Eur Respir J 2000; 15: 803–806
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European Respiratory Journal
ISSN 0903-1936

CASE STUDY

Chronic interstitial lung disease due to Epstein-Barr virus infection in two infants

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Chronic interstitial lung disease due to Epstein-Barr virus infection in two infants. A. Pfleger, E. Eber, H. Popper, M.S. Zach. ©ERS Journals Ltd 2000.

ABSTRACT: This case study reports on two infants, 5 and 6 months of age, respectively, with chronic interstitial lung disease who presented with failure to thrive, tachypnoea, rales and mild hypoxaemia.

Epstein-Barr virus (EBV) was detected by *in situ* hybridization in lung biopsy specimens and by EBV-deoxyribonucleic acid-polymerase chain reaction (PCR) in bronchoalveolar lavage (BAL) fluid in one patient and by *in situ* hybridization and PCR analysis in BAL fluid in the second patient. There was serological evidence of immunoglobulin G antibodies to EBV capsid antigen by indirect immunofluorescence in both patients.

After 7 months of respiratory symptoms one patient was successfully treated with a 10 day course of intravenous ganciclovir followed by oral acyclovir for 20 days. The other patient became symptom free after 3.5 months of respiratory symptoms, without any specific antiviral medication. During a follow-up of 2 and 1.5 yrs, respectively, both infants remained symptom free and showed normal physical development.
Eur Respir J 2000; 15: 803–806.

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Keywords: Chronic interstitial lung disease, Epstein-Barr virus, infant, ganciclovir

Received: July 20 1999
Accepted after revision January 12 2000

The spectrum of paediatric interstitial lung disease (ILD) comprises a heterogeneous group of mostly rare disorders. Two recent studies have described four out of 48 children who had ILD as the result of an infection (adenovirus, Mycoplasma pneumoniae, influenza B virus), and one other male who had positive results on serological studies for Epstein-Barr virus (EBV) [1, 2].

EBV is often found in the lungs of children with lymphocytic interstitial pneumonia (LIP) and acquired immunodeficiency syndrome (AIDS); consequently, a synergistic role for the pathogenesis of this disorder has been suggested [3, 4]. Using monoclonal antibodies against viral antigen, EBV replication within type II alveolar cells was shown to occur in adult cryptogenic fibrosing alveolitis (CFA; idiopathic pulmonary fibrosis, IPF) [5]. As these cells may have a critical role in the deposition of type I collagen in the lung, a direct relationship between viral injury and CFA was suggested [5]. A different study, using immunohistochemistry (IHC), *in situ* hybridization and polymerase chain reaction (PCR) analysis on lung biopsy samples from patients with CFA did not support this hypothesis [6]. However, a recently published paper, investigating lung tissue for the presence of EBV by IHC and PCR analysis, obtained surgically from 27 patients with IPF and 28 control subjects, strongly suggests an association between EBV and IPF [7]. In general, EBV antigen staining needs to be interpreted with caution, as some antibodies are related to viral latency, whereas others are specific for productive replication [8]. To date, a possible role for EBV in the pathogenesis of chronic ILD has mainly been proposed in adult patients. The present study reports on two cases in early infancy that were associated with an EBV infection, thus extending this discussion into the paediatric age range.

Case reports

Case 1

Patient 1, the first male child of two healthy, not consanguineous Caucasian parents, was born at term after an uncomplicated pregnancy. He was breastfed and initially showed a good weight gain. At the age of 3 months he gradually developed loss of appetite, failure to thrive and tachypnoea. The patient was admitted to a primary care hospital with tachypnoea, intercostal and sternal retractions, crackles over both lungs, and a slightly elevated body temperature. He required supplemental oxygen for several days. The chest radiograph showed a patchy infiltrate in the left lung. White blood cell (WBC) count was $6{,}500 \cdot \mu L^{-1}$ with lymphocytosis ($3{,}600 \cdot \mu L^{-1}$), and immunoglobulin (Ig)M was 52 $mg \cdot dL^{-1}$ (normal range 20–40). Treatment with *i.v.* ampicillin and *p.o.* erythromycin was administered for 2 weeks; in addition, a 3 day course of systemic steroids was given. Serological tests for viral pathogens, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* were negative. After a further increase in symptoms, the patient was transferred to a secondary care paediatric department. At admission he presented with tachypnoea ($60 \cdot min^{-1}$), crackles over both lungs and arterial desaturation (88% arterial oxygen saturation (Sa,O_2) in air). The weight was below the 10th percentile, C-reactive protein was negative, erythrocyte sedimentation rate was 5 $mm \cdot h^{-1}$, WBC count showed a lymphocytosis of 69% ($3{,}700 \cdot \mu L^{-1}$), and the IgM level was elevated (85 $mg \cdot dL^{-1}$). Serum antibody determinations against *Listeria*, *Candida*, human immunodeficiency virus, *Aspergillus*, and *Bordetella pertussis* yielded negative results. A sputum culture grew *Klebsiella* spp. The chest radiograph showed bilateral interstitial pneumonic infiltrates with a maximum in the middle lobe. A computed tomography (CT) scan revealed

a ground glass pattern over both lungs. After *i.v.* antibiotic therapy (ceftazidim) and systemic steroids for 14 days the patient was no longer oxygen dependent, but still tachypnoeic ($50 \cdot min^{-1}$) with retractions.

At this stage the patient, now 7 months old and with respiratory symptoms for 12 weeks, was transferred to the author's tertiary care centre. Clinically there was no involvement of other organs. Laboratory findings on admission were: 4,600 leukocytes$\cdot \mu L^{-1}$ (3,360$\cdot \mu L^{-1}$ lymphocytes); glutamic oxaloacetic transaminase (GOT) 29 mg$\cdot dL^{-1}$ (upper limit of normal = 21), other serum parameters were in the normal range. The chest radiograph on admission did not differ substantially from previous ones, and high-resolution (HR) CT revealed a ground glass pattern over both lungs plus small atelectatic areas in both the upper and in the left lower lobe. Arterial blood gas analysis revealed a pH of 7.36, an oxygen tension in arterial blood (P_{a,O_2}) of 9.04 kPa (68 mmHg), an alveolar-arterial oxygen gradient (A_{a,DO_2}) of 3.99 kPa (30 mmHg), a carbon dioxide tension in arterial blood (P_{a,CO_2}) of 5.32 kPa (40 mmHg) and an S_{a,O_2} of 92% in air. Ig levels and IgG subclasses were normal except for an IgM with 112 mg$\cdot dL^{-1}$ (normal range 36–104). Flow cytometry showed low values for natural killer- and T-suppressor cell subsets. To rule out a metabolic interstitial lung disorder (lysinuric protein intolerance) quantitative amino and organic acid tests were performed and yielded negative results. Sweat test results were normal. Antibodies against adenovirus, cytomegalovirus (CMV), influenza virus A and B, parainfluenza virus 1–3, parvovirus B19, respiratory syncytial virus (RSV), rubella virus, varicella-zoster virus, *C. pneumoniae, Chlamydia psittaci, M. pneumoniae*, and *Coxiella burneti* were negative. However, Epstein-Barr virus capsid antigen (EBV–VCA) IgG antibodies were found to be positive (1:64).

Echocardiography revealed mild pulmonary hypertension. A barium swallow showed no signs of a tracheoesophageal fistula. Flexible bronchoscopy revealed an accessory segment in the left lower lobe; a fistula communicating with the gastrointestinal tract was excluded by injecting contrast material. Bronchoalveolar lavage (BAL) demonstrated a lymphocytic and macrophagocytic alveolitis ($1.06 \times 10^5 \cdot mL^{-1}$ total cells) by a differential cell count that showed 69% alveolar macrophages (AM), 1% neutrophils (Ne), 30% lymphocytes (Ly) with 1.6% B-cells, 15% T-helper and 85% T-suppressor cells (ratio 0.17, normal ratio 0.6) [9]. A search for adenovirus, influenza virus A and B, parainfluenza virus 1–3, RSV, *M. pneumoniae, C. pneumoniae, Mycobacterium tuberculosis, Legionella*, CMV and *Pneumocystis carinii* remained negative. However, a positive staining for EBV by *in situ* hybridization was seen in 10% of AM. Macroscopically, the airway mucosa did not look swollen or inflamed.

An open (nonthoracoscopic) lung biopsy was performed; the obtained middle lobe specimen showed lymphocytic infiltration, interstitial fibrosis with immature collagen deposits in a few areas, and intraalveolar accumulation of macrophages and giant cells (fig. 1). Some of these contained nuclear inclusion bodies, suggesting a viral infection. IHC and *in situ* hybridization for CMV, herpes simplex virus, and adenovirus remained negative. *In situ* hybridization was performed using a commercially available system (Genius, Boehringer Mannheim, Indianapolis, IN, USA) and showed a positive signal for EBV in 5% of macrophages, in a few type II pneumocytes and in some endothelial cells. The probe used was an antisense probe to internal repeat 1 region of the EBV genome, labelled with digoxigenin-11-uridine diphosphate (UDP). Details of the technique have been described previously [10].

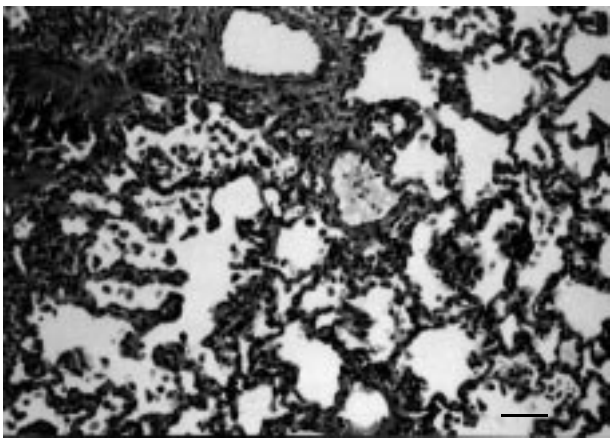

Fig. 1. – Open lung biopsy specimen from patient 1 showing a focal lymphocytic infiltration and and intraalveolar reaction of macrophages. Most interstitial lymphocytes are found around bronchioli and alveolar ducts. Haematoxylin and eosin staining. Internal scale bar=200 μm.

The patient only received supportive care and his respiratory status improved gradually. After clinical stabilization he was discharged home at age 8 months. There he did well for some weeks; then he developed symptoms of bronchopneumonia and again received antibiotic treatment (cefotaxim, netilmicin) in the local hospital. After discharge his respiratory symptoms waxed and waned. At an age of 10 months, 7 months after the beginning of his disease and 3 months after the initial exploration at the author's centre the patient was readmitted; he still presented with mild tachypnoea ($45 \cdot min^{-1}$) and an elevated A_{a,DO_2} of 4.12 kPa (31 mmHg); HRCT still demonstrated a ground glass pattern; BAL again revealed a lymphocytic alveolitis with polynuclear macrophages and multinucleated giant cells ($6.83 \times 10^4 \cdot mL^{-1}$ total cell count, 28% Ly, 70% AM, 1% Ne, 0.3% eosinophils (Eo)) and EBV-deoxyribonucleic acid (DNA) was detected in BAL-fluid. Detection of EBV-related small messenger ribonucleic acid (RNA) (EBER 1) and internal repeat region three of EBV genome were carried out as previously described [10, 11]. A lymphocyte transformation test with T- and B-cell mitogens showed a completely normal response to stimulation. An evaluation of EBV antibodies gave the following result: EBV-VCA IgG 1:64; EBV-VCA IgM, EBV-early antigen (EBV-EA), and EBV associated nuclear antigen antibodies (EBV-EBNA) were negative. The patient then received a 10 day course of *i.v.* ganciclovir (5 mg$\cdot$kg body weight^{-1} *b.i.d.*), followed by oral acyclovir for another 20 days (30 mg$\cdot$kg body weight^{-1} *t.i.d.*). There were no side effects of this treatment. At follow-up 5 weeks later the patient had gained weight and presented with a normalized oxygen saturation. A_{a,DO_2} was normal; BAL fluid analysis showed a mild lymphocytic alveolitis ($5.56 \times 10^4 \cdot mL^{-1}$ total cells, 22% Ly, 77% AM, <1% Ne) with negative *in situ* hybridization for EBV in macrophages, whereas PCR for EBV was found to be positive in some macrophages. HRCT demonstrated a markedly decreased ground glass pattern. Subsequent outpatient visits showed a healthy thriving infant without any further respiratory symptoms; he has now been followed-up for 2 yrs.

Case 2

Patient 2, the first male child of two healthy, not consanguineous Caucasian parents, was born at term after an uncomplicated pregnancy, and was breastfed. At the age of 6 months failure to thrive was observed and the parents as well as the patient′s paediatrician noticed episodes of tachypnoea. The infant then developed a febrile infection of 3 days duration and, after showing a typical rash, exanthema subitum was diagnosed. Subsequently, the child became more tachypnoeic and was referred to the author′s centre. On admission, the male presented with fine crackles over both lungs, a respiratory rate of $50 \cdot min^{-1}$, and mild arterial desaturation (S_{a,O_2} 89, 90% in air) without fur- ther clinical organ involvement. A chest radiograph showed peribronchial shadowing. HRCT revealed a diffuse ground glass pattern, that predominated in both upper lobes. A WBC count revealed transient neutropenia ($800 \cdot \mu L^{-1}$), and $4{,}850 \cdot \mu L^{-1}$ lymphocytes. Routine biochemical studies and a sweat test revealed normal results. The A_{a,DO_2} was found to be elevated (4.92 kPa; 37 mmHg), the pH was 7.38, the P_{a,O_2} 7.98 kPa (60 mmHg), the P_{a,CO_2} 5.45 kPa (41 mmHg). Cultures for respiratory viruses from nasopharyngeal secretion as well as serum titres for viruses, *M. pneumoniae* and *C. pneumoniae* were negative, as were results of serological tests for autoimmune diseases. A detailed immunological investigation, including serum Ig and IgG subclass levels, vaccination antibodies and isoagluttinine titres, assessment of activated component of complement (C)3, C4, and the 50% haemolyzing dose of complement (CH50), and a lymphocyte transformation test revealed completely normal results. Flexible bronchoscopy and BAL were performed and yielded the findings of a lymphocytic alveolitis ($1.1 \times 10^5 \cdot mL^{-1}$ total cells, 50% Ly, 48% AM, 1.5% Ne, 0.2% Eo, 0.2% basophils); AM showed intracytoplasmatic inclusion bodies. By *in situ* hybridization for different viruses, a positive reaction for EBV was obtained within AM. The clinical course of this patient′s respiratory disease remained mild; the patient only received supplemental oxygen and supportive care. After 14 weeks respiratory symptoms gradually disappeared.

In a follow-up HRCT scan a reduction of the ground glass pattern was observed. Five months after the initial hospitalization EBV-VCA IgG was 1:64, increasing after a further 5 months to 1:256. EBV-VCA IgM as well as EBV-EA and EBV-EBNA antibodies remained negative. BAL, performed 12 months after the acute disease, still showed a mild lymphocytic alveolitis (total cell count $9.07 \times 10^4 \cdot mL^{-1}$, 50% AM, 48% Ly, 1% Ne, 0.2% Eo). EBV-PCR was negative; however, a few AM still had positive EBV staining by *in situ* hybridization. The patient has remained symptom free and has shown a normal physical development in a 1.5 yrs follow-up.

Discussion

The authors observed two infants with chronic ILD of mild to moderate severity. The BAL and biopsy findings of EBV within AM strongly suggest that their respiratory disorder was caused by this viral infection.

It is well known that chronic ILD in children can be caused by viral infections. Furthermore, some forms of chronic ILD of unknown aetiology might have their origin in earlier, clinically unrecognized viral infections [1, 2]. A prospective study, performed to evaluate the diagnostic value of BAL in 29 immunocompetent children with chronic diffuse pulmonary infiltrates, identified two adenovirus and one CMV infection [12]. The present report is the first to suggest that EBV might have to be included in the list of viral pathogens with the potential to cause chronic ILD in children.

Usually virus-induced pneumonia shows dense lymphocytic infiltration and, depending on the type of virus, necrosis of pneumocytes and/or bronchiolar epithelium [13]. Other histological features are lymphocytic interstitial infiltration, follicular bronchiolitis and bronchus-associated lymphoid tissue hyperplasia [14]. In the current two patients the lymphocytic interstitial infiltration and the reactions of macrophages and pneumocytes that included giant cell formation were suggestive of a viral DNA integration.

One article has reported EBV-DNA found by Southern blotting in lung biopsy material from infants with LIP and AIDS [4]. The current two patients, however, were immunocompetent and not under immunosuppressive therapy. Cases of acute pneumonia in immunocompetent children have been linked causally to EBV on the basis of serological findings [15]. To the author′s knowledge, this report is the first to describe the use of a specific genomic probe for EBV (internal repeat region 1) by *in situ* hybridization and of EBER 1 and the internal repeat 3 (IR3) region of the EBV-genome specific amplification by PCR in BAL fluid (in two patients) and in lung biopsy specimens (in one patient) to diagnose EBV-induced chronic ILD in immunocompetent infants. EBERs are expressed during the latent phase of EBV infection [16]. As the respiratory tract is known to be a major reservoir for EBV, the question remains whether EBV is just a "passenger" or a pathogen, when localized in lung tissue [17]. However, atypical lymphocytes hybridized with a probe specific for internal repeat region 1 (BamHI W) of EBV indicate productive infection [18]. EBV infection in the first months of life is very uncommon [19]. Thus, it is highly likely that EBV had a causative role for the chronic ILD observed in these two infants. In the current two patients, EBV-VCA IgG was observed, but elevated EBV-EA and EBV-EBNA antibodies could also be expected. Such an incomplete serological response, however, is common in very young infants [19, 20]. Furthermore, a causative role of EBV is strongly suggested by the location of the viral antigen in lung cells and by the good clinical response of one patient to antiviral medication [21].

In a study of adults with CFA, EBV replication within type II alveolar cells was demonstrated by IHC in 14 out of 20 patients, compared with 2 out of 21 control subjects. There was no difference in EBV detection when comparing patients with, to those without, immunosuppressive therapy [5]. A later report, including 12 patients with IPF, two with IPF and associated systemic sclerosis, 10 with other pulmonary disorders and three healthy control subjects remained unable to confirm this finding; IHC showed inconsistent focal positive staining with anti-EBV antibodies, but there was neither evidence of EBV-RNA using *in situ* hybridization nor traces of EBV-DNA following gene amplification [6]. Although the latter paper included a smaller number of CFA patients and a smaller control group than the previous study, it could be expected that a low level background of EBV-DNA would be found in lung tissue, simply because of the blood volume in this organ [7]. Recently, EBV detection in lung

tissue from adult patients with IPF, using both IHC with antibodies specific for the productive cycle antigens (gp340/220 and VCA) and nested PCR analysis with oligonucleotide primers specific for EBV and sensitive to one copy of EBV-DNA, was reported. Eleven of the 27 patients (41%) with IPF and none of the 28 control subjects were positive with both techniques ($p<0.001$) [7]. In this study, by STEWART *et al*. [7] the DNA extraction procedure from lung tissue was optimized, a positive control PCR for a single copy human gene (P53) was included, ensuring that each extracted DNA sample was capable of being amplified. So the contradictory results might also reflect differences in the techniques applied. In general, it is important to know whether EBV exists in a latent or productively replicating form; the IHC antibodies used were specific for the replicative form, whereas PCR analysis detected both latent and productive EBV [7, 8].

IPF in infants is a disease with variable prognosis and response to treatment; mortality rate has been reported to range 30–90% [22, 23]. So far no association with EBV infection has been documented [2, 22, 23]. The chronic ILD observed in the current patients obviously did not progress into clearcut CFA. Patient 1, however, showed some fibrosing areas in the lung biopsy specimens, and the question remains whether these changes could have progressed into full blown CFA or not. After a prolonged disease course, both patients′ respiratory status returned to normal as evident by clinical, radiological and functional findings. Integration of EBV into B-lymphocytes might result in some risk for the development of lymphoproliferative disorders later in life. EBV-associated diffuse lymphoid proliferations have been observed to occur in the lungs of patients treated with immunosuppressive therapy after organ transplantation [24, 25]. Patients with various types of immunodeficiency are at increased risk for the development of potentially fatal EBV-related lymphoproliferative diseases, B lymphomas, and severe atypical EBV infections; most notably, this includes male children with the x-linked lymphoproliferative syndrome [26].

Although regarded as immunocompetent both infants will be followed-up carefully. In summary, the authors have documented two cases of chronic but ultimately benign interstitial lung disease in early infancy associated with an Epstein-Barr virus infection by detecting Epstein-Barr virus specific sequences within alveolar macrophages and epithelial cells of the lung.

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