A CASE OF PARANEOPLASTIC LIMBIC ENCEPHALITIS DUE TO GASTRIC CARCINOMA PRESENTING WITH PANHYPOPITUITARISM

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ABSTRACT
Paraneoplastic limbic encephalitis (PLE) is a rare disease probably caused by an immune reaction against central nervous system (CNS) structures. A 67 year old man, admitted for slurred speech, short-term loss of memory and intermittent confusions had findings compatible with limbic encephalitis and a thinned hypophysis stalk on cranial MRI. The diagnosis of limbic encephalitis was supported by cerebrospinal fluid (CSF) examination and electroencephalographic findings but anti-neuronal antibodies were negative. During the follow-up, panhypopituitarism requiring hormone replacement therapy developed and on repeated cranial MRI, new lesions were seen in the brainstem. The malignant lesion was found during gastroscopy at the gastric antrum and the histopathological diagnosis was adenocarcinoma. The patient died on the 36th day of admission.

Key Words: Limbic encephalitis, malignancy, hypopituitarism.
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INTRODUCTION
Limbic encephalitis is a rare paraneoplastic disease with findings of personality changes, epileptic seizures, memory loss, and dementia whose subtle clinical signs and symptoms cause great diagnostic difficulty. It generally precedes the clinical diagnosis of the malignant disease and its diagnostic criteria are; appropriate clinical picture, a period of less than 4 years between the onset of neurological symptoms and occurrence of the neoplastic disease, exclusion of other neuro-oncological complications and laboratory findings of at least one of the following: inflammatory changes in CSF examination, typical temporal lobe...
abnormalities in MRI, or epileptic activity in EEG. It is reported to occur most frequently with small cell carcinoma of the lung and anti-neuronal antibodies are considered to be a marker of the disease, though there is no pathological correlation between this marker and paraneoplastic limbic encephalitis.\textsuperscript{1, 2} In this article we present a case of paraneoplastic limbic encephalitis due to gastric carcinoma causing panhypopituitarism.

**CASE REPORT**

A 67 years-old male patient was admitted for slurred speech, short-term memory loss and intermittent confusions. His speech had progressively slowed in the last 6 months and auditory hallucinations developed recently. The chemistry panel 15 days prior to admission, showed glucose 35 mg/dl, Na: 132 mmol/l, K: 5.1 mmol/l, free T4: 11.6 pmol/l (12-22), TSH: 0.9 mIU/l (0.27-4.2). Cranial MRI and thorax CT scans were unremarkable. On mental evaluation, spontaneous speech was decreased, he could understand and obey simple one-step orders, space and time orientation were deficient. On neurological examination there was no focal neurological deficit. Nuchal rigidity and meningeal irritation signs were absent. Deep tendon reflexes were hypoactive in all 4 extremities but the reactivity to light of both pupils was normal and there were no pathological reflexes. There also was no cranial and peripheral nerve deficit. Blood pressure and pulse rate were within normal limits. The patient’s confusion was attributed to hyponatremia (119 mmol/l) and was admitted with the preliminary diagnosis of syndrome of inappropriate antidiuretic hormone (SIADH) secretion, adrenal insufficiency and a primary pathology in the CNS. Urinary sodium was 170 mmol/l, serum cortisol level was 21.8 µg/dl (>25). Prednisolone treatment with 20 mg/day was started. During the ensuing days, serum sodium level returned to normal without a concomitant improvement in the neurological picture which remained unchanged. On repeated cranial MRI, increased T2A-flair signal intensity was observed at both hippocampal-parahippocampal regions, at the left temporal pole, leg of left capsula interna, left capsula externa, and left pedunculus cerebri. Contrast enhancement after contrast injection was observed bilaterally in the mesial region, right pedunculus cerebri and interpeduncular cistern. Thickening and an increase in contrast uptake in the mesial region of the right hemisphere was observed (Figure 1-2).

On differential diagnosis lymphoma, sarcoidosis, meningoencephalitis and limbic encephalitis were considered. Absence of fever, normal CRP and normal thoracic CT excluded sarcoidosis and tuberculosis and CSF findings supported the limbic encephalitis.

On EEG, the main activity was of slow waves in theta and delta frequency bilaterally but predominantly on the right hemisphere. It also showed a severe and generalized organization defect at the right hemisphere and suspicious hypersynchronism at the right fronto-temporal region supporting the diagnosis of limbic encephalitis. On gastroscopy, an ulcerative lesion at the antrum was seen on biopsy adenocarcinoma was diagnosed. During follow-up the patient’s neurological deficits progressed. He became quadriplegic, unresponsive to painful stimuli and in the end in coma. In the ensuing month, cortisol (6.9 µg/dl), FSH (1.2 mIU/l), LH (1.2 mIU/l), TSH (0.1 mIU/l), fT4 (10.7 pmol/l) levels precipitately decreased and full blown panhypopituitarism developed. The patient was put on L-thyroxine and prednisolon dose was increased to 40 mg/day. Anti-neuronal antibodies were negative. On repeat cranial MRI the lesions progressed to involve the totality of the brain stem (Figure 3). The patient died on the 36\textsuperscript{th} day of follow-up.

![Figure 1. Contrast enhancement bilaterally in the mezial region, right pedunculus cerebri and interpeduncular cistern](image1)

![Figure 2. Thickening and an increasing in contrast uptake in the hypophysis stalk](image2)
DISCUSSION

The presumed etiology of limbic encephalitis is viral agents, malignancies and autoimmune diseases. Paraneoplastic limbic encephalitis is thought to arise as a result of an immunological reaction against CNS structures. It is commonly associated with lung (50%), testis (20%) and breast (8%) cancers.\(^5\) This condition was also reported in association with Hodgkin’s and non-Hodgkin’s lymphoma.\(^6\) There may be a lag of up to 4 years between the development of paraneoplastic limbic encephalitis and the clinical occurrence of the malignancy.\(^1\) The cure of the malignancy may stop the progression or partially resolve the encephalitic process with some residual neurological sequel.\(^5\) On the other hand, as the clinical progression is fast, it is not always possible to detect the malignancy before the terminal event. The long time interval between the occurrence of limbic encephalitis and detection of the malignancy makes the treatment of premalignant lesions equivocal. In our case the interval between PLE symptoms and detection of the malignancy was 6 months. An autoimmune disorder should also be considered in patients in whom a malignancy cannot be found after an exhaustive search. The presence of antibodies against intracellular molecules (Hu, Ma2 etc.) or neuronal cell membrane antigens (neuropilis of potassium channels, hippocampus and cerebellum, etc.) support the diagnosis of autoimmune limbic encephalitis.\(^3\) Immunohistochemical techniques were used to detect serum and cerebrospinal fluid antibodies.\(^7\) Type of antibodies found may have prognostic significance in that cases with antibodies against intracellular structures are relatively resistant to treatment while those with antibodies against membrane components are sensitive to therapy.\(^8\)

Antibodies were not detectable in 20% of patients in one study and the location of the underlying malignancy in such cases was pulmonary.\(^9\) Antibodies were negative in the present case whose primary was gastric adenocarcinoma. Clinical features, MRI findings and antineuronal antibodies are all important in the diagnosis of limbic encephalitis and our case was diagnosed depending on clinical and MRI findings without the additional help from anti-neuronal antibodies. Hyponatremia was a common finding at presentation in reported cases of limbic encephalitis and was known to develop suddenly and be resistant to treatment. Hyponatremia was corrected uneventfully in our case. However the neurological picture continued to deteriorate and cranial MRI findings showed limbic encephalitis. One month later, panhypopituitarism occurred. The treatment-resistant hyponatremia was probably due to panhypopituitarism which was caused by limbic encephalitis. Hypothalamic involvement which is rarely seen in limbic encephalitis is reported to occur more frequently in cases with anti-neuronal and anti-Ma2 antibodies.\(^9\) The underlying illness must be treated. Hormone replacement should also be done.

REFERENCES