Paraneoplastic cerebellar ataxia and the paraneoplastic syndromes

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Paraneoplastic cerebellar ataxia, also known as paraneoplastic cerebellar degeneration, is one of the wide array of paraneoplastic neurological syndromes in which neurological symptoms are indirectly caused by an underlying malignancy, most commonly gynecological, breast, or lung cancer or Hodgkin's lymphoma. We describe a patient with severe cerebellar dysfunction attributed to a paraneoplastic neurological syndrome. The case highlights the need to look for paraneoplastic syndromes—both to discover malignancies early, at a treatable stage, and, as in our case, to address very distressing symptoms for the patient's relief even if the malignancy is not curable.

The neurologic manifestations seen in cancer patients are mostly the consequence of direct tumor invasion of the nervous system or metastases. Other common causes of neurologic symptoms include neurotoxicity from cancer treatment, infections, and vascular or metabolic disorders. In less than 1% of cancer patients, an autoimmune response develops that targets normal neural tissues, which is termed paraneoplastic neurologic syndrome (PNS) (1, 2). Autoimmune neuronal degradation is believed to occur when systemic malignancies express proteins, called onconeural antigens, that are made only in neurons (3). Although no studies to date have conclusively proven that paraneoplastic antibodies are pathogenic, they are still useful markers of autoimmunity that categorize the PNS subtypes (1). We present a case of paraneoplastic cerebellar ataxia (PCA) associated with anti-Yo antibody (anti-Purkinje cell antibody) due to an underlying gynecologic malignancy.

CASE DESCRIPTION

A 67-year-old white woman presented with a 3-day history of headache, severe imbalance, nausea, and binocular double vision limiting her mobility. Two weeks earlier, she had been diagnosed with a left 4 cm adnexal mass following a 6-week history of pelvic pain. She was known to have hypertension, coronary artery disease, aortic stenosis (mild), left ear cholesteatoma, and mastoiditis. Neurological examination revealed intact language and cognition, significant bilateral diplopia and nystagmus worse to the right, bilateral dysmetria worse on the left, and broad-based gait ataxia. No focal weakness or change in muscle tone was noted. Deep tendon reflexes were brisk at all

Table 1. Laboratory blood work

Result	Tests
Paraneoplastic antibodies panel: positive results	Purkinje cell cytoplasmic antibody, type 1: 1:61,440
Paraneoplastic antibodies panel: negative results	ANNA-1, ANNA-2, ANNA-3, AGNA-1, PCA-2, PCA-Tr, amphiphysin antibody, CRMP-5, striational antibodies, P/Q-type calcium channel antibody, AChRab, ganglionic AChR autoantibody, VGKC, NMDA-R Ab
Other pertinent positive results	EBV IgG
Other pertinent negative results	Serum Lyme, syphilis, CMV IgM, EBV IgM, HSV-1 PCR, HSV-2 PCR, fungal cultures, bacterial cultures
AChRab indicates anti-acetylcholine receptor antibody; AGNA, anti-glial/neuronal nuclear antibody; ANNA, anti-neuronal nuclear antibody; CMV, cytomegalovirus; CRMP, collapsin response mediator protein; EBV, Epstein-Barr virus; HSV, herpes simplex virus; Ig, immunoglobulin; NMDA-R Ab, anti-N-methyl D-aspartate receptor antibody; PCA, Purkinje cell cytoplasmic antibody; VGKC, voltage-gated potassium channel.	

sites, and the plantar reflexes were downgoing on the right and upgoing on the left. Routine laboratory work was unremarkable. A biopsy of the recently discovered pelvic mass disclosed a poorly differentiated adenocarcinoma of Mullerian origin. A computed tomography (CT) scan of the chest, abdomen, and pelvis revealed mediastinal lymphadenopathy.

The patient was started on chemotherapy with carboplatin and paclitaxel. A serum paraneoplastic panel was positive for anti-Yo antibody with a high titer (*Table 1*). Cerebrospinal fluid (CSF) examination showed lymphocytic pleocytosis, high protein, and positive anti-Yo antibodies (*Table 2*). Magnetic resonance imaging (MRI) of the head on admission showed no evidence of metastatic disease. MRI done 10 days after admission, however, showed enhancement along the bilateral cerebellar sulci. A diagnosis of anti-Yo-associated PCA was made, and the patient was started on high-dose methylprednisolone

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Table 2. Cerebrospinal fluid examination

	Analysis 1	Analysis 2 (9 days later)
Protein (mg/dL)	59	88
Glucose (mg/dL)	44	62
White blood cell (cells/ μ L): lymphocytes, neutrophils, monocytes	41 (86%, 3%, 11%)	45 (92%, 6%, 2%)
Red blood cell (cells/ μ L)	0	6650
Gram stain and cultures	Negative	Negative
IgG synthesis, cryptococcal Ag, Histoplasma Ag		Negative
Cytology for malignant cells	Negative	Negative
Venereal Disease Research Laboratory	Negative	
Paraneoplastic antibodies		PCA-1 positive, 1:4096
IgG indicates immunoglobulin G; PCA-1, Purkinje cell cytoplasmic antibody type 1.		

and intravenous immunoglobulin (IVIG) at 2 g/kg given over a period of 3 days along with her chemotherapy drugs. Her headache resolved, and her diplopia and dysmetria were slightly improved. The patient was transferred to a rehabilitation facility for continuation of palliative chemotherapy.

DISCUSSION

PNS are rare neurological syndromes that are not the consequence of direct invasion, metastasis, or side effects of cancer treatment (2). PNS can affect any level of the nervous system (*Table 3*). They can affect a single site, as in Lambert-Eaton myasthenic syndrome, a single cell type, as in PCA, or multiple areas, as in paraneoplastic encephalomyelitis. The association of many PNS with specific antibodies that recognize onconeural antigens suggests that PNS may be due to an initial autoimmune response against the tumor (1). However, one antibody can be associated with different neurological syndromes, and one syndrome can present with different antibodies as well (1). The antibodies are specific for the malignancy rather than being specific for a neurological syndrome (2).

Table 3. Paraneoplastic neurologic syndromes and their associated antibodies

Syndrome	Frequency	Associated tumor	Associated antibodies	Clinical manifestations
Lambert-Eaton myasthenic syndrome	60%	SCLC	VGCC-Ab	Proximal weakness, ocular and bulbar involvement, hypoactive deep tendon reflexes, mild dysautonomia
Subacute cerebellar ataxia	50%	Ovary, breast, uterus	Yo-Ab	Rapid development of severe pancerebellar ataxia
		SCLC	Hu-Ab CV2-Ab	
		Hodgkin disease	Tr-Ab	
		Others	Ma-Ab	
Opsomyoclonus	20%	Neuroblastoma	Hu-Ab	Spontaneous, chaotic saccades of gaze associated with myoclonus and ataxia and sometimes encephalopathy
		Breast, lung	Ri-Ab	
Sensory neuropathy	20%	SCLC	Hu-Ab CV2 Ab	Rapidly progressing and asymmetric onset of paresthesias, pain in upper extremity
Limbic encephalitis	20%	SCLC	Hu-Ab CV2 Ab Amphiphysin-Ab	Memory problems, confusion, seizures, mood and sleep abnormalities
Encephalomyelitis	10%	Testicular	Ma2-Ab	
		SCLC	Hu-Ab CV2 Ab Amphiphysin-Ab	Subacute involvement of multiple areas of CNS at the same time
		Others	Ma2-Ab	
Retinopathy (cancer-associated, melanoma-associated, uveitis, optic neuropathy)	NA	SCLC	Recoverin-Ab CV2-Ab	Symptoms vary depending on type of retinopathy
		Melanoma	Rod-bipolar-cell Ab	
Stiff person syndrome	20%	Breast	Amphiphysin-Ab	Fluctuating muscle rigidity in trunks and limbs, hypersensitivity to sensory stimuli causing painful muscle spasms
Chronic gastrointestinal pseudo-obstruction	NA	SCLC	Hu-Ab CV2 Ab	Subacute nausea, vomiting, weight loss, pain, abdominal distension, and constipation

Modified with permission from Honnorat J and Cartalat-Carel S, 2004 (1). Ab indicates antibodies; CNS, central nervous system; SCLC, small cell lung cancer; Tr-Ab, thyroid-stimulating hormone receptor antibody; VGCC-Ab, anti-voltage-gated calcium channel antibody.

Table 4. Paraneoplastic antibodies in paraneoplastic cerebellar ataxia and their associated malignancies

Antibody	Neurological syndrome	Associated cancer
Anti-Yo (PCA-1)	Cerebellar ataxia	Ovarian, breast
Anti-Hu	Cerebellar ataxia, PEM/SN	Small cell lung cancer
Anti-Ri	Cerebellar ataxia, OM	Breast, gynecological, small cell lung cancer
Anti-Tr	Cerebellar ataxia	Hodgkin's lymphoma
Anti-VGCC	Cerebellar ataxia, LEMS	Small cell lung cancer
Anti-Ma	Cerebellar ataxia, brainstem dysfunction	Many
Anti-CRMP5 (anti-CV2)	PEM/SN, cerebellar ataxia	Small cell lung cancer, thymoma, gynecological
Anti-mGluR1	Cerebellar ataxia	Hodgkin's lymphoma
Anti-Ta (anti-Ma2)	Limbic encephalopathy, cerebellar ataxia	Testis

Modified from Shams'ili et al, 2003 (6) with permission from Oxford University Press. CRMP5 indicates collapsin response mediator protein 5; LEMS, Lambert-Eaton myasthenic syndrome; mGluR1, metabotropic glutamate receptor 1; OM, opsoclonus/myoclonus; PEM, paraneoplastic encephalomyelitis; SN, sensory neuropathy; VGCC, voltage-gated calcium channels.

One of the most common PNS is PCA (4). PCA results in rapid (less than 12 weeks) development of severe pancerbellar dysfunction (1, 2). Since it can precede the presentation of neoplasms by several months to a year, a high index of

suspicion is required (2). Neurologic symptoms are the first manifestation of the tumor in about 70% of PNS patients (4). The diagnostic possibility should be considered in the setting of a family history of cancer or autoimmune disorder, subacute presentation, neuraxis involvement at multiple levels, and an insidious progression of the neurological condition with no clear alternative diagnosis (2). The hallmark of PCA is severe loss of cerebellar Purkinje cells with relative preservation of other cerebellar neurons and the presence of inflammatory infiltrates in the cerebellar cortex, deep cerebellar nuclei, and inferior olivary nuclei (1, 4–6). Prodromal symptoms, such as viral-like illness, dizziness, nausea, and vomiting, are followed acutely to subacutely by gait unsteadiness progressing rapidly to ataxia, diplopia, often nystagmus, dysarthria, and dysphagia (4, 5). Blurry vision, oscillopsia, transient opsoclonus, and cognitive impairment may be present (4, 5).

CT and MRI studies are initially normal in most cases, although some have transient diffuse cerebellar hemispheric enlargement or cortical meningeal enhancement, with eventual cerebellar atrophy (1, 4). Fluorodeoxyglucose positron emission tomography may show cerebellar hypermetabolism in early stages followed by hypometabolism as cerebellar atrophy develops (4). CSF often shows nonspecific abnormalities, such as mild to moderate lymphocytic pleocytosis, increased protein, a high IgG index, and CSF-specific oligoclonal bands in approximately 60% of PCA patients (2, 4, 5). Intrathecal synthesis of autoantibodies is a frequent finding in PCA patients with anti-Yo antibody (7). Only 60% to 70% will have detectable antibodies in their serum or CSF (2).

Figure 1. Paraneoplastic syndrome diagnosis and management flowchart. Modified with permission from Kannoth, 2012 (2).

It is preferable to look for the entire range of paraneoplastic antibodies, as nine specific antineuronal antibodies are associated with PCA (2, 6) (Table 4). Purkinje cell cytoplasmic antibody type 1 (PCA-1), also known as anti-Yo, is highly specific and the most frequently detected autoantibody in PCA (5, 8). The presence of paraneoplastic antibodies can direct the care team towards a tumor search using a CT scan of that region (1) (Figure 1). Most cases of anti-Yo PCA occur in women over 60 years (5).

PCA treatment includes tumor treatment, immunotherapy, and supportive therapy. Treating the tumor as soon as possible is the best approach for stabilization or symptom improvement with or without immunotherapy (2, 4). Immunotherapy includes steroids, IVIG, plasmapheresis, cyclophosphamide, azathioprine, and rituximab (2). In most cases of PCA, the neurological symptom has stabilized by the time treatment is started, meaning that Purkinje cell damage and neuronal loss have most probably already occurred (5). Multiple studies have shown that patients with anti-Yo antibodies have a worse neurologic prognosis, with most becoming bedbound within 3 months of diagnosis, compared with PCA patients with other antibody types (5, 9). However, immunotherapy has been reported to be effective in some cases, and hence a trial of IVIG, steroids, or plasmapheresis is indicated (1). Our patient with anti-Yo-associated PCA experienced clinical improvement in some of her neurologic symptoms and stabilization of other symptoms with high-dose steroids and IVIG. However, her relief was partial since her primary cancer was advanced and treatments were limited. Generally, it is the tumor progression and not the neurological disease that causes death in PCA patients (5). Nevertheless, in our patient, the PNS significantly

affected her quality of life, while the malignancy was largely asymptomatic. Despite successful treatment of the primary tumor in many cases, paraneoplastic symptoms often continue to negatively impact the patients' quality of life more so than the underlying tumor (9). This signifies the importance of early diagnosis, as delays in the start of treatment can lead to rapid progression and irreversible neurological damage (2).

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