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Chronic Enterovirus Meningoencephalitis in Prolonged B-Cell Depletion After Rituximab Therapy

Case Report

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Abstract

Objectives

Persistent impaired immunity is possible even years after B-cell depleting therapies. This may favor the occurrence of infections, including infectious meningitis and encephalitis. In this study, we report a case of chronic enterovirus meningoencephalitis in prolonged B-cell depletion years after rituximab therapy.

Methods

This is a case report from a German academic hospital. In addition to repeated clinical examinations, repeated brain MRI and extended CSF and laboratory diagnostics were performed. We used the CARE checklist when writing our report.

Results

A 38-year-old man presented with high fever (>40°C), severe headache, and progressive neurologic and cognitive deficits. As result of previous lymphoma therapy with rituximab years ago, prolonged B-cell aplasia was detected. To restore humoral immunity, the patient received repeated infusions of immunoglobulins. In the end, a complete restitution of the physical and mental condition was achieved with the established therapy.

Discussion

This case report should emphasize the importance of assessing humoral immunity even years after B-cell depletion therapy, especially in case of opportunistic infections.

Introduction

We present the case of a 38-year-old man with chronic enterovirus meningoencephalitis due to unrecognized, persistent B-cell depletion years after lymphoma therapy with rituximab.[1]

Case Report

The 38-year-old farmer first presented to a tertiary hospital in September 2021 with high fever (>40°C) and severe headache. Neurologic examination revealed no other neurologic deficits (modified Ranking scale, mRS: 1 point). He had a history of Burkitt lymphoma (diagnosed in 2017; cytogenetic findings: translocation t (8; 14) with IGH-MYC fusion, 1q duplication, and 6q deletion). The diagnosis included involvement of the liver, bone marrow, and right cervical lymph

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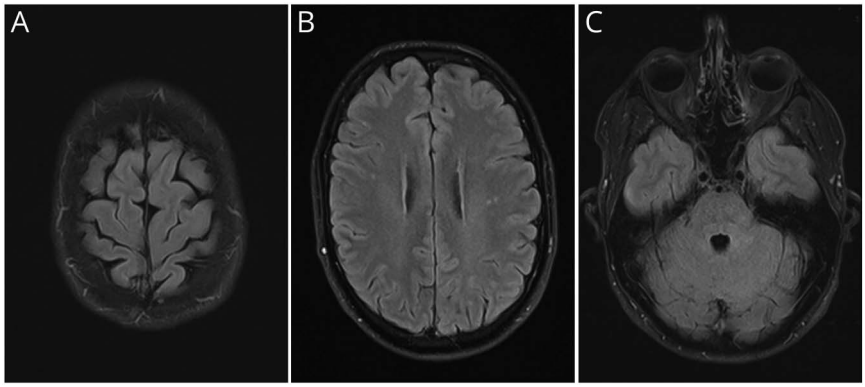
nodes. Between July and December 2017, the patient received 6 courses of short-intensity chemotherapy combined with the anti-CD20 antibody rituximab analogous to the GMALL B-ALL/NHL 2002 protocol (NCT00199082 at ClinicalTrials.gov). The protocol was established as part of a multicenter treatment optimization study in high-grade non-Hodgkin lymphoma.[2] Treatment consisted of 6 five-day cycles of high-dose methotrexate, high-dose cytarabine, cyclophosphamide, etoposide, ifosphamide, corticosteroids, and triple intrathecal therapy (cytarabine, methotrexate, and dexamethasone). Rituximab was given before each cycle. The last comprehensive hemato-oncologic staging in July 2021 still indicated sustained complete remission. Before the onset of our patient's symptoms, his children were experiencing *hand-foot-and-mouth disease*, which is caused by enteroviruses of the Picornaviridae family.[3]

Aseptic meningitis was suspected, and the CSF confirmed a mixed pleocytosis of 181 cells/μL (lymphocytes 11%, monocytes 39%, and neutrophils 45%; total protein 521 mg/L; lactate 1.7 mmol/L; and glucose 3.04 mmol/L). Rapid CSF multiplex PCR testing was positive for enterovirus (BioFire FilmArray®). A brain MRI disclosed single subcortical white matter lesions rated as unspecific (Figure 1). Symptomatic measures were initiated (lowering of the fever by medication and physical means and IV fluid administration), and the patient was discharged 9 days after admission. One month later, the patient presented again first to the tertiary hospital and 1 day later to our hospital with persistent general weakness and fatigue. Again, neurologic examination showed no focal neurologic signs; however, anamnesis revealed an ongoing anhedonia, lethargy, and sleep disturbances (mRS: 1 point). Brain MRI was unchanged, and the WBC count in the CSF remained elevated (60 cells/μL, lymphocytes 38%). Based on the observed psychiatric symptoms, a depressive disorder with obsessive compulsive traits was considered. Six months after the initial onset of symptoms, the patient was admitted for a third time to the same hospital due to a further dramatic deterioration in physical and mental condition with significant decreases in attention, concentration, and memory, severe motivational disturbances, and a flattening of emotions. Due to the progressive worsening of the condition, a five-day high-dose cortisone therapy was initiated suspecting autoimmune encephalitis without significant clinical benefit, and the patient was transferred to our neurologic clinic. On examination, a severely apathetic patient with marked concomitant apraxia, moderate aphasia, and mild tetraspasticity was observed. He was not able to walk independently anymore and needed full assistance for all activities of daily living (mRS: 4 points). Brain MRI now revealed multifocal T2 hyperintense lesions involving cortical, subcortical, and infratentorial structures without pathologic enhancement after application of contrast agent (Figure 2). The CSF showed persisting lymphocytic pleocytosis (19 cells/μL, lymphocytes 85%). Negative blood test results were obtained for hepatitis, syphilis, measles, yersinia, rickettsia, leptospires, HHV 6/7/8, bartonella, coxiella, HTLV-1/-2, schistosomes, leishmania, tuberculosis, ANA and ANCA screening, and thyroid autoantibodies. CSF results were negative for Bornavirus, cytopathologic analysis and, in addition, 14-3-3 and RT-QuIC to exclude prion disease. In both the CSF and blood, negative results were found for Borrelia, toxoplasmosis, JC virus, and antineuronal and onconeuronal antibodies. Flow cytometric analysis of the whole blood and CSF did not show CSF CD19 B cells arguing against B-cell lymphoma recurrence. Yet a complete B-cell aplasia and reduced levels of immunoglobulins (IgG: 5.41 IgA: 0.66 IgM: <0.1 levels in g/L) were found as a correlate of persistent humoral immunodeficiency years after lymphoma treatment. Furthermore, positive enterovirus PCR (BioFire FilmArray) was again identified in the CSF. Chronic persistence of enterovirus infection was supported by molecular typing, resulting in identification of enterovirus A71 (EV-A71), which was found in the current CSF sample and in the sample from the time point of first disease manifestation.

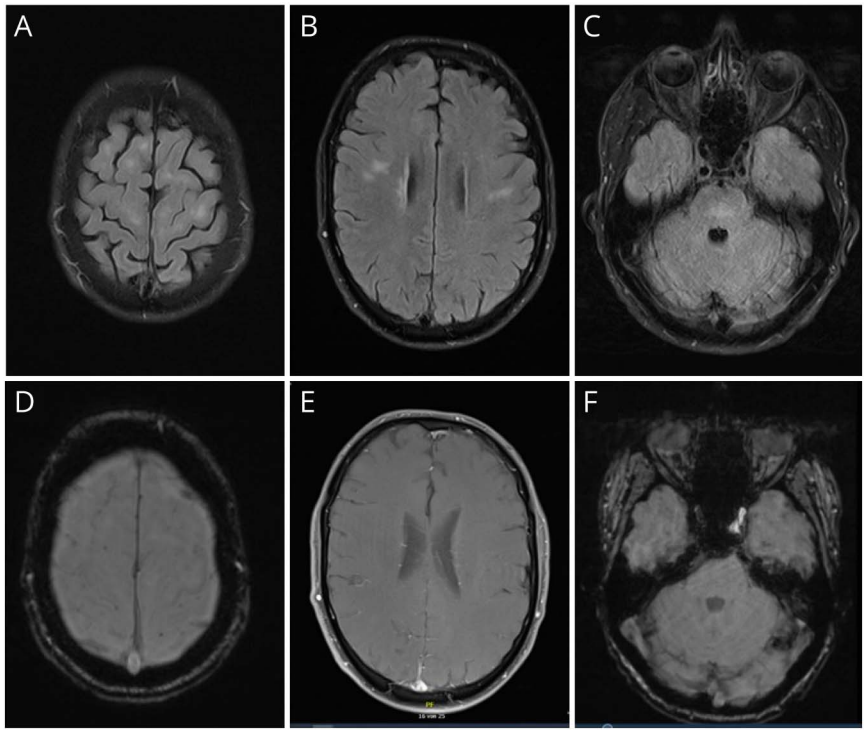
The diagnosis of chronic enterovirus meningoencephalitis under persistent B-cell depletion after lymphoma therapy

Figure 1 Brain MRI at First Presentation With Symptoms of Meningitis



Brain MRI (pictured: axial T2 dark fluid weighting) showed no anomalies in cortical (A) and infratentorial (C) structures and single subcortical white matter lesions rated as unspecific (B).

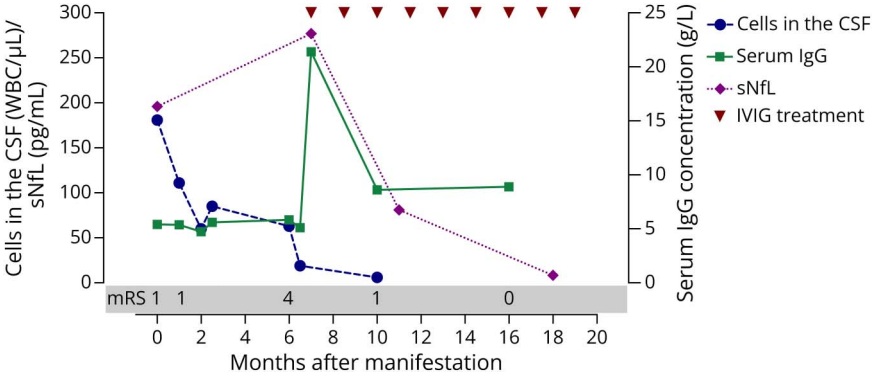
Figure 2 Follow-up Brain MRI After Development of Severe Neurologic Symptoms



Brain MRI (pictured: axial T2 dark fluid weighting) revealed multifocal T2 hyperintense lesions in different localization including (A) cortical, (B) subcortical, and (C) infratentorial structures without pathologic enhancement after application of contrast agent (D–F).

including rituximab therapy 4 years earlier was made and treatment with IV immunoglobulins (IVIGs) of 2g/kg bodyweight initiated. A few days later, aphasia and apathia improved, and he was able to walk again over short distances. IVIGs were substituted with 0.5g/kg bodyweight every 6 weeks, and after 3 months, the patient had almost returned to his physical and cognitive baseline level, with only slight memory gaps persisting from the period of illness itself (mRS: 1 point). CSF sampling between the 1st and 2nd IVIG dose revealed a further decrease in pleocytosis (6 cells/μL, lymphocytes 77%), see also Figure 3. Furthermore, enterovirus could not be detected anymore in the CSF. At follow-up 11 months after the start of IVIG treatment, the patient had fully recovered, was back to work (mRS: 0 points), and serum IgG levels were compensated under IVIG substitution (see also Figure 3). However, B-cell aplasia persisted, and IVIG substitution is still ongoing. In addition, serum neurofilament light (sNfL) was retrospectively assessed as a biomarker of neuroaxonal damage during the course of the disease. sNfL levels were measured using an ultra-sensitive assay (NF-light) on the HD-X analyzer (Quanterix). The patient had a markedly elevated sNfL level at first manifestation of the disease (196 pg/mL) and shortly before starting IVIG treatment (277 pg/mL). At follow-up 11

Figure 3 Overview Laboratory Parameters and Treatment in Clinical Course of the Disease



Overview on Serum IgG concentrations (g/L; green rectangles), white blood count (cells/μL; blue dots) in the CSF and serum neurofilament light concentration (sNfL, purple hexagons). The red triangles indicate the application of IV immunoglobulins (IVIG). Modified ranking score (mRS) identified in gray textbox above x-axis.

months after the start of IVIG treatment, a decrease in sNfL concentration was documented, which correlated with the positive clinical outcome (81 pg/mL). Treatment with IVIGs was well tolerated, with no relevant side effects.

Discussion

There is compelling evidence that adding rituximab to short-term intensive chemotherapy increases event-free survival in Burkitt lymphoma.[4] However, chronic B-cell deficiency has been described in individual cases up to 5 years after rituximab therapy.[5-7] Moreover, cases of chronic enterovirus infections after B-cell depleting therapy have also been described in the setting of other underlying diseases, for example, in the treatment of psoriatic arthritis.[8] We therefore conclude for this case that the severe neurologic symptoms were caused by a chronic enterovirus meningoencephalitis after an impaired humoral immunity due to prolonged B-cell depletion more than 5 years after rituximab therapy. Hand-foot-and-mouth disease in the home environment, which is often caused by EV-A71, was hypothesized as a possible source of infection. The restoration of humoral immunity using IVIGs resulted in a rapid control of enterovirus infection and symptom improvement. There is limited data in the literature on the treatment of chronic enterovirus infection. The most common treatment has been IVIG, with or without combination with pleconaril, with outcomes ranging from complete resolution to death.[9]

Taken together, this case report illustrates the high importance of examining humoral immunity even years after B-cell depletion therapy, if infections occur.

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