Subacute Horizontal Diplopia, Jaw Dystonia, and Laryngospasm

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Abstract

Jaw dystonia and laryngospasm in the context of subacute brainstem dysfunction have been described in a small number of diseases, including antineuronal nuclear antibody type 2 (ANNA-2, also known as anti-Ri) paraneoplastic neurologic syndrome. Severe episodes of laryngospasms causing cyanosis are potentially fatal. Jaw dystonia can also cause eating difficulty, resulting in severe weight loss and malnutrition. In this report, we highlight the multidisciplinary management of this syndrome associated with ANNA-2/anti-Ri paraneoplastic neurologic syndrome and discuss its pathogenesis.
Case Presentation

A 61-year-old White woman presented with horizontal binocular diplopia, progressive trismus with jaw pain, and jaw spasms causing tongue biting over 5 weeks. The trismus worsened to the point that she could only eat pureed food and had severe weight loss. She also experienced intermittent pressure headache over the left temporal area, loss of taste, and sometimes metallic taste. Her medical history included depression treated with duloxetine, a left ovarian cyst, a thyroid nodule, and shingles over the left eyelid 2 months earlier. She had never smoked, and her family history was unremarkable. On examination, she had severe horizontal gaze restriction of both eyes with preserved vertical gaze and mild bilateral ptosis but normal pupillary response. Limited mouth opening and intermittent jaw spasms were also observed. The rest of the cranial nerves were intact. She had full motor power and no sensory deficit. Reflexes were decreased in the lower extremities, and plantar response was down-going bilaterally. She had mild left hemiataxia on finger-to-nose testing, dysdiadochokinesia, and heel-to-shin dysmetria.

Brain and spine MRIs, CSF analysis, and extensive blood tests were obtained. An examination of the brain MRI revealed T2-hyperintense lesions in the dorsal pons and medulla with no associated enhancement or restricted diffusion (Figure 1, A and B). The spine MRI was unremarkable. CSF analysis showed no white cells (normal, 0–5/μL) but showed mildly elevated protein, 70 mg/dL (normal, 0–35 mg/dL), and 4 oligoclonal bands that were unmatched with serum (normal range, 0–1). CSF Gram stain, VZV IgG, HSV PCR, VDRL, IgG index, and cytology showed negative results. Blood test showed negative results for ACE, aquaporin-4 (AQP4), and interferon-gamma release assay. She was found to have a low thiamine level, suspected to result from difficulty eating due to jaw-opening dystonia.

Figure 1 Brain MRI of the Patient Before and After Acute Treatment With IV Methylprednisolone

(A and B) Initial brain MRI showing T2-hyperintense lesions in the dorsal pons and medulla. There was no associated enhancement (images not shown). (C and D) The T2-hyperintense lesions disappear after acute treatment with IV methylprednisolone.
Localization and Differential Diagnosis

The patient presented with subacute progressive bilateral horizontal ophthalmoplegia, bilateral ptosis, jaw dystonia and spasms, and dysgeusia, which could localize to the brainstem or cranial nerves. Within the brainstem, bilateral horizontal ophthalmoplegia could localize to the paramedian pontine reticular formation or the abducens nuclei in the dorsal pons, while bilateral ptosis localized to the central caudal nucleus, a midline subnucleus within the oculomotor nuclear complex (Figure 2). Excitation in the brainstem tegmentum could cause jaw dystonia.1 Left hemiataxia suggested involvement of the left cerebellar hemisphere or spinocerebellar tracts. Headache could either be associated with trismus or irritation of pain-sensitive structures, such as the dura, large blood vessels, or the cranial nerves. The combination of bilateral external ophthalmoplegia and headache could either result from direct involvement of the brainstem or be a false localizing sign from increased intracranial pressure. Considering the age at onset and the subacute progression of brainstem syndrome, differential diagnoses are outlined in the Table.2-4

The nonenhancing homogeneous T2-hyperintense lesion in the pons and medulla and inflammatory CSF profile made neurodegenerative causes less likely. The absence of supratentorial abnormalities also made multiple sclerosis, toxic/metabolic, prion, and genetic diseases less likely. The indistinct border of the lesion and absence of enhancement was not typical for tuberculosis, fungal infection, metastatic cancer, or lymphoma, which were often well-circumscribed. Primary brainstem tumor remained a possibility. The patient had no risk factors for an immunocompromised status and no travel history to suggest any specific infection. Among autoimmune and paraneoplastic brainstem encephalitis, jaw dystonia is a rare but characteristic feature of ANNA-2/anti-Ri paraneoplastic neurologic syndrome (PNS).1 Some patients with anti-Ma2 encephalitis can also develop jaw dystonia (Josep Dalmau, personal communication). Moreover, jaw dystonia and laryngospasm may occur with paraneoplastic brainstem encephalitis in the setting of lung cancer but without detectable antibodies (Francesc Graus, personal communication). Isolated brainstem syndromes can occur in AQP4-IgG–positive neuromyelitis optica spectrum disorder and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), which can be diagnosed by the presence of AQP4-IgG or...
MOG-IgG in the serum. On the contrary, serum ACE is insensitive for neurosarcoidosis, and thus, a negative result did not exclude the possibility. Neuro-Behçet disease also has a predilection for the brainstem.

Six weeks after the onset of neurologic symptoms, she noticed a lump in her right breast. Ultrasound and mammogram revealed an infiltrative mass in her right breast and axilla, which was pathologically confirmed to be a stage 2 invasive ductal carcinoma with estrogen receptor positive, progesterone receptor positive, and human epidermal growth factor receptor 2 (HER2) negative results.

Paraneoplastic panel revealed antineuronal nuclear antibody type 2 (ANNA-2, also known as anti-Ri) positivity in the serum (titer 1:7680) and CSF (titer 1:128) by tissue immunofluorescence, and both were confirmed with western blot positivity. She was also found to have a low thiamine level, suspected to result from difficulty eating due to jaw-opening dystonia. Subsequently, she reported a 60- to 90-second episode of cyanosis suspected to be secondary to laryngospasm. There were also episodes of coughing unrelated to oral intake.

**Final Diagnosis and Treatment**

This patient was diagnosed with ANNA-2/anti-Ri antibody–associated paraneoplastic brainstem encephalitis with a stage 2 breast carcinoma. The presence of a high-risk antibody accompanied by classical phenotypes and cancer for ANNA-2/anti-Ri consolidated the definite PNS diagnosis according to the 2021 Updated Diagnostic Criteria for PNS.5

The principles of management of PNS are early treatment of underlying cancer and immunotherapy.6 An oncologist, a general surgeon, and a radiation oncologist were consulted for the treatment of breast cancer. For immunotherapy, she received IV methylprednisolone for 5 days with minimal improvement and continued on 60 mg/d of oral prednisone. Repeated brain MRI showed resolution of lesions (Figure 1, C and D), so prednisone was tapered down to 10 mg/d before surgery. She underwent right mastectomy and axillary lymph node dissection, followed by adjuvant chemotherapy (docetaxel and cyclophosphamide for 4 cycles) and radiation therapy.

Symptomatic management with a multidisciplinary approach should be performed concurrently. A speech therapist was consulted for swallowing evaluation and oral diet modification to accommodate her jaw opening difficulty. Her weight was closely monitored, and thiamine was prescribed to supplement for its deficiency. Antispasticity medication for her jaw-opening dystonia included meloxicam, diazepam, and cyclobenzaprine, which did not provide improvement. Movement disorder specialists recommended botulinum toxin injection to the masseter, temporalis, medial pterygoid, and platysma, which enabled her to open her mouth to the point that she could properly brush her teeth for the first time. The dose of botulinum toxin injection was gradually titrated at each visit. Bacofer and clonazepam also provided some small additional benefits.

PNs associated with antibodies to intracellular antigens, such as ANNA-2/anti-Ri, have a variable prognosis but are generally less favorable than those associated with antibodies to cell surface antigens. Subsequently, she reported deterioration of trismus and a 60- to 90-second episode of cyanosis suspected to be secondary to laryngospasm. There were also episodes of...
coughing unrelated to oral intake. This progression prompted initiation of maintenance immunotherapy, so she was prescribed intravenous immunoglobulin (IVIg) every 3 weeks, before transitioning to rituximab. Cyclophosphamide, already given as a part of chemotherapy for breast cancer, was extended to 6 months. A trial of 5 cycles of plasma exchange was also undertaken.

Despite cancer treatment and immunotherapy, she continued to have 2–3 episodes of laryngospasm lasting 15–20 seconds a day, with occasional cyanosis. She had never lost consciousness or required intubation because of this. A whole-body fluorodeoxyglucose PET (FDG-PET) and CT scan showed no residual breast cancer.

Laryngospasm was the most concerning symptom for this patient that could potentially cause critical hypoxia. She felt that clonazepam helped her laryngospasms, but the mainstay of management is tracheostomy. The neuroimmunology team collaborated with otorhinolaryngologists, and tracheostomy and alternative management options including botulinum toxin injections in the larynx were being considered.

At the last follow-up, she had persistent bilateral horizontal ophthalmoplegia, ataxia, and jaw-opening dystonia with difficulty eating but to a milder degree. Treatment for breast cancer was completed with success, but she continued surveillance imaging as planned. Maintenance immunotherapy was continued with rituximab every 6 months and low-dose oral prednisone.

Discussion

ANNA-2/anti-Ri is a marker of CD8 T-cell–mediated PNS with a strong cancer association.5 Classically, patients present with neurologic syndromes involving the brainstem or cerebellum, such as ataxia, ophthalmoplegia, opsoclonus-myoclonus syndrome, jaw dystonia, and laryngospasm. The stepwise disease progression and variety of presentations can lead to delayed diagnosis. More recently, isolated confusion, syndrome of in-progressation and variety of presentations can lead to delayed diagnosis. A whole-body fluoro-deoxyglucose PET (FDG-PET) and CT scan showed no residual breast cancer.

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Outcomes of PNS with antibodies targeting intracellular neural antigens, such as ANNA-2/anti-Ri, are generally less favorable than those with antibodies against cell surface antigens, possibly due to CD8 T–cell associated cytotoxicity. However, prompt early treatment could potentially limit neuronal loss and stabilize neurologic symptoms, and improvement of ANNA-2/anti-Ri PNS with treatment has been observed in some patients.

Laryngospasm is an uncommon manifestation of brainstem syndromes that has been reported in the context of autoimmune/paraneoplastic, neurodegenerative, viral, and ischemic etiologies.1,13-15 Antibodies reported in association with laryngospasm include ANNA-2/anti-Ri and IgLONs.1,16 In neurodegenerative diseases, laryngospasm has been reported in multiple system atrophy, amyotrophic lateral sclerosis, and progressive supranuclear palsy and could also be an early presentation.14,15,17 The pathophysiology is unclear but could involve either the loss of inhibition of the laryngeal closure reflex or the stimulation of the superior laryngeal nerve.18 Prolonged episodes of laryngospasm could lead to sudden death from asphyxiation; therefore, prophylactic tracheostomy should be discussed.1,16 Caution should be taken in provocative circumstances such as airway manipulation, emergence from general anesthesia, or comorbid gastroesophageal reflux disease.13 Botulinum toxin injection has been explored for the management of spasmodic dysphonia and laryngeal dystonia causing stridor but is not yet standard for laryngospasm.19,20
Symptomatic therapy and comprehensive multidisciplinary care should always accompany PNS treatment. Jaw dystonia could be relieved by botulinum toxin injection and antispasticity medications. Nutritional deficiency from restricted jaw opening, also observed in this patient, is not uncommon.\(^1\) Gastrostomy tube might be required to improve intake in severe cases.

In summary, paraneoplastic etiologies should be considered in the differential diagnosis of subacute brainstem syndromes. The accompanying manifestations can be potentially life-threatening in the setting of laryngospasm. Jaw dystonia can be complicated by malnutrition and severely affect the quality of life. A multidisciplinary team is required for the optimal management in these patients, from treating the culprit cancer to addressing the downstream complications from PNS.

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