Clinical Reasoning: A 49-Year-Old Woman With Progressive Numbness and Gait Instability

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**Section 1**

A 49-year-old Caucasian woman, with no significant past medical history presented to an external neurology clinic with progressive hand and foot paresthesia and gait instability for over 6 months. Initially, she reported tingling and shooting electrical-type sensations involving her feet. Within several weeks of the onset of paresthesia, she noted a burning pain sensation involving the left hand. Sensory symptoms continued to worsen and she felt pressure like sensation around the neck and scalp region. This was shortly followed by right hand numbness and loss of dexterity. Over the next month, she developed progressive gait imbalance and transitioned to a cane for ambulation.

On examination, she had reduced sensation to pin prick, light touch, and temperature involving bilateral upper and lower extremities distally. She had asymmetrically reduced sensation to vibration and proprioception in her feet more prominently on the left. She also had pseudoathetosis and asymmetric sensory ataxia on finger nose testing with her eyes closed without appendicular ataxia when testing finger-to-nose or heel-to-shin with open eyes. Romberg sign was positive. She had a wide based gait and was unable to ambulate without support. Deep tendon reflexes in the bilateral lower extremities were absent. Strength and tone were normal in all extremities and cranial nerve examination was unremarkable.

Q1. What is the best localization of her deficit?
Q2. What is the differential diagnosis for a patient with progressive asymmetric sensory loss and ataxia?

Section 2

The patient’s sensory impairment with prominent sensory ataxia, absence of weakness, and depressed reflexes suggest a peripheral nerve localization, involving the large (proprioception and vibration) and small (pain and temperature) sensory fiber. The asymmetry and non-length dependent upper and lower extremity involvement further suggests involvement of the dorsal root ganglia, a sensory ganglionopathy/neuronopathy. Considering the localization and subacute onset, the differential diagnosis includes vitamin B6 toxicity, drug toxicity with platinum-based chemotherapy, neurological manifestations of systemic autoimmune diseases (Sjogren’s syndrome, mixed connective tissue disease, rheumatoid arthritis), paraneoplastic neurological syndromes, and infectious etiologies like human immunodeficiency virus (HIV) or varicella-zoster virus, and idiopathic sensory ganglionopathy.¹ ²

Pertinent laboratory testing to evaluate the etiology of sensory neuronopathy initially performed at external neurology clinic included unremarkable vitamin B6, anti-nuclear antibody (ANA), anti-Ro/SSA and anti-La/SSB antibodies, and HIV serology. Electrodiagnostic testing demonstrated asymmetric, non-length dependent low amplitude sensory nerve action potentials supportive of a sensory ganglionopathy, contrary to symmetric and length dependent sensory action potential amplitude changes observed in sensory axonal neuropathy. CSF evaluation showed protein 48mg/dl, total nucleated cells 1 cell/mcL, glucose 57 mg/dl, normal IgG index, and absence of supernumerary CSF oligoclonal bands. MRI brain and cervical, thoracic, and
lumbar spine with contrast were normal. A CT chest was performed to investigate for hilar adenopathy or occult malignancy and showed presence of enlarged mediastinal lymph nodes. An endobronchial ultrasound guided fine-needle aspiration biopsy (FNA-EBUS) was performed revealing non-necrotizing granulomas (Figure 1A, B).

Q3. What is the most likely diagnosis?

Q4. Is the patient’s neurological presentation consistent with histopathological findings?

Section 3

A sensory neuronopathy (ganglionopathy) secondary to neurosarcoidosis was presumed based on the patient’s neurological presentation and evidence of non-necrotizing granulomas on lymph node FNA-EBUS. She was started on oral prednisone (40mg daily), which was tapered over 6 weeks without clinical improvement.

She subsequently had a focal onset seizure with secondary generalization. An MRI brain obtained showed T2 hyperintensity of the left medial temporal region suggestive of post-ictal change but routine EEG did not demonstrate epileptiform abnormalities or slowing. She was initially started on levetiracetam (500mg twice daily) but due to adverse effects (increased agitation) was transitioned to lacosamide (200mg twice daily). A four day course of IV methylprednisolone 500mg daily was also initiated followed by oral prednisone 80 mg daily. As she developed neuropsychiatric side effects on oral prednisone, it was tapered off. She was started on 7.5mg once weekly methotrexate and infliximab (5mg/kg IV at 0, 2, and 6 weeks, followed by 5mg/kg every 8 weeks thereafter).
Soon after, she developed bilateral sensorineural hearing loss, initially right sided hearing impairment followed by involvement of the left side. She also developed facial numbness, diplopia, and dysarthria. Her gait instability continued to deteriorate, eventually requiring a wheelchair for safety.

Q5. What additional investigations would you pursue at this stage?

Section 4

Due to new, progressive, multi-focal neuroaxis deterioration with seizure and brainstem involvement suggestive of encephalitis, the patient was referred to a tertiary center for further management. Comprehensive history and laboratory investigations were performed including a paraneoplastic panel. The patient was positive for amphiphysin autoantibody in serum and CSF by tissue-based indirect immunofluorescence assay (serum titer 1:7680, CSF titer 1:256) and commercial EUROLINE immunodot (Euroimmun).

Amphiphysin autoantibodies are associated with breast cancer and lung cancer. Thus, to evaluate for occult malignancy, mammography and a Positron Emission Tomography - Computed Tomography (PET CT) scan were performed. Mammography revealed scattered densities in the breast but no masses. On PET-CT, several enlarged hypermetabolic right axillary lymph nodes were detected. An ultrasound-guided core needle biopsy of a right axillary lymph node was performed with pathology confirmation of metastatic invasive ductal carcinoma.

Q6. What is the diagnosis?

Q7. What is the most appropriate treatment strategy?
The patient was diagnosed with a paraneoplastic sensory neuronopathy and encephalitis consistent with the diagnosis of paraneoplastic encephalomyelitis, a multi-focal neurological disorder considered a classical paraneoplastic neurological syndrome. Her paraneoplastic encephalomyelitis was due to amphiphysin autoantibodies, in association with metastatic invasive ductal breast carcinoma. She underwent five sessions of plasmapheresis and five days of 1gram intravenous methylprednisolone, which were well tolerated. Infliximab and methotrexate were discontinued. She underwent surgical removal of the axillary lymph nodes, with 15 of 18 resected lymph nodes were positive for metastatic invasive ductal carcinoma. Following initial immunotherapy and cancer resection, she reported significant improvement in neuropathic pain, numbness, hand dexterity, coordination and gait. She transitioned from a wheelchair to a walker for ambulation. To prevent cancer recurrence, intravenous adriamycin and cyclophosphamide (4 cycles) followed by weekly paclitaxel has been planned.

**Discussion:**

Amphiphysin autoantibodies were first identified in patients with paraneoplastic stiff-person syndrome. Since the initial description, its phenotypic associations have broadened to include peripheral neuropathy, particularly polyradiculoneuropathy or sensory neuronopathy. The majority of the amphiphysin neuropathy cases have been reported to have co-existing central nervous system involvements (57%). Breast adenocarcinoma and small cell lung cancer are the most commonly reported malignancies among amphiphysin IgG seropositive patients. Our amphiphysin IgG seropositive patient shared many of the described associations including sensory neuronopathy at disease onset, progressive course with CNS involvement and new diagnosis of breast adenocarcinoma supporting the final paraneoplastic diagnosis.
Granulomatous inflammation, or a sarcoidosis-like reaction, has been reported among various malignancies, including breast cancer. This is hypothesized to be due to the host's anti-tumor immune response, that may limit tumor growth or metastasis. Not surprisingly, sarcoidosis-like reactions have also been demonstrated after administration of immune checkpoint inhibitors.

Paraneoplastic autoimmunity is often associated with tumors that can incite a strong host immune response. An immune response directed at the tumor and neural antigens may result in more favorable oncologic responses in paraneoplastic neurological syndromes. Regressed or “burnt out” germ cell tumors among patients with paraneoplastic rhombencephalitis may be another example of a strong host anti-tumor response. Immunogenic tumors like breast cancer may similarly develop sarcoidosis-like reactions and such findings among patients presenting subacute progressive neurological syndrome should prompt evaluation for paraneoplastic disease.

This clinical vignette highlights that all patients presenting with subacute, non-length dependent and asymmetric sensory complaints should be carefully evaluated by comprehensive electrodiagnostic studies. Among patients presenting with sensory neuronopathy paraneoplastic neurological syndrome should be a part of differential diagnosis and onconeural antibody evaluation should be considered. Common autoantibodies associated with sensory neuronopathy presentation include anti-neuronal nuclear antibody type-1 (ANNA1 or anti-Hu) and collapsin response-mediator protein 5 (CRMP5 or anti-CV2), and less often amphiphysin or Purkinje cell cytoplasmic antibody type-2 (PCA2). Additionally, progressive neurological deterioration after administration of tumor necrosis factor-alpha inhibitors in patients with presumed neurosarcoidosis should lead to consideration of alternative autoimmune etiologies. Finally, sensory neuronopathy with multifocal neurological axis-involvement is uncommon for
neurosarcoidosis. \textsuperscript{13} Granulomatous inflammation can be seen in paraneoplastic diseases due to potent anti-tumor immune responses. For such atypical presentations onconeural antibody testing should be considered.
Figure 1 (A-B) Histopathology of the biopsied lymph nodes.

Non-necrotizing microgranuloma (arrow shows cohesive aggregate of spindled and epithelioid macrophages) detected on fine needle aspiration of mediastinal lymph node and direct smear: modified giemsa (differential quick), 200X (A), hematoxylin and eosin 400X (B).
### Appendix 1: Authors

<table>
<thead>
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References

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