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Fatal Coxsackie meningoencephalitis in a patient with B-cell lymphopenia and hypogammaglobulinemia following rituximab therapy

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Enteroviruses (EVs) are the most common circulating viruses and cause of viral meningoencephalitis in the United States. In the general population, enteroviral infection is usually a self-limited disease. However, in patients with humoral immunodeficiency, infections can be fatal. The present case is that of a woman with Evans syndrome treated with splenectomy and rituximab who developed hypogammaglobulinemia and, despite antibody replacement, a fatal Coxsackie B3 virus meningoencephalitis.

Enteroviruses are positive-sense single-stranded RNA viruses with a capsid composed of 4 structural proteins (VP1eVP4).[1,2] Although EV meningoencephalitis (EM) is typically self-limited, in patients with humoral immunodeficiency, chronic EM has been reported often with fatal outcome.[3,4] The use of intravenous immunoglobulin (IVIG) has dramatically decreased the incidence of chronic EM in congenital agammaglobulinemic conditions. Unfortunately, there are limited pharmaceutical treatment options available once chronic EM develops, all with varying degrees of success, including pleconaril (a picornavirus capsid protein inhibitor), high-dose IVIG, intrathecal immunoglobulin, and use of immunoglobulin preparations selected to contain high titers of enteroviral antibody.

A 28-year-old white woman presented to the University of Virginia Hospital. At 15 years of age, she was diagnosed with Evans syndrome (autoimmune hemolytic anemia) and idiopathic thrombocytopenic purpura.[5] Workup at that time was negative for immunodeficiency (Table 1). She was initially treated with danazol and corticosteroids. Then, she received high-dose (1 mg/kg) IVIG and a total of 8 doses of 375 mg/m^2 of

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rituximab during a 10-month period for severe idiopathic thrombocytopenic purpura. At 23 years, she received pneumococcal and meningococcal vaccines and underwent splenectomy for refractory idiopathic thrombocytopenic purpura.

She did well until 27 years of age, when she was hospitalized for aseptic meningitis (Table 1, lumbar puncture [LP] 1). She subsequently developed idiopathic bilateral sensorineural hearing loss. At 28 years, she was hospitalized for influenza A (H3) with concurrent facial *Pseudomonas* cellulitis and again for *Streptococcus pneumoniae* sepsis. Then, she was found to have marked hypogammaglobulinemia with impaired antibody response and profound B-cell lymphopenia (Table 1). She was started on replacement IVIG (Privigen, CSL Behring, King of Prussia, Pennsylvania) at a dose of 400 mg/kg every 4 weeks.

One month later, she developed a steady decline in neurocognitive function. The following month, she developed persistent fever. Brain magnetic resonance imaging displayed white matter changes concerning for encephalitis, but no focal lesions. Cerebrospinal fluid (CSF) from an LP was remarkable for an elevated opening pressure with slight lymphocytic pleocytosis and elevated protein. Flow cytometry of the CSF demonstrated a paucity of B cells but no aberrancy in the T-cell population. CSF infectious workup was negative (Table 1, LP 2). Stereotactic brain biopsies were performed. Histopathology on all specimens demonstrated meningoencephalitis with no evidence for granulomatous inflammation, but extensive $CD68^+$ macrophages and $CD5^+$ T-cell reaction and minimal to no $CD20^+$ B cells. Viral inclusions and micro-organisms were not present. Computed tomography of the head showed no evidence of intracerebral hemorrhage.

Her cognitive function continued to deteriorate despite empiric treatment with broad-spectrum antibiotics. LP was remarkable for an elevated opening pressure, and repeat CSF studies, including EV polymerase chain reaction (PCR), were negative except for persistent lymphocytic pleocytosis and elevated protein (Table 1, LP 3 and LP 4). Repeat brain magnetic resonance imaging showed no intracranial abscess, but there was slight progression of the symmetric abnormal white matter signal. Given the lack of clinical improvement despite appropriate medical therapy, a repeat brain biopsy examination was performed. In addition, tissues from the first brain biopsy and CSF were sent to the Centers for Disease Control and Prevention for immunohistochemistry and PCR for *Toxoplasma* species, *Mycoplasma* species, EV, Japanese encephalitis, and flaviviruses. Results were positive for EV by immunohistochemistry and PCR.

Unfortunately, the patient had a left middle cerebral artery ischemic stroke several days after her second brain biopsy examination. She was transitioned to hospice and expired a few days later. Postmortem brain uncal and parietal tissue for PCR testing were positive for human Coxsackie virus B3, with positive VP2, VP4, and 5′ untranslated region. The VP2 and VP4 sequences showed 93% nucleotide identity with the human Coxsackie virus B3. Thus, her final cause of death was determined to be diffuse meningoencephalitis secondary to human Coxsackie virus B3 owing to an immunocompromised state.[1]

We hypothesize that this patient's previous treatment with rituximab for Evans syndrome caused persistent profound B-cell lymphopenia and secondary hypogammaglobulinemia,

predisposing her to EM. Although she also had a splenectomy, asplenia is not considered a high-risk condition for EM.

The present case adds to an increasingly recognized, but incompletely understood, association between rituximab therapy and EM. Rituximab is a chimeric monoclonal antibody targeting CD20, which is expressed on B cells from the late pro–B-cell to memory B-cell stage.[6] Given the absence of CD20 expression on plasmablasts and plasma cells, most patients treated with rituximab develop only transient, mild hypogammaglobulinemia and naive B-cell recovery occurs by12 months,[7] with memory B-cell recovery after recapitulating normal B-cell ontogeny.

Increased susceptibility to enteroviral infections has been observed in primary immunodeficiencies associated with defective B- and T-lymphocyte interactions such as X-linked agammaglobulinemia, hyper-IgM syndrome, and major histocompatibility class II deficiency.[8] In X-linked agammaglobulinemia, congenital absence of B lymphocytes is associated with defective antigen presentation and decreased ability of B lymphocytes to sequester and destroy circulating virus.[4] In contrast, patients with common variable immunodeficiency typically retain circulating B cells and are at lower risk for EM.[9,10] Therefore, in patients with persistent marked B lymphopenia after rituximab, we would predict an increased risk of EM similar to patients with X-linked agammaglobulinemia.

Routinely obtaining immunoglobulin levels and peripheral B-cell numbers before and after rituximab treatment should be considered to monitor for pre-existing and secondary immunodeficiency. Prompt immunoglobulin replacement intravenously or intrathecally should be initiated in patients with persistent B-cell absence because this might avert severe EM infections in these high-risk patients. As the present case illustrates, immunoglobulin replacement might be inadequate salvage therapy in established EM.

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Table 1

Laboratory results before and after rituximab treatment

Time point	Laboratory results (normal range)
15 y of age Diagnosed with Evans syndrome	antinuclear antibody negative
	anti–double-stranded DNA 1:40
	DAT, broad-spectrum Coombs (+)
	DAT anti-IgG serum (+)
	DAT anti-C3 (+)
	Hb 7.0 g/dL, platelet count 4,000 k/μL bone marrow biopsy result: erythroid hyperplasia
16 y of age Before treatment with rituximab	IgG 1,140 mg/dL (700–1,450 mg/dL)
	IgA 256 mg/dL (70–370 mg/dL)
	IgM 172 mg/dL (30–210 mg/dL)
	IgE 124 IU/mL (10–130 IU/mL)
	HIV-1 and -2 IgG negative
27 y of age CSF results (LP 1)1	fluid colorless and clear
	WBC count 118 μL (55% lymphocytes)
	RBC count 2/μL
	protein 87 mg/dL (15–40 mg/dL)
	glucose 41 mg/dL (40–70 mg/dL)
	oligoclonal bands not detected
28 y of age Diagnosed with hypogammaglobulinemia	IgG 259 mg/dL (700–1,450 mg/dL)
	IgA 38.9 mg/dL (70–370 mg/dL)
	IgM <4.2 mg/dL (30–210 mg/dL)
	IgE 2.8 IU/mL (10–130 IU/mL)
	tetanus toxoid IgG 0.24 IU/mL (protective)
	Streptococcus pneumoniae IgG <0.1–<0.8 μg/mL (0 of 7 serotypes protective)
	April 2013
	0% $CD19^+$ cells (5%–24%)
	86% $CD3^+$ cells (57%–84%)
	46% $CD4^+$ cells (30%–61%)
	absolute $CD4^+$ count 430/μL (400–1,500/μL)
	37% $CD8^+$ cells (12%–37%)
	13% $CD16^+$ cells (2%–22%)
	September 2013
	87% $CD3^+$ cells (57%–84%)
	44% $CD4^+$ cells (30%–61%)
	absolute $CD4^+$ count 907 μL (400–1,500/μL)
	36% $CD8^+$ cells (12%–37%)
28 y of age CSF results (LP 2)	opening pressure 319 mm H_2O (60–250 mm H_2O)
	WBC count 8/μL (89% lymphocytes)
	RBC count 4/μL

Time point	Laboratory results (normal range)
	protein 44 mg/dL (15–40 mg/dL)
	glucose 53 mg/dL (40–70 mg/dL)
	lactate 1.9 mmol/L (0.5–2.2 mmol/L)
	CSF gram stain and culture negative
	cryptococcal antigen negative
	CMV PCR negative
	EBV PCR negative
	HSV PCR negative
	HHV-6 PCR negative
	JCV PCR negative
	Lyme IgG/IgM PCR negative
	VZV PCR negative
	VDRL negative
28 y of age CSF results (LP 3)	CMV PCR negative
	EV PCR negative
	EBV PCR negative
	HSV PCR negative
	HHV-6 PCR negative
	JCV PCR negative
	Toxoplasma IgG and PCR negative
28 y of age CSF results (LP 4)	opening pressure 95 mm H_2O (60–250 mm H_2O)
	WBC count 17/μL (82% lymphocytes)
	RBC count 120/μL
	protein 51 mg/dL (15–40 mg/dL)
	glucose 49 mg/dL (40–70 mg/dL)
	lactate 2.1 mmol/L (0.5–2.2 mmol/L)
	Toxoplasma PCR negative
	HHV-6 PCR negative
	CMV PCR negative
	HSV PCR negative
	anti–N-methyl D-aspartate receptor antibody negative

Abbreviations: CMV, cytomegalovirus; CSSF, cerebrospinal fluid; DAT, direct anti-globulin test; EBV, Epstein-Barr virus; EV, enterovirus; Hb, hemoglobin; HHV-6, human herpes virus 6; HIV, human immunodeficiency virus; HSV, herpes simplex virus; JCV, John Cunningham virus; LP, lumbar puncture; PCR, polymerase chain reaction; RBC, red blood cell; VDRL, Venereal Disease Research Laboratory; VZV, varicella zoster virus; WBC, white blood cell.