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ENCEPHALOMYELONEUROPATHY WITH CRMP-5 ANTIBODIES IN A PATIENT WITH A PRIMARY MEDIASTINAL SERINOMA

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Case report. A 23-year-old nonsmoking man presented with difficulty walking, numbness, and weakness progressing over several months. By the time of presentation, the patient was not ambulatory. He was afebrile with normal vital signs and general examination. Neurologic examination demonstrated normal vision, mildly decreased strength, and severely diminished sensation to vibration and proprioception in both lower extremities. His temperature and pinprick sensation were mildly diminished in both legs and arms. Reflexes were diffusely diminished but not absent. He exhibited significant dysmetria in both upper and lower extremities. No tremor or other abnormal movements were noted.

MRI of the spinal cord demonstrated increased T2 signal extending from the craniocervical junction to the conus medullaris with gadolinium enhancement (figure, A–D). MRI of the brain demonstrated a heterogeneous region of contrast enhancement in the cerebellum (figure, E–F). CSF analysis showed a nucleated cell count of 187 (87% lymphocytes), no red blood cells, glucose 75 mg/dL, and protein elevated to 165 mg/dL. Oligoclonal bands were elevated at 2 (normal 0–1), albumin index was 24.2 (normal 0–9), and IgG index was 0.71 (normal 0.28–0.66). (Additional laboratory values are presented in the supplemental appendix at Neurology.org/nn.) Approximately 2 months prior to presentation, the patient underwent a nerve conduction study at another facility, which demonstrated a demyelinating polyneuropathy. Extensive rheumatologic and infectious workup was negative. Aquaporin-4 antibody was negative in serum and CSF. Serum paraneoplastic studies demonstrated a positive IgG antibody (titer 1:30,720) to collapsing response-mediator protein 5 (CRMP-5). While awaiting these results, the patient received steroids and plasma exchange. CT of the chest revealed a 3.4-cm anterior mediastinal soft tissue mass, with biopsy and pathology results consistent with seminoma (figure, G–H). There was no evidence of testicular neoplasm on ultrasound.

The patient demonstrated some improvement in strength and sensation after steroids and plasmapheresis.

He received 4 cycles of etoposide and cisplatin and continued to improve with treatment of the primary seminoma. Repeat imaging demonstrated resolution of the inflammation seen previously in the cerebellum and spinal cord, and repeat serum studies were negative for the CRMP-5 antibody. Follow-up PET did not reveal any fludeoxyglucose uptake in the mediastinum. Nerve conduction studies performed approximately 6 months later revealed a sensory ganglionopathy with absent sensory responses. He continues to have some difficulty with ambulation related primarily to severe proprioceptive deficits.

Discussion. Antibodies to CRMP-5 were first described clinically in a series of patients presenting with a wide variety of neurologic symptoms, including (from most to least common) peripheral neuropathy, autonomic neuropathy, cerebellar ataxia, subacute dementia, cranial neuropathy, and neuromuscular junction dysfunction.¹ Subsequent reports have shown an association of CRMP-5 with optic neuritis and retinitis,² chorea,³ and a neuromyelitis optica–like syndrome of transverse myelitis with optic neuritis.⁴ The patient described in this report had a combination of cerebellar ataxia, longitudinally extensive transverse myelitis involving primarily the dorsal columns, and demyelinating polyneuropathy.

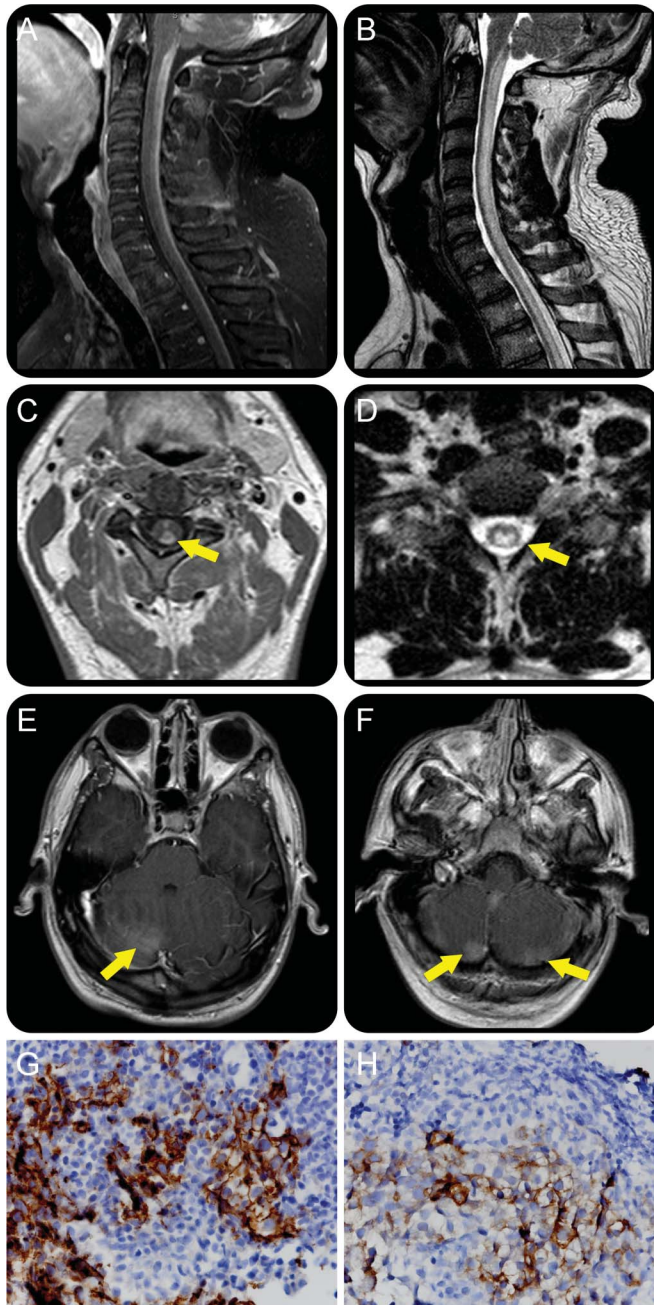
In the reported cases of anti-CRMP-5 paraneoplastic disorders, the primary tumor was most commonly small cell lung cancer (SCLC). However, association with renal cell carcinoma, thymoma, thyroid papillary carcinoma, lymphoma, and prostate adenocarcinoma has also been described. We report the association of anti-CRMP-5 with a seminoma.

Seminomas have been associated rarely with anti-Ma2 antibodies affecting the limbic system, diencephalon, or brainstem.⁵ Primary mediastinal germ cell tumors have been recently reported as being associated with paraneoplastic disorders in 2 cases.^{6,7} The first presented with encephalitis associated with anti-Ma2, whereas the second had encephalitis, sensorimotor polyneuropathy, vasculomyositis, and cerebellar ataxia associated with anti-NMDA and anti-neuronal nuclear autoantibody type 1.

In this case, the patient responded clinically to immunosuppression followed by treatment of the underlying cancer with cisplatin and etoposide, although

Supplemental data
at Neurology.org/nn

Figure MRI demonstrating cerebellar encephalitis, longitudinally extensive transverse myelitis, and pathology of seminoma



(A) Parasagittal T1 postcontrast images of the cervical spine demonstrate homogeneous enhancement of the spinal cord from the craniocervical junction that extends through the midthoracic spine and also several ill-defined mass-like areas of enhancement in both cerebellar hemispheres involving both cortex and white matter. (B) Parasagittal T2 image demonstrating increased signal in these same areas. (C) Axial T1 postcontrast image demonstrating that the enhancement is primarily dorsal. (D) Axial T2 image with increased signal in the dorsal cord. (E, F) Axial T1-weighted postcontrast images demonstrating multifocal areas of patchy enhancement in the cerebellum. (G) Mediastinal soft tissue mass demonstrates positive immunohistochemistry for placental alkaline phosphatase and (H) CD 117. These are characteristic of seminoma.

his recovery was complicated by the chemotherapeutic agents' possible role in neuropathy/ganglionopathy. In cases of subacute onset syndromes of neurologic dysfunction involving multiple components of the nervous system in which initial evaluation for infection and primary autoimmunity does not reveal a cause, paraneoplastic studies should be considered, even in nonsmokers. Chest CT should be considered as first-tier testing for primary neoplasm, as many paraneoplastic syndromes are associated with SCLC.^{1,2,4,5} However, as paraneoplastic syndromes including CRMP-5 become increasingly recognized, it is important to expand the differential diagnosis of tumors associated with paraneoplastic syndromes to include seminomas and other primary neoplasms.

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1. Yu Z, Kryzer TJ, Griesmann GE, et al. CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. *Ann Neurol* 2001;49:146–154.
2. Cross SA, Salomao DR, Parisi JE, et al. Paraneoplastic autoimmune optic neuritis with retinitis defined by CRMP-5-IgG. *Ann Neurol* 2003;54:38–50.
3. Vernino S, Tuite P, Adler CH, et al. Paraneoplastic chorea associated with CRMP-5 neuronal antibody and lung carcinoma. *Ann Neurol* 2002;51:625–630.
4. Jarius S, Wandinger KP, Borowski K, Stoeker W, Wildemann B. Antibodies to CV2/CRMP5 in neuromyelitis-optica-like disease: case report and review of the literature. *Clin Neurol Neurosurg* 2012;114:331–335.
5. Dalmau J, Graus F, Villarejo A, et al. Clinical analysis of anti-Ma2-associated encephalitis. *Brain* 2004;127:1831–1844.
6. Bosemani T, Huisman TA, Poretti A. Anti-Ma2-associated paraneoplastic encephalitis in a male adolescent with mediastinal seminoma. *Pediatr Neurol* 2014;50:433–444.
7. Pohley I, Roesler K, Wittstock M, et al. NMDA-receptor antibody and anti-Hu antibody positive paraneoplastic syndrome associated with a primary mediastinal seminoma. *Acta Neurol Belg* 2014;1–3.

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Encephalomyeloneuropathy with CRMP-5 antibodies in a patient with a primary mediastinal serinoma

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CORRECTION

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In the Clinical/Scientific Note “Encephalomyeloneuropathy with CRMP-5 antibodies in a patient with a primary mediastinal serinoma” by C.W. Hampton et al. (*Neurology® Neuroimmunology & Neuroinflammation* 2015;2:e82), “serinoma” was misspelled in the title. The publisher regrets the error.