SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Neurology

A Case Series of Paraneoplastic Neurologic Syndromes

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DOI: 10.36347/sasjm.2022.v08i04.003 | **Received:** 25.02.2022 | **Accepted:** 05.04.2022 | **Published:** 08.04.2022

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Abstract **Case Report**

Paraneoplastic neurologic syndromes are a group of rare disorders that are triggered by an abnormal immune system response to a neoplasm. In order to increase our knowledge about these rare syndromes, we present three cases with paraneoplastic neurologic syndrome after breast cancer, small cell lung cancer and esophagogastric junction adenocarcinoma.

Keywords: Paraneoplastic, Neurologic, Syndrome, Autoimmune, Antibodies.

INTRODUCTION

Paraneoplastic neurologic syndromes (PNSs) are remote effects of cancer with an immune-mediated pathogenesis [1-3]. The diagnosis of PNS can be difficult and requires careful exclusion of direct involvement of the nervous system by cancer, such as brain metastasis or carcinomatous meningitis, and indirect involvement caused by coagulopathy, treatment-related neurotoxicity, metabolic problems, or infections [1, 4]. PNSs develop in approximately 1 of 300 patients with cancer [4]. Few population based epidemiologic studies have been performed in the field of PNS. Yet, stated incidence varies from 1.6 to 8.9 per million person-years, suggesting that underdiagnosis and underreporting are still relevant issues [4, 5]. In this article, we report our experience with three cases of PNS.

CASE PRESENTATION

Case 1

A 62-year-old postmenopausal woman presented with symptoms dating back three months, consisting of progressive unsteady walking, dysarthria, and difficulty performing daily tasks. Her medical history included high blood pressure. There were no other systemic or neurological symptoms during this period. The cerebellar syndrome was predominant, including disorders of balance, walking and rapid execution of voluntary movements. The remainder of the neurological and physical examination was unremarkable.

Standard laboratory tests, vitamins E and B12, thyroid hormones, folic acid and tumor markers such as cancer antigen15-3 (CA15-3), α-fetoprotein (AFP), β-human chorionic gonadotropin (BHCG), carcinoembryonic antigen (CEA), cancer antigen 125 (CA125) and cancer antigen 19-9 (CA19-9) in serum were normal. Extensive studies including Sjögren's serology, ANA, ANCA, antibodies to gliadin, ceruloplasmin, Lyme and toxoplasmosis serology, Venereal Disease Research Laboratory (VDRL) test and antibodies against the human immunodeficiency virus (HIV) were all negative. Magnetic resonance imaging (MRI) of the brain and electroencephalogram (EEG) were unremarkable. Cytological, biochemical and microbiological studies of cerebrospinal fluid (CSF) were normal. Since the above investigations failed to make a diagnosis, she was then assigned for a possible paraneoplastic etiology given the rapidly evolving symptoms. Serum and CSF were studied for anti-Yo, anti-Hu, anti-Tr, anti-Ma, and anti-Ri antibodies, with positive results for anti-Ri antibodies in both samples. This prompted a wide search for malignancy, including computed tomography (CT) chest/abdomen/pelvis, mammography, breast ultrasound and MRI-breast, all normal. Whole-body positron emission tomography (PET) using 10-mCi fluorodeoxyglucose (FDG) intravenously showed an abnormal hot spot in the upper outer quadrant of the left breast (Figure 1).

The patient initially received intravenous methylprednisolone (1 g daily for 4 days) with subjective improvement in her symptoms. After careful

discussion, a quadrantectomy and ipsilateral axillary lymphadenectomy were performed. Intraoperative and postoperative pathology study confirmed a diagnosis of oestrogen and progesterone receptor-positive infiltrating ductal carcinoma corresponding to 1.2 cm with overexpression of human epidermal receptor-2 (HER2). The patient then received a qualified adjuvant comprising anthracyclines and taxanes in combination with Trastuzumab. A neurological follow-up 5 months after the start of treatment showed a partial clinical improvement in dysarthria and gait. No anti-Ri antibody immunoreactivity was demonstrated in serum or CSF and there was no local or systematic relapse of his neoplastic pathology at this time.

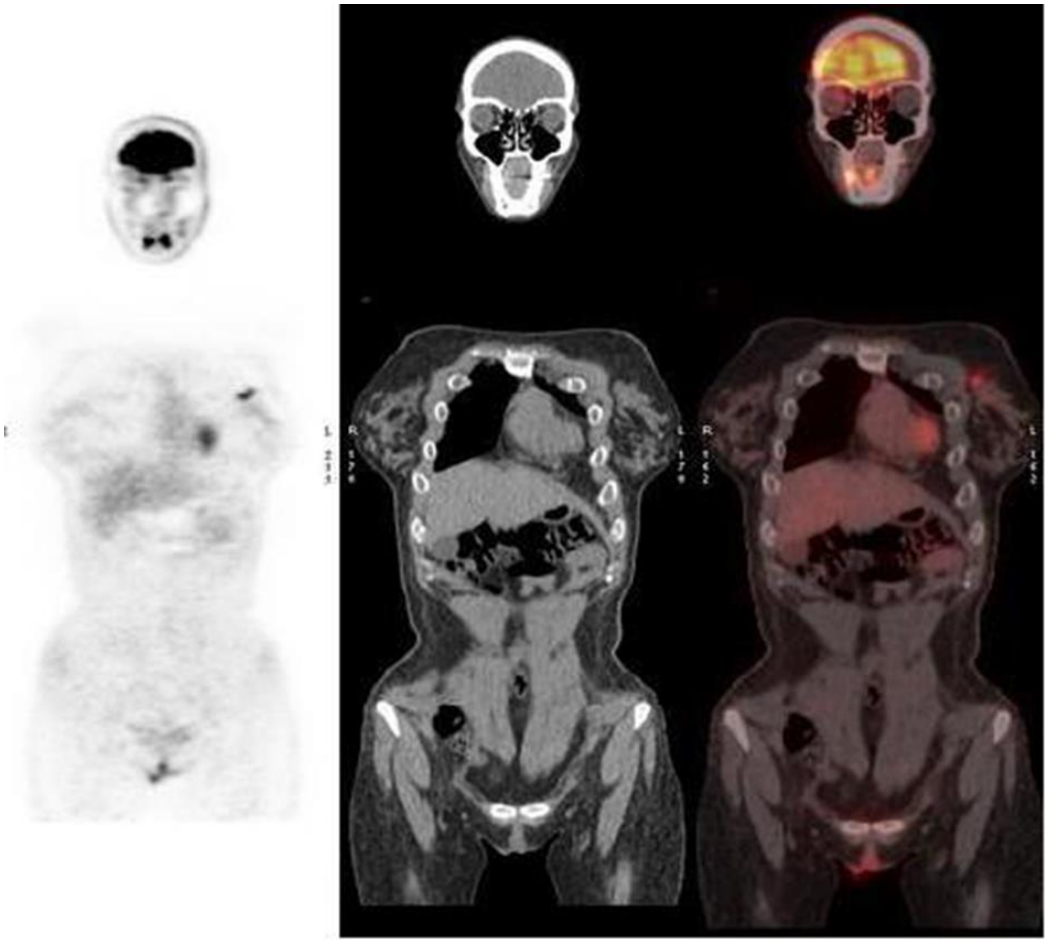

Figure 1: Coronal view of PET, full-body CT, and fused patient images showing an abnormal hot spot in the outer upper quadrant of the left breast

Case 2

This is a 58-year-old patient, known to be a chronic smoker for 40 pack-years. He was admitted for balance disorders of subacute installation for a month, affecting posture, walking and speech, without sensory signs or HTIC, all evolving in a context of apyrexia and preservation of the 'condition.

The examination found an isolated statokinetic cerebellar syndrome. The rest of the clinical examination was unremarkable.

Brain MRI and lumbar puncture were normal. The infectious, metabolic and toxic assessment was negative. The search for neuronal antibodies was not done and the thoracic-abdominopelvic CT scan was also normal. The PET scan showed proximal hyperfixation of the anterior segment of the left upper lobe (Figure 2). This led to a bronchoscopy which revealed an endo-bronchial tumor bud whose anatomopathological examination was in favor of a bronchial carcinoma with small cells on the morphological aspect and confirmed by immunohistochemistry (Chromogranin + and Synaptophysin +).

The diagnosis of paraneoplastic cerebellar degeneration was then retained. The treatment consisted of concomitant radiochemotherapy based on cisplatin and etoposide.

The evolution was marked by a hepatic metastatic recurrence after three months with deterioration of the general state. The patient received supportive care and died after one month.

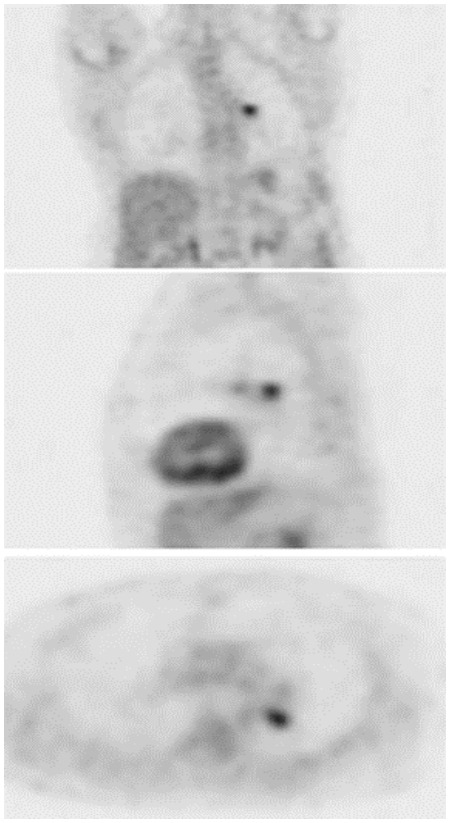

Figure 2: Proximal hyperfixation of the anterior segment of the left upper lobe on PET-scanner

Case 3

This is a 49-year-old patient followed for arterial hypertension. She consults for memory and behavioral problems, partial epileptic seizures and abnormal movements evolving for 15 days.

Examination found anterograde amnesia and pyramidal syndrome. The rest of the clinical examination was normal.

A brain MRI showed a bi-hippocampal hypersignal (Figure 3). The infectious assessment, in particular the lumbar puncture, was negative. The blood ionogram was also normal including thyroid function. A thoracic-abdominopelvic CT scan and tumor markers were unremarkable. The search for onconeuronal antibodies in the blood was not carried out.

After a comparison of anamnestic and paraclinical data, the diagnosis of limbic encephalitis of autoimmune origin was retained. The evolution under corticosteroids was marked by a partial improvement of the neurological symptoms.

Two years later, the patient presented with progressive low dysphagia, first to solids and then to liquids. An esophagogastroduodenoscopy objectified a tumoral process of the esophagogastric junction. Biopsies were performed, the pathological examination of which was in favor of an adenocarcinoma. The diagnosis of paraneoplastic limbic encephalitis was then retained a posteriori.

The extension assessment was negative and the patient was treated by surgery supervised by perioperative chemotherapy based on Folfox (Oxaliplatin, 5 Fluoro-Uracil, Calcium folinate) with a good evolution after a two-year follow-up.

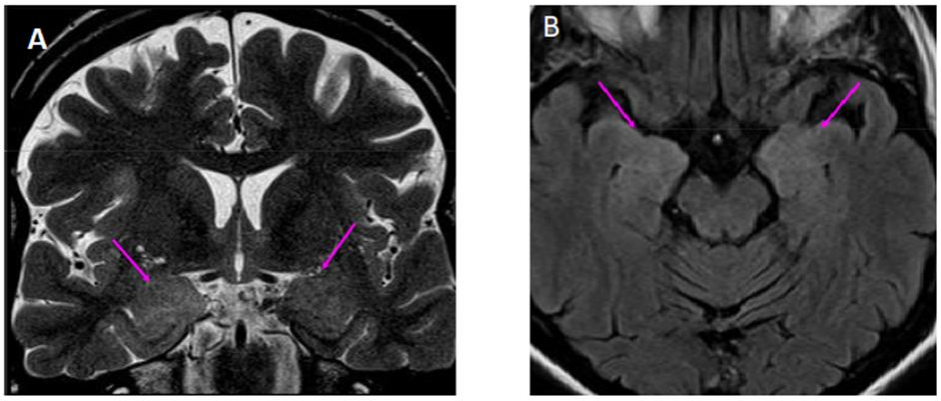

Figure 3: MRI aspect in favor of a bi-hippocampal hypersignal (A) Coronal T2-weighted slice (B) Axial T2-weighted Flair slice

DISCUSSION

PNS which can affect some areas of the nervous system from the cerebral cortex to the neuromuscular junction and the muscle, is a rare clinic. However, it is important because it appears before cancer is diagnosed or when cancer is very small and can be treated. While neurological symptoms develop as the first signs of tumor in 70% of PNS cases, and tumor can be detected in approximately 70%–80% of these cases during the initial evaluation [6].

Initial clues that a patient has a PNS are found in the history and symptom presentation and include the patient's age, cancer risk factors, or known cancer history (Table 1). Most PNS develop acutely or subacutely and may resemble a viral process. Although the same neurologic syndromes seen in PNS also occur without a cancer association, some syndromes, such as LEMS or limbic encephalitis, are so commonly cancer associated they are referred to as classical PNS and a

paraneoplastic cause should be suspected when one of these syndromes is seen. Other disorders have a more variable association with cancer and for some this association is age and sex dependent. It is important to keep in mind that the co-occurrence of a neurologic syndrome and cancer may simply be coincidental. The presence of cerebrospinal fluid (CSF) pleocytosis, elevated protein concentration, intrathecal synthesis of immunoglobulin, and/or oligoclonal bands is supportive of paraneoplasia, although normal CSF studies do not rule out PNS. Neuroimaging is helpful to exclude other nonparaneoplastic causes but may be normal. An exception is limbic encephalitis in which MRI often shows unilateral or bilateral mesial temporal lobe abnormalities best seen on T2-weighted and fluid-attenuated inversion recovery images [7, 8].

Table 1: Classical PNSs

Syndrome	Clinical feature	Investigations
Paraneoplastic encephalomyelitis (PEM)	Subacute involvement of more than one area of the CNS – includes cortical, limbic or brainstem encephalitis, cerebellar dysfunction, myelitis	MRI of the relevant part. CSF-pleocytosis, elevated protein and OCB
Limbic encephalitis (LE)	Memory problems, seizures, mood and sleep abnormalities	MRI brain T2/FLAIR HI involving limbic structure. Abnormal CSF as above, EEG epileptiform abnormality/focal slowing
Paraneoplastic cerebellar degeneration (PCD)	Severe pan cerebellar ataxia developing in less than 12 weeks, onset appendicular	Initial MRI brain usually normal. Later cerebellar atrophy
Opsoclonus myoclonus	Involuntary chaotic saccades in all directions of gaze, associated with myoclonus and ataxia frequently	MRI brain usually normal. EMG diagnosis of myoclonus
Chronic gastrointestinal pseudoobstruction	Subacute progressive nausea, vomiting, abdominal distension, pain and constipation	GI motility study and autonomic reflex screen, thermoregulatory sweat test for associated autonomic dysfunction
Subacute sensory neuronopathy	Numbness and pain onset in upper extremity, asymmetric. Progression in less than 12 weeks	NCS-absent or reduced SNAPs, MRI spine enhancing nerve roots. Abnormal CSF as mentioned above
Lambert eaton myasthenic syndrome (LEMS)	Proximal weakness with ocular and bulbar involvement. Hypoactive DTRs and mild dysautonomia helps clinical differentiation from myasthenia gravis (MG)	EMG-incremental response on repetitive stimulation

CSF = Cerebro spinal fluid; DTR = Deep tendon reflex; EEG = Electroencephalography; EMG = Electromyography; FLAIR = Fluid attenuation inversion recovery; GI = Gastrointestinal; HI = Hyperintensity; MRI = Magnetic resonance imaging; OCB = Oligoclonal band; SNAP = Sensory nerve action potential; NCS = Nerve conduction study

Onconeuronal antibodies are helpful for the diagnosis. Presence of these autoantibodies, alone or in combination, helps to detect the tumor as they are more tumor specific than for neurological syndrome. This can guide the search for the primary cancer. These antibodies establish the autoimmune nature of the disease, helping the clinician to differentiate the new neurological symptoms of PNS from treatment related-complications like toxic neuropathies, metastasis or infiltration. They are of help in detecting the recurrence of the disease in already seropositive patients [7].

If PNS is suspected tumor screening should proceed. The search may initially be focused to those tumor types more commonly associated with the patient's syndrome or type of antineuronal antibody, but should be expanded if no tumor is found because unexpected cancer-antibody associations may occur. Similarly, if the tumor found is not a histologic type that typically associates with the syndrome or antibody, a search for a second neoplasm should be undertaken. Because PNS onset often precedes the cancer diagnosis or occurs when the tumor is small and difficult to detect, a multidisciplinary approach to cancer diagnosis is warranted. The investigating team should be informed that PNS is suspected and that questionable or inconclusive results of tumor screening should be thoroughly investigated. If no cancer is found but PNS remains the likely diagnosis, cancer screening should be repeated periodically up to 4 years. The frequency of cancer screening depends on the type of disorder. For example, for classical paraneoplastic syndromes (anti-Hu usually related to SCLC and similar), cancer screening every 6 months seems reasonable, but for other disorders (eg, anti-NMDAR encephalitis) less frequent and shorter duration of screening is reasonable (evaluation for ovarian teratoma yearly for 2 years). In greater than 90% of patients with solid tumors and PNS, the tumor is found within 1 year of PNS presentation [9].

There are limited studies evaluating treatment efficacy for PNS. Accordingly, treatment is largely based on expert opinion. The two major principles for PNS management are treatment of the underlying cancer and immunotherapy initiation. This combined oncologic and immunologic therapy should be initiated as soon as possible to minimize irreversible neuronal loss and severe neurological disability [10]. Immunotherapy includes steroids, intravenous immune globulins (IV IgG), plasma exchange, cyclophosphamide, azathioprine and rituximab. Supportive therapy includes symptomatic treatment like analgesics, antiepileptics, psychiatric medications, dysautonomia medications, physiotherapy, occupational therapy and speech and swallowing therapy. Respiratory support and nutritional support are important [7].

CONCLUSION

If etiological diagnosis is unclear in patients presenting with different neurological symptoms and findings, it should be considered that this clinical picture can be associated with PNS. It should be kept in mind that neurological findings can occur many months, even years, before the diagnosis of cancer. Furthermore, it should be understood that early detection of PNS is important for the early treatment of tumor and early initiation of rehabilitation through rapid diagnosis of tumor [6].

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