Simon Faissner, MD
Carsten Lukas, MD
Anke Reinacher-Schick, MD
Andrea Tannapfel, MD
Ralf Gold, MD
Ingo Kleiter, MD

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AMPHIPHYSIN-POSITIVE PARANEOPLASTIC MYELITIS AND STIFF-PERSON SYNDROME

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Finding the underlying etiology of transverse myelitis (TM) can be challenging, as several disorders, including multiple sclerosis (MS), neuromyelitis optica, acute disseminated encephalomyelitis, postvaccine myelitis, Sjögren disease, neurosarcoidosis, infectious myelopathies, or idiopathic TM, may be causative.[1] Paraneoplastic myelopathy, another differential diagnosis, is associated with a broad range of neoplasms and bears a severe risk to develop disability.[2] Stiff-person syndrome (SPS) can occur as a result of some neoplasms and is characterized by skeletal muscle rigidity and spasms.

We present the case of a patient with suspected MS who eventually was diagnosed with paraneoplastic TM and SPS, both associated with antibodies to amphiphysin.

Case report. A 44-year-old otherwise healthy woman was admitted in September 2012 for increasing gait difficulties for several weeks. She had grade 4 Medical Research Council paraparesis, gait ataxia, and hypesthesia of both legs, and intermittently used a wheelchair. At the time of presentation, she had been treated with 4 infusions of natalizumab, which was started for suspected MS after 2 exacerbations (weakness of the right arm in March 2012, deterioration of walking in May 2012) had occurred under glatiramer acetate therapy. The initial manifestation was hypesthesia of DI–DIII in her right hand in September 2011. Since November 2011, she had noticed an emerging weakness of both legs, and she was able to walk for approximately 30 minutes with bilateral assistance in January 2012. In February 2012, MRI had revealed cervical myelitis C2–C3 and lumbar puncture positive oligoclonal bands and 84/3 cells.

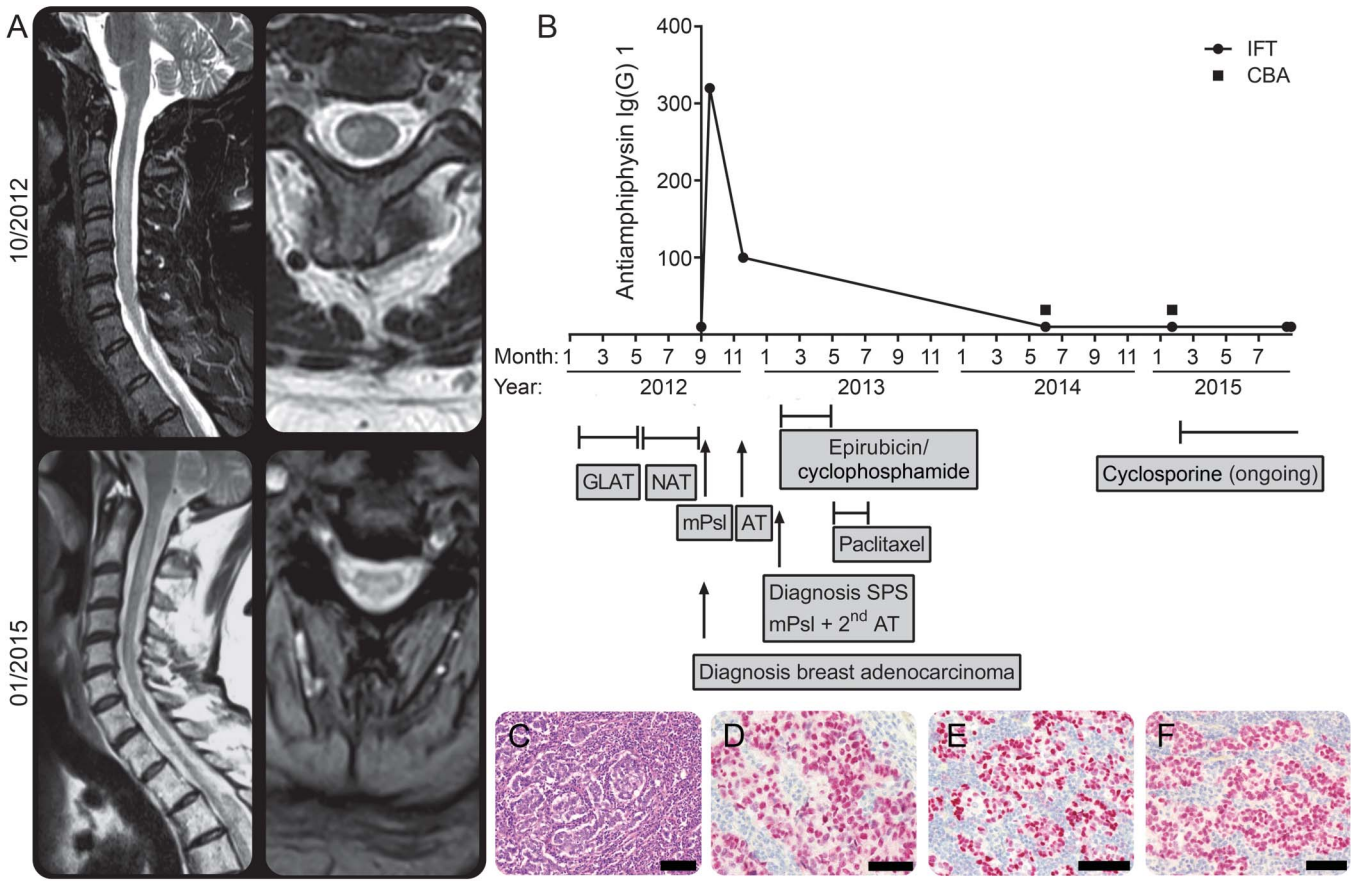
In October 2012, spinal MRI showed a longitudinally extensive TM extending from C2 to C7 (figure, A); the remaining spinal cord and brain imaging were normal. Laboratory workup showed positive anti-amphiphysin 1 immunoglobulin G (IgG) (titer 1:320) (figure, B). A screening for neoplasia including whole-body PET-CT exhibited a suspicious lymph node in the right axilla, which was surgically removed. Histologic workup revealed a poorly differentiated adenocarcinoma (figure, C–F), highly suspicious of invasive breast cancer spread to the locoregional lymph node. Further examinations failed to detect other metastases or a mammary primary tumor.

The diagnosis of paraneoplastic anti-amphiphysin IgG-positive TM was made and corticosteroids (500 mg IV/3 d) were given, leading to transient improvement of neurologic symptoms. Subsequently, the patient had deterioration of paraparesis and received 6 sessions of combined plasma exchange (PLEX) and immunoadsorption (IA), again with only transient improvement. In January 2013, she developed painful muscle cramps of the arms and generalized muscle rigidity with cervical involvement, and was bedridden. Based on clinical symptoms, SPS was diagnosed and the patient was treated with corticosteroids (500 mg IV/3 d), followed by PLEX/IA (5 sessions). Antispastic medication with baclofen and diazepam was started. Although further imaging studies failed to show a primary tumor, our interdisciplinary tumor board decided to initiate adjuvant chemotherapy with epirubicin and cyclophosphamide (4 cycles), followed by paclitaxel, assuming occult hormone receptor–positive breast cancer. In the following months, symptoms gradually improved, and after rehabilitation the patient was able to walk some steps. Immunosuppressive therapy with cyclosporine was initiated. In January 2015, MRI showed marked atrophy of the cervical spinal cord. Until last follow-up (March 2016), the patient has remained in complete remission, titers of anti-amphiphysin IgG had declined to 1:10, and the patient was able to walk approximately 30 meters with a wheeled walker.

Discussion. A paraneoplastic origin of TM is rare and might be preceded by episodes typical for demyelinating diseases. Sometimes, only therapeutic failure triggers diagnostic reevaluation. In our patient, MS drugs were inefficacious before paraneoplastic etiology of TM and SPS was established. Notably, natalizumab therapy, which blocks lymphocyte migration to the CNS, failed to prevent further deterioration of disease.

Paraneoplastic neurologic syndromes require tumor therapy;[3] in our case, removal of a lymph node

Figure Clinical and diagnostic features of a 44-year-old woman with amphiphysin-positive paraneoplastic myelitis and stiff-person syndrome (SPS)



(A) MRI performed in October 2012 shows a longitudinally extensive transverse myelitis extending from C2 to C7 (sagittal STIR and axial T2-weighted on the level of C2/3). Follow-up MRI performed in January 2015 reveals progressive atrophy of the cervical spinal cord (sagittal and axial T2-weighted). (B) Anti-amphiphysin 1 immunoglobulin (Ig) G titers as 1:x and therapies performed. At 2 time points, data of a cell-based assay (CBA) were available. (C–F) Histology of an axillar lymph node metastasis shows a typical expression profile for a poorly differentiated breast adenocarcinoma. Scale bar = 100 μM. (C) Hematoxylin & eosin. (D) Estrogen receptor. (E) Progesterone receptor. (F) GATA3. AT = apheresis therapy; GLAT = glatiramer acetate; IFT = immunofluorescence test; mPsl = methylprednisolone; NAT = natalizumab.

metastasis, chemotherapy, and immunotherapy. Apart from steroids and apheresis therapies, immunosuppressants are used. We applied cyclosporine, since calcineurin inhibitors were suggested to be useful in paraneoplastic neurologic syndromes associated with intracellular antigens.[4]

To our knowledge, this is the second case of anti-amphiphysin IgG-associated paraneoplastic TM and SPS. Chamard et al.[5] reported a 65-year-old woman with breast cancer who presented with stiffness and difficulty in walking. Diagnostic workup revealed SPS, TM, and positive anti-amphiphysin antibodies. The authors postulated that anti-amphiphysin antibodies could target epitopes expressed in the spinal cord, leading to 2 different clinical presentations. Recently, it was suggested that also cytotoxic CD8+ T cells are involved in the pathology of SPS.[6] Histologically, the internalization of anti-amphiphysin IgG into neurons was demonstrated using a murine model of SPS.[7]

This case illustrates that hormone receptor–positive adenocarcinoma detected in a lymph node can lead to a paraneoplastic syndrome with devastating neurologic deterioration; therefore, in patients with myelitis not responding to anti-inflammatory treatment, further oncologic workup should be considered.

From St. Josef-Hospital (S.F., C.L., A.R.-S., R.G., I.K.) and Institute of Pathology (A.T.), Ruhr-University Bochum, Germany.

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Correspondence to Prof. Kleiter: ingo.kleiter@rub.de

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