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Case Report

A rare occurrence of progressive encephalomyelitis with rigidity and myoclonus in a case of breast carcinoma on treatment: a case report

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ABSTRACT

Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a subtype of Stiff-Person syndrome (SPS) and it is characterized by progressive muscle rigidity, painful spasms, and stimulus sensitive abnormal involuntary movements (myoclonus). PERM is distinct from classical SPS in view of its more rapid progression, additional neurological symptoms, and poorer prognosis. It is an autoimmune-mediated disorder of the central nervous system (CNS), particularly affecting inhibitory pathways and can present as a paraneoplastic syndrome. We present the case of a 65-year-old woman with metastatic breast cancer who initially presented with spasmodic abdominal contractions misdiagnosed as intractable hiccups. Her symptoms progressed to include jaw stiffness, dysarthria, dysphagia, and generalized myoclonus, requiring invasive mechanical ventilation. Investigations showed normal brain imaging, unremarkable cerebrospinal fluid analysis, and positive amphiphysin antibodies in paraneoplastic encephalitis panel thus confirming PERM. She was treated with methylprednisolone (500 mg/day for 5 days) followed by intravenous immunoglobulin (IVIG) (2 g/kg over 5 days), resulting in complete resolution of symptoms and ventilator weaning. This case highlights the importance of recognizing PERM in cancer patients and demonstrates the potential efficacy of immunotherapy in its management.

Keywords: Amphiphysin antibodies, Carcinoma breast, Myoclonus, Paraneoplastic syndrome, PERMS, Stiff person syndrome

INTRODUCTION

Stiff-person syndrome (SPS) is a rare neurological disorder characterized by progressive muscle stiffness, rigidity, and painful spasms, primarily affecting the axial muscles and significantly impairing mobility.[1] A more severe variant, PERM, presents with additional symptoms such as brainstem dysfunction, seizures, encephalopathy, and stiff-limb syndrome, where one or more limbs develop distal rigidity.[2,3] This causes marked disability profoundly impacting patient's quality of life with significant morbidity. Early diagnosis and treatment are crucial as it is progressive and sometimes fatal, but can be challenging due to its varied spectrum of presentation and rarity.

Clinical suspicion is based on neurological signs and symptoms of rigidity and myoclonus with hallmark triggers backed with presence of specific paraneoplastic antibodies. The mainstay of treatment is immunosuppressive therapy.

CASE REPORT

A 65-year-old woman diagnosed with invasive carcinoma of the right breast (ER 90%, PR 90%, HER2-2+, Ki-67 index 60%) with lymph node and skeletal metastases was receiving Palbociclib and Letrozole since April 2024. She was in a stable condition as per PET scan done in July 2024. Other co morbidities include type 2 diabetes mellitus and hypertension, both of which were well-controlled on regular medications. Initially admitted elsewhere with hiccups and chest pain; managed conservatively for intractable hiccups and discharged after partial relief. Two weeks later, presented to our facility with worsening hiccups, dysphagia, slurred speech, and altered sensorium. Neurological examination revealed drowsiness, dysarthria, dysphagia with oral pooling of secretions, grade 2 rigidity of the upper limbs as per modified unified Parkinson's disease rating scale and brisk deep tendon reflexes. Other system examination was normal. She was managed for intractable hiccups with chlorpromazine, baclofen, and benzodiazepines but without relief. CT head, neck, thorax and abdomen were done to look for any mass lesions, abscesses and diaphragmatic involvement as a part of work up for hiccups which was normal. She then gradually developed synchronous jerky movements of upper limbs and trunk with frequency of around 30-40 per minute along with stiffness of jaw suggestive of brainstem myoclonus which earlier resembled hiccups. Further workup with contrast-enhanced MRI revealed metastatic lesions in the vertebral column with normal brain parenchyma. Cerebrospinal fluid (CSF) analysis was unremarkable, with no evidence of infection identified on the multiplex PCR panel for common bacterial, viral, and fungal pathogens associated with meningoencephalitis. Other potential etiologies, including toxic and metabolic causes, were also ruled out. Electroencephalogram showed generalised slowing with no epileptiform discharges. Suspecting paraneoplastic encephalitis, serum for paraneoplastic antibodies (qualitative immunoblot method) was sent which was positive for amphiphysin antibodies and negative for CV2.1, PNMA2 (Ma2/Ta), ANNA-1/Hu, ANNA-2/Ri, PCA-1/Yo, Recoverin, SOX1, and Titin. Based on the clinical findings, normal brain imaging, normal CSF analysis, and a positive serum amphiphysin antibody, a final diagnosis of PERM was established. The patient was initially treated with levetiracetam, clonazepam, valproate, perampanel, and baclofen, in addition to empirical intravenous methylprednisolone (500 mg/day for 5 days). Despite this regimen, there was minimal clinical improvement, and myoclonic jerks persisted (around 5-10 per hour)-particularly in response to tactile stimuli. Due to partial response to steroids, IVIG therapy was initiated at 400 mg/kg/day for 5 days. During this period, the patient required mechanical ventilation for airway protection and was later tracheotomised. A significant clinical improvement was observed on day 2 of IVIG therapy, with reduced rigidity in the jaw and upper limbs (improving from grade 2 to grade 0) and completes resolution of myoclonus. By day 4, the patient was successfully weaned from ventilator support and mobilized to a wheelchair. Subsequently, the tracheostomy was decannulated, and the patient was discharged ambulating independently.

DISCUSSION

PERM is a variant of SPS ("stiff-person-plus" syndrome) or a form of brainstem myoclonus which is considered to originate from the brainstem and spinal cord.[3]There is excessive excitation of alpha motor neurons due to loss of spinal inhibitory interneurons similar to SPS.[4] Presence of antibodies to glycine receptors (GlyR) has a strong association with degeneration of long descending motor tracts along with brainstem involvement.[5] PERM is characterized by painful muscle spasms and typically involves the neck, trunk or lower limbs and is often rapidly progressive which is frequently stimulus sensitive. Other brainstem signs such as nystagmus, dysarthria, and dysphagia can be present. Patients may also present with an excessive startle and oculomotor dysfunction, whereas cognitive dysfunction and seizures are less frequently observed.[6]

Our patient initially presented with focal myoclonus, manifesting as rhythmic contractions mimicking hiccups, for which symptomatic treatment was initiated. Over time, the myoclonic activity progressed in a synchronous manner, involving the trunk and upper limbs. This was accompanied by progressive jaw rigidity, which subsequently led to dysarthria and dysphagia, with evidence of oral pooling of secretions. As the condition advanced, the patient exhibited deterioration in sensorium, ultimately requiring mechanical ventilation for airway protection.

Paraneoplastic SPS is more common in patients with breast cancer and small cell lung cancer. The serum of these patients often contains antibodies against amphiphysin whereas; patients with SPS who do not have malignancy (but who usually develop diabetes and other symptoms of endocrinopathy) have antibodies against glutamic acid decarboxylase (GAD). Amphiphysin 1 is an onconeural antigen expressed in both tumor and normal nervous tissue. Both humoral and cellular immune responses to tumors can contribute to the pathogenesis of autoimmune injury in the CNS.[7] Amphiphysin antibodies, for example, interfere with clathrin-mediated presynaptic endocytosis, resulting in reduced GABAergic transmission. This disruption leads to widespread disinhibition of CNS circuits, manifesting clinically as rigidity, exaggerated startle responses, painful spasms, and myoclonus (Figure 1).

Antibodies targeting the alpha-1 subunit of the GlyR, with or without concurrent GAD autoimmunity, have also been reported in some patients with stiff-person but are more characteristic of PERM.[8] Although most patients with GlyR antibodies do not have an associated malignancy, a study of 52 patients with PERM and GlyR antibodies found that 5 had a prior history of neoplasms, and 4 were

diagnosed with tumors during the evaluation for PERM. The most commonly identified tumors were breast cancer, lymphoma, and thymoma. In older adults who present with features of limbic encephalitis, encephalomyelitis, or opsoclonus-myoclonus-especially in combination with marked neck and arm rigidity-a paraneoplastic etiology should be strongly considered.

There are currently no internationally recognized guidelines, standards, or consensus on how to diagnose PERM. However, in 2022, Newsome and Johnson proposed diagnostic criteria for the spectrum of SPS-related disorders-including classic SPS, partial SPS, pure cerebellar ataxia, SPS-plus, and PERM. The proposed criteria for PERM include six major and seven minor diagnostic features (Table 1).[9] Our patient exhibited characteristic rigidity involving the neck and trunk, tactile stimulus-induced myoclonus, generalized EEG slowing, and tested positive for amphiphysin antibodies-thereby fulfilling all major diagnostic criteria.

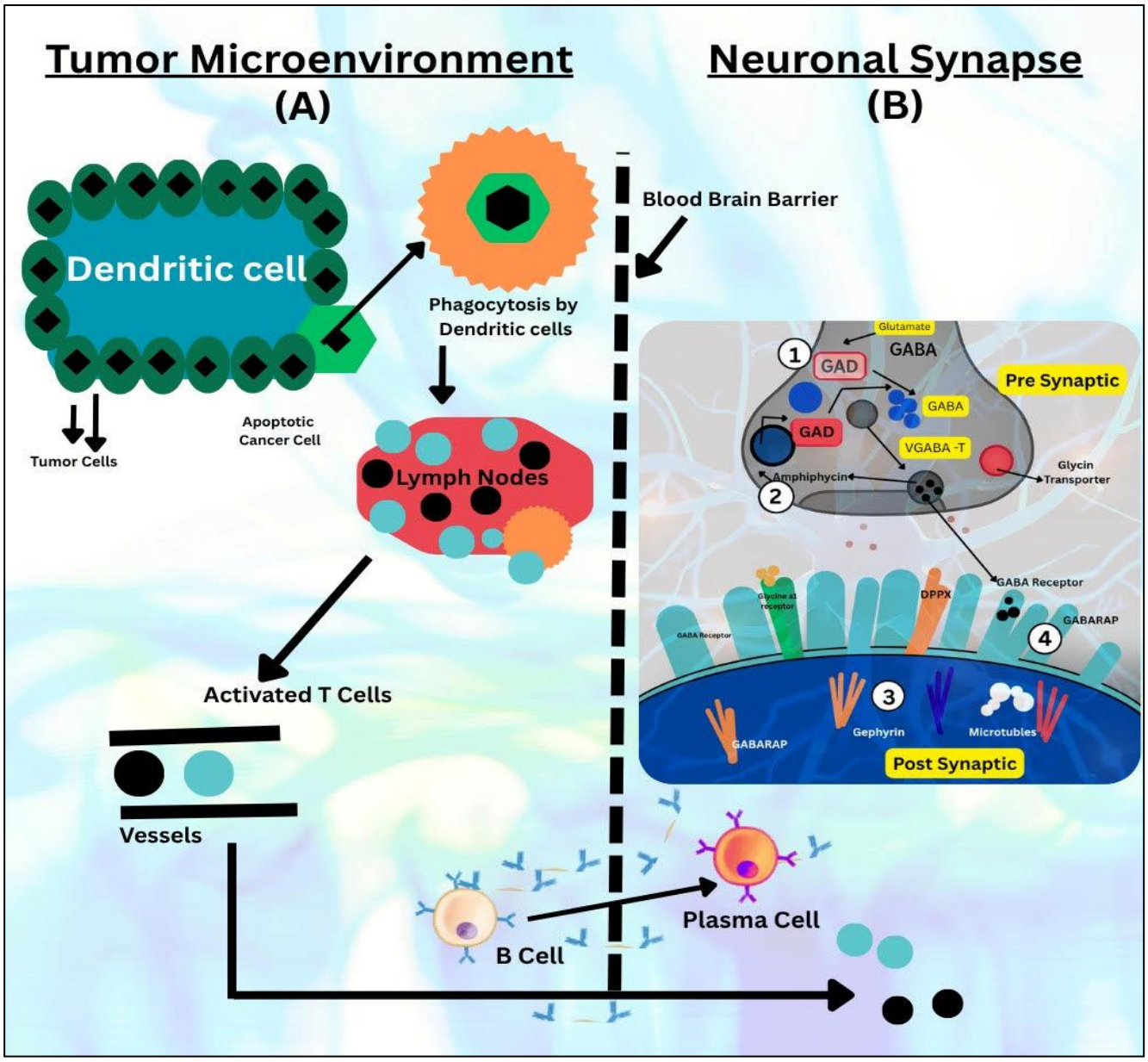

Figure 1: (A) Tumor expressing onconeural antigens can trigger an immune response through cross-presentation, where dendritic cells engulf apoptotic tumor cells and present their antigens to T and B cells in lymph nodes. This leads to activation of cytotoxic T lymphocytes and plasma cells that produce onconeural antibodies. They cross blood–brain barrier and attack healthy neurons expressing similar antigens, resulting in inflammation and damage. (B) Presynaptic antigens are (1) GAD-enzyme that synthesizes GABA, and (2) Amphiphysin-synaptic vesicle protein responsible for endocytosis of plasma membrane following GABA release. Post synaptic targets are, (3) Gephyrin, GlyR, DPPA (dipeptidyl peptidase like protein) and (4) GABARAP (GABA A receptor associated protein).

Table 1: Diagnostic criteria.

Major criteria	Minor criteria
Clinical presentation of rigidity involving typical regions like neck, torso and extremities, brainstem and/or cerebellar symptoms)	Autonomic dysfunction
Hallmark triggers for spasms/increased rigidity	Presence of CSF autoantibody to GAD65, GlyR or amphiphysin
Exam findings: features of other SPS spectrum disorder plus encephalopathy and severe rigidity or myclonus, may be generalised or focal	CSF pleocytosis
Positive serum autoantibody to GAD65 (high titre), GlyR, or amphiphysin	CSF-restricted Oligoclonal bands
EEG (generalized slowing and/or epileptic discharges)	Electromyography demonstrating co-contraction of agonist and antagonist muscles and/or continuous motor unit activity in affected muscles (paraspinal/abdominal musculature and/or legs/arms)
Exclusion of alternative diagnoses	Brain MRI demonstrates T2/contrast-enhancing lesion(s) in brainstem
	Brain FDG-PET demonstrates hyper-or-hypo metabolism within cortices

*Meets all major and minor criteria-Definitive diagnosis, meets all major criteria and no minor criteria-Definitive diagnosis, meets 4 major criteria (must include positive serum autoantibody and exclusion of alternative diagnoses) and at least 2 minor criteria-definitive diagnosis, meets 3 major criteria (must include positive serum autoantibody and exclusion of alternative diagnoses and at least 2 minor criteria-definitive diagnosis, meets 3 major criteria (must include exclusion of alternative diagnoses) and at least 2 minor criteria-probable diagnosis, meets 3 major criteria (must include exclusion of alternative diagnoses) and less than 2 minor criteria- possible diagnosis and meets 2 major criteria (must include exclusion of alternative diagnoses) and at least 2 minor criteria- possible diagnosis.

Immunosuppressive therapy remains the cornerstone of treatment. Corticosteroids are the most commonly used agents, typically initiated with intravenous pulse methylprednisolone at 500-1000 mg/day for 3-5 days, followed by oral prednisolone at 1 mg/kg/day, gradually tapered over time. Alternative or adjunctive immunosuppressive strategies include: IVIG-0.4 g/kg/day for 3-5 days, plasma exchange: 3-6 sessions depending on disease severity, rituximab: 375 mg/m² weekly for 4 weeks, cyclophosphamide: 750 mg/m² every 4 weeks and mycophenolate mofetil: 1000-1500 mg orally, twice daily.

Despite these approaches, treatment outcomes remain variable and are influenced by underlying serological markers and tumor associations. Predictors of favorable response and lower relapse rates have yet to be clearly defined.[10]

Identification of an underlying malignancy and timely initiation of appropriate treatment is of paramount importance in cases of paraneoplastic encephalitis. In situations where no tumor is initially detected, active surveillance and periodic screening for occult malignancy are warranted for at least four years, as PERM can precede the diagnosis of an associated malignancy. It is also important to consider alternative etiologies, such as drug-induced encephalitis. For instance, palbociclib, a CDK4/6 inhibitor used in cancer therapy, has been implicated in cases of AMPA receptor antibody-positive encephalitis.[11] These patients often present with ataxia, nystagmus, and confusion-clinical features that can mimic but are distinct from PERM. However, further research is necessary to establish clearer understanding of drug-induced autoimmune encephalitis.

CONCLUSION

PERM is a rare, autoimmune-mediated neurological disorder that requires a high index of clinical suspicion for timely and accurate diagnosis. It is often associated with occult or untreated progressive malignancies. Initial symptoms may be subtle and misleading, as seen in our patient, who presented solely with persistent hiccups while undergoing treatment for breast carcinoma with good response, making this a particularly rare and atypical presentation. Although significant advances have been made in understanding the autoimmune pathophysiology of PERM, further research is needed to determine the most effective therapeutic strategies and optimal treatment durations to achieve sustained symptom resolution.

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