Pearls & Oy-sters: Gait Instability, Jaw Dystonia, and Horizontal Diplopia in a Woman With Anti-Ri Antibodies and Breast Cancer

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Abstract

A 40-year-old woman was admitted for 6 months of progressive gait disturbance, lower limb–predominant weakness, stiffness, falls, jaw dystonia, horizontal diplopia, and weight loss. Neurologic examination revealed horizontal gaze paresis, limited jaw opening with palpable masseter hypertrophy, and spastic paraparesis with sustained clonus and upgoing plantar responses. MRI revealed T2-hyperintense signal abnormalities in the dorsal pons, medulla, and upper cervical cord central gray matter extending to C3, without gadolinium enhancement. CSF showed mildly elevated protein and immunoglobulin (IgG) index with CSF-specific oligoclonal bands. Neural autoantibody testing was positive for anti-Ri in CSF and serum by mouse brain indirect immunofluorescence and immunoblot. Testing for aquaporin-4 (AQP4)-IgG and myelin oligodendrocyte glycoprotein (MOG)-IgG by cell-based assay was negative. The patient received methylprednisolone 1 g for 5 days and IV immunoglobulin 2 g/kg over 2 days with prednisone taper and botulinum toxin injections for jaw dystonia. PET-CT revealed an enlarged left axillary lymph node with high FDG uptake. Left axillary lymph node biopsy confirmed high-grade, locally invasive breast adenocarcinoma. Neurologic stabilization was documented at 2-week follow-up after hospital discharge before modified radical mastectomy. Our case demonstrates a clinical triad highly suggestive of anti–Ri-associated paraneoplastic neurologic syndrome (Ri-PNS): gait instability, jaw dystonia, and horizontal gaze paresis. The more slowly progressive course and poor response to immunotherapy help distinguish it from AQP4-IgG–seropositive neuromyelitis optica spectrum disorder (NMOSD) and MOG-IgG–associated disease (MOGAD) that share similar radiographic features. Early diagnosis, prompt immunotherapy, and cancer treatment are paramount for disease stabilization.

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Pearls

- The triad of progressive gait instability, jaw dystonia, and horizontal diplopia is highly suggestive of Ri autoimmunity and coexisting breast or lung cancer.
- Neurologic symptoms often antedate cancer diagnosis or suggest recurrence.

Oy-sters

- Despite overlapping radiologic features, symptom progression over weeks to months favors Ri-PNS over NMOSD and MOGAD where nadir is typically less than 21 days.
- Malnourishment related to jaw dystonia and paroxysmal laryngospasm can contribute to morbidity and mortality.

Case Report

A 40-year-old woman presented with a 6-month history of progressive gait disturbance, lower limb–predominant weakness, stiffness, falls, jaw dystonia, and horizontal diplopia. She initially developed subtle gait instability that progressed to stiffness in her legs and falls. Within 2 months, she started using a cane and by 3 months developed more gait difficulty, lower limb weakness, and cramping and required bilateral assistance to ambulate. She endorsed insomnia sleeping only a few consecutive hours each night.

She developed jaw opening difficulty that progressed over 2 months until she could only use a straw for nourishment and lost 20 kg. Two weeks later, she developed blurry vision that became binocular horizontal diplopia. She was admitted for workup.

Neurologic examination revealed tachycardia up to 135, left eye esotropia, near-absent bilateral horizontal saccades and smooth pursuit, preserved convergence, limited jaw opening with palpable masseter hypertrophy, and lower limb–predominant weakness and spasticity. She had trace 5−/5 shoulder abduction and 4+/5 elbow extension weakness in the upper extremities and 3/5 right hip flexion, 4−/5 left hip flexion, 4−/5 right knee flexion, 4+/5 left knee flexion, 2/5 right dorsiflexion, and 4−/5 left dorsiflexion weakness in the lower extremities. Spasticity was worse in the legs than arms. Sensation was intact to pinprick, temperature, joint proprioception, and vibration. Deep tendon reflexes were diffusely hyperactive (3+ to 4+) with sustained ankle clonus and bilateral Babinski signs. Finger-to-nose testing revealed a subtle action tremor, and her gait was unsteady and spastic requiring bilateral assistance.

MRI revealed high T2-weighted signal in the dorsal pons and medulla (Figure 1 A.a, A.b) and upper cervical cord predominantly involving central gray matter (Figure 1 A.c, A.d), without gadolinium enhancement. CSF showed inflammatory changes including mildly elevated protein (487 mg/L), immunoglobulin (IgG) index (1.94), and CSF-specific oligoclonal bands, otherwise no pleocytosis (4 cells/μL) and normal glucose (4.2 mmol/L).

Neural autoantibody testing was positive for anti-Ri in serum by mouse brain indirect immunofluorescence (IIF) and immunoblot (serum titer >1:7,680 by IIF). Positivity for anti-Ri in CSF by IIF and immunoblot was also demonstrated (tested at 1:2 using IIF; additional dilutions for CSF titer were not performed because of limited sample volume). Testing for aquaporin-4 (AQP4)-IgG and myelin oligodendrocyte glycoprotein (MOG)-IgG in serum by cell-based assay was negative. Vitamin B1 (111 nmol/L), B6 (37 nmol/L), and B12 (900 pmol/L) levels were normal. Additional laboratory studies were negative for acid-fast bacilli, cryptococcus, herpes simplex virus, varicella zoster virus, *Treponema pallidum*, and *Borrelia burgdoferi*.

PET-CT revealed mass-like densities in the left breast without significantly increased FDG uptake (maximum SUV 1.9) most in keeping with benign fibroadenomas, but also an enlarged left axillary lymph node with significantly increased FDG uptake (maximum SUV 6.0) suspicious for malignancy. Left axillary lymph node histopathology confirmed high-grade, locally invasive breast adenocarcinoma that was estrogen receptor positive, progesterone receptor weakly positive, with HER2 gene amplification by fluorescence in situ hybridization (FISH).

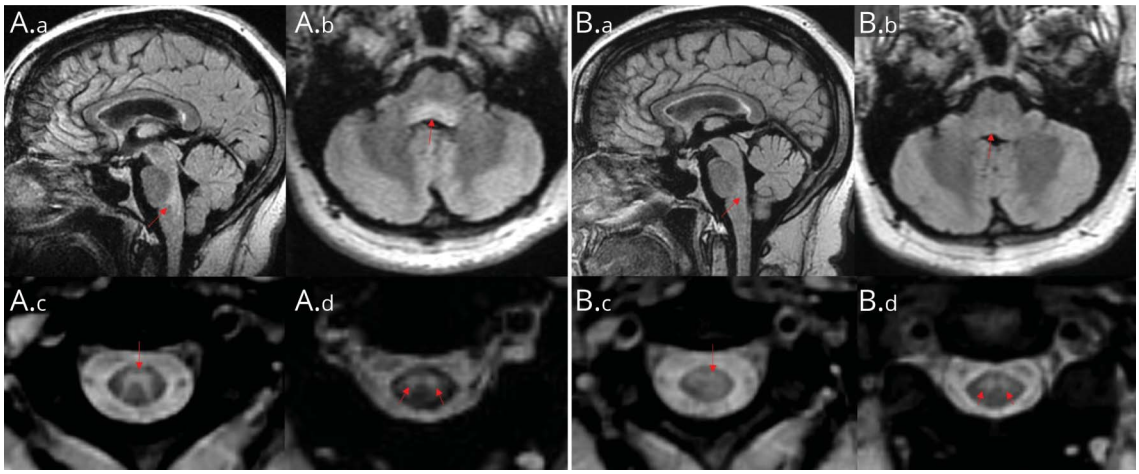
The patient received IV methylprednisolone 1 g for 5 days and IV immunoglobulin 2 g/kg over 2 days, followed by oral prednisone 60 mg with 5-mg taper every 2 weeks. She received botulinum toxin injections (20 units, masseter muscles; 10 units, lateral pterygoids) for jaw dystonia with minimal improvement before discharge.

At the 2-week follow-up, despite subtle improvement in horizontal gaze and lower limb strength, she required a walker and demonstrated persistent horizontal gaze deficits, jaw dystonia, and had lost 5 additional kilograms. Two weeks later, she had a left modified radical mastectomy, complicated by hypercapnic hypoxic respiratory failure, requiring nasotracheal intubation on postoperative day 3 in the setting of ineffective mucus clearance/atelectasis, left lower lobe pneumonia, and right lower lobe segmental pulmonary embolus, treated with apixaban 5 mg twice a day, piperacillin/tazobactam for 7 days, chest physiotherapy, and tracheostomy to secure a long-term airway. Possible paroxysmal laryngospasm cannot be ruled out. Repeat MRI demonstrated improvement in T2-hyperintense signal abnormalities in the brainstem (Figure 1 B.a, B.b) and upper cervical cord (Figure 1 B.c, B.d), despite limited neurologic improvement.

Discussion

We highlight a triad of gait instability, horizontal diplopia, and jaw dystonia that should prompt consideration of testing for

Figure 1 MRI Signal Abnormalities in the Brainstem and Upper Cervical Cord at Initial Presentation (A.a–A.d) and 1 Month Later (B.a–B.d) Following Immunotherapy



T2-hyperintense signal (arrows) in the periependymal dorsal pons and medulla on sagittal (A.a) and axial (A.b) T2/fluid-attenuated inversion recovery (FLAIR) and upper cervical spinal cord central gray matter at C2 (A.c) and C2-C3 (A.d) levels on axial T2-weighted imaging. One month later, T2-hyperintensities were less conspicuous in the brainstem (B.a, B.b) and upper cervical cord at C2 (B.c) and C2-3 (B.d) levels. No enhancement after gadolinium administration on T1-weighted imaging or restricted diffusion on diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) images observed (not shown).

antineuronal nuclear autoantibody type 2 (ANNA-2, also termed anti-Ri). Most patients with anti–Ri-associated paraneoplastic neurologic syndrome (Ri-PNS) are women (66%–78%) presenting with progressive brainstem, cerebellar, and/or spinal cord dysfunction, evolving over weeks to months with an underlying breast or lung cancer found in the large majority (>70%).[1-3]

Clinical manifestations result from CNS injury to neuroanatomic regions expressing neuro-oncologic ventral antigen (NOVA)-1 and NOVA-2, which are RNA-binding proteins that regulate neuronal pre-mRNA expressed in the brainstem and ventral spinal cord.[1,4] Paraneoplastic autoantibodies, ANNA-2/anti-Ri, result from an immune-mediated response against processed onconeural polypeptides presented to T helper cells on MHC Class I. The pathogenesis is primarily driven by Ri-specific cytotoxic $CD8^+$ T cells, which produce cytotoxic factors (e.g., perforin and granzymes), targeting tumor and neurons expressing a common onconeural antigen.[5] Response to immunotherapy in Ri-PNS is often poor, although stabilization is possible with early cancer-directed therapy and immunotherapy.[5]

In a retrospective case series of 28 patients with Ri autoimmunity, the most common initial symptom was gait instability (86%).[6] Horizontal gaze palsy (21%) and jaw dystonia (14%) were also common accompaniments.[6] These findings parallel that of our patient who developed progressive gait disturbance, loss of conjugate horizontal eye movements, and oromandibular dystonia over a span of 6 months. In a prospective clinical follow-up, among 6 patients with jaw dystonia, 5 had severely impaired nutrition and profound weight loss.[1] All 6 patients with jaw dystonia had horizontal gaze paresis, suggesting that both these findings, when found together, may be a useful clinical clue for Ri-PNS. Likewise, in a retrospective French cohort of 36 patients with anti-Ri, the most common pattern at onset was a cerebellar syndrome (39%) presenting with gait instability/ataxia and action tremor, followed by subsequent brainstem involvement causing oculomotor disturbances (17%) and oromandibular or cervical dystonia (17%), similar to that in our patient.[2] Dysautonomia (e.g., cardiac arrythmias), paroxysmal laryngospasm, and central hypoventilation during sleep (Ondine syndrome) may occur in a minority of Ri-PNS cases but can cause significant harm when present, suggesting the need to evaluate for these complications when suspected.[2,7]

In the French cohort, cancer was diagnosed in 33 patients (92%).[2] The neurologic syndrome antedated cancer diagnosis in 24 patients (73%). Misdiagnosis occurred in 8 patients (22%), mistaken for chronic neurodegenerative (e.g., atypical parkinsonism) or neuroinflammatory (e.g., multiple sclerosis) conditions of the CNS, during which time an underlying cancer would go undetected.[2] In our patient, early unprovoked falls, rigidity, ophthalmoparesis, and tremor could have been mistaken for atypical parkinsonism.[5,8] However, progression over weeks to months would suggest the need to investigate for alternative causes.

In terms of differential diagnosis, patients with autoantibodies targeting Hu, Ma2/Ta, and neurochondrin may also present with a progressive rhombencephalitis, with or without evidence of broader neurologic dysfunction.[3] AQP4-IgG–seropositive neuromyelitis optica spectrum disorder (NMOSD) and MOG-IgG–associated disorder (MOGAD) may present with encephalomyelitis and share certain radiographic features to Ri-PNS yet can be distinguished by the temporal profile and

Table 1 Comparison of Ri-PNS and Inflammatory CNS Demyelinating Disorders in Adults

	Ri-PNS	AQP4-IgG NMOSD	MOGAD
Most common neurologic manifestations (in decreasing frequency)	Cerebellar, brainstem, and spinal cord syndromes presenting with gait instability, ataxia, tremor, opsoclonus myoclonus, oculomotor disturbances, oromandibular or cervical dystonia with or without laryngospasm, weight loss, rarely (~5%) cardiac arrythmias, and central hypoventilation during sleep (Ondine syndrome)[1,2,6]	Single/recurrent longitudinally extensive myelitis associated with painful tonic spasms, unilateral/bilateral optic neuritis, area postrema syndrome, brainstem syndromes, diencephalic syndromes (narcolepsy, hyponatremia, and anorexia), and symptomatic cerebral syndrome[9,10]	Recurrent bilateral (~50%), sequential optic neuritis with optic disc edema (86%), acute flaccid myelitis associated with bowel/bladder and sexual dysfunction, brainstem syndromes, acute disseminated encephalomyelitis (ADEM), and unilateral cortical FLAIR-hyperintense Lesions in Anti-MOG-associated Encephalitis with Seizures (FLAMES). Antecedent infectious or inflammatory prodrome common[9,10]
Mode of onset	Progressive/insidious	Subacute (time to nadir 1–21 d)[9]	Subacute (time to nadir 1–21 d)[9]
Course	Progresses over weeks to months, commonly in a gradual and less often (30%) stepwise manner[2]	Relapsing; usually no progression between relapses[10]	Monophasic or relapsing; usually no progression between relapses[10]
Oncologic associations	High-risk autoantibody associated with breast > lung cancer (>70%)[3]	Low risk (<5%)[3]	Low risk (5 case reports)[3]
CSF analysis	Pleocytosis (36%), elevated protein (68%), and oligoclonal bands (80%) are common[2]	Variable. Usually, lymphocytic pleocytosis but can be neutrophilic or eosinophilic; oligoclonal bands in <30%[9]	Usually, lymphocytic; oligoclonal bands in <10%[9]
MRI findings	Mainly T2-weighted and FLAIR hyperintensities with prominent brainstem and upper cervical cord involvement, rarely enhances[2]	T2-weighted and FLAIR hyperintensities often enhancing. Predilection for posterior optic nerve/chiasm; longitudinally extensive (>3 vertebral length, 85%) myelitis with prominent swelling, central (gray and white matter) involvement, ring-like or patchy enhancement; and periependymal lesions adjacent to lateral, third, or fourth ventricles[9,10]	T2-weighted and FLAIR hyperintensities with faint/no enhancement. Predilection for anterior optic nerve; longitudinally extensive (70%) myelitis with central gray matter restriction (H-sign (30%) on axial scans accompanied by a sagittal T2-hyperintense line) and conus involvement. Multifocal acute disseminated encephalomyelitis (ADEM-like) large, fluffy white matter, deep gray matter, and brainstem lesions; and unilateral cortical FLAMES[9]
Treatment approaches	No consensus or randomized controlled trial data, only expert opinion. Cancer-directed treatment when cancer detected, combined with immunotherapies (e.g., IV methylprednisolone 1 g for 3–5 d and then weekly for 5–11 wk; prednisone 60 mg for 2–3 mo, followed by taper 10 mg/mo; IV immunoglobulin (IVIG) 0.4g/kg for 5 d and then 1 dose weekly for 5–11 wk, plasma exchange 1–1.5 times plasma volume for 5–7 sessions; rituximab 1 g paired dose separated by 2 wk; cyclophosphamide 0.6–1 g/m^2 monthly for 6 mo). Sometimes steroid-sparing agents such as mycophenolate mofetil or azathioprine are considered for maintenance therapy[5]	Acute treatment: methylprednisolone 1 g for 5 d, plasma exchange often required, 1–1.5 times plasma volume for 5–7 sessions Maintenance: 3 FDA-approved treatments available including eculizumab (900 mg IV weekly for 4 doses and then 1200 mg every 2 wk); inebilizumab (300 mg IV on days 1 and 15, every 6 mo); and satralizumab (subcutaneous injections 125 mg weeks 0, 2, and 4 and then monthly). Other off-label options include azathioprine, mycophenolate mofetil, and rituximab	Lack of clinical trial evidence Acute treatment: Methylprednisolone 1 g for 5 d alone or in combination with plasma exchange 1–1.5 times plasma volume for 5–7 sessions Maintenance (when relapse): optimal preventive therapy unknown, but options include corticosteroids, azathioprine, mycophenolate mofetil, rituximab, or monthly IVIG
Treatment response	Poor outcomes, although exceptions occur	Often incomplete	Typically good

response to immunotherapy. The neuroimaging appearance of a lesion that involves the dorsal periependymal pons/medulla and extends down into the cervical spinal cord with central predilection may mimic AQP4-IgG NMOSD. Likewise, brainstem and central gray matter–predominant spinal cord involvement without enhancement on MRI may mimic MOGAD, yet a relapse associated with these demyelinating conditions would be expected to reach nadir of neurologic dysfunction within days to weeks (i.e., less than 21 days).[9] In contrast, paraneoplastic neurologic disorders typically progress more slowly over weeks to months,[9] often with a poor response to immunotherapy.[5] These disorders are summarized and compared in Table 1.

The clinical spectrum and oncologic accompaniments of Ri autoimmunity are being elucidated through detailed case reports and case series, but clinician recognition of this rare disease may be lacking. We highlight a triad of symptoms highly suggestive of Ri autoimmunity that should prompt testing for this disease in the appropriate clinical context. This

may facilitate early diagnosis and management of neurologic autoimmunity but also cancer-directed therapy. Although evidence is limited, early immunotherapy and cancer treatment are likely paramount for preventing irreversible CNS injury. Furthermore, early detection of known complications, such as malnourishment from jaw dystonia and paroxysmal laryngospasm, may help mitigate elements of preventable morbidity and mortality associated with anti-Ri.

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