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Letter to the Editor

A case of anti-NMDA receptor encephalitis in a woman with a NMDA-R$^+$ small cell lung carcinoma (SCLC)

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1. Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder characterized by IgG autoantibodies directed against the NR1 subunit of the NMDA glutamate receptor [1]. The disease commonly occurs in young females and in this range of sex and age is associated in about 50% of cases with ovarian teratoma [1–3]. Cases have also been reported in older patients, predominantly men, but cancer is less frequent in this age range [4]. Other tumors than teratoma are rare. They represent less than 5% of cases [1] and can develop from a wide range of organ [1,3]. We report here a case of anti-NMDAR encephalitis associated with small cell lung cancer (SCLC).

2. Case history

A 62 years old, heavy smoker (30 packs/year), woman experienced mood and behavioral changes four weeks prior to hospitalization in the intensive care unit. She was diagnosed with a severe depression and received antidepressant, benzodiazepines and neuroleptic treatments but her condition rapidly deteriorated with catatonic state, mutism, oppositional attitude, followed by complex partial seizures, orofacial dyskinesia, dystonic movements in the left side of the body and finally severe hypoventilation needing intubation. Initial electroencephalography (EEG) showed a right hemispheric epileptic activity followed in the next days by extreme delta-brush waves. Flair weighted sequence of brain MRI performed at referral showed cortical high signals in the temporal and occipital lobes extending in the insula, cingulum, internal pallidum and sub-thalamic regions (Fig. 1). CSF contained 0.46 g/l protein with intrathecal IgG production and 20 lymphocytes/mm^3. PCR was negative for HSV and anti-nuclear antibody (ANA) was positive with titer 640. Anti-NMDAR antibodies were detected in the serum and the CSF while anti-Hu, CV2/CRMP5, amphiphysin, Yo, LGI1 and CASPR2 antibodies were negative. A chest CT scan found a mass in the inferior lobe of the left lung and bronchoscopy yielded a cytological diagnosis of SCLC. Pelvic CT-scan was normal and ovarian biopsy did not detect teratoma. The patient received high doses of corticosteroids for 3 days with a course of 2 g/kg intravenous immunoglobulins followed by 1 g Rituximab in parallel with 2 courses of chemotherapy by cisplatin and etoposide. After six weeks the CT scan showed partial tumor regression but the neurological status remained unchanged and the patient died from intractable infectious complications after two months of hospitalization.

3. Small cell lung cancer cells immunoreactivity with the patient serum

Detection of autoantibodies against the NR1 subunit of the NMDA glutamate receptor was performed in the serum or CSF by indirect immunofluorescence with NMDAR HEK transfected cells (Euroimmun, Germany). IgG from the patient and from a control normal subject diluted 1:10 in PBS-Tween 0.1% and revealed with FITC labelled anti-human IgG were used to detect NMDAR expression in the patient's tumor and in four SCLC from patients without neurological syndrome. Tumor cells were taken from lymph node biopsy by needle aspiration. The patient's IgGs but not the control serum strongly immunolabelled tumor cells from the patient and from two of the four SCLC of patients without brain encephalitis (Fig. 2).

4. Discussion

The case reported here had the typical clinical and chronological pattern of anti-NMDAR AB encephalitis marked by initial psychiatric symptoms followed within a few weeks by loss of consciousness, seizures, dysautonomia, abnormal movements and central hypoventilation [3]. Extreme delta brush on EEG was also typical of the disorder [5] and anti-NMDAR antibodies were detected both in the serum and the CSF. However, this case displays several unusual features. First the encephalitis affected a patient older than 45 years, a situation which occurs in 5% of cases only [3]. Second, the extension and severity of lesions on brain MRI was also unusual since MRI is abnormal in only one third of cases and usually shows only transient and mild changes [1,3]. Finally the associated tumor was a SCLC. This association is rare and has been reported in less than 15 patients so far, but there is no details concerning their case reports [1–3].

The current hypothesis to explain the development of paraneoplastic neurological disorders is that the tumor expresses neural antigens that are recognized by the immune system leading to the development of the autoimmune disease. Todays, two categories of paraneoplastic disorders can be distinguished [6,7]. In the first group, cellular immunity is probably responsible for the neurological diseases and antibodies which recognize neural intracellular antigen are only biomarkers. These antibodies, called onconeural antibodies, almost universally occur with cancer. In the second group, the antibodies react with neuron cell surface antigens such as receptors or ion channels and are the effectors of the neurological disorders. At the difference of the first group, tumor is inconstant and many cases occur without cancer.

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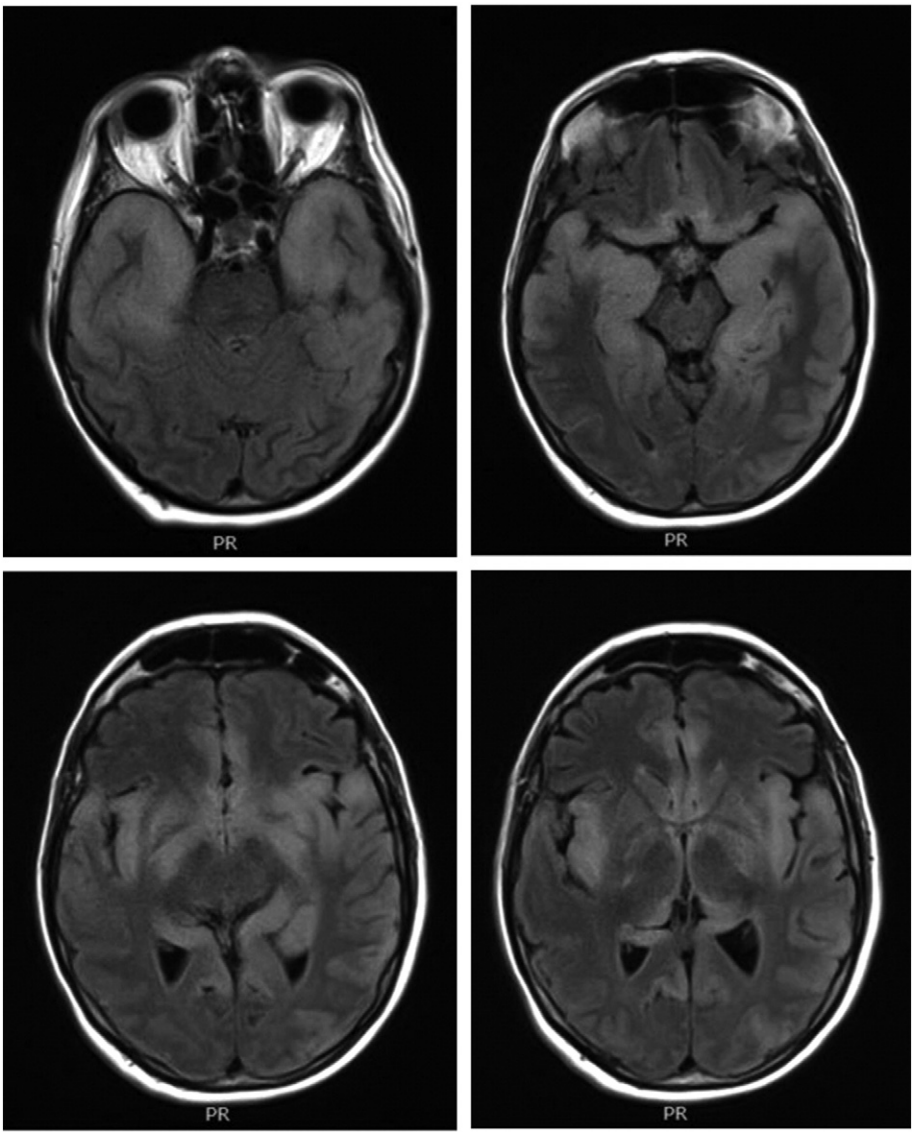

Fig. 1. Brain MRI. FLAIR weighted sequences showing diffuse high signals in the limbic system extending in the pallidum, the sub-thalamic region and the occipital lobe.

Teratoma, the most frequent tumor with anti-NMDAR encephalitis has been reported to express NMDAR subunits [8,9] while intratumoral inflammatory cell reaction is more important in those patients who develop encephalitis suggesting that the tumor is the source of the immune reaction [9]. At the difference of teratoma, SCLC occurs with onconeural or cell surface antibodies. They express the onconeural antigens HuD [10] or CV2/CRMP5 [11], or cell surface proteins including $GABA_BR$ [12], GluR1 or GluR2 subunits of the AMPAR [13] or subunits of the voltage gated calcium channels [14]. This may explain the wide spectrum of paraneoplastic disorders with SCLC and the association of several onconeural or cell surface antibodies in a same patient [15].

Using the patient's serum we observed that serum IgGs containing anti-NMDAR antibodies immunolabelled the patient's own tumor and half of the four SCLCs not associated with a paraneoplastic disorder suggesting that expression of NMDAR subunits by SCLCs is frequent in keeping with North et al. who reported the expression of functional NMDAR1 and 2 in most SCLC cell lines and tumors [16]. The reason why only some patients with SCLC develop anti-NMDAR encephalitis is unclear and other factors including the expression of MHC molecules by the tumor and personal susceptibility may be requested to trigger the development of the neurological disorder [10].

Conflict of interest

No conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.clim.2016.03.011.

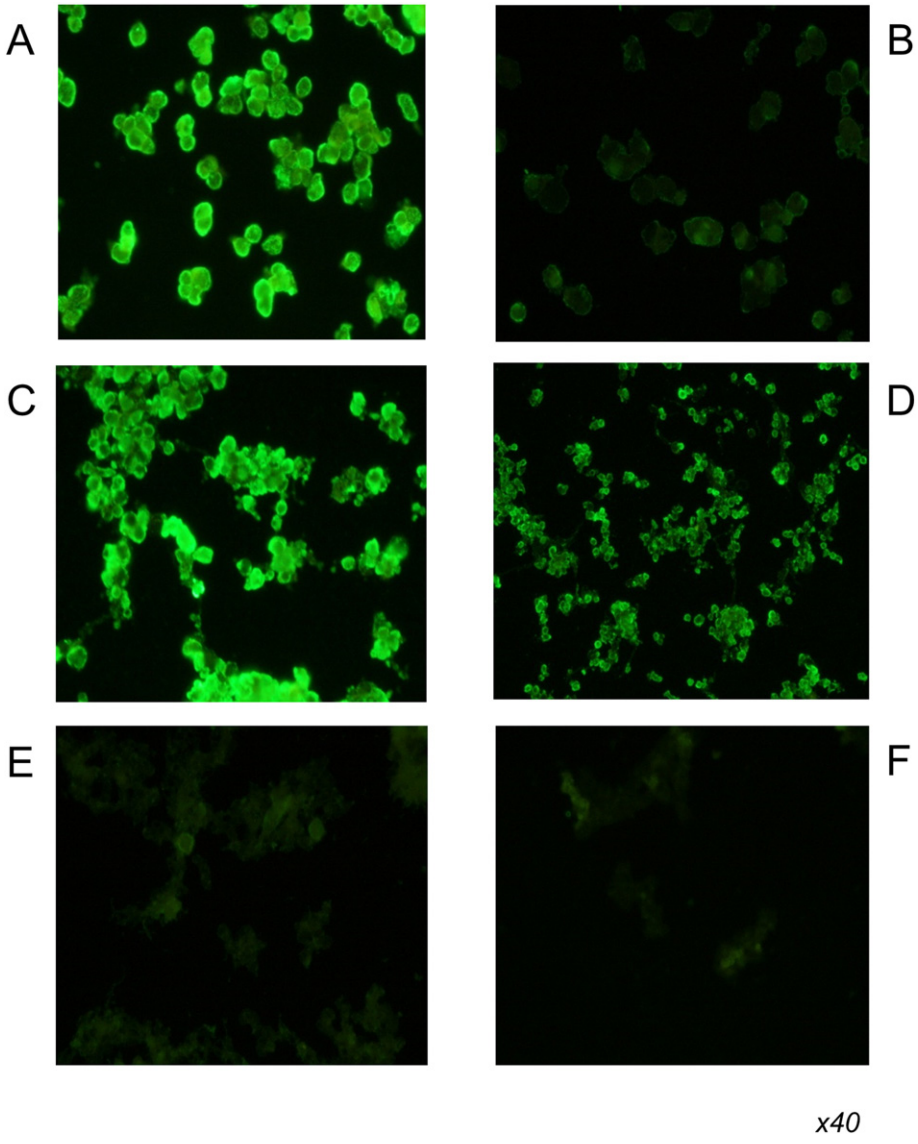

Fig. 2. NMDA-R expression by indirect immunofluorescence on SCLC tumor cells. (A) Strong expression of NMDA-R in SCLC tumor cells from our patient after staining with positive anti-NMDA-R Abs. (B) Negative control serum staining on tumor cells from our patient (C–D) High expression of NMDA-R on two SCLC control tumor cells (E–F) No expression of NMDA-R on two SCLC control tumor cells.

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M. Jeraiby
A. Depincé-Berger
V. Bossy
GIMAP EA3064, Laboratory of Immunology and Immunomonitoring, CIC 1408 Inserm Vaccinology, Hopital Nord, CHU Saint-Etienne, France

J.C. Antoine
Neurology Department, Hopital Nord, CHU Saint-Etienne, France

S. Paul
GIMAP EA3064, Laboratory of Immunology and Immunomonitoring, CIC 1408 Inserm Vaccinology, Hopital Nord, CHU Saint-Etienne, France
Corresponding author.
E-mail address: stephane.paul@chu-st-etienne.fr.

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