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...
Table 1. Laboratory Data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Adults*</th>
<th>On Admission</th>
</tr>
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<tr>
<td>Erythrocyte sedimentation rate</td>
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<td>22</td>
</tr>
<tr>
<td>Sodium (mmol/liter)</td>
<td>135–145</td>
<td>133</td>
</tr>
<tr>
<td>Potassium (mmol/liter)</td>
<td>3.4–4.8</td>
<td>3.6</td>
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<tr>
<td>Chloride (mmol/liter)</td>
<td>100–108</td>
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<tr>
<td>Carbon dioxide (mmol/liter)</td>
<td>23.0–31.9</td>
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<tr>
<td>Glucose (mg/dl)†</td>
<td>70–110</td>
<td>119</td>
</tr>
<tr>
<td>Creatine kinase (U/liter)</td>
<td>40–150 (women)</td>
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<tr>
<td>Aspartate aminotransferase (U/liter)</td>
<td>9–32</td>
<td>52</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/liter)</td>
<td>7–30</td>
<td>50</td>
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* 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.

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 T₂-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.

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...
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. These autoantibodies are usually not associated with underlying cancer (<1% in one series), but patients often have diabetes mellitus and other autoimmune diseases. 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.

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). Other paraneoplastic syndromes include limbic encephalitis, subacute cerebellar degeneration, opsoclonus–myoclonus, subacute sensory neuronopathy, the Lambert–Eaton myasthenic syndrome, and dermatomyositis. The direct pathogenicity of anti-amphiphysin antibodies was shown in a patient with breast cancer who had a response to plasmapheresis.

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
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<sup>2*</sup>-weighted gradient-recalled echo images (Fig. 2C) to suggest the presence of hemorrhage. No abnormal enhancement is seen on T<sup>1</sup>-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.

**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<sub>2</sub>*-weighted gradient-recalled echo image (Panel C) to suggest the presence of hemorrhage. An axial T<sub>1</sub>-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 immuno-
profile 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 lack-
ing in colonic adenocarcinomas. Estrogen recep-
tor is usually expressed in breast and gynecolo-
tic tumors and in some tumors of the skin and
its appendages. Thyroid carcinomas and lung
adenocarcinomas typically express thyroid tran-
scription 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 meta-
static 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 can-
cer. 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 as-
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 diagno-
sis. 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 fo-
cused on the family history of cancer, the change
in bowel habits, and the constitutional symp-
toms, 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 par-
ents. She had had annual mammograms that were
normal, but there was no record of screening
colonoscopies. Physical examination was impor-
tant, 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 ad-
dition, 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 carcinoem-
bryonic 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 oc-
cult 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 stud-
ies 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 de-
cscribed; 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 iden-
tifying the tumor origin and because it has treat-
ment 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 re-
placed 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 pri-
mary origin in the breast.
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. 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%. 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. 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%. 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. Byrne: According to the diagnostic recommendations of an international panel, this patient meets the criteria for a definite diagnosis of paraneoplastic stiff person syndrome, 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.
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, 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.

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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.

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REFERENCES

Case Records of the Massachusetts General Hospital

Lantern Slides Updated: Complete PowerPoint Slide Sets from the Clinicopathological Conferences

Any reader of the Journal who uses the Case Records of the Massachusetts General Hospital as a teaching exercise or reference material is now eligible to receive a complete set of PowerPoint slides, including digital images, with identifying legends, shown at the live Clinicopathological Conference (CPC) that is the basis of the Case Record. This slide set contains all of the images from the CPC, not only those published in the Journal. Radiographic, neurologic, and cardiac studies, gross specimens, and photomicrographs, as well as unpublished text slides, tables, and diagrams, are included. Every year 40 sets are produced, averaging 50-60 slides per set. Each set is supplied on a compact disc and is mailed to coincide with the publication of the Case Record.

The cost of an annual subscription is $600, or individual sets may be purchased for $50 each. Application forms for the current subscription year, which began in January, may be obtained from the Lantern Slides Service, Department of Pathology, Massachusetts General Hospital, Boston, MA 02114 (telephone 617-726-2974) or e-mail Pathphotoslides@partners.org.

References: