Post-transplantation swelling of the lower eyelid

Case

An 11-year-old boy with end-stage renal disease due to diarrhoea-associated haemolytic uraemic syndrome was seen by a paediatrician for swelling of the lower eyelid. He had a history of treatment with peritoneal dialysis for 11 months, followed by cadaveric kidney transplantation 4 months earlier. Immunosuppression consisted of cyclosporin A (blood trough levels: 120–200 ng/ml), mycophenolate mofetil (1.2 g/m²/day) and prednisolone (4 mg/m²/day). Prophylactic oral ganciclovir was given for 40 days post-transplantation in view of a high-risk status for CMV (CMV antibody-positive donor and -negative recipient). Two months earlier, a severe CMV disease with enterocolitis had been successfully treated with intravenous ganciclovir. At this time, EBV seroconversion was noted (EBV DNA, EBV-IgM-antibody positive).

On presentation, the child was afebrile and the swelling was indolent. The boy was initially diagnosed with conjunctivitis of the left eye, DD haematoma because of a possible trauma. However, he developed increasing swelling and livid discoloration of the left lower eyelid (maximum diameter: 3.5 cm) within the following 3 weeks (Figure 1), which was first treated with local steroid cream and later systemic antibiotic therapy for suspected bacterial blepharitis/orbital cellulitis. Since this therapy failed, a biopsy from the lower eyelid was performed.

Questions

What is the diagnosis?
What are the treatment options?
The differential diagnosis of inflammatory lesions of the eyelids includes blepharitis, hordeolum and chalazion, all usually caused by staphylococcal infection. In an immunosuppressed patient, however, other microorganisms (including *Pseudomonas aeruginosa*) and herpetic blepharitis may occur. In addition, periorbital and orbital cellulitis (e.g. due to local streptococcal, staphylococcal or *Haemophilus influenzae* infection) should be considered. Tumorous lesions of the eyelids include infections with *Molluscum contagiosum* and verruca viruses, dermal tumours (e.g. basal cell carcinoma, adenoma sebaceum or haemangioma) and tumours of the orbita (e.g. retinoblastoma or neuroblastoma) with involvement of the eyelid.

In the present case, progressive swelling of the eyelid and lack of a response to antibiotic therapy necessitated biopsy of the eyelid. The histological analysis demonstrated a clonal expansion of B and T cells with immunohistochemical proof of EBV with the diagnosis of an EBV-associated post-transplant lymphoproliferative disease (PTLD; differential diagnosis: highly malignant B cell lymphoma).

The performed bone marrow and CSF puncture showed no pathological findings. Serology for EBV demonstrated a slight increase in EBV-IgM and positive results for EBV-IgG, EBV DNA virus load and for EBV early antigen.

The ultrasound of the orbita showed an inhomogeneous non-encapsulated dense structure below the left lower eyelid with increased arterial perfusion. Magnetic resonance imaging of the head described a solitary tumour of the left lower eyelid (diameter: 3 cm) with enhanced surrounding, e.g. organized haematoma (Figure 2). There were no signs of infiltration. Ultrasound of the neck and the abdomen and chest X-ray were normal and showed no signs of mediastinal lymphoma.

Therapeutic immunosuppression was reduced, with a stepwise withdrawal of mycophenolate mofetil over 6 weeks and a decrease of daily prednisolone (3 mg/day). Additionally, the patient received intravenous foscarnet for 3 weeks, resulting in a decrease in EBV virus load.

A steroid pulse-therapy was required in week 3, because of a mild allograft rejection (Banff classification: type Ia), and a mild gastritis (*Helicobacter*-negative) was treated with amoxicillin, metronidazole and omeprazole. Our patient remained asymptomatic and was discharged from the hospital after 7 weeks, after complete disappearance of the facial swelling had been achieved (Figure 3).

Immunosuppression was continued with cyclosporin A and prednisolone. Until now, our patient has maintained a stable renal function (current serum creatinine: 0.9 mg/dl).

PTLD is defined as an abnormal lymphocyte proliferation in transplanted patients under immunosuppressive medication, usually associated with EBV infection. Resolution of EBV infection in immunocompetent patients is carried out by cytotoxic T cells by elimination of infected cells. In patients receiving powerful immunosuppressive agents, like cyclosporin or mycophenolate mofetil, T-cell function is impaired. This may lead to uncontrolled lymphoproliferation. Because of a high rate of EBV seronegativity in young children, there is a tendency for primary EBV infection and PTLD after transplantation. Furthermore, reactivation of a latent virus is also a possible mechanism.

The outcome of paediatric patients with PTLD is guarded. In the largest study so far (the North American Pediatric Renal Transplant Cooperative Study), counting 56 kidney recipients with PTLD, 48% patients died from their neoplasm or from infection and 66% lost their graft function [1].

The diagnosis of PTLD can be hampered by an uncommon extranodal localization. Involvement of the eye and orbita is rare; there are only eight PTLD cases in children documenting involvement of the eye [2–7].
In addition, there is no reported case of PTLD involvement of the eyelid as in our patient. Symptoms are unspecific and may mimic a common uveitis. Because of the rarity of a PTLD of the eye, exact diagnosis may be delayed.

Treatment options for PTLD are reduction or discontinuation of immunosuppression, antiviral therapy and/or chemotherapy; the latter is often not needed in children. Holmes and Sokol [8] suggest an algorithm for the management of EBV-associated PTLD with the combination of reduction of immunosuppression and antiviral therapy. After initiation, success of the therapy is monitored by a decrease of EBV DNA and remission of PTLD. If this is achieved, antiviral therapy is stopped and immunosuppression is resumed up to the full dose. Other therapeutic measures, e.g. chemotherapy, interferon and anti-CD20 antibody, are indicated when EBV DNA is increasing or PTLD is progressive.

Commonly used antiviral agents for EBV are acyclovir and ganciclovir, but there are no controlled trials on their effectiveness in EBV-associated PTLD. Biochemically, these drugs need conversion into the monophosphate form to utilize their biologically active triphosphate form. This conversion is dependent on viral thymidine kinase, which is not expressed by EBV-infected lymphocytes [9]. Foscarnet has the ability to bypass phosphorylation of monophosphates by viral thymidine kinase and to directly inhibit the DNA polymerase. Therefore, it is active in EBV-associated lymphoproliferations [10]. There is one published report of three cases using foscarnet in treatment of EBV-associated PTLD [11]. Our report is the first one documenting the use of foscarnet in a paediatric patient with EBV-associated PTLD after solid organ transplantation; however, the resolution of PTLD in our case cannot be attributed to a single agent.

In conclusion, PTLD may present in many forms, requiring a high level of suspicion by physicians treating patients with solid organ transplants. An uncommon localization can delay the diagnosis and the beginning of therapy. Reduction of immunosuppression in combination with foscarnet antiviral therapy may be a promising treatment strategy and, in selected patients, it may be sufficient to achieve complete remission of PTLD and uncompromised transplant function.

References


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