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CASE REPORT

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NMDA receptor encephalitis with cancer of unknown primary origin

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ABSTRACT

Purpose: N-methyl-D-aspartate receptor (NMDAR) encephalitis may present as a paraneoplastic syndrome in young women and is often associated with ovarian teratoma.
Methods: We report 2 male cases of NMDAR encephalitis presenting with metastatic cancer of unknown primary origin.
Results: Both patients showed cognitive dysfunction as well as other neurological symptoms, slow waves on EEG, and NMDAR antibodies in sera and CSF. Symptoms were effectively treated by pulse steroid and intravenous immunoglobulin treatment. The patients developed metastatic small cell neuroendocrine carcinoma of the parotid gland and inguinal metastatic squamous cell cancer shortly after their neurological episodes. Follow-up PET studies showed small cell lung cancer in the first patient while no primary origin could be found in the second patient.
Conlusions: Our cases imply that NMDAR encephalitis may present with metastatic cancers that display slow progression rates and occur after encephalitis attacks.

Keywords: Autoimmune encephalitis, Ion channel antibody, Metastatic tumor, NMDA receptor

Introduction

Paraneoplastic neurological syndromes (PNS) constitute a rare group of disorders caused by the remote effects of cancer (1). In adults, PNS are mostly associated with small cell lung cancer (SCLC), lymphoma, thymoma and gynecological tumors (1). Antibodies to ion channel and synapse proteins have recently been recognized as important contributors to PNS pathogenesis. Among the various known PNS, N-methyl-D-aspartate receptor (NMDAR) encephalitis is most commonly associated with ovarian teratoma. Tumors related to NMDAR encephalitis generally have a relatively benign nature, although neuroendocrine tumors and lung cancers with a high risk of metastasis have been encountered in rare cases (2, 3).

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Case presentations

Case 1

A 62-year-old man presented with a 2-month history of amnesia, complex partial seizures and hallucinations. Neurological and psychiatric examinations were normal and neuropsychological examination showed impaired verbal-visual memory and visual-spatial function. Routine blood tests, an extensive screen for rheumatological, vasculitic and viral disorders, and cranial magnetic resonance imaging (MRI) were normal, whereas EEG showed widespread slow waves. Cerebrospinal fluid (CSF) examination showed 1 lymphocyte/mm^3, normal protein (38 mg/dL) and glucose (55 mg/dL) concentrations, and no oligoclonal bands. NMDAR antibody was found positive in serum and CSF. Whole-body computed tomography (CT) and positron emission tomography (PET) scans were normal. The patient's symptoms promptly regressed with intravenous administration of steroids (1,000 mg for 5 days) and immunoglobulin (IVIG) (total dose 30 g). Following subsequent monthly steroid and IVIG treatment, the symptoms completely disappeared in 4 months. Three months later, the patient developed a right parotid gland mass that was surgically removed. Pathological examination demonstrated small cell neuroendocrine carcinoma of the parotid gland (Fig. 1). Although his PET examination at the time did not reveal any additional lesions, 6 months after surgery a repeat PET scan

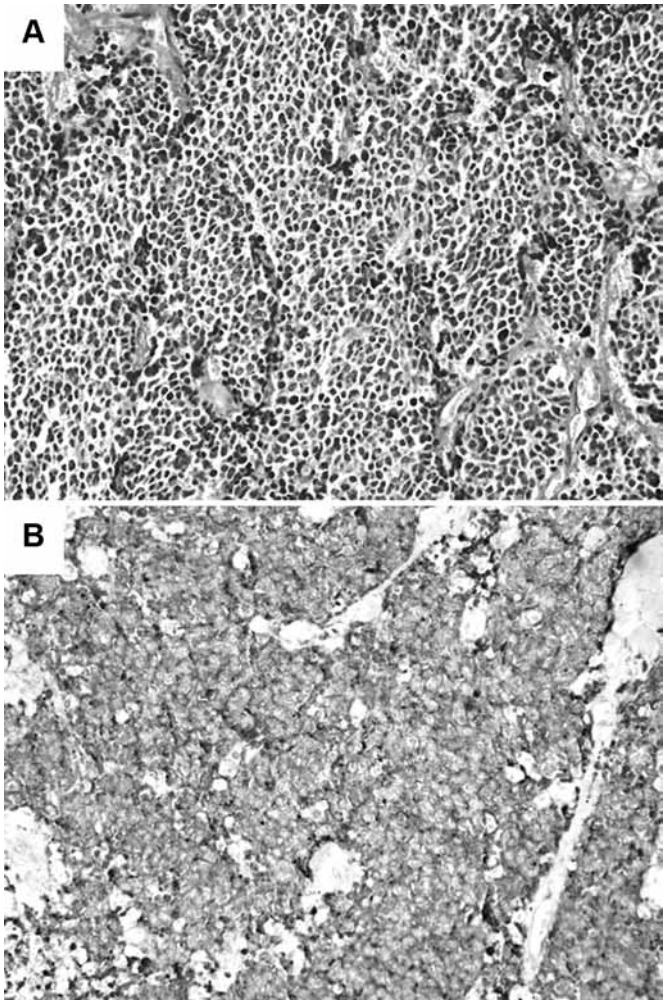

Fig. 1 - Histopathological image of small-cell carcinoma of the parotid gland. (**A**) Tumor cells forming solid nests with hyperchromatic nuclei, inconspicuous nucleoli and scanty cytoplasm. Mitotic figures are frequent and the stroma is vascular (hematoxylin and eosin stain, magnification ×400). (**B**) The tumor cells are immunoreactive for synaptophysin, confirming the neuroendocrine origin of the tumor (magnification ×400).

showed a lung mass, which was diagnosed as SCLC. He did not develop any neurological symptoms after immunotherapy.

Case 2

A 64-year-old man was admitted with a 2-month history of generalized weakness, ataxia, confusion and excessive daytime sleepiness, which progressed to coma and respiratory failure requiring mechanical ventilation. The patient and his relatives did not report any psychiatric symptoms. EEG showed widespread slow waves and brain MRI revealed hyperintensity in both medial temporal lobes with no contrast enhancement. CSF examination showed 2 lymphocytes/mm^3, normal protein (42 mg/dL) and glucose (61 mg/dL) concentrations. Oligoclonal IgG bands were found in CSF but not in serum (pattern 2). While routine blood tests and an extensive screen for rheumatological, vasculitic and viral disorders were normal, NMDAR antibody was found positive in serum and CSF. Following treatment with intravenous steroids (1,000 mg for 5 days), IVIG (total dose 28 g) and plasma exchange, the neurological symptoms completely regressed in 2 months. One month later, PET revealed a left inguinal mass, which on pathological examination was found to be a metastatic squamous cell carcinoma. PET studies failed to reveal the underlying primary tumor. After chemotherapy and radiotherapy the inguinal mass was reduced in size. In a 5-year follow-up period, the inguinal mass did not recur, the primary tumor could not be detected despite several repeat PET studies, and no neurological relapses were observed.

Discussion

NMDAR encephalitis occurs most commonly in young women and is associated with an underlying ovarian teratoma in approximately half of the patients. Aggressive and potentially metastatic tumors are observed very rarely in patients with NMDAR encephalitis. Therefore, the outcome is expected to be good, especially when tumor resection is performed at an early stage (2, 3). By contrast, both of our NMDAR encephalitis cases presented with metastatic lesions shortly after the encephalitis episodes. Also, in 1 patient no primary tumor could be detected despite an extensive investigation. To our knowledge, cancer of unknown origin has never been reported in NMDAR encephalitis. Moreover, parotid gland metastasis of SCLC (4) was reported for the first time in association with NMDAR encephalitis.

Our study implies that NMDAR encephalitis may occur with metastatic cancer and metastasis might even be the initial presentation of the cancer. Moreover, the underlying cancer in NMDAR encephalitis may show a very insidious course and may potentially affect the lifetime survival rate and prognosis of the patient. Therefore, so-called tumor-free NMDAR encephalitis patients should be closely followed with regular examinations for underlying undetected primary tumors over a long follow-up time.

Disclosures

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Conflict of interest: The authors declare that they have no conflict of interest related to this article.

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