Seronegative encephalitis in a patient with follicular B-cell non-Hodgkin lymphoma: possible complication related to Obinutuzumab

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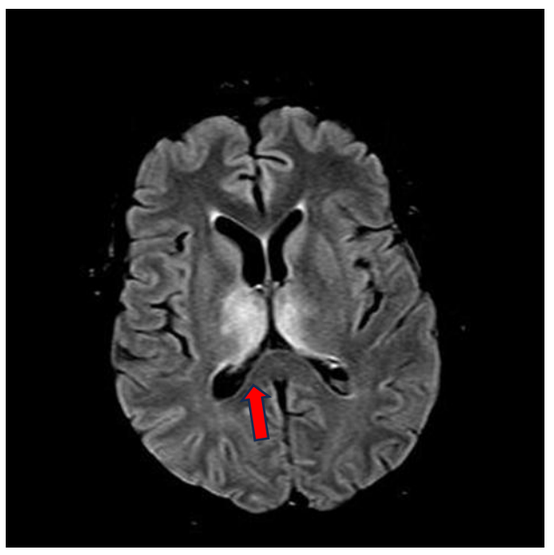
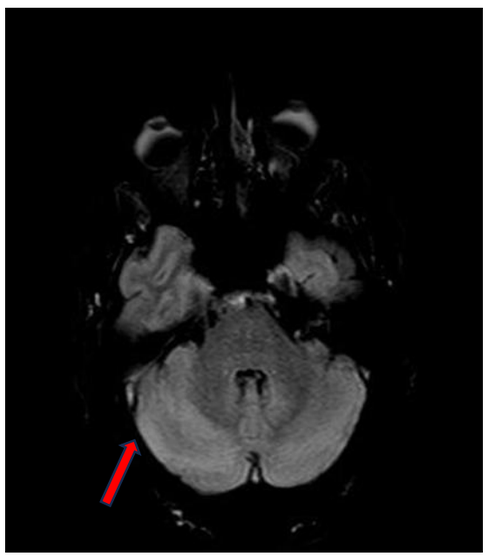
Introduction

Seronegative encephalitis is an heterogeneous group of dysimmune encephalitis in which there is a subacute onset of cognitive disorders, behavioral alterations, seizures in the presence of neuroradiological pictures compatible with immune-mediated encephalitis, having excluded the presence of known autoantibodies or infectious agents in biological fluids (serum or CSF). Anti-CD 20 immunosuppressive drugs such as Obinutuzumab can paradoxically trigger or promote dysimmune reactions due to their ability to deplete B cells and activate pathological T cells.





CASE REPORT

Anamnesis

- 60-year-old male patient
- B-cell follicular non-Hodgkin lymphoma in remission after radiotherapy and chemotherapy according to the CHOP protocol followed by maintenance therapy with Obinutuzumab
  About two months after the last administration of the anti CD 20 antibody, the patient presented hyperpyrexia and gastrointestinal symptoms. About three days later, bradysepsychism, nystagmus, tremor, dysphagia for liquids and difficulty walking appeared

Instrumental examination

- **encephalic MRI with gadolinium:** shaded signal hyperintensity in FLAIR of the medial portion of the right thalamus in the absence of post contrastographic enhancement.
- **CSF**: pleiocytosis (70 cells mm2) and minimal protidorrachia (59 mg/dl), the infective examination (included JCV) was negative, cytopathological examination of CSF excluded the presence of cell atypia
- **immunohistochemistry (performed on CSF and serum):** negative for anti-mGlur5, igLon5, Caspr2, NMDAr, LGI1, GABA-B, GABA-A, AMPA1 and 2, mGLUR1, DPPX antibodies

The patient presented fluctuations in consciousness alterations in the sleep-wake rhythm and myoclonus ans tonic clonic seizures. The picture quickly became worsening..

- **EEG:** slowing of cerebral electrogenesis and the presence of both paroxysmal and slow and multifocal abnormalities
- **Second encephalic MRI with gadolinium:** involvement of the contralateral thalamus and the appearance of a hyperintensity in FLAIR of the cerebellar cortex

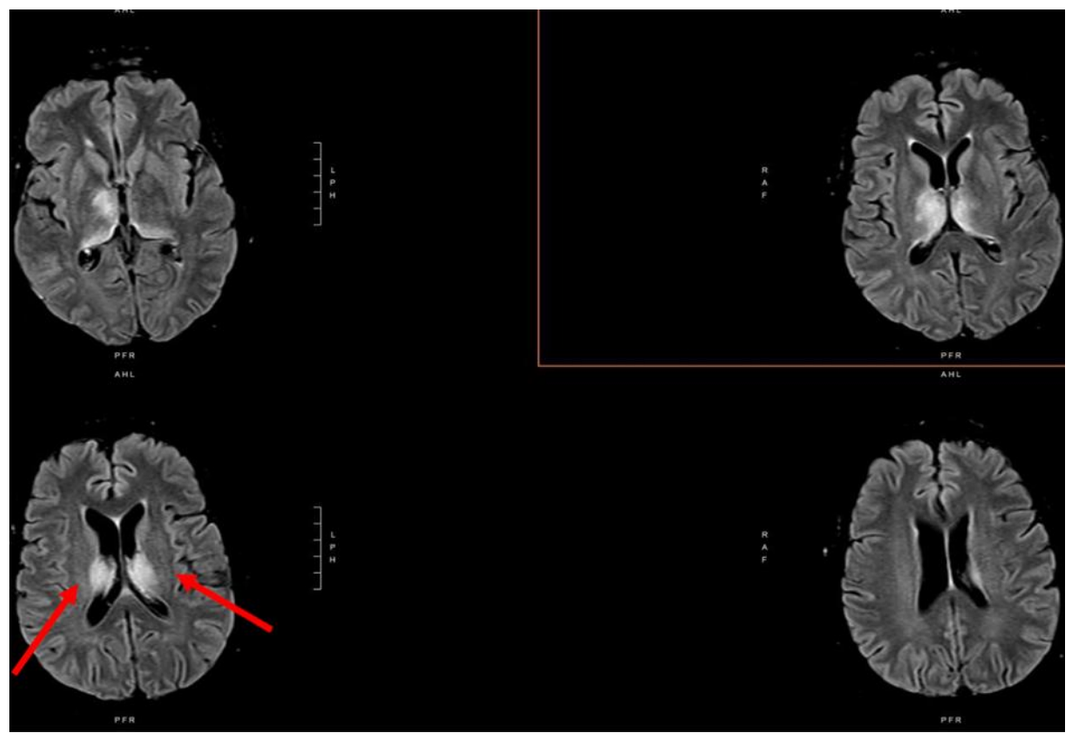
Therapy

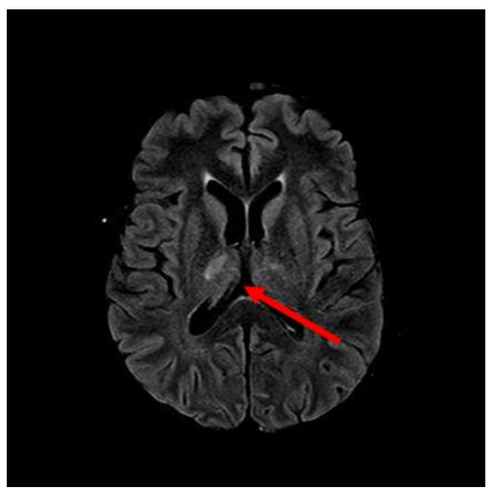
- **methylprednisone 1 g for five days**: no clinical improvements
- **intravenous immunoglobulins:** clinical and neuroradiological improvements from the third day

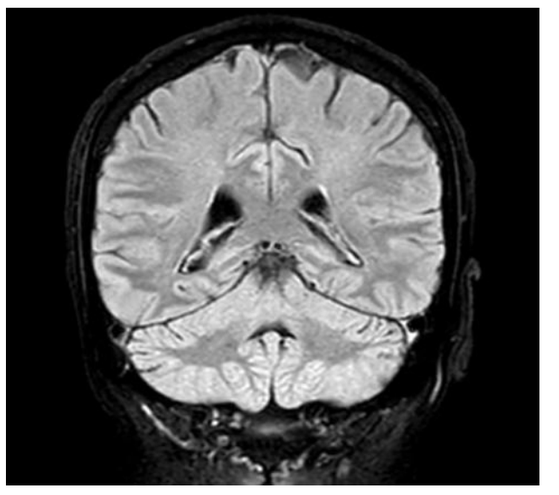
Clinical and neuroradiological evolution

After 10 months…

- **Clinic:** the patient is alert, partially oriented and cooperative. Slight motor slowing and disturbances of the sleep-wake rhythm persist
- **encephalic MRI with gadolinium**: resolution of detectable signal alterations in the thalami and cerebellar hemispheres on both sides.







Discussion

The absence of a clear infectious aetiology, the negativity of the autoantibodies known to date, and the neuroradiological data associated with a clear diencephalic syndrome depict a seronegative encephalitis. The good response to immunotherapy further confirmed this hypothesis.

Conclusions

We believe that such syndromes, although rare, may represent a delayed and unpredictable complication of biologic therapies in immunocompromised patients. Early recognition and targeted treatment are crucial to improve outcome.

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