Chorioretinal post-transplant lymphoproliferative disorder induced by the Epstein-Barr virus

P F Demols, P M Cochaux, T Velu, L Caspers-Velu

Abstract
Background—The Epstein-Barr virus (EBV) is responsible for the lymphoproliferative disorders observed in transplanted patients.

Methods—The case history is described of a 59 year old man with a chorioretinal lesion who had received a single lung transplant and was on immunosuppressive treatment. Immunoglobulin gene rearrangement and EBV detection by polymerase chain reaction (PCR) with semiquantification were used on the vitreous material.

Results—A proliferation of B lymphocytes with a monoclonal subpopulation was found by PCR on the vitreous sample. The large amounts of EBV genomes found in the vitreous suggest that EBV was the cause of the lymphoproliferation. Healing of the lesion was achieved by a decrease in immunosuppressive treatment and the use of nucleotide analogues.

Conclusion—The diagnosis of ocular post-transplant lymphoproliferative disorder (PTLD) can be made by PCR on vitreous material. Early diagnosis and treatment can lead to regression of limited monoclonal lesions.

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The use of immunosuppressive agents following transplantation has already saved many lives, but the incidence of neoplasms has increased.1 Lymphomas which occur in allo-
graft recipients are mainly of B cell origin. Post-transplant lymphoproliferative disorders (PTLD) include a number of diseases ranging from infectious mononucleosis-like syndrome to malignant lymphoma.

We report a case of chorioretinal PTLD in whom large amounts of Epstein-Barr virus (EBV) DNA were detected by semiquantitative polymerase chain reaction (PCR) in the vitreous.

Case report
A 59 year old man received a single lung transplant for emphysema in December 1992 and was treated with immunosuppressive drugs (cyclosporin, azathioprine, and methylpred-
nisolone). He had already needed treatment for CMV lung infections, relapsing herpes zoster, and cytomegalovirus (CMV) retinitis or toxoplasmic retinochoroiditis and treatment with intravenous ganciclovir was continued. Two days later the dose of cy-

closporin was further reduced. After 2 weeks the chorioretinal lesion extended to the macular region with the appearance of a few haem-

orrhages.

The diagnosis was thought to be atypical CMV retinitis or toxoplasmic retinochoroiditis and treatment with intravenous ganciclovir was continued. Two days later the dose of cy-

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product with amplified dilutions of decreasing amounts of EBV control plasmid DNA mixed with DNA from uninfected cells. The plasmid pBA-W containing the Bam HI fragment from the B95-8 EBV genome was kindly provided by A Sergent (CNRS, Lyons, France).

Further molecular study with PCR revealed rearrangement of a clonal immunoglobulin gene at the heavy chain locus, showing that a monoclonal cell population had emerged among the EBV positive proliferating B lymphocytes.

Serological tests showed an increase in the EBV viral capsid antigen (VCA) antibodies (IgG 1/320 → 1/1280) between August and October 1994 which strongly supported the diagnosis of chorioretinal EBV induced monoclonal PTLD.

EBV genomes decreased in the vitreous fluid with intravitreous administration of ganciclovir and foscavir in association with intravenous ganciclovir, although the lesion continued to grow. This antiviral treatment was then replaced with intravenous aciclovir (1 g twice daily) for 3 weeks from 26 December 1994 followed by oral administration (800 mg three times daily) because of chronic renal failure. This led to clinical improvement of the lesion until total scarring was achieved in June 1995, 6 months after the start of treatment (Fig 1B-D). There has been no ocular recurrence to date.

Discussion

EBV induced lymphoproliferative disorders are observed in both iatrogenically and congenitally immunosuppressed patients. The discovery of significant amounts of EBV genomes in the immunodeficient tissues of patients with lymphoproliferative disorders suggests that EBV is the responsible agent.

The pathogenesis of PTLD is complex and multifactorial. It is caused by a breakdown in the balance between B cell stimulation and the anti-EBV immune response. B lymphocyte proliferation is induced by chronic antigenic stimulation from the allograft, by the presence of an oncogene in the genome of the EBV, and by the degree of immunosuppression.

When there is an imbalance, polyclonal B lymphocyte proliferation occurs that may develop into an oligoclonal or monoclonal lymphoma. Some clones are susceptible to genetic modifications—for example, oncogene or tumour suppressor gene alterations which result in the development of a true lymphoma.

The clonal state is not the only criterion for malignancy. In the case presented here, a monoclonal state occurred with no malignancy. The major risk factors for developing PTLD are the intensity, type, and duration of immunosuppressive therapy. Non-clonal PTLD and a subpopulation of clonal PTLD regress when the dose of immunosuppressive treatment is decreased, with or without aciclovir.

Clinical, morphological, immunological, and cytogenetic analysis enables the therapeutic response to be predicted. Patients with stage I PTLD (lymphoid hyperplasia) respond to treatment with aciclovir, often without a reduction in the dose of immunosuppressive treatment, thus avoiding any risk of graft rejection.

At the other extreme, stage III PTLD (true lymphoma) progresses in spite of a decrease in immunosuppressive treatment, with or without aciclovir. These lesions require standard antineoplastic treatment (chemotherapy, radiotherapy, surgery) and the discontinuation of immunosuppressive drugs if...
possible. Aciclovir has been shown to be ineffective when the tumour is monoclonal, probably because it consists of latent infected B cells which no longer depend on EBV replication to proliferate but have acquired a malignant autonomous growth potential. Nevertheless, an early clonal subpopulation (stage II PTLD) may respond to aciclovir treatment associated with a reduction in immunosuppression if the autonomous growth potential has not yet been reached.

Some cases of chorioretinitis with serologically determined acute EBV infection have been observed, but without solid evidence of their cause. A few cases of intraocular lymphoproliferation associated with AIDS have been reported, and EBV has recently been found by in situ hybridisation in a retinal biopsy specimen of an HIV positive patient with multifocal chorioretinitis. EBV has been suspected but its presence has not been confirmed in another four cases of intraocular lymphoproliferative disease following transplantation.

The case reported here is the first documented case of chorioretinal PTLD in whom a large number of EBV genome copies have been found in vitreous cells by PCR semi-quantification associated with monoclonal proliferation. This case also confirms that a monoclonal proliferation can regress with decreased immunosuppressive therapy associated with nucleotide analogues. It also shows that the diagnosis of intraocular EBV induced PTLD can be made from the vitreous alone using a PCR amplification technique which permits semiquantification of the virus.

Early detection and treatment are essential for the regression of limited monoclonal lesions. Identification of patients who are at high risk for this kind of complication might lead to a decrease in morbidity and mortality in this population.

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