Paraneoplastic encephalitis as a rare paraneoplastic syndrome of adrenocortical carcinoma: A rare case report.

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Abstract

Paraneoplastic neurologic syndromes (PNS) are rare in pediatrics and are understood to be consequences of cross-reactivity against various neuroendocrine antigens expressed on cancer cells. Here, we report a case of autoimmune encephalitis, a type of paraneoplastic neurologic syndrome that was associated with a case of adrenocortical carcinoma and had some clinical response to immunosuppressive therapy. Adrenocortical carcinoma is a rare tumor with controversial tissue of origin but expresses various neuroendocrine antigens that could be the possible mechanism for this rare yet interesting association.

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Abbreviations

PNS	Paraneoplastic neurologic syndromes
ACC	Adrenocotical carcinoma
PET	Positron emission tomography
NSE	Neuron specific enolase
IVIG	Intravenous immunoglobulin

ABSTRACT

Paraneoplastic neurologic syndromes (PNS) are rare in pediatrics and are understood to be consequences of cross-reactivity against various neuroendocrine antigens expressed on cancer cells. Here, we report a case of autoimmune encephalitis, a type of paraneoplastic neurologic syndrome that was associated with a case of adrenocortical carcinoma and had some clinical response to immunosuppressive therapy. Adrenocortical carcinoma is a rare tumor with controversial tissue of origin but expresses various neuroendocrine antigens that could be the possible mechanism for this rare yet interesting association.

MAIN TEXT

Introduction

Paraneoplastic neurologic syndromes (PNS) are rare in pediatrics and are reported in only a few pediatric malignancies like Hodgkin lymphoma, neuroblastoma and teratoma (1). Opsoclonus-myoclonus, encephalitis, cerebellar syndrome and encephalomyelitis are some of the reported paraneoplastic neurological syndromes. Paraneoplastic encephalitis is usually associated with neuroendocrine tumors and lymphomas (2). We report a case of possible paraneoplastic encephalitis in a patient of adrenocortical carcinoma (ACC).

Case description:

A 6year old male, presented with left flank swelling and excessive facial, axillary and pubic hair, increased appetite and weight gain for 2 months. On examination he had hyper tension, flank mass and virilization. Abdomen and chest CT was suggestive of a left sided adrenal mass with calcification and pulmonary metastasis. Serum dehydroepiandrosterone level was $>$ 1500.0 ug/dL leading to the diagnosis of adrenocortical carcinoma. Due to upfront un-resectability he was started on mitotane and CED (Cisplatin-Etoposide-Doxorubicin) chemotherapy.

Two weeks after starting chemotherapy he had multiple episodes of left focal seizure with secondary generalisation. Patient also had behavioural alterations, frightfulness, deterioration of sensorium, dystonia and overall increased extremity tones. MRI brain showed focal areas of hyperintensity and diffusion restriction in thalami, posterior parietal and subcortical and insular cortex. FDG-PET of the brain was suggestive of hypermetabolism in frontal-temporal lobe and thalami with hypometabolism in occipital lobes (Fig-1). EEG was suggestive of left hemispheric near continuous discharges with occipital predominance (Fig-2).

The patient was started on antiepileptics bud had poor responses in EEG. Ultimately the patient went on to require five antiepileptics: valproate, levetiracetam, topiramate, lacosamide and lorazepam. Initial cerebrospinal fluid (CSF) analysis was suggestive of neutrophilic pleocytosis, and was sent for both infective and autoimmune panel. All the CSF workup including biochemistry, bacterial, tubercular, viral, parasitic and autoimmune panel were negative. With the clinical possibility of seronegative autoimmune encephalitis, child received IVIG and pulse steroids. Child showed neurological improvement in the form of improved sensorium, normalization of behaviour and seizure control. Unfortunately, interim response was suggestive of progression of ACC at primary and metastatic site, hence parents opted for palliation.

Discussion:

Paraneoplastic syndromes are rare in ACC, with occasional reports of hypoglycaemia(3), Cushing syndrome and polycythaemia(4). To the best of our knowledge, paraneoplastic neurologic syndromes (PNS) has never been reported in ACC. Malignancies usually reported with PNS include lung cancers, breast cancer, teratomas, lymphomas, neuroendocrine tumours and malignant thymomas. Paraneoplastic encephalitis is one of the PNS that is usually associated with tumors of neuroendocrine origin and has a debilitating course(5). Though the exact mechanism of immune-tolerance breakdown that leads to paraneoplastic encephalitis is not known, cross reaction between tumor antigen and neural antigens is the most plausible explanation(2). Interestingly ACC despite not being of direct neuroendocrine origin, is positive for neuroendocrine markers like synaptophysin and NSE(6). This raises the possibility that some unknown neuroendocrine antigens could also be expressed over the ACC cells, that cross-reacts with neural antigens leading to autoimmune encephalitis.

For diagnostic certainty of PNS, updated PNS-Cares score was proposed in 2021 (Table-1), with the known limitation that it will be false negative if the cross-reactant antigen is a novel one(7). The index patient will be "possible PNS" as per the score, but it is fairly possible that the clinical syndrome in him could be due to some novel antigen not detected by the current antibody panel.

In addition to CSF auto-antibody panel, MRI is an important modality to diagnose autoimmune encephalitis, but findings can be normal or non-specific in a sizable number of cases(8). Multiple studies have reported increased sensitivity of FDG-PET over MRI in assessment of autoimmune encephalitis (9) (10) (11). As paraneoplastic encephalitis is a form of autoimmune encephalitis the patterns of involvement in imaging is often similar. Common patterns reported in FDG-PET are mesial temporal hypermetabolism, bilateral occipital lobes hypometabolism with hypermetabolism of the frontal-temporal lobe, and basal ganglia (11) (12). Though mesial temporal hypermetabolism is the most common pattern in PET, index patient had hypermetabolism of the frontal lobe and basal ganglia with nonspecific findings on MRI of same time point.

First-line therapy of paraneoplastic encephalitis begin with high-dose methylprednisolone, IVIG and plasmapheresis given individually or in combination(13). Cases refractory to initial therapy are treated with, second-line drugs like cyclophosphamide and/or rituximab(14). To conclude, paraneoplastic encephalitis should be kept as a rare differential of an unexplained encephalitis in a case of adrenocortical carcinoma. Exploration of the inciting antibody will give more information on the exact antigen and the pathogenesis of this clinically interesting process.

Conflict of Interest statement: The authors declare no conflict of interest.

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Legends:

Table-1 : PNS-Care Score

Figure-1 : Axial FDG-PET/CT image showing left sided adrenal origin calcified, solid, cystic mass with calcifications and FDG uptake in the solid component diagnosed as ACC (A) increased uptake in the basal ganglia, frontal-temporal lobe and thalami with decreased uptake in occipital lobes (B)

Figure-2 : Bipolar children montage epoch showing left hemispheric near continuous discharges with occipital predominance (A). Unipolar montage showing the left occipital predominance of the discharges (B).

Table-1: PNS-Care Score

Clinical level
High-risk phenotypes Intermediate-risk phenotypes Defined phenotype epidemiologically not associated with cancer
Laboratory level
High-risk antibody (>70% cancer association) Intermediate risk antibody (30%–70%) Lower risk antibody (<30%) or negat
Cancer
Found, consistent with phenotype and (if present) antibody, or not consistent but antigen expression demonstrated Not fou
Diagnostic level

Clinical level				
Definite	Probable	Possible	Non-PNS	

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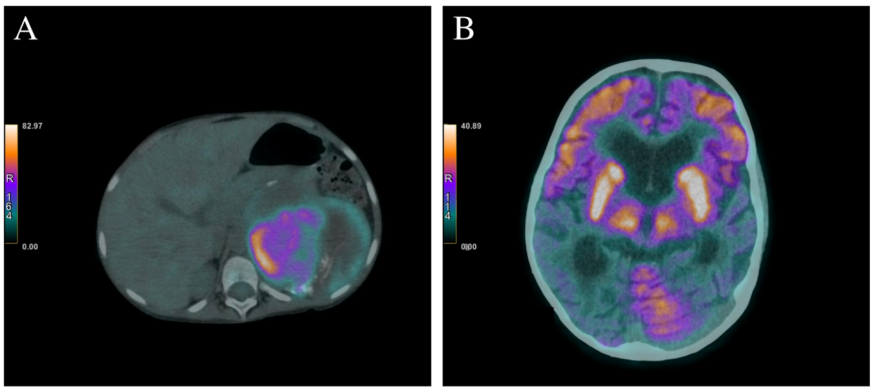
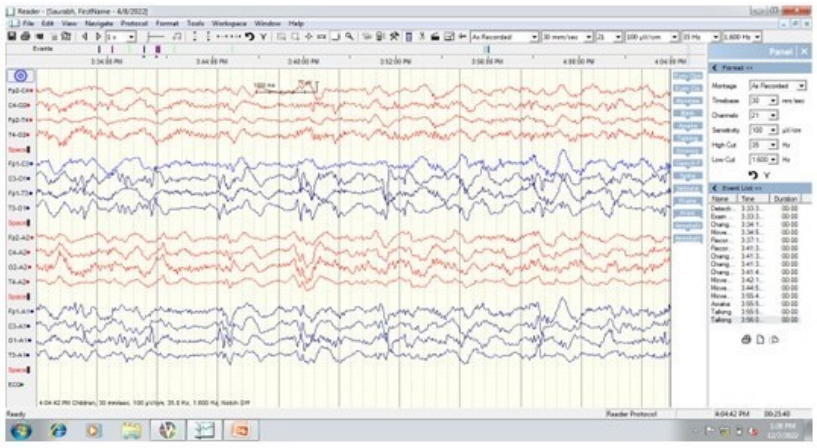
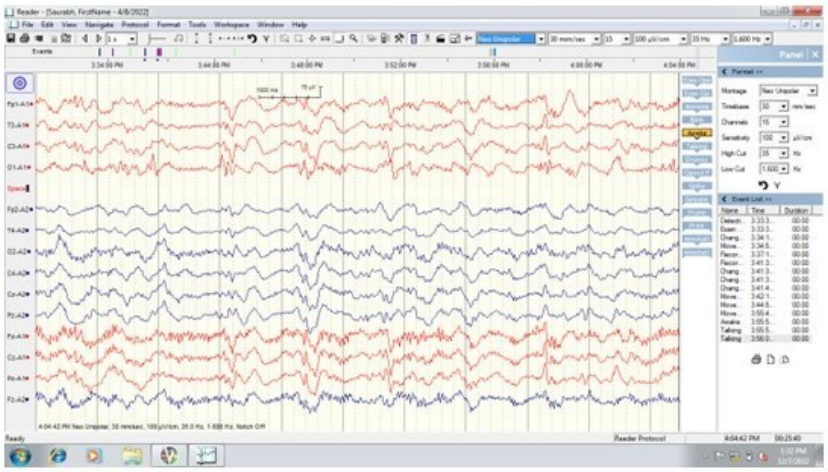


Figure-2 : Bipolar children montage epoch showing left hemispheric near continuous discharges with occipital predominance (A). Unipolar montage showing the left occipital predominance of the discharges (B).



A



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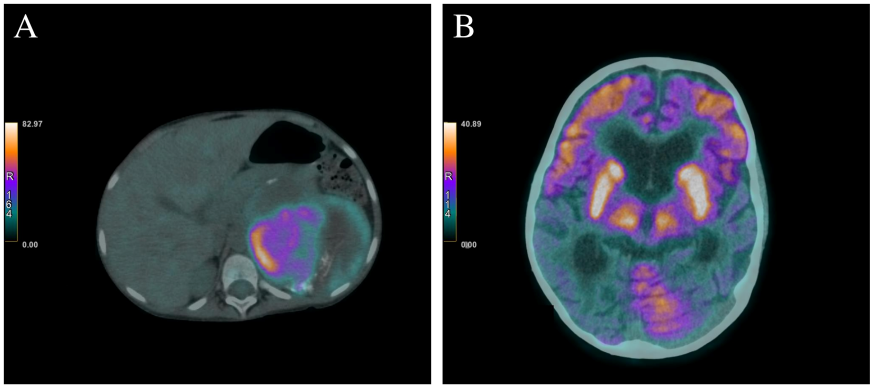
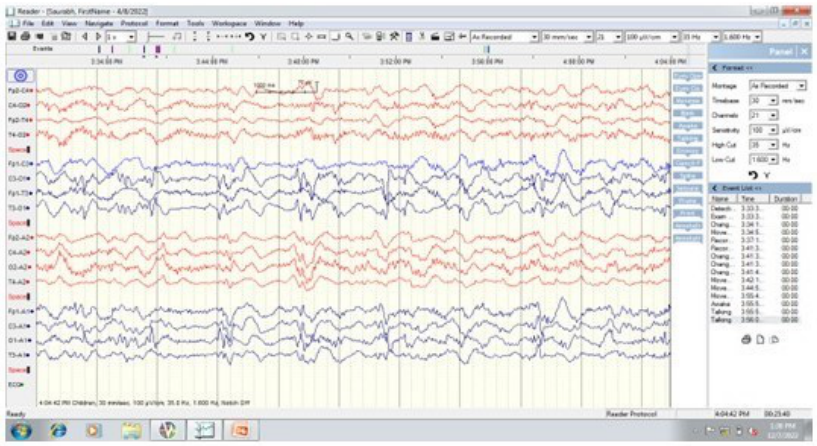
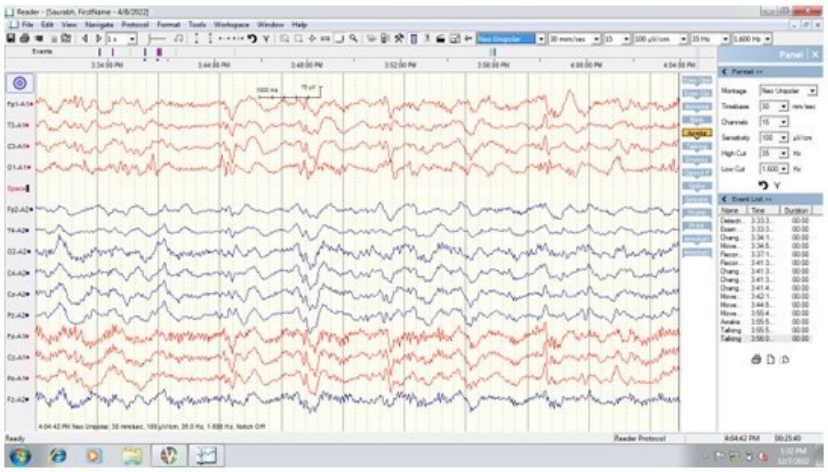




A



B