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Severe invasive β haemolytic group A streptococcal cellulitis and eyelid necrosis treated with linezolid

Fewer than 50 cases of invasive group A streptococcal (iGAS) eyelid infections have been reported.[1] Predisposing factors include skin trauma or surgery[2–7] and immunosuppression.[3 4] iGAS preseptal cellulitis can be devastating; potentially leading to streptococcal gangrene of the eyelids,[1] which can be fatal with a mortality of 40% in the presence of bacteraemia, and an overall mortality of 18%.[1]

Case report

An 80 year old man with rheumatoid arthritis presented with rapidly spreading periorbital erythema involving both eyes within 12 hours, having started at the left pinna which was markedly swollen and discharging (fig 1).

Empirical treatment was begun for possible necrotising streptococcal infection with clindamycin 900 mg four times daily and imipenem 500 mg four times daily. Features suggestive of iGAS infection included the elevated creatine kinase (243 IU/l) and, in particular, marked blistering and a serosanguinous discharge rarely found in staphylococcal infections.

GAS sensitive to penicillin, clindamycin and linezolid was cultured from eye and ear swabs. Despite aggressive treatment, on day 3 he remained pyrexial, the C reactive proyein (CRP) peaking at 374 g/l.

However, within 24 hours of adding oral linezolid, 600 mg twice daily, the CRP fell to 208, with a dramatic improvement in the cellulitis. Examination of the right eye was impossible because of gross swelling, subcutaneous emphysema and thick scab. Very limited left eye examination was possible; visual acuity was 6/9. There was no relative afferent pupil defect.

Computed tomography imaging (fig 2) confirmed the clinical impression of preseptal infection.

By day 8, the cellulitis had largely resolved, exposing a tense right upper lid abscess yielding sterile pus on drainage. There was localised eyelid necrosis but debridement was unnecessary. By day 21, both eyes could close adequately despite upper lid skin defects (right larger than left, fig 3). On discharge at 3 weeks, the right upper lid had mild ectropion secondary to healing, and corrective lid surgery was deferred.

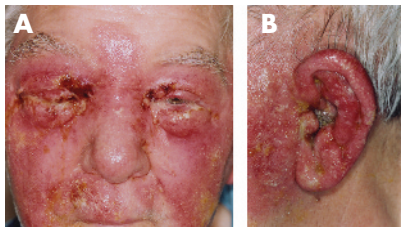

Figure 1 Preseptal cellulitis with pinna involvement.

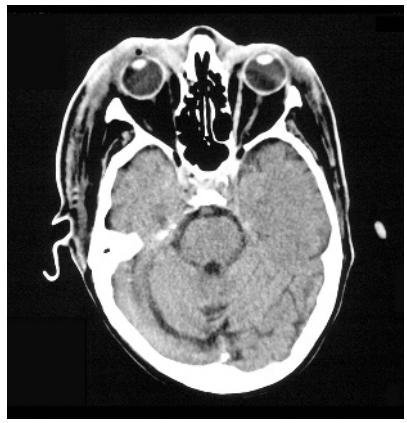

Figure 2 Computed tomography showing preseptal cellulites.

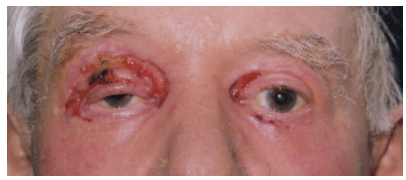

Figure 3 Upper lid skin defects after cellulitis resolution.

Comment

Our patient presented with a severe iGAS infection, his only risk factor was rheumatoid arthritis. Fortunately he did not develop orbital cellulitis where more serious surgical intervention has been necessary—for example, multiple drainage of abscesses or evisceration[8] and even exploration of the neck.[3]

Our case demonstrates how difficult iGAS can be to treat. Although the creatine kinase was raised, there were no other features of myositis or toxic shock syndrome.[6]

Penicillins are largely ineffective in severe iGAS infection because of the Eagle[9] effect; bacteria in the non-dividing or stationary phase being immune to cell wall active antibiotics.

Debridement being unnecessary once linezolid was added, there was no definitive histopathological evidence of necrotising fasciitis.

This is the first case of iGAS periorbital infection treated successfully with linezolid. A novel synthetic oxazolidinone antibiotic, linezolid is equally active orally and intravenously, and effective against Gram positive organisms, including streptococci and methicillin resistant *Staphylococcus aureus* (MRSA).[10] Both clindamycin and linezolid prevent toxin production by inhibiting bacterial protein synthesis initiation at the ribosome, but linezolid acts earlier in the process.

Clindamycin has been the drug of choice for severe iGAS infections. In our experience, the delayed response to high dose clindamycin was unusual. The addition of linezolid had a dramatic clinical effect, but we are uncertain whether linezolid's earlier mechanism of action explains why it appeared to be more effective than clindamycin in our patient. The suggestion[11] that using both agents together dramatically decreases toxin release could equally be borne out in this case.

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The patient has given full verbal and written consent for publication of the case and of the included photographs and scan image.

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Intraocular soluble IL-2 receptor alpha in a patient with adult T cell leukaemia with intraocular invasion

It has been reported that human T cell lymphotropic virus type I (HTLV-I) infection is related to a wide range of ocular disorders, such as intraocular lymphoma,[1 2] uveitis,[3] and cytomegalovirus (CNV) retinitis.[4] The diagnosis of adult T cell leukaemia (ATL) cell infiltration in the eye is often difficult, even when characteristic ocular findings are present and cytological examinations of intraocular fluids are performed. It is well

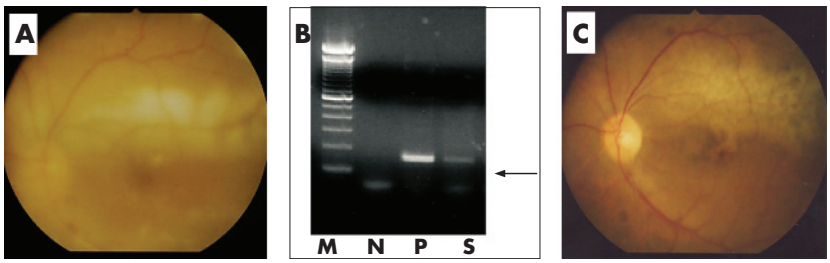

Figure 1 Fundus photographs and PCR results. (A) Fundus photograph showing retinal whitish lesions along retinal vessels and dense vitreous opacities. (B) Detection of proviral DNA of HTLV-I tax gene in vitreous of our ATL patient. M, molecular size marker, N, negative control, P, positive control (HTLV-I infected cells), S, vitreous sample of our ATL patient. (C) Fundus photograph after treatment with chemotherapy of anticancer medication and CHOP therapy. The cells are not present.

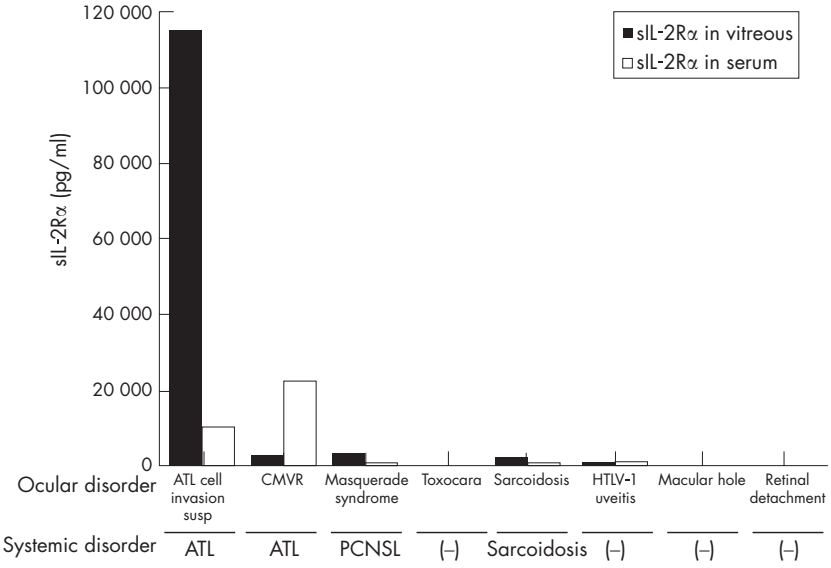

Figure 2 Soluble IL-2 receptor alpha (sIL-2Rα) concentrations in the vitreous and the serum of patients with various ocular diseases. CMVR, cytomegarovirus retinitis; ATL, adult T cell leukaemia/lymphoma; PCNSL, primary central nervous system lymphoma (malignant B cell lymphoma); Toxocara, toxocariasis; HTLV-I uveitis, HTLV-I associated uveitis; Macular hole, idiopathic macular hole.

known that determination of patient serum interleukin 2 receptor alpha (sIL-2Rα) levels is critical in the evaluation of the clinical status of the disease.[5] We report here a patient with systemic ATL who developed vitreous opacities and subretinal lesions and in whom vitreous measurement of the soluble form of sIL-2Rα provided information that could be used in making a diagnosis and in treating associated ocular disorders.

Case report

A 69 year old man with a 2 year history of systemic ATL developed a sudden onset of decreased vision and vitreous floaters in the left eye. Funduscopic examination of the left eye revealed dense vitreous opacities and whitish retinal exudates along with superior vascular arcade (fig 1A). Based on the ocular manifestations and the presence of systemic ATL, intraocular infiltration of ATL cells was suspected and a diagnostic pars plana vitrectomy was performed in the left eye. After informed consent was obtained, a vitreous sample from the patient was analysed using research protocol. The cytopathology of the vitreous sample was class III with many atypical lymphoid cells. The extra cell pellet of the sample was used for polymerase chain reaction (PCR). Proviral DNA for the HTLV-I tax gene was amplified using previously described PCR methods.[3] The proviral DNA was amplified by PCR (fig 1B). We also examined detection of CMV-DNA using quantitative PCR, because diffuse dot retinal haemorrhages like a CMV retinitis were seen in the left eye. The result of quantitative PCR was undetectable levels in the vitreous. Since the HTLV-I tax gene was detected in the vitreous sample, the vitreous fluid was assayed for sIL-2Rα levels using ELISA (R&D system, Minneapolis, MN, USA). Data for the vitreous samples of seven patients with various retinal disorders, who served as controls, can be seen in figure 2. In this patient, the concentrations of sIL-2Rα were extremely high (115 114 pg/ml) in the vitreous and considerably high in the serum. The concentrations of sIL-2Rα in the vitreous and the serum of another ATL patient with CMV retinitis, in a patient with intraocular B cell lymphoma, and in a patient with sarcoidosis or HTLV-I associated uveitis (HTLV-I carrier, no ATL) were also high, although the concentrations were much less than that observed in the vitreous of this case (fig 2). In addition, detectable levels of sIL-2Rα were not observed in patients with toxocariasis, idiopathic macular hole or non-PVR retinal detachment.

Our ATL patient had received conventional CHOP therapy before observation of the ocular symptoms. After identification of the ocular ATL infiltrates and documentation of sIL-2Rα, a cerebrospinal injection of anticancer medication containing a combination of methotrexate, cytarabine, and prednisolone was added to the CHOP therapy because the patient had central nervous system involvement. One month later, a dramatic improvement was noted in the patient with regard to the retinal exudates and haemorrhages (fig 1C).

Comment

In the current case, the sIL-2Rα level was much higher than the level observed in the serum or in the vitreous of patients with other retinal disorders. These data strongly suggest that the infiltrating T cell leukaemic cells constitutively express IL-2Rα on their surface, and secrete soluble forms of IL-2Rα into the vitreous. Also, the results of this case suggest that the measurement of sIL-2Rα in the vitreous could be a useful tool in the diagnosis of direct invasion of ATL in the eye, which is critical in the prognosis for the eye and for death.

HTLV-I infection is endemic in Japan, the Caribbean islands, and South America. Known ophthalmic manifestations of HTLV-I include malignant infiltrates in patients with ATL, neuro-ophthalmic disorders, and HTLV-I associated uveitis. Most of the published information on HTLV-I ocular manifestations comes from cases in south western Japan, which currently has the highest incidence of infection worldwide. Routine evaluation of HTLV-I infected patients is important because immune mediated or neoplastic ocular involvement may occur during the course of the disease. In different populations, genetic and environmental factors may also have a role in the ocular manifestations of HTLV-I.

Unlike ocular ATL infiltrates, HTLV-I associated uveitis is not a serious disorder, as this condition is responsive to corticosteroid therapy. However, since patients with ATL infected by HTLV-I are immunocompromised and subject to invasion of retinal lesions[1 2] and cytomegalovirus retinitis,[4] early diagnosis and treatment are very important. In the present ATL case, the early diagnosis helped to ensure that the patient was able to receive an appropriate course of therapy.

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Severe persistent nasolacrimal duct obstruction: a typical finding in ADULT syndrome

The acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome was first described in 1993 by Propping and Zerres.[1] The main manifestations of the syndrome are ectrodactyly, excessive freckling, onychodysplasia, lacrimal duct obstruction, hypodontia, and/or early loss of permanent teeth. Other clinical signs may include frontal alopecia, syndactyly, hypoplastic nipples and breasts, and typical neurodermitic signs such as exfoliative dermatitis of the fingers and toes. It belongs to the group of developmental disorders (EEC, ectrodactyly, ectodermal dysplasia; cleft palate syndrome; LMS, limb mammary syndrome; UMS, ulnar-mammary syndrome) that are based on mutations in the *TP63* gene.[2] Propping and Zerres[1] have traced symptoms of ADULT syndrome through five generations of one particular family. The expression of the described clinical signs is variable. A linkage study had mapped the gene to chromosomal region 3q27 where the gene of LMS had been located.[3 4] The responsible gene proved to be *TP63*.[5] Except for this particular family the ADULT syndrome has so far only been described in four single non-related cases.[6–9] We report on the clinical course of nasolacrimal duct obstruction in the youngest member of the above mentioned family (fig 1).

Case report

A 7 month old girl presented with severe discharge from both eyes and crusting of the eyelashes, which had been there since birth (fig 2). These symptoms are typical of congenital nasolacrimal duct obstruction. Probing of the nasolacrimal duct was only possible on the left side. Aplasia of the right nasolacrimal duct was assumed. Local therapy with antibiotics and xylometazoline hydrochloride was unsuccessful. Apart from the nasolacrimal duct obstruction ocular findings were within normal limits. None of the other symptoms of ADULT syndrome could be detected at that time; however, the child also suffered from severe otitis (fig 3).

At the age of 11 months, in a second attempt, both nasolacrimal ducts could be probed and silicone tubes were placed through the upper and lower punctum on both sides and passed all the way into the nose where they were secured by a knot. Microbiological examination of the nasolacrimal discharge revealed *Corynebacterium urealyticum* and *Haemophilus influenzae*. Local treatment with both drops and ointment was carried out according to microbiological recommendations based on the result of sensitivity testing of the organisms.

Within 3 months after nasolacrimal intubation with silicon tubes the situation had still not improved. The silicon tubes were then removed and the heavy discharge continued. Owing to the persistent and treatment resistant otitis a surgical shortening of the lower nasal conchae was scheduled in the ENT department, which might also improve the eye symptoms.

The affected father of the patient as well as several other affected members of the family, were reported to have also had chronic discharge due to nasolacrimal obstruction. The father had undergone multiple nasolacrimal duct operations and was wearing permanent silicon tubes.

Comment

Congenital nasolacrimal duct obstruction is found relatively often at birth, but in the majority of cases opens spontaneously in the first few months of life under local antibiotic therapy and digital massage of the lacrimal sac. If not, nasolacrimal duct probing with or without placing silastic tubing is done after the sixth month of life and will usually keep the nasolacrimal duct open. In patients with ADULT syndrome the nasolacrimal duct obstruction seems to be much more complicated than usual. Extremely severe discharge and tearing occurs, and even duct probing and tubing do not improve any of the symptoms.

Except for otitis with chronic discharge, our patient appeared to be completely healthy. Evidently, none of the other clinical manifestations of ADULT syndrome were apparent in our patient; however, some of them (hypodontia, early loss of permanent teeth, alopecia) could not be determined at that age. Although no case of persistent otitis was remembered throughout five generations of the family, two members of the last generation had otitis, which was as resistant to treatment as the nasolacrimal duct obstruction. It still has to be verified whether this could be an additional symptom of ADULT syndrome. Nasolacrimal duct obstruction was present in most of the affected members of the ADULT syndrome family and was resistant to therapy.

A large Dutch family with autosomal dominant limb mammary syndrome with at least 27 affected members has been described. These patients presented many of the signs of ADULT syndrome, such as ectrodactyly, hypoaplasia of mammary gland and nipple, nail dysplasia, and hypodontia as the main clinical features, with variable expression.[3] Lacrimal duct atresia was found in seven out of 15 patients with limb mammary syndrome. Mutations in the *TP63* gene lead to a group of disorders characterised by a spectrum of developmental defects.[10] It is likely that in all these syndromes nasolacrimal duct atresia is a common feature.

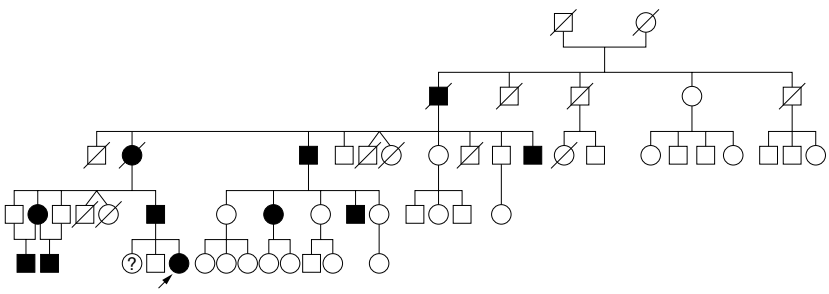

Figure 1 Pedigree of the family with ADULT syndrome. Solid symbols represent affected members. The index patient is indicated by an arrow (for further details see Propping and Zerres[1]).

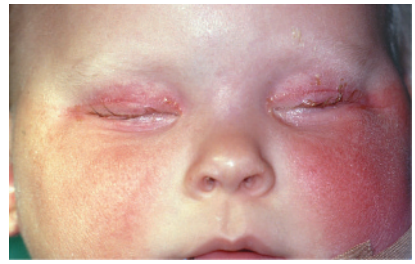

Figure 2 Severe discharge, left eye more than right eye, and crusting of the eyelashes.

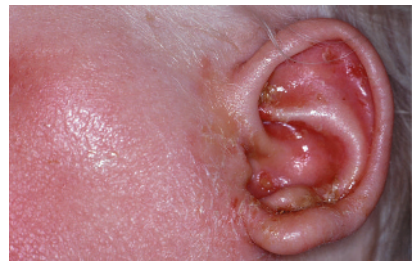

Figure 3 Left ear with severe discharge.

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