

# A case of Epstein–Barr virus (EBV) meningoencephalitis in a patient with rheumatoid arthritis

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## Abstract

A case of Epstein–Barr virus (EBV) meningoencephalitis in a 74-year-old white man with rheumatoid arthritis is reported. The potential predisposing factors for EBV meningoencephalitis, the diagnostic approach and the management highlighted by this case are discussed.

## Keywords

Epstein–Barr virus; EBV meningoencephalitis; rheumatoid arthritis.

## Introduction

Epstein–Barr virus (EBV) infection commonly manifests as infectious mononucleosis. The association between EBV and infective mononucleosis was first described in the late 1960s. It is a common cause of viral sore throat and cervical lymphadenopathy in patients of all ages but is particularly frequent in children and young adults. Clinical features include fever, tonsillopharyngitis, lymphadenopathy, hepatosplenomegaly and the presence of leucocytosis with predominant lymphocytosis in peripheral blood. Moderately raised transaminase levels may occur. Neurologic involvement occurs in 1–10% of patients with EBV infections<sup>[1]</sup>. There are often features of lymphocytic meningitis, encephalitis, meningoencephalitis, transverse myelitis and polyradiculoneuritis. Spontaneous recovery occurs in most cases of uncomplicated infectious mononucleosis.

We report a case of EBV meningoencephalitis in an immunocompromised elderly patient with underlying rheumatoid arthritis. The pathogenesis of EBV meningoencephalitis is not completely understood but may be due to direct virus invasion or an immunocytotoxic effect mediated by infiltration of cytotoxic CD8<sup>+</sup> lymphocytes into neural tissue or deposition of antibody–antigen complexes. This case provides clinicians with information on the recognition, laboratory diagnosis and treatment of EBV meningoencephalitis.

## Case report

A 74-year-old man was referred to the Infectious Diseases Unit with a 4-day history of intermittent confusion, headache, fever, neck stiffness and photophobia. He had a past medical history of rheumatoid arthritis, stable ischaemic heart disease, epilepsy and peptic ulcer. His medication included oral prednisolone 5 mg once daily, methotrexate 10 mg weekly, adcal D3 1 tablet once daily, folic acid 5 mg once daily, clopidogrel 75 mg once daily, atorvastatin 20 mg every night, bisoprolol 2.5 mg once daily, isosorbide mononitrate XL 60 mg once daily, telmisartan 40 mg once daily and carbamazepine CR 200 mg twice daily. He is an ex-smoker and does not drink alcohol. He lives with his wife; there was no history of recent foreign travel or close contacts with any infections.

On examination, he was pyrexial at 38.5°C. Mental test score was 10/10. He had signs of meningism. Cardiorespiratory, abdominal and funduscopy examinations were normal. He did not have a rash. He had chronic changes on his hands consistent with rheumatoid arthritis without active synovitis.

Initial investigations showed a haemoglobin (Hb) level of 14.8 g/dL, total leucocyte count  $6.9 \times 10^9$ /L with lymphocytosis (neutrophil count  $3.80 \times 10^9$ /L, lymphocyte count  $6.3 \times 10^9$ /L, atypical lymphocytes  $1.18 \times 10^9$ ), platelet count  $127 \times 10^9$ . Biochemistry showed  $\text{Na}^+$  130 mmol/L,  $\text{K}^+$  4.3 mmol/L, urea 7.2 mmol/L, creatinine 143  $\mu\text{mol}$ /L, random plasma glucose 7.1 mmol/L and C-reactive protein 73 mg/L. Liver function tests were abnormal with albumin 34 g/L, alanine transferase 155 IU/L, alkaline phosphatase 406 IU/L, total bilirubin 23  $\mu\text{mol}$ /L and gamma-glutamyl transferase 101 IU/L. Alkaline phosphatase isoenzyme analysis showed predominantly liver isoenzymes. Clotting screen was normal with an internationalized normalized ratio of 1.1 and a prothrombin time of 10.9 s. Autoimmune profile was negative,  $\text{C}_3$  0.94 g/L,  $\text{C}_4$  0.09 g/L, IgG 20.9 g/L, IgA 7.51 g/L, IgM 4.28 g/L and no monoclonal band was detected on serum electrophoresis. Blood, urine, faecal and throat cultures were negative for bacteria, fungi and viruses.

In view of the abnormal liver function tests, an ultrasound scan of the hepatobiliary tree and spleen was performed and found to be normal. HIV, hepatitis B and C serology were negative and a computed tomography (CT) scan of the head was normal.

A lumbar puncture was performed which showed lymphocytic meningitis with clear colourless cerebrospinal fluid (CSF). Microscopy examination revealed total red cells of  $12 \times 10^6$ /L, white cells of  $101 \times 10^6$ /L (differential count 1% polymorphs and 99% lymphocytes). No organisms were seen on gram staining. CSF protein was mildly increased at 0.87 g/L; glucose level was 2.5 mmol/L (random glucose of 7.1 mmol/L). Tuberculosis microscopy was negative for acid-alcohol fast bacilli (AAFB) and cytology examination was normal.

The working diagnosis was lymphocytic meningitis with a differential diagnosis of viral meningitis, tuberculosis meningitis, *Listeria monocytogenes* meningitis and lymphoma. He was started on intravenous antibiotics and antiviral agents with ceftriaxone 2 g once daily, benzyl penicillin 2.4 g six times daily and acyclovir 10 mg/kg three times daily. Methotrexate was temporary discontinued since there was no clinical active synovitis.

On the second day, he was noted to have continuous low grade pyrexia of 37.5°C and frontal headache. He was disorientated in time and place with a Mental Test Score of 6/10. Neurologic examination showed features of cerebellar signs with an intension tremor on the finger to nose test, dysdiadochokinesia and an ataxic gait. There was no focal weakness, reflexes were brisk on the lower limbs with normal plantar responses. Cranial nerve examination was normal.

In view of the clinical deterioration, a repeat lumbar puncture was performed. Microscopic examination showed red cells  $10 \times 10^6$ /L, white cells  $169 \times 10^6$ /L (differential counts 100% lymphocytes). CSF protein was at a higher level at 1.40 g/L and his glucose level was within normal limit at 3.1 mmol/L (plasma glucose 7.3 mmol/L) confirming an earlier impression of viral meningoencephalitis. An urgent magnetic resonance imaging (MRI) brain scan was normal. An ethylenediamine tetraacetic acid (EDTA) blood sample and CSF were investigated by polymerase chain reaction (PCR) for Epstein-Barr virus (EBV) DNA, cytomegalovirus (CMV) DNA, enterovirus RNA, herpes simplex virus (HSV) DNA and varicella zoster (VZV) DNA. A clotted serum sample for EBV, CMV, HSV and VZV serology testing were also sent to the laboratory.

The EBV DNA quantitation revealed 85,000 copies/mL in CSF; all other investigations were negative by PCR. An EDTA blood specimen was investigated for EBV DNA by PCR and revealed 750,000 copies/mL. Serology showed undetectable EBV virus capsid antigen (VCA) and nuclear antigen (EBNA) immunoglobulin G; EBV virus capsid antigen (VCA) immunoglobulin M was detectable.

The clinical manifestations and laboratory results led to a diagnosis of EBV meningoencephalitis. Intravenous ceftriaxone, benzyl penicillin and acyclovir were discontinued. The patient was commenced on intravenous gancyclovir at a dosage of 5 mg/kg twice daily after adjusting for the patient's epidermal growth factor level. The patient showed significant clinical improvement after 11 days of treatment with intravenous gancyclovir with resolution of clinical symptoms. He was discharged on oral valganciclovir 450 mg twice daily for a further 2 weeks and continued on oral prednisolone 5 mg once daily.

At the 1-month follow-up in the outpatient department, the patient has no residual neurologic sequelae. His liver function tests normalized. A repeat EDTA blood sample for EBV PCR testing showed undetectable copies of EBV DNA quantification. Repeat serology showed undetectable EBV (VCA) immunoglobulin M with detectable (VCA) and (EBNA) immunoglobulin G.

## Discussion

EBV, along with all other herpes viruses, is a  $\gamma$ -herpes virus present in more than 90% of the general population and is characterised by persistence in sharing the same hallmark of latency. The virus can infect T and B lymphocytes. B lymphocytes are a major cellular reservoir, with healthy virus carriers harbouring 1–50 EBV genomes per million blood mononuclear cells<sup>[2]</sup>. EBV replicates in the pharynx and nasopharynx with nearly all seropositive individuals actively shedding virus in the saliva. It is also capable of infecting glandular epithelium of the thyroid, stomach, salivary gland, smooth muscle cells and follicular dendritic cells. Infection usually occurs through contact with oral secretions especially in children. Primary infection often results in infectious mononucleosis<sup>[3]</sup>. The virus persists for life in its human host by cleverly balancing its ability to hide from the immune system via latent infection of B lymphocytes with its ability to replicate and shed from oral mucosa. Around 20% of carriers are shedding salivary virions, which results in nearly universal propagation of the virus in human populations<sup>[4]</sup>.

Acute primary infection is marked by a rise in immunoglobulin M against VCA, which usually disappears after 2 months of infection. This is followed by the appearance of immunoglobulin G against VCA and nuclear antigen (EBNA) at least 1 month after primary infection and persists for many years or throughout life<sup>[4]</sup>.

The patient in this case report had the clinical features and laboratory results indicative of acute EBV meningoencephalitis from primary infection. He was immunocompromised from his underlying rheumatoid arthritis, long-term corticosteroid and methotrexate use although he was not lymphopenic or neutropenic on admission. Corticosteroid prevents interleukin 1 (IL-1), IL-2 and IL-6 production by macrophages. This inhibits all stages of T cell activation and T cells lose their ability to proliferate and react to specific antigens. However, antibody production is not suppressed by corticosteroids<sup>[5,6]</sup>. Methotrexate prevents T cell activation by inhibiting IL-1 production in vivo and induces IL-1 receptor antagonist (IL-1ra)<sup>[7]</sup>. It is also proposed that methotrexate decreases the expression of IL-2 and interferon  $\gamma$  (IFN- $\gamma$ ), which inhibits the activities of T-helper 1 cells<sup>[8]</sup>. Recent reports in the literature have suggested that there is an increased risk of B cell non-Hodgkin lymphoma in patients with rheumatoid arthritis, most likely due to monoclonal expansion of EBV-infected B lymphocytes seen in these patients. It remains controversial whether the risk of lymphoma increases in patients with rheumatoid arthritis treated with disease modifying agents for rheumatoid arthritis (DMARDs) especially with methotrexate. However, a recent literature review from a 3-year prospective study in France and a matched case-control study of 378 consecutive patients with rheumatoid arthritis in Sweden suggested the risk of lymphoma is substantially increased in those with very severe disease, high inflammatory activity rather than treatment with DMARDs<sup>[9,10]</sup>.

The pathogenesis of EBV-associated neurologic complications is not completely understood. Encephalitis and meningitis are the most commonly observed neurologic complications associated with infectious mononucleosis. There have been suggestions that immunocytotoxicity is caused by infiltration of catatonic CD8<sup>+</sup> cells into the neural tissue. Alternatively, deposition of circulation antibody-antigen complexes is suggested as a cause of endothelial changes leading to tissue damage. A recent literature review using neuroimaging studies with CT and MRI in patients with EBV-associated meningoencephalitis showed abnormal radiologic findings in up to 60% of the patients; 70% made a full recovery, 20% had neurologic sequelae and 10% died<sup>[11]</sup>. The regions most frequently involved in EBV-associated meningoencephalitis are presented in Table 1<sup>[11]</sup>.

The effectiveness of antiviral therapy on EBV has been validated in post-transplant recipients and haematologic patients to prevent serious complications from reactivation of EBV and CMV.

Table 1. Locations and outcomes involved in EBV-associated meningoencephalitis

Location	No. of cases	Outcome (%)		
		Good	Sequelae	Death
<b>Cerebellum</b>	13	8 (61)	1 (8)	4 (31)
Isolated cerebellitis	112	8	1	2
+ other location involvement				2
<b>Basal ganglia</b>	13	10 (77)	1 (8)	2 (15)
Isolated basal ganglia involvement	3	2	1	
+ other location involvement	10	8		2
<b>Cerebral hemisphere</b>	19	15 (79)	2 (10.5)	2 (10.5)
Gray matter involvement	3	3		
White matter involvement	4	4		
Combined or non-specific	12	8	2	2
<b>Thalamus</b>	10	3 (30)	4 (40)	3 (30)
Isolated thalamus involvement	2	1	1	
+ basal ganglia involvement	1		1	
Basal ganglia and other location	7	2	2	3
<b>Brain stem, mesencephalon</b>	10	5 (50)	2 (20)	3 (30)
Isolated brain stem involvement	4	1	1	2
+ other location involvement	6	4	1	1
<b>Limbic system, insula</b>	8	2 (25)	3 (37.5)	3 (37.5)
Isolated involvement	2		1	1
+ other location involvement	6	2	1	3
<b>Spinal cord</b>	3	3		
<b>Others</b>	11	8 (72)	3 (27)	
<b>Unspecified location</b>	5	4 (80)	1 (20)	

However, in our patient, treatment with gacyclovir and valganciclovir therapy can be justified in view of the immunosuppression as a results of his underlying rheumatoid arthritis together with clinical and laboratory evidence of acute EBV infection complicated by meningoencephalitis. Ganciclovir and its prodrug, valganciclovir, are acyclic nucleotide analogues. This group of antiviral drugs inhibits EBV replication by targeting EBV DNA polymerase<sup>[13]</sup>. The effectiveness of antiviral therapy in our patient was shown by a rapid clinical response and undetectable EBV DNA quantification in EDTA blood.

### Teaching point

Viral meningoencephalitis should always be considered in patients who are immunocompromised and present with clinical features of meningitis and confusion. Patients with underlying rheumatoid arthritis on DMARDs have a high prevalence of EBV infection and reactivation of latency. Advancement in molecular diagnostic techniques using PCR testing of CSF and EDTA blood samples provides prompt diagnosis; as immunocompromised patients have inconsistent humoral responses against viral infection, serology is not as reliable a marker of clinical status. Neuroimaging with MRI provides neuroanatomic localization of EBV meningoencephalitis, which may be a predictive factor for its clinical outcome.

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