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**Title: Report of two cases of tocilizumab induced recurrent meningitis or meningoencephalitis**

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**Key words:**

Tocilizumab, rheumatoid arthritis, juvenile idiopathic arthritis, meningitis, encephalitis, meningoencephalitis

Dear editor,

Tocilizumab (TCZ) is a humanized monoclonal antibody which has shown significant efficacy both in rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA). We report two cases of neurologic disorders following TCZ administration.

**Case 1:** A 68-years-old woman with RA was treated by methotrexate associated successively with rituximab, abatacept, etanercept, TCZ, infliximab, with insufficient response. Due to high activity of the RA, TCZ was reintroduced. On the day after the first infusion of TCZ 8 mg/kg, she developed confusion with altered consciousness, aphasia, vomiting, right hemiparesia. The CRP was elevated (37 mg/l). Cerebrospinal fluid (CSF) assessment showed 48 elements (98% neutrophils), and an elevated protein level at 0.59 g/L. Microbiological cultures, herpes virus simplex (HSV) 1 and 2, Varicella-Zoster Virus (VZV), Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), adenovirus, Human-Herpes-Virus type 6 (HHV-6), JC virus, Anti-NMDA-receptor antibodies and Lyme-specific antibody were negative. Cerebral magnetic resonance imaging (MRI) revealed an encephalitis (figure 1). An electroencephalogram (EEG) revealed continuous slow waves on the left fronto-temporal derivations. Probabilistic treatment by ceftriaxone, dexamethasone, and levetiracetam was initiated. Rapid recovery of consciousness and hemiparesia during the following 48 hours was obtained, but cognitive impairment remained.

**Case 2:** A 17-year-old woman with JIA, was regularly treated by indometacine, methotrexate, prednisone, and TCZ 10 mg/kg every 2 weeks. Fifteen days after the last administration, she presented a first episode of severe headache, vomiting and asthenia. Lumbar puncture showed aseptic meningitis (324 elements, 78% lymphocytes, protein level 0,63 g/l, normal glucose level). The patient recovered without antibiotic treatment. One month later, after a second TCZ administration, she presented intense headache progression, nausea, photo and phonophobia, widespread pain to back and legs, fever (38°C), and stiff neck without focal neurologic signs. CRP was not elevated. Lumbar puncture revealed an aseptic lymphomonocytic meningitis: 113 elements (41% lymphocytes, 50% monocytes, protein level 1.13 g/l). PCR EBV, CMV, HSV, VZV, HHV6, enterovirus and JC virus were negative. EEG revealed a slow and moderate diffuse dysrhythmia sometimes associated with vigilance's fluctuation. Cerebral MRI was normal. Antinuclear antibodies were negative. Meningeal syndrome disappeared in two days, without relapse after TCZ discontinuation.

## Discussion

Causes of aseptic meningitis with or without encephalitis are multiple. The main infectious causal agents in aseptic meningitis are enteroviruses, HSV-2 and VZV<sup>2</sup>, which were ruled out in both cases. A previous case of rhomboencephalitis due to listeria after TCZ was previously reported. 48% to 66% of aseptic meningitis remains without infectious etiologies<sup>2-4</sup>.

Inflammatory diseases such as connective tissue diseases, vasculitis or malignancy may also be responsible of meningitis or encephalitis. Herein, drug-induced aseptic meningitis (DIAM) seems probable for both reported cases. Recently, other monoclonal antibodies have been associated with aseptic meningitis, such as infliximab, adalimumab etanercept, efalizumab or cetuximab<sup>5-6</sup>. Pharmacovigilance assessment agreed to probable causality of TCZ in the absence of all other possible etiologies together with the rapid onset after administration. To the best of our knowledge, these are the first two cases of aseptic meningoencephalitis or recurrent meningitis under TCZ to be reported.

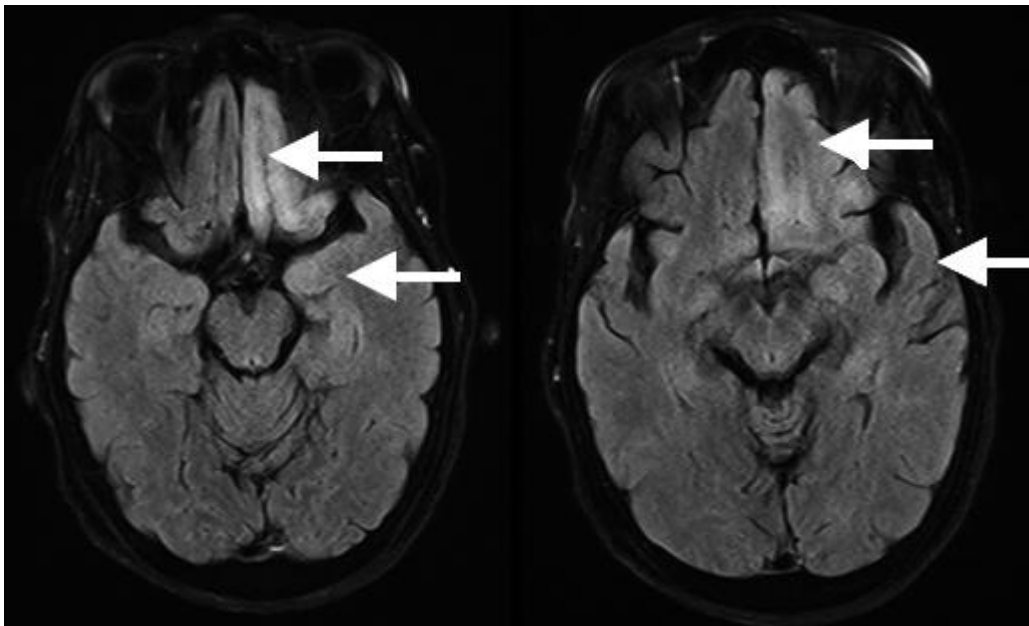


Figure 1: hypersignal in T2 FLAIR-weighted sequences (also present in T2-weighted sequences), in the left fronto-temporal lobe without enhancement after injection of gadolinium in T1-weighted sequences of cerebral MRI (image not shown).

### **Key messages:**

Tocilizumab may cause aseptic meningoencephalitis.

Confusion or neurological signs occurring after biologic agent infusion should raise the possibility of drug-induced aseptic meningitis.

Drugs commonly associated with meningo-encephalitis or encephalitis are nonsteroidal anti-inflammatory, antibiotics or immunosuppressive-immunomodulatory therapies.

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### **Conflict of interest statement**

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