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Case 4-2007: A 56-Year-Old Woman with Rapidly Progressive Vertigo and Ataxia

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PRESENTATION OF CASE

A 56-year-old woman was admitted to the hospital because of rapidly progressive vertigo and ataxia.

The patient had been well until approximately 10 weeks before admission, when occasional dizziness and nausea occurred, followed during the next several weeks by increasing positional vertigo and severe vomiting. Antiemetic agents were administered, the vomiting resolved, and her dizziness improved. Shortly thereafter, slurred speech, rapidly progressive ataxia, and difficulty with ambulation developed.

Approximately 6 weeks before admission, the patient saw a physician at another facility. Cranial magnetic resonance imaging (MRI) showed an increased T_2-weighted signal in the periventricular white matter that was thought to represent either ischemia or demyelination. Computed tomographic (CT) scanning of the brain showed no discrete lesions. Warfarin therapy was initiated but discontinued shortly thereafter, when coagulation studies yielded supratherapeutic results. Fresh-frozen plasma was infused, and the results of coagulation studies returned to normal. A lupus anticoagulant was not detected. A complete blood count, levels of serum protein, electrolytes, calcium, and phosphorus, and the results of renal- and liver-function tests were normal. A lumbar puncture revealed a normal opening pressure; the results of laboratory tests on the cerebrospinal fluid are shown in Table 1. No organisms were seen on staining or in cultures; a cryptococcal antigen test and a polymerase-chain-reaction test for herpes simplex virus were both negative. Tests for human immunodeficiency virus types 1 and 2, antinuclear antibodies, and rapid plasma reagin were also negative.

One week later, a second MRI study showed a new, small, linear area of increased signal in the left pontine region on fluid-attenuated inversion recovery (FLAIR) sequences. A magnetic resonance angiogram of the carotid arteries revealed an anatomical variant of the left vertebral artery, mild irregularities of the basilar artery without evidence of occlusion, and less than 15% stenosis of the carotid arteries. A 3-day course of high-dose methylprednisolone was administered, followed by a tapered course of prednisone, with no improvement.

Approximately 3 weeks before admission, the patient was evaluated in a neurology clinic at another hospital. On examination, she was seated in a wheelchair and had a to-and-fro head tremor, flat affect, and severely dysarthric speech. She was alert

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and oriented, with some deficiencies in performing multistep, sequenced commands. Visual testing revealed diminished pursuit and saccadic overshoot. Alternating movements of the hands were severely slowed, dexterity was diminished, and there was mild hip-flexor weakness and paratonia; strength and tone in other muscles were normal. Finger-to-nose testing revealed severe dysmetria bilaterally, and heel-knee-shin testing could not be performed. There was truncal titubation, and the patient was unable to walk. Reflexes were normal.

One week before admission, CT scanning of the chest revealed minimal thickening of the pleura of the right lung, strands of subsegmental atelectasis or fibrosis in the right posterior costophrenic sulcus, and oblique fissure of the left lung. Mammography and CT scanning of the abdomen and pelvis showed no abnormalities.

One week later, the patient saw a neurologist at this hospital. Her neurologic symptoms had been stable for the previous 2 weeks. She had hypertension and hypercholesterolemia. Her medical history included an episode of otitis media, 7 years earlier, and a bilateral tubal ligation. She did not use alcohol and had stopped smoking cigarettes 20 years earlier. She was married, with a 35-year-old daughter in good health. Her mother had had breast cancer in her eighth decade, and her father had Parkinson's disease. There was no family history of multiple sclerosis. Medications included atorvastatin, aspirin, and hydrochlorothiazide, with promethazine as needed for dizziness.

The vital signs were normal. The patient was alert and oriented, with tremors and stuttering speech. The score on the Mini–Mental State Examination was 27 (the highest possible score is 30), with points lost on calculations and on the recall of two out of three objects at 5 minutes. Her gaze had lost smooth pursuit, and saccadic overshoot was present. There was difficulty with pronunciation of the letter K, and the gag reflex was reduced. Cranial nerve I was not tested; cranial nerves II through VII were intact. Motor and sensory examinations were normal; reflexes were 2+ to 3+ throughout. Marked dysmetria and dysdiadochokinesia were present in the arms, and there was difficulty with the amplitude and velocity of fine finger movements and with the control of movement during strength testing. Examination of the legs revealed dysmetria with foot tapping; the heel-knee-shin test could not be performed. The patient was unable to stand unless given full assistance, and she was unable to walk. There was no response to plantar stimulation. The results of the remainder of the examination were normal.

Table 1. Results of Cerebrospinal Fluid Tests.

Test	Reference Range in Adults*	6 Weeks before Admission
Red-cell count (per mm³)	None	8
White-cell count (per mm³)	0–5	22
Differential count (%)		
Neutrophils	None	1
Lymphocytes	None	97
Monocytes	None	2
Protein (mg/dl)	12–60	86
Glucose (mg/dl)†	40–70	63
Venereal Disease Research Laboratory test	Nonreactive	Nonreactive
IgG (mg/dl)	0.0–6.0	16.1
IgG synthetic rate (mg/day)	0.0–8.0	60.1
IgG index	0.28–0.66	2.16, oligoclonal bands present
IgG:albumin ratio	0.09–0.25	0.50
Albumin (mg/dl)	0–35	32
Myelin basic protein (ng/ml)	0.00–2.10	2.27
Angiotensin-converting enzyme (U/liter)	0.0–2.5	2.3
Antineuronal nuclear antibodies (anti-Hu and anti-Ri antibodies)		Negative

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

† To convert the values for glucose to millimoles per liter, multiply by 0.05551.

The patient was admitted to the hospital that day. A complete blood count, prothrombin and partial-thromboplastin times, liver- and renal-function tests, and serum levels of electrolytes, immunoglobulins, CA 125, CA 19-9, carcinoembryonic antigen, thyroxine, and thyroid-stimulating hormone were normal; additional results were pending. On the second hospital day, MRI revealed a mass, 12 mm in diameter, in the inferior left breast. CT scanning of the chest and abdomen showed focal fatty change in the liver and a nodule, 11 mm in diameter, in the left adrenal gland that appeared to be an adenoma; no other abnormalities were seen. Ultrasonography of the pelvis showed no abnormalities.

On the fourth hospital day, MRI of the brain showed moderate volume loss in the cerebellar

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hemispheres without evidence of abnormal T_2-weighted signals or abnormal diffusion. There were multiple foci of T_2-weighted hyperintensity in the white matter, with subtle gadolinium enhancement in the right corona radiata. Two days later, positron-emission tomographic (PET) scanning showed hypermetabolic foci in both axillas and in a lower thoracic vertebra at approximately T10. However, a review of the chest CT scan obtained earlier in this hospitalization did not reveal any corresponding mass or lymphadenopathy in the axillary regions. Serum protein electrophoresis revealed an abnormal pattern, with one very-low-concentration band identified as IgG kappa M component. On the seventh hospital day, a biopsy of a hyperechoic solid mass in the inferior left breast, performed under ultrasonographic guidance, revealed atrophic breast tissue with no malignant cells. On the next day, an excisional biopsy of the lesion in the left breast revealed a myxoid fibroadenoma, with no evidence of cancer.

A diagnostic test result was received.

DIFFERENTIAL DIAGNOSIS

Dr. Josep Dalmau: May we review the imaging studies?

Dr. R. Gilberto Gonzalez: The MRI scan obtained on the patient's admission to this hospital revealed evidence of cerebellar and brain-stem atrophy and abnormal signals in the cerebral white matter. A sagittal midline T_1-weighted image of the brain (Fig. 1A) shows shrinkage of the cerebellar vermis with prominent fissures. Axial T_2-weighted images through the posterior fossa showed tissue loss in the cerebellum, extensive cerebrospinal fluid in the posterior fossa, and enlargement of the fourth ventricle. The cerebellar hemispheres, vermis, and pons were small. In the cerebrum, there were scattered foci of T_2-weighted hyperintensity in the subcortical white matter. The largest signal abnormality was a focus of about 8 mm in diameter in the right corona radiata that showed subtle enhancement on images obtained after the administration of contrast material.

An ^{18}F-fluorodeoxyglucose PET scan obtained on the sixth day showed three abnormal foci: one each in the right and left axillas (Fig. 1B) and a third in a thoracic vertebra at approximately T10.

Dr. Dalmau: In this adult with no history of immunodeficiency, the subacute development of a predominant cerebellar syndrome with inflammatory abnormalities of the cerebrospinal fluid and hypermetabolic foci on a body PET scan narrows the differential diagnosis to a few disorders. Diagnoses that could have been considered before the PET scan was obtained are shown in Table 2. The absence of a history of alcohol abuse and nutritional deficiencies, the rapid course of the disease, the inflammatory findings in the cere-

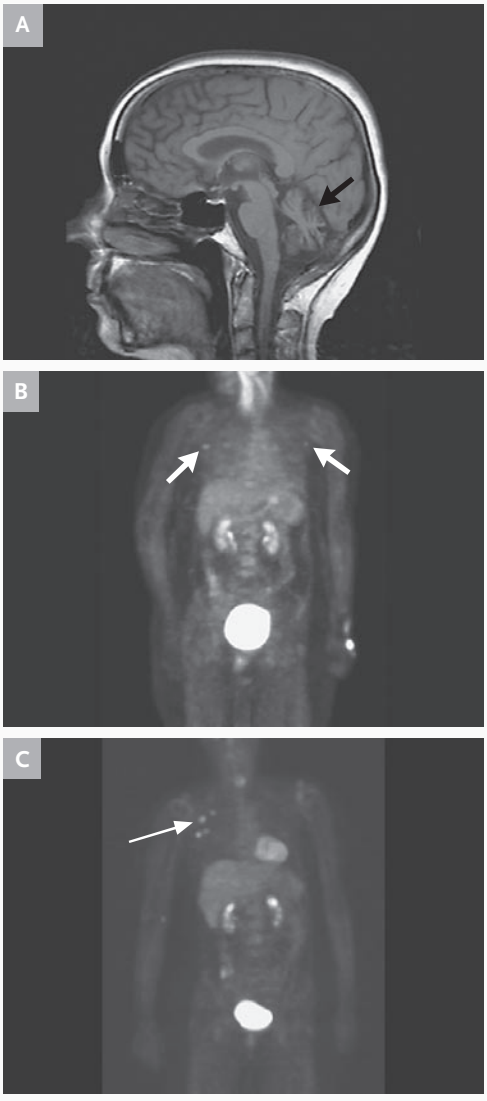

Figure 1. Imaging Studies.

A sagittal T_1-weighted MRI scan obtained on the patient's admission to this hospital (Panel A) shows shrinkage of the cerebellar vermis (arrow). A PET scan obtained after the administration of ^{18}F-fluorodeoxyglucose (Panel B) shows a small focus of uptake in the left axilla and a slightly larger one in the right axilla (arrows). A follow-up PET scan obtained 4 months later (Panel C) shows extensive abnormal uptake of tracer in the region of the right axilla and chest wall (arrow).

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brospinal fluid, the atrophic changes in the symptomatic regions on MRI, and the PET findings, either alone or in combination, readily rule out most of these disorders.

CEREBROVASCULAR DISEASE

The rapid development of dysarthria and ataxia and the presence of risk factors for cerebrovascular disease initially suggested a vertebrobasilar system stroke. Treatment with warfarin was begun, but a supratherapeutic effect was noted and the treatment was discontinued. The presence of a lupus anticoagulant was ruled out. These findings do not rule out the possibility of a subclinical tendency to fibrinolysis, which occurs in some malignant conditions.[1] In this patient, the results of magnetic resonance angiography ruled out vascular occlusion, and the cerebrospinal fluid findings suggested causes other than stroke.

DEMYELINATING DISORDERS

The patient was treated with corticosteroids, probably because a demyelinating disorder was considered. Among patients with multiple sclerosis, the median age at diagnosis is 30 years; this 56-year-old woman had no history of visual or neurologic deficits. The supratentorial findings on T_2-weighted MRI are more suggestive of small-vessel ischemic disease. Elevated levels of myelin basic protein in the cerebrospinal fluid can occur in disorders other than multiple sclerosis[2] and may also occur in paraneoplastic disorders. These findings and the absence of a clinical response to corticosteroids do not support the diagnosis of multiple sclerosis.

SARCOIDOSIS

Sarcoidosis should be included in the differential diagnosis. However, the symptoms of sarcoidosis are not as acute as those in this patient, and the cranial nerves, basal meninges, hypothalamus, and pituitary region are often involved, which is not the case in this patient. A CT scan of the chest is abnormal in 60 to 70% of patients with sarcoidosis. In this patient, the absence of such findings and the normal level of angiotensin-converting enzyme in the cerebrospinal fluid argue against the diagnosis of sarcoidosis.[3]

PARANEOPLASTIC SYNDROMES AFFECTING THE CENTRAL NERVOUS SYSTEM

I suspect that this patient has a neurologic complication of cancer. Metastatic involvement of the central nervous system is unlikely because of the absence of contrast-enhancing abnormalities in the posterior fossa. Rare tumors such as intravascular lymphoma[4] and so-called carcinomatous encephalitis caused by miliary metastases[5] may not be characterized by contrast enhancement or mass effect, but the predominant cerebellar syndrome and cerebrospinal fluid abnormalities in this patient do not support these diagnoses.

Paraneoplastic disorders can affect any part of the nervous system and are believed to be immune-mediated.[6] The likelihood that a disorder is paraneoplastic depends on the clinical syndrome (i.e., cerebellar degeneration or limbic encephalitis) and on whether paraneoplastic antibodies and a tumor are detected.[7] In 60% of patients with paraneoplastic disorders, the neurologic symptoms precede the diagnosis of cancer; the absence of a known cancer in this patient is therefore typical. It has been postulated that the antitumor immune response may contribute to the small size of the tumor, making detection difficult.[8] A combination of CT and body PET imaging facilitates detection of these tumors.[9]

Table 2. Possible Causes of Acquired, Rapidly Progressing Cerebellar Ataxia in Immunocompetent Patients.

Stroke
Multiple sclerosis
Sarcoidosis
Primary or metastatic tumors in the posterior fossa
Paraneoplastic neurologic disorders
Exposure to toxins and drugs (lead, anticonvulsants, salicylates, aminoglycosides, sedatives, fluorouracil, cytarabine)
Miller Fisher syndrome
Infection (human immunodeficiency virus infection, viral cerebellitis, Creutzfeldt–Jakob disease)
Alcoholic cerebellar degeneration
Vitamin deficiency (thiamine)
Autoimmune disease (systemic lupus erythematosus, Sjögren's syndrome, Hashimoto's disease, cerebellar ataxia with anti–glutamic acid decarboxylase antibodies, cerebellar ataxia with antigliadin antibodies)

Immunologic Features of Paraneoplastic Syndromes

The immune responses associated with paraneoplastic syndromes are shown in Table 3. Antibodies appear to be necessary but not sufficient alone to cause neurologic dysfunction, and cytotoxic T-cell responses are also involved.[10-12] In this patient, identification of any of the antibodies listed in Table 3 would confirm the diagnosis of a paraneoplastic syndrome; depending on the antibody identified, this finding would also direct the search for the tumor.[6] In approximately 40% of patients, no antibodies are identified.[13]

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Table 3. Antibodies Associated with Paraneoplastic Cerebellar Degeneration (PCD).*

Antibodies	Predominant Syndrome	Associated Cancer
Predominantly associated with PCD		
Anti-Yo (PCA-1) antibodies	PCD	Ovarian and breast cancers
Anti-Tr antibodies	PCD	Hodgkin's lymphoma
Anti-mGluR1 antibodies†	PCD	Hodgkin's lymphoma
Anti-Zic4 antibodies‡	PCD	Small-cell lung cancer
Sometimes associated with PCD		
Anti-VGCC antibodies	Eaton–Lambert syndrome, PCD	Small-cell lung cancer and lymphoma
Anti-Hu (ANNA-1) antibodies	Encephalomyelitis, PCD, sensory neuronopathy	Small-cell lung cancer and other cancers
Anti-Ri (ANNA-2) antibodies	PCD, brain-stem encephalitis, paraneoplastic opsoclonus–myoclonus	Breast, gynecologic, and small-cell lung cancers
Anti-CV2/CRMP5 antibodies	Encephalomyelitis, PCD, chorea, peripheral neuropathy, uveitis	Small-cell lung cancer, thymoma, and other cancers
Anti-Ma protein antibodies§	Limbic, hypothalamic, brain-stem encephalitis (infrequently PCD)	Testicular, lung, and other cancers
Anti-amphiphysin antibodies	Stiff-person syndrome, encephalomyelitis, PCD	Breast and small-cell lung cancers

* There is no uniform nomenclature for some of these antibodies; variant names appear in parentheses. mGluR1 denotes metabotropic glutamate receptor 1, Zic4 zing finger of the cerebellum 4, and VGCC voltage-gated calcium channel.
† Anti-mGluR1 antibodies have been identified in only two patients.
‡ Anti-Zic4 antibodies are predominantly associated with PCD only when no other paraneoplastic antibodies are detectable.
§ Ma proteins include Ma1 and Ma2. Patients with brain-stem and cerebellar dysfunction usually have antibodies against both Ma1 and Ma2.

Clinical Features of Paraneoplastic Cerebellar Degeneration

The development of paraneoplastic cerebellar degeneration is usually rapid, leaving the patient severely disabled in days to weeks.[14] This patient's presentation is typical, beginning with the dizziness, vertigo, and nausea that may suggest a peripheral vestibular problem. These symptoms are followed by ataxia of the trunk and limbs, variable oscillopsia, blurry vision, diplopia, nystagmus, dysarthria, tremor, and sometimes dysphagia. The ocular motor abnormalities can be complex because there is always some degree of brain-stem involvement, as shown in autopsy studies.[15] The clinical features in this patient indicate predominant cerebellar dysfunction; the decreased gag reflex with no other abnormalities on cranial-nerve examination suggests mild involvement of the brain stem. Mild memory and cognitive deficits, detected during the examination, occur in about 20% of patients with paraneoplastic cerebellar degeneration.[14]

The abnormalities in the cerebrospinal fluid suggest an inflammatory or immune-mediated process; similar abnormalities are found in approximately 70 to 80% of patients with paraneoplastic cerebellar degeneration. Paraneoplastic antineuronal nuclear antibodies (anti-Hu and anti-Ri antibodies) were not detected in this patient's cerebrospinal fluid; we do not know whether tests for other antibodies were performed. The two antibodies that have the highest specificity for cerebellar dysfunction are anti-Yo[16,17] and anti-Tr antibodies.[18] The remaining antibodies listed in Table 3 either are associated with syndromes that frequently affect other areas of the nervous system in addition to the cerebellum or are infrequently detected in patients with paraneoplastic syndromes (i.e., mGluR1).

In most patients with paraneoplastic cerebellar degeneration, MRI scans are normal early in the disease whereas subsequent studies reveal cerebellar atrophy, as occurred in this case.[13,14,16,19] The clinical significance of the other MRI findings in this patient is unclear. The abnormality in the FLAIR signal in the brain stem could be related to transient inflammation, which occurs in the hippocampus in patients with limbic encephalitis.[20] The subtle enhancement in the right corona radiata suggests telangiectasia, and the

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abnormalities on T_2-weighted images are probably nonspecific findings or manifestations of small-vessel ischemic disease.

Tumors Associated with Paraneoplastic Syndromes of the Central Nervous System

What neoplasm is responsible for this woman's disorder? At her age, the most common tumors associated with paraneoplastic cerebellar degeneration are cancers of the ovary, breast, and lung and lymphoma.[13,14,16,19] The absence of abdominal symptoms, the negative results of tests for cancer markers, and the distribution of findings on the PET scan do not suggest an ovarian cancer. The patient has a family history of breast cancer, and there is weak evidence that fibroadenoma may be a risk factor for cancer.[21] However, simultaneous bilateral axillary involvement and a metastasis at T10 would be a very unusual presentation for breast cancer. A small single focus of ^{18}F-fluorodeoxyglucose uptake in the axilla on the side of the injection can result from subcutaneous radioactive tracer infiltration and may lead to a false positive result.[22]

Lung cancer, particularly small-cell lung cancer, is the cancer most frequently associated with paraneoplastic syndromes of the central nervous system. These syndromes can be manifested as cerebellar dysfunction that remains isolated or progresses to involve other parts of the central nervous system (encephalomyelitis) and are often associated with anti-Hu antibodies.[23] About 40% of patients who have small-cell lung cancer and cerebellar degeneration without anti-Hu antibodies have voltage-gated calcium-channel antibodies, which are also present in patients with the Eaton–Lambert myasthenic syndrome.[24] Except for mild proximal leg weakness, this patient did not have symptoms suggestive of the Eaton–Lambert myasthenic syndrome. The remote history of smoking, the absence of abnormalities in the lungs and mediastinum on PET scanning, and the absence of anti-Hu antibodies make lung cancer unlikely.

Lymphomas are the next most common tumors associated with paraneoplastic cerebellar degeneration. The distribution of the PET findings and the presence of an IgG kappa M component could suggest non-Hodgkin's lymphoma, although the latter finding also occurs in 1% of the healthy population. A monoclonal IgG gammopathy is typical of multiple myeloma, but this tumor is rarely associated with cerebellar degeneration and does not involve the axillary nodes. Patients with cerebellar degeneration and Hodgkin's lymphoma usually have anti-Tr antibodies,[18] whereas those with non-Hodgkin's lymphoma rarely have any of the antibodies known to be associated with paraneoplastic cerebellar degeneration.[25] In addition to the cerebellar degeneration, this patient may have had a paraneoplastic coagulopathy that contributed to the supratherapeutic effect of warfarin. Coagulopathy may occur in association with diverse types of cancers or B-cell neoplasms.[1] The serum level of lactate dehydrogenase in this patient is not provided, but an elevated level would support the diagnosis of lymphoma.

SUMMARY

I believe that the diagnosis in this case is a paraneoplastic syndrome with predominant cerebellar degeneration. Breast cancer in association with anti-Yo antibodies would be my leading diagnosis. The diagnostic procedure was probably a biopsy of the lesion in the right axilla or the lesion in the T10 vertebral body, detected by PET scanning.

Dr. Nancy Lee Harris (Pathology): Dr. Batchelor, would you summarize your thinking and tell us about additional testing that was done?

Dr. Tracy T. Batchelor (Neuro-oncology): In this patient, a diagnosis of a paraneoplastic cerebellar degeneration was strongly suspected. The anti-Yo antibody test performed at the first hospital was eventually received and was reported to be positive. We repeated the panel of paraneoplastic antibody tests.

CLINICAL DIAGNOSIS

Paraneoplastic syndrome with predominant cerebellar degeneration.

DR. JOSEP DALMAU'S DIAGNOSIS

Paraneoplastic syndrome with paraneoplastic cerebellar degeneration, probably associated with anti-Yo antibodies and a primary breast cancer.

PATHOLOGICAL DISCUSSION

Dr. Batchelor: Tests for MaTa antibodies, CV2/CRMP5 antibodies, antineuronal nuclear (Hu, Ri) antibodies, anti-CAR antibodies, and anti–voltage-

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gated calcium-channel antibodies (associated with the Eaton–Lambert myasthenic syndrome) were negative. A test for anti–Purkinje-cell (Yo) antibodies was positive.

A 5-day trial of intravenously administered immunoglobulin did not lead to improvement in the patient's neurologic condition, and she was discharged to a rehabilitation center on hospital day 12. Because of concern about the possibility of an occult ovarian cancer, laparoscopic hysterectomy and salpingo-oophorectomy were performed 2 months after discharge; no malignant tumor was found. We then repeated the CT and PET scans.

Dr. Gonzalez: A PET scan obtained 4 months after the initial PET scan revealed abnormalities in the right axilla and chest wall (Fig. 1C). There was still an abnormality in the T10 area. The left axilla showed no abnormalities. CT scanning showed the presence of an enlarged lymph node, 1.4 cm in diameter, in the right axilla, which was enhanced after the administration of contrast material.

Dr. Melinda F. Lerwill: Excision of the patient's enlarged right axillary lymph node revealed a poorly differentiated malignant neoplasm (Fig. 2A); the malignant cells were large, with abundant eosinophilic cytoplasm and marked nuclear pleomorphism (Fig. 2B). The differential diagnosis included carcinoma, lymphoma, and melanoma. Immunohistochemical studies showed that the tumor cells were positive for cytokeratin, supporting a diagnosis of carcinoma and negative for the lymphoid marker leukocyte common antigen and the melanoma marker S-100. The tumor cells were positive for cytokeratin 7 and negative for cytokeratin 20, a profile common to carcinomas from diverse sites, including the breast, lung, and ovary. The cells were diffusely positive for gross cystic disease fluid protein-15 (Fig. 2C), a marker of apocrine differentiation that is expressed in 62 to 77% of breast carcinomas as well as in salivary gland and skin adnexal tumors.[26] Gross cystic disease fluid protein-15 is only rarely positive in other cancers and is therefore a fairly specific marker of cancer originating in the breast when salivary gland and skin adnexal tumors are not likely. In conjunction with the clinical picture, the immunohistochemical findings in this case supported a diagnosis of metastatic breast carcinoma. The tumor cells did not express either estrogen or progesterone receptor, but they did show 3+ overexpression of Her-2/neu (Fig. 2D).

Less than 1% of patients with breast cancer present with an axillary metastasis as the first clinical indication of disease.[27] Clinical and radiographic evaluation of the breasts often shows no abnormalities in such patients even with the use of MRI.[27,28] A primary carcinoma is detected in the breast on pathological examination in 50 to 80% of cases,[27] sometimes months to years after the axillary metastases are detected. In nearly two thirds of cases in which axillary metastasis is the first clinical indication of breast cancer, the carcinoma is poorly differentiated, has a diffuse growth pattern, and is composed of large cells with abundant eosinophilic cytoplasm, pleomorphic nuclei, and macronucleoli, all features of this patient's tumor.[29]

Dr. Harris: Dr. Schmahmann, would you comment on your evaluation of this patient?

Dr. Jeremy D. Schmahmann (Neurology): I saw this patient during her first admission and was struck by the impairment in mental flexibility combined with poor set shifting, deficient verbal working memory, decreased verbal fluency, poverty of initiation, limited verbal learning and short-term recall, and flattening of affect. Because of the cerebellar involvement, the presence of anti-Yo antibodies, and the absence of demonstrated involvement of the cerebral hemispheres, I believed this patient had the cerebellar cognitive affective syndrome.[30] This neurobehavioral disorder is characterized by deficits in executive, visual–spatial, and linguistic performance, with disordered regulation of affect. Treatment with sertraline was instituted, and the patient's mood and comportment improved. The recognition of the cerebellar cognitive affective syndrome in this case was thus clinically relevant, since it resulted in specific treatment that improved her quality of life.

Dr. David P. Ryan (Medical Oncology): Tumor-marker studies were repeated; the CA 15-3 level was 45 U per milliliter (normal range, 0 to 30), and the carcinoembryonic antigen level was 14.8 ng per milliliter (normal value, <3.4). Repeated MRI showed progressive cerebellar volume loss. The patient was treated with vinorelbine and trastuzumab for 6 months. Follow-up CT scans showed complete regression of the axillary and chest-wall abnormalities, with no new metastatic disease; the levels of tumor markers returned to normal values. However, the patient's neurologic status was unchanged. Two years after the onset of symptoms, she remained free of cancer; al-

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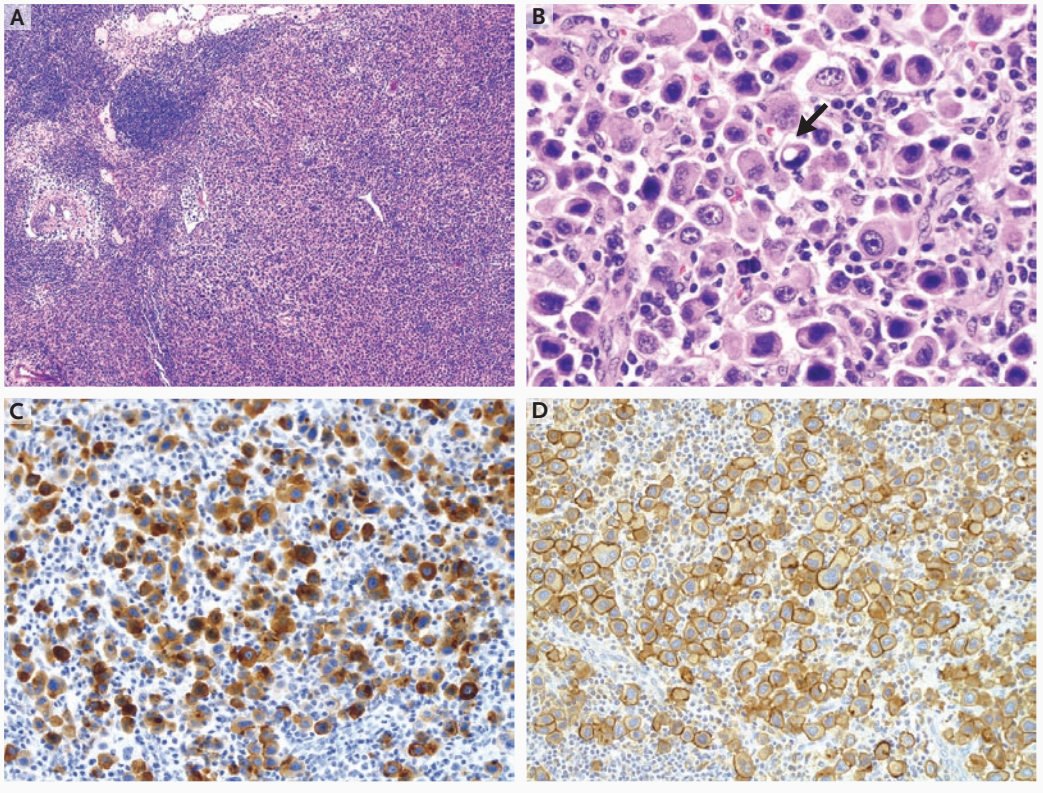

Figure 2. Biopsy Specimen from an Axillary Lymph Node Showing Diffuse Tumor Involvement.

Most of the lymph-node architecture is effaced by a diffuse infiltrate of large tumor cells (Panel A, hematoxylin and eosin). The tumor cells have abundant eosinophilic cytoplasm, pleomorphic nuclei, and macronucleoli (Panel B, hematoxylin and eosin). Occasional cells contain intracytoplasmic vacuoles (Panel B, arrow), raising the possibility that the cells contain mucin and suggesting a diagnosis of metastatic carcinoma. The tumor cells show diffuse cytoplasmic staining for gross cystic disease fluid protein-15 (Panel C, immunoperoxidase stain for gross cystic disease fluid protein-15), a finding seen in breast, salivary gland, and skin adrenal cancers. Most of the tumor cells show strong immunoperoxidase staining of the entire cell membrane for HER-2/*neu*, constituting a score of 3+ overexpression (Panel D).

though her neurologic status did not improve, it did not deteriorate further.

A Physician: Do the tumors in such patients express the Yo antigen?

Dr. Dalmau: Yes, the tumors in patients with anti-Yo antibodies express the Yo antigen.[31]

Dr. Robert H. Brown, Jr. (Neurology): What are the proteins to which the antibodies are directed? Is there any correlation between their distribution in the nervous system and the phenotype of the paraneoplastic syndrome?

Dr. Dalmau: In most of these syndromes, the antigens have been identified, and the genes cloned.[32] The Yo antigen is a cytoplasmic protein called CDR2 that interacts with c-Myc. The protein is expressed predominantly in the Purkinje cells of the cerebellum and the large neurons of the brain stem. Studies suggest that CDR2 sequesters c-Myc in the neuronal cytoplasm and downregulates its activity. Disruption of this interaction by anti-Yo antibodies may increase c-Myc activity, leading to apoptosis of the Purkinje cells. Antibodies could therefore play an initial pathogenic role, although it is believed for the most part that the T-cell immune response is the major effector of neuronal degeneration.[33]

ANATOMICAL DIAGNOSIS

Paraneoplastic cerebellar degeneration due to anti-Yo antibodies.

Metastatic poorly differentiated carcinoma, involving a right axillary lymph node, consistent with metastasis from a primary cancer in the breast

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(estrogen receptor negative and progesterone receptor negative, with overexpression of HER2/*neu*).

Dr. Dalmau reports receiving royalties from a patent held by Memorial Sloan-Kettering Cancer Center, New York, licensed to Athena Diagnostics (Ma-family polypeptides and anti-Ma antibodies) and consulting fees, advisory board payments, and lecture fees from Athena Diagnostics. No other potential conflict of interest relevant to this article was reported.

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