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Case Report

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A Rare Case of Paraneoplastic Encephalitis in Association With Breast Cancer

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Abstract

We present a case of a 47-year-old female who presented with diffuse dysesthetic pain in both legs for past 3 months. She described the sensation as of pins and needles. She also had balance difficulty and developed progressively worsening back pain and spasms. Relatives reported that the patient had memory difficulties. The patient would repeat questions even after the questions had already been answered. Magnetic resonance imaging (MRI) of cervical, thoracic and lumbosacral spine with and without contrast showed mild multilevel degenerative changes in cervical spine and minimal disc bulges from L1 to S1 levels with no areas of significant spinal canal or neural foraminal stenosis. MRI of brain was performed which showed abnormal T2/FLAIR hyperintensity along the left medial temporal lobe and additional small foci in the right centrum semiovale/corona radiate and bilateral periventricular white matter. Based on the MRI findings, a diagnosis of limbic encephalitis was made. A lumbar puncture was also done. Cerebrospinal fluid (CSF) showed 14 oligoclonal bands with elevated IgG synthesis. Paraneoplastic antibody panel showed high titers of amphiphysin antibody (1:15,360). Since this is a paraneoplastic antibody, computed tomography of chest, abdomen and pelvis was performed. It showed several enlarged right axillary lymph nodes. Ultrasound of right breast showed 4 mm hypoechoic nodule at 2 o'clock axis (upper inner quadrant). The biopsy of this lesion and axillary lymph node showed invasive ductal carcinoma of the breast. For further evaluation, MRI of bilateral breast was performed. It revealed additional areas of enhancements in upper outer and lower outer quadrants of right breast. Biopsy of the upper outer area of enhancement revealed invasive ductal carcinoma and ductal carcinoma *in situ* (DCIS). Biopsy of the lower outer aspect showed infiltrating lobular carcinoma and lobular carcinoma *in situ* (LCIS). Our report highlights a rare patient presenting with paraneoplastic limbic encephalitis with underlying breast cancer. When encountering a patient with unexplained neurologic symptoms, paraneoplastic neurological syndromes (PNSs) should be considered as part of the differential. And a thorough search of autoantibodies associated with PNS should be considered. If such autoantibodies are present, search for an underlying malignancy should be undertaken.

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Introduction

Paraneoplastic neurological syndromes (PNSs) are syndromes of nervous system disorder associated with cancer (that are not explained by other diagnoses). They are not caused by metastasis or direct tumor invasion of the nervous system. The spectrum of PNS includes paraneoplastic encephalomyelitis (PEM), paraneoplastic cerebellar degeneration (PCD), limbic encephalitis (found in our patient), opsoclonus myoclonus, subacute sensory neuronopathy and Lambert-Eaton myasthenic syndrome (LEMS). The neurologic dysfunction of PNS can precede (60% of cases) or follow (40% of cases) a diagnosis of cancer. The current hypothesis is that PNS is autoimmune in nature. An array of autoantibodies have been identified, some of which are associated with specific PNS and malignancies.

Case Report

A 47-year-old female presented with constant diffuse dysesthetic pain in both legs for the past 3 months. She described the pain as burning with pins and needles sensation. She also had progressively worsening back pain and spasms. It was associated with increasing balance difficulties. Initially, her symptoms were attributed to neuropathy (and worked up accordingly, Table 1). She was given a trial of amitriptyline and gabapentin with no noted improvement and her symptoms continued to worsen. A month after presentation, the patient's mother started noticing memory difficulties. The patient would repeat questions even after the questions had already been answered. She denied fever, chills, visual problems, headaches, rash, arthralgias, joint swelling, focal motor or sensory deficits, and bladder or bowel incontinence.

The patient had a past medical history of bacterial meningitis treated at age of 4. She had gastric sleeve surgery 5 years ago. She had no known allergies. Her medications included vitamin B12 and vitamin D supplements. She denied smoking, alcohol use or illicit drug use. She denied any family history of autoimmune, rheumatologic or demyelinating disease.

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Table 1. Laboratory Data

Test	Results	Reference range
Workup for neuropathy and encephalitis		
Vitamin B12	760	193 - 986 ng/dL
Folic acid	65.7	4 - 18 ng/mL
TSH	0.86	0.340 - 4.820 µIU/mL
Homocysteine	8.6	5.0 - 12.0 µmol/L
Gliadin IgAb	9.0	Negative < 20
Ganglioside antibody panel	Negative	
Zinc	0.73	0.66 - 1.10 µg/mL
Erythrocyte sedimentation rate	27	0 - 30 mm/h
Rapid plasma regain	Non-reactive	
Lyme disease antibody, serum	0.02	< 0.90 index
Blood parasites	Negative	
Epstein-Barr virus antibody panel	Negative	
Spotted fever antibody IgG, IgA, IgM	Negative	
Bartonella antibody panel	Negative	
Ehrlichia antibody panel	Negative	
Babesia microti antibody IgG, IgM	Negative	
Antinuclear antibody (ANA)	Positive 1:640 speckled	
ANA reflex antibodies	Negative	
Rheumatoid factor	< 10	0 - 15 IU/mL
Cardiolipin antibody IgA, IgG, IgM	Negative	
Neuromyelitis optica NMO/Aqua4-IgG	Negative	
Heavy metals screen, serum		
Arsenic	2.0	0 - 12 ng/mL
Lead	< 1.0	0.0 - 4.9 µg/mL
Mercury	< 1.0	0.0 - 9.0 ng/mL
Cadmium	0.2	0.0 - 4.9 ng/mL
Copper	1.36	0.75 - 1.45 µg/mL

Physical exam revealed an overweight female with no apparent distress. Her pulse was 78 beats per minute, blood pressure was 111/70 mm Hg, respiratory rate was 16 breaths per minute, and oxygen saturation was 99% on room air. The speech was fluent without errors. On mini-mental state examination (MMSE), she recalled two out of three names at 15 min and had difficulty doing serial threes. Direct fundoscopic exam showed pink optic discs with sharp margins. Cranial nerves I-XII were grossly intact. Tone and strength in all extremities was normal. Deep tendon reflexes were 1+ and symmetric in bilateral upper extremities but unelicitable at bilateral knees and ankles. Sensory exam to soft and painful stimulus was normal in all four extremities. Her gait was very cautious and unsteady, although sufficiently strong to rise on heels and toes. Tandem walk was difficult. Romberg test was unsteady with both eyes opened and closed. Neck was supple with full range of motion. Lung, heart and abdomen exam was normal.

Magnetic resonance imaging (MRI) of cervical, thoracic and lumbosacral spine with and without contrast showed mild multilevel degenerative changes in cervical spine and minimal disc bulges from L1 to S1 levels with no areas of significant spinal canal or neural foraminal stenosis. MRI of brain was performed due to memory difficulties. It showed abnormal T2/FLAIR hyperintensity along the left medial temporal lobe involving areas of hippocampus and amygdala, additional small foci in the right centrum semiovale/corona radiate and bilateral periventricular white matter (Fig. 1a). Based on the above findings, a diagnosis of limbic encephalitis was made. She also underwent extensive laboratory workup (Table 1) which was negative.

She underwent lumbar puncture. Cerebrospinal fluid (CSF) showed 44 white blood cells per microliter with 90% lymphocytes. Glucose and protein levels were within normal limits. CSF showed elevated oligoclonal bands and increased CNS IgG synthesis. Testing for PNS autoantibodies showed elevated anti-amphiphysin antibodies (1:15,360, Table 2). CSF

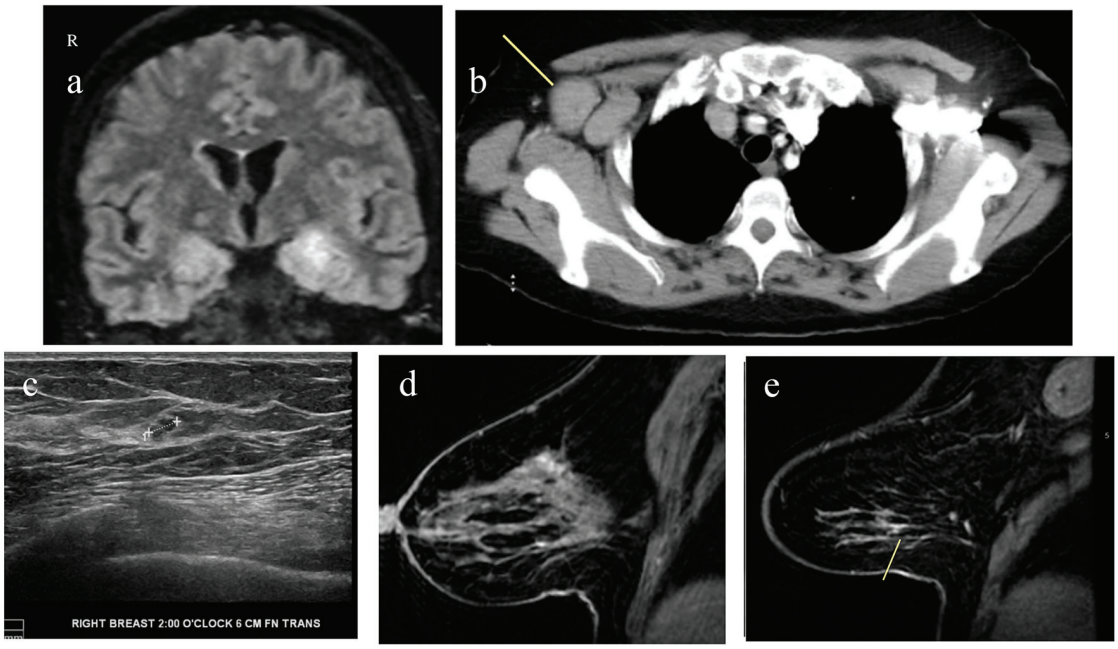

Figure 1. (a) MRI of brain with and without contrast showing T2/FLAIR hyperintensity along the medial temporal lobe involving portions of the hippocampus and amygdala. (b) CT of chest with contrast showing markedly enlarged axillary lymph nodes. (c) Ultrasound of right breast and axilla showing 4 × 4 × 3 mm hypoechoic lobulated nodule at 2 o'clock axis. (d) MRI of bilateral breast with and without contrast showing clumped enhancement in the upper outer quadrant of the right breast. (e) MRI of bilateral breast with and without contrast showing a small 8 mm area of patchy non-mass enhancement in the lower outer right breast.

meningitis/encephalitis panel was negative (Table 2). Since this is a paraneoplastic antibody, the patient underwent computed tomography (CT) of chest, abdomen and pelvis to rule out underlying malignancy. It showed right axillary lymphadenopathy (Fig. 1b). This raised concern for an underlying breast cancer that had spread to the axillary region. Ultrasound of right breast showed 4 mm hypoechoic nodule at 2 o'clock axis (Fig. 1c). The biopsy of this lesion and axillary lymph node showed invasive ductal carcinoma. For further evaluation, MRI of bilateral breast was performed. It revealed additional areas of enhancements in upper and lower outer quadrants of right breast (Fig. 1d, e). Biopsy of the upper outer area of enhancement revealed invasive ductal carcinoma and ductal carcinoma *in situ* (DCIS). Biopsy of the lower outer aspect showed infiltrating lobular carcinoma and lobular carcinoma *in situ* (LCIS). Our report highlights a rare case of PNS associated with breast cancer.

Discussion

PNSs are syndromes of nervous system disorder associated with cancer (that are not explained by other diagnoses). They are not caused by metastasis or direct tumor invasion of the nervous system [1, 2].

The current hypothesis regarding the pathogenesis of PNS is that they are immune mediated [2, 3]. Our immune system generates antibodies or T cells response against tumor antigens. These antibodies or T cells cross-react with our normal neuronal tissues causing PNS. The theory is supported by CSF study in these patients. In one European study, lymphocytic pleocytosis was present in 39%, elevated protein in 67% and oligoclonal bands of IgG in 63% [4]. Two of these findings were present in our patient's CSF.

Specific cancers have been associated with eliciting certain autoantibodies. These antibodies, in turn, are associated with dysfunction of specific parts of the nervous system. The symptoms of PNS vary based on the part of the nervous system affected. Symptoms can present acutely or sub-acutely and include tremors, visual complaints, ataxia, seizures, autonomic dysfunction, peripheral neuropathy and others (Table 3) [5]. Based on the symptoms, affected region of nervous system on imaging studies and types of autoantibodies elicited, the subtypes of PNS include PEM, PCD, limbic encephalitis (found in our patient), opsoclonus myoclonus, subacute sensory neuronopathy and LEMS [5].

PNS precedes (60% of cases) or follows cancer diagnosis (40% of cases) [2]. In a few instances, cancer cannot be found in a patient whose clinical syndrome is otherwise consistent with PNS. Such patients need to be on surveillance if cancer was not found on the initial workup. When encountering a patient with unexplained neurologic symptoms, PNS should be considered as part of the differential. A thorough search of autoantibodies associated with PNS should be considered (Table 4) [6, 7]. If such autoantibodies are present, search for an underlying malignancy should be undertaken.

The Purkinje cell antibody (PCA-1) was the first antibody described in relation to PNS in 1893 by Greenlee and Brashear. It was found in two patients with ovarian carcinoma and paraneoplastic cerebellar degeneration [8]. In our discussion, we

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Table 2. Cerebrospinal Fluid Analysis

CSF	Results	Reference range
Appearance	Clear	Clear
WBC	44	0 - 5/UL
Lymphocytes	90	63-99%
Monocytes	10	3-37%
RBC	< 1,000	/UL
Glucose	110	40 - 70 mg/dL
Protein	58	12 - 60 mg/dL
Cytology	Negative for malignant cells	
Oligoclonal bands	14	< 4 bands
IgG index, CSF*	1.22	≤ 0.85
IgG	9.4	≤ 8.1 mg/dL
Albumin	33.9	≤ 27.0 mg/dL
IgG/albumin	0.28	≤ 0.21
Synthesis rate	28.77	≤ 12 mg/24 h
Meningitis/encephalitis panel, PCR		
Escherichia coli K1	Not detected	
Hemophilus influenzae	Not detected	
Listeria monocytogenes	Not detected	
Neisseria meningitidis	Not detected	
Streptococcus agalactiae	Not detected	
Streptococcus pneumoniae	Not detected	
Cytomegalovirus	Not detected	
Enterovirus	Not detected	
Herpes simplex virus 1 and 2	Not detected	
Human herpesvirus 6	Not detected	
Varicella zoster virus	Not detected	
Cryptococcus neoformans/gatti	Not detected	
Paraneoplastic panel		
Amphiphysin antibody	1: 15,360	< 1:240 titer
ANNA-1, S	Negative	< 1:240 titer
ANNA-2, S	Negative	< 1:240 titer
ANNA-3, S	Negative	< 1:240 titer
AGNA-1, S	Negative	< 1:240 titer
PCA-1, S	Negative	< 1:240 titer
PCA-2, S	Negative	< 1:240 titer
PCA-TR, S	Negative	< 1:240 titer
CRMP-5-IgG	Negative	< 1:240 titer
Striated muscle Ab	Negative	< 1:120 titer
P/Q-type calcium channel Ab	Negative	≤ 0.02 nmol/L
N-type calcium channel Ab	Negative	≤ 0.03 nmol/L
Ach receptor binding Ab	Negative	≤ 0.02 nmol/L
ACHR ganglionic neuronal Ab, S	Negative	≤ 0.02 nmol/L
Neuronal (V-G) K^+ channel Ab, S	Negative	≤ 0.02 nmol/L
GAD65 Ab assay, S	Negative	≤ 0.02 nmol/L

*CSF IgG index: CSF IgG to CSF albumin ratio compared to the serum IgG to serum albumin ratio. An increase in the index is an indicator of IgG production in the central nervous system. In our patient serum albumin 3.5 g/dL and serum IgG 814 mg/dL (Reference: https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8271)

Table 3. Clinical Features and Investigations Associated With Various PNS [5]

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 oligoclonal bands
Limbic encephalitis (LE)	Memory problems, seizures, mood and sleep abnormalities	MRI brain T2/FLAIR hyperintensity 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
Chronic gastrointestinal pseudoobstruction	Subacute progressive nausea, vomiting, abdominal distention, pain and constipation	GI motility study and autonomic reflex screen, thermoregulatory sweat test for associated autonomic dysfunction
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 distention, 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	Nerve conduction studies (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 deep tendon reflexes and mild dysautonomia helps clinical differentiation from myasthenia gravis	EMG-incremental response on repetitive stimulation

will focus on antiamphiphysin antibodies (AAs) which were found in our patient. AAs are autoantibodies that react with 128 kD protein amphiphysin I found in synaptic vesicles [9]. They were first reported in patients with Stiff-man syndrome and breast cancer [10]. More studies have shown that they can also be found in other PNS and malignancies. In 1999, Antoine et al performed testing to detect autoantibodies on 2,800 serum samples from patients with paraneoplastic syndromes. Of the five patients with AA, three had small cell lung cancer (one was diagnosed with cancer after 24 months of follow-up), one had breast cancer and one had ovarian cancer. In this group, PNS included sensory neuronopathy, limbic encephalitis, encephalomyelitis and LEMS [10].

The diagnosis of PNS is challenging especially in cases where a malignancy may not be initially apparent. However, in a patient with a consistent neurologic syndrome (as described above), PNS should be considered if no alternate diagnosis is apparent. The presence of personal or family history of cancer or autoimmune diseases provides clues to the diagnosis of PNS. On CSF analysis, presence of lymphocytic pleocytosis, increased protein or oligoclonal IgG are consistent with PNS. Depending on the syndrome, MRI of brain/spine will reveal T2/FLAIR hyperintensity in limbic structures, cerebellar atrophy or enhancing nerve roots. Depending on the syndrome, electromyography (EMG) will reveal findings such as incremental response on repetitive stimulation or myoclonus. Positive autoantibodies associated with PNS also make this diagnosis more likely. Therefore, a combination of clinical features, laboratory and imaging findings can help with the diagnosis of PNS (Tables 3 and 4) [5-7].

Our patient presented with pain in both legs and back associated with short term memory deficits. CSF analysis showed lymphocytic pleocytosis, oligoclonal bands, elevated IgG protein and positive AAs. MRI of brain showed hyperintensity along the left medial temporal lobe involving limbic structures. This led to a diagnosis of limbic encephalitis. A search was initiated to find out underlying malignancy with imaging. She was found to have right axillary lymphadenopathy and hypodensity in the right breast. This was subsequently proved as right breast cancer on biopsy. Patient underwent right mastectomy and was started on chemotherapy. This report illustrates a rare case of paraneoplastic limbic encephalitis associated with breast cancer.

Conclusion

Our report illustrates a rare case of a 47-year-old female who presented with neurological symptoms and diagnosed with paraneoplastic limbic encephalitis associated with breast cancer. A good clinical judgment based on different clinical, imaging and laboratory findings (as described above) can lead to early diagnosis of PNS and underlying malignancy. This is very important for prompt treatment to prevent irreversible neurological damage.

Conflict of Interest

The authors declare that there is no conflict of interest regard-

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Table 4. Paraneoplastic Antibodies Associated With Cancers and PNS [6, 7]

Antibody	Neoplasm predicted by autoantibody	Neoplasm (%)/frequency of coexisting antibody (%)	Clinical features
Nuclear antibodies			
Anti-neuronal nuclear antibody-1 (ANNA-1) (anti-Hu)	Small cell lung cancer (SCLC), neuroblastoma, thymoma	81/43	PEM- limbic, cortical, brainstem encephalitis, PCD, myelitis, PSN, autonomic dysfunction
ANNA-2 (anti-Ri)	Lung cancer, breast cancer	86/73	Brainstem encephalitis, opsoclonus - myoclonus, PCD
ANNA-3	Lung cancer, upper airway cancer	90/30	Sensory/sensorimotor neuropathy, cerebellar ataxia, myelopathy, brainstem and limbic encephalopathy
Anti-glial nuclear antibody (AGNA 1)	SCLC	90/50	LEMS, PCD, sensory neuronopathy, limbic encephalitis, sensory motor neuropathy
Anti-Ma2	Germ cell tumor of testis, lung, GIT, breast, non-Hodgkin's lymphoma	Unknown	Cerebellar/brainstem syndrome, limbic encephalitis. Narcolepsy like, cataplexy, hypnogogic hallucination
Zic 4	SCLC	92/27	Limbic encephalitis, cerebellar/ brainstem syndrome
Cytoplasmic antibodies			
Purkinje cell cytoplasmic antibody (PCA-1)	Ovarian, fallopian, endometrial and breast cancer	90/9	PCD
PCA-2	SCLC	80/63	Brainstem/limbic encephalitis, PCD, LEMS, motor neuronopathy
PCA-Tr	Hodgkin's lymphoma	90/unknown	PCD, limbic encephalopathy
Amphiphysin	Breast cancer, lung cancer	80/38	Stiff-man syndrome, PEM
CRMP-5 (collapsin response mediated protein)	SCLC, thymoma, thyroid, renal cancer	80/57	PEM, PCD, chorea, optic neuropathy, myelopathy and peripheral neuropathy
Striational (sarcomeric proteins)	SCLC, thymoma, breast cancer	Unknown	Myasthenia gravis
Cell membrane antibodies			
Voltage gated calcium channel (VGCC) N	Lung, breast, ovarian cancer	Unknown	LEMS, cerebellar degeneration
VGCC P/Q	SCLC	Unknown	LEMS, cerebellar degeneration
AchR, muscle	Thymoma, SCLC	Unknown	Myasthenia gravis
AchR, ganglionic	Thymoma, SCLC	Unknown	Autonomic neuropathy
Voltage gated potassium channel (VGKC) related protein	Thymoma, SCLC	Unknown	Limbic encephalitis, Morvan's syndrome, PCD, GI dysmotility, parkinsonism, tremor, chorea, sensory motor neuropathy, hyponatremia, dyssomnia and hyperphagia
NMDA receptor	Ovarian teratoma	59/unknown	Psychiatric features and memory loss, orofacial dyskinesia, choreoathetoid movements, abnormal posturing or increased tone, catatonic state and central hypoventilation
AMPA receptor	SCLC, thymoma, breast	Unknown	Limbic encephalitis, atypical psychosis
GABA B receptor	SCLC	Unknown	Limbic encephalitis
Glycine receptor	Lung cancer	Unknown	Progressive encephalomyelitis with rigidity and myoclonus (PERM)
MgluR1	Hodgkin's lymphoma	Unknown	PCD

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