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Case report

Paraneoplastic limbic encephalitis revealing a small cell carcinoma of the lung

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ABSTRACT

Introduction: Paraneoplastic limbic encephalitis is a rare disease, usually associated with small cell lung cancer.
Case report: We report in this publication the cases with different age brackets, who presented with various neurological symptoms such as repetitive seizures or anterograde amnesia. Cerebral CT-scan, cerebral MRI and anti onco-neural paraneoplastic antibodies were suggesting the diagnosis of paraneoplastic limbic encephalitis. Etiological exploration lead to the diagnosis of locally advanced small cell carcinoma of the lung. We started rapidly a curative protocol associating chemotherapy and sequential thoracic radiotherapy.
Conclusions: we insist on the diversity of the imaging findings, immunological analyses and outcome on treatment of this entity. Prognostic impact remains also unclear.

1. Introduction

Paraneoplastic limbic encephalitis (LE) is a rare neurologic syndrome that is difficult to diagnose. This entity is clinically characterized by a cognitive disorder, amnesia, confusion, psychiatric symptoms or seizures. It is described in patients presenting with lung cancer (50%), genital cancer (20%) and breast cancer (8%). To be qualified as paraneoplastic, diagnosis of the underlying neoplasia should imperatively be done within a four year period. Although there is currently no well-established treatment for LE, therapeutic management of the malignant tumor is the first option if no metastases were found. Symptomatic treatment includes corticosteroids which are the most frequently used, followed by high-dose immunoglobulins. We report two cases of paraneoplastic LE associated with small-cell lung carcinoma in two male patients with different ages.

2. Case 1

A 53-year-old man, a taxi driver, active smoker, hypertensive for 10 years, presented to the emergency department with a status epilepticus with generalized tonicoclonic seizures associated with anterograde amnesia. The patient has been smoking for 30 years at a rate of 10 cigarettes a day. Neurological examination found a bradypsychia, with preserved motricity and sensitivity. The subjective assessment of cognitive function via the Montreal Cognitive Assessment (MoCA) score was 21/30. The brain scan showed a right para-sagittal meningioma of the superior sagittal sinus, measuring 8mm. Lumbar puncture and the electroencephalogram were normal. Cerebral MRI with T1, T2 and FLAIR sequences showed no abnormalities (Fig. 1a and b). An immunological test for anti-neuronal antibodies showed the presence of *anti*-Hu antibodies, anti-SOX 1 antibodies and *anti*-GABAr B1/B2 antibodies (Table 1). Chest X-ray showed a retro-cardiac opacity with irregular boundaries. Bronchial fibroscopy showed a budding formation completely obstructing the left lower lobe. Bronchial biopsies concluded to a small cell carcinoma. The body scan objectified a tumor mass obstructing the left lower lobe with left hilar and sub carinal adenomegalies, and a suspicious retro-esophageal lymph node. The tumor would be classified T2bN3M0 (see Fig. 2). Through clinical, biological and radiological data, we established the diagnosis: paraneoplastic limbic encephalitis revealing a locally advanced small cell carcinoma of the lung. Chemotherapy associating carboplatin and Etoposide was started promptly. Anticonvulsant therapy was also prescribed: a combination of oral corticosteroid (prednisone 40mg/day), phenobarbital 50mg three times daily and levetiracetam 500mg in the morning and 1000mg at night. Despite the treatment, the patient had a seizure every two weeks. The onset of chemotherapy had a positive impact with disappearance of the seizures. During chemotherapy sessions, the patient was still bradypsychic but with a more sustained

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Abbreviations:

MRI	magnetic resonance imaging
CT-scan	computed tomography scan
LE	limbic encephalitis
MoCA	Montreal Cognitive Assessment
PNS	paraneoplastic neurological syndromes
CSF	cerebro-spinal fluid
GABA	Gamma-Aminobutyric Acid Receptor
VGCC	voltage-gated calcium channels
VGKC	voltage-gated potassium channels

memory. The MoCA score was 25/30. After 4 cycles of chemotherapy based on carboplatin and etoposide, we noted a stability of the tumor. Sequential thoracic radiotherapy was proposed but refused by the patient. Progression-free survival already reached seven months.

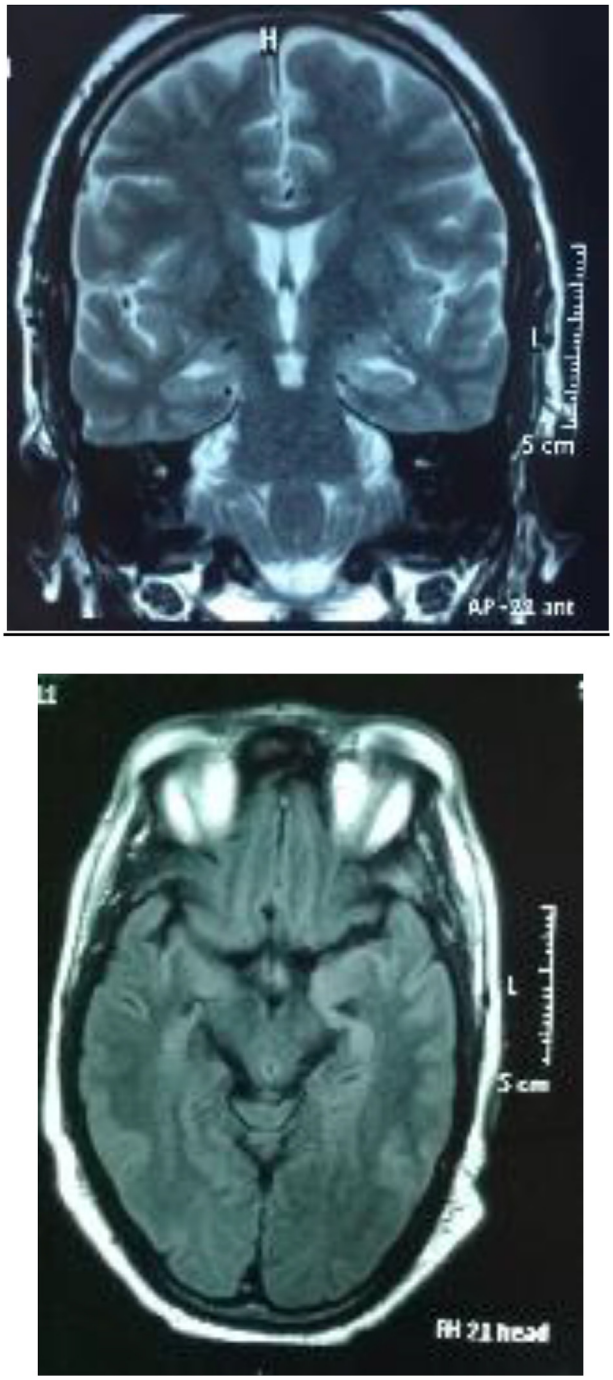

Fig. 1. :(a) and (b) Cerebral MRI (T2 + FLAIR) shows no abnormal signal within the limbic regions.

3. Case 2

A 73 years old man, former smoker, was admitted to pulmonology department for exploration of a chronic dry cough. The patient has been smoking for 42 years at a rate of 10–20 cigarettes a day. He had past medical history of a treated gastric ulcer. He was complaining of progressively emerging cough with retrosternal burn sensation. His family members signaled anterograde amnesia with neither humor trouble nor suicidal tendency. Physical examination showed a normal cardio-pulmonary status, normal sensitivity and motricity. Chest X Ray revealed a right hilar opacity with spiculated margins. Bronchial fibroscopy showed a budding formation partially obstructing the right upper lobar bronchus. Bronchial biopsies concluded to small cell carcinoma. The thoracic CT scan objectified a tissue mass extending from the hilus to the right upper lobe, measuring 59 mm of diameter, associated with sub-pleural speculated nodules of the right lower lobe, mediastinal lymph nodes in the zones 4R, 7 and 10. Cerebral MRI revealed bilateral high signal intensity on T2-weighted and FLAIR image in the hippocampus (Fig. 3a and b). We concluded on paraneoplastic limbic encephalitis. Serum or CSF paraneoplastic antibodies were not checked since the diagnosis was obvious. The tumor was classified T4N3M0 according to the 8th edition of TNM classification. No treatment was prescribed for the encephalitis. Four cycles of chemotherapy including carboplatin and etoposide, then sequential thoracic radiotherapy was proposed.

4. Discussion

Paraneoplastic neurological syndromes (PNS) are rare neurological syndromes associated with cancer with no obvious metastatic, metabolic, infectious, deprivative or iatrogenic cause [1]. The pathogenesis of this condition is not completely understood, but the strongest hypothesis describes an immune response directed against the central nervous proteins which are similar to tumor antigens. It leads to lymphocyte infiltration of perivascular and microglial cells followed by neuronal loss [1]. The presence of circulating serum autoantibodies or abnormal cerebrospinal fluid (CSF), specifically associated with PNS is one of the hallmarks of these syndromes. They are found in more than 80% of patients with PNS. Depending on the target of the antibodies found, there are two types of PNS. There are intracellular targets (onco-neuronal) and membrane targets [1]. *Anti*-onco-neuronal antibodies such as *anti*-Hu, *anti*-Ri, *anti*-Yo, anti-Ma/Ta, *anti*-amphiphysin, anti-Sox 1 and *anti*-CV-2 are specific of small cell lung cancer, breast, ovarian or testicular cancer [2]. The best described membrane targets are ionotropic glutamate receptors: *N*-Methyl D-Aspartate Receptor (NMDAr) or Gamma-Aminobutyric Acid Receptor (GABAr), either ion channels such

Table 1
Serum immunoassay for *anti*-onco-neuronal and anti-membrane antibodies.

Antibodies	Results	Antibodies	Results
Anti Cv2	–	Anti Titin	–
Anti PNMA	–	Anti Amphiphysin	–
Anti Ri	–	Anti AMPA1/AMPA2	–
Anti Yo	–	Anti CASPR2	–
Anti Hu	+	Anti LG11	–
Anti Recoverin	–	Anti GABAr B1/B2	++
Anti SOX1	++		

as voltage-gated calcium channels (VGCC) or voltage-gated potassium channels (VGKC) [2]. The clinical presentations vary from case to case. The onset is mostly sub-acute. In 65% of cases, paraneoplastic neurological involvement precedes the discovery of cancer for several months or years.

Autoimmune encephalitis is one of the most common PNS, involving mainly the limbic system but may also involve other extra limbic structures. The term autoimmune encephalitis is preferred to LE which is too restrictive [1]. Neurological symptoms vary from anterograde memory disorders, confusion to dementia and convulsive seizures that may precede cognitive impairment for several months (temporal, psychomotor impairment, generalized tonic-clonic seizures). Changes of behavior, personality and psychiatric symptoms (irritability, anxiety, depression, hallucinations and aboulia) are also described. Sleep disorders (hypersomnia or insomnia, narcolepsy, cataplexy), weight change along with disturbance of the sensation of satiety can be found [3–5]. Further tests are necessary to make the diagnosis but also to rule out the differential diagnoses (infectious cause, deficiency, metastatic …). The analysis of the cerebrospinal fluid contributes to the diagnosis by showing the absence of malignant cells. Cerebral MRI shows no metastatic lesion. The electroencephalogram shows a non-specific aspect of epileptic activities at the temporal lobes in 50% of cases [6]. MRI plays also a prominent role in diagnosis by detecting single or bilateral (60%) amygdalo-hippocampal signal abnormalities [3,6]. Typically, it shows a high-intensity signal on T2-weighting sequences, more visible on the FLAIR and on the diffusion sequences. T1-weighting sequences may show a hyposignal or isosignal with temporal atrophy at a later stage. Enhancement after gadolinium injection can be seen in 15–20% of cases [3,6]. MRI may be normal at the beginning, as in the first case, hence the importance of imaging follow-up [7]. FDG-PET scan is useful when the EEG and MRI show no abnormalities. It shows a hyper-metabolism of the temporal lobes, midbrain, cerebellum or frontotemporal lobes [8], indicating an acute phase of the inflammatory process. The presence of anti-neuronal *anti*-GABAr B1 antibodies is suggestive of small cell cancer. The presence of *anti*-Hu antibodies is associated in 94% of cases with small-cell lung carcinoma [3]. Alamowitch et al. [9] found *anti*-Hu antibodies in 50% of patients with limbic encephalitis associated with small cell lung carcinoma. Anti-SOX1 antibodies are found in the Lambert-Eaton myasthenic syndrome and less frequently in patients with *anti*-Hu syndrome or small-cell lung carcinoma without neurological signs [10]. GABAr B antibody assay should be considered in all cases of LE, with or without associated small cell carcinoma, in cases of cerebellar dysfunction, opsoclonus-myoclonus. The evolution and prognosis of paraneoplastic LE depends on the nature of the primary tumor and its treatment. The presence of anti-neuronal antibodies is often associated with poor neurological functional prognosis despite the proposed therapeutic arsenal. It is currently considered that the treatment of the tumor is the only pathway to stabilize the evolution by suppressing the antigenic stimulation [1]. In the presence of a membrane antibody, treatments targeting humoral immunity (immunoglobulin IV, plasmapheresis, and anti-CD20) can be proposed as well as systemic corticosteroids. However, no therapeutic protocol could be validated by a randomized controlled study because of the small number of patients concerned [1].

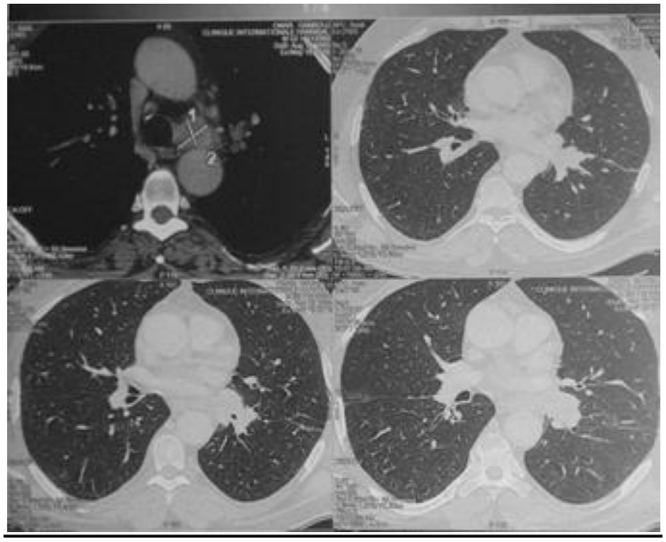

Fig. 2. Thoracic CT shows a tumor mass that obstructs the left lower lobe bronchus with left hilar and sub-carinal adenomegalies.

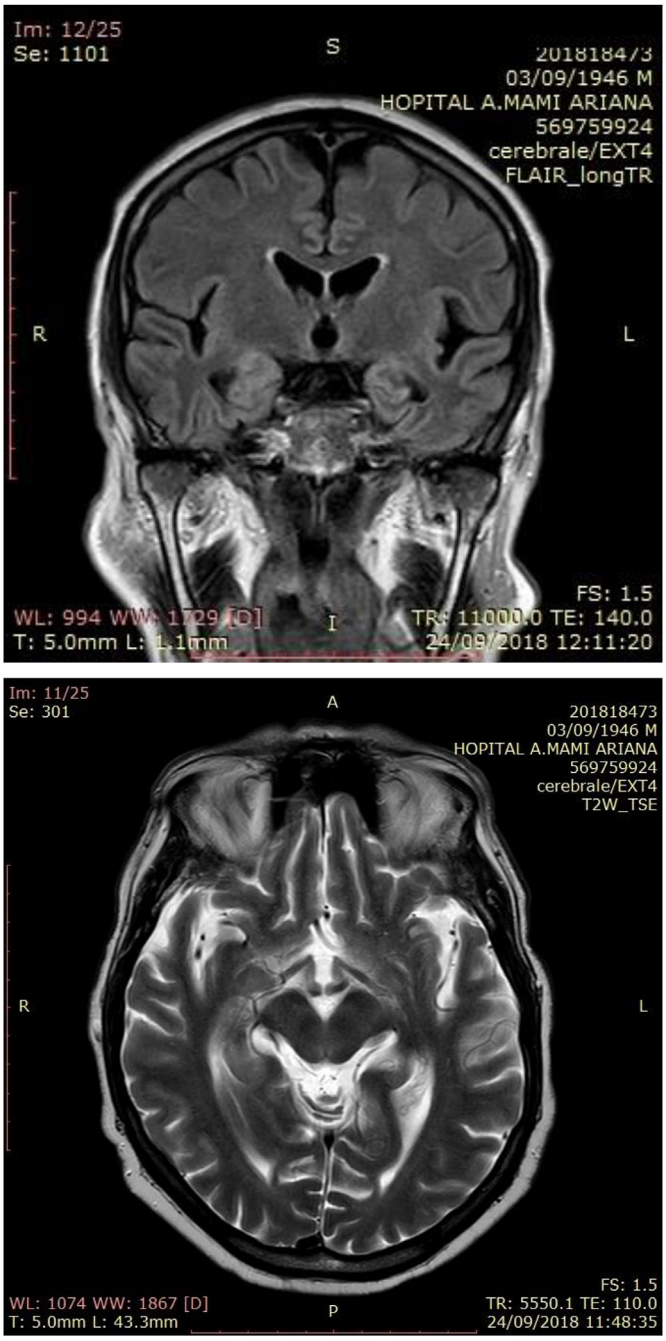

Fig. 3. (a) and (b) Cerebral MRI revealing bilateral high signal intensity on T2-weighted and FLAIR image in the hippocampus.

5. Conclusion

The reported cases highlight the diversity of paraneoplastic syndromes, which can be the first symptom of a malignant tumor. The review of the literature confirms the crucial importance of the anti-tumor immune response that can generate temporary or permanent dysimmunitary or endocrine disorders. The complexity of the pathophysiology explains the difficulty of treatment. It is also difficult to describe predictive elements of response of paraneoplastic neurological signs to the proposed therapies, apart from regression of the tumor. Tumor control remains the best alternative.

Consent for publication

A written consent for publication was obtained from the patients and their legal tutors.

Conflicts of interest

Interests related to the manuscript theme: None

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Authors' contributions

Marwa KACEM: 1st case redaction, scientific content discussion.
Nidhal BELLOUMI: article redaction, correction, scientific content discussion.
Imene BACHOUCHE: scientific content discussion.
Mariem MERSNI: 2nd case redaction.
Fatma CHERMITI BEN ABDALLAH: scientific content discussion.
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