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Fatal pulmonary complications in an immunodeficient child with chronic active Epstein-Barr virus infection

Śmiertelne powikłania płucne u dziecka z niedoborem odporności i przewlekłym aktywnym zakażeniem wirusem Epsteina-Barra

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Abstract

Primary Epstein-Barr virus infection in children typically presents as infectious mononucleosis and in immunocompetent individuals severe pneumonitis proves to be a rare complication. Chronic active Epstein-Barr virus infection (CAEBV) is associated with multiple life-threatening conditions, including interstitial lung disease with fibrosis and lymphoid and lymphohistiocytic infiltrations. We report on a pediatric patient in whom CAEBV resulted in severe pneumopathy with a fatal outcome.

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Key words: Epstein-Barr virus, pneumonia, children

Streszczenie

Pierwotne zakażenie wirusem Epsteina-Barra u dzieci manifestuje się najczęściej jako mononukleoza zakaźna i u osób immunokompetentnych zapalenie płuc o ciężkim przebiegu jest rzadkim powikłaniem. Przewlekłe aktywne zakażenie wirusem Epsteina -Barr (CAEBV) jest związane z licznymi zagrażającymi życiu powikłaniami, takimi jak śródmiąższowa choroba płuc z włóknieniem i nacieki limfohistiocytarne. W pracy przedstawiono przypadek dziecka z CAEBV i powikłaniami płucnymi o śmiertelnym przebiegu.

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Słowa kluczowe: wirus Epsteina-Barra, zapalenie płuc, dzieci

Epstein-Barr virus-associated clinical syndromes

Epstein-Barr virus (EBV) belongs to the *Herpesviridae* family (human herpesvirus 4, HHV-4) and its acquisition, like other herpesviruses, results in lifelong infection after the initial viral replication has been contained. In the vast majority of healthy individuals, the EBV infections are subclinical and cause no disease owing to the delicate balance between the host's immune system, limiting viral replication and the persistence and transmission of the virus. Inappropriate control of viral replication leads to chronic active EBV (CAEBV) infection, characterised by infectious

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mononucleosis (IM)-like symptoms, high anti-EBV antibody titres and detection of EBV genomes DNA in affected tissues, including peripheral blood. More severe and fatal clinical manifestations (SCAEBV) occur predominantly in children under the age of 15 years and are accompanied by a tendency toward pancytopenia as well as T- and NK-cell lymphoproliferative disorders and hemophagocytic lymphohistiocytosis [1].

In this paper we report on pediatric patient in whom CAEBV resulted in severe pulmonary complications with fatal outcome.

Fatal pulmonary complications in a child with CAEBV infection

A 15-year-old boy was referred to the pediatric pneumonology, allergology and clinical immunology department of the university hospital because of persistent fever and lower airway infection with increasing signs of respiratory and circulatory insufficiency.

He was the first child of middle-aged, nonconsanguineous parents, born from the second pregnancy in the 38th week of gestation; the perinatal period was uncomplicated. Since the second year of life he gradually presented with multiorgan autoimmune disorders – celiac disease, hypothyroidism, hypopituitarism and growth hormone deficiency as well as autoimmune hepatitis with positive antinuclear and smooth muscle antibodies (ANA and SMA, respectively). He required immunosuppressive treatment with systemic corticosteroids (prednisone, methylprednisolone) and azathioprine, along with substitution therapy with thyroxin and growth hormone. At the age of four years he underwent the surgical treatment of a non-neoplastic tumour of the right temporal lobe resulting in drug-resistant epilepsy. Since early infancy he had suffered from recurrent airway infections – pharyngitis, bronchitis and otitis media, which led to the formation of a cholesteatoma requiring surgical removal. Furthermore, at the age of ten, a cochlear implant was engrafted to the left ear because of deep sensory-neural hypoacusis.

Two years later, the boy developed a disseminated HSV (*herpes simplex virus*) infection with papular eruptions on the skin and mucous membranes. Simultaneously, an infection with *Epstein-Barr virus* was diagnosed based on positive anti-EBV antibodies (VCA IgM and IgG, EA IgG) and detection of EBV-DNA in peripheral blood mononuclear cells (3,727 × 10^4 copies/mL) and with *cytomegalovirus* (CMV) because of elevated anti-CMV IgM antibody titres and positive CMV-DNA in qualitative polymerase chain reaction (PCR) of peripheral blood and urine. Treatment with ganciclovir, followed by oral aciclovir led to clinical improvement as well as to negative PCR for CMV-DNA. Along with antiviral therapy, intravenous polyvalent immunoglobulin transfusions and antibiotic prophylaxis with amoxicillin, followed by azithromycin, were instituted because of the demonstrated IgG4 subclass deficiency. Major immunoglobulin isotypes, complement component levels as well as B- and T-cell subsets in peripheral blood flow cytometric immunophenotyping did not show any significant abnormalities. Until the age of 15 years the boy suffered from recurrent respiratory tract infections which were successfully treated in an outpatient setting.

On admission to hospital, the child presented with fever, dyspnea, tachypnea, candidal stomatitis and dental caries, symptoms of bronchial obstruction and disseminated bilateral fine rales on auscultation as well as hepatomegaly. In gasometry hypoxemia, desaturation and hypocapnia were found (pO_2: 52.3 mm Hg, sO_2: 82.0%, pCO_2: 30.4 mm Hg, respectively). Laboratory tests revealed pancytopenia (leukopenia — WBC 0.16 × $10^3/\mu$L, anemia — HGB 8.6 g/dL, RBC 3.02 × $10^6/\mu$L, thrombocytopenia 17.0 × $10^3/\mu$L), lymphopenia 0.002 × $10^3/\mu$L (12.5%) in peripheral blood smear, significantly elevated markers of inflammation (C-reactive protein 39.19 mg/dL, procalcitonin > 0.5 ng/mL, ferritin 158.2 ng/mL, d-dimer 1.84 mg/L) and a high EBV-DNA load in peripheral blood (9.11 × 10^4 copies/mL). In peripheral blood lymphocyte flow cytometric immunophenotyping, decreased absolute count and relative number of B, T CD4 and CD8 as well as NK cells were revealed. On a chest radiograph, disseminated bilateral patchy and stranded parenchymal and interstitial infiltrations with blurred borders of the heart shape and the diaphragm were present (Fig. 1). HRCT (high-resolution computed tomography) imaging showed massive confluent patchy opacities in both lungs, with irregular cavities indicating a decay of the lung parenchyma, accompanied by fibrosis and dilation of the peripheral portions of the bronchi and mediastinal lymphadenopathy (Fig. 2). Infections with *respiratory syncytial virus* (RSV) *A* and *B*, *rhinovirus A* and *B*, *adenovirus*, *metapneumovirus, influenza A* (including A H1N1) and *B viruses*, *parainfluenza 1, 2 and 3 viruses*, *coronavirus OC43* and *229E*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Le-*

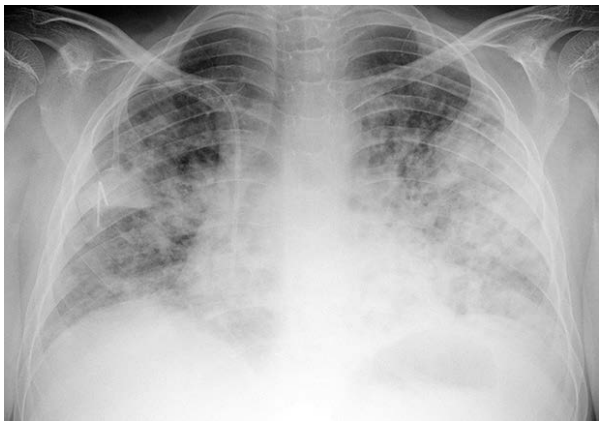

Figure 1. Chest radiograph showing disseminated bilateral patchy and stranded parenchymal and interstitial infiltrations with blurred borders of the heart shape and the diaphragm

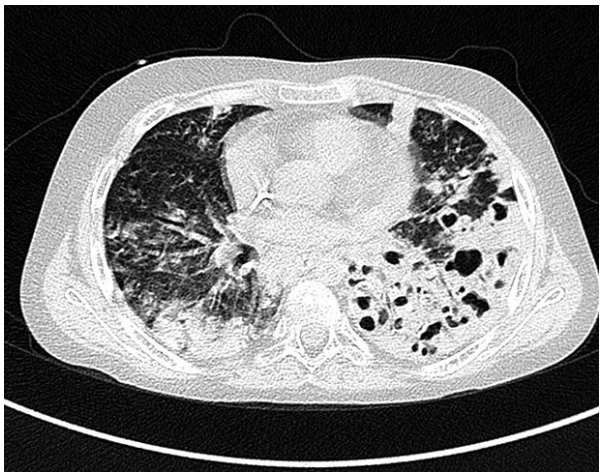

Figure 2. Transaxial HRCT imaging of the chest showing massive confluent patchy opacities in both lungs, with irregular cavities indicating collapse of the lung parenchyma, accompanied by fibrosis and dilation of the peripheral portions of the bronchi and mediastinal lymphadenopathy

gionella pneumophila and *Pneumocystis jiroveci* were excluded on negative PCR examinations of tracheal aspirate samples and infection with *human immunodeficiency virus* (HIV) was excluded on a negative ELISA test of peripheral blood. Sputum and blood cultures did not show any pathological bacterial flora. Despite intensive, multiple drug therapy with aciclovir, antibiotics (ciprofloxacin, vancomycin), trimethoprim/ /sulfamethoxazole, antifungal agent (fluconazole), immunoglobulins and systemic corticosteroids, deterioration of the child's state and development of the respiratory and circulatory insufficiency were observed. The patient died in the pediatric anesthesiology and intensive care unit because of multiorgan failure.

Discussion

Impaired immune control of the infection resulting from primary immune deficiencies may lead to significant EBV-related clinical pathology, including a life-threatening primary infection and EBV-associated lymphoproliferative disorders [2].

In healthy young children, the primary EBV infection is usually asymptomatic, and in 50% of adolescents it presents as an infectious mononucleosis (IM). Complications resulting from viral tissue invasion or from excessive immune-mediated damage are uncommon. These include upper airway obstruction, meningoencephalitis and other neurological complications, pancreatitis, pericarditis, myocarditis, pneumonitis and splenic rupture, as well as autoimmune phenomena such as hemolytic anemia and thrombocytopenia [3]. In immunocompromised children, such as those affected by the X-linked lymphoproliferative syndrome (XLPS), with mutations in the gene encoding the signalling lymphocyte activation molecule (SLAM-associated protein, SAP), a fulminating, fatal primary EBV infection may occur [4].

Chronic active EBV infection may result in life--threatening complications, such as accelerated hematological phase also referred to as hemophagocytic lymphohistiocytosis, hematological malignancies and hepatic failure [5]. EBV pneumonia is rare in immunocompetent subjects [6–8]. While mild, usually asymptomatic pneumonitis occurs in about 5-10% of all immunocompetent cases of infectious mononucleosis; severe pulmonary involvement predominantly in the form of interstitial pneumonitis has also been reported to date [9–11]. CAEBV infection has been associated with often life-threatening pulmonary complications most often in adult patients; however, severe fatal EBV-related prominent atypical lymphoid or lymphohistiocytic infiltrates have also been reported in an immunodeficient pediatric patient [12] as well as in immunocompetent young children [13]. Certainly, an immunosuppressive therapy with systemic corticosteroids and azathioprine may have had an important impact on the immune response, defective control of viral replication and development of CAEBV infection in the reported case. The boy presented with severe systemic inflammatory response evolving signs of hemophagocytic syndrome as well as unusually extensive parenchymal and interstitial pneumopathy with necrosis. Since bacteria such as *Streptococcus pneumoniae* or *Staphylococcus aureus* are the most frequent etiological factors of necrotic pneu-

monia in children, which may be characterised by a congenial clinical course and radiographic presentation [14, 15], infections with these pathogens must primarily be taken into account in the differential diagnosis despite negative cultures. Among other causative agents, such bacteria as *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter lwoffii* must also be considered in differential diagnostics [16]. In children with viral respiratory infections, in particular with recently emerged pandemic influenza A (H1N1), the interactive mechanisms between viruses and bacteria predispose to bacterial superinfections and development of necrotic pulmonary lesions [17]. In immunocompromised children, fungal infections with *Candida*, *Aspergillus fumigatus*, *Cryptococcus neoformans* as well as *Scedosporium prolificans* must be taken into account as causative agents of necrotic pneumonia [18].

In conclusion, CAEBV infection may result in pulmonary involvement with a fatal outcome; therefore, any suspicion of its presence should lead to immediate investigation in order to secure an early diagnosis and treatment.

Conflict of interest

The authors declare no conflict of interest.

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