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CASE REPORT

Paraneoplastic Limbic Encephalitis: A Diagnostic Challenge

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ABSTRACT

Paraneoplastic limbic encephalitis (PLE) is probably underdiagnosed, because of diversity of its symptoms and lack of specific diagnostic markers. A case of 29-year-old woman with complaints of persistent headache, behavior and memory changes has been discussed. Efforts have been made to establish all those diagnostic steps required to be applied before proceeding empirical therapy for PLE.

The overall poor outcome of PLE likely stems from both the delay in recognition and treatment, and thus resulting in immune-mediated neuronal injury. The prognosis is dependent upon the type of associated paraneoplastic onconeuronal antigen. In general, cytotoxic T-cell mediated process connected with intracellular antigens e.g. Hu is less responsive to two-pronged approach of tumour removal and immune therapy in comparison to immune process related to cell surface antigens which carries a worse neurological outcome.

Keywords: Antibodies, Antigens, Inflammatory, Limbic encephalitis.

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INTRODUCTION

Paraneoplastic limbic encephalitis (PLE) is a rare disorder characterized by features of personality changes, irritability, seizures, depression, memory loss, and sometimes dementia. This disorder is commonly associated with tumors in lung (50%), testis (20%), or breast (8%). The diagnosis is difficult because clinical markers are lacking, and symptoms usually precede the diagnosis of cancer or mimic other complications.[1]

The list of differential diagnosis with similar clinical presentation includes viral encephalitis [e.g., herpes simplex virus (HSV)], lupus cerebritis, toxic and metabolic encephalopathies, multiple sclerosis, Hashimoto's encephalopathy, Wernicke's encephalopathy, neurosyphilis, primary vasculitis of the central nervous system, and leptomeningeal involvement of malignancy.[2] A revised set of criteria for diagnosis proposed by Graus and Saiz[3] in 2005 are as follows:

- Subacute onset (<12 weeks) of seizures, short-term memory loss, confusion, and psychiatric symptoms
- Neuropathologic or radiologic evidence [magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), computed tomography (CT), positron emission tomography (PET)] shows involvement of the limbic system.
- Exclusion of other possible etiologies of limbic dysfunction
- Demonstration of a cancer within 5 years of the diagnosis of neurologic symptoms, or the development of classic symptoms of limbic dysfunction in association with a well-characterized paraneoplastic antibody (Hu, Ma2, CV2, amphiphysin, Ri) changes.

There is no evidence-based recommendation for the treatment of PLE. Current opinion favored applying a two-pronged approach for our patient with PLE, using a combination of tumor removal to eliminate the source of paraneoplastic onconeural antigens and immune therapy [e.g., intravenous steroid, intravenous immunoglobulin (IVIG), or plasma exchange], to prevent further immune-mediated neuronal injury.[2,4] The prognosis for recovery in patients with PLE is poor if immune therapy is administered without concomitant treatment of the underlying malignancy.[1]

However, here we present a case with unconstitutional symptoms, but after careful choice of investigations revealed presence of an ovarian teratoma, highlighting the importance of high index of suspicion of PLE and to look for the tumor.

CASE REPORT

A 29-year-old female came with complaints of persistent headache, behavior and memory changes, and sensations of "déjà vu" for 3 weeks. Headache was bilateral in fronto-occipital region worsening early in the morning, but relieved with analgesics. Patient had a vaginal delivery 11 weeks earlier. Physical examination showed vitals within normal limits and unremarkable cardiopulmonary

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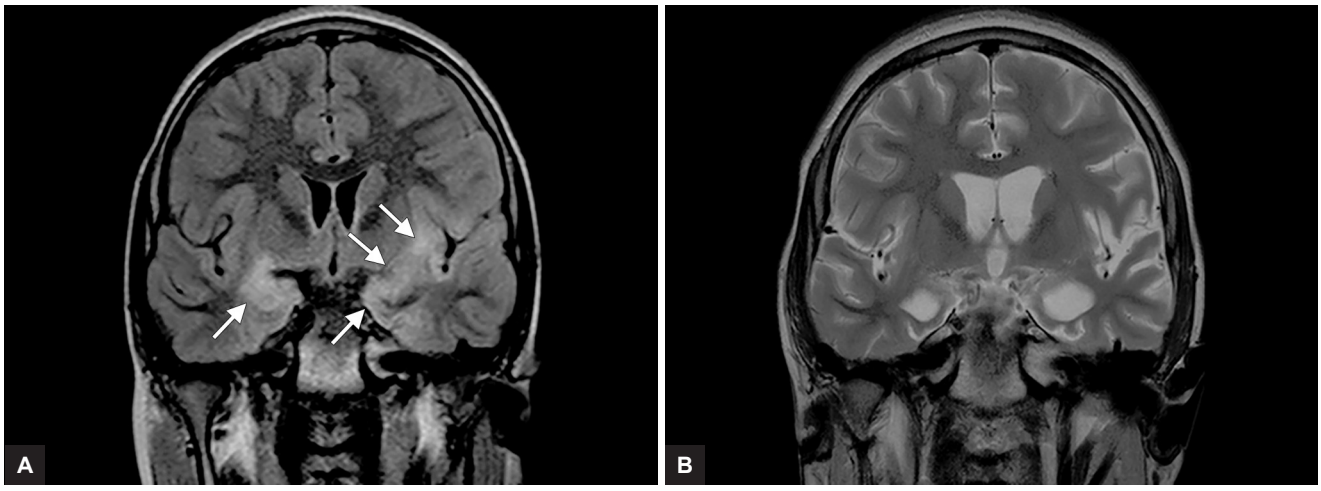

Figs 1A and B: (A) MRI FLAIR image; (B) MRI T2 weighted image (Note: MRI FLAIR (Fig. 1A) and T2 coronal images (Fig. 1B) of brain at the level of bilateral sylvian tissues and mesial lobes shows hyperintensity involving the bilateral hippocampal and parahippocampalgyrus on FLAIR images. On left side hyperintensity is extending up to left subcortical white matter of sylviangyrus. These lesions appear hyper on T2-weighted images s/o edematous changes)

and abdominal examination. Neurological examination revealed that patient had poor recall with blunted effect and muttering. Other higher functions were normal. Fundus examination was within normal limits. Motor system showed normal tone, 5/5 power, and 3+ reflexes symmetrically with no sensory involvement and limb dysmetria. Gait was normal.

Post admission, the patient gradually deteriorated to catatonic state with minimal oral intake and abnormal movements and generalized tonic clonic seizures on day 3 of admission. Seizure was also associated with frothing, uprolling of eye balls, tongue bite and bladder incontinence. She was started on antiepileptics. On day 7 post admission, she went into status epilepticus. She was electively intubated and intravenous lorazepam was given and phenytoin (20mg/kg body weight) was loaded. Levetiracetam and topiramate were subsequently added in increasing doses (up to maximum dosages) to treat persistent seizures.

Routine blood investigations were normal. Computed tomography brain was suggestive of diffuse cerebral edema. Cerebrospinal fluid (CSF) analysis showed normal proteins and sugars. Gram stain and culture were negative HSV and enterovirus polymerase chain reaction (PCR). Viral culture was negative, MRI of brain with gadolinium showed three nonspecific fluid attenuation inversion recovery (FLAIR) hyper intensities (mesial temporal region L>R) nonenhancing on gadolinium, magnetic resonance venogram revealed no venous thrombosis (Figs 1A and B). Electroencephalogram (EEG) showed epileptiform discharges.

Other blood investigations revealed antinuclear antibody, double-stranded DNA, C-antineutrophil cytoplasmic antibody (ANCA), and P-ANCA to be negative. Coagulation profile, including activated partial thromboplastin time, antiphospholipid antibody, antithrombin3, protein-C, protein-S, was normal. Ultrasonography (USG) of Abdo/pelvis revealed a cystic adnexal mass in pelvis. Contrast-enhanced CT (Fig. 2) of abdomen and pelvis revealed a right ovarian teratoma. CSF and serum was positive for anti-N-methyl D-aspartate receptor (NMDAR) antibodies. No other paraneoplastic antibodies [including binding, ganglionic, and striational acetylcholine (Ach) receptor antibodies, Purjinke cell antibodies type 1 (PCA-1 or anti-Yo), PCA-2, PCA-Tr (anti-Tr, immune response marker for Hodgkin's lymphoma), anti-neuronal nuclear antibodies type 1 (ANNA-1 or anti-Hu), ANNA-2 (anti-Ri), ANNA-3, anti-Ma1, anti-Ta, collapsin response-mediator protein-5 (CRMP-5 or CV2),

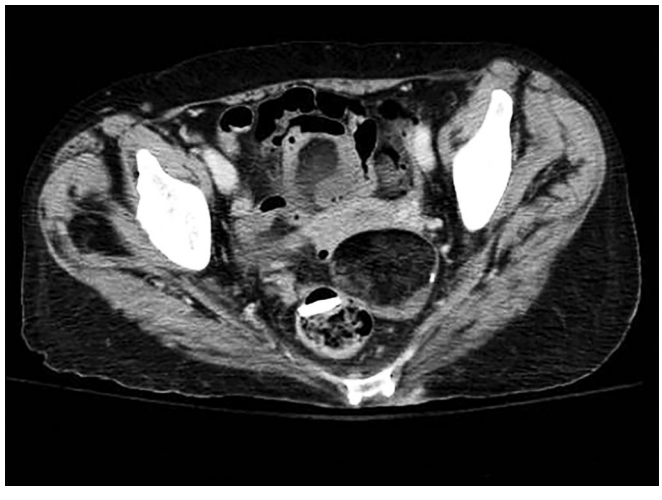

Fig. 2: Contrast-enhanced computed tomography of abdomen (Note: CT contrast (Fig. 2) at the level of bilateral iliac bones show well-defined hypodense round mass lesion posterior to fundus and body of uterus with calcific foci on the lateral aspect and fat attenuation within it with thickened posterior wall s/o dermoid cyst of ovary)

amphiphysin, anti-glial/neuronal nuclear antibody, type 1 AGNA-1] were detected.

After diagnosis the patient was started on azathioprine 1 mg/kg/day and steroids in the form of prednisolone and underwent bilateral oophorectomy for ovarian teratoma. The patient improved within 3 months of tumor treatment.

DISCUSSION

Paraneoplastic Limbic Encephalitis

Paraneoplastic limbic encephalitis results from production of neuronal protein by a tumor, which precipitates an immune mediated reaction against both tumor and central nervous system. There are two types of PLE, one with antibodies to intracellular antigens such as Hu, Ma2, CRMP5, and amphiphysin that is considered to be T cell mediated, and PLE with antibodies to cell membrane antigens such as: leucine-rich glioma inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2), N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and gamma-aminobutyric acid (GABA). These antibodies are more likely to be directly involved in the pathogenesis; thus these forms are more responsive to immune based treatment. PLE follows typically sub acute or chronic course with progression of symptoms within weeks to months.

The current hypothesis for the pathogenesis of PLE implicates an autoimmune process involving antigens shared by tumor cells and neuronal cells in the mesial temporal and limbic structures, including cingulated gyrus, orbitofrontal cortex, and mammillary bodies.[2] The most frequently associated neoplasm is small-cell lung cancer, followed by germ cell tumor of the testis, breast cancer, Hodgkin's lymphoma, thymoma, and immature teratoma of the ovaries.[1]

Paraneoplastic limbic encephalitis is associated with onconeuronal antibodies, which result in psychiatric and neurological manifestations. Anti-Hu antibody results in short-term memory loss, and confusion with seizures. Anti-Ma2 antibody is associated with short-term memory loss, nervous breakdown, and obsessive compulsive disorders with involvement of brainstem, hypothalamus, and diencephalon. Anti-CV2/CRMP results in cognitive defects, maniac mood, obsessive compulsive disorders with chorea, apraxia, optic neuropathy, dysgeusia, and anosmia. Anti-amphiphysin antibody leads to short-term memory loss, confusion with rigidity, and stiff man syndrome. Anti-NMDAR antibody results in psychosis, anxiety, paranoid behavior, catatonic state, and seizures. AMPA causes memory loss and aggression. GABA antibody results in psychosis, hallucinations, and seizures. Magnetic resonance imaging shows mesial temporal lobe changes in anti-Hu and anti-Ma2. Relapses are more common in AMPA antibodies.

Although PLE is rare (with a slightly greater predominance among women), the disease is under-reported due to the difficulty in establishing the diagnosis. Several factors render the diagnosis of PLE challenging. First, many other cancer-related complications, including brain metastases, toxic and metabolic encephalopathies, and adverse effects of cancer therapy, may have similar insidious neuropsychiatric presentations. Second, diseases other than PLE, particularly those of an infectious etiology, such as, HSV, share similar initial clinical features to PLE. Third, there is no "gold standard" method of establishing a diagnosis. The pathological findings of neuronal loss, perivascular inflammatory infiltrates, microglial activation, and reactive astrocytosis in the temporal and limbic structures are nonspecific and do not establish a paraneoplastic etiology.

Early immune treatment is particularly important with the emergence of rituximab, an anti-CD20 antibody that depletes B-cells and potentially the source of paraneoplastic antibody production.[5] B-cells cross the blood–brain barrier and intrathecal production of antibodies correlates with clinical severity in paraneoplastic disease. There is early evidence that rituximab is safe and may improve neurological outcomes, as seen in adjunct therapy in children with paraneoplastic opsoclonus-myoclonus syndrome,[6] as well as in paraneoplastic syndromes related to intracellular auto-antigens.[7] Since these studies are small and nonrandomized, we cannot make conclusive statements about the role of rituximab in the management of paraneoplastic diseases.

We recommend that in most patients the risks of immune therapy (IVIG or plasma exchange, steroids) are low enough to warrant early empiric intervention if there is sufficient clinical suspicion of PLE. We recommend the following tests before proceeding with empirical therapy for PLE: MRI of the brain, CSF analysis for bacterial and viral agents (in particular, HSV-PCR), measurement of ammonia levels and thyroid-stimulating hormone, a metabolic and electrolyte panel, EEG, and a paraneoplastic panel of both blood and CSF.[8]

CONCLUSION

A case of PLE in a young woman is reported. She presented with headache and behavioral changes, and later seizures. Diagnosis was established with detection of NMDAR antibodies in CSF and blood. Computed tomography scan abdomen showed an ovarian teratoma. Literature on this disease has been reviewed and treatment discussed. This patient improved after bilateral oophorectomy.

REFERENCES

1. Gultekin SH, Rosenfeld MR, Voltz R, Eichen J, Posner JB, Dalmau J. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumor association in 50 patients. Brain 2000 Jul;123(Pt 7):1481-1494.
2. Dalmau J, Rosenfeld MR. Paraneoplastic and autoimmune encephalitis. Available from: http://www.uptodate.com/contents/paraneoplastic-and-autoimmune-encephalitis.
3. Graus F, Saiz A. Limbic encephalitis: a probably under-recognized syndrome. Neurologia 2005;20(1):24-30.
4. Vedeler CA, Antoine JC, Giometto B, Graus F, Grisold W, Hart IK, Honnorat J, Sillevis Smitt PA, Verschuuren JJ, Voltz R. Management of paraneoplastic neurological syndromes: report of an EFNS Task Force. Eur J Neurol 2006 Jul;13(7):682-690.
5. Dalakas MC. B cells as therapeutic targets in autoimmune neurological disorders. Nat Clin Pract Neurol 2008 Oct;4(10):557-567.
6. Pranzatelli MR, Tate ED, Travelstead AL, Barbosa J, Bergamini RA, Civitello L, Franz DN, Greffe BS, Hanson RD, Hurwitz CA, et al. Rituximab (anti-CD20) adjunctive therapy for opsoclonus-myoclonus syndrome. J Pediatr Hematol Oncol 2006 Sep;28(9):585-593.
7. Shams'ili S, de Beukelaar J, Gratama JW, Hooijkaas H, van den Bent M, van't Veer M, Sillevis Smitt P. An uncontrolled trial of rituximab for antibody associated paraneoplastic neurological syndromes. J Neurol 2006 Jan;253(1):16-20.
8. Xia Z, Mehta BP, Ropper AH, Kesari S. Paraneoplastic limbic encephalitis presenting as a neurological emergency: a case report. J Med Case Rep 2010 Mar 24;4:95.