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ORIGINAL INVESTIGATION

Epstein-Barr virus-associated pneumonia and bronchiolitis obliterans syndrome in a lung transplant recipient

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Abstract We report the case of a 25-year-old lung and liver transplant recipient who developed respiratory failure. High levels of Epstein-Barr virus (EBV) genome copies were detectable in respiratory tract specimens, while the search for various other viral, bacterial or fungal pathogens remained empty. Post-transplant lymphoproliferative disease was excluded. Due to the rapid progression of respiratory insufficiency, a re-transplantation of the lung was performed. EBV-encoded small RNAs could be demonstrated by in situ hybridization within pneumocytes and lymphocytes of the explanted lung tissue. The clinical situation improved soon after re-transplantation, and the EBV load detected in the lower respiratory tract decreased significantly.

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Introduction

Epstein-Barr virus (EBV) is a ubiquitous human lympho- and epitheliotropic gamma-1 herpesvirus [1]. Initially, EBV infects B lymphocytes and epithelial cells of the oropharynx [2]. This primary infection is usually asymptomatic with the exception of acute infectious mononucleosis in adolescents and young adults. Thereafter, EBV establishes a lifelong latent infection of B lymphocytes [3]. A prolonged excretion of EBV via saliva was observed in approximately 20% of healthy individuals and in 50–80% of immunocompromised patients [4, 5]. The virus is associated with several human malignancies including Burkitt's lymphoma and nasopharyngeal carcinoma. In immunocompromised patients, post-transplant lymphoproliferative disease (PTLD) and AIDS-related lymphomas are observed. Several studies further demonstrate that EBV is involved in the development of certain T-cell and Hodgkin's lymphomas [6, 7] and some malignant skin neoplasms in transplant recipients [8, 9].

The laboratory diagnosis of EBV infection is based widely on serological methods. However, in the state of immunosuppression, EBV serology might be less useful. The qualitative detection of viral DNA is not useful since EBV causes a latent infection in B lymphocytes. Therefore, measurement of EBV load has become an important tool for the prediction and monitoring of EBV-associated diseases, and a variety of quantitative assays have been published [10–16]. These protocols mainly refer to the

quantitation of EBV in peripheral blood mononuclear cells (PBMCs), whole blood, plasma, or serum [15]. The most desirable specimens for measuring EBV load differ among the EBV-associated diseases: While plasma or serum is recommended in patients with nasopharyngeal carcinoma, the usage of DNA preparations obtained from PBMCs and whole blood is strongly suggested in patients with PTLD [15].

EBV is frequently detected in respiratory specimens, but its pathogenic role in respiratory tract infections remains still unclear [17]. The present case report highlights the general clinical impact of EBV in patients under immunosuppression. Furthermore, the significance of this pathogen in the development of respiratory failure and its contribution to the development of a bronchiolitis obliterans syndrome (BOS) is discussed.

Case report

A 25-year-old male lung and liver transplant recipient was referred with the presumptive diagnosis of bronchiolitis obliterans for extracorporeal photopheresis. He had been transplanted 4 years ago for a treatment of congenital multiple arteriovenous fistula. For about 2 months, the patient suffered from a continuous aggravation of breathing. At the onset of these symptoms, various bacterial pathogens had been found in a bronchoalveolar lavage (BAL; Table 1). On examination, his forced expiratory volume in 1 s (FEV_1) was measured at 0.9 l (reference approx. 3.5–4.5 l). He had to use his auxiliary respiratory muscles and required 5 l oxygen per minute. Initially, results of bronchoscopy and computer tomography of the chest were interpreted as a chronic graft rejection (bronchiolitis obliterans grade IV). In consideration of the previous microbiological findings, a variety of specimens were taken at readmission to the hospital. In tracheal wash, respiratory swab or blood samples, there was no evidence for the presence of relevant bacteria, fungi and cytomegalovirus (CMV) antigen pp65.

Respiratory samples were also analyzed by multiple polymerase chain reaction (PCR) protocols to exclude further bacteria and viruses: *Chlamydia spp.*, influenza A and B virus, adenovirus, herpes simplex virus types 1 and 2, varicella-zoster virus, CMV and EBV. With the exception of the latter one, no pathogen could be demonstrated. While high copy numbers of EBV were evident in bronchial and tracheal secretions, only a few viral copies were detectable in whole blood preparations (Table 1). Since this constellation could originate from an EBV-associated lymphoproliferative disease restricted to the lung, a bone marrow aspirate was taken. The histological examination revealed no evidence for the presence of a lymphoproliferative disease. Furthermore, PTLD was largely excluded by a computer tomography of the chest. At that time, serological results of EBV immunoblot revealed a long-lasting loss of anti-EBNA-1 IgG combined with the presence of virus-specific IgA and IgM antibodies indicative for an endogenous reactivation of EBV (Table 1). Due to the rapid progression of dyspnoea, a re-transplantation of the lung was indicated. The macroscopic and microscopic examination of the explanted lung lobes revealed signs of a chronic obliterative bronchiolitis and bronchitis. An underlying PTLD was excluded. The application of in situ hybridization technique on lung tissue sections demonstrated the presence of isolated cells bearing EBV-encoded RNAs (EBER). These cells were identified to represent pneumocytes and interstitial lymphocytes (Fig. 1). In addition, DNA extracted from that tissue was tested positive for EBV by a PCR protocol following the recommendations of Stocher et al. [18] (data not shown).

After re-transplantation, only low copy numbers of EBV were detectable by quantitative PCR of follow-up respiratory samples obtained from the lower respiratory tract, while EBV was continuously present in saliva. Serological data revealed the presence of anti-EBNA-1 IgG and the absence of EBV-specific IgM (Table 1).

Approximately 20 days after re-transplantation, the patient developed pneumonia with an extended-spectrum beta-lactamase-producing *Klebsiella pneumonia* strain. Concomitant to this situation, EBV was detectable again in high copy numbers within respiratory fluid. The clinical symptoms reclined rapidly under the administration of meropenem accompanied by a significant decrease in EBV load. An acute graft rejection was treated by the administration of methylprednisolone and standard immunoglobulin. Furthermore, a plasmapheresis therapy was started due to the presence of anti-HLA-A1 and A36 antibodies. The patient recovered completely from re-transplantation and post-operative complications.

Discussion

The implication of EBV to infections of the lower respiratory tract is still unclear [17]. It was demonstrated that the lower respiratory tract might represent a major reservoir for EBV [19]. Furthermore, EBV genomes were detected frequently in broncheoalveolar lavages obtained from 100 immunocompromised and 94 immunocompetent patients [17]. However, several authors reported a diffuse severe pneumonia occurring as a rare complication of EBV primary infection in adults [20, 21]. By the application of in situ hybridization technique, Sriskandan et al. were able to demonstrate that this condition is associated with EBER-1-positive lymphoid cells located within the pulmonary

Table 1 EBV loads, results of EBV immunoblot and further findings

Time point	Viral load in copies/ml (specimen)	EBV IgG (against EBV-specific proteins)	EBV IgA (against EBV-specific proteins)	EBV IgM (against EBV-specific proteins)	Further pathogens (specimen)	Interpretation
3 months before onset of symptoms	Negative (serum)*	Positive (p18, p23, BZLF1, p138, p54)	Positive (p18, p23, BZLF1, p138, p54)	Weakly positive (p54)	–	EBV reactivation
At onset of symptoms	1.3×10^4 cop/ml (BAL)	n.d.	n.d.	n.d.	*Pseudomonas aeruginosa*, *Citrobacter freundii*, *Staphylococcus aureus.* (BAL)	Bacterial pneumonia and EBV reactivation
2 months after onset of symptoms (admission to hospital)	9.8×10^5 cop/ml (BAL) $7.2x10^6$ cop/ml (TF) 127 cop/ml (wb)	Positive (p18, p23, BZLF1, p138, p54)	Positive (p18, p23, BZLF1, p138, p54)	Weakly positive (p54)	–	EBV-associated pneumonia
4 days after re-transplantation	2.6×10^3 cop/ml (BAL)	n.d.	n.d.	n.d.	–	EBV-associated pneumonia, significant decrease in EBV load (BAL)
11 days after re-transplantation	650 cop/ml (BAL)	n.d.	n.d.	n.d.	–	EBV-associated pneumonia, significant decrease in EBV load (BAL)
3 weeks after re-transplantation	1.6×10^5 cop/ml (BAL)	Positive (p72, p18, p23, BZLF1, p138, p54)	Weakly positive (p18, p23)	Negative	*ESBL-producing Klebsiella pneumoniae* (BAL)	*Klebsiella pneumoniae* pneumonia associated with significant increase in EBV load (BAL)
1 month after re-transplantation	1.0×10^4 cop/ml (BAL)	n.d.	n.d.	n.d.	–	Significant decrease in EBV load (BAL)
3 months after re-transplantation	Negative (wb)	Positive (p72, p18, p23, BZLF1, p138, p54)	n.d.	Negative	–	Past EBV infection

Note the loss of anti-EBNA-1 IgG (p72) combined with the strong reactivity of IgA against viral capsid (p18, p23) and early antigens (p138, p54) as well as the weak reactivity of IgM against EBV early antigen (p54) before re-transplantation. Note the disappearance of EBV-specific IgM after re-transplantation combined with the drop of EBV load observed in follow-up BALs

BAL bronchoalveolar lavage; *TF* tracheal fluid; *wb* whole blood; *BZLF1* EBV immediate early protein; *n.d.* not done; * whole blood was not available

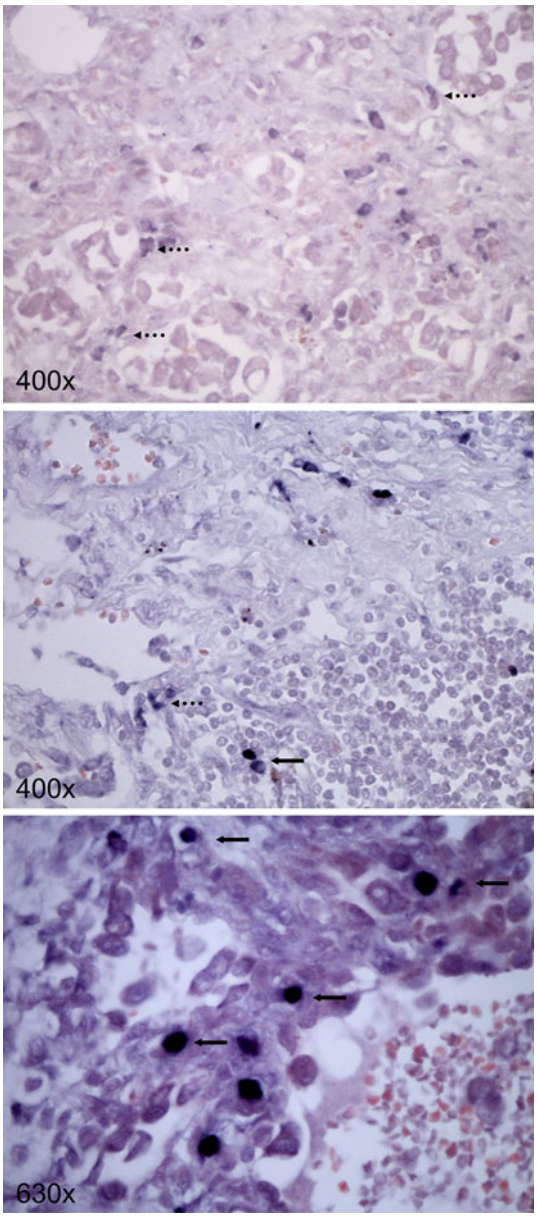

Fig. 1 In situ hybridization of lung tissue (magnification ×400, ×630) indicates EBV-encoded small RNA (EBER-1) in lymphocytes (*arrow*) and pneumocytes (*dotted arrow*)

interstitium [22]. In situ hybridization was further used to verify the contribution of EBV to lymphocytic interstitial pneumonia (LIP) observed in immunocompromised patients [23]. In addition, Egan et al. provided evidence for EBV replication within type II alveolar cells obtained from patients with cryptogenic fibrosing alveolitis [24].

By contrast, the role of EBV in the development of PTLD is largely accepted. PTLD represents a heterogenous group of lymphoproliferative disorders [25] and is associated to deficiencies in EBV-specific cellular immune response [26]. The incidence of PTLD in lung transplant recipients was given by several authors to range from 1.8 to 10% [27–29]. The risk to develop PTLD depends on EBV and CMV seromismatch as well as on the applied immunosuppression regime [30]. Measuring of EBV DNA in whole blood preparations has become an indispensable tool to prevent, diagnose and monitor PTLD [15]. However, its predictive value in solid organ transplantation recipients is controversial [15].

The case presented in this report suggested three major causes of the progressive respiratory failure: (1) an underlying PTLD, (2) transplant rejection and/or (3) a pneumonia that might be associated with EBV reactivation and might have triggered BOS.

1. PTLD was largely excluded by computer tomography as well as by the histological examination of a bone marrow aspirate. Furthermore, high copy numbers of EBV DNA were not detectable in whole blood preparations. Nevertheless, several authors reported PTLD with low or non-detectable EBV DNA in the peripheral blood [31, 32]. However, the most important evidence for absence of PTLD comes from the histopathological examination of the explanted lung as well as from in situ hybridization. While EBER-bearing B-cells are a typical finding in PTLD, EBER-positive pneumocytes can normally not be found. In addition, the clinical course after re-transplantation further argues against PTLD. Taken together, an underlying PTLD was excluded in our patient.
2. In general, it is difficult to exclude a chronic graft rejection which is a frequent cause of death beyond the first year of transplantation. The incidence of chronic lung rejection was estimated by several authors to approach 50% within 5 years of transplantation [33–35]. The unimpaired function of the concomitant liver transplant, the poor responses to high doses of corticosteroids and to extracorporeal photopheresis as well as the rapid progress of respiratory failure within a few weeks might be arguments against an acute or chronic graft rejection. However, the histopathological examination of explanted lung revealed some evidence for a chronic bronchiolitis that is indicative for a chronic graft rejection and organ dysfunction [36].
3. In the case presented in this report, an underlying EBV-associated pneumonia is a further explanation for the rapid progress of dyspnoea that might also be caused by progressive BOS. The most important finding indicating EBV-associated pneumonia was the detection of EBER-1-positive pneumocytes and interstitial lymphocytes by in situ hybridization. Previous studies have used in situ hybridization technique with an EBER-1 probe for the detection and quantitation of EBV-infected cells [15]. EBER-based in situ hybridization is considered as gold standard for proving any relation between histopathological lesions and EBV

[37]. The abundant production of EBV-encoded small RNAs is characteristic for latently infected lymphocytes, but EBER signals were also evident after induction of EBV replication [38].

The high EBV load of about 10^6 copies per ml in specimens obtained from the lower respiratory tract is also supporting the hypothesis of an EBV-associated pneumonia as etiology of respiratory failure. This especially refers to the fact that at this time no other pathogens were found in respiratory fluids, and EBV load was clearly reduced after re-transplantation. However, it cannot be generally ruled out that other rare microorganisms or noxa contributed to pneumonia. The transient increase in EBV load that occurred 3 weeks after re-transplantation is most likely associated with pneumonia caused by *Klebsiella pneumoniae*. In contrast, prolonged EBV DNA secretion within saliva is frequently observed in immunocompromised patients [5]. Thus, the high EBV DNA concentrations (about 10^7 copies/ml) detected in all available upper respiratory samples of our patient were not predictive for EBV disease. In addition, it is worthy to discuss that BAL and saliva do not represent a standardized clinical specimen.

Before re-transplantation, the EBV immunoblot demonstrated a loss of anti-EBNA-1 IgG combined with a strong IgG reactivity against both viral capsid (VCA) and early antigens (EA) of EBV. For virus-specific IgA, reactivity against VCA and EA was evident. These findings are indicative for an endogenous EBV reactivation although serological data on immunocompromised patients have to be judged cautiously. Soon after re-transplantation, anti-EBNA-1 IgG was detectable in several follow-up sera. The last was obtained almost 6 months after re-transplantation (data not shown). Thus, a blood transfusion–mediated appearance of anti-EBNA-1 IgG seems to be unlikely. It is hypothesized that EBV affection of the lung was related to imbalances of anti-EBV-specific immune response. This fact might also explain the rapid drop in EBV load observed in follow-up specimens of the lower respiratory tract, while viral load in saliva remained unaffected.

In conclusion, the diagnostic findings of the presented case argue for a contribution of EBV to respiratory failure and pneumonia that might have triggered BOS even though other causes cannot be ruled out completely. Thus, the presented case supports previous suggestions that EBV itself (like various other viruses) is associated with the development of BOS [39, 40]. These findings challenge our current concepts of BOS pathogenesis and therapy.

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