LETTERS TO THE EDITOR

Bilateral cavernous haemangiomas of the orbit

EDITOR,—The great majority of orbital tumours are unilateral. However, some conditions, such as idiopathic orbital inflammation (“pseudotumour”), granulomatous inflammation, lymphoid tumours, or metastases sometimes can be bilateral. Orbital cavernous haemangioma is almost always unilateral.1 2 We report a patient with bilateral orbital cavernous haemangiomas that caused unilateral proptosis and visual distortion.

CASE REPORT

A 37 year old man developed distorted vision in the inferior field of his left eye and was found to have mild left proptosis. There was mild swelling of the left optic disc and a small inferonasal visual field defect. Orbital computed tomography (CT) revealed bilateral orbital masses and the patient was referred to the oncology service for another opinion and management. His visual acuity was 6/6 in each eye and colour vision was normal in both eyes. The only positive findings were 3 mm of left proptosis, mild swelling of the left optic disc, and a subtle inferonasal field defect. The orbital CT showed a round, soft tissue mass in the inferior field of his left eye and was computed tomography (CT) showed a round, soft tissue mass in the left orbit temporally that displaced the retrolubular portion of the optic nerve nasally. A similar but smaller mass was present in the right orbit lateral to the medial rectus muscle (Fig 1). Both masses showed slight contrast enhancement. The clinical diagnosis was bilateral cavernous haemangioma. The left orbital mass was removed intact by a superolateral extraperiosteal approach. Gross and microscopic studies revealed a benign tumour composed of large endothelial lined vascular channels separated by fibrous stroma, consistent with cavernous haemangioma (Fig 2). The patient had an unremarkable postoperative course with good visual acuity.

COMMENT

Cavernous haemangioma of the orbit is a common, benign tumour that almost always occurs unilaterally. There are rare reports of bilateral cavernous haemangiomas. Friis and Char reported a case that was very similar to ours.3 They excised the tumour in one orbit and elected to follow the asymptomatic tumour in the opposite orbit. Sullivan and associates reported an unusual case of multiple bilateral orbital haemangiomas.4 Johnson and co-workers reported bilateral orbital haemangiomas as part of Maffucci’s syndrome, a condition characterised by enchondromatosis and multiple systemic haemangiomas.5 Our patient was otherwise normal with no evidence of Maffucci’s syndrome. There was also a recent report of bilateral orbital vascular masses, presumed orbital varices, that caused intravascular papillary endothelial hyperplasia.6 The widespread use of CT and magnetic resonance imaging to evaluate unrelated problems, such as headache, has led to the recognition of asymptomatic lesions compatible with orbital cavernous haemangioma. We have seen several such cases and have elected to follow without treatment these small, asymptomatic tumours, presumed to be orbital cavernous haemangiomas. Consequently, it is possible that orbital cavernous haemangioma may be more common than previously believed. If so, additional cases of bilateral orbital cavernous haemangioma will probably be recognised. In our case, the asymptomatic tumour in the right orbit most likely is a cavernous haemangioma, but periodic observation, rather than surgical excision, would seem to be the best management. In summary, the ophthalmologist should include orbital cavernous haemangioma in the differential diagnosis of bilateral, as well as unilateral, orbital tumours.

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Choroidal neovascularisation at a demarcation line: an immunopathological study

EDITOR.—We describe a patient presenting with a choroidal neovascular membrane (CNVM) at the demarcation line of a longstanding rhegmatogenous retinal detachment (RRD), and characterise its immunopathological features following surgical removal.

CASE REPORT

A 46 year old myopic woman attended the vitreoretinal service with a 3 month history of a shadow in the superior half of her left visual field. Her visual acuity was 6/9 right and 6/12 left, with a refractive error of −13.0D and −9.50D effective spheres respectively.

Examination of the left fundus revealed longstanding detached and thinned retina inferiorly and a broad heavily pigmented demarcation line passing through the macula with associated retinal pigment epithelial (RPE) hypertrophy. An area of paravenous retina adjacent to the tide mark appeared elevated and a fundus fluorescein angiogram

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Figure 1 Orbital computed tomograms with axial cut (A) and coronal cut (B), showing bilateral circumscribed orbital soft tissue masses, with a larger tumour in the left orbit and a small tumour in the right orbit.

Figure 2 Pathology. (A) Gross photograph of pseudocapsulated reddish blue mass. (B) Photomicrograph, showing large cavernous vascular channels typical of orbital cavernous haemangioma (haematoxylin and eosin ×100).
(FFA) revealed a juxtafoveal CNVM emerging from the edge of RPE hypertrophy. Three months later she reported decreased vision and metamorphopsia in her left eye, with a best corrected left visual acuity reduced to counting fingers. A subfoveal extension of the CNVM with bordering haemorrhage was present, confirmed by FFA (Fig 1A, B). She subsequently underwent pars plana vitrectomy, parafoveal retinotomy, and removal of subfoveal CNVM, together with external scleral buckling, argon laser retinopexy, and 20% sulphur hexafluoride gas tamponade.

Postoperatively, an area of inferior retinal detachment persisted and further surgery with silicone oil tamponade was undertaken. Subsequently, a posterior subcapsular cataract developed and she underwent left phacoemulsification with intraocular lens implantation and removal of silicone oil. Postoperatively, visual acuity improved to 6/18 and the retina remained flat with no clinically apparent CNVM (Fig 1C). Four months later, her visual acuity was reduced to 6/36. Fundal examination showed an elevated area at her fovea and FFA confirmed a recurrent CNVM. We are treating this conservatively as the fovea and FFA confirmed a recurrent CNVM.

The distribution of basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), macrophages (PGM1), and von Willebrand factor (vWF) were investigated using a standard biotin-streptavidin-biotin, alkaline phosphatase complex method (Dako Ltd). The alkaline phosphatase label was visualised as a red final reaction product (Vector Ltd). Nuclei were weakly stained with Mayer’s haematoxylin. A normal human donor eye was used as a positive control, while the negative control used was normal rabbit serum diluted to give a final protein concentration equivalent to that of the primary antibody used.

Histopathological examination revealed a CNVM consisting of numerous endothelial lined vascular channels and chronic inflammatory cells. The CNVM was lined by an incomplete layer of RPE cells on its posterior aspect, as determined by the clinical orientation of the membrane at the time of removal (Fig 2A).

A large portion of the CNVM consisted of vascular channels lined by endothelial cells displaying immunoreactivity for von Willebrand antigens (Fig 2B). There was staining for VEGF (Fig 2C) and bFGF (Fig 2D) in the extracellular matrix, with a similar distribution of immunoreactivity.

COMMENT
Choroidal neovascularisation occurs in a wide spectrum of conditions, including degenerative, inflammatory, traumatic, and hereditary disorders—all characterised by breaks in Bruch’s membrane. A few cases of CNVM developing at the edge of a demarcation mark have been reported in both chronic rhegmatogenous and tractional retinal detachments; however, the immunopathology does not appear to have been previously described. A demarcation mark (“high watermark”) is characteristically found in longstanding retinal detachments that either progress very slowly or remain static. In this setting, RPE cells may detach from Bruch’s membrane to proliferate and undergo metaplasia in the subretinal space at the junction of attached and detached retina. Clinically, a demarcation line appears as a line of increased pigmentation in this area and may form a sufficiently firm adhesion to prevent progression of a retinal detachment. The local wound healing response at the edge of the detached retina may also lead to excessive RPE proliferation. In our patient, such chorioretinal adhesion may have allowed the transmission of mechanical vitreoretinal traction forces to Bruch’s membrane. This could potentially have compromised the integrity of Bruch’s membrane, allowing the formation of a CNVM. High myopia was a further predisposing factor for choroidal neovascularisation in this patient, making Bruch’s membrane more susceptible to disruption.

Grossniklaus and Gass have described two fundamentally different types of choroidal neovascular growth patterns—type 1, with growth of new vessels beneath the retinal pigment epithelium, and type 2, with growth of new vessels in the sub-sensory retinal space. In our patient, the presence of RPE cells on the posterior surface of the CNVM indicates that it represented a type 2 membrane, as determined by its clinical orientation at the time of removal.

Experimentally detached retina in cats has been shown to possess higher angiogenic activity than normal attached retina. Indeed, peripheral retinal neovascularisation has been described in chronic rhegmatogenous retinal detachment. Retinal detachment is likely to lead to compromised metabolism and hypoxia of the outer retinal layers due to elevation of the retina from the choriocapillaris. RPE cells may...
secrete VEGF in response to this hypoxic insult and also secondary to mechanical stress incurred at the edge of the demarcation line. 4,5 VEGF may then stimulate the recruitment and activation of monocytes, which in turn could promote mediators of angiogenesis.6 It is therefore possible that the liberation of neovascular growth factors in this setting may have contributed further to the development of CNVM in our patient.

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Simultaneous metastases of cutaneous malignant melanoma to conjunctiva and choroid

Editor,—We report an unusual case of a cutaneous malignant melanoma which metastasised to the conjunctiva in one eye and the choroid in both eyes nearly 2 years after the initial presentation.

Case report

A 42 year old white man presented with a history of a small superficial black mark in the temporal aspect of the right eye, which had increased in size for the past 2 months. There was no significant ocular history. Two years earlier he had had a large malignant melanoma, 4.5 × 3.5 cm, removed from his lower back. On histopathology, this had been diagnosed as a superficial spreading type (Clarke’s level IV with Breslow thickness of 3.5 mm). The mitotic count was 5 per 10 high power field (HPF) with a sparse lymphocytic infiltrate seen at the edges. It had been excised completely with no vascular or lymphatic invasion seen in the section. He had been thoroughly screened and a computed tomograph (CT) scan of the abdomen and head thoroughly screened and a computed tomograph (CT) scan of the abdomen and head had not revealed any metastases. Subsequently, he had been followed up on a 4 monthly basis over the next 2 years and no recurrences had been found. During this period he developed a severe form of asthma which was controlled by oral prednisolone 25 mg per day. He otherwise felt well and on examination seemed to be in good general health. An enlarged lymph node was found in his left axilla. Visual acuity was 6/6 in the right eye and 6/5 in the left eye. Examination of the choroid revealed metastatic deposits in the choroid.

Figure 1 Fundus photograph of the right (A) and the left (B) eye, respectively, showing extensive metastatic deposits in the choroid.
present with pain and redness due to secondary glaucoma caused by infiltration of the trabecular meshwork or angle closure due to an annular haemorrhagic choroidal detachment. Retinal deposits are very rare and may cause blunted vision. Differentiation between secondary melanomas in the choroid and a primary melanoma is important in order to decide on the type of management. Bilateral diffuse uveal melanocytic proliferation is an important differential diagnosis in our patient but he had no associated cataract, retinal detachment, or severe visual impairment. The time interval between the initial presentation of the skin lesion and the occurrence of metastases may vary from months up to 10 years. The occurrence of ocular metastases usually indicates grave prognosis owing to widespread visceral disease, as was the case in our patient. He had undergone regular thorough screening for 2 years but signs of metastases were found during this period. The first external sign of secondary disease was the presence of the conjunctival lesion, which led to the discovery of the intraocular metastases (from cervical node involvement. Metastases to the conjunctiva from a cutaneous malignant melanoma is again very rare (less than 1%) and is usually associated with secondaries elsewhere in the eye. These lesions are often differentiated from other conditions such as primary acquired melanosis, naevus, adrenochrome deposits, direct extensions from ciliary body melanomas, and foreign body granulomas. The mode of treatment of metastatic cutaneous malignant melanoma in the eye can range from local excision as in small localised iris tumours, and enucleation for a painful blind eye or palliative treatment comprising chemotherapy and radiotherapy if the disease is widespread, as is often the case. Patients with a single choroidal metastasis may be considered for radioactive plaque treatment.

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Acute sixth nerve palsy in vitamin A treatment of xerophthalmia

CASE REPORT

A 5 month old male infant with a long history of feeding intolerance was admitted to our hospital for severe irritability and failure to thrive. In the course of his examination, a sweat test was performed confirming the diagnosis of cystic fibrosis. Appropriate nutritional therapy and pancreatic enzyme replacement was commenced.

The infant had also been treated by his paediatrician for “conjunctivitis” of his right eye for the preceding 2 months with topical antibiotics. On the ophthalmic examination, the infant’s visual acuity was fix and follow bilaterally. Extraocular motility was full and the eyes were orthophoric. Anterior segment examination revealed conjunctival xerosis of both eyes, and an inferior corneal ulcer of the right eye measuring 2x4 mm. Fundus examination was normal in both eyes. A diagnosis of xerophthalmia was made.

Vitamin A therapy was promptly commenced, with 50 000 IU (water miscible retinyl palmitate) intramuscularly to be given immediately and then to be repeated on the following day. After the first 50 000 IU, prominent bulging of the fontanelle was observed, although the infant remained alert and happy, and was feeding well. The second dose of 50 000 IU was therefore postponed for 48 hours, to be administered in two divided doses over 2 consecutive days. These doses were well tolerated, with gradual improvement of the bulging fontanelle noted a week. Five days after the initial vitamin A dose, a complete abduction deficit of the infant’s left eye was noted, in keeping with an acute sixth nerve palsy of the left eye. The infant still remained alert and happy, and
Successful treatment of ocular invasive mould infection (fusariosis) with the new antifungal agent voriconazole

EDITOR,—Voriconazole is a new, highly potent, triazole with broad spectrum activity against fungi, including moulds, as well as fluconazole resistant Cândida spp. Like other azole antifungal agents it interferes with ergosterol biosynthesis. Its antifungal activity has been shown in several experimental as well as clinical studies.

CASE REPORT
In November 1998, a 16 year old girl was transferred to the university eye hospital in Düsseldorf with a severe ulcerative hypopyon keratitis in the left eye from which she had been suffering for 3 months after swimming in a lake in Italy. Smears, scrapings, and serology gave no hint of the aetiology. Despite intensive topical antibacterial, anti-acanthamoebal, antifungal, and antitherpetic therapy, as well as cryoapplication, her clinical situation had deteriorated continuously before admission to our hospital. As an optical rehabilitation was unlikely, owing to the severely infiltrated cornea, a perforating keratoplasty was performed. Postoperatively, the patient was given systemic as well as topical antibiotics. The first 3 days postoperatively were inconspicuous, but from the sixth day on a hypopyon could again be seen. The hypopyon progressed and finally took place, and the patient was released by mouth twice daily. Voriconazole was also injected intracamerally, at a dosage of 10 µg/0.1 ml. Topical antifungal therapy was switched from amphotericin B 0.3% every hour to voriconazole 1% every half hour. In addition, any remaining suspicious intracorneal material was again excised and the anterior chamber was irrigated with a 3 µg/ml voriconazole solution. After this procedure, healing was accomplished. Its obvious antifungal activity and favourable pharmacological properties, especially the low range of side effects, were no local or systemic adverse effects during this highly potent antifungal regimen. A transient elevation of liver enzymes (a known adverse event of azole antifungal agents) at the end of therapy and after cessation has been attributed to the study drug. Topical administration was well tolerated.

COMMENT
This is the first time that the efficacy of voriconazole in the treatment of ocular invasive fungal infection has been demonstrated. Topical administration has been tolerated well even when injected into the anterior chamber. Its obvious antifungal activity and favourable pharmacological properties, especially the low range of side effects, will make this new drug attractive for future studies on invasive ocular infections.

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Figure 1 Grocott methenamine silver positive hyphae in the excised corneal button.

Figure 2 Ultrasound biomicroscopy discloses relapse of intraocular fungal disease.

Severe intraocular inflammation after a change of HAART

EDITOR,—Patients with previous cytomegalovirus retinitis (CMVR) and immune recovery vitritis who developed further severe intraocular inflammation 6 weeks after changing HAART.

CASE REPORT

A 43 year old man, diagnosed as HIV positive in 1984, was treated in January 1996 for bilateral CMVR that responded to systemic ganciclovir. In April 1996 he started saquinavir, stavudine and lamivudine, and ritonavir was added in December 1996. In February 1997 he developed immune recovery vitritis in both eyes. Best corrected visual acuities (BCVA) were 6/6, N5 right; 6/6, N6 left. A viral load was now 7800 copies x10^6/l and CD4+ count 40 cells x10^6/l. In December 1996 ritonavir was added. We present a patient with previously treated CMVR and immune recovery vitritis who developed further severe intraocular inflammation 6 weeks after changing HAART.

We postulate that this is due to the improved CD4+ function that occurs with HAART.

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Six weeks after changing HAART, he complained of blurred left vision. Visual acuity was 6/6 right, 6/9 left. There was a left vitritis with a white retinal lesion along the inferotemporal vessels at the margin of inactive CMVR (Fig 3). A diagnosis of relapse of CMVR was made and he was treated with intravenous ganciclovir.

Two weeks later vision was counting fingers, the vitriris was worse, and the retinal lesion had extended with more haemorrhage. He was treated for presumed toxoplasmosis with sulphadiazine, pyramethamine, and folic acid but 1 week later his vision was hand movements and the lesion was larger (Fig 4). A diagnostic vitrectomy was performed. Polymerase chain reaction (PCR) was negative for CMV, toxoplasmosis, varicella zoster, and Epstein–Barr viruses. Cytology did not reveal lymphoma.

One week later the eye was painful and vision was perception of light. A retinal biopsy was performed in an area of active inflammation. Histology showed retinal necrosis and exudates. No viral inclusion bodies were found and stains for acid fast bacilli, fungi, and toxoplasma cysts were all negative. A few atypical lymphocytes were seen and PCR for


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B cell clonality showed oligoclonal banding. A contrast enhanced magnetic resonance imaging of the brain and orbits was normal.

Eighteen months later the BCVAs are 6/6, N5 right; perception of light, left. A chorioretinal scar persists in the macular and temporal retina of the left eye but there is no active inflammation in either eye.

COMMENT
In this patient it failed to identify any cause for the intraocular inflammation; however, the cessation of the inflammatory process in the absence of any specific treatment is similar to the clinical course of immune recovery vitritis and suggests a non-infectious mechanism. The temporal association with changes in HAART, together with the PCR findings, both imply an immunological cause. It is unclear why this response was unilocular.

The presence of multiple discrete bands on PCR may indicate a premalignant lymphoproliferation but 18 months later the eye is quiet with no recurrence and the patient remains well. Our hypothesis is that the intraocular inflammation occurred because the new combination HAART produced a second, very exaggerated immune response to pre-existing antigens.

Clinicians should be aware that changing the combination of HAART may be associated with aggressive intraocular inflammation with an oligoclonal lymphocyte response. Early recognition and treatment with systemic steroids may have prevented blindness in our patient.

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Oriental herbal medicine induced epithelial keratopathy

EDITOR,—“Kampo” is the name given to an oriental herb medicine which has been used in China and Japan for more than 2000 years. Kampo is believed to be very mild and a safe medicine and so far there has been no report of kampo induced keratopathy.

We report a case of epithelial keratopathy, which occurred in a patient who had taken oriental herbal medicine for 5 years. To the best of our knowledge, this is the first report of oriental herbal medicine (kampo) induced keratopathy.

CASE REPORT
A 30 year old Japanese woman was referred to Juntendo University Hospital with the complaint of bilateral photophobia. Visual acuity was 20/20 in both eyes. Slit lamp examination disclosed dust-like opacities in the epithelial layer in both central corneas, and brown coloured precipitates, which spread radially from the central cornea (Fig 1A). No corneal staining was observed with fluorescein. No other ocular abnormality was found. There were no remarkable findings in her past or family history.

The patient underwent therapeutic and diagnostic superficial keratectomy that provided epithelial layer for ultrastructural study. The corneal epithelial layer was processed for routine electron microscopy. Electron microscopic examination disclosed corneal epithelial cells with numerous lamellar inclusion bodies formed by series of concentrically arranged lamellae suggestive of lipid-like material (Fig 1B).

The patient was submitted to laboratory tests in order to investigate a possible metabolic disease. No abnormal data were detected except for slightly high level of total blood cholesterol. Concerning the drug history, the patient informed us that she had been taking an oral oriental herbal medicine for chronic constipation for about 5 years. The composition of the drug is shown in Table 1. Two years before the present complaint, the patient had the same symptom of photophobia which gradually disappeared several months after withdrawal of the herbal medicine. One month before the present complaint, she started taking the herbal medicine for constipation. The patient was advised to withdraw the herbal medicine. Three months after withdrawal, the corneal opacities decreased and the patient noticed relief of symptoms. One year after withdrawal, the corneal lesions had disappeared completely. No sign of recurrence was observed until now, 4 years after the first examination.

COMMENT
Although oriental herb medicines have been beneficial to patients, scientific explanation of their pharmacological mechanisms has lagged behind the widespread use of kampo in clinical practice.1 In this case, the clinical and morphological findings were similar to those observed in Fabry’s disease2 and in drug induced keratopathy.3,4 In drug induced lipid storage keratopathy, the corneal deposits are bilateral, dose and duration related, and gradually disappear after the drug is withdrawn.5 Although kampo is believed to be very safe, it seems advisable to dictate caution with respect to this possible adverse effects.

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Table 1 Composition of the herbal medicine (7.5 g of this product contains 5.7 g of dried extract obtained from mixed raw herbs in the above ratio)

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<thead>
<tr>
<th>Herb name</th>
<th>Amount (g)</th>
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<tbody>
<tr>
<td>JP Scutellaria root</td>
<td>2.0 g</td>
</tr>
<tr>
<td>JP Glycyrrhiza root</td>
<td>2.0 g</td>
</tr>
<tr>
<td>JP Platycodon root</td>
<td>2.0 g</td>
</tr>
<tr>
<td>JP Gypsum</td>
<td>2.0 g</td>
</tr>
<tr>
<td>JP Atractylodes rhizome</td>
<td>2.0 g</td>
</tr>
<tr>
<td>JP Rhubarb rhizome</td>
<td>1.5 g</td>
</tr>
<tr>
<td>JP Schionepeta spike</td>
<td>1.2 g</td>
</tr>
<tr>
<td>JP Gardenia fruit</td>
<td>1.2 g</td>
</tr>
<tr>
<td>JP Peony root</td>
<td>1.2 g</td>
</tr>
<tr>
<td>JP Cadmium rhizome</td>
<td>1.2 g</td>
</tr>
<tr>
<td>JP Japanese angelica root</td>
<td>1.2 g</td>
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<tr>
<td>JP Mentha herb</td>
<td>1.2 g</td>
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<tr>
<td>JP Napoleonia root</td>
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<td>JP Forsythia fruit</td>
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</tr>
<tr>
<td>JP Ginger rhizome</td>
<td>0.8 g</td>
</tr>
<tr>
<td>Talc</td>
<td>3.0 g</td>
</tr>
<tr>
<td>Anhydrous mirabilum</td>
<td>0.75 g</td>
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Figure 1 (A) Slit lamp examination shows numerous dust-like opacities in the epithelium at central cornea and brown coloured precipitates spreading radially from central cornea in both eyes. (B) Numerous membranous lamellar inclusion bodies in the corneal epithelial cells, suggestive of lipid-like material (>16 000).

Branch retinal artery occlusion; another complication of sildenafil

EDITOR,—Sildenafil is the oral treatment for erectile dysfunction and was licensed throughout Europe in September 1998. It is a potent, selective inhibitor of the isoenzyme phosphodiesterase type 5 (PDE5). Inhibition of PDE5 leads to prolongation of cyclic guanosine monophosphate (cGMP) activity in erectile tissue and increases the natural cGMP levels in the corpus cavernosum.

In this case, sildenafil was used for the treatment of erectile dysfunction in a 72-year-old man with advanced HIV disease. After 4 months, he presented with a subacute branch retinal artery occlusion in the nasal retina of the left eye.

The patient was started on sildenafil, and sildenafil was stopped after 4 months. After stopping the medication, the branch retinal artery occlusion resolved. The authors suggest that sildenafil might cause branch retinal artery occlusion.

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CASE REPORT

A 69 years old man presented with a sudden painless loss of vision in the left eye 2 days previously. The patient was fit and healthy otherwise and had no history of glaucoma, diabetes, hypertension, or other systemic vascular diseases. Visual acuity was 6/6 in the right eye and 6/24 in the left eye. Anterior segment examination was normal apart from a mild relative left afferent pupillary defect. Fundus examination of right eye was normal whereas fundus examination of the left eye revealed a superotemporal branch retinal artery occlusion. As the patient did not have any of the risk factors predisposing to arterial occlusion a more detailed history was sought and the patient informed us that he had taken a dose of Viagra (100 mg) a few hours before he experienced loss of vision in left eye. Cardiac examination revealed sinus rhythm, normal heart sounds, and there was no carotid bruit or thrill. 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