornea department of the eye clinic, University of Athens, in March 1997. Examination detected epithelial lesions in the centre of the cornea in the right eye (Fig 2) and at 11 clock hours in the periphery of the left eye. The patient had had treatment with latanoprost once daily for primary open angle glaucoma during the past 3 months. There was no history of herpes keratitis. Latanoprost treatment was discontinued. The samples of the corneal epithelium from the ulcerated area of both eyes demonstrated the presence of herpes simplex virus, using immunofluorescence. After antiviral treatment, trabeculectomy was carried out in the right eye, when latanoprost treatment was continued in the left eye. After a small period of time, in the right eye—without latanoprost treatment—there was no herpetic infection, while in the left eye—with latanoprost treatment—herpetic infection presented again.

### COMMENT
Both patients presented with herpes keratitis during latanoprost treatment. After discontinuing the latanoprost treatment, there was no recurrence of the keratitis.

Latanoprost is a prostaglandin analogue. It is an esterified predrug inactive until its enzymatic hydrolysis in the cornea, where it becomes a biologically active acid. Owing to the biochemical disturbance in the cornea, and the keratopathy confirmed with staining, we can suppose that the presence of latanoprost predisposes the appearance of herpes keratitis.

More cases must be studied before we can reach more specific conclusions.

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**References**

Optic neuropathy and cerebellar ataxia associated with a rare missense variation (A14510G) of mitochondrial DNA

EDITOR,—Mitochondrial diseases manifest a variety of syndromic signs. Skeletal muscle, central nervous system, heart, eye, ear, liver, kidney, pancreas, bone marrow, and colon are the common target organs in mitochondrial diseases. The mitochondrial DNA (mtDNA) is responsible for the mitochondrial diseases through molecular defect of oxidative phosphorylation enzymes in conjunction with the nuclear genome.1 Optic neuropathy and cerebellar ataxia are a frequent association in mitochondrial diseases. We report a sporadic case of bilateral optic neuropathy, cerebellar ataxia, and peripheral neuropathy associated with a rare missense variation at np 14510 which replaced Val by Ala in the ND 6 coding sequence of mtDNA.

CASE REPORT
A 52 year old Japanese man first noted writing tremor of hands, and mild gait disturbance at the age of 49 years. The patient had a 30 year history of drinking (daily alcohol consumption 125 g) and smoking (daily 20 cigarettes). Physical examination revealed a complex of neurological signs including cerebellar ataxia and peripheral neuropathy. The gait was broad based and ataxic. There was mild ataxia of the lower extremities on heel to knee test. Deep tendon reflexes were hyperactive with normal plantar responses. Peripheral nerve conduction velocity studies revealed sensory polyneuropathy in the upper and lower limbs. Muscular strength and volume of the limbs were normal. Magnetic resonance imaging showed cerebellar atrophy with dilatation of the fourth ventricle (Fig 1). The cerebrospinal fluid was normal without any inflammatory signs. Peripheral blood examination showed mild macrocytic anaemia. The serum levels of vitamin B-1, vitamin B-12, and folic acid were within the normal range. Red blood cell folate level was also normal. The patient had suffered from a progressive loss of central vision in both eyes since 51 years of age. At presentation, best corrected visual acuity was 0.1 in the right eye and 0.08 in the left. Pupils were round, isocoric, and sluggishly to light. There was no blepharoptosis. Ocular motility was normal. Anterior segments and media were clear. Funduscopy disclosed dilatation of small retinal vessels neighbouring the optic nerve head in both eyes. The nerve heads were not hyperemic but slightly atrophic with temporal pallor. Static and kinetic visual field testing showed central scotomas. Farnsworth’s panel dichotomous test showed untreated amnicon (C1, C2, and C3 = negative control; □ = A14510G variant). The amplicon (243 bp) spanning from np 14429 to 14671 of mtDNA is treated with Alu I which recognizes allele G and the mutant fragment is digested into 82 bp and 161 bp. The patient has homoplastic A14510G mutation. C1, C2, and C3 show only the wild type fragments.

COMMENT
The nucleotide at np 14510 of mtDNA is most usually adenine (14510A). A literature survey reveals that 193 individuals in east Asia, 411 in an aboriginal Siberian population, 60 in a native American population, and 173 in a white population all had 14510A.1 Only one Australian among 147 individuals of African, Asian, white, aboriginal Australian, and aboriginal New Guinean was reported to have guanine at np 1450 (14510G).1,2 The A14510G mutation in the present patient was found in none of 468 Japanese patients without neurological symptoms and found in none of 468 Japanese patients with other mitochondrial disorders such as chronic progressive external ophthalmoplegia, MELAS, and MERRF. Occasionally we could not dismiss the diagnosis of a mitochondrial disease subtype because of the bilateral optic neuropathy accompanied by cerebellar ataxia. Peripheral blood was obtained after informed consent and examined for common pathogenic mtDNA point mutations by polymerase chain reaction (PCR) restriction method described elsewhere.3 The nucleotide sequence of sense and antisense strands of ND1, ND4, and ND6 genes of mtDNA from the patient were evaluated by autosequence methods. In the patient, no major pathological mutation was found by PCR restriction detection at np 3243 for mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), 3460 for Leber’s hereditary optic neuropathy (LHON), 8344 for myoclonic epilepsy and ragged red fibres (MERRF), 8993 for neurogenic weakness, ataxia, and retinitis pigmentosa, 11778 for LHON, or 14484 for LHON. There was no known mutation in ND1, ND4, or ND6 gene of mtDNA by nucleotide sequencing. Instead, nucleotide sequencing and Alu I restriction detection confirmed a homoplasmic missense mutation at np 14510 (A14510G) that replaced Val by Ala in the ND 6 gene of mtDNA (Fig 2). The DNA samples reserved by us were examined for the relevant mtDNA mutation. The A14510G mutation was not detected in 468 Japanese individuals, including 39 LHON patients with 11778 mutation, 24 healthy carriers with 11778 mutation, one LHON patient with 3460 mutation, 78 patients with neurogenic weakness, ataxia, and retinitis pigmentosa reported by Bondy et al,3 and 86 unrelated healthy individuals.

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Figure 1 Magnetic resonance imaging of the brain in the patient with A14510G mutation of mtDNA. A 52 year old Japanese man with bilateral optic neuropathy and cerebellar ataxia. T1 weighted imaging shows cerebellar atrophy with dilatation of the fourth ventricle.
characterised by insidious, chronic progressive optic nerve disease.1 Our patient developed a late onset, insidious bilateral optic neuropathy with mildly atrophic optic nerve heads and tortuous retinal vessels, being compatible with features of LHON.2 Cerebellar ataxia and/or cerebellar atrophy are caused by mutations of mtDNA—for example, large scale deletions or tRNA mutations.3 An extensive review of the literature demonstrates a variety of neurological abnormalities in LHON patients, including cerebellar ataxias and peripheral nerve disorders.4 Our patient had cerebellar ataxia and sensory polyneuropathy, with evidence of cerebellar atrophy on magnetic resonance imaging. Similar neurological complications were rarely found in a LHON family with G11778A mutation.5

Although epigenic factors have been considered for the disease expression and visual outcome of LHON patients in association with mtDNA mutations, it has yet to be proved. A retrospective analysis of LHON sibships has failed to demonstrate a significant deleterious association between tobacco or alcohol consumption and vision loss among individuals at risk with the major mtDNA mutations.6 In the present clinical isolate, it remains unknown whether the nutritional condition provided a potential risk factor in the clinical manifestation associated with the underlying mtDNA defect. The A14150G mutation of mtDNA is expected to be found in other independent patients especially with unknown optic neuropathy and cerebellar ataxia.

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Table 1 Main clinical manifestations of the patients. Their HLA phenotype is also shown

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>49</td>
<td>80</td>
</tr>
<tr>
<td><strong>First symptoms</strong></td>
<td>Nausea and anorexia</td>
<td>Asymptomatic, coincidental finding</td>
</tr>
<tr>
<td><strong>Uveitis</strong></td>
<td>Bilateral AAU</td>
<td>Bilateral AAU with papillitis</td>
</tr>
<tr>
<td><strong>Onset of uveitis</strong></td>
<td>4 months after the nephritis (A24, A32, B62, B39, Bw6, Cw7, Cw3)</td>
<td>Unknown, at the time or possibly prior to the nephritis (A28, B57, Bw4, DR11, DR14, DR52, DQ5)</td>
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AAU = acute anterior uveitis.
An 80 year old white woman presented complaining of sudden deterioration in vision in her left eye. Her ocular history was remarkable for atrophic AMD. Visual acuity was measured at 6/6 in the right eye and counting fingers in the left eye. On fundus examination of the right eye diffuse soft confluent drusen, some calcified, and geographic atrophy (GA) were detected (Fig 1A). In the left, the most striking feature was the presence of marked and diffuse cystoid macular oedema (CMO), and a serosanguineous pigment epithelial detachment (PED) associated with large amounts of hard exudates (Fig 1B). Soft and calcified drusen and GA were also present. Fluorescein angiography (FA) disclosed diffuse pooling of dye in the macula in the left eye, and an area of hyperfluorescence corresponding to the PED (Fig 2A). Window defects corresponding to areas of atrophy were detected in both eyes. On indocyanine green angiography (ICG) a choroidal vascular network of polypoidal structures was observed in the left eye (Fig 2B, C).

After informed consent was obtained, focal laser photoocoagulation using an argon laser was applied to polypoidal vessels. The parameters used were a laser power of 200 mW, an exposure time of 0.2 seconds, and a spot size of 200 µm. This resulted in resolution of the CMO and PED (Fig 2D) on FA, closure of the choroidal vascular network on ICG (Fig 2B, E), and on a subjective improvement in vision 2 weeks following laser treatment.

COMMENT
IPCV is characterised by the presence of recurrent serosanguineous PEDs and neuro-sensory retinal detachments (NSRD). The vascular abnormality underlying the disorder appears to be in the inner choroid. Dilated networks of vessels terminating in aneurysmal dilatations or “polyps” can be observed on ICG angiography. Polypoidal lesions may arise from the peripapillary region, macula, or peripheral areas. Histopathological evaluation of a case of IPCV showed extensive...
fibrovascular proliferation in the subretinal space and within Bruch’s membrane, and a marked lymphocytic infiltration with both B and T cells. Although laser photocoagulation appears to be very effective in preserving visual acuity in patients with IPCV, spontaneous resolution of PEDs and NSRDs can also occur.

The patient described in this report had evidence of atrophic AMD. However, the diagnosis of IPCV was suspected by the presence of a marked NSRD, extensive and diffuse hard exudates, and a serosanguineous PED. Since it was not clear whether GA was involving the fovea in the left eye, laser treatment was applied in an attempt to achieve resolution of subretinal fluid and hard exudates and in the hope that an associated visual improvement will occur. Rapid resolution of all subretinal fluid was noted and, more spectacularly, resolution of the serosanguineous PED, distantly located from the treated area, was also observed 2 weeks after laser treatment. Although no objective improvement in visual acuity was measured, the patient perceived a gain in vision after the treatment.

Although probably rare, IPCV can occur in pregnant females being treated with subcutaneous heparin. Pregnant females treated with subcutaneous heparin appear to have a cause to which the haemorrhage could be referred to like venous anomalies of the orbit such as lymphangiomas or systemic haematological disorders.1,2 Rarely, it has been reported in pregnant females being treated with subcutaneous heparin. In this case report, we describe a woman who developed a spontaneous orbital haemorrhage in the perioperative period following cardiac angioplasty.

CASE REPORT
A 48 year old woman awoke with blurred vision and diplopia in her left eye 1 day after percutaneous coronary angioplasty for coronary stenosis. Before angioplasty she received...
Herpes simplex dendritic keratitis after treatment with latanoprost for primary open angle glaucoma

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