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LETTER TO THE EDITORS

HSV-2-encephalitis in a patient with multiple sclerosis treated with ocrelizumab

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Dear Sirs,

The treatment of multiple sclerosis, especially with monoclonal antibodies is a balance between efficacy and safety [1]. Ocrelizumab leads to a depletion of CD20 B cells and was approved by the US Food and Drug Administration in March 2017 and by the European Medicines Agency in January 2018 for the treatment of active relapsing and progressive multiple sclerosis. To the best of our knowledge no cases of viral encephalitis under treatment with ocrelizumab have been reported so far [2]. Here, we report the case of a 61-year-old man (K.H.) with secondary progressive multiple sclerosis, who suffered from HSV-2-encephalitis under treatment with ocrelizumab. First symptoms of a relapsing–remitting multiple sclerosis occurred in 1997. In November 2005 he developed a secondary progressive course, and hence next year the diagnosis of that type of multiple sclerosis was established. He had developed left-sided spastic hemiparesis and neurogenic bladder dysfunction. Despite treatment with mitoxantrone until May 2015 he developed spastic tetraparesis and in 2017 dysarthria. In September 2018 ocrelizumab was started with an initial dose of 300 mg and a second dose of 300 mg at the end of the month. Against spasticity he had received 4-aminopyridine for several years and triamcinolon intrathecally once a year. No other immunosuppressive or immunomodulatory drugs were applied between the termination of mitoxantrone and the start of ocrelizumab. The last treatment with triamcinolon was 3 months before the first administration of ocrelizumab. Nevertheless, he was unable to walk and his left arm was almost plegic. About 4 weeks after the second application of ocrelizumab he developed severe headache and the following day a bilateral clonic seizure with movements mainly of the right arm. He was referred to our emergency room, where some other seizures without lateralizing signs occurred. Seizures stopped after treatment with lorazepam 2 mg and a loading dose of levetiracetam 2000 mg. Initially he had a temperature of 38.4° and altered consciousness, which was regarded as a postictal condition. The cerebrospinal fluid (CSF) showed a pleocytosis of 559/µl with 546/µl mononuclear cells, a blood-CSF barrier dysfunction (QAlb 20,7) and an elevated lactate (3,2 mmol/l) without a quantitative intrathecal synthesis of immunoglobulins. In a polymerase chain reaction (pcr) (RealStar HSV PCR Kit 1.0®) performed in our laboratory 9×10^6 copies of HSV-2 were found. The pcr was negative for HSV-1. Unfortunately we have no information about prior HSV serologies. Whereas CD19 lymphocytes had been 15.9% after the first dosage of ocrelizumab, they now had decreased to 5%. Aciclovir 750 mg every 8 h was given intravenously for 21 days, 4-aminopyridine was stopped and he recovered clinically within a few days. With levetiracetam 500 mg bis in die he remained free of seizures. A MRI 5 days after beginning of treatment was performed with axial DWI, FLAIR, T1-, T2 sequences, sagittal T2 sequences and isometric 3D-volume sequences after contrast medium. It revealed no acute encephalitic lesions. After 13 days of treatment pleocytosis in CSF was reduced to 381/µl, the blood-CSF barrier dysfunction decreased and just 1206 copies/µl of HSV-2 were detected by pcr. After another week of treatment with aciclovir the patient was discharged in his habitual condition.

HSV-2 encephalitis with normal MRI brain imaging is a rather rare condition. In one 68-year-old patient with known B cell chronic lymphatic leukaemia the CSF pleocytosis was very similar to the finding in our patient (540/µl with > 90% lymphocytes) [3]. Some years later even an

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immunocompetent adult with symptoms of dementia, similar CSF findings and normal MRI brain imaging was published [4]. Therefore, in patients with acute focal neurological signs like seizures with a focal onset MRI cannot rule out acute encephalitis and if encephalitis is suspected CSF should be obtained.

Compliance with ethical standards

Conflicts of interest JRösche reports speaker honoraria from Eisai unrelated to this work. J Bösel reports speaker honoraria and travel support from Bard, Zoll, and Boehringer Ingelheim unrelated to this work. The other authors have nothing to declare.

Ethical standards This case report is in accordance with the ethical standards laid down in the declaration of Helsinki and its later amendments.

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