

Transverse Myelitis: Amphiphysin Autoimmunity Paraneoplastic Syndrome in a Woman with Breast Cancer

Shamsuddin Virani, MD¹

Meng Tan, MD²

Jame Abraham, MD¹

¹*Department of Medicine, Section of Hematology/Oncology, West Virginia University, Morgantown, West Virginia;*

²*Department of Neuroimmunology, Mayo Clinic, Rochester, Minnesota*

Case Report

A 39-year-old Caucasian woman presented to a neurologist with 3 months of progressive left-greater-than-right lower extremity stiffness and spasms. These symptoms had gradual onset around the time of an unexplained fall. She also reported back pain and spasms and experienced increasing impairment of mobility and activities of daily living. She denied urinary or fecal incontinence. Physical therapy had provided minimal relief.

She had previously been in good health except for pregnancy-induced hypertension, gestational diabetes mellitus, and hypercholesterolemia. There was no family history of neurologic or autoimmune disease. The patient's maternal aunt was diagnosed with breast cancer at age 70 and her paternal aunt was diagnosed with breast cancer around age 30.

Physical examination revealed a moderately severe spastic gait and moderate spastic paraparesis, more severe on the left. Although generally hyporeflexic, she had bilateral extensor plantar responses and loss of pinprick sensation below T6 dermatomal level. She had mild slowing of alternating movements in the left hand, with mild weakness of intrinsic hand muscles. Magnetic resonance imaging (MRI) showed extensive multifocal T2 hyperintensities throughout the thoracolumbar spinal cord from T1 down to the conus medullaris, but without cord expansion or gadolinium enhancement. Brain MRI was normal. Lumbar puncture revealed a lymphocytic pleocytosis (leukocytes 16/mL; 94% lymphocytes) with increased immunoglobulin G (IgG) index (0.98; normal 0.85 or less).

Address correspondence to:

Jame Abraham, MD, Associate Professor of Medicine, Chief, Section of Hematology/Oncology, Department of Medicine, West Virginia University, Morgantown, WV 26505; Phone: (304) 293-4229; Fax: (304) 293-2519; E-mail: jabraham@hsc.wvu.edu.

The patient was diagnosed with an inflammatory myelopathy consistent with transverse myelitis, and commenced on intravenous corticosteroids. After 3 weeks, she reported moderate improvement and was prescribed baclofen for residual spasticity. At 3 months after treatment, she had minimal weakness confined to left iliopsoas, intrinsic muscles of the left hand, and a sensory level at T9.

Approximately 6 months after the onset of neurologic symptoms, the patient noticed a right axillary mass for which she was evaluated at a surgical clinic. She denied nipple discharge, breast tenderness, or previous history of breast masses.

Her mammogram and subsequent ultrasound showed a lobular mass in the right breast measuring 15 mm. Core needle biopsy revealed right breast infiltrating ductal carcinoma, which was estrogen receptor (ER)- and progesterone receptor (PR)-positive and human epidermal growth factor receptor 2 (HER2)-Neu-negative.

The patient underwent right quadrantectomy and right axillary lymph node dissection. Pathology revealed poorly differentiated infiltrating ductal carcinoma with lymphovascular invasion, 1.5 cm in maximum dimension, high nuclear grade, with a modified Bloom-Richardson (MBR) score of 6–7, ER 99% positive, PR 92% positive, and HER-2-Neu negative. One of 13 lymph nodes was positive for disease, measuring 0.5 cm; pathologic stage was IIA, T1cN1M0.

A comprehensive paraneoplastic serologic evaluation was ordered. Her serum was strongly positive for amphiphysin-IgG, detected by indirect immunofluorescence at a titer of 1:245,760. The patient underwent 4 cycles of cyclophosphamide/doxorubicin chemotherapy initially. She showed neurologic improvement, as well as a moderate reduction of amphiphysin-IgG titer to 1:30,720. Subsequently, she received 4 cycles of chemotherapy with docetaxel followed by further neurologic improvement,

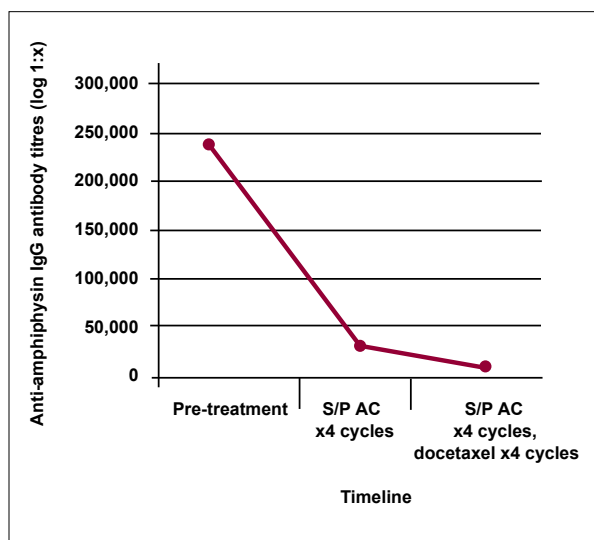


Figure 1. Chronology of anti-amphiphysin immunoglobulin G (IgG) titers.

AC=cyclophosphamide + doxorubicin.

and further decline in amphiphysin-IgG titer to 1:7,680 (Figure 1). The patient is currently undergoing radiation therapy and reports improvement in strength and a decrease in back pain.

Discussion

Though associated with malignancies, paraneoplastic disorders are not caused by metastases.¹ Paraneoplastic neurologic syndromes (PNS) manifest as a variety of disorders such as paraneoplastic limbic encephalitis, paraneoplastic sensory and motor neuropathy, paraneoplastic cerebellar degeneration, Lambert-Eaton myasthenia syndrome (LEMS), paraneoplastic opsoclonus myoclonus ataxia (POMA), and stiff-person syndrome. Several immunologic processes have been proposed to explain the development of the above-mentioned disorders, but the etiology remains unclear.

Amphiphysin protein was first described in 1992 by Lichte and colleagues² as a synaptic vesicle protein with a critical role in retrieving vesicle membranes from the axon terminal's plasma membrane after exocytosis. In the subsequent year, Folli and coauthors³ reported anti-amphiphysin antibodies in the sera of 3 women with stiff-person syndrome and breast carcinoma.

It has now been established that amphiphysins are a group of proteins belonging to the BAR (Bin/Amphiphysin/Rvs) family of proteins. These SH3 domain-containing proteins are thought to function as multifunctional

adapters that cooperate in recruitment and targeting of clathrin mediated endo- and exocytosis.⁴ Whereas, amphiphysin-I is primarily found in the central nervous system, amphiphysin-II has been isolated in the central as well as the peripheral nervous system, which could explain the wide spectrum of neurologic manifestations in patients with anti-amphiphysin autoimmunity.⁵

A number of publications have outlined the role of anti-amphiphysin autoimmunity, in conjunction with other neuronal autoantibodies in paraneoplastic neurologic disorders. We reviewed literature published in the past 14 years using keywords: paraneoplastic neurologic syndromes, anti-amphiphysin antibodies, and breast cancer.

In our review, anti-amphiphysin antibodies were found in 0.07% of patients with known or suspected PNS, mostly in association with sensory motor neuropathy and stiff-person syndrome. A total of 28% of patients with amphiphysin autoimmunity were diagnosed with breast cancer, as summarized in Table 1.

Of the 7 patients with amphiphysin autoimmunity and breast cancer in whom response to treatment was observed (n=6), 5 reported some improvement in neurologic symptoms with cancer treatment. Treatment was based on surgery and chemotherapy or chemotherapy alone, often in combination with anti-estrogen therapy. Worsening was reported in 1 case.

Conclusion

Although a significant proportion of patients with breast cancer and neurologic symptoms may have autoantibodies, the diagnosis of PNS still remains clinical; a negative paraneoplastic panel does not rule it out. In our review, anti-amphiphysin antibodies were found in a minority of cases, mostly in association with sensory motor neuropathy and stiff-person syndrome; however, they are not specific to a particular PNS. Although a temporal relationship has not been established, neurologic manifestations may precede the diagnosis of a carcinoma, as hypothesized by Georgian-Smith and coworkers⁶ and observed in our patient. We suggest that paraneoplastic disorder be considered as differential for any constellation of unexplained neurologic symptoms, as it could trigger an inquiry into the cause; autoantibody testing may aid to augment the diagnosis. Patients can be treated with standard chemotherapy, which seems to be effective in most cases. However, further studies are needed to ascertain the effectiveness of chemotherapy. Whether the levels of anti-amphiphysin autoantibody can be used as a predictor for subsequent neurologic improvement remains another unexplored area.

Table 1. Published Literature on PNS, Anti-amphiphysin Autoantibodies, and Breast Cancer

Authors (year published)	Number of case(s) with suspected PNS	Anti-amphiphysin IgG +	Breast cancer in anti-amphiphysin IgG +	Treatment	Response	Remarks
Folli et al ³ (1993)	3	3	3	Excision + Hormonal therapy (3)	2 Improved 1 Deteriorated	
Rosin et al ¹³ (1998)	1	1	1	Excision + Hormonal therapy	Improvement	
Antoine et al ⁸ (1999)	2,800	5	1	Surgery + XRT	Improvement	
Georgian-Smith et al ⁶ (2003)	1	1	1	Mastectomy + adjuvant hormonal therapy	Improvement	
Altaha et al ⁷ (2003)	1	0	0	Chemotherapy	Improvement	
Rojas-Marcos et al ¹² (2003)	92	3	3	NR	NR	49/92 had breast cancer
Pittock et al ¹⁵ (2004)	60,000 (553 IgG +)	18	8	NR	NR	10 had SCLC
Petzold et al ¹¹ (2004)	1	1	1	NR	NR	10 had SCLC
Pittock et al ⁹ (2005)	120,000	63 (71 but 8 excluded)	16	NR	NR	50/63 with histologic diagnosis
Coppens et al ¹⁴ (2006)	NR	2	1	NR	NR	1 patient had SCLC

IgG+=immunoglobulin G positive; NR=Not reported; PNS=paraneoplastic neurologic syndrome; SCLC=small cell lung cancer; XRT=radiation therapy.

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Review

Amphiphysin Autoimmunity in Paraneoplastic Neurologic Disease

Lakshmi Nayak, MD

Michael Rubin, MD, FRCP(C)

*Department of Neurology and Neuroscience,
Weill Cornell Medical College, New York Presbyterian
Hospital-Weill Cornell Medical Center, New York, New York*

Paraneoplastic neurologic syndromes (PNS) are rare, occurring in 0.01% of cancer patients. PNS do not result from damage to neural structures caused by a direct effect of cancer or metastases. Rather, they develop remotely, possibly through an immune-mediated mechanism, whereby the primary tumor, expressing an onconeural antigen normally expressed in the nervous system, provokes an ill-fated, immune-mediated, by-product (the paraneoplastic syndrome) in the body's attempt to destroy or contain the cancer.¹ Most patients present neurologically, with cancer neither evident at onset nor previously diagnosed, but the astute clinician considers a paraneoplastic diagnosis and proceeds accordingly, searching for antibodies to onconeural antigens in serum and cerebrospinal fluid. Each antibody is associated with a spectrum of paraneoplastic neurologic disorders and varied types of cancer, with no antibody predicting a specific neurologic syndrome. One such onconeural antigen is the 128-kD synaptic vesicle protein, amphiphysin.

Autoantibodies to amphiphysin were first described in the cerebrospinal fluid and sera of 3 women with stiff-person syndrome and breast cancer. Subsequently, they were also identified in patients with limbic encephalitis and opsoclonus-myoclonus. Magnetic resonance imaging (MRI) of amphiphysin antibody-positive PNS patients has shown inflammatory changes in the brain or spinal cord in the form of hyperintensity on T2-FLAIR (fluid attenuated inversion recovery) sequence or gadolinium enhancement. Cerebrospinal fluid analysis demonstrates inflammatory cells, elevated protein, or positive oligoclonal bands or both, in addition to the specific amphiphysin

antibody. Involved areas of the nervous system appear atrophic to the naked eye and, microscopically, there is diffuse microgliosis. Infiltrates predominantly of CD8-positive T lymphocytes have been noted within the parenchyma, with B lymphocytes seen in perivascular regions.² Treatment of amphiphysin antibody-related paraneoplastic syndromes is similar to that of other PNS, and includes treatment of the underlying cancer and immunosuppression with corticosteroids, plasma exchange, intravenous immunoglobulin, tacrolimus, rituximab (Rituxan, Genentech) or alemtuzumab (Campath, Bayer Healthcare).

The case reported by Virani and colleagues³ presents a 39-year-old woman with a 3-month history of back pain, spastic paraparesis, mild upper extremity weakness, and a T6 sensory level with cerebrospinal fluid pleocytosis, and multifocal T2-hyperintense lesions on thoracolumbar spinal MRI, consistent with inflammatory myelopathy. Intravenous corticosteroids were administered with moderate improvement. Six months later, she noted a right axillary mass, and a diagnosis of infiltrating ductal carcinoma of the right breast was made. Serum paraneoplastic antibody panel was positive for amphiphysin antibody. She underwent quadrantectomy and axillary lymph node dissection, was staged as IIa, TcN1M0, received 4 cycles of cyclophosphamide and doxorubicin, followed by 4 cycles of docetaxel, and was receiving radiation therapy at time of writing. She improved neurologically throughout the course of chemotherapy and demonstrated a consistent decline in amphiphysin-immunoglobulin G (IgG) titer.

Amphiphysin exists in 2 forms. Amphiphysin I, associated with clathrin-mediated synaptic vesicle endocytosis and highly concentrated in the cortical cytoplasm of nerve terminals, is expressed in the brain at high concentration and in the anterior pituitary and adrenal medulla at lower concentration.⁴ Amphiphysin II localizes to cortical axon initial segments, nodes of Ranvier, and T-tubules, and is expressed in brain and skeletal muscle. What pathogenic role amphiphysin antibodies play in PNS and whether they are directly responsible for neurologic damage remains unclear. Sommer and coauthors produced a stiff-person-like syndrome in rats by injecting them with human amphiphysin-IgG, arguing for a direct pathogenic role of amphiphysin antibodies in this condition.⁵ Enhanced expression of amphiphysin I in breast cancer has been reported in a patient with sensory neuronopathy and amphiphysin antibodies, supporting this contention.⁶ Others argue, however, that the humoral response against amphiphysin and expression of amphiphysin I in cancer may be an epi-phenomenon.^{6,7} At the other end of the spectrum, genetic investigations in yeast and rodents suggest that by integration of cell polarity signals

Address correspondence to:
Michael Rubin, MD, FRCP(C), Professor of Clinical Neurology, Weill Cornell Medical College, Director, Neuromuscular Service and EMG Laboratory, New York-Presbyterian Hospital, 520 East 70th Street, Rm K-615, New York, NY 10021; Tel: (212) 746-2320; Fax: (212) 746-8984; E-mail: mprubin@med.cornell.edu.

generated by actin and vesicle dynamics—with central regulators of cell-cycle arrest, apoptosis, and immune surveillance—amphiphysin-like adapter proteins may serve a cancer-suppression role.⁸ Hence, amphiphysin antibodies may actually promote cancer growth and development. Confusion persists and the jury is still out as we await further developments with piqued interest.

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