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CASE REPORT

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New-onset seizures misdiagnosed as psychogenic non-epileptic seizures: a case of paraneoplastic limbic encephalitis with primary testicular cancer

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Abstract

Background Behavioral psychiatric symptoms can be the only warning signs of more serious conditions such as paraneoplastic limbic encephalitis. Differentiating between primary psychiatric disorders and paraneoplastic neurological syndromes is crucial as they require distinct treatment approaches. In this case report, we provide an overview of paraneoplastic encephalitis and introduce a unique case that showcases a misdiagnosis of psychogenic non-epileptic seizures (PNES) in a male as the primary symptom of paraneoplastic encephalitis due to pure seminoma. This case highlights the underlying pathophysiology of antibody-mediated paraneoplastic encephalitis and its significance.

Case presentation A 31-year-old male with no known past medical history presented due to recurrent seizures. There was no prior history of epilepsy or exposure to seizure-triggering agents. Imaging and electroencephalogram findings during his initial hospitalizations pointed to a potential diagnosis of PNES. The patient continued to experience seizures following discharge, leading to repeat hospitalizations. During the fourth hospitalization, the patient received mood-stabilizing anti-seizure medications and benzodiazepines, but he deteriorated and required intubation. It was during this time that the patient was transferred to our facility. Magnetic resonance imaging of the brain revealed multifocal areas of hyperintensity and restricted diffusion with avid enhancement. Immunotherapy was initiated with improvement of non-epileptic spells and encephalopathy. Outpatient workup uncovered malignant pure seminoma with metastases to the retroperitoneum. The authors theorize that paraneoplastic neurological disorders stemming from testicular cancer led to the neurological symptoms seen in this case.

Conclusion This report highlights a rare occurrence of paraneoplastic limbic encephalitis associated with pure testicular seminoma, clinically manifested as PNES. The diagnostic challenge posed by variability of presenting symptoms in paraneoplastic encephalitis emphasizes the importance of accurate differentiation from conditions such as autoimmune encephalitis. Current diagnostic approaches for paraneoplastic and autoimmune etiologies involve detection of known antibodies, as well as brain imaging. Notable antibodies associated with psychogenic non-epileptic seizures symptoms include anti-GAD-65, anti-Ma2, KLH11-antibodies, anti-Hu, and NMDA receptor antibodies. Recognizing paraneoplastic limbic encephalitis symptoms is challenging and often leads to misdiagnosis or overlooking of malignancies highlighting the need for awareness, comprehensive evaluation and timely treatment. Through this comprehensive case analysis, we enhance the understanding of underlying mechanisms, associated symptoms, and treatment options.

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Keywords PNES, Paraneoplastic encephalitis, Paraneoplastic syndrome

Background

Psychogenic non-epileptic seizures (PNES) have an estimated prevalence of 33 per 100,000 individuals with a mean age of 31. It was also found to be around 80% predominantly women, based on a study that followed 367,566 people over 3 years [1]. Signs of PNES are characterized by brief seizure-like episodes that lack the abnormal cortical activity typically seen in epileptic seizures. They are believed to stem from psychological distress, depression, and post-traumatic stress disorder (PTSD), which may manifest in physical symptoms, including convulsions, loss of consciousness, or involuntary movements [2]. Additional causes of PNES include conditions such as syncope, complex migraines, panic attacks, and transient ischemic attacks [3]. A diagnosis of PNES includes a thorough history and video electroencephalogram (EEG) to confirm the diagnosis [4]. Consideration of other underlying pathologies should be carefully taken into account, as PNES and their associated signs and symptoms have been documented in the literature as being potentially linked to neoplasms or other malignancies as an early indication [5]. Previous literature has shown an association, with 40% of patients with PNES having anti-NMDA receptor antibodies with an underlying tumor; the most common being small cell lung cancer and ovarian teratoma [6, 7] with brain tumors also been implicated [8]. Anti-neuronal antibodies can induce immune-mediated damage to neural tissue as a distant unintended effect of T-cell-mediated immune responses targeting the neoplasm. These unintended antibodies have the potential to induce destructive and detrimental effects on CNS neurons, resulting in inflammation characterized by the infiltration of T and B cells, as well as antibody deposition [9, 10]. Antibodies targeting intracellular synaptic epitopes, including NMDA receptors, anti-Hu, anti-gamma-aminobutyric acid (GABA), anti-Ma2 (targeting paraneoplastic Ma antigen family like 2), Kelch-like protein 11 (KLHL11) and glutamic acid decarboxylase-65 have been detected in individuals diagnosed with paraneoplastic limbic encephalitis (PLE) [10, 11]. These specific antibodies have also been associated with solid tumors, such as testicular tumors. KLHL11 antibodies are distinct as they have been proposed as a biomarker for paraneoplastic brainstem syndromes and directly associated with testicular seminomas [11]. It is important to note that the absence of these antibodies does not definitively exclude the presence of a paraneoplastic syndrome [10].

Paraneoplastic encephalitis can manifest as psychiatric symptoms, seizures, and short-term memory deficits. This condition is considered rare, with a prevalence of less than 1 per 10,000 patients [12]. Among these cases, approximately half are associated with lung cancer and a quarter of patients are associated with testicular cancer [12]. The specific antibody involved determines the cellular mechanisms that are impaired, giving rise to corresponding symptoms.

Glutamic acid decarboxylase 65 kDa (GAD-65) antibodies target intracellular synaptic epitopes and disrupt the GABAergic transmission. GAD autoimmunity impairs GABA synthesis by hindering the uptake of newly synthesized GABA into synaptic vesicles, resulting in reduced inhibitory GABA release. This can cause a state of neuronal hyperexcitability, which may lead to seizures involving the limbic regions [10, 13]. However, the understanding of GABAergic transmission and its relationship to PLE is still limited. GAD-65 has also been linked to specific conditions such as cerebellar ataxia, stiff-person syndrome, and as previously mentioned PLE. Only patients with GAD-related neurological disorders will have GAD antibodies detected in cerebrospinal fluid (CSF) establishing an association with GAD antibodies and neurological disorders, no correlation between titer levels and severity have been implicated [10, 13].

Neuroimaging should be performed to rule out brain metastases or other unusual seizure etiologies. In PLE, magnetic resonance imaging (MRI) may display T2 fluid-attenuated inversion recovery (FLAIR) signal on bilateral mesial temporal lobes [10]. Older age, male gender, and the presence of antibodies to neuronal antigens are established risk factors for underlying malignancy [13]. Individuals with these risk factors should undergo regular tumor screening.

The primary treatment for paraneoplastic encephalitis is dependent on the location of the antigens. Intracellular and cell surface/synapse antibodies involve the use of high-dose corticosteroids, plasmapheresis (PLEX), and intravenous immunoglobulins (IVIg), either individually or in combination. In cases where an adequate response is not observed, rituximab or cyclophosphamide is the next line of treatment [10]. Currently, there is not enough evidence to favor one treatment over another. Oncological or surgical intervention is necessary to achieve neurological improvement in the long term of paraneoplastic neurological syndromes [10].

Case presentation

A 31-year-old male with no known past medical history presented due to new-onset seizure. He described his first seizure events in which he would stand and shake without loss of consciousness. Although the patient had no history of common precipitants of epilepsy, he reported recently experiencing high levels of stress, anxiety, and depression leading to consideration of PNES as a differential diagnosis. He was eventually admitted to an outside hospital due to multiple convulsive events. Episodes were described as generalized tonic–clonic convulsive activity. Autonomic fluctuations related to these events were reportedly treated as indications of agitation or psychosis. Neuroimaging was reportedly unremarkable. Long-term EEG results at the outside facility led to a diagnosis of PNES, and the patient was discharged with mood-stabilizing anti-seizure medication. However, the patient's seizure activity persisted, leading to multiple readmissions to the hospital. During his latest admission, the patient experienced frequent seizure events and psychomotor agitation, followed by a decrease in consciousness after receiving benzodiazepines for agitation, necessitating intubation for respiratory support. The seizures were described as generalized tonic–clonic activity with presumed autonomic fluctuations that were treated as agitation or psychosis rather than a true seizure. He was subsequently transferred to our facility for higher level care and continuous EEG monitoring. Upon arrival, the patient presented with a severe and sudden onset of renal and hepatic failure. The precise cause of the liver and renal failure remains uncertain, yet it is reasonable to speculate that it may be linked to the incident that necessitated intubation, be it a genuine seizure or an iatrogenic effect resulting from the administration of benzodiazepines.

Initial computed tomography (CT) of the head was unrevealing. Brain MRI revealed multifocal bilateral areas of symmetric hyperintensity and restricted diffusion with areas of avid uniform enhancement involving the bilateral globus pallidi, mesial temporal lobes, and portions of the bilateral cerebellar gray matter (Fig. 1). CT of chest, abdomen and pelvis was notable for a few prominent retroperitoneal nodes but otherwise unremarkable. Iodine contrast was deferred due to renal failure. EEG studies at our facility showed mild to severe encephalopathic slowing of the background, ranging from 1–2 cycles per second to 6–7 cycles per second depending on the level of sedation. A convulsive seizure lasting approximately 14 s

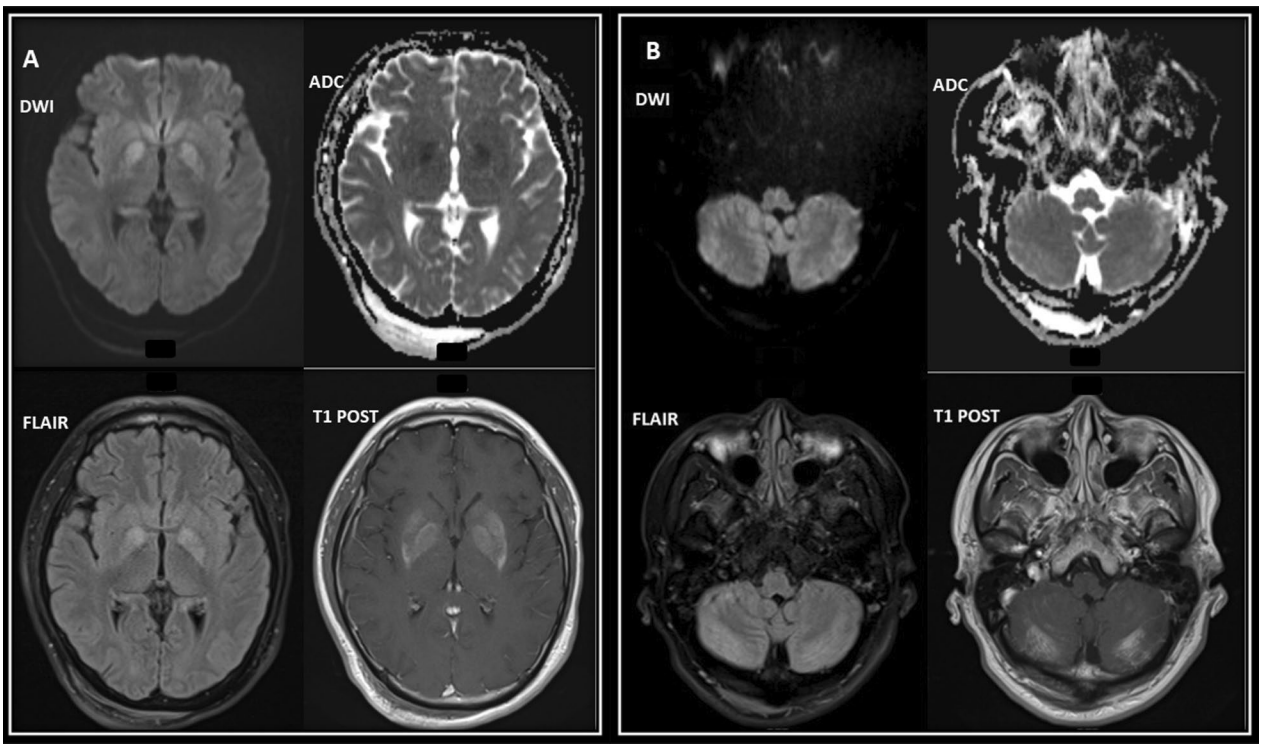

Fig. 1 MRI characteristics of paraneoplastic limbic encephalitis. MRI brain showing uniform bilateral symmetric restricted diffusion, hyperintensity and avid post-contrast enhancement involving the bilateral caudate (**A**), globus pallidus (**A**), and cerebellum (**B**) (*DWI* diffusion-weighted imaging, *ADC* apparent diffusion coefficient, *FLAIR* fluid-attenuated inversion recovery). Mild right posterior scalp edema noted here is thought to be related to self-injurious behavior as it resolves in subsequent MRIs and is not commented on by reading radiologist

was recorded on continuous EEG showing generalized tonic–clonic activity throughout the ictus. During the event a generalized spike-and-wave complexes between 1 and 3 Hz were noted. Extended serum and CSF studies were conducted to investigate his persistent encephalopathy, aiming to provide clarity on the condition. Serology for infectious and inflammatory causes were negative. Autoimmune and paraneoplastic antibodies for NMDA, AMPAR1/R2, GABA-B, LGI-1, CASPR2, DPPX were negative. Titers for serum GAD-65 antibodies during initial hospitalization were 77 units/mL (normal < 5 uM/L). CSF cellular composition was notable for a lymphocyte-predominant pleocytosis. CSF meningoencephalitis panel and cytology were unrevealing. A diagnosis of autoimmune encephalitis was considered for which a trial of corticosteroids, PLEX and intravenous IVIg were subsequently initially with notable improvement. Rituximab was started in the hospital and in the outpatient setting. Treatment led to near-complete resolution of encephalopathy, allowing for liberation from the ventilator. After a prolonged hospitalization of approximately 26 weeks, he was eventually transferred to an acute rehabilitation facility. A repeat GAD-65 antibody was performed prior to his hospital discharge which was persistently elevated and higher than previous at 127 u/mL (normal < 5).

The patient continued to receive outpatient follow-up care with neurology, rheumatology, and primary care, with no recurrence of encephalopathy, seizures or reported PNES. At follow-up with neurology several months following hospital discharge, he reported paresthesia and weakness of his extremities. Neuro-axis MRI incidentally found a soft tissue mass in the retroperitoneum. Further workup ensued including a PET/CT scan which raised concerns for primary testicular carcinoma with metastatic disease to the retroperitoneum. He underwent orchiectomy with excision of retroperitoneal lymph nodes. Biopsy revealed a malignant pure seminoma with extensive tumor necrosis strongly positive for CD117, D240 and PLAP, negative for pankeratin and CD30. He completed combination chemotherapy with bleomycin, etoposide, cisplatin without recurrence of his cancer, encephalopathy, mood disturbances, seizures or PNES.

Conclusions

Paraneoplastic limbic encephalitis due to pure testicular seminoma is a rare phenomenon. The clinical presentation of suspected PNES makes this phenomenon further uncommon. In our patient, anti-Ma2 and KLH11 antibodies, associated with paraneoplastic limbic encephalitis due to testicular cancer, were not able to be obtained. GAD-65 antibodies have also been shown to be involved in testicular tumors [11, 14]. Interestingly, our patient's repeated GAD-65 levels increased after treatment with immunotherapy. Although this may be related to the iatrogenic effect of IVIg [15], an underlying untreated neoplasm may also be causative.

As more clinical information was gathered, it became clearer that the diagnosis of PNES was likely inappropriate.

Furthermore, the literature and this case presentation show an association between paraneoplastic syndromes leading to seizures in germ cell tumors [5, 9]. This highlights the need to identify underlying malignancies for proper disease management.

Healthcare professionals should keep a high level of suspicion when encountering patients with new-onset psychiatric or neurological symptoms such as seizures. To proactively identify a neoplasm as a potential cause of PLE, a comprehensive evaluation should be conducted to rule out malignancy. Early identification, heightened awareness, and prompt treatment of PLE can significantly mitigate the risks of detrimental outcomes, including permanent neurological damage or fatality, thereby paving the way for improved patient outcomes. Further collaboration among healthcare professionals, including neurologists, psychiatrists, and oncologists is essential to ensure that patients receive the appropriate diagnostic and therapeutic interventions.

Abbreviations

CSF	Cerebrospinal fluid
CT	Computed tomography
EEG	Electroencephalogram
FLAIR	Fluid-attenuated inversion recovery
GAD-65	Glutamic acid decarboxylase 65 kDa
GABA	Gamma-aminobutyric acid
IVIg	Intravenous immunoglobulins
KLHL11	Kelch-like protein 11
PLE	Paraneoplastic limbic encephalitis
MRI	Magnetic resonance imaging
PNS	Paraneoplastic neurological disorders
PLEX	Plasmapheresis
PTSD	Post-traumatic stress disorder
PNES	Psychogenic non-epileptic seizures

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Author contributions
AR analyzed patient data and was a major contributor in the writing of the manuscript. DL analyzed patient data and was a major contributor in the writing of the manuscript. AV was a major editor of the manuscript. CN was an editor of the manuscript. MM was an editor of the manuscript. PJ was an editor of the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
In conducting this case report, patient privacy and consent were adhered to. This case report did not undergo ethical committee review due to the nature of the study, which incorporated the retrospective analysis of clinical data without any experimental intervention or deviation from normal practices. Full consent was acquired from the patient for publication.

Consent for publication
Patient has given full written consent for publication.

Competing interests
The authors declare that they have no competing interests.

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