New onset refractory status epilepticus (NORSE) in a patient with paraneoplastic limbic encephalitis associated with craniopharyngioma: A rare case report

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Abstract

New onset refractory status epilepticus (NORSE) is a clinical presentation in patients, not a specific diagnosis characterized by the occurrence of a prolonged period of refractory seizures. NORSE is the presenting clinical feature in some patients with paraneoplastic etiology. Paraneoplastic limbic encephalitis (PLE) is a rare disorder of the nervous system associated with malignant disease. It presents as a subacute disease with symptoms like seizures, cognitive dysfunction, irritability, hallucination, and short-term memory loss. In our study, we reported a case of a 30-year-old woman with PLE associated with craniopharyngioma and serum anti-Hu antibodies. The patient presented with NORSE. Initial therapy with antiepileptic drugs failed to control seizures. The patient presented with short-term or recent memory loss, cognitive dysfunction, and behavioral changes (anger/apathy) for the last three months, suggesting a rapidly progressing dementia. Baseline investigations (blood counts, renal function, thyroid function, liver function, serum B12/folate level, serum cortisol, and urinalysis) were normal, and she had no background comorbidities. Computerized tomography (CT) scan and magnetic resonance imaging (MRI) revealed a sellar/suprasellar lesion suggestive of craniopharyngioma. The tumor was successfully removed and repeat imaging after surgery was clear and did not result in further seizures. Now the patient is on follow-up with tapering doses of prednisolone. This is a rare condition; we treated our patient successfully via surgical resection and postoperative chemotherapy. Also, we considered that her new onset refractory epilepsy was associated with her craniopharyngioma. Hence a high degree of suspicion is required, which can be guided by clinical findings and imaging.

Key words: NORSE, paraneoplastic limbic encephalitis, craniopharyngioma, refractory seizure.

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Introduction

Paraneoplastic limbic encephalitis (PLE) is a malignancy-associated central nervous system disorder. New onset refractory status epilepticus (NORSE) is observed in some patients with paraneoplastic etiology. PLE is a rare disorder with a subacute onset that affects the medial temporal lobe and presents symptoms such as cognitive dysfunction, seizures, irritability, hallucination, short-term memory loss, disorientation, limb paresis, and altered consciousness level. (1) The patients with PLE have several specific antibodies isolated in plasma and cerebrospinal fluid (CSF), of which anti-Hu is the most common type. PLE is one of the central nervous system paraneoplastic syndromes that occur in less

than one per ten thousand patients. Among these, 50% of patients have lung carcinoma, 20% have testicular tumors, and 8% will have breast carcinoma. (2,3)

Young individuals typically present with germ cell tumors of the testis or ovarian teratomas. (4) Germ cell tumors have more dominant limbic, diencephalic, and upper brainstem dysfunction. Hodgkin's lymphoma, immature teratoma, and thymoma are the most frequently associated tumors. CSF analysis or neuroimaging evidence provides a definite diagnosis of involvement of the limbic system besides the clinical features.

The mechanism reported in PLE is systemic neoplasia, where antigen expresses within the central nervous system, producing antibodies that target neoplastic tissue (onconeural antigens). (5) Early diagnosis of PLE is often important because that helps in the recognition of underlying malignancy. In PLE, cancer control is an important step because it is usually followed by remission of the paraneoplastic syndrome. (6) Fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) or T2 sequences show hyperintense signals in the medial portion of one or both temporal lobes. Tumor management, either by chemotherapy or surgical removal, results in a gradual improvement of signs and symptoms of PLE, considered the first line of treatment. In most patients, if primary malignancy is treated, PLE will recover. PLE is best treated by an interprofessional team. This study presents a detailed case report of a patient presenting PLE associated with craniopharyngioma.

Case report

A 30-year-old woman presented with a NORSE. She was initially treated with antiepileptics drugs, including benzodiazepines, levetiracetam, and fosphenytoin. But treatment failed to control seizures. She was then treated with intravenous (IV) general anesthesia (GA) (+ intubation) to control the seizures. She was admitted to the Intensive Care Unit (ICU) in our hospital and was under observation with continuous electroencephalography (EEG) monitoring. Despite continuous IV GA (propofol) and ongoing levetiracetam/fosphenytoin, the patient still had occasional seizures. At the same time, we collected her past medical history from relatives. They revealed she had increased memory loss (short-term/recent memory), cognitive dysfunction, and behavioral changes (anger/apathy) in the last three months, suggesting a rapidly progressing dementia.

Baseline investigations like renal function test, complete blood count, liver function test, thyroid function test, B12/folate, cortisol, and urinalysis were done and were normal. She did not have any background of comorbidities. An electroencephalogram of this patient revealed background abnormality in the form of generalized theta range slowing along with right hemispheric periodic lateralized epileptiform discharges (PLEDs).

A paraneoplastic encephalitis panel was done in both CSF and blood. The patient tested positive for anti-Hu antibodies. CSF analysis revealed inflammatory changes with mild lymphocyte predominance.

The computerized tomography (CT) scan of the head showed a well-defined hyperdense lesion with calcification in the sellar/suprasellar region. T1/T2 weighted brain MRI revealed a sellar/suprasellar lesion consistent with a craniopharyngioma (solid areas were hypointense and cystic regions were hyperintense in T1). FLAIR imaging showed hyperintensities in the bilateral medial part of the temporal lobe (**Figure 1**).

Hence a diagnosis of paraneoplastic limbic encephalitis was made. She was acutely treated with corticosteroids + intravenous immunoglobulin (IVIg) with slow tapering of antiepileptics, started on IV methylprednisolone 1 g/day for 3 days, and then prednisolone 60 mg/day. IVIg was given at a dose of 0.4 g/kg/day for 5 days. Seizures were remitted with the therapy, and the patient had a significant improvement in cognitive functions.

She was then posted for surgery after a neurosurgery consultation. The tumor was successfully removed by neurosurgery (extended endonasal endoscopic approach) and an excision biopsy of the tumor confirmed it to be a craniopharyngioma (adamantinomas). Tapering of antiepileptics continued (starting from 2 months post-surgery) while the patient continued to be on immunosuppression (prednisolone 40 mg/day).

Repeat imaging ensured good tumor clearance, and cessation of antiepileptics (by month 6) did not result in any further seizures. She is currently on follow-up with tapering doses of prednisolone.

For cancer screening, positron emission tomography CT (PET-CT) or focused investigations (like mammogram/transvaginal ultrasound/testicular ultrasonography) for cancer search were done and showed no evidence of metastasis.

Discussion

PLE is a rare neurological syndrome affecting limbic areas. PLE has a subacute onset with symptoms including short-term memory loss, dementia, altered mental status, mood changes, and seizures. (7) The subacute progression of short-term memory

loss of less than three months is the hallmark of PLE. (5)

Gaspard et al. evaluated NORSE cases between 2008 and 2013 and reported that in some patients with NORSE, a paraneoplastic or an autoimmune etiology was identified. (8) In our case, we also identified NORSE, a rare clinical presentation with paraneoplastic etiology.

CSF analysis showed mild to moderate lymphocytic pleocytosis in 60-80% of patients, and an elevated immunoglobulin G (IgG) index of oligoclonal bands in 50% of cases was noted in some studies. In our study, CSF analysis revealed inflammatory changes with mild lymphocyte predominance.

Hiroshi Nagafuji et al. found that PLE was associated with mixed olfactory neuroblastoma, and craniopharyngioma was a unique association. (9) Our study found that PLE was associated with one tumor element, craniopharyngioma. There have been very few case reports in the literature with a craniopharyngioma associated with limbic encephalitis.

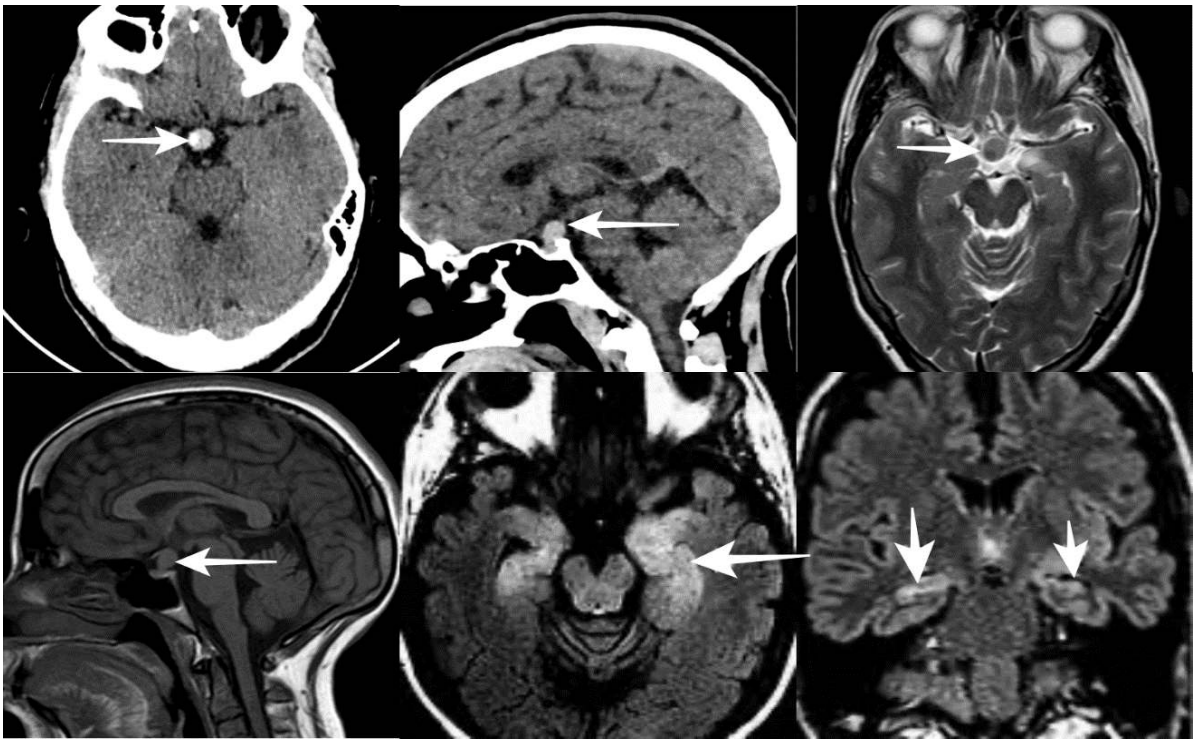
Several studies explained the pathogenic role of antineuronal antibodies in PLE. PLE with temporal seizures is associated with onconeural autoantibodies (anti-Hu, anti-Ma2/Ta, anti-CV2/collapsin response mediator protein [CRMP]-5, anti-amphiphysin). Recently many autoantibodies to neuronal extracellular epitopes (anti-N-methyl-D-aspartate [NMDA], anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA], anti-γ-aminobutyric acid-B [GABAB], anti-voltage-gated potassium channel [VGKC] [leucine-rich glioma inactivated 1 {LGI1}, contactin-associated protein-like 2 {CASPR2}) have been described. (10) Gultekin SH et al. found out in PLE that 60% of patients have antibodies in CSF or serum against antigens related to the nervous system and underlying cancer. (2) In our case, we confirmed that our patient was positive with antigen Hu.

The treatment of PLE is mainly surgical removal of the tumor and immunotherapy, such as plasma exchange, intravenous immunoglobulin therapy, or administration of immunosuppressive agents (e.g. corticosteroids). This treatment method helps to reduce the signs and symptoms of PLE. In our case, we also treated the patient with tapering of antiepileptics continued (starting from 2 months post-surgery). In contrast, the patient continued to be on immunosuppression (prednisolone 40 mg/day), and cessation of antiepileptics (by month 6) did not result in any further seizures. Now the patient is currently on follow-up with tapering doses of prednisolone. We treated our patient successfully via surgical resection and postoperative chemotherapy. Also, we consider that her limbic encephalitis was associated with her craniopharyngioma.

Conclusion

PLE due to anti-Hu antibodies is usually associated with small-cell lung cancer. But association with other tumors is uncommon with only a handful of cases reported in the literature. MRI has revolutionized neuroimaging and is almost indispensable in any patient with seizures to rule out a structural brain lesion. Antibody testing can be extremely useful for patients with suspected autoimmune/paraneoplastic encephalitis, and the number of associated antibodies is evolving and likely to increase. A high degree of suspicion is required, which can be guided by clinical findings and imaging.

Figure 1. Brain magnetic resonance imaging



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