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CASE REPORT

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Epstein–Barr virus reactivation-related meningoencephalitis with transverse myelitis in pregnancy

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Key Clinical Message

Consider the differential of Epstein–Barr virus (EBV) reactivation in pregnant women who develop progressive meningoencephalitis and transverse myelitis. EBV nucleic acid amplification should be considered in immunosuppressed patients.

Abstract

A 32-year-old G10P6M3K22 pregnant female presented to a regional hospital with progressive severe neurological and behavioral deficits. Magnetic resonance revealed cervical transverse myelitis. Lumbar puncture confirmed Epstein–Barr virus (EBV) DNA on a background of IgG-positive EBV serology. A diagnosis of EBV reactivation-related meningoencephalitis with transverse myelitis in pregnancy was concluded.

KEYWORDS

Epstein–Barr virus, meningoencephalitis, pregnancy, transverse myelitis

1 | INTRODUCTION

Epstein–Barr virus (EBV)-related reactivation resulting in cerebrospinal nervous system (CNS) manifestations is rare and is most associated with immunocompromised clinical states.[1–3] Though pregnancy has been associated with EBV reactivation, the existing literature for this demographic remains poor in describing severe meningoencephalitis cases. This paper describes in detail the complicated clinical course of a 32-year-old female with no prior predisposing factors except pregnancy, progressing to PCR-confirmed EBV meningoencephalitis with transverse myelitis confirmed on MRI brain and spine.

2 | CASE HISTORY

A 32-year-old G10P6M3K22 pregnant female of Maori ethnicity with no previous medical history, presented with 4 days of fever, headache, nausea and vomiting, photophobia, rigors, and neck stiffness to a regional hospital in southern Queensland, Australia. Her presentation occurred before the onset of the COVID-19 pandemic. On initial physical examination, she had no focal neurological deficits and remained alert, though complaining of a dull, throbbing headache of gradual onset without photophobia.

Pathology revealed a white cell count (WCC) 6.3×10^9/L and lymphopaenia 0.68×10^9/L with no remarkable blood

film or biochemistry findings besides normocytic anaemia since the advent of pregnancy. Haemoglobin A1c was not elevated. She was treated on admission with intravenous (IV) ceftriaxone, benzylpenicillin, aciclovir, and dexamethasone, to which she initially clinically responded. Her foetal morphology scan was unremarkable. Multiple blood cultures were negative before and after antibiotics were started, and cerebrospinal fluid (CSF) results 2 days after admission were noted (Table 1).

An extensive workup for infectious and noninfectious aetiologies ensued. The cerebrospinal fluid did not detect enterovirus RNA, herpes simplex virus (HSV) 1 and 2, varicella-zoster virus (VZV), nor bacterial or cryptococcal DNA. Similarly, India ink stain was negative, as was the serum cryptococcal antigen. Mycobacterial CSF cultures had no growth. Barmah Forest, Ross River, and other arbovirus serologies were negative, as were *Mycoplasma pneumoniae* antibodies and *Streptococcus pneumoniae* antigens. Syphilis, mumps, human immunodeficiency virus, and hepatitis B and C serologies were negative. Both Q fever DNA and serology were not detected. The rest of her TORCH screen was unremarkable. The autoimmune screen was negative including complement studies, angiotensin-converting enzyme, antinuclear antibodies, extractable nuclear antigens, double-stranded DNA, and antineutrophil cytoplasmic antibodies. Flow cytometry and cytology analysis of CSF were unremarkable except for numerous lymphocytes, monocytes, and neutrophils. Following her CSF results, dexamethasone and antibiotics were ceased on the presumption of viral meningitis.

Over the next 6 days, she deteriorated with persistent fevers, neck and shoulder pain, fatigue, confusion, and a decreased level of consciousness. She developed metabolic acidosis with respiratory compensation. Despite this, her C-reactive peaked at 22 mg/L and her procalcitonin 0.12 uq/L, indicating systemic bacterial infection was unlikely. Antibiotics were restarted to include IV ceftriaxone and meropenem, and she was transferred to the intensive care unit (ICU) for monitoring, intubation, and inotropic support. Following this, a repeat CSF specimen was obtained from a further lumbar puncture (Table 2).

Further fungal cultures and anti-neuronal antibodies were negative. Viral DNA for HSV, VZV, rabies virus, and lyssavirus was not detected, with no oligoclonal bands present. In the context of her pregnancy, EBV DNA was tested and found positive in the CSF, but EBV viral capsid antibody immunoglobulin M (IgM) was negative with immunoglobulin G (IgG) positive on serology.

She developed global and symmetrical brisk deep tendon reflexes, bilateral lower limb weakness with upgoing plantar reflex responses, and horizontal nystagmus. She remained nonresponsive and intubated. Electroencephalography revealed generalized slowing at 6–7 Hz, low in amplitude, posterior, and nonreactive, consistent with mild to moderate encephalopathy. Brain MRI revealed increased signal intensity in the cervical spinal cord associated with oedema indicating longitudinally extensive transverse myelitis but without cortical or subcortical lesions (Figure 1).

An opinion of EBV reactivation-related meningoencephalitis with transverse myelitis was made. Due to concerns regarding high-dose steroids in early pregnancy, she initially commenced plasmapheresis. Following the development of transfusion-related associated lung injury, her plasmapheresis was ceased. Instead, IV methylprednisolone 1 g daily was commenced for 5 days, followed by IV immunoglobulin for a further 5 days.

TABLE 1 Cerebrospinal fluid (CSF) assessment on initial assessment.

CSF parameter (units)	Patient value	Reference range
Protein (mg/L)	970	150–500
Glucose (mmol/L)	2.8	2.2–3.9
White cell count ($\times 10^6$)	50	<5
Red cell count ($\times 10^6$)	440	0
Differential	Polymorphs 15% Mononuclears 85%	
Gram stain	No organisms seen	
India ink	Negative	
Cryptococcal antigen	Nonreactive	
Culture	No growth	

TABLE 2 Cerebrospinal fluid on subsequent assessment.

CSF parameter (units)	Patient value	Reference range
Protein (mg/L)	2800	150–500
Glucose (mmol/L)	1.3	2.2–3.9
White cell count ($\times 10^6$)	980	<5
Red cell count ($\times 10^6$)	60	0
Differential	Polymorphs 3% Mononuclears 89%	
Gram Stain	No organisms seen	
India ink	Negative	
Cryptococcal antigen	Nonreactive	
Culture	No growth	
Cytology	No malignant cells seen	
Streptococcus pneumoniae antigen	Not detected	

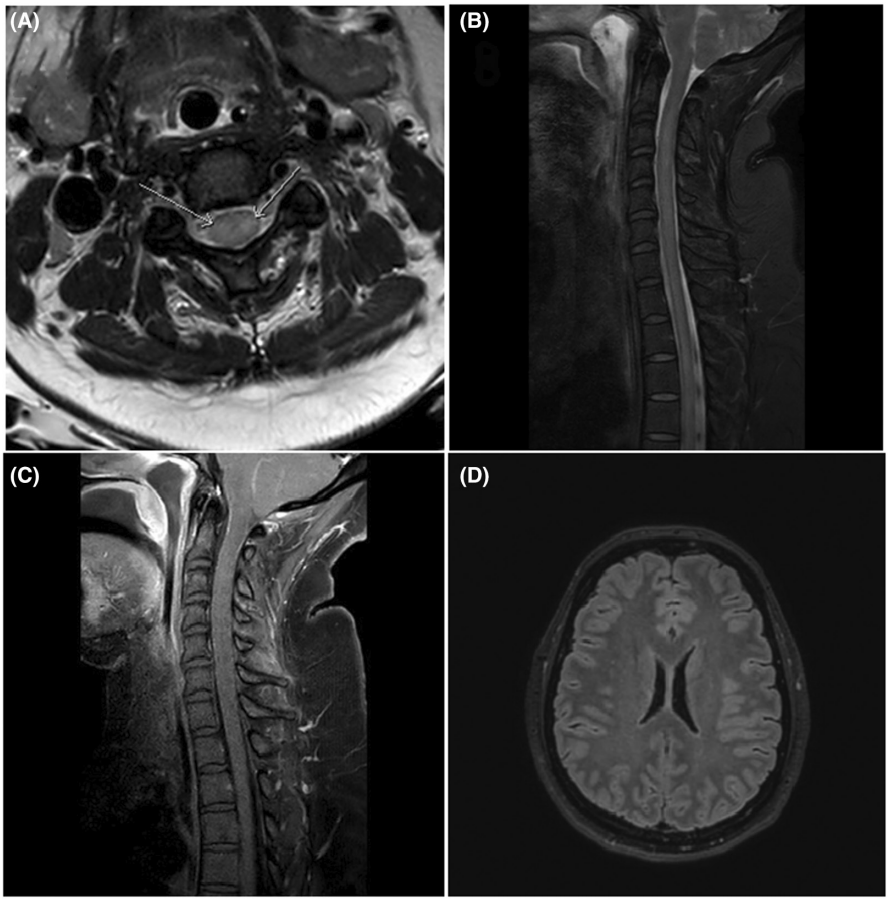

FIGURE 1 Pre-treatment MRI brain and spine. Clockwise from left upper quadrant, (A) axial T2 hyperintensity in the cervical spinal cord; (B) sagittal T2 hyperintensity in the cervical spinal cord with associated oedema; (C) sagittal T2 post-contrast with no enhancement; (D) axial FLAIR of the brain without hyperintensities.

2.1 | Outcome and follow-up

Repeat MRI imaging 10 days later revealed improvement in the spinal cord hyperintensity and oedema (Figure 2). Radiological improvement correlated with clinical resolution of the patient's upper motor neuron signs and conscious state. She was eventually extubated without complications. Her EBV DNA tested negative following clinical recovery. The foetus remained viable on ultrasonography with morphology, movements, and heart rate remaining within normal limits. She was discharged after 13 days in the ICU and stepped down to rehabilitation for reconditioning, with safe delivery of the foetus without further complications. Since neonatal delivery, she has recovered back to her baseline level of neurological function.

3 | DISCUSSION

Epstein–Barr virus is a near-ubiquitous pathogen that has been known to reactivate during periods of immunosuppression.[1] During reactivation, clinical manifestations have included encephalitis and transverse myelitis.[2,3] Pregnancy is known to be associated with a decline in lymphocytes, correlated with progesterone increases.[4,5] Reactivation of EBV is known to occur in pregnancy; however associated meningoencephalitis with transverse myelitis remains novel.

Meningoencephalitis in pregnancy is rare and has only been described in small case series associated with an infective aetiology including HSV, cytomegalovirus, tick-borne encephalitis, and toxoplasmosis.[6] Noninfective etiologies may include anti-NMDA receptor encephalitis, but again, only case series predominate.[7] Despite the rarity of these conditions, it is important to recognise and exclude these differentials in the workup of pregnant patients presenting with encephalopathy, given early recognition may allow for prompt treatment and reduce the risk of sequelae. The patient described in this case report was screened for these causes and was negative, except for EBV.

In this presentation, EBV DNA was detected in the CSF but negative for EBV viral capsid IgM serology. Viral capsid IgG serology was positive indicating past EBV exposure. Previous literature has indicated cases of EBV reactivation with discordance between serology and DNA, questioning the utility of EBV serology in cases of reactivation.[5,8] The clinical signs of meningoencephalitis, high proportion of CSF mononuclear cells, and exclusion of other causes for this presentation likely indicate a novel case of EBV reactivation with neurological sequelae, detected by PCR in a pregnant female with no other cause for immunosuppression

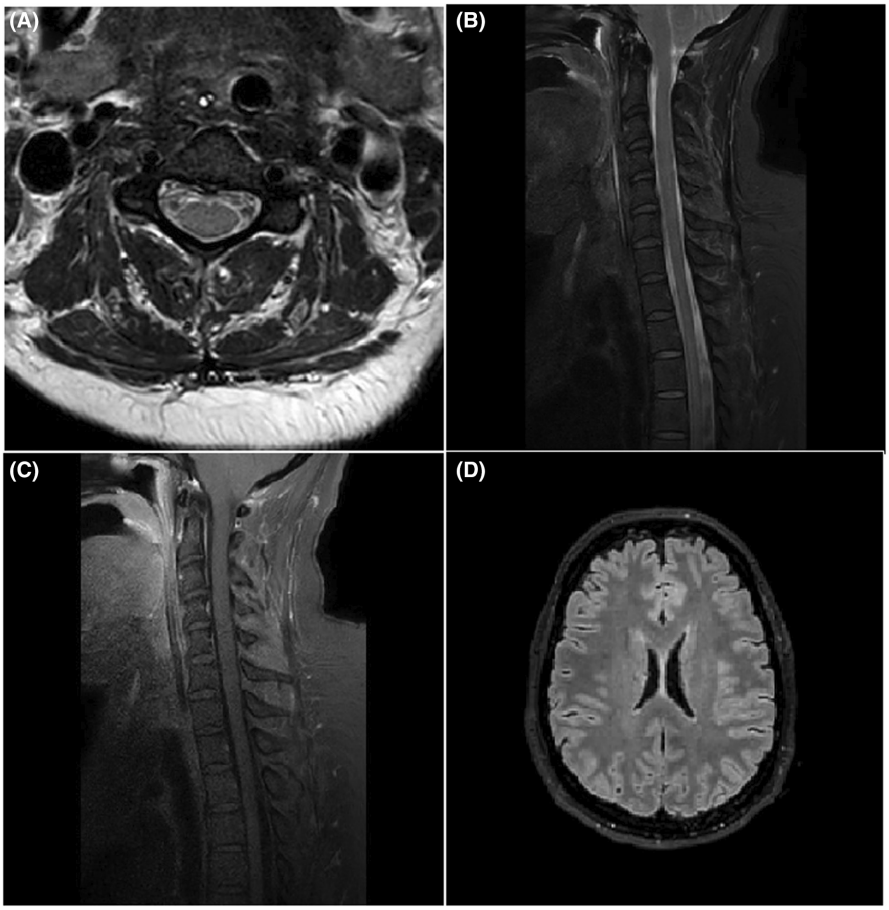

FIGURE 2 Post-treatment MRI brain and spine. Clockwise from left upper quadrant, (A) resolving axial T2 hyperintensity in the cervical spinal cord; (B) sagittal T2 hyperintensity in the cervical spinal cord with oedema also resolving; (C) sagittal T2 post-contrast with again no enhancement; (D) axial FLAIR of the brain again without hyperintensities.

detected. Further to this, the patient's EBV-detectable viraemia disappeared on the resolution of her illness. Head and neck MRI is an important tool to demonstrate brain abnormalities in EBV infection, including in showing related changes of bilateral and symmetric increased T2-weighted signal changes in the caudate nuclei, putamina, and thalami, given neurotropism for the basal ganglia.[9] Involvement of the brainstem, white matter, and splenium is rarer, but changes in the cervical spinal cord were identified in this case. The true prevalence of infection-associated transverse myelitis, especially postinfectious transverse myelitis, is probably underestimated.[10] The immune system appears to play a role in the pathogenesis of postinfectious transverse myelitis.[11] The true presence of the virus in the spinal cord cannot be proven without histological methods, but molecular and serological methods can be used to increase the pretest probability that a pathogen is implicated in disease, such as in this case.

The management of infection-related transverse myelitis in pregnancy is also fraught with complexity. Steroid use prior to 23 weeks has been associated with oral cleft formation.[12] Steroid use can have implications on the course of infection. Given that this patient was unable to tolerate plasmapheresis, IV methylprednisolone in combination with IV immunoglobulin was used with appreciable clinical resolution and radiological improvement. A safe delivery outcome for the fetus was also demonstrated following treatment of her condition.

This case study was limited to a qualitative discrete result of EBV DNA. Due to logistical and processing challenges, quantitative titres of EBV DNA were unable to be performed to assess the level of viraemia. However, the detectable EBV viral load resolved on resolution of her illness, thus increasing the likelihood of EBV reactivation-related encephalitis and transverse myelitis that improved following treatment. Given the rarity of this presentation, the study's findings will be best confirmed with documentation of other similar syndromes. This study adds to the wider literature of EBV-related clinical sequelae by presenting a unique occurrence of EBV reactivation in pregnancy associated with encephalitis and myelitis.

4 | CONCLUSION

Meningoencephalitis with transverse myelitis in pregnancy without any other significant history has rarely been reported. Though there is a wide spectrum of differentials for meningoencephalitis and postinfectious transverse myelitis, cerebrospinal fluid PCR was accurate in

identifying EBV in this case, and other potential causes of this patient's radiology were appropriately excluded. With EBV-related reactivation known to occur in pregnancy, it is therefore important to recognize the differential of EBV reactivation in pregnancy when a presentation of transverse myelitis with meningoencephalitis occurs, and the implication this has on treatment options.

AUTHOR CONTRIBUTIONS

Andrew Dang Khai Nguyen: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; validation; visualization; writing – original draft; writing – review and editing. **Ronald Siu:** Conceptualization; supervision; validation; writing – review and editing. **Grant Kleinschmidt:** Conceptualization; investigation; supervision; validation; writing – review and editing. **Bimal Prakash Sood:** Conceptualization; investigation; supervision; validation; writing – review and editing. **Ehsan Esmaili Shandiz:** Conceptualization; formal analysis; investigation; project administration; resources; supervision; validation; visualization; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest in the formulation of this paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONSENT

Written informed consent was obtained from the patient for publication of this report. A copy of the written consent is available to the Editor of this journal for review.

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