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Case Report

"Limbic encephalitis with acute onset and Hu antibodies treated with rituximab: Paraneoplastic or non-paraneoplastic disorder?"

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ABSTRACT

Paraneoplastic limbic encephalitis (PLE) associated with Hu antibodies is a rare autoimmune disorder usually characterized by subacute onset of slowly progressive neurocognitive symptoms. Small cell lung carcinoma is the most frequent PLE-associated cancer, which negatively affects the prognosis of the disease. We report on a patient with acute onset of confusional state and disorganized speech. Cerebrospinal fluid analysis and brain MRI temporal lesions corroborated the diagnostic suspects toward infectious or autoimmune encephalitis but testing for onconeural antibodies suggested the alternative diagnosis of PLE, in the absence of cancer (total-body CT and PET were negative). The patient's serum was positive for Hu antibodies, thus leading to a diagnosis of PLE. First-line immunotherapies were ineffective on the neurocognitive symptoms, which improved after rituximab. Six months later, a retropharyngeal peri-jugular mass was histopathologically diagnosed as a metastasis of lung neuroendocrine tumor. Still clinically improved, the patient died from the oncological disease-related complications. Testing for onconeural antibodies should be considered in patients with clinico-radiological features of acute infectious or autoimmune encephalitis.

1. Introduction

Hu antibody-seropositive paraneoplastic limbic encephalitis (PLE) usually associates with small cell lung carcinoma (SCLC) [1] and, more rarely, with neuroendocrine tumors [2]. The onset is subacute, the course slowly progressive, and the outcome poor, despite aggressive anti-tumor and immunosuppressive treatments [3]. Very preliminary findings suggest that rituximab, an anti-CD20 monoclonal antibody used to treat B-cell malignancies and many autoimmune diseases, might be effective in Hu antibody-associated PLE [4].

We report on a patient with limbic encephalitis that resulted seropositive for Hu antibodies, without showing the typical clinical feature of the paraneoplastic LE.

2. Case report

A 69-year-old male developed confusional state, disorganized speech and behavior, without fever or meningeal signs, in 2 h. The patient was immediately admitted to the Emergency Department, where neurological examination was remarkable only for cognitive deficits. He was alert, but not oriented in space and time, with severe impairment of short-term memory, attention, and verbal fluency. In the following 4 h, Mini Mental Status Examination (MMSE) score deteriorated to 17/30, and the modified Rankin Scale (mRS) score reached a value of 5. Brain CT showed mild chronic ischemic vascular microangiopathy. Brain MRI, performed immediately after CT due to the rapid deterioration of the clinical status, revealed bilateral hyperintense lesions in the amygdalo-hippocampal areas (the largest lesion located on the left side; Fig. 1: A, B), with moderate swelling and slight reduction of signal intensity on diffusion-weighted imaging. Transferred to the Neurology Department, the patient underwent EEG that showed paroxysmal epileptic activity on the left temporal region. Extensive laboratory tests were normal, with the exception of serum neuron specific enolase concentration that was slightly increased (16.2 ng/ml; range, 0–14.7). Cerebrospinal fluid (CSF) analysis was remarkable for pleocytosis (40 cells/mm^3; lymphocytes, 90%), high total protein

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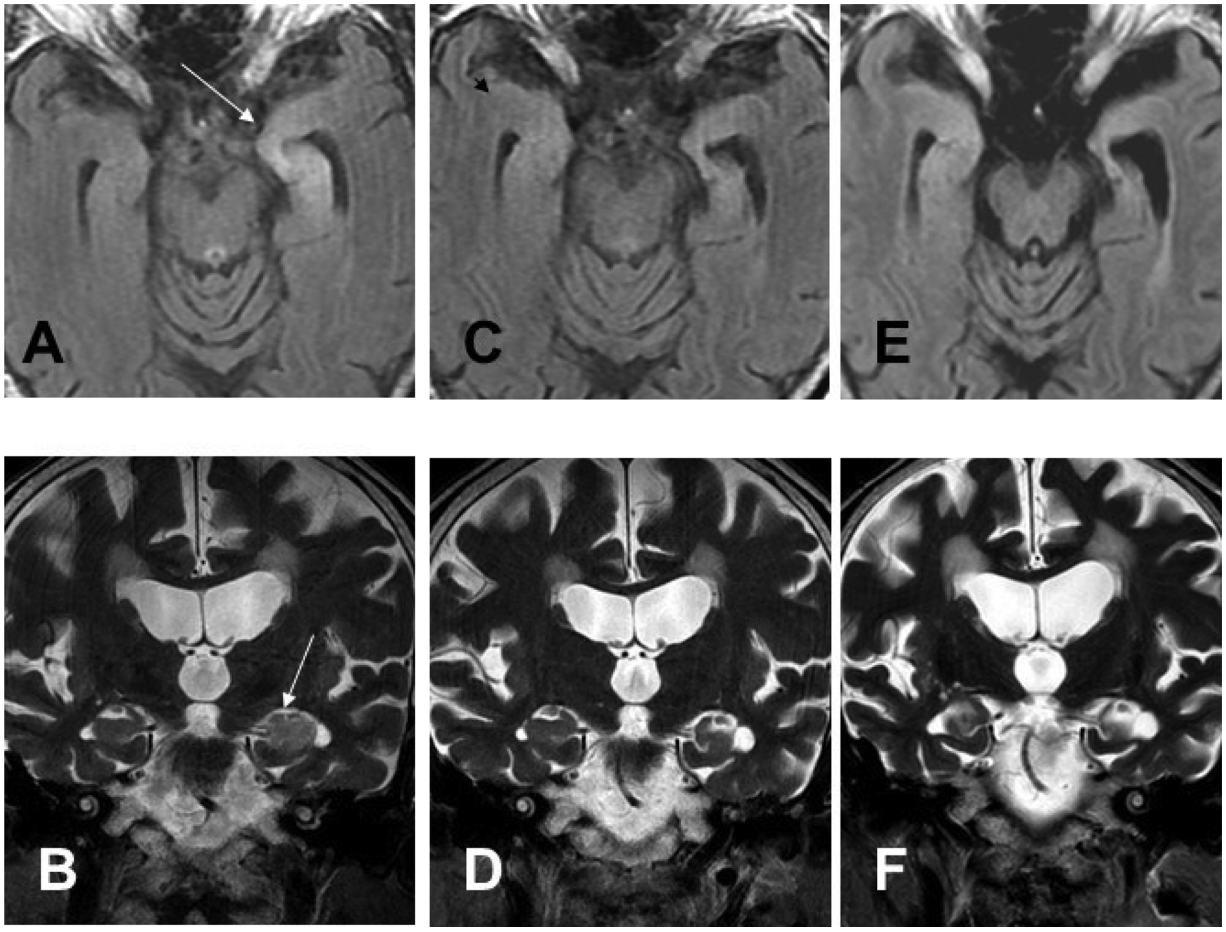

Fig. 1. MRI scans at the onset of the limbic encephalitis and during the follow-up.
Fluid-attenuated inversion recovery axial (A, C, E), and T2-weighted turbo spin-echo coronal images (B, D, F); left mesial temporal hyperintensity (A, arrow), with enlargement and signal hyperintensity in the hippocampus (B, arrow) before rituximab; marked decrease of the temporal hyperintensity (C), and of the signal intensity in the hippocampus (D) two months after rituximab; mesial temporal atrophy (E), and temporal atrophy (F) ten months after rituximab

concentration (600 mg/dL), and oligoclonal IgG bands. Pleocytosis led us to start empirical therapy with intravenous (iv) acyclovir. Serological tests, PCR on CSF for neurotropic pathogens (Herpes Simplex virus-1/2, Varicella-Zoster virus, Human Cytomegalovirus, Human Herpes virus-6, Epstein-Barr virus), and CSF bacterial, mycotic and mycobacterial cultures were all negative. The localization of the lesions in limbic areas prompted us to search for onconeural (Hu, Yo, Ri, CV2, Tr, Ma1/2, PCA-2, GAD, amphiphysin), and for neuropil/synaptic (NMDA-R, LGI1, CASPR2, AMPA-R1/2, $GABA_B$-R) antibodies. The serum resulted positive for Hu IgG antibodies (indirect immunofluorescence on primate cerebellum, and dot-blot; Euroimmun, Germany), which led to the formal diagnosis of PLE (3). The search for an underlying tumor with total-body CT and PET was negative. Fulfilling the diagnostic criteria for paraneoplastic neurological syndromes (PNS) [4], and after the negative CSF results of PCR tests for neurotropic virus and of culture tests, one week after the onset of symptoms the patient was treated with intravenous (iv) methylprednisolone (1 g/day for 5 days). Two days after the end of the steroid cycle, and due to its inefficacy, a cycle of iv immunoglobulins (ivIg) (0.4 g/kg/day for 5 days) was started, together with carbamazepine to prevent seizures. The antiepileptic drug was continued for the whole course of the disease. After one week the patient's cognitive symptoms improved only slightly, so we attempted to treat him with iv rituximab (375 mg/m^2, once a week for 4 weeks). Two months after the end of rituximab cycle, the patient improved substantially and turned able to perform, although with the necessity of assistance, most of his daily activities, after a short period in a Rehabilitative Unit (MMSE score, 24/30; mRS score, 3). Neuropsychometric testing confirmed improvements in recent memory, cognitive efficiency, and executive functions. Brain MRI showed a reduction of the lesions, with initial ventricular enlargement (Fig. 1: C, D). No epileptic activity was detectable on EEG. As for the oncologic follow-up, six months after the end of rituximab therapy, a chest CT showed a mixed-density mass in the retropharyngeal peri-jugular space, which was histologically diagnosed as a metastasis of a neuroendocrine tumor. One month later, a small lung mass was detected at chest CT. Despite chemotherapy with cisplatin and vepesid q21, followed by paclitaxel, the lung mass increased in size on chest CT. One year after the onset of symptoms, brain MRI showed medial temporal atrophy without hyperintensity (Fig. 1: E, F), and the clinical picture remained stable, with the maintenance of the post-rituximab improvements. However, 3 months later, the patient developed severe hyponatremia due to a syndrome of inappropriate antidiuretic hormone secretion and died from tumor-related cachexia.

3. Discussion

Our patient's sudden onset of neurocognitive symptoms is typical of infectious or autoimmune encephalitis rather than of PNS, which is characterized by gradual onset and slow progression of symptoms over weeks or months [3]. Similarly to our case, sudden onset of symptoms has been described in patient with PLE resembling acute herpetic encephalitis [5]. Following the detection of Hu antibodies, our patient underwent a strict oncologic follow-up that enabled us to discover a small neuroendocrine cancer 8 months after the onset of the

neurological syndrome. The association between Hu antibody-associated PNS and neuroendocrine tumors is very rare [2]. Despite aggressive oncological therapies, the patient died from tumor-related complications, as expected in the majority of PNS [3]. As for the limbic encephalitis, following the results of an uncontrolled trial in PNS [4], we treated the patient with rituximab, which reversed the symptoms almost completely, with the improvement of the brain MRI lesions. The clinical improvement persisted throughout the chemotherapy. This is another unexpected feature of our case, as prompt and sustained responses to rituximab are more typical of autoimmune encephalitis. However, spontaneous remissions of Hu antibody-associated PLE following the activation of the immune system have been also described [1,3].

The atypical characteristics of our patient's manifestations of PLE challenge the current diagnostic criteria for PNS, which greatly emphasize the diagnostic role of the well-defined onconeural antibodies [3]. We had no opportunity to test whether his neuroendocrine cancer cells expressed the Hu antigen, as a proof of principle favoring the paraneoplastic hypothesis.

4. Conclusion

Our case of limbic encephalitis with atypical sudden onset of symptoms and prompt response to rituximab, but with seropositivity for Hu antibodies and the presence of cancer falls into a grey zone between non-paraneoplastic autoimmune encephalitis and PNS. Anyway, early diagnosis is fundamental to start oncologic follow-up and prompt treatments. Rituximab could be an effective therapy even in these 'borderline disorders', whose prognosis remain substantially poor in the presence of cancer.

Consent statement

A written informed consent was obtained from a relative of the patient.

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Author contribution statement

BL and GM were the treating neurologists of the patient; FD performed the immunologic laboratory evaluations and contributed to the final version of the manuscript; TC performed brain MRI scan; LC and BL wrote the first draft and the sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

Declaration of Competing Interest

None.

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