Case Report

Unusual PSMA uptake in seronegative paraneoplastic brainstem encephalitis: A case report

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ABSTRACT

Paraneoplastic encephalitis, especially seronegative, is a heterogeneous group of disorders with varied symptoms at presentation. We present the case of a 63-year-old male who presented with motor weakness and altered sensorium. Magnetic resonance imaging of the brain showed altered signal intensity in the midbrain, pons, anterior part of the medulla, and bilateral middle cerebellar peduncle. T2 hyperintensity was also seen in the bilateral basal ganglia and internal capsule region. 18 fluoro-deoxyglucose positron emission tomography/computed tomography (18 FDG PET/CT) showed increased FDG uptake in the brain stem, left thalamus, and periventricular location. 68Ga-prostate-specific membrane antigen (PSMA) PET/CT done in view of elevated serum Prostate-specific antigen levels show a focal PSMA-avid lesion in the prostate gland and increased PSMA uptake in the brain stem, which is an atypical site of PSMA uptake. Our study highlights the importance of paraneoplastic syndromes with varied clinical presentation and low specificity to antibodies. These spectra of diseases are fatal but treatable and therefore should be evaluated diligently to reduce morbidity.

Key words: Brain, Encephalitis, Magnetic resonance imaging, Prostate specific membrane antigen

Encephalitis is an inflammation of the brain characterized by progressive encephalopathy. The main causes of encephalitis are infections (40–52%) and immune-mediated phenomena (21%), which include paraneoplastic syndromes [1]. The first population-based study found an incidence of paraneoplastic syndromes that approximates 1/100,000 person-years and a prevalence of 4/100,000 [2]. Paraneoplastic neurological syndromes are a group of diseases that are associated with malignancy and may or may not have the presence of antibodies against neuronal antigens. The evolution and discovery of various methods to detect these antibodies have led to a new entity called paraneoplastic neurological disorders. These onconeural antibodies also suggest the possibility of a tumor. On the other hand, the absence of these neuronal antibodies does not rule out the possibility of paraneoplastic neurological syndromes. The role of imaging like magnetic resonance imaging (MRI) contrast and positron emission tomography (PET) can be useful tools in conjunction with other investigations for the diagnosis of seronegative immune-mediated disease. The rationale for reporting this case is the unusual uptake of prostate-specific membrane antigen (PSMA) in the brain, despite its specificity to the prostate. The presenting complaints of the patient were non-specific with respect to CA prostate, and this chance finding gave a diagnosis that differed from the clinical diagnosis.

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CASE REPORT

A 63-year-old male with a known case of hypertension for 6 years presented in emergency with altered sensorium, inability to swallow, hoarseness of voice, and imbalance while walking, slowly progressing for 1 month.

On examination, the patient was hemodynamically stable and afebrile, with normal vitals and a Glasgow coma scale (GCS) of E2V1M4. The patient was drowsy, arousable, and disoriented by time, place, and person. There was no meningeal irritation (Kernig's and Brudzinski's signs were negative). Motor examination revealed 3/5 on the Medical Research Council sum score (MRC SS) on both upper limbs and lower limbs without sensory involvement. Myotatic reflexes were normal in all four limbs with a bilateral extensor plantar response.

A clinical diagnosis of encephalitis was kept, and the patient was started empirically on Acyclovir, Ceftriaxone,

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Methylprednisolone, and other supportive drugs. Routine blood investigations were suggestive of microcytic hypochromic red blood cells with neutrophilic leucocytosis. Inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) and metabolic and electrolyte parameters were normal. Urine cultures were sterile. In view of the altered sensorium, an electroencephalogram was done, which was suggestive of electrophysiological dysfunction in the form of a symmetrical slowing of background to theta. The MRI brain showed altered signal intensity in the midbrain, pons, anterior part of the medulla, and bilateral middle cerebellar peduncle. T2 hyperintensity was also seen in the bilateral basal ganglia and internal capsule region. MRI contrast showed hyperintensity in the basal ganglia and internal capsule region, which was suggestive of inflammation of the brainstem (encephalitis) (Fig. 1).

Cerebrospinal fluid (CSF) examination showed raised proteins (106 mg/dL) and mild pleocytosis (10 cells–all lymphocytes) with a normal glucose level (73.5 mg/dL). There were no malignant cells in the CSF. India Ink (*Cryptococcus*), Gene Xpert (tuberculosis), and autoimmune encephalopathy panels were negative. The bacterial and viral polymerase chain reaction for the commonly associated bacterial and virus-causing meningoencephalitis panel was negative. His serum paraneoplastic panel, NMO MOG antibody, ganglioside antibody panel, and vasculitis profile were negative. ACE and serum ammonia levels were normal. Tumor makers (CA 19-9, CA 125, CEA, beta HCG) were negative.

Fluoro-deoxyglucose PET whole body was advised to further investigate, which showed increased uptake seen in the brainstem (Fig. 2). Prostate-specific antigen (PSA) was done, and the levels were found to be 14 ng/dL and 16 ng/dL, increasing over the span of 7 days. The MRI pelvis was suggestive of possible prostate malignancy (PIRADS-5) with an apparent diffusion coefficient (ADC) value of 7×10^{-3} mm^2/s (normal values of ADC $\geq 9 \times 10^{-3}$) (Fig. 3). There was increased uptake of PSMA, Ga-PSMA-11,

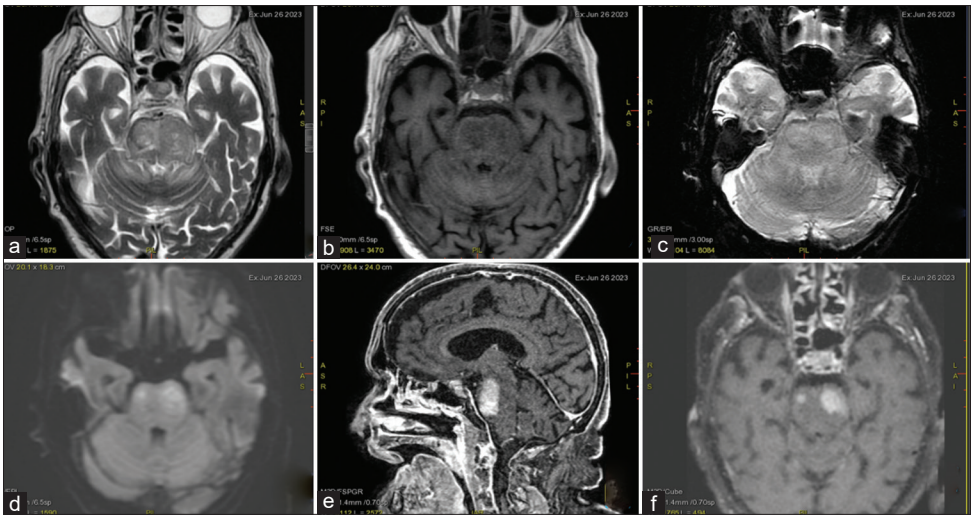

Figure 1: Areas of parenchymal swelling with signal change appearing hyperintense on T2 (a), hypointense on T1 (b) showing intense enhancement in both halves of pons on post contrast T1W Sagittal and axial images(d,e). Some of these areas show slight restricted diffusion and rest show facilitated diffusion on DWI (d). No haemorrhage on GRE(c) in these areas

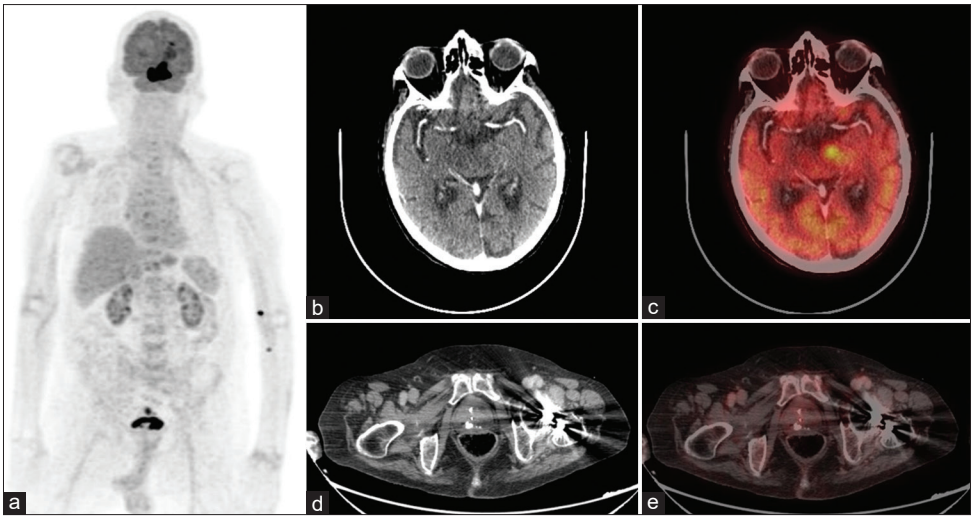

Figure 2: Maximum intensity projection images (a), axial computed tomography (CT) (b and d) and axial fused positron emission tomography/CT (d and e) sections of 18 F-fluoro-deoxyglucose (FDG) PET/CT done in a patient with encephalitis under evaluation. Scan shows heterogeneously enhancing foci with increased FDG uptake in periventricular region (not shown), left thalamus (not shown) and brain stem involving mid brain (white arrow image c, SUVmax- 19.4) and pons. Pelvic sections show ill-defined hypodense foci in left lobe of prostate gland with no significant FDG uptake. No significant focal FDG avid hypermetabolic lesion noted in whole body survey

in the prostate and brainstem, which is an unusual presentation in a patient with encephalitis with seronegative autoimmune and paraneoplastic profiles (Fig. 4).

The patient was advised to undergo a biopsy of the prostate gland lesion to confirm prostate malignancy. However, based on imaging findings, i.e., a PIRAD- 5 prostate gland lesion on pelvic MRI and corresponding increased PSMA avid lesion in the prostate gland on 68Ga PSMA PET/computed tomography, a provisional diagnosis of carcinoma of the prostate gland (a biopsy result was awaited) with paraneoplastic brain stem encephalitis was kept (Fig. 5).

On 3rd day of admission, the patient was empirically started on intravenous immunoglobulin (IVIG) (2 g/kg of body weight) for 5 days. The patient improved neurologically on the 7th day

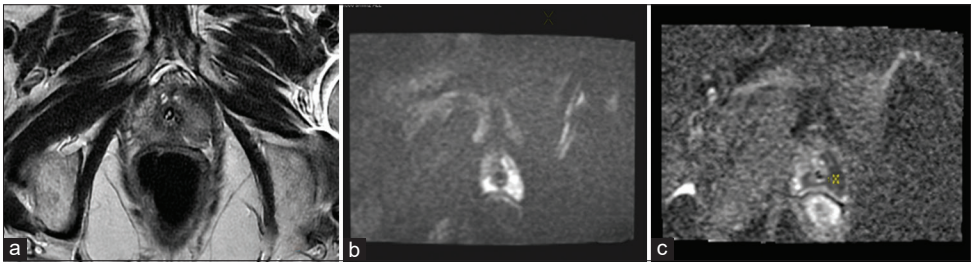

Figure 3: T2 axial image of pelvis reveals hypointense signals in left peripheral zone (a) which shows restricted diffusion (b) with ADC maps (c). ADC values 0.7 × 10^{-3} mm^2/s

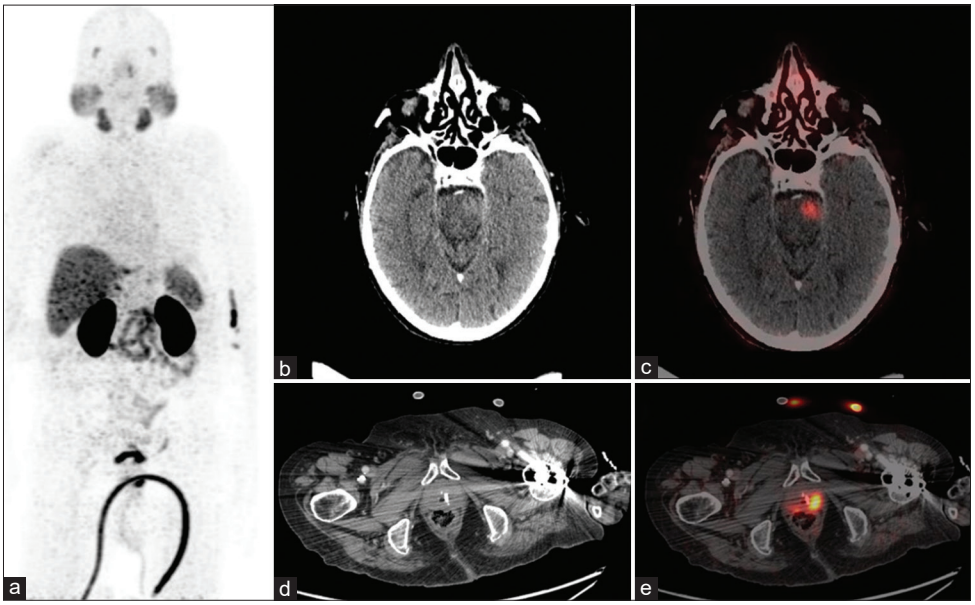

Figure 4: Maximum intensity projection images (a), axial computed tomography (CT) (b and d) and axial fused positron emission tomography/CT (d and e) sections of 68Ga-prostate specific membrane antigen (PSMA) PET/CT. Scan shows heterogeneously enhancing foci with increased FDG uptake in brain stem involving mid brain (white arrow image c, SUVmax- 7.3) and pons. Note is made of focal PSMA avid lesion in left lobe of prostate gland (thick white arrow image e, SUVmax-19.1)

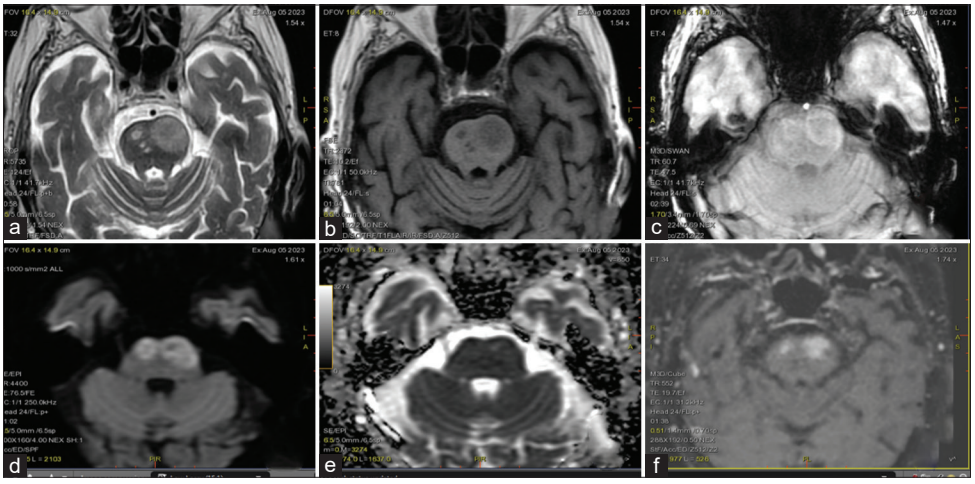

Figure 5: (a-f) Regression of swelling, signal change and enhancement in pons on follow up scan

of admission, with better sensorium and responsiveness to verbal commands. On discharge, his GCS was 15, and motor weakness in bilateral upper and lower limbs improved to 4/5 on the MRC SS. A prostate biopsy showed acinar adenocarcinoma, Grade 5 (Gleason score 5+4=9**).** Based on prostate biopsy reports, a final diagnosis of paraneoplastic encephalitis with secondary CNS changes was drawn.

DISCUSSION

Paraneoplastic syndromes, in the form of encephalitis, are novel and rarer forms of antibody-mediated manifestation involving the CNS. The widespread availability of these antibody tests has led to better diagnosis and treatment strategies [3]. However, still, there is a group of antibodies not yet recognized and yet to be explored. This is a challenge for clinicians. Therefore, correlating the clinical manifestation of these groups with newer and more advanced investigative techniques and biomarkers may be helpful in corroborating the diagnosis, prognostication, and treatment plan of the patient. It can be further useful in pediatric and older age groups where disease monitoring can be better and faster with minimal intervention. In our study, higher PSA levels, PI-RADS >5, and increased PSMA uptake in the prostate are indicative of the possibility of CA prostate with a seronegative paraneoplastic disorder in the form of brainstem encephalitis [4].

PSMA ligand uptake is not specific to the prostate; its uptake is seen to be increased in the lacrimal glands, nasal mucosa, salivary glands, glottis, spleen, liver, kidneys, and small intestines [5]. However, PSMA ligand uptake is also reported to be increased in the neovascularization of solid tumors such as lymphoma, multiple myeloma, small-cell carcinoma, and thyroid cancer, as well as in benign tumors such as Paget's disease, sarcoidosis, and neuronal ganglia. Ga PSMA 11 is known to be sensitive to prostate cancer. The sensitivity of Ga PSMA 11 PET is dependent on PSA values at the time of scanning. At PSA levels >2 ng/mL, the possibility of a pathological scan is around 90–95% [6,7]. There are various studies suggesting that PSMA ligand uptake is not specific to the prostate but is present in other cells as well. Our study, to the best of our knowledge, is the first case report for PSMA ligand uptake seen in the brainstem, suggesting "prostate-specific" in PSMA is a misnomer. There is a need to further implore the threshold of PSMA ligand uptake quantitatively and establish a standardized uptake value to discriminate the pathology of the various cells involved and to further acknowledge PSMA as a novel and sensitive marker [8].

Studies suggest the empirical use of corticosteroids or other immunotherapies is controversial. However there is evidence supporting the usage of corticosteroids in the initial stages. Immunotherapy includes IVIG and oral prednisolone, gradually withdrawn over six months. Suggested alternatives include plasma exchange and monthly pulsed intravenous methylprednisolone [9].

CONCLUSION

Identifying and treating seronegative paraneoplastic antibody patients can be challenging, as only a few antibodies are identified. The spectrum of undiscovered antibodies is still vast, and it is a challenge to elucidate them. With the advent of new techniques (MRI, PET) and investigations (immunological assays) available, faster diagnosis, timely intervention (immunomodulatory therapy), and prognostication are possible. Our study highlights the importance of paraneoplastic syndromes with varied clinical presentation and low specificity to antibodies. These spectra of diseases are fatal but treatable and, therefore, should be evaluated diligently to reduce morbidity.

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