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Case Report

# Human Herpesvirus-7 Encephalitis Following Treatment with Obinutuzumab-CHOP in a Patient with Non-Hodgkin Follicular Lymphoma: A Case Report

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## Abstract

Human herpesvirus-7 (HHV-7) is a lymphotropic virus that belongs to the Betaherpesviridae subfamily. Along with febrile disease and cutaneous manifestations, it can also cause neurological complications, including encephalitis, mostly in immunocompromised patients. The anti-CD20 monoclonal antibody, Obinutuzumab is increasingly used, in combination with chemotherapy, for the treatment of patients with chronic lymphocytic leukemia and follicular lymphoma (FL). We report a case of HHV-7 encephalitis in a young female patient with FL after receiving Obinutuzumab-based immunochemotherapy. Although it is quite rare in the clinical practice, physicians should be aware of the possibility of HHV-7 encephalitis in those who have received anti-CD20 monoclonal antibodies and develop signs of neurological deterioration.

**Keywords:** Anti-CD20 monoclonal antibody; Encephalitis; Follicular lymphoma; Immunochemotherapy; Human herpesvirus-7; HHV-7; Obinotuzumab

## Introduction

Human herpesvirus-7 (HHV-7) is a lymphotropic virus that belongs along with HHV-6 and Cytomegalovirus (CMV) to the Betaherpesviridae subfamily [1,2]. Primary infection, in the majority of people, occurs in childhood, causing febrile disease with usually cutaneous manifestations (exanthem subitum) and is followed by a lifelong latent state [1,3,4]. Neurological complications of HHV-7 infection, including encephalitis, might occur, mainly in children as a primary infection or in immunocompromised hosts after reactivation [1-3,5,6]. Obinutuzumab is a glycoengineered type II anti-CD20 monoclonal antibody, which induces direct cell death and has better antibody-dependent cellular cytotoxicity than rituximab. Obinutuzumab has been approved, in combination with chemotherapy, for the treatment of patients with chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL). However, the use of anti-CD20 monoclonal antibodies is accompanied by severe hypogammaglobulinemia and the development of opportunistic infections.

Despite several cases of roseolavirus-associated encephalitis occurring after combined immunochemotherapy (ICM), our patient with FL is, to the best of our knowledge, the first reported case who developed HHV-7 encephalitis after receiving obinutuzumab-based treatment.

## Case Report

A 37-year-old woman was diagnosed in October 2018 with Follicular Lymphoma (FL) grade 1-2, Ann Arbor clinical stage IIIA and Follicular Lymphoma International Prognostic Index (FLIPI) score 3. After initial "watch and wait" strategy, the patient presented clinical and radiological progression and was treated with ICM with Obinutuzumab-CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Methylprednisolone) in September 2020.

Immediately after the 4$^{th}$ cycle of ICM, the patient reported transient episodes of horizontal diplopia although ophthalmologic examination was normal. After the 5$^{th}$ cycle of ICM and the reappearance of the symptoms she underwent magnetic resonance imaging (MRI) of the brain which revealed periventricular white matter increased signal on T2 weighted images in the frontal lobes bilaterally, with involvement of the genu of corpus callosum, interior right capsule, cerebral right peduncle, midbrain, cerebellar peduncles and the medulla oblongata (Figure 1A-C). Neurological examination and the electroencephalography (EEG) were unremarkable.

Laboratory workup was within normal range (except for mild anemia, Hb 10.6 mg/dl), as were thiamine levels, thereby excluding Wernicke encephalopathy. We performed cerebrospinal fluid (CSF) analysis (Table 1) which revealed only a slightly elevated total protein, with negative polymerase chain reaction (PCR) based tests (film array panel as performed in our institution including Escherichia coli, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae, CMV, Enterovirus, Herpes simplex virus 1 and 2, HHV6, Varicella zoster virus, Cryptococcus neoformans/gatti). CSF culture did not show any growth of bacteria, mycobacteria, or fungi and a cytological examination did not show any malignant cells. Moreover, there was a negative PCR test for JC virus. At that point, CSF was not tested for HHV-7. A serological test for human immunodeficiency virus (HIV) was negative. Similarly, serological tests for autoantibodies including rheumatoid factor and antinuclear antibodies, were all negative, as was myasthenia antibodies testing (anti–acetylcholine receptor-AChR, Muscle specific tyrosine kinase- MuSK, anti-titin). Repetitive nerve stimulation testing was negative for neurological function disorder.

In less than 2 weeks, the patient deteriorated regarding cognitive, visual and memory function, also showing transient amnesia and instability. The laboratory work-up revealed mild hyponatremia (127 mEq/L, normal range: 236-146 mmol/L) and on physical examination the patient had bradycardia. Following hospital admission, she presented an episode of aphasia followed by mild hyperthermia. The patient was treated with dexamethasone (24 g/day), ceftriaxone (2 g/day, 7 days), acyclovir (1,500 mg/day), amphotericin-B (350mg/day), vancomycin (2 g/day) and

ampicillin (12 g/day) as a probable CNS infection.

A new MRI was performed which revealed extensive leukoencephalopathy sparing the subcortical U fibers, involving the cerebral white matter frontally, now extending into the temporal lobes, including the anterior commissure and extending into the body and splenium of corpus callosum which appeared enlarged, the corticospinal tracts including internal capsule, cerebral peduncles, midbrain, superior cerebellar peduncles, left middle cerebellar peduncle and left side of the medulla. There was moderate diffusion restriction in the corpus callosum (Figure 1D). No hemorrhage or contrast enhancement were seen. The differential diagnosis included toxic leukoencephalopathy, possible relapse of lymphoma and were not typical of PML. A second spinal tap was performed and the CSF analysis (Table 1) revealed pleocytosis with predominance of lymphocytes (94%), high protein levels, normal glucose, and normal LDH. CSF culture, cytological and PCR based tests including JC virus were all-negative, except for the HHV-7 DNA test which came out positive. Antibiotic treatment was stopped and the antiviral treatment was changed to foscarnet 3g three times per day (60 mg/kg every 8h) for 21 days with gradual tapering of dexamethasone.

New MRI and Magnetic Resonance Spectroscopy (MRS) were performed 15 days after the previous MRI. Conventional sequences revealed lesions expansion (Figure 1E-F) mainly in the external capsule bilaterally, subcortical white matter, cingulate, medial bilateral thalami, midbrain, pons, vermis and right cerebellar hemisphere. New finding was the appearance of contrast enhancement with areas of linear and nodular appearance (Figure 1G-H). MRS showed increased Choline (Cho) / Creatine (Cr) and Choline / N-Acetylaspartic acid (NAA) ratios, which were calculated 2.40 and 2.54 respectively (Figure 1I). However, these abnormalities were attributed to the low concentrations of Cr and NAA, given the constant concentrations of Cho and the reduction of Cr and NAA compared with the normal appearing brain parenchyma. There were no significant differences of relative cerebral blood volume and relative cerebral blood flow in MR perfusion. Imaging findings were suggestive of an inflammatory process, including a high possibility of immune reconstitution inflammatory syndrome (IRIS) associated with PML or another inflammatory process. Based on imaging findings, lymphoma relapse was considered less likely, however it could not be excluded. Due to the uncertainty of the diagnosis and the need to definitely exclude disease relapse in the CNS, the patient underwent a stereotactic brain biopsy. Microscopically, brain tissue showed a mainly perivascular lymphocytic inflammatory infiltrate, composed of CD3+ T cells and CD68+ histiocytes, whereas PAX5+CD20- B cells were very rare (Figure 2). These findings were considered compatible with the diagnosis of encephalitis. Repeated CSF tests confirmed the positive HHV-7 DNA result. Unfortunately, our laboratory could not perform a quantitative analysis of the HHV-7 DNA in the CSF neither HHV-7 serology, and a PCR test performed in a blood sample was negative for HHV-7 DNA. The patient showed total remission of symptoms and follow-up brain MRI after 3 weeks and after 3 months showed significant improvement of the lesions of the leukoencephalopathy (Figure 1J-K). CSF tests for HHV-7 DNA continued to produce positive results throughout the follow-up period. Neurological examination after 9 months of follow-up did not reveal any residual disability or signs of neurologic disorder.

| CSF analysis (Normal values) | Day -32 | Day -20 | Day 0 | Day 6 | Day 22 |
|---|---|---|---|---|---|
| Color | Clear | Clear | Clear | Clear | Clear |
| Leukocyte count (0-5/mm3) | 0 | 2 | 30 | 0 | 5 |
| Total Protein (15-45 mg/dL) | 57.3 | 61 | 77 | 41 | 38.2 |
| Albumin (mg/dL) | 42 | 47.5 | 48 | 22 | 21.9 |
| Glucose (45-80 mg/dL) | 52 | 54 | 77 | 78 | 63 |

| | | | | | |
|---|---|---|---|---|---|
| LDH (U/L) | 15 | 24 | 17 | 16 | 12 |
| Gram stain (Negative) | Negative | Negative | Negative | NA | NA |
| Culture (Sterile) | Sterile | Sterile | Sterile | NA | NA |
| Film array +JC Virus | Negative | Negative | Negative | Negative | NA |
| West Nile | NA | NA | Negative | NA | NA |
| HHV-7 | NA | NA | Positive | Positive | Positive |

**Table 1:** CSF analysis of patient. Therapy was initiated on the day of the diagnosis (Day 0) (CSF: cerebrospinal fluid, NA: not applicable)

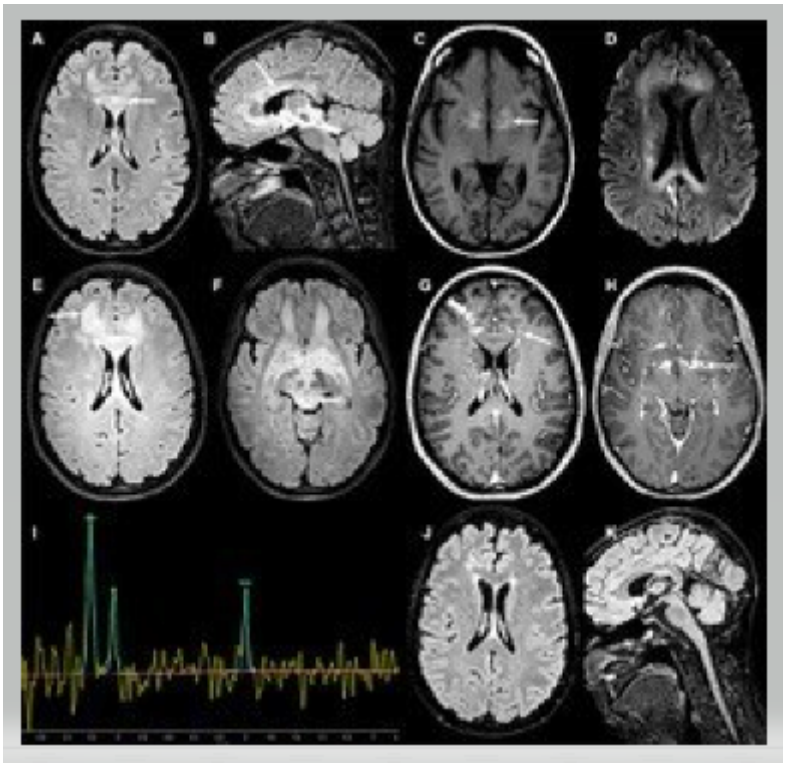

**Figure 1:** Serial MRI of HSV-7 encephalitis following Obinutuzumab-CHOP treatment.

Axial (A) and sagittal (B) FLAIR images demonstrate increased signal intensity in the frontal white matter bilaterally, corpus callosum (arrows A, B) anterior longitudinal ligament, midbrain (thick arrow B) and medulla oblongata. Axial T1 image (C) reveals hyperintensities in the basal ganglia (arrow C). Mild restriction is noticed on diffusion weighted imaging (DWI), mainly in the corpus callosum (arrow D). Lesions expansion is noticed 15 days later on axial FLAIR images (E, F) in the frontal subcortical white matter (arrow E), basal ganglia and midbrain (arrow F). Axial T1 images post contrast administration (G, H) reveal nodular (thin arrows G,

H) and linear (thick arrow G) enhancement. Increased ratios of Choline (Cho) on MR spectroscopy (I) were attributed to the reduced concentrations of Creatine (Cr) and N-Acetylaspartic acid (NAA) compared with normal parenchyma. Follow up axial (J) and sagittal (K) FLAIR images demonstrate resolution of the abnormal signal.

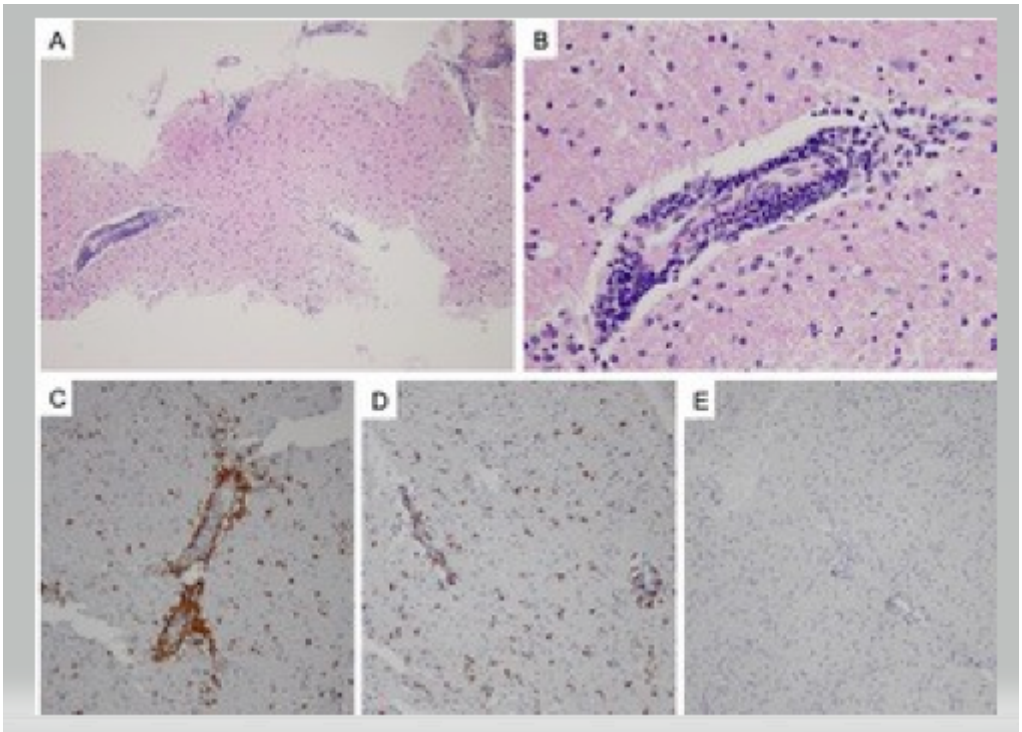


**Figure 2:** Brain tissue showing moderate to dense perivascular lymphocytic inflammation (H&E, A:10x, B:20x), comprising mostly CD3+ T cells (C), CD68+ histiocytes (D) and rare PAX-5+ (E) CD20- B cells.

## Discussion

To the best of our knowledge, this is the first case report of a patient with FL who suffered from obinutuzumab-associated HHV-7 encephalitis. There are several cases of roseolavirus-associated encephalitis in patients that have received ICM and have undergone hematopoietic stem cell transplantation (HSCT) or solid-organ transplant (SOT) [3, 7-9], cases of progressive multifocal leucoencephalopathy and CMV after receiving anti-CD20 monoclonal antibodies (including rituximab and obinutuzumab) [8, 10-11], and even a case of HHV-6 encephalitis after receiving rituximab for dermatomyositis [12]. Viral encephalitis is an aseptic inflammatory process of the brain parenchyma associated with clinical symptoms of brain dysfunction. It is a medical emergency with significant morbidity and mortality [3].

HHV-7, is a member of the Herpesviridae family, subfamily Betaherpesvirinae, and genus Roseolavirus and along with HHV-6A and HHV-6B have been regarded as lymphotropic viruses. Similarly, to other human herpesviruses, they are ubiquitous and establish a lifelong latent infection. CD4+ T lymphocytes are assumed the sites of latent infection of HHV-7 [1-2, 5, 13]. Roseolaviruses primary infections cause acute febrile disease associated with fever, skin rash, seizures, gastrointestinal and respiratory symptoms in children, with the most manifestation disease being exanthema subitum [1-2, 4].

Defects of cellular immunity seem to be the most prominent favoring factor of the emergence of active HHV-6 and HHV-7 infections [1]. Reactivation of HHV-7 is frequently observed in HSCT and SOT recipients [1, 3], and roseola virus-associated encephalitis is observed in other immunocompromised individuals, such as HIV-infected patients [1, 4]. Since the seroprevalence of HHV-6 and HHV-7 infections is very high in adults, the vast majority of active infections among adult patients is thought to be due to viral reactivations [1, 5]. In our case, a delayed primary infection by HHV-7 cannot be excluded, since serology for HHV-7 was not available, but considering the patient's age, reactivation seems the most probable scenario.

Disease spectrum may involve many organ systems, with the CNS being a major target, taking into consideration roseola viruses' neurotropism [1, 5]. Several brain functions, including visual, verbal, behavioral, and cognitive and memory functions, can be disturbed, presented as amnesia (especially short-term), disorientation or even delirium. There also can be evidence of focal neurological signs, insomnia, seizures and dysesthesia. Moreover, other common findings that have been reported include autonomous and hypothalamic disturbances, as also hyponatremia [3]. Our patient presented with mild disorientation, short-term memory loss, visual dysfunction, and with hyponatremia and bradycardia, all supporting the diagnosis.

EEG might show abnormalities earlier before neuroimaging abnormalities are observed. In several cases of roseola virus infection, computed tomography (CT) and MRI have detected cerebral lesions with the brain stem (midbrain, pons, medulla oblongata), the limbic area (amygdala and hippocampus), and the temporal lobe being the most common sites [3]. The radiological examination of our patient also revealed lesions in the midbrain, medulla oblongata and temporal lobe among other sites, which resolved after treatment. The examination of the CSF might show pleocytosis with lymphocyte predominance and normal or elevated protein and glucose levels [3], as was observed in our case.

Detection and quantification of viral nucleic acids have become the gold standard of diagnostic procedures applied to HHV-6 and HHV-7 [1]. Detecting genomic DNA by polymerase chain reaction (PCR) is currently the reference technique. Due to the sensitivity and specificity of current PCR techniques, detection of roseola virus DNA in CSF is highly indicative of an active infection of the CNS, especially in the presence of encephalopathy. The diagnosis must be considered even if the results of the concomitant DNAemia analysis are negative as limited local viral reactivations in CNS is possible [13]. In our case, the role of HHV-7 as the cause of the neurological disorder is supported by the sustained amplification of HHV-7 in three separate CSF samples, although detectable viremia was not present.

Anti-roseola virus medication has to be initiated by the time reactivation of HHV-6 or HHV-7 is recognized [3]. Foscarnet and ganciclovir are used as first line therapy, and cidofovir as second but with insufficient data. Generally, foscarnet 60 mg/kg i.e. every 8 h or 90 mg/kg every 12 h (180 mg/kg/day), or ganciclovir 5 mg/kg i.e. every 12 h are recommended. Antiviral therapy should be for at least three weeks and immunosuppressive medications should be reduced if possible [3, 7].

**Ethics Approval and Consent to Participate:** Ethical approval is not appropriate. The authors obtained patient's consent to participate.

**Consent for Publication:** The authors obtained informed consent from the patient to publish information on his disease and clinical course.

**Competing Interests:** The authors declare that they have no competing interests.

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