Case report

Brainstem encephalitis caused by Coxsackie A16 virus in a rituximab-immunosuppressed patient

Ruaridh Cameron Smail,[1] John H O'Neill,[2] David Andresen[2]

[1]Neurology, Royal North Shore Hospital, Saint Leonards, New South Wales, Australia
[2]Neurology, Saint Vincent's Hospital Sydney, Darlinghurst, New South Wales, Australia

Correspondence to
Dr Ruaridh Cameron Smail, ruaridh.cameronsmail1@health.nsw.gov.au

Accepted 3 August 2019

SUMMARY

Rituximab and other B cell depleting agents are increasingly used for haematological, immunological and neurological diseases. In a small minority, immunosuppression leads to increased virulence of normally mild infections. Brainstem encephalitis has been described occurring after infection from enteroviruses, more commonly in the paediatric population, but also in immunosuppressed adults. In this paper, we describe an enteroviral brainstem encephalitis in a rituximab-immunosuppressed patient. The enterovirus identified was Coxsackie A16, which has never yet been reported to cause brainstem encephalitis in an adult.

BACKGROUND

The *Enterovirus* genus, within the family *Picornaviridae*, comprises common endemic viruses such as Coxsackie viruses, echoviruses and other enteroviruses. While enteroviruses are common in the human population, they rarely result in serious infections. Most human infections are asymptomatic or lead to non-specific febrile illnesses with or without rash. Enteroviruses are the most common cause of viral meningitis, but encephalitis is rare. Brainstem encephalitis is a rare but often devastating complication of enterovirus infection. Enterovirus serotypes such as Coxsackievirus A9, A10 and B5; Echoviruses 4, 5, 9, 11, 19 and 30 and Enterovirus 71, 75, 76 and 89 have been reported in encephalitis cases around the world.[1–5]

Several previous outbreaks of Enterovirus 71 have resulted in a small proportion of children developing brainstem encephalitis as well as life-threatening non-cardiogenic pulmonary oedema. A prospective clinical trial in Sarawak identified several outbreaks of enterovirus 71, with 10%–30% of children developing central nervous system (CNS) complications, of which 58% were brainstem encephalitis.[6] An outbreak of enterovirus 71 has also been documented in Sydney.[7] In the absence of effective antiviral therapy, intravenous Ig for treatment of brainstem encephalitis has evolved although no randomised efficacy data are available.

Enterovirus rarely causes brainstem encephalitis in adults, presumably due to immunological maturation and acquired immunity due to prior enteroviral exposure. Humoral immunity is believed to be central to the control of enteroviral infection and replication. Several case reports of enteroviral brainstem encephalitis exist in adult patients with defects of humoral immunity, such as those treated with the anti-CD20 B cell-depleting agent rituximab. Here, we describe a case of rituximab-associated brainstem encephalitis. The enterovirus identified was Coxsackie A16 rather than the more common Enterovirus 71. Only two other cases of brainstem encephalitis associated with this serotype, both in children, have been reported in the literature.[8]

CASE PRESENTATION

A 41-year-old male patient presented to our hospital complaining of 1 week of intermittent fever, headache, double vision and gait unsteadiness. Stage 4 follicular lymphoma had been diagnosed 4 years prior. He had initially received six cycles of R-CHOP chemotherapy (a regimen consisting of rituximab, cyclophosphamide, doxorubicin,vincristine and prednisolone) followed by 3-monthly maintenance rituximab. He was considered to be in remission. He had no CNS involvement by his lymphoma. He had developed mild vincristine-related peripheral neuropathy but had not suffered any other side effects.

Six weeks prior to presentation, the patient's son had developed a febrile illness consistent with hand, foot and mouth disease but did not require hospitalisation. The patient himself was noted to have developed a rash in his mouth and hands when he was reviewed for his rituximab dose 4 weeks prior to presentation. Approximately 1 week later, his rash had settled but he began to develop fevers. Initially, these were managed with antipyretics but gradually worsened to the point of presentation. Fever was accompanied by chills and low back pain, and he was advised to take prednisolone 25 mg for 3 days by his haematologist.

On presentation, the patient was febrile at 39.0°C. The patient complained of intermittent slurred speech, gait unsteadiness and double vision, but no objective neurological signs other than mild ataxia were found. The patient was not meningitic. Blood tests demonstrated a mild neutrophilia, lymphopaenia and anaemia. Chest X-ray and CT of the brain were normal. A lumbar puncture showed an elevated cerebrospinal fluid (CSF) protein level (1.06 g/L) and CSF lymphocytosis (26 white cell count/mm^3 89% mononuclear cells, 11% polymorphs), with CSF glucose 66 mg/dL (3.7 mmol/L). He was treated initially with empiric antibacterial therapy and acyclovir. No organisms were seen on Gram stain of the CSF, and no bacterial growth was obtained.

To cite: Cameron Smail R, O'Neill JH, Andresen D. *BMJ Case Rep* 2019;**12**:e230177. doi:10.1136/bcr-2019-230177

Table 1 Previous cases of enterovirus encephalitis in adults with/without immunosuppression

Reference	Year	Country	Enterovirus identified (if reported)	Age	Underlying disease	Time since rituximab	MRI change?	Symptoms/signs	Treatment	Outcome
9	2003	France	Echovirus 13	53	Follicular lymphoma	6 months	Myelitis	Fever, headache, paraesthesia, diplopia	Intravenous Ig pleconaril	Recovered fully
10	2006	UK		75	DLBCL	7 months	Nil	Confusion, fever,	Intravenous Ig	Died at 14 wks
11	2006	USA		46	DLBCL	1 month	1st: nil 2nd: FLAIR hyperintensity in thalamus, basal ganglia	Dysarthria, nystagmus	Intravenous Ig planned not given	Died of lymphoma
12	2008	Japan	EV71, C4	37	Nil	N/A	Pons, midbrain hyperintensity	Diplopia, dysarthria, ataxia, hyporeflexia	Methylprednisolone	Recovered fully
13	2009	UK		53	DLBCL	1 week	Left temporal lobe enhancement	Fever, ataxia, dysarthria	Intravenous Ig	Died at 3 months (sepsis)
14	2009	Belgium		61	DLBCL	4 months	T2 hyperintensities?incidental	Confusion, ataxia, dysphasia	Intravenous Ig	Recovered fully
15	2010	Holland		64	Marginal zone lymphoma	1 month	Nil	Fever, nausea, fatigue	Intravenous Ig	Recovered fully
16	2011	Australia	EV71	63	NHL	3 months	Thalamus, frontal hyperintensities	Fever, myoclonus, hemiparesis, aphasia	Intravenous Ig	Died 12 weeks
17	2011	Canada	Coxsackie A9	65	Follicular	5 months	Not reported	Fever, hepatitis, rash	Nil	Recovered fully
18	2012	France		66	Follicular	2 months	Day 6: normal Day 13: myelitis	Fever, asthenia, aphasia Facial paralysis, spasticity	Intravenous Ig	Died day 32
19	2015	USA	Coxsackie B3	28	Evan's syndrome ITP	13 years	White matter changes	Fever, cognitive decline	Intravenous Ig	Died at 3 months

DLBCL, diffuse large B-cell lymphoma; EV71, Enterovirus 71; FLAIR, fluid-attenuated inversion recovery sequence; ITP, immune thrombocytopaenic purpura; N/A, not applicable; NHL, non-Hodgkin's Lymphoma.

The following day the patient's condition worsened with increasing drowsiness, dysarthria and ataxia. MRI of the brain performed on day 2 of admission was normal. Enterovirus PCR on his CSF returned as positive. This was subsequently identified by sequencing as Coxsackie A16 virus. By day 3 of admission, he required transfer to the intensive care unit due to drowsiness, confusion, hypertonia, hyper-reflexia and gaze-evoked nystagmus. A diagnosis of brainstem encephalitis was made.

TREATMENT, OUTCOME AND FOLLOW-UP

Though he remained persistently obtunded, with hypertonia and hyper-reflexia, the patient remained haemodynamically stable and did not require endotracheal intubation. Based on previous experience in immunosuppressed children, and in the absence of targeted antiviral therapy, he was managed with high-dose intravenous immunoglobulin (Ig) at a dose of 2 g/kg per day for 3 days.

An electroencephalogram (EEG) performed on day 4 showed an absent alpha rhythm and persistent symmetrical slow wave activity. By day 5, he gradually began to become more alert. A progress MRI brain scan on day 8 was also normal. EEG performed on day 9 had improved, with more evident alpha rhythm. He was discharged to a rehabilitation facility on day 12. At follow-up after 1 month, he continued to have impairment of fine motor tasks, mild intention tremor as well as the inability to tandem gait. He ultimately made a complete recovery within 6 months.

DISCUSSION

Rituximab is a chimeric monoclonal antibody which targets B cells which express CD20. The B cell suppression can last for months and induced hypogammaglobulinaemia can occur despite a limited effect on plasma B cells. Several cases of rituximab-related brainstem encephalitis have been reported in the literature (see table 1).[9–19] Many of these cases were also undergoing concurrent immunosuppression with other chemotherapeutic agents or as part of a previous stem cell transplant. Nevertheless, the rituximab was often the most recent agent, as in our case.

This case highlights the susceptibility of humorally immunosuppressed patients to endemic viral infections. Previous reports of rituximab-treated adults have described various enteroviruses causing brainstem encephalitis and outcomes are often fatal (see table 1). Although both Enterovirus 71 and Coxsackie A16 cause hand, foot and mouth disease, Enterovirus 71 is considered to have greater virulence in the CNS. We were surprised when the result returned as Coxsackie A16 virus since this enteroviral serotype has been less commonly associated with CNS complications.[8]

Learning points

- In the immunosuppressed population, normally indolent viruses, such as *Coxsackie* can cause severe infections of the central nervous system.
- Viral PCR testing should be swiftly sought if viral encephalitis is suspected.
- Brainstem encephalitis may occur in the absence of MRI changes, particularly in the early stages.
- Early use of intravenous Ig may be lifesaving.
- The use of high-dose intravenous Ig has not been trialled in viral brainstem encephalitis, yet remains our most suitable treatment, based on past experience in the paediatric population.

The extent of humoral suppression and low immunoglobulin levels are likely the best predictor of susceptibility to this type of infection and, conversely, antibody production (or exogenous administration) may assist recovery. Enterovirus encephalitis in children has been reported to improve after administration of high-dose intravenous immunoglobulin. Despite this, the disease carries a high mortality rate.

Clinicians are advised to consider this condition in patients manifesting a brainstem syndrome while being immunosuppressed after rituximab administration. Enterovirus PCR testing should be swiftly sought, since early use of intravenous immunoglobulin may be lifesaving.

Contributors All three authors cared for the patient in hospital. The case report was conceptualised and designed by RCS and JHO'N. The draft manuscript and literature review was written by RCS. The manuscript was reviewed and revised by JHO'N and DA.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Dalwai A, Ahmad S, Pacsa A, *et al*. Echovirus type 9 is an important cause of viral encephalitis among infants and young children in Kuwait. *J Clin Virol* 2009;44:48–51.
2 Fowlkes AL, Honarmand S, Glaser C, *et al*. Enterovirus-associated encephalitis in the California encephalitis project, 1998-2005. *J Infect Dis* 2008;198:1685–91.
3 Kumar A, Shukla D, Kumar R, *et al*. An epidemic of encephalitis associated with human enterovirus B in Uttar Pradesh, India, 2008. *J Clin Virol* 2011;51:142–5.
4 Lewthwaite P, Perera D, Ooi MH, *et al*. Enterovirus 75 Encephalitis in Children, Southern India. *Emerg Infect Dis* 2010;16:1780–2.
5 Sapkal GN, Bondre VP, Fulmali PV, *et al*. Enteroviruses in patients with acute encephalitis, uttar pradesh, India. *Emerg Infect Dis* 2009;15:295–8.
6 Ooi MH, Wong SC, Podin Y, *et al*. Human enterovirus 71 disease in Sarawak, Malaysia: a prospective clinical, virological, and molecular epidemiological study. *Clin Infect Dis* 2007;44:646–56.
7 Zander A, Britton PN, Navin T, *et al*. An outbreak of enterovirus 71 in metropolitan Sydney: enhanced surveillance and lessons learnt. *Med J Aust* 2014;201:11.
8 Xu W, Liu CF, Yan L, *et al*. Distribution of enteroviruses in hospitalized children with hand, foot and mouth disease and relationship between pathogens and nervous system complications. *Virol J* 2012;9:8.
9 Quartier P, Tournilhac O, Archimbaud C, *et al*. Enteroviral meningoencephalitis after anti-CD20 (rituximab) treatment. *Clin Infect Dis* 2003;36:e47–e49.
10 Padate BP, Keidan J. Enteroviral meningoencephalitis in a patient with non-Hodgkin's lymphoma treated previously with rituximab. *Clin Lab Haematol* 2006;28:69–71.
11 Ganjoo KN, Raman R, Sobel RA, *et al*. Opportunistic enteroviral meningoencephalitis: an unusual treatable complication of rituximab therapy. *Leuk Lymphoma* 2009;50:673–5.
12 Hamaguchi T, Fujisawa H, Sakai K, *et al*. Acute encephalitis caused by intrafamilial transmission of enterovirus 71 in adult. *Emerg Infect Dis* 2008;14:828–30.
13 Kiani-Alikhan S, Skoulidis F, Barroso A, *et al*. Enterovirus infection of neuronal cells post-Rituximab. *Br J Haematol* 2009;146:333–5.
14 Servais, *et al*. Enteroviral meningoencephalitis as complication of Rituximab therapy in a patient treated for diffuse large B-cell lymphoma. *BJ Haem* 2010.
15 Schilthuizen C, Berenschot HW, Levin MD, *et al*. Enteroviral encephalitis in a patient with a marginal zone lymphomatreated with rituximab. *Neth J Med* 2010;68:221–3.
16 Ahmed R, Buckland M, Davies L, *et al*. Enterovirus 71 meningoencephalitis complicating rituximab therapy. *J Neurol Sci* 2011;305:149–51.
17 Moreau B, Bastedo C, Michel RP, *et al*. Hepatitis and encephalitis due to coxsackie virus a9 in an adult. *Case Rep Gastroenterol* 2011;5:617–22.
18 Kassab S, *et al*. Fatal Case of Enterovirus 71 infection and rituximab therapy, France, 2012 Emerging Infectious Diseases. 2013;19: http://www.cdc.gov/eid.
19 Palacios T, Bartelt L, Scheld W, *et al*. Fatal Coxsackie meningoencephalitis in a patient with B-cell lymphopenia and hypogammaglobulinemia following rituximab therapy. *Annals of Allergy, Asthma & Immunology* 2015;115:148–50.