

LETTERS TO THE EDITOR

Sympathetic ophthalmia associated with high frequency deafness

EDITOR.—Sympathetic ophthalmia with deafness has been reported rarely.^{1,2} We describe one such case and explore a hypothesis whereby genetic susceptibility may be associated with cross reactivity of antigens derived from common neural crest tissue.

CASE REPORT

A 72 year old woman who had previously undergone a left trabeculectomy had a fall in which she sustained a Colles fracture and a left total hyphaema. By 14 days the blood had cleared sufficiently to reveal that she had expelled the entire left iris into the trabeculectomy bleb, with extensive dispersion of uveal pigment into the subconjunctival space. She was also found to have dislocated the lens, and had sustained a choroidal detachment (confirmed by ultrasonography). A non-granulomatous anterior uveitis was noted in the left eye at this time. The initial visual acuity was light perception in the left eye and 6/12 in the right eye.

On the 25th day after the original injury, she experienced pain and blurring of vision in her right eye, with the simultaneous onset of bilateral deafness (with an initial high frequency hearing loss of 60 dB). She was found to have a brisk anterior uveitis, with a dense vitritis in this eye, through which rugose choroidal thickening could just be discerned. At this stage, the right visual acuity had declined to 6/24, and the left eye achieved hand movements.

A diagnosis of sympathetic ophthalmia was made. She received two infusions of intravenous methylprednisolone (1 g each) and oral prednisolone (20 mg daily) was started. Cyclosporin A was commenced, and the dose adjusted to achieve a trough level of 200 µg/l (despite a history of breast cancer in remission). In view of the severity of the injury to

the left eye, a left pars plana lensectomy and vitrectomy were performed to assess the visual potential of this eye. The retina was found to be flat, and the macula healthy; therefore, enucleation was not performed. By 3 months she had regained a visual acuity of 6/6 in the sympathising eye, and 6/12 in the exciting eye (with a contact lens incorporating a pupil and an aphakic correction).

However, at 4 months post-injury, reduction of the prednisolone dose to 12.5 mg, and reduction of cyclosporin A to give a trough level of 70 µg/l, was followed by a flare of anterior uveitis in both the exciting and sympathising eyes. This responded to increased prednisolone (15 mg) and an increase in the dose of cyclosporin A to achieve a trough level of 140 µg/l. At this time the exciting eye began to display white choroidal lesions consistent with the appearance of Dalen Fuchs nodules (Fig 1). Prednisolone was gradually reduced to 12.5 mg without further complications and she ultimately achieved a visual acuity of 6/9 in both eyes. Despite treatment, her hearing loss gradually progressed to 90 dB; this has not recovered.

COMMENT

Sympathetic ophthalmia with features of Vogt-Koyanagi-Harada disease (VKH), was initially reported in the 19th century.³ More recently, Nirankari *et al* have reported one case of sympathetic ophthalmia with profound high frequency deafness which did not recover.² Rao and Marak³ have performed a clinicopathological survey of 100 pathological specimens of eyes enucleated because of sympathetic ophthalmia. Four of these had VKH overlap features, of which two had hearing loss. The association of sympathetic ophthalmia and deafness is clearly rare, which raises the question of what such overlap cases can teach us about the pathogenesis of VKH. Woods⁴ attempted to explain why deafness could occur in VKH, hypothesising that pigment present in the auditory labyrinth and the eye could be common targets of autoimmunity. The auditory labyrinth and the uvea are known to have a common embryological origin in the neural crest. Could a genetic predisposition facilitate the recognition of such shared antigens? Sugita *et al*⁵ have recently reported that cytotoxic T cells from three

patients with VKH and one with sympathetic ophthalmia reacted against the MART 1 melanoma antigen (an antigen carried by skin and eye melanocytes), when presented in association with HLA-A2. Interestingly, two of their three VKH patients carried HLA-A2, HLA-B51, HLA-DR4, and a further VKH patient carried the HLA-A2, and HLA-DR4 antigens. Their sympathetic ophthalmia patient was also A2 positive, but was not positive for either HLA-B51 or HLA-DR4. Our patient was HLA typed and found to carry HLA-A2, HLA-B51, HLA-DR4.

HLA-A2 and HLA-DR4 are common and linked antigens, occurring together in approximately 33% of the population, but HLA-B51 is less common. From 537 random transplant organ donors HLA typed over 3 years, we calculated the frequency of HLA-A2, HLA-B51, HLA-DR4 in the regional population. These specificities were present together in only seven donors, giving a frequency of 1.3%. We propose that patients carrying HLA-A2, HLA-B51, and HLA-DR4 are at increased risk of damage arising in melanocytes of diverse tissues when one tissue is injured, whether in VKH or sympathetic ophthalmia.

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Similarities in the packaging of cyanoacrylate nail glue and ophthalmic preparations: an ongoing problem

EDITOR.—We would like to raise concern over an ongoing problem—namely, the similarity between the packaging used for fingernail extension glue (cyanoacrylate “superglue”) and topical ophthalmic preparations.

These concerns were raised as long as 16 years ago¹ and yet no action or progress has since been instituted by the manufacturers of these containers.

Both nail glue and ophthalmic preparations are almost identically packaged in 5–10 ml clear, round bodied, soft plastic dropper type bottles with a white non-locking twist cap which are often manufactured in the same factory.¹ The caps are even interchangeable.

Discrimination between these products is therefore made unnecessarily difficult, particularly for patients who need to use regular topical medication—for example, glaucoma and contact lens wearers² and patients who are partially sighted or blind.

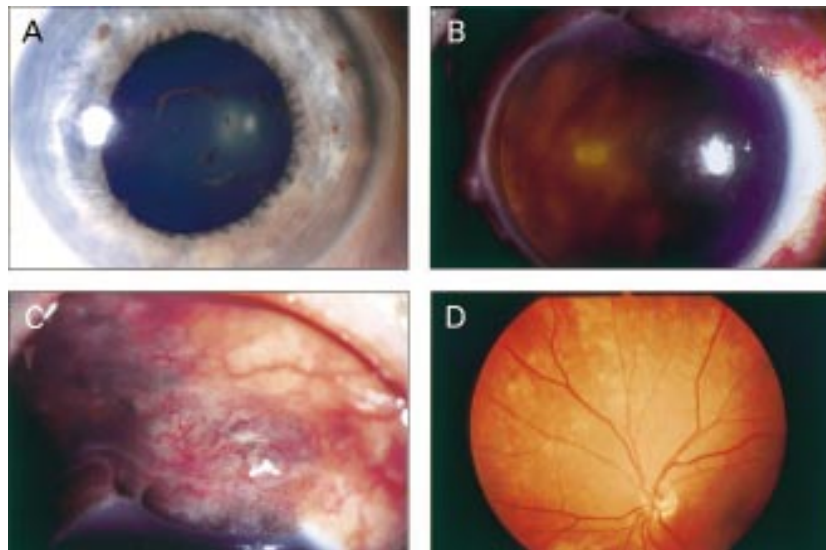


Figure 1 (A) Sympathising eye: acute uveitis (pigment ring after pupillary dilatation). (B) Exciting eye: aniridia and hyphaema. (C) Exciting eye: iris pigment in trabeculectomy bleb. (D) Exciting eye: multifocal pale subretinal lesions, representing early Dalen Fuchs nodules.

Furthermore, once superglue has been installed into the eye, it undergoes instantaneous polymerisation,¹ so that no therapeutic window of opportunity exists to irrigate the glue from the eye.

Ocular injuries reported following superglue administration have included corneal abrasions, punctate epithelial keratopathy, eyelash loss, skin excoriation, and conjunctivitis.³ There is also the initial fear of blindness generated by an instant tarsorrhaphy.⁴

CASE REPORT

There have been multiple reports of the mistaken ocular use of nail adhesive in adults.¹⁻⁴

We have recently treated two paediatric patients for accidental ocular administration of nail adhesive glue, in one case a direct result of confusion about the packaging. The youngest was a baby aged 3 months, who had been prescribed chloramphenicol 0.5% eye drops for conjunctivitis. The mother confused the antibiotic eye drops with the nail adhesive drops which were mistakenly installed into the left eye, causing a partial tarsorrhaphy, eyelash clumping, and a corneal abrasion.

The second case was of a 3 year old child whose brother was receiving antibiotic eye drops for conjunctivitis. The child imitated her mother's actions by installing drops in her own eye but used nail adhesive instead. This led to misdirection of her eyelashes and a corneal abrasion.

Both children responded well to the mechanical removal of the glued lashes and chloramphenicol 1% ointment.

COMMENT

Sixteen years have now passed since this issue was first raised, and we feel that the manufacturers of nail glue products should be forced to address some remedial action, to ensure that these preparations are packaged differently from therapeutic preparations in the future.

At the very least, nail glue products should be fitted with child safety caps to prevent any further unnecessary anxiety and ocular trauma.

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Disconjugate vertical ocular movement in a patient with locked-in syndrome

EDITOR,—Locked-in syndrome is a rare paralytic state in which voluntary movements are affected. This uncommon de-efferent state results in quadriplegia, loss of gestural or vocal communication with a defect in horizontal eye movements. However, consciousness and vertical eye movements are spared, which enable

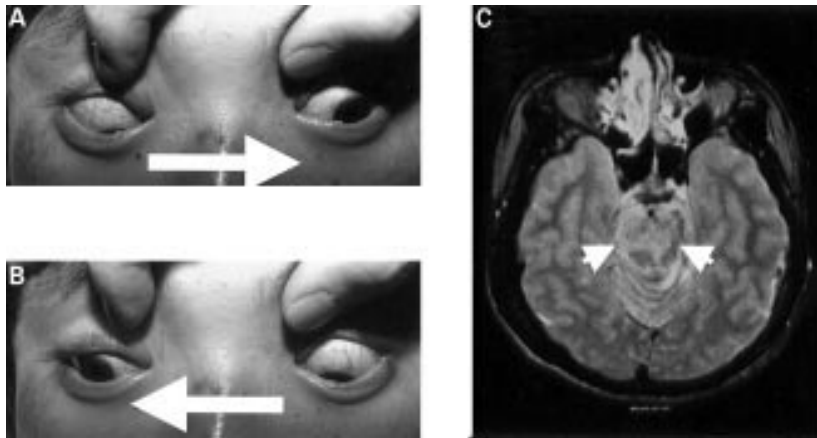


Figure 1 (A) and (B) show disconjugate vertical and torsional eye movement when the patient is asked to look to one side (direction of arrow). Horizontal gaze and upward movement above the midline are limited. (C) Axial T2 weighted magnetic resonance imaging shows a high signal intensity in pons (arrows) due to infarction.

the patient to communicate by way of ocular movement, either conjugate upward or downward.

Here, we report an unusual case of locked-in syndrome presenting disconjugate vertical and torsional ocular movement, mimicking seesaw nystagmus (SSN).

CASE REPORT

A 30 year old man was brought to the emergency room. He was unable to move his extremities at all. Verbal communication was not possible because he could not speak. Increased deep tendon reflex with bilateral extensor toe signs were noted. He could open his eyes. Visual acuity was uncheckable. Visual field appeared to be normal by a threatening test. Pupil size was equal and light reflex was prompt. Funduscopic examination did not show any remarkable findings.

On command, he showed conjugate vertical eye movements but he could not make horizontal gaze. Instead, full conjugate horizontal leftward deviation was obtained with cold water irrigation in the left ear, but nystagmus to the opposite direction was absent. Caloric stimulation on the right ear was not performed because eardrum perforation was suspected. Doll's eye manoeuvre showed full range of horizontal eye movements except for the adduction of the left eye, presumably due to left internuclear ophthalmoplegia. Convergence for near target was not possible. When the patient was asked to look to the right side, the right eye moved upward with intorsion, and at the same time, left eye moved downward and extorsion. It appeared to be a half cycle of SSN. When the patient was asked to look to the left side, the reverse half cycle of SSN was observed—the left eye moved upward with intorsion whereas right eye moved downward with extorsion. Horizontal gaze was limited, although there seemed to be minimal movement. The eyes that moved upward didn't cross above the midline (Fig 1A, B).

In addition to the above findings, intermittent irregular jerky eye movements were detected. These also consisted of elevation with intorsion of one eye and synchronous depression and extorsion of the other eye. They appeared in a clustered pattern containing four to five cycles of SSN, beating at between 0.5 and 1 Hz. Whether this phenomenon was purely voluntary or involuntary was not confirmed. It had persisted for 1 month.

Brain MRI revealed an extensive infarct in the ventral pons (Fig 1C).

COMMENT

We report an unusual non-concomitant vertical and torsional eye movements with a large brainstem infarction that rendered him "locked-in". The main finding was intermittent disconjugate vertical eye movement with rising and intorting on one side while falling and extorting on the opposite side. It appeared to be SSN but it has not been previously reported in locked-in syndrome. Unlike the previously reported SSN cases, the half cycle of SSN was also induced when the patient attempted to look to the side.

Studies on SSN have suggested that interstitial nucleus of Cajal (INC) mediate this phenomenon. The INC, a centre of integration of vertical and torsional eye movements, has extensive rostral and caudal connections.^{1,2} It receives ipsilateral input from the frontal cortex through the zona incerta, and contralateral input from the deep cerebellar nuclei and pretectum. The INC itself sends outputs to the ocular motor nuclei, the ipsilateral medial vestibular nucleus, and the contralateral INC. In animal experiments, stimulation near the INC³ or stimulation of semicircular canals^{4,5} produced one half cycle of SSN. The underlying mechanism for a half cycle of SSN in our patient is not known. Horizontal conjugate deviation by cold caloric stimulation or oculocephalic reflex did not produce SSN, suggesting a vestibular mechanism may not explain SSN in this patient. Instead, we suggest that supranuclear control for horizontal gaze inappropriately sends signals to the INC, but a disturbance of neural integration in the INC may be responsible for the development of SSN.^{6,7}

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Conjunctival CD5+ MALT lymphoma

EDITOR.—Primary ocular non-Hodgkin's lymphoma (NHL) may be found in the conjunctiva, eyelids, and lacrimal glands, but the majority occur in the orbit.¹ Most primary ocular NHL are of B cell origin, either of the follicular, diffuse small, or mixed cell type.¹

According to the Revised European American classification of lymphoid neoplasms (REAL classification)² the most common ocular NHL, arising from mucosa associated lymphoid tissue (MALT) and the marginal zone of lymph follicles, is included in the group of extranodal peripheral B cell lymphomas.¹ Histopathological features of marginal zone lymphoma (MZL) of the MALT type consists of a diffuse and parafollicular growth pattern and the presence of lymphoepithelial lesions.² The tumour cells express monotypic surface Ig (sIg) and sometimes cytoplasmic Ig (cIg) (usually IgM), moreover the pan B cell antigens CD19, CD20, CD22, and CD79a.² Typically, they are negative for CD5, CD10, and CD23.²

Characteristically, MZL of the MALT type affects older patients and may remain localised for years,² while disseminated disease involving bone marrow and peripheral blood is rare.² Localised tumours may be cured with local irradiation, whereas disseminated stages of the disease are not curable and transformation into a large cell NHL may occur.²

We report a case of conjunctival MZL of the MALT type with an unusual clinical appearance, an CD5+ immunophenotype, and a history of idiopathic non-specific anterior uveitis.

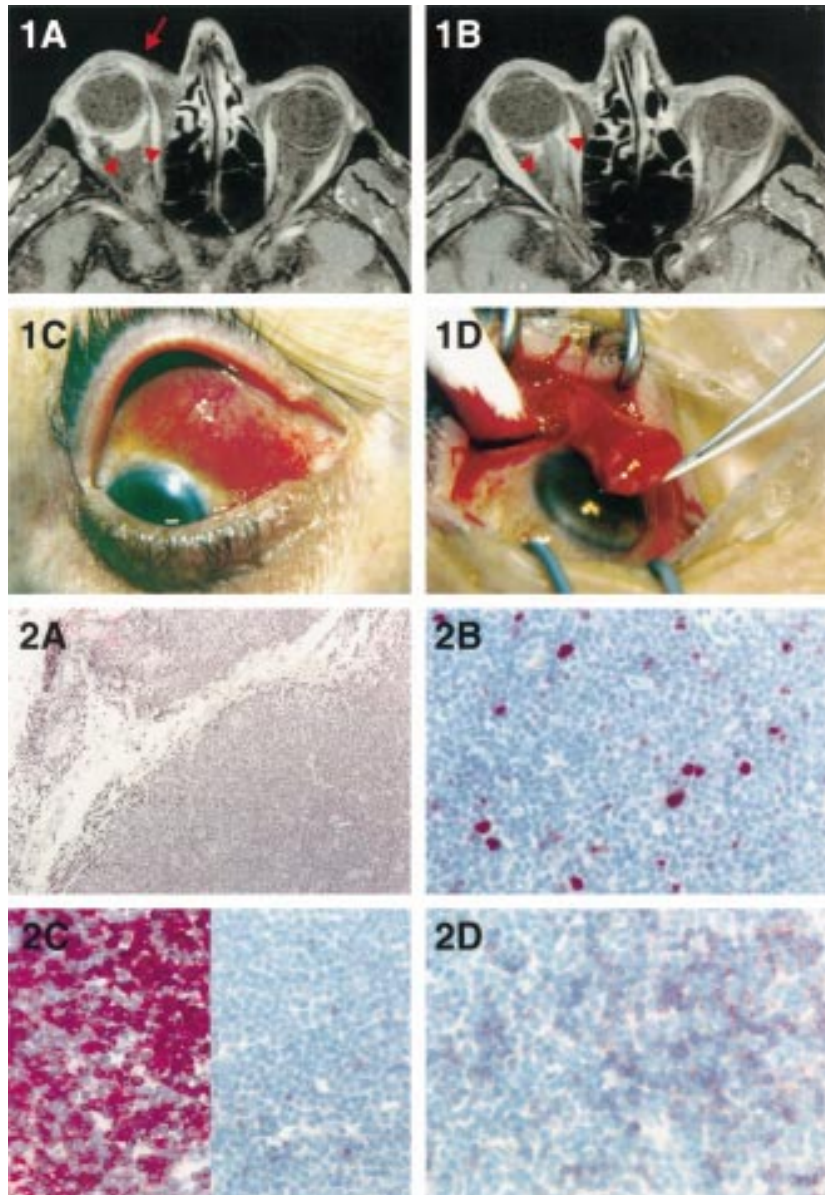
CASE REPORT

A 79 year old man was referred to our hospital with a 3 month history of right eye discomfort and an epibulbar mass below the upper eyelid. Ophthalmological examination of the right eye revealed a reddish palpable tumour, 1.5 cm in diameter, located in the upper conjunctiva (Fig 1C). The extraocular movements were normal. Cornea and anterior chamber appeared clear; however, cortical and nuclear opacities were noted in the crystalline lens. Posterior segment examinations showed areas of confluent drusen and retinal pigment epithelium atrophy, with a normal optic disc. The patient's left eye had suffered from a severe anterior uveitis 30 years earlier and some recurrences, resulting in subsequent phthisis bulbi. Slit lamp examination revealed

a low flare without cells in the anterior chamber, an indication of persisting vascular damage, moreover posterior synechiae. Lens opacification and age related macular degeneration were similar to the right eye. Because of the age related macular degeneration and the cataract visual acuity was "only" 20/100 for the right eye, for the phthisic left eye counting fingers/1 metre. The intraocular pressure was normal for the right eye (17 mm Hg), but hypotonic for the left eye (7 mm Hg). Because the uveitis was not due to any systemic or ocular disorder (characterised by

blood chemistry tests and anterior chamber tap) it has to be diagnosed as idiopathic non-specific uveitis.

Orbital magnetic resonance imaging (MRI) showed a supraequatorial lesion that surrounded the right eyeball (Fig 1A and B). Computed tomography (CT) scans demonstrated an intact bone structure of the orbit and no abnormalities were seen in the remaining skull, body or abdomen. As extensive as possible the anterior, visible part of the epibulbar lesion was surgically resected (Fig 1C and D), formalin fixed and paraffin



Figures 1 and 2 Clinical and diagnostic presentation of a rare conjunctival MALT lymphoma. (1A) Orbital magnetic resonance imaging (MRI) shows a supraequatorial and epibulbar tumour mass (arrow) with extension to the deep orbit of the right eyeball (arrowheads). (1B) On equatorial sectional plane, MRI revealed tumour masses surrounding the optical nerve (arrowheads). The optical nerve appears not to be infiltrated. (1C and 1D) Excisional biopsy showed a well defined tumour. Histological presentation of conjunctival MALT lymphoma. (2A) Diffuse and homogeneous infiltration of the conjunctival connective tissue by small sized lymphoid cells. Haematoxylin and eosin staining, magnification $\times 40$. (2B) Monoclonal antibody MIB1 recognises a relatively low tumour growth fraction of about 10%. Proliferating cells are indicated by a red nuclear or cytoplasmic signal. APAAP technique, counterstaining by haematoxylin, magnification $\times 240$. (2C) Almost all cells of the tumour mass are immunoreactive for the B cell marker CD79a (left), whereas only few intermingled normal T cells express CD3 (right). Immunoreactive cells are indicated by a red membranous signal. APAAP technique, counterstaining by haematoxylin, magnification $\times 240$. (2D) About 50% of the tumour cells express the T cell antigen CD5. Immunoreactive cells are indicated by a red membranous signal. APAAP technique, counterstaining by haematoxylin, magnification $\times 240$.

embedded sent to the pathology department of Justus-Liebig-University Giessen, Germany, for immunohistological studies (Fig 2). Immunohistochemistry was done on the routinely formalin-fixed, paraffin embedded biopsy specimen after microwave pretreatment of the prepared 3–4 µm tissue sections. In the absence of analysable epithelium or mucosal glands, lymphoepithelial lesions were not assessed. However, general expression of CD20 and CD79a revealed the B cell nature of the tumour infiltrate, but it was interesting that CD5 expression in about 50% of tumour cells was positive (Fig 2D), while only few intermingled reactive T lymphocytes were observed (Fig 2C). Hints for a plasma cellular differentiation were not detected by VS38c and reactivity for CD10, CD23, and CD30 was negative.

General physical examination of the patient showed no abnormality. There were no lymphadenopathy or hepatosplenomegaly. Peripheral blood smears as well as bone marrow aspiration biopsy showed no signs for a disseminating lymphoma. All haematological and biochemical parameters were within the normal range with the exception of slightly elevated thymidine kinase (8 U/l) and β₂-microglobulin levels (2.9 µg/l) suggestive for intensified cell growth. In conclusion, the final diagnosis of a low malignant conjunctival MLZ of the MALT type was established and confirmed by the German reference centre (Prof M-L Hansmann, University of Frankfurt). The patient underwent radiotherapy (40 Gy) of the right orbit (fractionated to 5 × 2 Gy/week). After radiotherapy, the lesion decreased markedly. No recurrence of the orbital lesion or any systemic involvement was noted during the follow up period of 18 months.

COMMENT

The immunophenotypic profiles of low grade B cell NHL are complex and still under investigation. Especially the T cell antigen CD5 is used to subclassify this group of B cell lymphomas. Since CD5+ B cells were found in normal liver, spleen, and lymph node, CD5+ B cell NHL are considered to be a malignant clonal proliferation of a specific stage of B cell differentiation.⁷ The T cell antigen CD5 has been reported in B cell NHL between 3% and 40%.^{1,4,9} In extranodal MZL the presence of CD5 is described in one of 35 cases, in two of 63 cases, respectively in one of nine cases.^{6–8} Only three cases were disclosed which affected the eye.^{9,10}

Since increased numbers of CD5+ B cells are found in blood of patients with autoimmune diseases,¹¹ CD5+ B cells are thought to exert an immunoregulatory function. Whether CD5 expression is relevant to the prognosis of patients with MALT lymphoma is controversial.^{6,9,10}

The association of MALT lymphomas with diverse autoimmune disorders, especially Sjögren's syndrome and Hashimoto's thyroiditis is well known.^{12,13} Until now, the pathogenetic link of this relation is not clear, but an influence of a long standing inflammation and a lack of a regulatory lymphocytic subset are discussed to promote the development of MALT lymphoma.¹⁴ Perhaps there is also a (autoimmune) correlation of anterior uveitis (of the contralateral eye) and MALT lymphoma as demonstrated here, but it cannot be proved and is perhaps incidental.

The differential diagnoses of our patient are MZL, bearing the unusual CD5+ phenotype, chronic lymphocytic B cell leukaemia (B-CLL), and mantle cell lymphoma (MCL).

The last were excluded because of different morphological and phenotypic features.² Furthermore, B-CLL and MCL are usually widespread at diagnosis showing diffuse lymphadenopathy, substantial lymphocytosis, and bone marrow involvement. Both diseases are more aggressive than MALT lymphoma and usually not curable.² Although there was an extended growth from the epibulbar conjunctiva towards the deep orbit, our patient showed a localised stage of the disease, an indolent clinical course, and a favourable response to radiotherapy. Thus, we demonstrated an exceptional case of a conjunctival MZL of the MALT type with unusual CD5+ phenotype.

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Autosomal dominant microcephaly—lymphoedema-chorioretinal dysplasia syndrome

EDITOR.—We describe a family with chorioretinal dysplasia, microcephaly, mental retardation, and lymphoedema.

The proband presented with a severe multiple malformation syndrome, with anomalies of the brain, heart, and eyes. Ocular anomalies included microphthalmia and chorioretinopathy. Pedal lymphoedema was obvious at birth. These features overlap with three previously distinguished conditions (microcephaly with chorioretinopathy (MIM 156590), microcephaly with microphthalmia and retinal folds (MIM180060), and microcephaly and lymphoedema (MIM152950), and this suggests that they can be the variable expression of a single entity. In all children with microcephaly, a history of pedal oedema and detailed eye examination are essential.

CASE REPORTS

The index patient, a male, was born as the second child, to unrelated parents. He was born at a gestational age of 37 weeks by elective caesarean section for unexplained intrauterine growth retardation. He was severely microcephalic and had marked lymphoedema of the dorsum of both feet. Facial features were peculiar with, in addition to the microcephaly, low set ears and retrognathia. There was a transverse palmar groove on the left side, a right sided hydrocele and cardiac examination revealed the presence of an atrial septal defect, a small ventricular septal defect, and a right aortic arch. Neurological examination revealed axial hypertonia and severe developmental delay. Axial T1 weighted MR image at 4 months showed microcephaly and microlissencephaly. Asymmetry of the eyes was noted and the right eye had an abnormal leucocoric appearance. Corneal diameters were 11.5 mm on the right and 9 mm on the left. There was an iris bombans on the cataractous right eye with pressure of 30 mm Hg. Ultrasound showed the characteristics of a persistent hyperplastic primary vitreous (PHPV). After a surgical procedure with iridectomy the pressure normalised. On funduscopy of the left eye a dystrophic retina with punched out lesions was seen (Fig 1). The second patient is the 3 year old brother of the index patient. He was microcephalic and showed marked lymphoedema of both feet at birth. Development was moderately retarded. Ophthalmological examination revealed bilateral chorioretinal dysplasia with the punched out lesions being localised in the periphery and midperiphery. Optic discs had a waxy pale aspect, macular reflex was dull (Fig 2). A fERG performed under sedation using contact lens electrodes showed a severely attenuated cone and rod response. The third patient is the 27 year old father of both patients. He was mildly mentally retarded. Physical examination revealed microcephaly and dilated veins on the dorsal side of his feet. On funduscopy subtle atrophic pigment epithelial changes could be noted temporally from the optic disc on the right eye; on the left eye atrophic changes were prominent. A fERG



Figure 1 Patient 1. On funduscopy of the left eye a dystrophic retina with punched out lesions became obvious.

was performed and showed a normal rod and cone response.

In all three patients high resolution chromosomal analysis on a peripheral blood lymphocyte culture revealed a 46,XY normal male karyotype after G-banding.

COMMENT

In literature, three distinct conditions have been delineated—microcephaly with chorioretinopathy (MIM 156590) microcephaly with microphthalmia and retinal folds (MIM180060), and microcephaly and lymphoedema (MIM152950). The features in the present family overlap with these three disorders. This suggests that, in at least some instances, they can be the variable expression of a single genetic condition.

In the syndrome with microcephaly with chorioretinopathy variable expressivity and the presence of mental retardation as an associated feature have repeatedly been reported.¹ Male to male transmission of microcephaly, chorioretinal dysplasia, and mental retardation has also been described.^{2,3} Microcephaly with microphthalmia and retinal folds (MIM180060) has been reported as an apparently separate condition. However, microcephaly and microphthalmia were also present in the youngest child in the present family, but

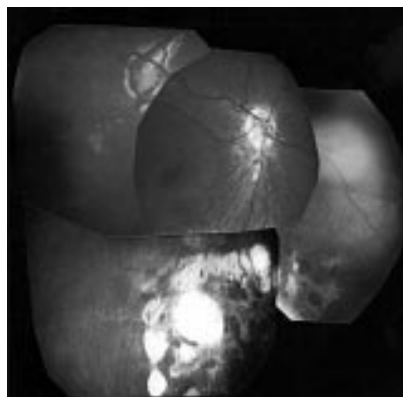


Figure 2 Patient 2, right eye. On funduscopy, chorioretinal dysplasia was evident in both eyes with the punched out lesions being localised in the periphery and midperiphery.

not in his father and brother, suggesting that both conditions might belong to the same spectrum of a single genetic disorder. Microcephaly and lymphoedema (MIM152950) was first described by Leung in 1985 in five individuals in a four generation family.⁴ There was no mental retardation. Congenital lymphoedema has also been described in three other isolated cases of microcephaly-chorioretinopathy.^{5,7} In the present family, the microcephaly and lymphoedema of the feet in patients 1 and 2 was associated with mental retardation as well as chorioretinopathy. This suggests that the three disorders previously distinguished could be the variable expression of a single genetic condition.

Ophthalmological findings reported in the autosomal dominant syndrome of microcephaly-chorioretinal dysplasia syndrome (MIM156590) include chorioretinal dysplasia, myopic astigmatism, and retinal dystrophy. Chorioretinal dysplasia represents the most common ocular abnormality seen in all patients of this report. Microphthalmia as seen in the proband has been reported before.^{5,8} Closed angle glaucoma secondary to a persistent primary hyperplastic vitreous (PHPV) has not been described. The spectrum of eye anomalies seen in the three patients of a single family clearly indicate the wide variety of eye anomalies that can be associated with a single genetic entity.

Feingold and Bartoszesky and Limwongse *et al* suggested before that the three entities might represent the variable expression of a single entity.^{7,7} The clinical variability in the expression of this syndrome is remarkable. The proband of the present family had a severe multiple malformation syndrome, with anomalies of the brain, heart, and eyes. The presence of marked lymphoedema of the feet suggested the diagnosis which was confirmed upon examination of his brother and father, who had milder manifestations with microcephaly and developmental delay. Interestingly, the eye anomalies had not been diagnosed in either of them, and in addition the pedal oedema had disappeared. This suggests that in all children with microcephaly, a careful eye examination is warranted.

Counselling in microcephaly is difficult, and in the absence of a specific aetiological diagnosis, an empirical recurrence risk of 15–20% is often cited.^{9,10} Chorioretinal dysplasia-microcephaly-mental retardation syndrome (CDMMS) with autosomal recessive inheritance was described by McKusick *et al*.¹⁰

In a sporadic patient with microcephaly, chorioretinal dysplasia, and mental retardation the clinical distinction between and autosomal dominant and recessive inheritance is not possible.⁸ However, the association with pedal lymphoedema could indicate probable autosomal dominant inheritance, since this has not been described in the autosomal recessive families.

Koen Devriendt is a senior clinical investigator of the Fund for Scientific Research-Flanders (Belgium) (FWO).

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Uveitis associated with OKT3 therapy for renal transplant rejection

EDITOR,—OKT3 (Ortho Biotech, Inc, Raritan, NJ, USA) is a murine monoclonal antibody to the CD3 receptor of human T lymphocytes, used in treatment of acute cellular graft rejection.¹ Adverse effects of OKT3 include flu-like symptoms, hypotension, pulmonary oedema, cardiac dysfunction, aseptic meningitis, and visual complications.² We describe uveitis following administration of OKT3.

CASE REPORT

A 51 year old man with polycystic renal disease underwent renal transplant from an unrelated donor. He was treated with antithymocyte globulin and steroid in the immediate postoperative period, and was discharged 7 days after surgery, with a nadir creatinine of 1.1, on cyclosporine 100 mg twice daily, prednisone 200 mg/day, amiodipine, nystatin, and famotidine.

Creatinine rose to 1.9 on postoperative day 30, and renal biopsy demonstrated lymphocytic interstitial infiltration, tubulitis, and endothelialitis. The patient was diagnosed

with BANFF 2B rejection, and given intravenous methylprednisolone 500 mg on the first day, tapered over 5 days to prednisone 30 mg/day. Creatinine level rose to 2.4 on day 35, and OKT3 (5 mg/day, intravenous) was begun.

On the fifth day of OKT3 therapy, the patient complained of right eye discomfort and redness. Over 2 days, the discomfort worsened and visual acuity fell, to 6/24— on the right and 6/9 on the left. Marked conjunctival injection, keratic precipitates, iris vessel congestion, white cells in the anterior chamber, hypopyon, and trace anterior vitreous cells were present in the right eye. Inflammation obscured fundus details, but abnormalities were not detected by B-mode ultrasonography. The left eye exhibited conjunctival injection without intraocular inflammation.

Anterior chamber paracentesis from the right eye revealed white blood cells and no organisms. Cultures of aqueous humour and conjunctival swab were negative. Topical prednisolone 1% every 2 hours and hyoscine (scopolamine) 0.25% twice daily were begun in the right eye, and OKT3 was discontinued. Three days later, acuity improved to 6/18, conjunctival injection decreased, and the hypopyon resolved. Prednisolone drops were tapered and, within 5 days, vision improved to 6/7.5 in both eyes, and ocular inflammation cleared. Over the next week, topical medications were tapered, then discontinued, without return of inflammation.

COMMENT

OKT3 is implicated as a cause of anterior uveitis in our patient because of onset of inflammation soon after initiating OKT3 therapy, accelerated resolution of inflammation following discontinuation of OKT3, and lack of identifiable infectious aetiologies. We did not further pursue a cause and effect relation through OKT3 rechallenge because renal status had improved. It is unclear whether OKT3 acted alone or in combination to induce uveitis. This type of synergistic drug interaction is reported for rifabutin induced uveitis, which may be potentiated by concurrent administration of fluconazole.³

Ocular side effects of OKT3 include optic neuritis, abducens nerve palsies, conjunctivitis, scleritis, and blindness presumed due to photoreceptor toxicity.^{4,6} Non-infectious uveitis in patients taking OKT3 is not reported or known to the manufacturer.

While efficacy of OKT3 against allograft rejection is based on suppression of CD3 T lymphocytes, OKT3 side effects may result from stimulation of separate immune pathways. For instance, aseptic meningitis and encephalitis may result from activation by OKT3 of non-CD3 T cells that then attack neural antigens.² OKT3 induces a cytokine release syndrome in which interleukin-6, tumour necrosis factor, and other mediators are released by lymphocytes⁵; these agents are also implicated in uveitis.⁷ Production of anti-OKT3 and other antibodies, and complement activation, also occur with OKT3 therapy, and may contribute to inflammation by immune complex formation with ocular or other antigens.² Although vitritis may develop during immune recovery in patients with AIDS and retinitis,⁸ it is unlikely that enhanced immune activity associated with acute rejection is relevant in our patient, since uveitis began only after additional immunosuppressive therapy was given. A direct toxic effect of OKT3 in ocular tissues has not been reported.

In conclusion, severe anterior uveitis occurred during treatment with OKT3, and resolved with OKT3 withdrawal and topical therapy.

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Maxillary sinus non-Hodgkin's lymphoma with orbital and intraocular involvement in the acquired immunodeficiency syndrome

EDITOR.—In spite of its rare occurrence there is a well established association between the acquired immune deficiency syndrome (AIDS) and lymphoma, which most of the time is a highly malignant B cell type affecting the central nervous system (CNS).¹

Rare cases of lymphomas involving paranasal sinus, orbit, and intraocular structures have been described. This report describes a case of primary lymphoma of the maxillary sinus with orbital and intraocular secondary involvement.

CASE REPORT

A 28 year old man with AIDS presented with right proptosis and recurrent sinusitis. His CD4+ count was 3 cells $\times 10^9/l$ and viral load 1 343 145 copies. Skull and orbital computed tomograph (CT) scans demonstrated right maxillary sinus opacification, mild right proptosis, and an anterior superotemporal mass in the right orbit. Cerebral image was unremarkable. The ocular examination disclosed right eye proptosis, ptosis, and a visible mass on the temporal area of superior right lid, restricting spontaneous lid opening (Fig 1). There was bilateral lid oedema but no mass could be found on the left side. Right eye movements were restricted. Pupillary reflexes were normal in both eyes, and visual acuity reached 6/12 right eye and 6/6 left eye. Fundus examination revealed a left choroidal lesion measuring approximately one disc diameter superior to the disc (Fig 2). Lid infiltration prevented right fundus examination, but a B-scan



Figure 1 Mass on the temporal area of superior right lid.

revealed a serous retinal detachment and an intraocular mass.

Since a lymphoma was highly suspected specific treatment was started, and 5 days after the first chemotherapy, a significant reduction in the size of the mass was noted. Examination of the right fundus disclosed a large temporal scar and surprisingly, the left choroidal lesion had completely disappeared.

One month after the last chemotherapy, a drastic recurrence of the right mass occurred, causing total ophthalmoplegia, paralytic mydriasis, and amaurosis. An elevated lesion was found on the bulbar conjunctiva from which a tissue specimen was easily obtained. Left visual acuity had also decreased to 6/60. At this moment, an extensive yellowish temporal choroidal lesion was found in the right fundus. Left fundus examination disclosed a serous retinal detachment involving the superior retina along the supratemporal arcade. CT scan showed that the right orbital mass expanded towards the apex, with cavernous sinus involvement. It also detected a left retro-orbital mass associated with a posterior scleral thickening, as well as multiple cerebral lesions. The patient's condition rapidly deteriorated and he died a few days later. Postmortem examination was not performed.

The specimen removed from the right bulbar conjunctiva revealed a large cell, poorly differentiated neoplasm. Neoplastic cells with plasmocytoid differentiation were found in a scattered distribution. Immunohistochemical studies were done using the indirect immunoperoxidase method with diaminobenzidine (DAB), and the antigen retrieval method using heat or protease. The following markers were used: CD3, CD20, CD30, Kappa, Lambda, Vimentin, Citoceratina pan, HMB45, Protrina S-100. The tumour cells showed nucleolar immunopositivity for anti-CD20 antibody.

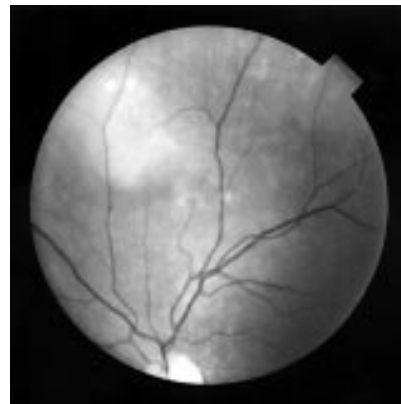


Figure 2 Left fundus showing choroidal lesion measuring approximately 1 disc diameter superior to the disc.

COMMENT

Classically, the AIDS associated lymphomas are of the B cell type and involve the CNS and the abdominal cavity, as opposed to the preferential ganglion involvement seen in immune competent patients.¹⁻³ Such cases usually develop at advanced disease stage. Primary maxillary sinus lymphoma is rare, as is secondary orbital involvement.⁴ Malignant paranasal sinus tumour secondarily involves the orbit in 45% of the cases, but lymphomas are uncommon.⁵ Primary and secondary orbital lymphomas are rare, and bilateral occurrence is very unlikely.⁶ Rare cases of intraocular primary lymphomas were also previously described.⁷⁻⁸ Our patient had bilateral involvement of the sinuses, orbit, and intraocular structures, which was confirmed by CT scan, and although we didn't obtain a specimen from the choroidal lesions for histological confirmation, the disappearance of the left lesion and the scarring on the right fundus just after treatment supports lymphoma as the diagnosis for the intraocular lesion. The immunohistochemistry was CD20 (L26) positive, and negative for all the other markers (CD3, CD30, Lambda, Kappa, S-100 protein, HMB45), confirming the B cell origin.

Non-Hodgkin's lymphoma in HIV infected patients tends to be of high grade malignancy, being very aggressive most of the times, with a mean survival of around 8 months.^{4,9} Our patient died after 3 months in spite of initial good response to chemotherapy.

Lymphoma treatment is still controversial. Radiotherapy has demonstrated good results for treatment of both systemic disease and in cases of orbital and intraocular involvement. On the other hand, chemotherapy has been good for systemic disease but has not been successfully used for intraocular disease.¹⁰ Interestingly, our patient had a significant improvement after chemotherapy, but that was shortly followed by an intense reactivation, which was probably due to the high grade of malignancy.

Isolated or associated paranasal sinus, orbital, and intraocular lymphomas are considered to be very rare tumours, and even though their incidence has decreased in the HAART era, clinicians should be aware of this potential manifestation of non-Hodgkin's lymphoma.

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Pythium insidiosum keratitis confirmed by DNA sequence analysis

EDITOR.—*Pythium insidiosum* is an unusual but serious ocular pathogen. Although the organism grows as a mycelium in tissue, it is not a member of the fungal kingdom and its identification can be a challenge for a routine laboratory. We report a case of *Pythium* keratitis in which the organism was confirmed by nucleic acid sequencing.

CASE REPORT

A 32 year old man was referred from Kuala Lumpur having suffered with intractable keratitis of the left eye for 4 weeks. He gave a history of diabetes, disposable contact lens wear, and swimming in the Kelang River. Routine microbiological investigations had been negative. At presentation to Flinders Medical Centre, he was on topical antibacterial, antifungal, and antiamebic medication. He had a large epithelial defect, a deep stromal infiltrate approaching the limbus, and hypopyon (Fig 1, top). His visual acuity was hand movements and there was considerable pain. The drops were stopped and corneal scrapings were

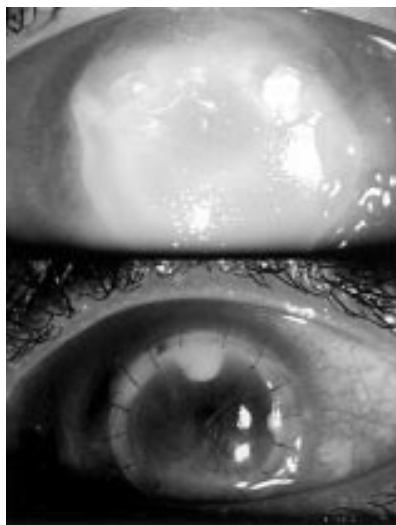


Figure 1 *Pythium insidiosum* keratitis. Top, the patient at presentation. Bottom, proliferative material in the anterior chamber after corneal transplantation.

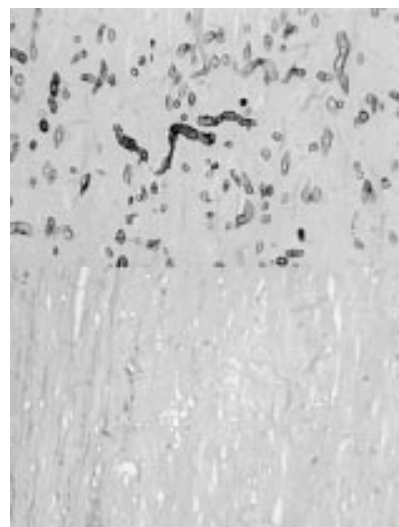


Figure 2 Histopathology of the excised cornea ($\times 625$). Top, silver stain. Bottom, PAS. The organisms have not stained with PAS; their presence is indicated by the spaces in the section.

taken. Gram and Giemsa stains were negative. A biopsy was performed the following day and hyphae were observed in sections. A filamentous organism appeared in cultures of the original scrapings. There was no response to continued antifungal treatment and a penetrating graft was performed 4 days after the biopsy. Postoperatively, the patient received oral itraconazole and topical natamycin. Prednisolone phosphate drops were introduced 10 days later. Twice in the first 3 weeks after surgery the patient returned to theatre for an anterior chamber washout of proliferative material invading from the peripheral cornea (Fig 1, bottom). Hyphae were seen in these specimens, but cultures were negative. The patient returned to Malaysia and, 7 months postoperatively, had a clear graft, useful vision in the eye, and no recurrence of infection.

The histopathology revealed a florid keratitis with necrotic stroma and degenerate neutrophils and monocytes. Massive numbers of hyphae were seen in silver-stained sections, particularly in the anterior stroma (Fig 2, top). Hyphae were also observed penetrating Descemet's membrane. The organisms were not stained by the periodic acid-Schiff (PAS) method, also commonly used in suspected fungal infection, giving these sections the appearance of Swiss cheese (Fig 2, bottom).

Colonies grew rapidly on the primary fungal medium (plain Sabouraud's agar, 28°C). They were white with a yellowish tinge, unusually flat, and difficult to cut and separate from the agar. Few septae and no spores were seen. The isolate was sent to a reference laboratory under suspicion of being a zygomycete. However, no further taxonomic clues were induced by standard measures so a molecular approach was employed. The methods have been described.¹ Initially, a 510 base segment of the 18S ribosomal RNA gene was amplified (universal primers NS1 and NS2)² and sequenced (Model 373A DNA sequencer, Applied Biosystems Inc). A search of databases (GenBank, EMBL) revealed homology to oomycetes. The isolate was then incubated for 48 hours in water containing autoclaved grass. Motile zoospores were observed, indicative of *P insidiosum*. Other characteristics consistent with this identification were colony morphology, optimal temperature of growth (35°C), hyphal diameter (4-6 mm),

intercalary swellings in viable hyphae, vesicles at the end of spore discharge tubes, and spores germinating by means of germ tubes.³

To confirm the identification, the internal transcribed spacer (ITS) region defined by primers TW81 and AB28 (incorporating ITS1, the 5.8S gene and ITS2) was amplified. The 900 base pair product was sequenced by a direct double stranded DNA cycle method using primers 1–6 as detailed¹ except for the substitution of primer 3 with 3c (5'-GCGACTTCGGTTAGGACATT). The sequences were checked between complementary strands and shown to be 99.0% homologous with *P. insidiosum* reference strain CBS777.84 using CLUSTAL V software⁴ (CA Lévesque, personal communication). In comparison, the sequence was ~95% homologous with other *Pythium* species and ~90% homologous with other genera of oomycetes (BLAST database, NIH, Bethesda, MD, USA).

COMMENT

P. insidiosum is an aquatic, filamentous organism that produces heterokont, biflagellate zoospores, placing it as an oomycete in the kingdom *Chromista*. The only other human pathogen in this kingdom is *Rhinosporidium seeberi*, the agent of rhinosporidiosis. Oomycetes have a diploid genome and a cell wall consisting of cellulosic compounds and glycan, features which distinguish them from the fungal groups of the kingdom *Fungi*. The identification of an oomycete in our patient can explain the PAS result and the lack of response to antifungals, there being no chitin or ergosterol in the cell wall, respectively. In addition to our genetic approach to confirming the identification, serological tests have been developed in Bangkok⁵ and at the Centers for Disease Control, Atlanta.

Oomycetes play an important part in the decomposition and recycling of decaying matter. Some species are parasitic on crops and

fish. In mammals, *P. insidiosum* causes a granulomatous disease ("swamp cancer") in several species including horses and dogs. A number of cases of human pythiosis have been reported, mostly subcutaneous infections and arteritis in thalassaemic patients in farming communities of South East Asia.⁶ With respect to the eye, *P. insidiosum* has been responsible for periorbital infections in Australia⁷ and the USA⁸ and corneal ulcers in Thailand,⁶ Haiti,⁹ and New Zealand.¹⁰ Some patients have had no other medical history. Contact lens wear, exposure to river water, and diabetes were possible predisposing factors in our patient.

No cases of *Pythium* keratitis have been cured medically. A boy with facial pythiosis was cured without surgery by a 1 year course of terbinafine and itraconazole.⁸ For the cornea, however, it would be difficult to imagine a successful outcome given the destructive nature of the organism, the slow response if any to most antimicrobial agents, the probable delay in identification, and the need to prevent further tissue invasion. Transplantation may be the best option.

The introduction of corticosteroids in the management of fungal keratitis and, presumably, *Pythium* infection, must be approached with great caution. We gave prednisolone in the hope of reducing inflammation in the grafted cornea without encouraging a recurrence of the disease. It was fortunate that, apparently, no infectious elements had been left in the eye.

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