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Case report

Chronic enteroviral meningoencephalitis in a patient on rituximab for the treatment of psoriatic arthritis: A case report and brief literature review

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\section*{ARTICLE INFO}

Article history:
Received 16 April 2019
Received in revised form 7 May 2019
Accepted 7 May 2019

Keywords:
Rituximab
Enterovirus
Enteroviral meningoencephalitis
Viral encephalopathy
Psoriatic arthritis

\section*{ABSTRACT}

Enteroviruses are RNA viruses within the Picornaviridae family. Enteroviruses derive their name from the way they are typically transmitted via the intestinal tract. They commonly infect millions of people every year and often do not cause severe disease in immunocompetent patients with few exceptions. Aseptic meningitis is a classic manifestation and is usually self-limited, however, can lead to severe neurological complications in an immunocompromised individual. It has been well-described that patients with hypogammaglobulinemia are predisposed to developing chronic enteroviral meningoencephalitis \cite{1}. This is the first reported case of enteroviral meningoencephalitis in a patient being treated for psoriatic arthritis with rituximab. Here we describe a 46-year-old female who presented with altered mental status, fever, and myalgia. Polymerase chain reaction (PCR) of her cerebrospinal fluid (CSF) confirmed the presence of enterovirus. In the immunocompromised patient with encephalopathy, it is important to consider an enteroviral infection. This case adds to the present body of knowledge about enteroviral infections in immunocompromised hosts.

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\section*{Introduction}

Rituximab is a chimeric anti-CD20 monoclonal antibody that induces a long-lasting B-cell depletion. It is presently FDA-approved for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis, and most recently pemphigus vulgaris \cite{2}. It has also been successfully used as a second-line agent in the treatment of psoriatic arthritis \cite{3}. Typically, the drug has a respectable safety profile. There is a Black Box Warning for rituximab for a potentially fatal first-time infusion reaction, severe mucocutaneous reaction, hepatitis B virus reactivation, and progressive multifocal leukoencephalopathy. Enteroviral meningoencephalitis is a lesser known but clinically significant complication of rituximab that has been recognized in the recent years.

Enteroviruses remain the most common cause of viral meningitis in the United States with encephalitis recognized as a potential complication. Among immunocompetent individuals, children are affected more frequently than adults. Typical meningitis presentation in adults can include fever, headache, stiff neck, vesicular lesions, and lymphocytic pleocytosis on CSF. Rapid viral detection is imperative in establishing a proper diagnosis that can ultimately improve patient outcome and avoid unnecessary antibacterial usage and testing.

There have been several cases of enteroviral meningoencephalitis described in patients on rituximab since the first reported case in 2003 \cite{4--14} (Table 1). All of these patients were receiving rituximab in the setting of hematologic diseases. We report a novel case of enteroviral meningoencephalitis in a patient on prolonged rituximab therapy for psoriatic arthritis.

\section*{Case presentation}

A 46-year-old African American female presented to an outside hospital in late November 2017 due to altered mentation and flu-like symptoms. Her past medical history was significant for bipolar disorder, 1 seizure episode at age 17, and psoriatic arthritis treated with rituximab infusions since 2014. Her last known rituximab infusion was July 2017. Prior to seeking medical care, the patient tried multiple doses of Therafus (acetaminophen, dextromethorphan, and...
<table>
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<tr>
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<td>-Gastroenteritis -Septicemia -Low GCS -Fever</td>
<td>-Lymphocytosis -Increased protein -CSF initially negative</td>
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phenylephrine) because she attributed her symptomatology to influenza.

She complained of a subjective tactile fever, myalgias, and cough. Initial physical exam revealed the patient to be normotensive and afebrile, but she did have nuchal rigidity, was obtunded and showed generalized stiffness with her arms flexed and legs extended. Initial emergency department workup included a CT scan of the brain without contrast that showed no mass effect or hemorrhages and normal gray-white differentiation. Complete blood count (CBC) on admission showed a leukocytosis of 18,000/uL with an absolute neutrophil count of 15,600/uL. C-reactive protein (CRP) was elevated at 156.8 mg/L. A lumbar puncture showed a high WBC count of 161/uL with 70% lymphocytes, 25% PMNs, 98 mg/dL protein, and 55 mg/dL glucose. The patient was placed on isolation precautions and empirically started on ceftriaxone, vancomycin, and acyclovir. A CSF BioFire Meningitis/Encephalitis Panel revealed the presence of enterovirus. As a result, empiric antimicrobials were discontinued. On subsequent hospital days, the patient continued to have generalized stiffness, was unable to follow commands, and remained nonverbal. She experienced recurrent febrile episodes as well as multiple witnessed generalized tonic-clonic seizures. An EEG showed abnormal bitemporal slowing suggestive of nonspecific diffuse encephalopathy. Attempted brain MRI on hospital day 5 was not successful. The patient did not improve, had recurrent febrile episodes with leukocytosis, and frequent seizures. A brain MRI under sedation revealed restricted diffusion in the bilateral cortical and subcortical regions of the parietal and posterior temporal lobes, splenium of the corpus callosum, and bilaterally in the posterior thalamus (Fig. 1). These findings raised concern for posterior reversible encephalopathy syndrome (PRES) at the outside facility.

The patient was transferred to our tertiary care facility. On arrival, the patient remained altered with disorientation to person, place, and time. She showed left gaze preference and was unable to follow simple one-step commands. Her reflexes, muscle tone, and sensorium were normal. CRP was elevated at 64.2 mg/L. Her liver function studies and pancreatic studies were unremarkable. Intracranial and extracranial CT angiography showed no abnormalities. Brain MRI showed restricted diffusion in the splenium of the corpus callosum. Left greater than right restricted diffusion in the temporoparietal cortex was present. Subtle leptomeningeal enhancement on the left was also observed. Folate, vitamin B12, vitamin B1, and TSH levels were all within the normal reference ranges.

The patient improved clinically and was able to follow one-step commands. However, she had intermittent episodes of agitation requiring four-point restraints. She was placed on olanzapine as needed with haloperidol for breakthrough agitation. Follow-up brain MRI two weeks later showed stable FLAIR and T2 signal abnormalities within the splenium of the corpus callosum and thalami with no residual hypointensity on ADC map images, indicating no persisting restricted diffusion in these locations. Previous temporoparietal diffusion hyperintensities also had returned to normal and no new areas of signal abnormalities were identified (Fig. 2). At this point, the patient was awaiting placement in a skilled nursing facility. Her mentation and orientation continued to improve. Her episodes of aggression and agitation lessened.

A month after admission, the patient complained of decreased visual acuity. She was found to have decreased bilateral blink-to-threat reflexes with left-gaze preference. However, she was able to distinguish colors and track around the room. As a result, a repeat brain MRI was done on January 10, 2018. New cortical-restricted
**Fig. 1.** MRI Brain: **A** Axial DWI. Restricted diffusion in posterior temporal, parietal, and bilateral occipital lobe cortex. Restricted diffusion in splenium of corpus callosum and bilateral posterior thalami. **B** Axial DWI. Restricted diffusion in parietal lobe cortex. **C** Axial T1. Leptomeningeal enhancement.

Diffusion was present in the bilateral parietal and occipital lobes. Stable abnormal diffusion abnormality within the splenium of the corpus callosum and thalami remained (**Fig. 3**). These findings were concerning for Creutzfeldt-Jakob Disease but a 14-3-3 protein analysis was found to be within the normal reference range and real-time quaking-induced conversion failed to detect abnormal prion proteins.

Repeat CSF PCR for enterovirus was negative as well as a swab of the oropharynx. Cerebrospinal fluid testing for California (La Crosse) encephalitis, John Cunningham virus, *Mycobacterium tuberculosis*, Eastern equine encephalitis virus, *Cryptococcus neoformans*, VZV, HSV-1, HSV-2, CMV, VDRL for neurosyphilis, and angiotensin converting enzyme for neurosarcoidosis all proved to be negative. An India ink stain was performed and proved to be negative. Serum and plasma testing for hepatitis B virus, hepatitis C virus, HIV-1, HIV-2, John Cunningham virus, *Borrelia burgdorferi*, *Borrelia mayonii*, *Borrelia Garinii*, and *Borrelia afzelii* were all negative. The prior hospital had tested a CSF sample for West Nile virus and *Streptococcus pneumoniae* antigen, both of which were negative. Blood and CSF cultures showed no growth for bacteria or fungi. However, a follow-up chest X-ray was negative, AFB sputum culture ultimately showed no growth for 42 days, and sputum PCR for *Mycobacterium tuberculosis* was negative.

A serum Epilepsy Autoimmune Evaluation (Mayo Clinic Laboratories) failed to reveal any of the 19 autoantibodies tested. A serum NeoCerebellar Degeneration Paraneoplastic Profile with Recombx (Quest Diagnostics) was unremarkable for any autoantibodies indicative of cerebellar degeneration. CSF and serum paraneoplastic autoantibody evaluations were negative. The patient’s IgM, IgG, and IgA levels were all within the normal reference ranges. She ultimately received a five-day course of 400 mg/kg/day IVIG. Although the patient was not at baseline, she was discharged in an improved clinical condition with decreased visual acuity. She was instructed to follow-up as an outpatient with neurology, psychiatry, and infectious disease.
The presence of enterovirus in the patient’s CSF was established with the use of a CSF BioFire Meningitis/Encephalitis Panel. This panel is a molecular test used to assess the presence of 14 bacterial, viral, and fungal pathogens. It has an overall sensitivity of 94.2% and specificity of 99.9% [15]. The patient later had a repeat CSF PCR analysis that was negative for the presence of enterovirus. However, there are documented cases in the literature in which a CSF PCR for enterovirus was negative yet positive confirmation was obtained through a brain biopsy [5,14]. Our patient did not undergo a brain biopsy.

The cortical and subcortical parietal and posterior temporal lobe diffusion abnormalities observed on brain MRI (Fig. 1) prior to transfer to our facility raised concern for posterior reversible encephalopathy syndrome (PRES). PRES typically has an acute presentation and commonly manifests as seizures, visual disturbances, headache, and altered mental status [17]. Hypertension is seen in over 70% of patients, and renal injury is frequently present [18]. There are cases in the literature of PRES occurring within hours to days after the infusion of rituximab with resolution of symptoms in 1–2 days and no lasting residual deficits [19]. Our patient persistently had a blood urea nitrogen level under 12 mg/dL and a creatinine under 0.90 mg/dL. Her last rituximab infusion was 4 months prior to presentation which is inconsistent with prior cases of PRES after rituximab. In addition, she continues to have neurological deficits including decreased visual acuity. Given the aforementioned, PRES is an unlikely etiology.

Determining the etiology of encephalitis can be diagnostically challenging and even careful examination of a brain biopsy specimen can fall short [16]. Prior reported cases of enteroviral meningoencephalitis in association with rituximab have demonstrated thalamus and basal ganglia involvement on MRI, which is similar to what we have observed in our patient [6,7,9]. Autoimmune encephalitis was considered highly unlikely as all neurologic antibody studies were negative. Although this does not completely exclude autoimmune encephalitis as a possible etiology, it is interesting to note that rituximab is recommended as part of the treatment for autoimmune encephalitis, even in the absence of an identified antibody [20].

Previously, the administration of high-dose IVIG and pleconaril, an antipicornaviral agent, were the mainstay of treatment for enteroviral meningoencephalitis [11,4,10]. However, there is very little evidence in the present body of medical literature to support this. In addition, pleconaril is no longer available in the United States. Previous reports of patients with rituximab related enteroviral meningoencephalitis describe lasting neurologic residual deficits and behavioral problems [4,7,8]. This is consistent with our patient’s current state. She has cortical blindness, episodes of altered mental status with agitation and visual hallucinations, aphasia requiring speech therapy, altered balance and discoordination requiring physical therapy. Her most recent MRI done 10 months after discharge shows ex vacuo dilatation of the occipital horns of the lateral ventricles and bilateral occipital lobe encephalomalacia (Fig. 4). Chronic meningoencephalitis is a rare and potentially fatal complication of a typically nonthreatening pathogen. It should be an important clinical consideration in an immunocompromised patient on prolonged rituximab therapy.

**Conflict of interests**

On behalf of all authors, there are no conflicts of interests to declare.
References


