Anti-neuronal Nuclear Autoantibody Type 1 (Anti-Hu) Paraneoplastic Neurologic Syndrome Causing Jaw Dystonia

Joseph Conway MD[1], Katherine Havard MD[1], Emily F. Maly MD[1], James Liao MD[2], Amy Kunchok MD PhD[3], Payal Soni MD[2], Albert Aboseif DO[1], Justin R. Abbatemarco MD[3]

[1] Department of Neurology, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA
[2] Center for Neurologic Restoration, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA
[3] Mellen Center for Multiple Sclerosis Treatment and Research, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA

ABSTRACT

Anti-neuronal nuclear autoantibody type 1 (ANNA-1), or anti-Hu, paraneoplastic neurologic syndrome (PNS) classically manifests with sensory neuronopathy and encephalomyelitis. We describe a rare case of anti-ANNA-1 PNS presenting with marked jaw dystonia and cognitive impairment. The patient's symptoms complicated the evaluation for an underlying malignancy and severely impacted her functional status due to malnutrition and increased disability. Symptomatic management focused on reducing the severity of jaw dystonia, which improved her overall function and allowed for treatment of her underlying malignancy.

Introduction

Anti-neuronal nuclear autoantibody type 1 (ANNA-1), or anti-Hu neurologic syndrome, classically presents with encephalomyelitis, frequently with concomitant sensory neuronopathy in the setting of small cell lung cancer (Graus et al., 1985). We present an atypical case of a woman with jaw dystonia who tested positive for ANNA-1 antibodies. While trismus and oromandibular dystonia have been described with other autoimmune syndromes including ANNA-2/anti-Ri and anti-Ma2 (Tisavipat et al., 2023; Dalmau et al., 2004), ANNA-1 is rarely associated with jaw dystonia (Malek and Damian, 2018). This report is intended to expand our understanding of the phenotypic spectrum of ANNA-1 PNS and the potential complications involved in the management thereof.

Case Report

A 62-year-old woman with history of chronic obstructive pulmonary disease and a 20 pack-year smoking history presented with one year of progressive incoordination, diplopia, difficulty opening her jaw, and 40 pounds weight loss that led to admission for failure to thrive. She also reported four weeks of numbness starting in her left hand that progressed to involve her entire left arm. She had no other constitutional symptoms of night sweats, lymphadenopathy, or fevers. There was no history of cognitive decline, personality changes, or episodes concerning for seizures. On general examination she was cachectic, without lymphadenopathy or hepatosplenomegaly. There was no medication or substance use contributing to her jaw dystonia. Her neurologic exam revealed jaw closing dystonia (Figure 1, photograph taken after obtaining written consent from the patient), *geste antagoniste* (i.e., speech facilitation when the patient touched her chin), bilateral upper extremity ataxia, diminished light touch and proprioception in a length-dependent pattern involving all four extremities, and a conjugate left gaze palsy. Deep tendon reflexes were normal and symmetric. The Scale for the Assessment and Rating of Ataxia (SARA) quantified her degree of ataxia as 7/40. Her Montreal Cognitive Assessment (MoCA) score was 23/30, consistent with mild cognitive impairment.

Figure 1. Photograph of our patient with anti-ANNA-1 paraneoplastic syndrome attempting to open her mouth as wide as possible, with limitation reflective of her jaw dystonia.

Due to the patient's smoking history, significant weight loss, and the sub-acute onset of her neurologic symptoms, a paraneoplastic syndrome was suspected. Workup commenced with routine blood work including Complete Blood Count (CBC) and Complete Metabolic Panel (CMP) which showed no significant findings. Nutritional labs showed normal levels of copper, zinc, vitamin D, thiamine, pyridoxine, folate, and cyanocobalamin. Contrasted brain MRI showed no acute pathology (Figure 2). On electromyogra-

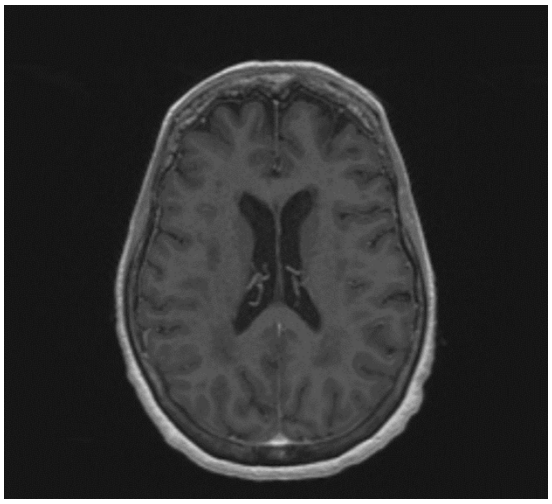

Figure 2. T1 post-contrast MRI Brain without abnormal findings or pathology.

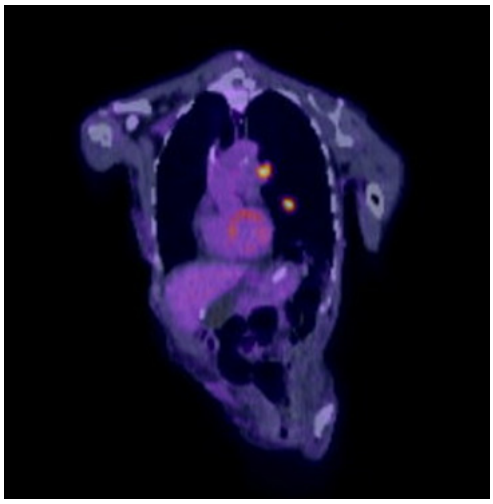

Figure 3. Whole Body Pet demonstrating FDG uptake in 2 lung nodules.

phy, sensory and motor nerve conduction studies were normal. Needle electrode examination of the upper and lower limbs, paraspinal muscles, orbicularis oris muscle and tongue were normal. Needle exam of the masseter muscle revealed a severe and persistent involuntary contraction, as can be seen in the setting of a dystonic contraction. Serology testing identified a positive serum ANNA-1 IgG with a titer of 1:3840 (Mayo Clinic Laboratories, MN USA). Her CSF studies showed normal protein and cell count and no CSF-specific oligoclonal bands (OCB), but did show a high immunoglobulin G (IgG) index of 0.77 mg/dL (reference range: 0.00-0.61). CSF was positive for ANNA-1 IgG at a titer of 1:64. ANNA-2/anti-Ri antibody. All other neural autoantibodies (Mayo Clinic Laboratories, MN USA) were negative in both serum and CSF. CT Chest revealed a left lower lobe lung nodule, which demonstrated increased fluorodeoxyglucose (FDG) uptake on a PET CT scan (Figure 3). A bronchoscopic fine-needle aspiration guided by endobronchial ultrasound was needed to confirm the diagnosis of a suspected pulmonary malignancy. This procedure was delayed due to her marked jaw dystonia. She required increasing doses of baclofen, gabapentin, clonazepam, and trihexyphenidyl, followed by botulinum toxin injections to relieve her dystonia before successfully undergoing the procedure. The biopsy pathology was consistent with small cell lung carcinoma. Given a high-risk neurologic phenotype (e.g., sensory neuronopathy), positivity of a high-risk antibody (anti-ANNA1), and identification of the most commonly associated tumor with this autoantibody, PNS was determined to be the definite diagnosis (Graus et al., 2021).

In addition to symptomatic management, she was treated with five days of IV methylprednisolone 1000 mg per day, and five cycles of plasma exchange (PLEX). Following biopsy results, her cancer was determined to be Stage 2B (T1cN1M0) SCLC. She initiated inpatient chemotherapy with cisplatin and etoposide with plans for radiation therapy with subsequent cycles. Unfortunately, her first cycle of chemotherapy was truncated due to bacteremia for which she was treated with IV antibiotics. Her jaw stiffness and pain improved with treatment, and upon discharge eight days later she was able to tolerate a full liquid diet and was trialing mechanical-soft solid foods. After discharge, the patient elected to proceed with care at a different facility.

Discussion

Anti-ANNA-1 PNS most often presents with symptoms of encephalomyelitis, but other clinical manifestations can include sensory neuronopathy, limbic encephalitis, chronic gastrointestinal pseudo-obstruction, brainstem syndromes, dysautonomia, and cerebellar ataxia (Graus et al., 2001). ANNA-1 IgG is associated with malignancy in about 85% of cases, with small cell carcinoma identified as the tumor type in around 55% of this subpopulation (Graus et al., 2001). Furthermore, the presence of a tumor at the time of PNS diagnosis is associated with a higher predicted mortality rate (Smitt et al., 2002). Our patient developed prominent sensory neuropathy followed by progressive sensory ataxia and was found to have small cell lung carcinoma, consistent with previous reports of ANNA-1 PNS. However, her prominent jaw dystonia was unusual as this has not been widely reported in association with ANNA-1.

The differential diagnosis for trismus is broad and etiologies include brainstem stroke, meningitis, tetanus, toxic exposures, and functional movement disorder (Malek and Damian, 2018). Paraneoplastic brainstem encephalitis caused by ANNA-2/anti-Ri or anti-Ma2 have been associated with jaw dystonia (Tisavipat et al., 2023; Dalmau et al., 2004). Our patient and that described by Malek and Damian (2018) are the only reports of jaw dystonia associated with ANNA-1 IgG we could find in our review of the relevant literature. Our two patients shared several interesting similarities, including the clinical finding of horizon-

tal conjugate gaze palsy. Together, our reports indicate that onco-neuronal antibodies, including ANNA-1, should be considered when a PNS is suspected in relation to subacute development of jaw dystonia.

Patients with ANNA-1 PNS may have limited benefit from immunosuppressive therapies and prognosis often depends on patient disability, performance status, and severity of disease (Graus et al., 2001). A single-center Dutch study found that anti-tumor therapy had a higher but statistically insignificant probability of successful maintenance or return of ambulatory function even after adjusting for factors indicating poorer prognosis (e.g., age at onset, level of disability at time of diagnosis) (Sillevis Smitt et al., 2002). Our patient's jaw dystonia limited her ability to receive adequate nutrition resulting in failure to thrive. She experienced significant jaw pain which negatively impacted her quality of life. Despite her relatively young age and lack of comorbidities, her limited ability to receive oral nutrition increased her overall level of disability and likely worsened her overall prognosis.

Conclusion

We report a case of jaw dystonia in the setting of ANNA-1 PNS. Jaw dystonia is an uncommon feature of PNS but has significant implications for morbidity. Although rare among the general population, this case serves as a reminder for practicing neurologists to maintain a broad differential and consider PNS in the diagnostic evaluation when progressive or atypical neurologic symptoms remain unexplained.

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