CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL



# Case 27-2012: A 60-Year-Old Woman with Painful Muscle Spasms and Hyperreflexia

Thomas N. Byrne, M.D., Steven Jay Isakoff, M.D., Ph.D., Sandra P. Rincon, M.D., and Thomas M. Gudewicz, M.D.

## PRESENTATION OF CASE

*Dr. Mikael L. Rinne* (Neurology): A 60-year-old woman was admitted to this hospital because of painful muscle spasms, weakness, and hyperreflexia.

The patient had been well until approximately 4 months before admission, when stiffness and cramping developed in both legs, associated with pain in the back. She saw a rheumatologist; a diagnosis of fibromyalgia was made, and gabapentin was administered, without improvement. Two weeks before admission, muscle cramps in the legs progressively worsened. The cramps were more severe proximally, occurred after movement or pressure on the legs, and awakened the patient from sleep. In the days before admission, spasms and stiffness led to multiple falls and required use of a walker. She came to the emergency department at this hospital.

The patient rated the pain at 10 on a scale of 0 to 10, with 10 indicating the most severe pain. She reported recent increased forgetfulness and intense generalized pruritus; during the previous 1 to 2 weeks, diaphoresis was associated with the episodes of pain. She did not have weakness or cramping in the arms, fever, headache, sensory loss, weight loss, rashes, bladder or bowel incontinence, or constitutional symptoms. She had hypertension, hypercholesterolemia, and chronic low back pain that radiated down her right leg to the midcalf. Medications on admission included atorvastatin, lorazepam, and atenolol, as well as opioid analgesic agents for pain and cetirizine and diphenhydramine as needed for pruritus. She had no known allergies, drank alcohol in moderation, and did not smoke or use illicit drugs. She was widowed and had recently retired from a professional position. Her parents had had dementia, had reportedly had colon cancer, and had died in their 90s; her father had had melanoma; her maternal grandmother had had breast cancer in her 70s; and a maternal cousin had had breast cancer in her 30s. The patient's three adult children were well.

On examination, the patient was anxious and in pain. The blood pressure was 170/111 mg Hg, the pulse 97 beats per minute, the temperature 37.5°C, and the oxygen saturation 93% while she was breathing ambient air. A large bruise on the right arm was the result of a fall. A mental-status examination was limited because

From the Departments of Neurology (T.N.B.), Hematology–Oncology (S.J.I.), Neuroradiology (S.P.R.), and Pathology (T.M.G.), Massachusetts General Hospital; and the Departments of Neurology (T.N.B.), Medicine (S.J.I.), Neuroradiology (S.P.R.), and Pathology (T.M.G.), Harvard Medical School — both in Boston.

N Engl J Med 2012;367:851-61.
DOI: 10.1056/NEJMcpc1114036

**Table 1. Laboratory Data.**

| Variable | Reference Range, Adults* | On Admission |
|---|---|---|
| Erythrocyte sedimentation rate (mm/hr) | 0–17 | 22 |
| Sodium (mmol/liter) | 135–145 | 133 |
| Potassium (mmol/liter) | 3.4–4.8 | 3.6 |
| Chloride (mmol/liter) | 100–108 | 98 |
| Carbon dioxide (mmol/liter) | 23.0–31.9 | 21.9 |
| Glucose (mg/dl)† | 70–110 | 119 |
| Creatine kinase (U/liter) | 40–150 (women) | 1498 |
| Aspartate aminotransferase (U/liter) | 9–32 | 52 |
| Alanine aminotransferase (U/liter) | 7–30 | 50 |

* 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.

of drowsiness, which was attributed to medications; the patient's attention was poor, and she had difficulty subtracting from 100 by serial 7s, naming the months, or spelling "world" backward. The tone, bulk, and strength of the arms were normal. Motor testing of the legs was limited because of pain and spasms induced by movement or stimulation. There was extreme rigidity of the flexor and extensor muscles bilaterally; the patient was unable to flex her right leg at the knee or fully extend her left leg. She was unable to flex her left hip against gravity and could not flex the right hip. Reflexes were 3+ at the biceps, triceps, brachioradialis, and knees and 4+ at the Achilles' tendons, with three or four beats of clonus at both ankles. Plantar reflexes were mute. She was unable to arise from a supine or sitting position or walk without assistance. The remainder of the neurologic and general physical examinations was normal.

Results of a complete blood count and white-cell differential count were normal, as were serum levels of calcium, phosphorus, magnesium, alkaline phosphatase, total and direct bilirubin, C-reactive protein, total protein, globulin, albumin, cholesterol, triglycerides, and lipoproteins and tests of coagulation and renal function; other test results are shown in Table 1. Urinalysis showed 1+ ketones, was positive for benzodiazepines and opiates, and was otherwise normal. Atorvastatin was discontinued, and morphine and diazepam were administered, followed by lorazepam and cyclobenzaprine hydrochloride, with improvement in the spasms and rigidity and decreased pain.

Magnetic resonance imaging (MRI) of the brain, performed without the administration of gadolinium, revealed a few nonspecific foci of hyperintensity in the frontal subcortical white matter, seen on $T_2$-weighted and fluid-attenuated inversion recovery (FLAIR) images. MRI of the cervical, thoracic, and lumbar spine, performed without the administration of gadolinium and limited by patient discomfort, showed degenerative changes of the cervical and lumbar spine, without cord or nerve-root compression.

A diagnostic test was performed.

## DIFFERENTIAL DIAGNOSIS

*Dr. Thomas N. Byrne:* I am aware of the diagnosis in this case. This 60-year-old woman had subacute progressive back and leg pain, an inability to walk, increased muscle tone in the legs, spasms, and unsustained ankle clonus, which suggested an upper-motor-neuron dysfunction localized to the spinal cord. There was no sensory level; however, in a patient who is drowsy or confused, it is difficult to obtain a reliable sensory examination.

A key point of the examination was that the patient had increased tone of the flexors and extensors, suggesting rigidity, rather than spasticity due to a myelopathy. Nonetheless, with this clinical presentation, a progressive myelopathy was suspected, and MRI of the spine was urgently performed. The lumbar spine was included because of the patient's history of sciatica; MRI of the brain was performed because of the cognitive dysfunction. With the exclusion of a compressive lesion or an obvious intraparenchymal abnormality, consideration was given to the diagnosis of the stiff person syndrome.

### THE STIFF PERSON SYNDROME

The clinical presentation of the stiff person syndrome is progressive stiffness and rigidity of the axial muscles extending into the proximal limbs, with superimposed spasms, leading to impairment of voluntary movements and gait. It is exacerbated by emotions and sensory stimuli. The syndrome is due to diminished function of

γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. In the spinal cord, a reduced level of GABA leads to hyperexcitable motor neurons, rigidity, and spasms of both agonist and antagonist muscles.

The stiff person syndrome may be idiopathic or due to a paraneoplastic syndrome. Approximately 90% of patients with the stiff person syndrome have autoantibodies directed against glutamic acid decarboxylase (GAD), the rate-limiting enzyme for GABA synthesis.[1] These autoantibodies are usually not associated with underlying cancer (<1% in one series), but patients often have diabetes mellitus and other autoimmune diseases.[1,2] In contrast, 5 to 10% of patients have an autoantibody against amphiphysin, a protein involved in regulation of synaptic-vesicle endocytosis after the release of GABA. Fifty to 90% of patients with anti-amphiphysin antibodies have an underlying cancer, usually of the breast.[2,3]

Paraneoplastic syndromes, including the stiff person syndrome, are believed to be mediated by antibodies to antigens on the neoplasm that also react to antigens expressed by the nervous system, causing clinical neurologic damage (onconeural antibodies).[4] Other paraneoplastic syndromes include limbic encephalitis, subacute cerebellar degeneration, opsoclonus–myoclonus, subacute sensory neuronopathy, the Lambert–Eaton myasthenic syndrome, and dermatomyositis.[5-7] The direct pathogenicity of anti-amphiphysin antibodies was shown in a patient with breast cancer who had a response to plasmapheresis.[8] When her serum was injected into laboratory animals, dose-dependent muscle spasms developed in the animals, and the spinal cords of those receiving high-titer antibodies were found to contain human IgG.

Clinical clues that should lead to consideration of a paraneoplastic syndrome include a severe neurologic syndrome that evolves subacutely over a period of a few weeks to months, as in this patient, and a cerebrospinal fluid (CSF) profile that includes inflammatory markers; measurement of IgG and oligoclonal bands is often helpful in determining that the disorder is inflammatory.[9]

This patient had no evidence of cancer; approximately two thirds of patients presenting with a paraneoplastic syndrome have no known cancer. Patients who are suspected of having a paraneoplastic syndrome undergo imaging of the nervous system, testing for characteristic antibodies, evaluation for an underlying neoplasm, and examination of the CSF, including analysis for IgG and oligoclonal bands and cytologic examination. In patients with antibodies that strongly suggest a specific cancer — such as anti-amphiphysin, which points to breast cancer — the diagnosis should be pursued even if testing (e.g., mammogram and MRI) is negative. If no cancer is found, follow-up studies are suggested.

## SUMMARY

In this patient, the clinical presentation was most compatible with the stiff person syndrome. Although she had no evidence of cancer, the rapid onset of symptoms raised suspicion for a paraneoplastic syndrome. To confirm the diagnosis, blood was sent for testing for anti-GAD and anti-amphiphysin antibodies.

*Dr. Rinne:* It took several weeks for the results of antibody testing to return; the patient was discharged. In the meantime, while awaiting the results, the patient received treatment with diazepam and cyclobenzaprine, which reduced her spasms; however, new memory loss developed and she had increasing confusion and confabulation, features thought to be side effects of the medication. The dose of diazepam was tapered, and the administration of baclofen was begun for treatment of spasticity.

Six weeks after discharge, marked short-term memory loss and progressive confusion developed, as well as severe orthostatic light-headedness that was thought to be the proximate cause of several falls. The patient returned to this hospital and was found to be severely disoriented and inattentive and to have confused speech. At that time, routine laboratory testing, cultures, and toxicologic screening were negative. A specimen of CSF from a lumbar puncture showed a lymphocytic pleocytosis, with 13 white cells and 749 red cells. The CSF glucose level was normal, but the protein level was slightly elevated and the IgG level was elevated, with oligoclonal bands. Cytologic examination showed only lymphocytes, with no malignant cells.

The results of antibody testing revealed no anti-GAD antibodies but confirmed the presence of anti-amphiphysin antibodies in the blood. This result prompted the search for an underlying neoplasm with computed tomography (CT) of the

chest, abdomen, and pelvis. A brain MRI was also obtained.

*Dr. Sandra P. Rincon:* CT of the chest after the administration of contrast material (Fig. 1) shows a mildly enhancing left axillary lymph node, 9 mm in greatest dimension. No other suspicious lymph nodes are identified, and CT of the abdomen and pelvis is normal. A diagnostic mammogram and MRI of the breast reveal no abnormalities. MRI of the brain (Fig. 2A and 2B) reveals ill-defined hyperintensity on FLAIR images in the amygdala, hippocampus, and parahippocampal gyri bilaterally, more prominent in the left temporal lobe than in the right temporal lobe. There is mild local mass effect, with effacement of the adjacent sulci. There is no susceptibility effect on $T_{2*}$-weighted gradient-recalled echo images (Fig. 2C) to suggest the presence of hemorrhage. No abnormal enhancement is seen on $T_1$-weighted images (Fig. 2D) after the administration of gadolinium.

The differential diagnosis for this appearance of the brain on MRI includes limbic encephalitis and herpes encephalitis, which can be indistinguishable on imaging studies. Bilateral, asymmetric involvement of the medial temporal lobes and inferior frontal lobes is seen in both conditions. Hemorrhage is not a feature of limbic encephalitis but is usually seen in herpes encephalitis and can be a late feature. Patchy enhancement of the involved brain is seen in limbic encephalitis and in herpes encephalitis early in the disease process; later, herpes encephalitis typically shows gyriform enhancement. Other differential considerations include an infiltrating neoplasm, such as gliomatosis cerebri, which can be multifocal and can show areas of signal abnormality and mild expansion of the involved brain. However, in this case, an infiltrating neoplasm was considered unlikely given the normal appearance of the earlier MRI. Finally, seizures can disrupt the blood–brain barrier and can be a cause of signal abnormality and cortical enhancement in the brain. Since these findings are usually transient, follow-up imaging can be helpful.

### LIMBIC ENCEPHALITIS

*Dr. Byrne:* In this patient with the stiff person syndrome and anti-amphiphysin antibodies, the development of memory loss and confusion and the presence of abnormal findings in the amygdala, hippocampus, and parahippocampal gyri are diagnostic of limbic encephalitis, which is most likely due to anti-amphiphysin antibodies.

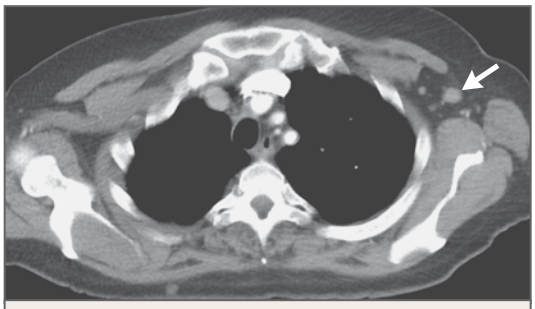

**Figure 1. CT of the Chest.**

An image from a CT of the chest after the administration of contrast material shows a mildly enhancing left axillary lymph node measuring 9 mm in greatest dimension (arrow).

*Dr. Rinne:* The patient's mental status and confusion fluctuated. During one of her periods of confusion, an electroencephalogram was obtained to rule out seizure activity; it showed good organization with no epileptiform activity. The decision was made to obtain a biopsy specimen of the 9-mm left axillary lymph node.

## DR. THOMAS N. BYRNE'S DIAGNOSIS

Paraneoplastic stiff person syndrome and limbic encephalitis with anti-amphiphysin antibodies, most likely due to an underlying malignant tumor.

## PATHOLOGICAL DISCUSSION

*Dr. Thomas M. Gudewicz:* Specimens from ultrasound-guided fine-needle aspiration and core needle biopsy were obtained from the left axillary lymph node. Both specimens contained large, atypical epithelial cells with a high nuclear-to-cytoplasmic ratio, irregular nuclear contours, and prominent nucleoli in a background of lymphocytes (Fig. 3A). Special attention was paid to whether the specimens had features of epithelial tumors that commonly occur in women in this patient's age group (i.e., tumors of the breast, lung and bronchus, corpus uteri, colon and rectum, ovary, kidney and renal pelvis, and thyroid). The histologic features of the biopsy specimens

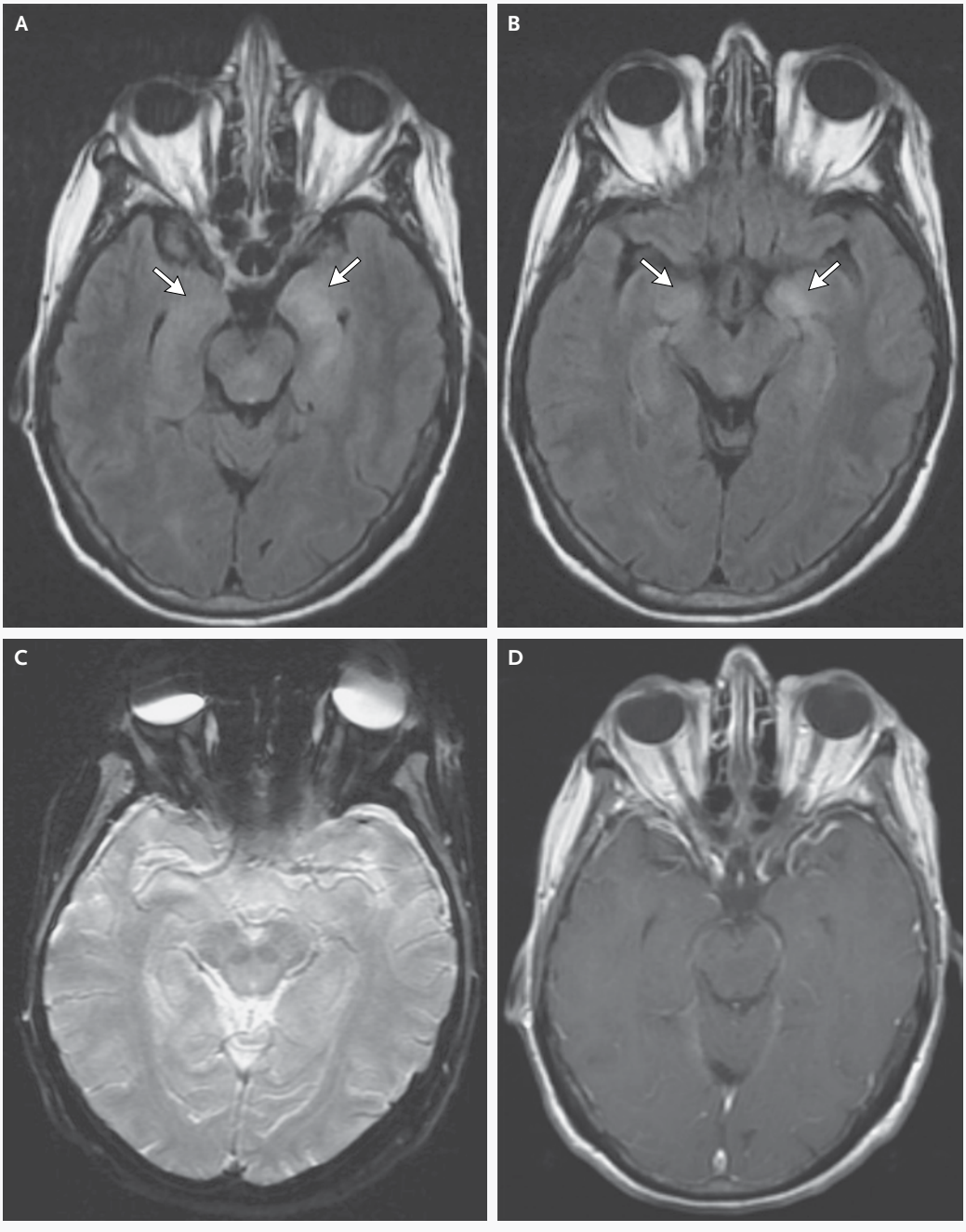


**Figure 2. MRI of the Brain.**

Axial fluid-attenuated inversion recovery (FLAIR) images (Panels A and B) show ill-defined, hyperintense signal abnormalities in the medial temporal lobes bilaterally (arrows), more pronounced in the left temporal lobe than in the right temporal lobe. There is mild local mass effect, with effacement of the adjacent sulci. There is no susceptibility effect on a $T_2$*-weighted gradient-recalled echo image (Panel C) to suggest the presence of hemorrhage. An axial $T_1$-weighted image obtained after the administration of gadolinium (Panel D) shows no appreciable enhancement in the regions of signal abnormality seen on the FLAIR images.

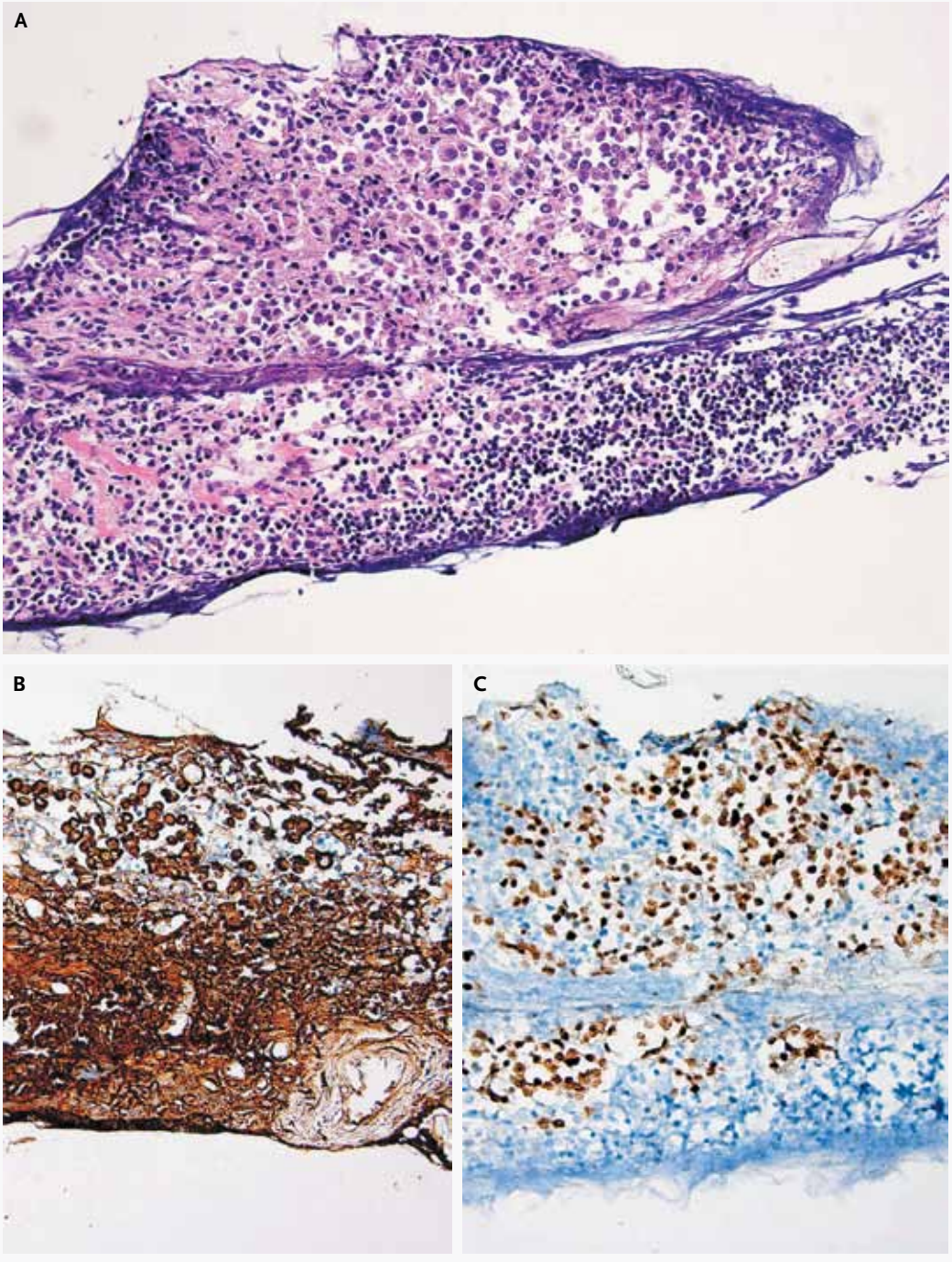


**Figure 3. Core-Biopsy Specimen from the Left Axillary Lymph Node.**

A core-biopsy specimen from the left axillary node, at medium magnification, shows enlarged atypical cells and scattered small lymphocytes (Panel A, hematoxylin and eosin). In Panel B (immunohistochemical stain for cytokeratin 7), strong cytoplasmic staining indicates an epithelial origin of the atypical cells. In Panel C, immunohistochemical staining for estrogen receptor shows strong nuclear staining.

were not discriminating, and a select immunoprofile of the tissue cores showed membrane and cytoplasmic staining with cytokeratin 7 (Fig. 3B), nuclear staining for estrogen receptor (Fig. 3C), and no staining with thyroid transcription factor 1 (not shown). There was insufficient tissue for additional studies.

Cytokeratin 7 is expressed in cells from breast, lung, and ovary tumors, but it is generally lacking in colonic adenocarcinomas. Estrogen receptor is usually expressed in breast and gynecologic tumors and in some tumors of the skin and its appendages. Thyroid carcinomas and lung adenocarcinomas typically express thyroid transcription factor 1. These findings thus favor but do not confirm a cancer originating in the breast; because of the small tissue sample, it was not possible to determine whether this was metastatic disease in a lymph node or possibly in situ carcinoma in the axillary tail of the breast, with associated inflammation.

*Dr. Steven Jay Isakoff:* Oncology was consulted after the fine-needle aspirate from the axilla showed cells that were suspicious for breast cancer. In women, breast cancer is the most common carcinoma of unknown primary site appearing in an axillary lymph node. In addition, as Dr. Byrne noted, it is the cancer most commonly associated with anti-amphiphysin antibodies.[2,10] Patients with lung cancer may also present with a metastasis in an axillary lymph node, albeit less commonly, and may also have associated anti-amphiphysin antibodies; in this patient, there was no evidence on lung CT to support this diagnosis. Other carcinomas of unknown primary site that on rare occasions are initially manifested in axillary lymph nodes include ovarian, gastric, esophageal, head and neck, thyroid, endometrial, apocrine, and renal carcinomas.

### EVALUATION OF THE PATIENT WITH A CANCER OF UNKNOWN PRIMARY SITE

Our team evaluated the patient's history. We focused on the family history of cancer, the change in bowel habits, and the constitutional symptoms, and we confirmed that the patient had had age-appropriate cancer screening. She had no first-degree relatives with breast cancer, but there was a possible history of colon cancer in her parents. She had had annual mammograms that were normal, but there was no record of screening colonoscopies. Physical examination was important, with attention to the other nodal areas and a breast examination, all of which were normal. Pelvic examination may be indicated in women. Men should have a prostate examination. This patient's laboratory studies were reviewed. In addition, serum tumor markers may be helpful in the diagnostic workup for a cancer of unknown primary site. The CA 15-3 level can be elevated in approximately 50 to 60% of breast cancers, the CA-125 level in ovarian cancers, the CA 19-9 level in pancreatic cancers, and the level of carcinoembryonic antigen in colon, lung, or breast cancer. The levels of these markers were all normal in this patient.

CT of the chest, abdomen, and pelvis should be performed in cases of carcinoma of unknown primary site; in this case, the axillary node was the only lesion identified. For breast imaging, a diagnostic mammogram should be obtained first. If the mammogram is normal, a breast MRI should be performed; a scan can reveal occult breast cancers in about 76% of cases.[11] Both the diagnostic mammogram and the breast MRI were normal in this case. The literature does not support routinely performing positron-emission tomography (PET) unless the results of other studies are unrevealing. Bone scans are generally not recommended unless there is bone pain or other indications to suggest bone disease. Neither PET scans nor bone scans were obtained in this case.

Immunohistochemical analysis of the tissue sample may be helpful, as Dr. Gudewicz described; in this case, the results supported but did not confirm a primary origin in the breast. Human epidermal growth factor receptor type 2 (HER2) is important because it may aid in identifying the tumor origin and because it has treatment implications in breast cancer.

At this point, we recommended excision of the axillary node.

*Dr. Gudewicz:* The left axillary lymph node was 1 cm in greatest dimension and was nearly replaced by metastatic adenocarcinoma. Additional immunohistochemical staining showed that the tumor was negative for progesterone receptor (PR) and HER2. The diagnosis was metastatic adenocarcinoma, which is consistent with a primary origin in the breast.

## DISCUSSION OF MANAGEMENT

*Dr. Isakoff:* Breast cancer presenting in a lymph node, with an occult primary cancer, was first described in 1907, when Halsted reported on three patients who presented with axillary lymph-node involvement by occult breast cancers.[12] This phenomenon appears to occur in 0.1 to 0.4% of all breast cancers.[13-15] However, much of the available data antedate the availability of breast MRI; with contemporary imaging, the incidence is most likely lower. Without evidence of distant metastatic disease, management in this case is the same as that for early-stage breast cancer. The two areas to consider are local therapy, which involves therapy to the breast and regional nodal areas (e.g., the axilla), and systemic therapy.

### MANAGEMENT OF EARLY-STAGE BREAST CANCER WITH AN OCCULT PRIMARY TUMOR

For local management, the first consideration is treatment of the breast. The choices are observation, mastectomy with or without postmastectomy irradiation, and whole-breast irradiation without mastectomy. The second consideration is whether an axillary lymph-node dissection should be performed.

In general, there is agreement in the literature about proceeding with axillary lymph-node dissection in cases such as this one. About half of such patients will have one to three positive lymph nodes, and the other half will have more than three positive lymph nodes.[16] When mastectomy is performed in such patients, the frequency of finding an occult breast cancer varies widely but is probably on the order of 60 to 80%.[16]

Several retrospective studies of patients presenting with an axillary-node metastasis without evidence of a primary breast tumor indicate a significant survival benefit associated with treatment of the breast and axillary dissection, as compared with either observation or axillary dissection with no treatment to the breast.[13-15] Survival among patients without treatment to the breast ranges from 15 to 50% at 10 years. With treatment (either irradiation or mastectomy), the 10-year survival rate is approximately 65%.[13,15]

In this patient in whom no lesion was identified on breast imaging, the literature supports treatment of the breast with either irradiation or mastectomy. She should also undergo a complete axillary lymph-node dissection. She presented with the paraneoplastic stiff person syndrome, limbic encephalitis, and anti-amphiphysin antibodies, and a primary goal of treatment was to completely remove the offending antigens by removing the primary tumor and any remaining positive nodes. On the basis of this reasoning and the findings on pathological examination of the lymph node that was removed from the left axilla, we recommended that she undergo a left mastectomy with axillary lymph-node dissection. Consideration of adjuvant chemotherapy would depend on the final results of pathological examination and the extent of the patient's postoperative recovery from the paraneoplastic symptoms. We also recommended adjuvant endocrine therapy with an aromatase inhibitor and referral to a radiation oncologist for consideration of postmastectomy irradiation.

*Dr. Gudewicz:* Modified radical mastectomy of the left breast and axillary dissection were performed. The breast was sectioned at intervals of 2 to 3 mm. No masses were visible or palpable. A focus of invasive ductal carcinoma, 1 mm in greatest dimension, was identified (Fig. 4A). The cytologic and architectural features of the invasive carcinoma (Fig. 4B) were similar to those of the metastasis to the left axillary lymph node (Fig. 4C), confirming the origin of the metastasis. Numerous representative sections of the breast that were sampled for microscopical evaluation revealed multiple small foci of ductal carcinoma in situ (Fig. 4D and 4E). Three of 15 additional lymph nodes contained metastatic carcinoma; therefore, a total of 4 of 16 lymph nodes were positive for metastasis.

### MANAGEMENT OF PARANEOPLASTIC STIFF PERSON SYNDROME

*Dr. Byrne:* According to the diagnostic recommendations of an international panel, this patient meets the criteria for a definite diagnosis of paraneoplastic stiff person syndrome,[5] including the presence of a classic clinical syndrome, a well-characterized onconeural antibody, and cancer. Approaches to the treatment of paraneoplastic syndromes include symptomatic therapy, which was done in this case with diazepam and baclofen, which are GABA agonists; treatment of the underlying cancer, which was also done in this case; and immunosuppression, which may include the administration of glucocorticoids, other immunosuppressant agents such as cyclophosphamide and rituximab, intravenous immune globulin, and plasmapheresis.[17-19]

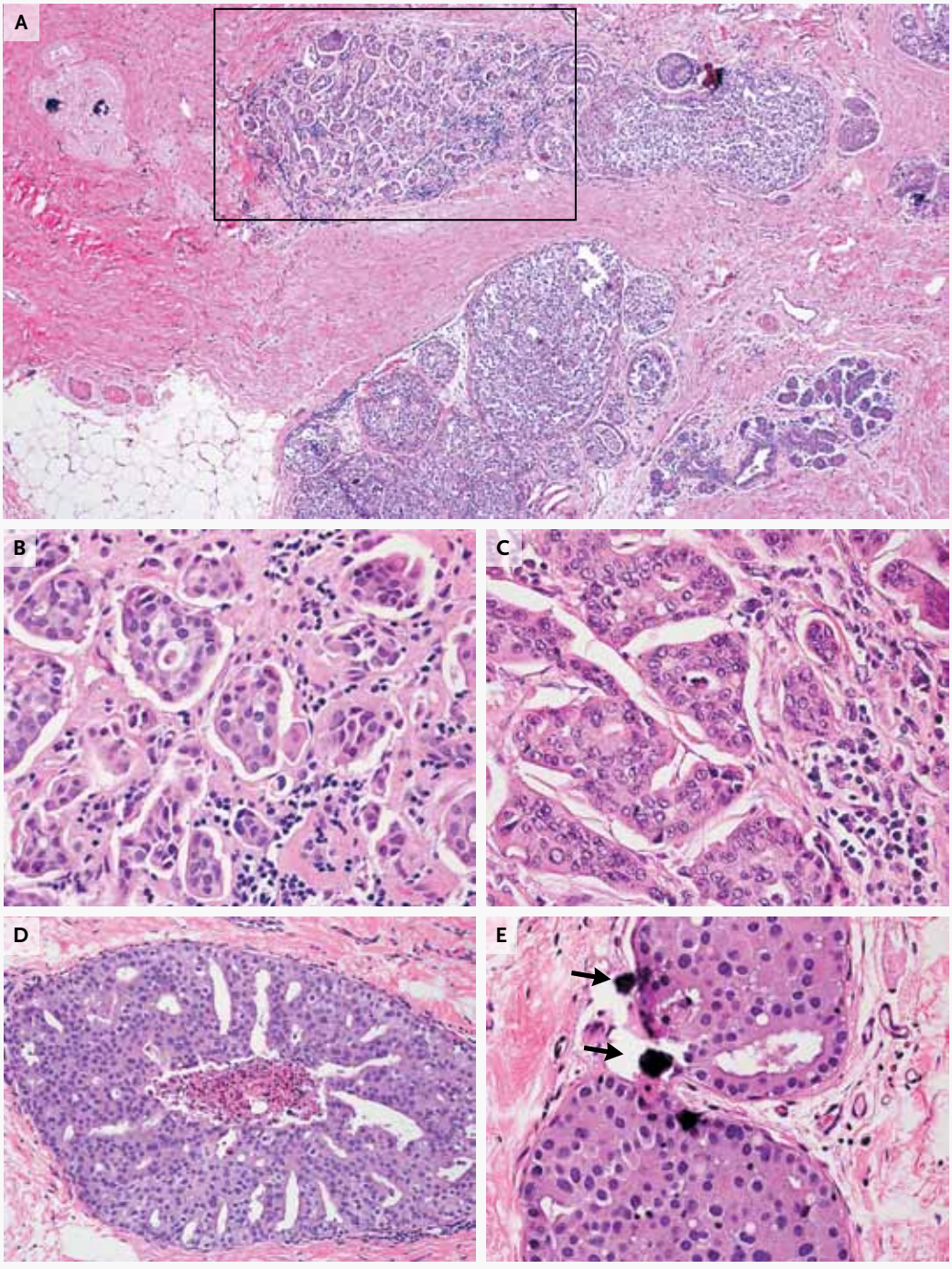


**Figure 4. Mastectomy Specimen.**

At low magnification, a 1-mm focus of invasive ductal carcinoma (Panel A, box; hematoxylin and eosin) is shown within a region of ductal carcinoma in situ and normal glands. At high magnification, the histologic features of the invasive component (Panel B, hematoxylin and eosin) are similar to those of the metastases to the lymph node (Panel C, hematoxylin and eosin). Foci of ductal carcinoma in situ were identified centrally and in the upper inner, upper outer, and lower outer quadrants of the breast. At medium magnification, the ductal carcinoma in situ shows expanded ducts with central necrosis (Panel D, hematoxylin and eosin) and, at high magnification, scattered calcifications (Panel E, arrows; hematoxylin and eosin).

### FOLLOW-UP

*Dr. Rinne:* By the time the diagnosis was established, the patient could not walk, and she had profound amnesia and psychosis. She was treated with 5 days of intravenous immune globulin and high-dose glucocorticoids, followed by a gradual taper. After the mastectomy, a planned course of adjuvant dose-dense chemotherapy with cyclophosphamide and doxorubicin, followed by paclitaxel,[20] was begun; the patient was discharged after a 1-month hospitalization. She initially made a miraculous recovery, and at follow-up 2 months after discharge, she was virtually back to baseline, with only minimal confusion. Unfortunately, 5 days later, she returned to the emergency department with confusion, agitation, paranoia, and psychosis. Brain MRI was aborted because of the patient's inability to cooperate but showed no evidence of intracranial hemorrhage, infarction, or masses; CT of the brain was unchanged from previous studies. An electroencephalogram showed nonconvulsive status epilepticus. She was readmitted to this hospital and treated with intravenous immune globulin, high-dose glucocorticoids, an anticonvulsant agent, and two doses of rituximab, with a return of her mental status to normal. She completed adjuvant chemotherapy with cyclophosphamide and doxorubicin but was unable to receive the intended course of adjuvant paclitaxel because of recurrent symptomatic limbic encephalitis. The chemotherapy was followed by anastrozole and radiation therapy to the chest wall and axilla. Almost 2 years after her initial admission, she continues taking prednisone (5 mg daily), her mental status is normal, and she lives independently and performs all activities of daily living.

## ANATOMICAL DIAGNOSES

Paraneoplastic stiff person syndrome and limbic encephalitis with anti-amphiphysin antibodies.

Invasive ductal carcinoma (grade 2), 0.1 cm in greatest dimension; ductal carcinoma in situ (grade 2), adjacent to and beyond the region of invasion; 4 of 16 lymph nodes positive for metastasis.

Presented at the postgraduate course Internal Medicine: Comprehensive Review and Update 2011, course directors Drs. Dennis A. Ausiello, Sekar Kathiresan, and Ravi Thadhani; sponsored by the Harvard Medical School Department of Continuing Medical Education and Massachusetts General Hospital.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Drs. Tracy Cho and Mikael Rinne for assistance with preparing the case history.

### REFERENCES

1. Solimena M, Folli F, Aparisi R, Pozza G, De Camilli P. Autoantibodies to GABA-ergic neurons and pancreatic beta cells in stiff-man syndrome. N Engl J Med 1990;322:1555-60.
2. Murinson BB, Guarnaccia JB. Stiff-person syndrome with amphiphysin antibodies: distinctive features of a rare disease. Neurology 2008;71:1955-8.
3. Alexopoulos H, Dalakas MC. A critical update on the immunopathogenesis of Stiff Person Syndrome. Eur J Clin Invest 2010;40:1018-25.
4. Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. N Engl J Med 2003;349:1543-54.
5. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 2004;75:1135-40.
6. Roberts WK, Darnell RB. Neuroimmunology of the paraneoplastic neurological degenerations. Curr Opin Immunol 2004;16:616-22.
7. Case Records of the Massachusetts General Hospital (Case 26-2008). N Engl J Med 2008;359:842-53.
8. Sommer C, Weishaupt A, Brinkhoff J, et al. Paraneoplastic stiff-person syndrome: passive transfer to rats by means of IgG antibodies to amphiphysin. Lancet 2005;365:1406-11.
9. Psimaras D, Carpentier AF, Rossi C. Cerebrospinal fluid study in paraneoplastic syndromes. J Neurol Neurosurg Psychiatry 2010;81:42-5.
10. Pittock SJ, Lucchinetti CF, Parisi JE, et al. Amphiphysin autoimmunity: paraneoplastic accompaniments. Ann Neurol 2005;58:96-107.
11. Buchanan CL, Morris EA, Dorn PL, Borgen PI, Van Zee KJ. Utility of breast magnetic resonance imaging in patients with occult primary breast cancer. Ann Surg Oncol 2005;12:1045-53.
12. Halsted WS. I. The results of radical operations for the cure of carcinoma of the breast. Ann Surg 1907;46:1-19.
13. Walker GV, Smith GL, Perkins GH, et al. Population-based analysis of occult primary breast cancer with axillary lymph node metastasis. Cancer 2010;116:4000-6.
14. Foroudi F, Tiver KW. Occult breast carcinoma presenting as axillary metastases. Int J Radiat Oncol Biol Phys 2000;47:143-7.
15. Masinghe SP, Faluyi OO, Kerr GR, Kunkler IH. Breast radiotherapy for occult breast cancer with axillary nodal metastases — does it reduce the local recurrence rate and increase overall survival? Clin Oncol (R Coll Radiol) 2011;23:95-100.

**16.** Rosen PP, Kimmel M. Occult breast carcinoma presenting with axillary lymph node metastases: a follow-up study of 48 patients. Hum Pathol 1990;21:518-23.
**17.** Dalakas MC. Stiff person syndrome: advances in pathogenesis and therapeutic interventions. Curr Treat Options Neurol 2009;11:102-10.
**18.** Donofrio PD, Berger A, Brannagan TH III, et al. Consensus statement: the use of intravenous immunoglobulin in the treatment of neuromuscular conditions: report of the AANEM ad hoc committee. Muscle Nerve 2009;40:890-900.
**19.** Greenlee JE. Treatment of paraneoplastic neurologic disorders. Curr Treat Options Neurol 2010;12:212-30.
**20.** Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer. J Clin Oncol 2003;21:1431-9. [Erratum, J Clin Oncol 2003;21:2226.]