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CASE REPORT

Chronic active Epstein-Barr virus infection in an adult with no detectable immune deficiency

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ABSTRACT

Introduction: Epstein-Barr virus (EBV) establishes lifelong latent infection. In some patients the host-virus balance is disturbed, resulting in a chronic active EBV infection. The following case illustrates the difficulty in diagnosing and treating chronic EBV infection.

Case: A 30-year-old woman was referred because of recurrent swellings of lymphatic tissue of both eyelids, orbit and lymph nodes and general malaise since the age of 19. In the past, repeated biopsies showed MALT lymphoma and nonspecific lymphoid infiltrations. Now, a biopsy of an axillary lymph node showed paracortical hyperplasia with a polymorphous polyclonal lymphoid proliferation, and large numbers of EBV-encoded small RNA (EBER) positive cells, consistent with EBV infection. Laboratory investigation showed a high EBV viral load. No evidence of immunodeficiency was found. Chronic active EBV infection (CAEBV) was diagnosed. Treatment with high-dose acyclovir did not significantly reduce the viral load. Rituximab was given in an attempt to reduce the amount of EBV-infected B lymphocytes. However, soon after the second dose the patient died of a subarachnoidal haemorrhage.

Conclusion: This case report illustrates CAEBV as a rare manifestation of EBV-induced disease, which will be detected more frequently with the use of EBV-EBER hybridisation of lymph nodes and polymerase chain reaction (PCR) for EBV DNA. The prognosis is poor with no established therapeutic strategies.

INTRODUCTION

Almost every adult (90 to 95%) will have acquired Epstein-Barr virus (EBV) and will be seropositive for this herpes virus. The majority of primary infections pass unrecognised, but roughly 10% of EBV infections present as acute infectious mononucleosis, particularly in adolescence and adulthood.[1] The oropharynx is thought to be the primary site of entry, where the virus binds to epithelial cells which are generally believed to be permissive for viral replication.[2,3] The latter has recently been disputed and it might well be that B lymphocytes in the oropharynx instead of epithelial cells are the primary reservoir for replication as well as viral latency.[4-6] EBV survives by maintaining a delicate balance with the host resulting in a latent infection,[7] restricted to B lymphocytes. Sometimes, also T lymphocytes, epithelial cells and myocytes can be infected, usually with expression of a restricted set of latent gene products.[8] Spread to new hosts is ensured by intermittent reactivation and productive replication at epithelial surfaces.[9]

Several patterns of latency have been recognised in which up to ten viral genes are expressed and are thought to be involved in establishing and maintaining the immortalised state of the infected cell. Six nuclear proteins belong to this group, of which EBNA-1 (Epstein-Barr virus nuclear antigen-1) is essential for episome replication and maintenance of the viral genome[10] and EBNA-2 (Epstein-Barr virus nuclear antigen-2) for the process of B-lymphocyte immortalisation.[11-13]
Three membrane proteins belong to the latency state,

latent membrane protein-1 (LMP-1), LMP-2A (latent membrane protein-2A) and LMP-2B (latent membrane protein-2B). LMP-1 protects EBV-infected B cells from programmed cell death (apoptosis).[14,15] LMP-2A and LMP-2B are integral membrane proteins which co-localise with LMP-1 in the plasma membrane of EBV-infected lymphocytes,[16] EBV-encoded small RNAs (EBERs) are most abundantly present in latently infected B cells.[17]
Productive EBV replication results in expression of early antigens (EA), which are part of the replication machinery, and viral capsid antigens (VCA),[18] which are structural constituents of the virion itself. The first antibodies produced during primary EBV infection, such as infectious mononucleosis, are IgM and IgG antibodies against VCA and EA, which can be detected together with the appearance of circulating atypical lymphocytes and heterophile antibodies.[18-20] Increase of pre-existing IgG antibody titres against VCA and EA indicate reactivation of EBV infection.[18] Antibodies against EBNA are usually produced somewhat later in time, e.g. during convalescence, but many exceptions exist where EBNA antibodies are found together with those against EA and VCA. *Figure 1* shows the expression of different viral antigens and antibodies during primary EBV infection, during latency and during chronic active EBV infection (*figure 1*).
Because EBV is a persisting virus, it must have strategies to elude the immune system. EBV-specific cytotoxic T lymphocytes (CTL) are thought to constitute the most important defence against EBV infection.[9,21] However, the latency-associated protein EBNA-1[11] has evolved into a protein that escapes antigen processing (proteasome degradation, an essential step to form peptides, which can be presented in the context of HLA molecules to the immune system) and thus recognition by CTL, thereby promoting EBV latency, while immune surveillance by CTL can still abort viral proliferation.[1,9]
The EBV BCRF1 protein shares 70% of its amino acid sequence with interleukin-10[22] and can mimic the activity of IL-10 by inhibiting the interferon-γ synthesis by human peripheral blood mononuclear cells *in vitro*.[23] The EBV BARF1 protein can inhibit the expression of interferon-α by monocytes.[24] Interferon-γ and interferon-α inhibit the

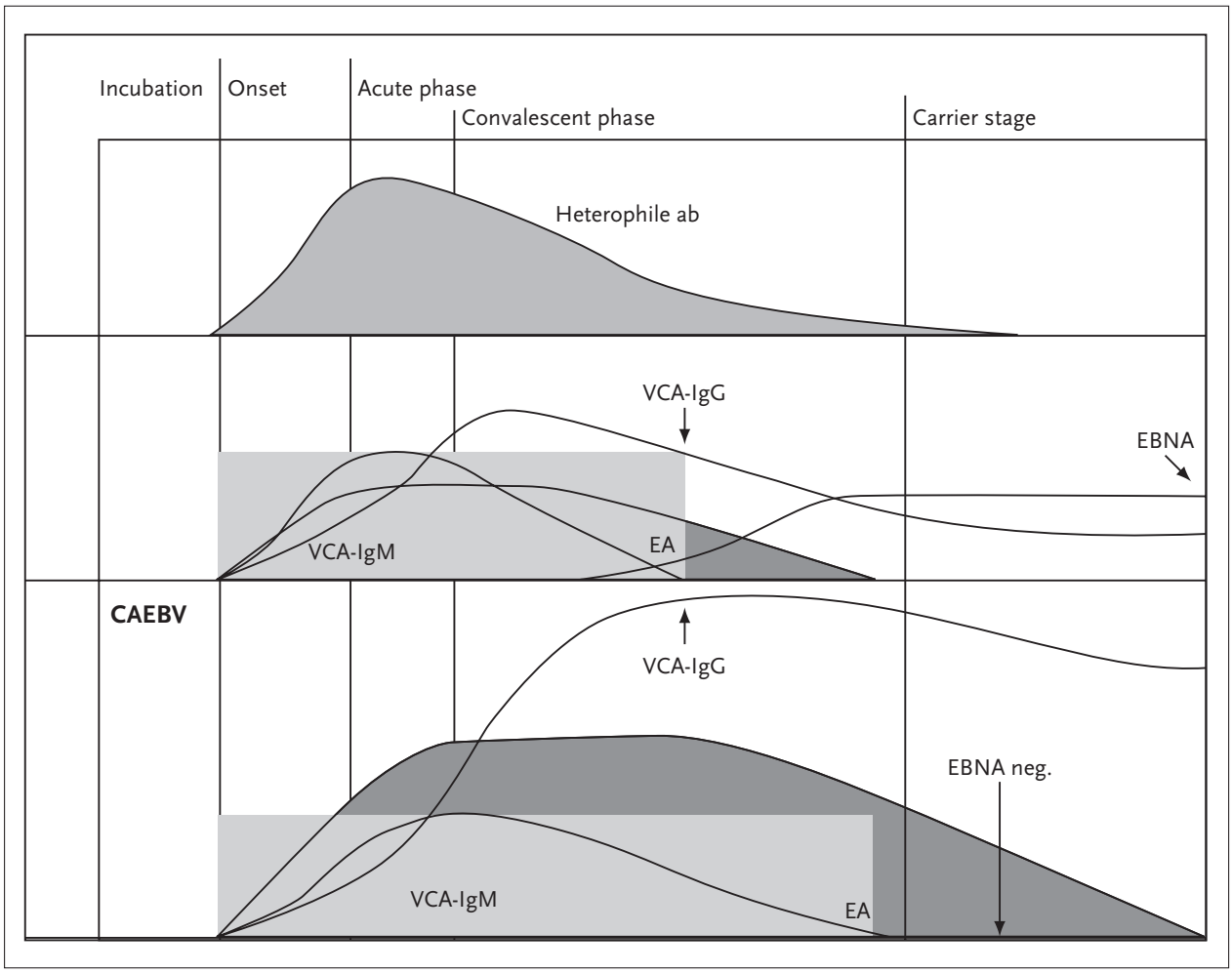

Figure 1
Antigen and antibody response during the different phases of EBV infection

outgrow of EBV-infected cells, so BCRF1 and BARF1 proteins probably help the virus to evade the host's immune system during acute EBV infection or reactivation of virus from latency.[25]
EBV is associated with a large range of inflammatory and proliferative diseases as summarised in *table 1*. Chronic active EBV infection (CAEBV infection) is one of the manifestations of EBV-induced disease. The following case illustrates the difficulty in diagnosing and treating CAEBV.

Table 1
Complications of primary EBV infection[18,40,41]

General	Mononucleosis infectiosa (Necrotising) lymphadenitis/tonsilitis Hepatitis Mesenteric adenitis Interstitial pneumonia Pancreatitis Myocarditis Myositis Glomerulonephritis Splenomegaly (with splenic rupture) Arthritis
Haematological	Haemolytic anaemia Aplastic anaemia Thrombocytopenia Thrombotic thrompocytopenic purpura, haemolytic-uremic syndrome Disseminated intravascular coagulation
Neurological	Guillain-Barré syndrome Facial nerve palsy Meningo-encephalitis Aseptic meningitis Transverse myelitis Peripheral neuritis Optic neuritis
Ophthalmological	Retinitis Uveitis
Dermatological	Rash Genital ulceration

CASE REPORT

A 30-year-old female was referred to the internal medicine department with recurrent unexplained orbital swelling and general symptoms. At the age of 19 she developed the first swelling in the left orbita and eyelid. A biopsy was nonconclusive because of extensive damage to the tissue. No additional therapy was instituted. At the age of 22 a similar swelling developed in the left orbit and eyelid. A biopsy of the mass in the eyelid showed a monotonous lymphoplasmacellular infiltration with light chain restriction (>10 times more lambda than kappa positive cells) consistent with a diagnosis of low-grade malignant orbital MALT lymphoma. Another biopsy in the same year, taken from the left orbita, showed lymphoid follicles with germinal centres and a lymphoplasmacellular proliferation with only moderate prevalence of lambda positive cells, consistent with a reactive lymphoid hyperplasia. EBV staining was not performed and no material for additional staining was available. She was treated with prednisone and when the swelling increased 18 months later, at the age of 24 years, she received local radiotherapy. At the age of 27, she was seen in our hospital to find an explanation for the increasing exophthalmus of her left eye. No indication was found for thyroid disease. A cerebral CT scan showed no abnormalities, and in particular no protrusio bulbi. A wait-and-see policy was adopted.

On referral she presented with a palpable mass in her *right* eyelid which had become obvious during the previous week. She was 14 weeks pregnant. She complained of fatigue and night sweats, but had no fever. Physical examination showed a palpable mass in the right eyelid of 0.8 x 0.2 cm, a protruding eye-bulb and firm, elastic submandibular and cervical lymph nodes up to 2 cm in diameter. No enlarged lymph nodes were found at other stations. Physical examination of heart, lungs and abdomen revealed no abnormalities: there was no hepatosplenomegaly. Laboratory investigations showed the following results (normal values in brackets): haemoglobin 7.2 mmol/l (7.5-10.0 mmol/l), leucocytes 7.8*10^9/l with a normal leucocyte differentiation (4.0-11.0 e^9/l), thrombocytes 281*10^9/l (150-400 e^9/l) , ESR 85 mm/h (1-19 mm/h). There was an elevated, oligoclonal γ-globulin of 25 g/l. The IgG was raised to 30 g/l (6.9-16.2 g/l), the IgA was 0.98 g/l (0.7-3.8 g/l), and the IgM 0.55 g/l (0.6-2.6 g/l). Liver enzymes and creatinine levels were normal. Serological examination revealed the following: Paul-Bunnell, CMV and Waaler-Rose serology were negative. Antinuclear antibodies (ANA) were also negative. IgG antibodies against toxoplasmosis were present, toxoplasmosis IgM antibodies were negative. Biopsy of the mass in the eyelid revealed a lymphoplasmocellular infiltration without evidence for malignancy. At that time, hybridisation for EBERs was not performed. Since a MALT lymphoma of the left orbita and eyelid has been diagnosed eight years before, lymphoma staging was done. Sternal aspirate and crista biopsy showed no localisation of a malignant lymphoma. Ultrasound of the abdomen and chest X-ray showed no intra-abdominal or mediastinal lymphomas. Because she was 14 weeks pregnant no CT-scanning was performed and a wait-and-see policy was adopted.
During the last month of her pregnancy, the cervical and axillary lymph nodes increased in size. Several weeks after an uncomplicated delivery and the birth of a healthy child she complained of progressive fatigue, arthralgia without signs of active arthritis and volatile erythematous skin lesions. Pathological examination of a skin biopsy revealed a focal increase in lymphocytes perivascularly, not meeting criteria for the diagnosis of vasculitis. CT scanning

of chest and abdomen showed axillary, mediastinal, retroperitoneal and iliacal lymph node proliferation, but all smaller than 1 cm. Biopsy of an axillary lymph node showed, apart from reactive follicles, a predominantly paracortical hyperplasia with large atypical cells among which many large B cells and positive hybridisation for EBERs. LMP-1 staining was negative. This finding is consistent with a histological diagnosis of EBV-induced lymphoproliferation or infectious mononucleosis. Three months later the exophthalmus of her right eye rapidly progressed and there was further enlargement of the lymph nodes. Prednisone (1 mg/kg) treatment was initiated. The exophthalmus and lymph nodes completely disappeared, but recurred when prednisone was tapered off. CT scanning of the right orbita revealed a soft tissue mass around the lacrymal gland. A second biopsy of an enlarged (cervical) lymph node was taken after the prednisone was stopped. Histology showed extensive paracortical and perisinusoidal infiltration of lymphocytes, plasma cells and eosinophils with scattered large activated lymphocytes and hybridisation for EBERs was positive, predominantly in the immunoblast-like cells. Now also LMP-1 staining was positive. The findings were grossly identical to the biopsy five months earlier. Because EBERs and LMP-1 were found in the lymph node biopsy more extensive EBV serology was performed. This showed an elevated titre of VCA-IgG of 512 E/ml, an EA-IgG of 128 E/ml, EBNA-IgG of 32 E/ml. The VCA-IgM was negative. Furthermore a high EBV viral load was measured by quantitative PCR: 10^4 genome equivalents (GEQ)/ml. Chronic active EBV infection (CAEBV) as cause of lymphadenopathy was considered, because EBV viral loads were high and there was a persisting lymphadenopathy with B-lymphocyte proliferation and expression of EBERs. We did several investigations to exclude an immunodeficiency. The total amount of T cells was low (0.58 x 10^9/l), but the CD4/CD8 ratio was normal (1.94). *In vitro* T-lymphocyte stimulation with phorbol myristate acetate (PMA) was normal, with normal production of IL-2, IL-4 and interferon-γ. There were normal numbers of B cells and natural killer (NK) cells. The CD4-CD45RA versus RO ratio was less than 1, suggesting less activated and naive T cells compared with memory T cells. Treatment with high-dose acyclovir (6 g/day orally) for three months resulted in a limited reduction of EBV viral load to 6*10^2 GEQ/ml, whereas the clinical symptoms increased. Rituximab (anti-CD20-antibodies) treatment (375 mg per dose) was given in an attempt to reduce the amount of EBV-infected B lymphocytes and to improve the clinical condition. However, six days after the second dose the patient was found comatose. Cerebral CT scanning showed subarachnoidal haemorrhage. There was no evidence of lymphoma localisation or an infectious focus. She died the same day, post-mortem evaluation was not allowed.

DISCUSSION

This case report describes a young woman who presented with recurrent periorbital swelling when she was 19 years of age. A low-grade malignant orbital MALT lymphoma was diagnosed on a biopsy from the orbital swelling when she was 23 years. Progressive symptoms during her first pregnancy and lymphadenopathy at the age of 30 were a reason for referral to our clinic for further evaluation. A lymph node biopsy showed a reactive histological picture consistent with viral infection and strong positive hybridisation for EBERs. This, together with the high plasma EBV titres, made us consider the diagnosis CAEBV, according to the criteria developed by Straus.[26] Straus defined three main criteria for the diagnosis CAEBV:

- Severe illness of greater than six months duration which began as a primary EBV infection or was associated with grossly abnormal EBV-antibody titres (IgG to VCA >1:5120; antibody to EA >1:640; or antibody to EBNA <1:2).
- Histological evidence of major organ involvement such as interstitial pneumonia, hypoplasia of some bone marrow elements, uveitis, lymphadenitis, persistent hepatitis or splenomegaly.
- Detection of increased quantities of EBV in affected tissues.

CAEBV is characterised by chronic or recurrent infectious mononucleosis-like symptoms persisting over a long period. The difference with latent EBV is viral replication and thus the presence of replicative antigens. In general, patients with this disease have no evidence of any prior immunological abnormality, as was the case in our patient. The pathogenesis of CAEBV is still unknown. There seems to be a deficiency in the specific T-cell response against EBV, but not a general immune deficiency. The interaction between EBV and adenovirus probably promotes the development of CAEBV by reducing the expression of human histocompatibility class 1 complex by adenovirus and transient immune suppression during acute EBV infection.[27,28] CAEBV is associated with the development of malignant lymphoma, especially T-cell lymphoma.[29] CAEBV is a disease with a high morbidity and high mortality.[1] The probability of five-year survival is 0.45 for older patients (≥8 years) and 0.94 for younger patients.[30] Our patient met the main criteria of Straus. Although the EBV-antibody titres of this patient did not meet the first criterion defined by Straus, titres cannot be compared between laboratories, particularly because our laboratory uses a test which deliberately results in low titres.[31] Although the antibody titres against EBV were elevated, the pattern of antibodies in this patient was normal, notably, with antibodies against EBNA being

present. This is in contrast with Miller's report[32] that patients with CAEBV have no detectable antibodies against EBNA. All the symptoms observed in our patient are consistent with CAEBV as is shown in *table 2*.

Table 2
Symptoms of chronic active Epstein-Barr virus infection (CAEBV)[1,27,35-41]

Low-grade fever	Intestinal perforation
High fever (T-cell type)	Large vessel arteritis
Sepsis	Coronary artery aneurysm
Pancytopenia	Exophtalmus*
Haemophagocytic syndrome	Uveitis
Malignant lymphoma	Cerebellar ataxia
Hepatosplenomegaly	Panencephalitis
Lymphadenopathy*	Calcification in basal ganglia
Hepatitis	Polyneuropathy
Tubulo-interstitial nephritis	Hypersensitivity to mosquito bites (HMB) (NK-cell type)
Interstitial pneumonia	Hydroa vacciniforme-like eruptions
Congestive heart failure	Erythema*
Myocarditis	Sicca syndrome
Pulmonary hypertension	Oral ulcers

* *Symptoms present in patient described in this case report.*

It is important to note that nowadays Epstein-Barr virus concentrations can be measured in plasma by quantitative PCR. This new technique, of which the diagnostic significance is rapidly growing, showed values of up to 10^4 GEQ/ml of the viral genome in blood, a value which strongly supports our diagnosis of CAEBV. At present atypical proliferations of lymphatic tissues are routinely stained on hybridisation for EBERs and LMP-1. Since quantitative PCR in plasma and tissue staining on EBV is possible it can be expected that the diagnosis of CAEBV will be made more frequently. Review of the criteria of CAEBV might be necessary, as Kimura *et al.* have also proposed.[1] They propose that a viral load exceeding $10^{2.5}$ GEQ/μg tissue DNA could be used as a diagnostic criterion for CAEBV. On the other hand, tissue EBV may be positive after EBV infection in normal individuals, while EBV plasma PCR levels should be negative. So we suggest the criterion of plasma, not tissue, PCR levels in the diagnosis of CAEBV.

Most but not all patients with CAEBV described in the literature have periods of low-grade fever. Our patient did not experience fever, but she complained of night sweats. Okano *et al.* describe 26 patients with severe active EBV infection (SCAEBV) of which three did not present with fever.[33] Almost all patients described in the literature are relatively young. The mean age of onset in Kimura's patient group was 8.3 years; the oldest patient was 27 years at onset of the disease. Our patient developed the first signs of the disease at the age of 19. The swelling of the left orbita in our patient, which was diagnosed as MALT lymphoma years before, might also be related to CAEBV, but unfortunately there is no material available for retrospective LMP1 and EBER staining. Low-grade malignant MALT lymphoma is in general a disease of the older age groups, but MALT lymphomas and low-grade plasmocytomas of the upper oropharynx, nasopharynx and orbit are not unusual in younger people in the third decade.[34] Whether these low-grade malignant tumours are related to EBV infection is not known but needs further investigation.

Because CAEBV is a disease with a poor prognosis, several treatment strategies have been proposed. Administration of immune-modulating agents such as interferon-α or interleukin-2 have been described to restrain the clonal development of EBV-associated T-lymphoproliferative disease (T-LPD) and (B-LPD).[35,36] It does not eradicate proliferation of EBV. Antiviral agents such as acyclovir, gancyclovir and vidarabine have been tried.[37,38] Our patient was treated with a high dose of acyclovir resulting in some reduction in EBV viral load, but with no clearance and with no effect on clinical signs and symptoms. Treatment with etoposide-based regimens or adoptive transfer of EBV-specific cytotoxic T lymphocytes have shown promising results.[7] Rituximab (anti-CD20 monoclonal antibody) has successfully been used in patients with EBV lymphoma after kidney and bone marrow transplantation, inducing clinical remissions.[39] Because a B-cell proliferation was seen in biopsies of lymph nodes, treatment with rituximab was instituted to reduce the amount of EBV-infected B cells. Unfortunately, we were not able to evaluate this therapy due to her sudden death. We can only speculate whether her sudden death, due to subarachnoidal bleeding, was related to CAEBV or was merely a coincidence. CNS involvement such as panencephalitis and cerebellar ataxia in CAEBV have been described, but cerebral bleeding is not mentioned. Since coronary artery aneurysms and arteritis have been described in CAEBV it is possible that cerebral vascular complications were the cause of death in our patient.

In conclusion, CAEBV is a rare manifestation of EBV-induced disease. It is based on an ineffective T-cell response against the EBV-infected cells, not due to a more generalised immune deficiency. The prognosis is poor with no established therapeutic strategies. If a patient presents with variable unexplained symptoms which fit in the spectrum of symptoms of CAEBV, EBV

viral loads should be measured and tissue should be stained on hybridisation for EBERs and LMP-1. Since currently atypical proliferations of reactive lymphatic tissues are routinely stained for EBV and serological tests are completed with measuring viral replication in (quantitative) PCR, it can be expected that the diagnosis of CAEBV will be made more frequently and review of the criteria of CAEBV might be necessary.

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ABOUT THE COVER

‘Studie van persoon’

Lex Loman

Lex Loman, the artist on this month’s cover, works and lives in Arnhem, the Netherlands. He also studied in Arnhem, at the Academy of Fine Arts. In addition to a series of individual expositions, he has shown his work at many group exhibitions in the region of Arnhem. Loman’s work is also presented in the offices of several companies, for example the PTT and AKZO Nobel, in Assen, Breda and Arnhem.

Since 1 January 2000 he has been active as printmaker assistant of the ‘Plaats Maken’ Printmaking Workshop.

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