

## 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.<sup>1</sup>

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.<sup>2</sup> Some cases of family uveal melanoma have been described in the literature, and they point to a dominant autosomal hereditary transmission.<sup>3,4</sup>

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.<sup>4,5</sup>

Unidentified mutations on the germinal line might be involved in its pathogenesis.<sup>4,6</sup> 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."<sup>7,8</sup>

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.<sup>9</sup>

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 progressive 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 which showed an external ocular melanoma with extrascleral invasion. Studies for stratification were negative for malignancy. Given the accessibility of the tumour, a biopsy confirmed a malignant melanoma. An exenteration of the right orbit was performed in April 2000. The histopathological report was of a mixed type (spindle B and epithelioid) malignant melanoma, with perineural and perivascular scleral infiltration. A liver ultrasound performed in November 2000 showed multiple, solid, round-shaped hypoechogenic images in both hepatic lobes, compatible with secondary metastasis in the liver, confirmed by CT scan, leading to plan a chemotherapeutic treatment with hepatic intra-arterial cisplatin.

Because of the clear tumour progression in such a short time, a painful hepatomegaly and

general deterioration and evidence of liver dysfunction, the previous treatment 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 episcleral 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 axillary 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 year 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 40% of in situ 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 tumour. 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 histopathology 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.

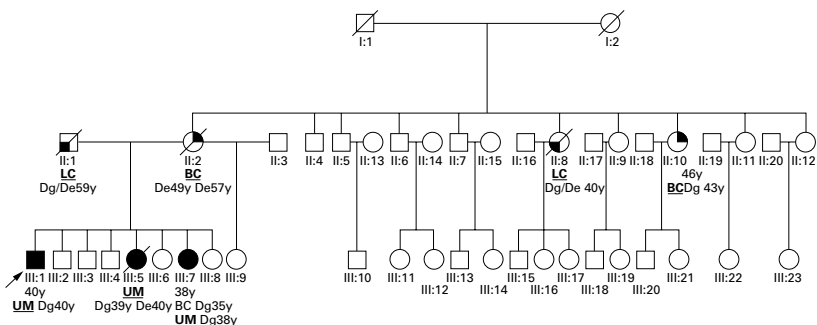


Figure 1 Geneological family tree. UM = uveal melanoma, LC = lung cancer, BC = breast cancer, Dg = diagnostic age, De = dead age, Dg/De = diagnostic and dead age, y = years, I = first generation, II = second generation, III third generation.

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.<sup>7</sup>

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.<sup>7</sup>

Based on the limited data available, an autosomal dominant mode of inheritance with incomplete penetration has been postulated to explain the family involvement in uveal melanoma.<sup>5</sup>

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.<sup>10</sup>

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.

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### Herpes simplex dendritic keratitis after treatment with latanoprost for primary open angle glaucoma

EDITOR,—Medications used to treat glaucoma can cause side effects such as irritation, redness, foreign body sensation, and pain in the eye.<sup>1</sup> There are reports that latanoprost has almost no serious side effects.

We present two patients treated with latanoprost for primary open angle glaucoma who developed herpes keratitis.

#### 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. The patient was treated again with latanoprost drops once daily in the right eye. Three months later she developed the same problems in the right eye. Latanoprost treatment was discontinued again and antiviral treatment with aciclovir ointments was recommended. There has been no recurrence of the herpetic infection.

##### 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.<sup>2</sup> The patient had had treatment with latanoprost once daily for primary open angle glaucoma during the past 2 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



Figure 1 Dendritic ulcer of the right eye.



Figure 2 Immunofluorescence demonstrates the presence of herpes simplex virus.

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.<sup>3,4</sup> It is an esterified predrug inactivate until its enzymatic hydrolysis in the cornea, where it becomes a biologically active acid.<sup>5</sup> 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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### 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.<sup>1</sup> 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 disturbance, 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 also had suffered from insidious, 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 sluggish 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. Optic nerve heads were not hyperaemic but slightly atrophic with temporal pallor. Static and kinetic visual field testing showed central scotomas. Farnsworth's panel D-15 test showed red-green colour vision defects. Full field scotopic electroretinograms and visual evoked cortical potentials were normal. The patient was the fourth of five siblings of non-consanguineous parents. Because of the alcoholism, he was divorced and lived alone. Family members were not accessible, but according to his statement, there was no relative having similar disease.

Although the clinical signs in this patient were not inconsistent with the effects of chronic alcoholism and tobacco abuse alone,



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.

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 methods described elsewhere.<sup>2</sup> The nucleotide sequences of sense and antisense strands of ND1, ND4, and ND6 genes of mtDNA from the patient were evaluated by autocycle sequencing 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, one LHON patient with 14484 mutation, 78 patients with aetiology undefined bilateral optic neuropathy, 239 patients with spinocerebellar ataxias who did not carry any abnormal trinucleotide repeats in the genes of spinocerebellar ataxia type 1, 2, 3, 6, 7, or 8, and 86 unrelated healthy individuals.

#### COMMENT

The nucleotide at np 14510 of mtDNA is most usually adenine (14510A). A literature survey reveals that 153 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.<sup>3</sup> Only one Australian among 147 individuals of African, Asian, white, aboriginal Australian, and aboriginal New Guinean was reported to have guanine at np 14510 (14510G).<sup>4,5</sup> The A14510G mutation in the present patient was found in none of 468 Japanese patients with genetically proved LHON, unexplained bilateral optic neuropathy, cerebellar ataxia, or

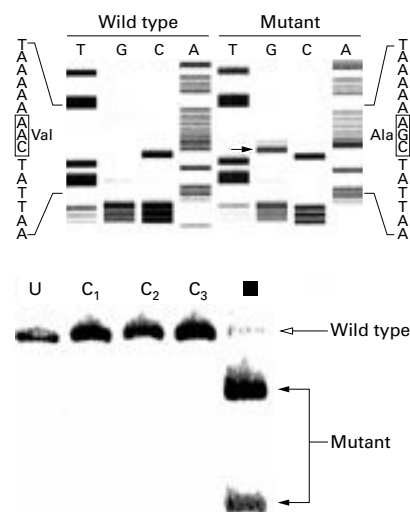


Figure 2 Identification of A14510G mutation of mtDNA. (Top) Sequencing result of ND6 in mtDNA in the patient. An A to G substitution at np 14510 replaces Val by Ala in the ND 6 coding sequence of mtDNA (arrow). (Bottom) PCR restriction detection for A14510G mutation. U = untreated amplicon; C1, C2, and C3 = negative controls; ■ = A14510G variant. The amplicon (243 bp) spanning from np 14429 to 14671 of mtDNA is treated with *Alu I* which recognises allele G and the mutant fragment is digested into 82 bp and 161 bp. The patient (■) has homoplasmic A14510G mutation. C1, C2, and C3 show only the wild type fragments.

healthy individuals. Thus, grouped with previous data in other populations, the frequency of A14510G is estimated to be two in 1413, or approximately one in 700. Noticeably, this frequency is remarkably rare compared with commonly found mtDNA polymorphisms that are innocent or not pathogenic. Although clinical information from the Australian with A14510G is not available, it is possible to assume that the mtDNA plays a part in the aetiology of a syndromic clinical disorder. We could not confirm maternal inheritance or heteroplasmy of the A14510G mutation in our family. According to the statements from the patient, the family members had normal vision but clinical and molecular genetic assessments in them may give significant information for the genotype phenotype correlation of the A14510G mutation.

Mutational effect of A14510G is unknown. Two of the primary mtDNA mutations, G14459A (Ala72Val) for LHON plus dystonia and T14484C (Met64Val) for LHON, have been verified near A14510G (Val55Ala) in the ND6 gene.<sup>3</sup> Another missense mutation (A14495G, Leu60Ser) has recently been found in the same gene in two LHON families, suggesting that the ND6 gene is a hot spot for LHON mutations.<sup>6</sup> The amino acid sequence relevant to A14510G (VFLI-YLGGMMVVFYGYTTA; letters in bold are replaced by the mutations) is highly conserved in mammalia including human, bovine, and mouse, but not strictly conserved in xenopus, sea urchin, or drosophila. This region is a part of hydrophobic transmembrane helices of the ND enzyme. Mutations in the ND6 gene may disturb the enzymatic stability of NADH CoQ reductase.

Optic neuropathy is the predominant sign of LHON and may also be developed in patients with other mitochondrial disorders such as chronic progressive external ophthalmoplegia, MELAS, and MERRF, occasionally

characterised by insidious, chronic progressive optic nerve disease.<sup>1</sup> 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.<sup>2</sup> Cerebellar ataxia and/or cerebellar atrophy are caused by mutations of mtDNA—for example, large scale deletions or tRNA mutations.<sup>3</sup> An extensive review of the literature demonstrates a variety of neurological abnormalities in LHON patients, including cerebellar ataxias and peripheral nerve disorders.<sup>8</sup> 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.<sup>9</sup>

Although epigenetic 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.<sup>10</sup> In the present clinical isolate, it remains unknown whether the malnutritional condition provided a potential risk factor in the clinical manifestation associated with the underlying mtDNA defect. The A14510G mutation of mtDNA is expected to be found in other independent patients especially with unknown optic neuropathy and cerebellar ataxia.

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### The tubulointerstitial nephritis and uveitis (TINU) syndrome is associated with HLA-DR14 in Spanish patients

EDITOR,—An uncommon association between tubulointerstitial nephritis and anterior uveitis was described in two adolescent female patients with non-caseating granulomas in both bone marrow and lymph nodes by Dobrin<sup>1</sup> and is referred to as TINU syndrome. Since then, some 50 cases (35 paediatric patients and 15 adults) have been described. Its distribution is typically in young girls aged 10–14 years. The kidneys are affected by tubulointerstitial nephritis with predominant mononuclear infiltrate in the majority of cases. The ocular lesion invariably consists of anterior uveitis and, exceptionally, panuveitis. Although the aetiology is still unknown, the laboratory findings reported suggest that TINU is a cell mediated immune disease.<sup>2</sup> Genetic markers (HLA alleles) have also been implicated as susceptibility risk factors.<sup>3</sup>

#### CASE REPORT

We describe the cases of three further female adult patients of Spanish origin who developed acute renal insufficiency secondary to idiopathic acute tubulointerstitial nephritis, and who, several months later, suffered a bilateral acute anterior uveitis. In all three patients, similar laboratory findings were found including slight anaemia, increase of the serum creatinine, blood urea nitrogen, and erythrocyte sedimentation rate. Glycosuria and proteinuria were found in the urinalysis. Hantavirus or hepatitis B, C antibodies were not found. Tuberculin and Bengal rose were negative. ANA, anti-DNA, anti-Sm Anti-RNP, anti-SSA, anti-SSB, and ANCA autoantibodies, detected by indirect immunofluorescence (IFI) or counterimmunoelectrophoresis (CIE), were all negative. RPR, antistreptolysin O, PCR, and rheumatoid factor were also negative. Thyroid function was normal, as were the chest and abdomen x rays and renal ultrasonography. Finally, polyclonal hypergammaglobulinaemia was found. Further details are given in Table 1. The HLA class I and class II phenotype of patients was carried out

by a microlymphocytotoxicity test and DNA typing techniques, respectively.<sup>4</sup> As a control group, 176 unrelated healthy individuals from Madrid were also HLA typed.

The distribution of the frequencies of HLA alleles in both groups was compared using the Fisher test. The aetiological fraction ( $\delta$ ) and the odds ratio (OR) value with the corresponding 95% confidence intervals (CI) was calculated.

#### COMMENT

In our series, HLA-A24 is found in 67% of the patients, compared with 14% in the Spanish control population ( $p > 0.05$ , Fisher test). No other HLA class I allele shows a remarkable deviation from the control population. Regarding HLA class II alleles, HLA-DR14 (a HLA-DR6 subtype) is found in two of our patients, whereas it appears in eight of our control individuals (67% v 4%,  $p = 0.006$ ; OR 48.2 (95% CI 5.5–258)). This finding would lend further support to the HLA-DR6 association previously reported in other populations.<sup>3</sup> The frequency of other HLA class II alleles is also increased in the diseased group when compared with the control group, although statistical significance is not reached: HLA-DQ5 (100% v 40%,  $p > 0.05$ , Fisher test) and HLA-DR52 (100% v 56%,  $p > 0.05$ )

When the aetiological fraction ( $\delta$ ) is considered, HLA-DR52 and HLA-DQ5 show the highest value ( $\delta = 1$ ), followed by HLA-DR14 ( $\delta = 0.74$ ) and HLA-A24 ( $\delta = 0.71$ ).

These data point to HLA class II antigens rather than HLA class I as the main TINU susceptibility markers. It may be worth recalling that HLA class II molecules are expressed in renal epithelial cells or in the uvea when inflamed. Thus, genetically predisposed individuals (that is, HLA-DR14) would be more prone to producing the lesions observed in the TINU syndrome upon activation of the immune system.

We are aware of the limited value of the statistical analysis carried out given the small number of patients studied, but this is inherent to the pathology itself, since scarcely 50 TINU patients have been described worldwide since its first description in 1975. We thus would use HLA phenotyping in future patients to assess the role of these HLA class II antigens in TINU susceptibility.

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

	Case 1	Case 2	Case 3
Sex	Female	Female	Female
Age	69	51	49
First symptoms	Nausea and anorexia	Upper respiratory infection	Asymptomatic, coincidental finding
Uveitis	Bilateral AAU	Bilateral AAU with papillitis	Bilateral AAU with retinal vasculitis
Onset of uveitis	4 months after the nephritis	Unknown, at the time or possibly prior to the nephritis	5 months after the nephritis
HLA phenotype	A24, A32, B62, B39, Bw6, Cw7, Cw3, DR14, DR8, DR52, DQ5	A28, B57, Bw4, DR11, DR14, DR52, DQ5	A3, A24, B35, B7, Bw6, Cw4, DR103, DR3, DR52, DQ5

AAU = acute anterior uveitis.

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### Idiopathic polypoidal choroidal vasculopathy in a patient with atrophic age related macular degeneration

EDITOR.—Since the initial description by Stern and colleagues in 1985,<sup>1</sup> the clinical entity now known as idiopathic polypoidal choroidal vasculopathy (IPCV)<sup>2</sup> has been increasingly recognised. Although it was initially described in black, middle aged, hypertensive women,<sup>1</sup> it is now widely accepted that IPCV can affect men and women of any race, and may represent a significant proportion of patients with age related macular degeneration (AMD).<sup>3,4</sup>

In this report, the case of a patient with atrophic AMD and evidence of IPCV is presented. To my knowledge, the co-existence of IPCV and atrophic AMD has not been previously reported.

#### CASE REPORT

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

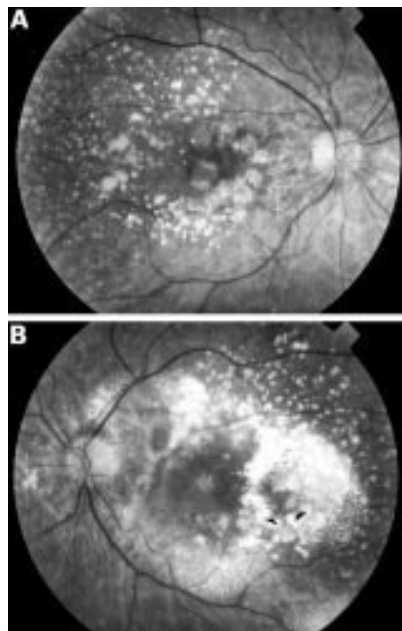


Figure 1 Fundus examination of both eyes disclosed soft confluent and calcified drusen and areas of geographic atrophy (A and B). In the left eye, a neurosensory detachment of the macula and a serosanguineous pigment epithelial detachment surrounded by extensive hard exudates were also present (B, arrowheads).

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 photocoagulation 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  $\mu$ m. 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 neurosensory retinal detachments (NSRD).<sup>1,5</sup> The vascular abnormality underlying the disorder appears to be in the inner choroid. Dilated networks of vessels terminating in aneurysmal dilations or "polyps" can be observed on ICG angiography.<sup>2,5</sup> Polypoidal lesions may arise from the peripapillary region,<sup>1,2</sup> macula,<sup>5</sup> or peripheral areas.<sup>4</sup> Histopathological evaluation of a case of IPCV showed extensive

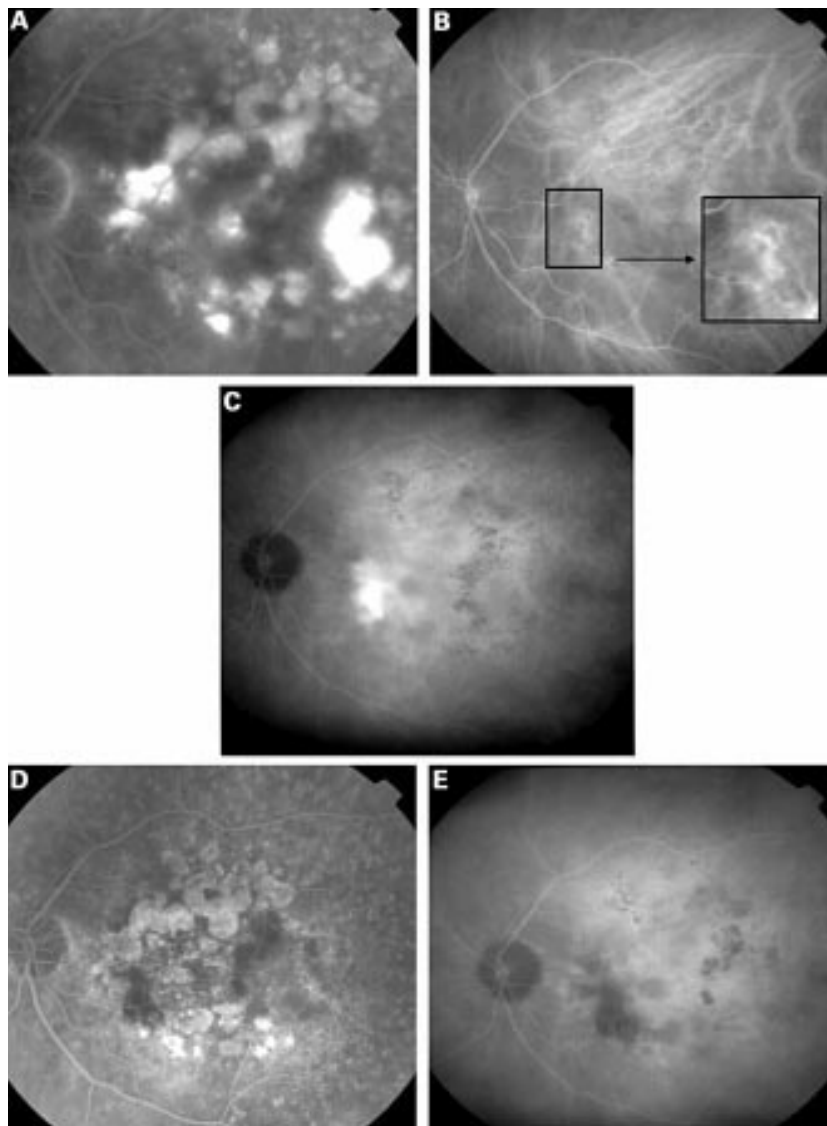


Figure 2 On fluorescein angiography pooling of dye at the macula was observed in late phases (A). An area of bright hyperfluorescence with late staining, corresponding to the serosanguineous pigment epithelial detachment, was also present (A). On indocyanine green angiography, a network of dilated channels terminating in aneurysmal dilations was observed in early frames of the angiogram (B), and leakage from this vascular network was detected in late frames (C). Laser photocoagulation was applied to cover the vascular network shown in B (inset). Following laser treatment, resolution of the neurosensory detachment of the macula and pigment epithelial detachment was noted on fundus examination and on fluorescein angiography (D). Closure of the polypoidal vessels was confirmed by indocyanine green angiography (E).

fibrovascular proliferation in the subretinal space and within Bruch's membrane, and a marked lymphocytic infiltration with both B and T cells.<sup>6</sup> 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.<sup>5</sup>

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 patients with atrophic AMD. A high index of suspicion may be required to establish the diagnosis in these cases.

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### Spontaneous orbital haemorrhage following cardiac angioplasty

EDITOR.—Orbital haemorrhage occurs most commonly following trauma, retrobulbar injection, or orbital surgery. Spontaneous orbital haemorrhage is a rare condition usually associated with vascular anomalies, lymphangiomas, or systemic haematological disorders.<sup>1–3</sup> Rarely, it has been reported in pregnant females being treated with subcutaneous heparin.<sup>4</sup> 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



Figure 1 Deviation of globe and left exophthalmos. (Reproduced with patient's permission.)

ReoPro (abciximab), a glycoprotein GP IIb/IIIa antagonist. There was no ocular history of note but she was known to have had treatment for hypertension and hypercholestaemia.

Her medication before angioplasty included subcutaneous heparin, aspirin, and clopidrogel—a P2 receptor antagonist.

On examination, her best corrected visual acuity was 6/9 left 6/6 right. There was no evidence of a relative afferent pupillary defect. There was no desaturation on field examination with a red target in either eye. The left eye was proptosed by 4 mm (Fig 1). There was evidence of limitation in elevation and dextroversion giving vertical and horizontal diplopia in those positions of gaze. Anterior segment was entirely normal but for slight chemosis (Fig 1) and the posterior segment examination including funduscopy did not reveal any abnormality. An MRI scan of the orbit (Fig 2) revealed an intraorbital extraconal acute haemorrhage measuring 1.7 cm and lying superior and lateral to the superior rectus muscle and displacing it. There was no evidence of optic nerve compression. She had a normal platelet count and clotting screen. She was managed conservatively and made a complete recovery with 6/6 vision in each eye at 4 months after haemorrhage.

#### COMMENT

This case represents a rare case of spontaneous orbital haemorrhage. Most cases of reported spontaneous orbital haemorrhage appear to have a cause to which the haemorrhage could be referred to like venous anomalies of the orbit such as lymphangiomas, haemangiomas or carotid cavernous fistulas.<sup>1,2</sup> Other predisposing factors include blood dyscrasias such as Von Willebrand's disease or haemophilia.<sup>3</sup> Heparin has been implicated in two cases of pregnant women treated with subcutaneous heparin and hypertension, and Valsalva manoeuvres have also been implicated as possible causes.<sup>4</sup> In this particular case, it is not clear what the predisposing factor may be. This woman was receiving



Figure 2 MRI scans showing retrobulbar haemorrhage not compressing optic nerve.

ReoPro (abciximab) a recent glycoprotein GP IIb/IIIa antagonist, which has marked antithrombotic effects.<sup>5</sup> Further, as well as aspirin and subcutaneous heparin, she was also receiving clopidrogel—a P2 receptor antagonist, which inhibits platelet aggregation.<sup>6</sup> We might speculate that one of these newer agents or combinations of these agents may have been responsible. Against this evidence, however, was the finding of a normal platelet count and clotting screen. In this particular case, the patient made a complete recovery probably as a result of venous bleed. However, many cases of spontaneous orbital haemorrhage reported have required surgical intervention with variable prognoses.<sup>7,8</sup> Ophthalmologists need to be vigilant and carefully monitor these rare cases.

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