LETTER TO THE EDITOR

To the Editor

Anti-Ma2-Associated Encephalitis Secondary to Hodgkin's Lymphoma

Keywords: Hodgkin's lymphoma, Paraneoplastic syndrome, Anti-Ma2 encephalitis, Vertical supranuclear gaze palsy, Anti-thyroperoxidase

The paraneoplastic syndrome (PNS) associated with anti-Ma2 antibodies presents with limbic, diencephalic, and/or brainstem encephalitis.[1] It is commonly reported in association with testicular germ cell tumors in young male patients, with non-small-cell lung cancer (SCLC) being the second most common associated tumor.[1,2] It has also been reported with breast, ovarian, parotid, colonic, esophageal, renal malignancies, melanoma, and non-Hodgkin's lymphoma,[1,2] but never in association with Hodgkin's lymphoma (HL). We report the first case associated with HL in a 60-year-old male presenting with neuropsychiatric symptoms, cataplexy, hypoglycemic episodes, and vertical supranuclear gaze palsy (VSGP).

A 60-year-old man with a 25-year history of well-controlled epilepsy developed subacute impairment in short-term memory and agitation that caused noncompliance with his anticonvulsants, resulting in an increase in his focal seizures, characterized by left- and occasionally right-side clonic movements preceded by alteration in speech and occasional postictal confusion. He developed new episodes of spontaneous sudden loss of tone, resulting in falls without loss of consciousness or difficulty speaking, suggestive of cataplexy. He also developed excessive daytime sleepiness (EDS) and unexplained hypoglycemic episodes, despite normal insulin, C-peptide, and a.m. cortisol. A year and a half later, he presented in the movement disorder clinic with difficulty reading due to an inability to look down. Family history was unavailable as he was adopted. Examination revealed reduced vertical gaze, which improved with oculocephalic maneuver, suggestive of VSGP. "Serpentine" saccades were observed on upgaze. There was mild upper limb ataxia, but no gait ataxia or parkinsonism (Video 1; see Supplementary Materials). His electroencephalogram showed asymmetrical bihemispheric frontotemporal slowing (left > right) without epileptiform discharges. A nonenhanced brain MRI showed mild generalized atrophy without any signal change or midbrain atrophy. Genetic testing for Niemann–Pick C (NPC) was negative. Serum lactate and muscle biopsy were normal. An abdominal CT done as part of a workup for his hypoglycemic episodes revealed a peripancreatic mass, subsequently diagnosed as HL (stage IA) on biopsy. A chest CT did not reveal any lung abnormality. He was treated with adriamycin, bleomycin, vinblastine, and dacarbazine chemotherapy and 22 cycles of radiation therapy, which improved short-term memory, mood, cataplexy, and hypoglycemic episodes, but not VSGP. A follow-up CT of thorax, abdomen, and pelvis showed no evidence of metastasis. A normal whole-body FDG–PET scan excluded other active malignancies. A paraneoplastic screen, including anti-Hu, Yo, Ri, Ma2, CV2, and amphiphysin, returned positive for anti-Ma2 antibodies in the serum; confirmed by immunoblot. For his epilepsy with unremarkable neuroimaging, anti-thyroperoxidase (TPO) was ordered, and found to be markedly elevated (>3000; ref: <34 IU/ml) with normal serum T3, T4, and TSH. Because of the cooccurrence of two known autoantibodies, HLA typing was done, which showed the presence of A2, A11, B39, B51, DR11, DR16, DQ5, DQ7, DR51, and DR52. He was subsequently treated with intravenous immunoglobulin (IVIg) 2 g/kg divided over 3 days, followed by 1 g/kg per month for 6 months with prednisone 20 mg p.o. daily for 6 months, which he tolerated well despite no further improvement in his VSGP.

The clinical presentation of anti-Ma2 PNS results from isolated or combined limbic, diencephalic, and/or brainstem involvement in 90% of patients.[1] While limbic involvement causes confusion, cognitive deterioration, and psychomotor seizures, brainstem dysfunction results in VSGP, diplopia, and dysarthria.[1,2] Diencephalic involvement leads to EDS, cataplexy, and hypnogogic hallucinations.[1,2] In 82% of patients, the PNS precedes tumor diagnosis by 2-36 months, while 18% develop PNS from 1 month to 14 years after tumor detection.[2] The subacute presentation with cataplexy, EDS, and VSGP preceding the diagnosis of HL and stabilization of the neurological syndrome after chemotherapy and radiation therapy for HL confirmed the association in our patient. His brain MRI was unremarkable, which can be seen in 18% of patients with anti-Ma2 encephalitis.[1,2] Cerebrospinal fluid examination was not done in our patient. Hypoglycemia has been reported with HL,[3] but never in association with anti-Ma2 encephalitis. HL is believed to produce a stimulating antibody to the insulin receptor, which has not yet been identified.[3]

More than 90% of patients with brainstem involvement, especially those with additional limbic and diencephalic dysfunction, develop eye movement abnormalities, with VSGP seen in 60% of them.[1] Due to the inability to generate a straight vertical saccade, our patient's eyes moved in a "serpentine" manner, likely related to intact horizontal saccades, adding up to move the eyes vertically. A similar phenomenon has been described as a "round-the-houses" sign in early progressive supranuclear palsy (PSP), where the eyes move in a lateral arc while generating a vertical saccade.[4] In our patient, there was no parkinsonism to suggest PSP, and genetic testing for the NPC that may present with VSGP, ataxia, and cognitive impairment was negative.[5] Patients with anti-Ma2 brainstem encephalitis fare relatively better than others with paraneoplastic brainstem encephalitis, such as those associated with anti-Hu and anti-Ri autoantibodies.[6] Improvement or stabilization of neurological features has been reported in 50-60% of patients with anti-Ma2 PNS after treatment of malignancy along with immunotherapy with steroid, IVIg, plasma exchange, or cyclophosphamide,[1,2] as was seen in our case. Although the paraneoplastic screen of our case did not include anti-Ma1 antibodies, it should be tested in patients with anti-Ma2 PNS, as its presence suggests a more likely association with nontesticular cancers and bears a worse prognosis.[1]

The presence of two clinically independent autoantibodies (anti-Ma2 and anti-TPO) in our patient along with a presumed third antibody causing hypoglycemic episodes suggests a likely predisposition to autoimmunity. Although specific PNS antibodies are associated with specific cancers,[7] no large studies have been conducted to identify HLA genotypes in patients with

https://doi.org/10.1017/cjn.2017.227 Published online by Cambridge University Press

specific cancers developing PNS versus those who do not. A single study found a significantly higher frequency of HLA-DQ2 and HLA-DR3 in patients with SCLC and anti-Hu PNS (n = 53), compared with healthy controls ($n = 2440$).[8] There was a trend toward a higher frequency of HLA-DQ2 in those with SCLC and anti-Hu versus those with SCLC alone ($n = 24$), but this was not statistically significant, likely related to the small size of the SCLC group.[8] No similar HLA studies have been performed in anti-Ma2 PNS patients. Interestingly, association with specific HLA alleles have been reported in patients with autoimmune encephalitis linked to IgLON5[9] and LGI1[10,11] antibodies, independent of malignancy. Larger studies involving patients with autoimmune encephalitis, with and without malignancies, may provide a link to screen for these disorders, leading to early diagnosis and improved clinical outcomes.

We report the first anti-Ma2 PNS case associated with HL and describe serpentine saccades. The presence of at least two separate autoantibodies in our patient (anti-Ma2 and anti-TPO) and probably a stimulating antibody to the insulin receptor associated with HL supports the need for further investigation into HLA genotypes and their relationship to the development of autoantibody-mediated PNS. Our patient's HLA genotypes may form the precedence for future HLA studies in similar cases.

Statement of Authorship

Dr. Rizek worked on study conception and design and on writing of the first draft of the manuscript. Dr. Kumar worked on study conception and design and on writing of the first draft of the manuscript. Dr. Jog worked on review and critiquing. Philippe Rizek and Niraj Kumar contributed equally to this manuscript.

Disclosures

Drs. Rizek and Kumar report no disclosures. Dr. Jog receives speaker and consultant honoraria from Merz Pharmaceuticals, Allergan, and AbbVie. He also receives research grants from CIHR, AMOSO, Allergan, Merz Pharmaceuticals, and Lawson Health Research Institute, and he is part of the AGE-WELL Network of Centers of Excellence of Canada program. From time to time, he serves on advisory boards for Allergan, Boston Scientific, AbbVie, and Merz Pharmaceuticals.

Philippe Rizek
Department of Clinical Neurological Sciences
Western University, London, Ontario, Canada

Niraj Kumar
Department of Clinical Neurological Sciences
Western University, London, Ontario, Canada

Mandar S. Jog
Department of Clinical Neurological Sciences
Western University, London, Ontario, Canada

Correspondence to: Mandar Jog, Department of Clinical Neurological Sciences, London Health Sciences Centre, Western University, 339 Windermere Road, A10-026, London, Ontario, N6A 5A5 Canada. Email: mandar.jog@lhsc.on.ca

Supplementary material

To view the supplementary materials for this article, please visit https://doi.org/10.1017/cjn.2017.227

References

1. Dalmau J, Graus F, Villarejo A, et al. Clinical analysis of anti-Ma2-associated encephalitis. Brain. 2004;127(Pt 8):1831-44.
2. Hoffmann LA, Jarius S, Pellkofer HL, et al. Anti-Ma and anti-Ta associated paraneoplastic neurological syndromes: 22 newly diagnosed patients and review of previous cases. J Neurol Neurosurg Psychiatry. 2008;79(7):767-73.
3. Kulkarni A, Zlabek J, Farnen J, Capla R. Recurrent hypoglycemia and hypothermia in a patient with Hodgkin's disease. Haematologica. 2006;91(Suppl 12):137-8.
4. Quinn N. The "round the houses" sign in progressive supranuclear palsy. Ann Neurol. 1996;40(6):951.
5. Salsano E, Umeh C, Rufa A, Pareyson D, Zee DS. Vertical supranuclear gaze palsy in Niemann–Pick type C disease. Neurol Sci. 2012;33(6):1225-32.
6. Blaes F. Paraneoplastic brain stem encephalitis. Curr Treat Options Neurol. 2013;15(2):201-9.
7. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry. 2004;75(8):1135-40.
8. de Graaf MT, de Beukelaar JW, Haasnoot GW, et al. HLA-DQ2+ individuals are susceptible to Hu–Ab associated paraneoplastic neurological syndromes. J Neuroimmunol. 2010; 226(1–2):147-9.
9. Sabater L, Gaig C, Gelpi E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. Lancet Neurol. 2014;13(6):575-86.
10. Kim TJ, Lee ST, Moon J, et al. Anti-LGI1 Encephalitis is associated with unique HLA subtypes. Ann Neurol. 2017; 81(2):183-92.
11. van Sonderen A, Roelen DL, Stoop JA, et al. Anti-LGI1 encephalitis is strongly associated with HLA-DR7 and HLA-DRB4. Ann Neurol. 2017;81(2):193-8.