VIA MEDICA

CASE REPORT

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Uncontrolled reactivation of EBV infection in a 26-year-old woman

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Oncology in Clinical Practice
2019, Vol. 15, No. 5: 269–274
DOI: 10.5603/OCP.2019.0030
Translation: dr n. med. Dariusz Stencel

ISSN 2450–1654

ABSTRACT

This report describes the case of a 26-year-old woman, who was admitted to oncological centre with symptoms of lymphoma, but final diagnosis indicated CAEBV virus infection. The patient had never been treated for chronic diseases before, and lymphoma was suspected due to: clinical symptoms (neck lymphadenopathy, febrile conditions), and imaging and endoscopic ultrasound examinations (CT, EUS). During the examinations in the oncological centre, lymphoma diagnosis was turned down and CAEBV infection was recognised. Despite the treatment applied in accordance with global standards, the patient developed multi-organ failure, which led to her death.

Key words: CAEBV, lymphoma, allo-HSCT

Oncol Clin Pract 2019; 15, 5: 269–274

Introduction

The Epstein-Barr virus (EBV) is a herpes virus that can cause acute and chronic infections; however, the first infection is usually asymptomatic. The virus primarily attacks B lymphocytes, in which it begins a latent (hidden) infection (in the form of an episome), lasting lifelong [1]. Reactivation can lead to monoclonal, uncontrolled proliferation. The virus also has oncogenic potential and is responsible for the endemic form of lymphoma in Equatorial Africa (Burkitt's lymphoma) and nasopharyngeal cancer. Humans are the only reservoir, and the source of infection is a sick or infected person. The infection occurs through contact with saliva, but it is also possible through blood transfusions, and transplantation of haematopoietic cells or solid organs [2, 3].

The incidence of uncontrolled reactivation is rare; only a few cases of the above syndrome are described in the literature.

Herein the case of a patient hospitalised in Department of *Cancer* and *Cardio-Oncology Diagnostics* of the Cancer Centre in Warsaw is presented.

Case report

On March 10, 2016 a 26-year-old woman was urgently admitted to our Department of *Cancer* and *Cardio-Oncology Diagnostics* and Palliative Medicine Clinic for diagnostics of lymphopoietic malignancy. From January 2016 the patient was diagnosed in various hospitals due to neck lymphadenopathy and febrile states. A computed tomography (CT) examination was performed in which a tumour-like lesion of the pancreas and retroperitoneal lymphadenopathy were described. The endoscopic ultrasound (EUS) evaluation revealed a lesion in the pancreatic body (suspected lymphoma infiltration, non-diagnostic result of previously performed biopsy). NK/T cell nasal type lymphoma was suspected in histopathological neck lymph node examination.

At admission the patient was in a good general condition (performance status ECOG 0). In the physical examination, attention was paid to a hard, painless infiltration within the right parotid and enlarged nuchal and neck lymph nodes.

Abnormalities in the laboratory tests included normocytic anaemia, leukopenia, elevated liver enzymes,

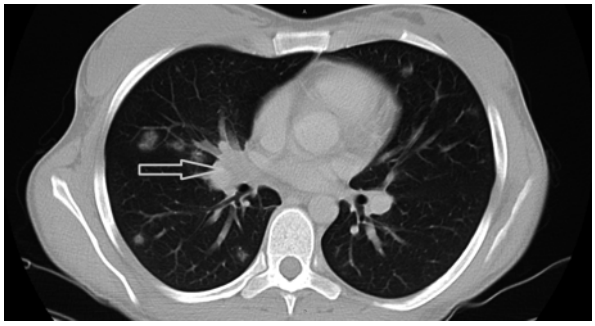

Figure 1. Computed tomography (CT) of the chest. Numerous focuses in the lung. Enlarged lymph nodes of the pulmonary hila

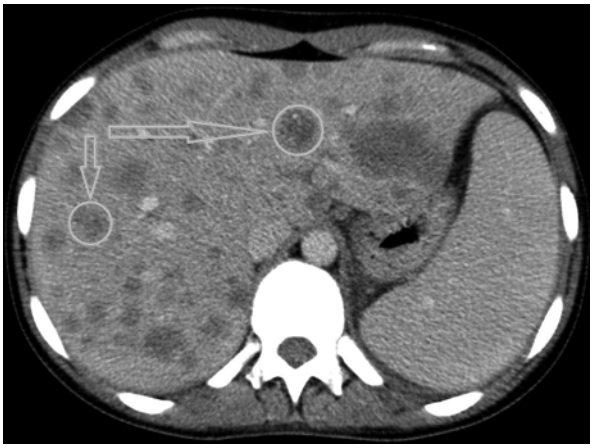

Figure 2. CT scan of the abdominal cavity. Enlargement of the liver and spleen. Numerous centres of reduced density in the whole liver

elevated D-dimer levels, and abnormalities in the coagulation system.

Computed tomography of the neck and chest (11/03/2016) showed heterogeneous nodal infiltration in the area of the right mandibular angle and branch, bilateral, numerous, poorly-separated mottled densities in lung parenchyma, nodal lesions in a right pulmonary hilum with suspected disintegration (Fig. 1), hepatosplenomegaly, numerous hypodense focal lesions in the liver, irregular hypodense area in the left kidney cortex — suspicion of infiltration, and, in addition, numerous lymph nodes of borderline size (Fig. 2, Fig. 3).

Due to the rare histopathological diagnosis and atypical course of the disease, the specimen from biopsy was consulted in Department of Pathology and the presence of neoplastic disease was not confirmed. *Lymphadenitis reactiva* associated with reactivation of EBV was diagnosed. The material provided was not eligible for testing to assess the presence of EBV RNA (EBV encoded RNA, EBER) by means of the FISH method.

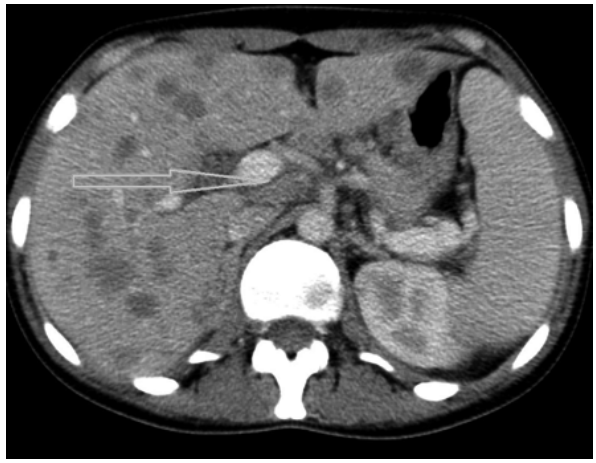

Figure 3. CT scan of the abdominal cavity. Enlarged lymph nodes of the liver hilum

Due to the suspicion of EBV infection, blood was collected for antibody testing. The serum level of beta-2-microglobulin was 9.04 mg/L (0.70–1.80) (Table 1).

On March 14, 2016, in order to perform flow cytometry, a fine-needle aspiration biopsy of the nodal lesion in the right parotid region was carried out under ultrasound (US) control. The result indicated an active EBV infection with associated lymphadenopathy. The predominance of CD4+/HLA DR+ lymphocytes over CD8+/HLA DR+ indicated no T-cell conversion, which may indicate the infection progression. In the trepanobiopsy, changes characteristic for bone marrow image in the course of EBV infection were found.

Histopathological examination of the material sampled during Tru-Cut biopsy from liver confirmed active hepatitis with extensive EBV-induced necrosis. Immunohistochemical reactions showed that EBV infected only large (blastic) T lymphocytes. The whole picture corresponded to a chronic, active EBV infection (CAEBV — chronic, active EBV) accompanied by a high titre of antibodies against EBV antigens, which corresponds to its active replication. The EBER result was positive in T-cell lymphoid cells.

Based on analysis of examinations performed, lymphoma was excluded (Table 2). CAEBV treatment was implemented in accordance with current guidelines together with the antibacterial and antifungal drugs (Table 3).

Laboratory tests showed stabilisation of morphological and biochemical parameters.

Continuation of the treatment resulted in the resolution of febrile conditions, reduction of infiltrative lesions within the right parotid, and a decrease in viraemia (15/03 — 21,150,115 copies/mL, 25/03 — 9,512,940 copies/mL).

On 26/03/2016 there was a sudden deterioration of the general condition of the patient with dyspnea,

Table 1. Differentiation of disease entities that may mask CAEBV

Feature	Lymphoma	CMV	EBV	Solid tumour in the generalised phase
Lymphadenopathy	+	+	+	Possible
Splenomegaly	+	+/–	+/–	–
Hepatomegaly	+	+/–	10–15% of patients	In the case of metastatic lesions
Febrile states	+	+	+	–
Weight loss	+	+/–	+/–	+/–
Pharyngitis and tonsillitis	–	+/–	+	–
Skin rash	Primary cutaneous lymphoma	–	5% of patients	Paraneoplastic syndrome
Changes in complete blood counts	+	+	+	With bone marrow infiltrations
Serological tests	–	Specific antibodies	Specific antibodies, EBV DNA/RNA	–
Increased inflammation parameters	+/–	+	+	–
Hepatitis	–	+	20–90% of patients	–
Changes in the bone marrow image (trepanobiopsy)	Characteristic for underlying disease	–	Characteristic image in CAEBV	With bone marrow infiltrations
Histopathological image of peripheral organ biopsy	Characteristic for underlying disease	Reactive	Reactive	Characteristic for underlying disease
LDH	Elevated	Could be elevated	Could be elevated	Normal
Flow cytometry	Characteristic for underlying disease	Not performed routinely	Not performed routinely, characteristic image in CAEBV	Not performed routinely, little usefulness
Imaging examinations	Organ infiltration changes	Not performed routinely	Organ infiltration changes in CAEBV	Solid tumour, metastatic lesions

CMV — cytomegalovirus; EBV — Epstein-Barr virus; LDH — lactate dehydrogenase

Table 2. Differentiation of CAEBV and lymphomas [3–5]

Feature	CAEBV	Lymphoma
General symptoms (febrile states, lymphadenopathy, hepatosplenomegaly, asthaenia, weight loss)	Present	Present
Abnormalities in complete blood counts	Non-specific lesions (in 98% of cases leukocytosis with a lymphocyte percentage > 50%, atypical lymphocytes in the history)	Depending on the type of lymphoma: increased leukocytosis (less frequently leukopaaenia), thrombocytopaenia, anaemia
Serological tests	Positive	Negative
Histopathological examination/flow cytometry	Characteristic for EBV infection	Characteristic for a given type of lymphoma
Indicators of inflammation	Elevated	+/–
Liver parameters	Hepatitis 20–90%	Elevated LDH level
Treatment	See the table 3	Immunochemotherapy depending on the type of lymphoma

EBV — Epstein-Barr virus; LDH — lactate dehydrogenase

Table 3. Treatment of EBV infection [3, 6, 7]

Treatment	Infectious mononucleosis	CAEBV
Symptomatic treatment	— Rest, avoiding injuries and effort, — Antipyretic drugs — Corticosteroids (for upper airway obstruction, anaemia, autoimmune thrombocytopaenia, rash with involvement of mucous membranes after penicillin)	— Ineffective
Causative treatment	— Not recommended — Ganciclovir or acyclovir for consideration in the lymphoproliferative syndrome — Immunological reconstruction with secondary immunodeficiency (reduction of doses of immunosuppressive drugs)	— Bone marrow transplantation as the most effective method — Antiviral drugs (ganciclovir, acyclovir, vidarabine) — Immunostimulatory drugs (IL-2, interferon alpha and gamma) — Immunosuppressants (corticosteroids, cyclosporine A, immunoglobulins) — Chemotherapy — Corticosteroids with etoposide (an inhibitor of topoisomerase II necessary for EBV replication)

EBV — Epstein-Barr virus; IL-2 — interleukin 2

jaundice, and features of haemorrhagic diathesis. In additional blood tests, pancytopenia occurred, bilirubin and transaminases level increased, and acute renal failure and electrolyte abnormalities were observed. The patient was transferred to the Intensive Care Unit (ICU), where further deterioration of the general condition was observed. Despite the intensive treatment implemented, no improvement was achieved and the patient died. In the autopsy multi-organ failure following CAEBV was indicated as the immediate cause of death.

Discussion

Chronic active EBV disease (CAEBV) is a lymphoproliferative disorder characterised by clearly elevated levels of anti-EBV or EBV DNA in the blood and EBV RNA or protein in the lymphocytes in the tissues. The disease was described for the first time by Virelizier et al. in 1978 [8].

The clinical picture of CAEBV mainly includes: fever, hepatomegaly, splenomegaly, lymphadenopathy, rash, hypersensitivity to mosquito bites, diarrhoea, urethritis, abnormal transaminase activity, thrombocytopaenia, and anaemia.

Rarer forms of CAEBV include: pancytopaenia, CNS involvement, intracranial calcifications, inflammation of the salivary glands, sinusitis, and oral mucosal ulcerations [9, 10].

Life-threatening complications in the course of the disease are: haemophagocytic syndrome, malignant lymphoma, disseminated intravascular coagulation (DIC), hepatic failure, gastrointestinal ulcer perforation, coronary artery aneurysms, myocarditis, interstitial pneumonia, and leukaemia [11].

CAEBV diagnostic criteria include:

— clinical manifestation (depends on which cell line is predominantly infected with EBV: T lymphocytes (worse prognosis) — fever, anaemia, lymphadenopathy, hepatomegaly, high titre of anti-EBV antibodies (Ab); NK lymphocytes (better prognosis) — mononuclear lymphocytosis, hypersensitivity to mosquito bites, high IgE titre);
— EBV viraemia;
— extremely high titre of IgG antibodies against capsid antigen (anti-VCA);
— absence of antibodies against nuclear antigens (anti-EBNA) [10].

The presence of EBV in CAEBV is also detected in CD4+ T cells, CD8+ T cells, and NK cells. CAEBV T-cell type is associated with an increased risk of coronary artery anomalies, and CAEBV NK cells type with hypersensitivity to insect bites and high titre of IgE antibodies [12].

The five-year survival in the CAEBV syndrome is 50–80% [13, 14].

The CAEBV treatment strategy consists of three steps:

1. stabilisation (immunochemotherapy);
2. cytoreduction (multi-drug chemotherapy);
3. reconstruction (allogenic haematopoietic stem cell transplantation — HSCT).

In the first stage, the treatment assumes the use of prednisolone 0.5–2 mg/kg/day 7 days a week, cyclosporine A 3 mg/kg × 2/day 7 days a week and etoposide 150 mg/m^2/day 1 day a week.

In the second stage, in cases presented in the literature, CHOP (vincristine 1.5 mg/m^2, maximum 2 mg day 1, cyclophosphamide 750 mg/m^2 day 1, pirarubicin 25 mg/m^2 day 1 and 2, prednisolone 50 mg/m^2 day 1–5) or ESCAP (etoposide 250 mg/m^2 day 1, cytosine ara-

Table 4. PTLD-EBV management [17, 18]

Procedure	EBV-DNA-aemia/pre-emptive therapy	PTLD-EBV
Rituximab	+	+
Reduction of immunosuppression	+	+
EBV-CTL	+	+
DLI	+	+
Chemotherapy	–	+
Antiviral drugs	–	–

EBV-CTL — human cytotoxic T lymphocytes against EBV-infected cells; DLI — donor lymphocytes infusion

binoside 1.5 g/m^2 2 times on days 1–5, L-asparaginase 6000 U/m^2/day on days 5–9, methylprednisolone 62.5 mg/m^2 2 times daily on days 1–5, prednisolone 30 mg/m^2 on days 6–9) were used [6].

The treatment of choice in these patients is bone marrow transplantation. Patients are at high risk of complications related to transplantation due to multi-organ failure that accompanies infection. In Japanese works, dozens of cases of such successful treatment have been presented.

The benefits of antiviral drugs (acyclovir, ganciclovir), vidarabine, interferon alpha, or interleukin 2 have not been demonstrated so far, although they may be useful in some cases of CAEBV [15]. Etoposide, corticosteroids, and cyclosporin A are reserved for patients with advanced EBV syndrome, but no clear benefits have been demonstrated. They can also be used to reduce the clinical symptoms associated with CAEBV [7].

Autologous LAK cells (interleukin-2-activated lymphocytes), EBV-specific cytotoxic T lymphocytes, and lymphocytes from identical HLA sublines are successfully used in the treatment of solid organ transplant recipients in whom EBV-dependent posttransplant lymphoproliferative disorders (EBV-PTLD) are a constant problem due to the continuous increase in the number of transplantations performed. The incidence of EBV-PLTD after allo-HSCT is 3.2% [16]. PLTD are heterologous lymphoproliferative disorders that develop after transplantation of haematopoietic cells or solid organs as a result of T-lymphocyte suppression. The diagnosis requires the presence of two of the three following factors:

1. biopsy and histological evaluation or flow cytometry for the presence of CD 19+ and CD 20+ antigens;
2. monoclonal or oligoclonal cell populations with virus markers;
3. presence of EBV in cells (DNA, RNA, or EBV protein).

The management strategy in these patients includes the following points:

1. prophylaxis of EBV-DNA-aemia reactivation in a seropositive patient with no symptoms of infection and without EBV-DNA-aemia;
2. therapy preceding the onset of EBV disease in individuals with present EBV-DNA-aemia disease without disease symptoms;
3. treatment of confirmed or probable EBV disease [17, 18] (Table 4).

In patients after haematopoietic stem cell transplantation, EBV therapy strategies include B-cell mass reductions, anti-CD20+ monoclonal antibodies (rituximab), and T-cell immunotherapy (donor lymphocyte infusion — DLI and cytotoxic T-EBV-CTL lymphocytes) [19].

It should be emphasised that antiviral therapy has no effect on the reduction of EBV-infected lymphocyte B cells and is of no clinical significance in the treatment of overt PTLD-EBV.

Conclusions

Chronic active EBV disease (CAEBV) is a rare systemic disease with a poor prognosis, with a mortality of app. 40%. It mainly affects Asian regions, causing the proliferation of T or NK cells in immunocompetent individuals. Due to the wide spectrum of symptoms, establishing the final diagnosis can be very difficult [20].

Acknowledgments

We would like to thank Dr. Jakub Pałucki for preparing the radiological images.

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