

Hodgkin Lymphoma Presenting with Anti-N-methyl-D-aspartate Receptor Encephalitis

Benjamin W. Hoyt, BS

Department of Surgery, Uniformed Services University, 4301 Jones Bridge Road, Bethesda, MD 20814
Phone: 301-502-8019; Email: Benjamin.hoyt@usuhs.edu

Abstract

Anti-N-methyl-D-aspartate Receptor (NMDAR) Encephalitis is a recently characterized autoimmune disorder defined by production of antibodies to NMDAR in the brain. It is thought to be responsible for many cases of previously misdiagnosed and unexplained neuropsychiatric disorders including seizures, acute psychosis, and other encephalitides.

Frequently associated with tumors, anti-NMDAR encephalitis is thought to be a paraneoplastic process. It most commonly occurs with ovarian teratomas, but has also been reported in patients with sex-cord stromal tumors, neuro-endocrine tumors, lung and breast carcinoma, neuroblastoma, and non-ovarian teratomas. To our knowledge, only one case of Hodgkin lymphoma-associated anti-NMDAR encephalitis exists in the literature, in a patient with tumor recurrence after treatment.

This case report details an episode of this paraneoplastic syndrome occurring in a patient with previously undiagnosed Hodgkin lymphoma. Diagnosis of the tumor was delayed due to initial presentation of neuropsychiatric illness. Neurologic prognosis in these patients is significantly improved by identification and early treatment of malignancy when present, and this report emphasizes the importance of maintaining a high index of suspicion for underlying malignancy, including Hodgkin lymphoma, in cases of anti-NMDAR encephalitis.

Keywords

Paraneoplastic Syndrome, Encephalitides, PET-CT, Autoimmune, Lymphoma, NMDAR

Abbreviations

NMDAR: N-methyl-D-aspartate Receptor; MRI: Magnetic Resonance Imaging; FLAIR: Fluid-Attenuated Inversion Recovery; CSF- Cerebrospinal Fluid; PET- Positron Emission Tomography; CT- Computed Tomography

Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a recently characterized autoimmune disorder that has caused many cases of previously misdiagnosed neuropsychiatric disorders [1, 2]. Commonly considered a paraneoplastic condition, to our knowledge, only one other case of anti-NMDAR encephalitis associated with Hodgkin lymphoma exists in the literature, in a patient with tumor recurrence after prior treatment [3]. This report details development of this encephalitis in a patient with first occurrence of Hodgkin lymphoma.

Case presentation

A 25-year-old Caucasian male presented to acute care in November 2011, complaining of insomnia, anorexia, and anxiety. He appeared disheveled but physical examination and basic laboratories were normal, and he was treated conservatively. He presented a few months later with suicidal ideation and paranoia. He was admitted and treated with olanzapine but left against medical advice. He returned a few weeks later and was admitted with myalgias, nausea, and hypotension. He became increasingly agitated and combative, and exhibited intermittent catatonic posturing. He was then transferred to tertiary care.

An MRI was performed and T2 FLAIR sequence demonstrated nonspecific, white-matter lesions in the frontal lobe. CSF analysis revealed elevated WBCs (23 cells/mm³) with positive NMDAR antibodies. CSF contained glucose and protein within normal limits and was negative for oligoclonal bands and viral nucleic acids. He was diagnosed with anti-NMDAR encephalitis. He was then treated with IV immunoglobulin, methylprednisolone, and a single dose of cyclophosphamide; followed by four weekly doses of rituximab. He also underwent testicular ultrasound and head/chest/abdomen/pelvis CT to evaluate for underlying malignancy; these were normal. He responded to therapy and did well for several months.

Within a few weeks after completion of therapy, he began to demonstrate manic symptoms, physical aggression, tremor, and loss of attention and visuospatial recognition. The patient was evaluated by neurology and started on divalproex and quetiapine and his behavior and thought process normalized. By September 2012, the patient began to report cognitive deficits in addition to insomnia, anxiety, headaches, and right-sided paresthesias. He received a whole body PET/CT scan, for concern of undiagnosed malignancy. This revealed increased metabolic activity in the right supraclavicular fossa (6.1SUVm) and cervical lymph nodes (5.37SUVm). Unfortunately, the patient failed to return for follow-up appointment and all further attempts to contact the patient were unsuccessful.

In March 2014, the patient presented with fever (103°F) and a 6-cm right neck mass. Neck CT evaluation showed a 6.4x2.5 cm lymph node conglomerate in the right supraclavicular fossa causing effacement of the internal jugular vein (Figure 1). Repeat PET/CT showed progression of hyper metabolic activity within the previously identified regions. He was referred to otolaryngology for excisional biopsy. Pathologic evaluation revealed effacement of normal lymph node architecture with broad bands of collagen fibrosis, dividing the lymph node into nodules containing Reed-Sternberg cells (Figure 2). The staining pattern, architecture, and findings were consistent with classical Hodgkin lymphoma nodular sclerosis subtype, EBV positive.

The patient was evaluated by hematology/oncology and staged as Ann Arbor stage IIA. He underwent ABVD chemotherapy. In June 2014, prior to starting his third chemotherapy cycle, an interim PET/CT scan indicated complete metabolic response, with Deauville score 2. He completed his final, sixth cycle of ABVD in December 2014 without complication and with no recurrence of psychiatric symptoms. Post-therapy PET/CT scan confirmed continued complete remission. He has had no recurrence of psychiatric, dysautonomic, or other presenting symptoms since this time.

Discussion

Anti-NMDAR encephalitis is an autoimmune disorder defined by production of antibodies against NMDAR in the brain, resulting in a decrease in NMDAR surface density and function [4]. The effect is to produce a disease with five characteristic and typically sequential phases, which include prodromal flu-like symptoms, psychosis, unresponsive state, hyperkinetic and autonomically unstable phase, and finally, recovery [1]. Characterized in 2007 [5], it has been increasingly identified as the cause of many cases of previously misdiagnosed neuropsychiatric disorders [1, 2].

A high index of suspicion for anti-NMDAR encephalitis is needed to distinguish it from other primary and secondary psychoses. Initial presentation may be missed as 70% of cases begin with a virus-like prodrome [1, 6, 7]. Patients may then develop symptoms mimicking other disorders such as seizures, dyskinesias, paresthesias, and autonomic instability [1]. Proper diagnosis can be further complicated in atypical presentations, such as in males, due to the absence of characteristic ovarian neoplasm [8].

Anti-NMDAR encephalitis is considered a paraneoplastic condition due to its frequent association with tumors, particularly ovarian teratomas [5]. Other cases report association with sex-cord stromal tumors, neuro-endocrine tumors [8], lung and breast carcinoma [1, 10], neuroblastoma [11], and non-ovarian teratomas [5]. To our knowledge, only one other case of Hodgkin lymphoma-associated anti-NMDAR encephalitis exists in the literature, in a patient with tumor recurrence after prior treatment [3].

In this case, at the time of diagnosis of anti-NMDAR encephalitis, no masses suspicious for lymphoma or other malignancy were seen on imaging. However this is a relatively common occurrence; the discovery of a neoplasm as far as many years after the onset of encephalitic symptoms is not unusual [12]. The presence of a neoplasm often portends a better outcome as definitive tumor therapy, including incision and/or chemotherapy, results in better neurologic recovery than immunotherapy of the isolated encephalitis [12]. Not surprisingly, the best reported outcomes have resulted from combination of immunotherapy with definitive tumor treatment [9, 13, 14]. However, despite appropriate therapy, resolution of cognitive deficits can be slow, incomplete, or temporary [9].

Patient outcomes in anti-NMDAR encephalitis are improved by early identification and treatment [14, 15], particularly resection, of neoplastic disease when present [1]. This report emphasizes the importance of including anti-NMDAR encephalitis in the differential of psychiatric illness and maintaining persistence in identification of underlying malignancy, which may include lymphoma.

Figures



Figure 1: CT axial image demonstrating 6.4X2.5cm right supraclavicular lymph node mass causing effacement of the right internal jugular and subclavian veins

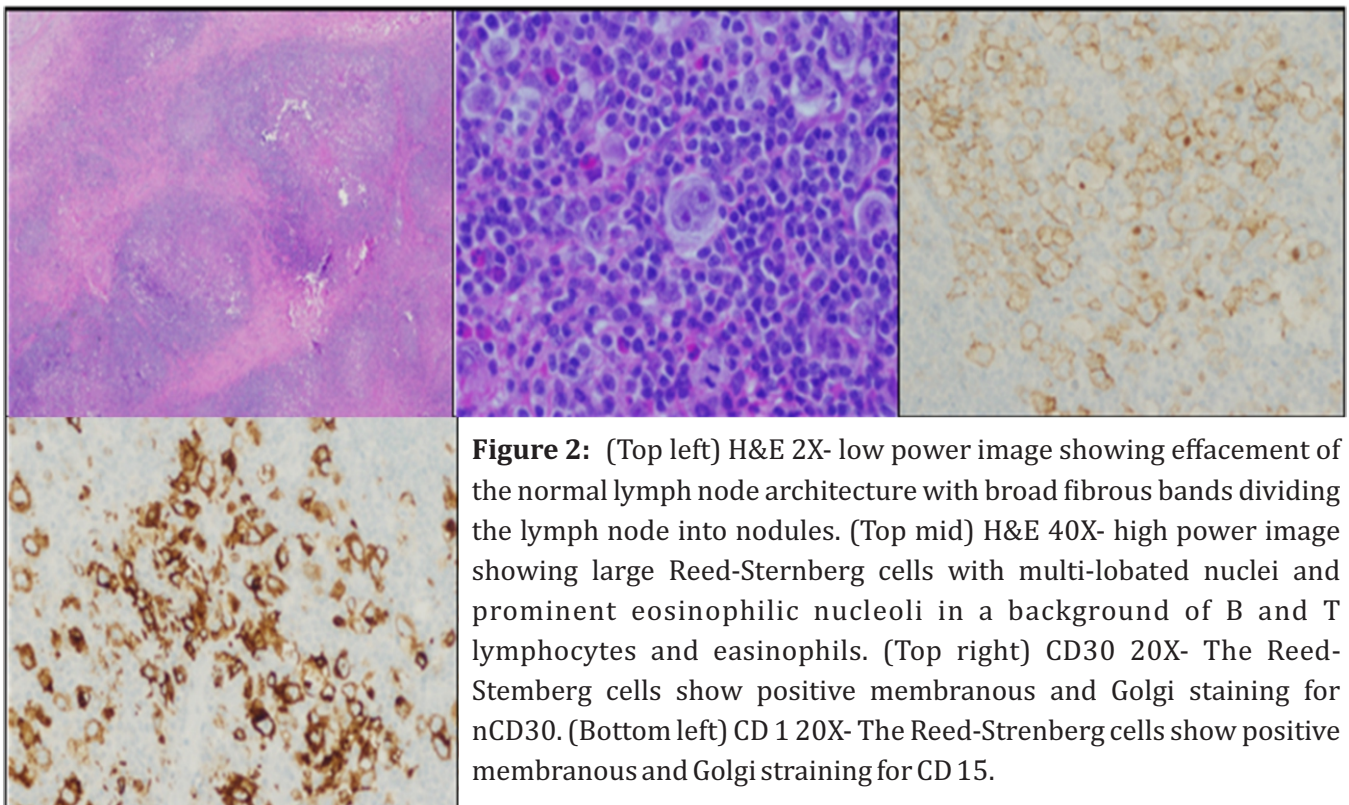


Figure 2: (Top left) H&E 2X- low power image showing effacement of the normal lymph node architecture with broad fibrous bands dividing the lymph node into nodules. (Top mid) H&E 40X- high power image showing large Reed-Sternberg cells with multi-lobated nuclei and prominent eosinophilic nucleoli in a background of B and T lymphocytes and eosinophils. (Top right) CD30 20X- The Reed-Sternberg cells show positive membranous and Golgi staining for nCD30. (Bottom left) CD 15 20X- The Reed-Sternberg cells show positive membranous and Golgi staining for CD 15.

References

1. Dalmau J, Tüzün E, Wu H, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic Anti-N-methyl-D-aspartate Receptor Encephalitis Associated with Ovarian Teratoma. *Ann Neurol*. 2007; 61(1): 25-36.
2. Pruss H, Dalmau J, Harms L, Holtje M, Ahnert-Hilger G, Borowski K, et al. Retrospective Analysis of NMDA Receptor Antibodies in Encephalitis of Unknown Origin. *Neurology*. 2010; 75(19):1735-1739.
3. Zandi MS, Irani SR, Follows G, Moody AM, Molyneux P, Vincent A. Limbic Encephalitis Associated With Antibodies To The NMDA Receptor In Hodgkin Lymphoma. *Neurology*. 2009;73(23):2039-2040.
4. Hughes EG, Peng X, Gleichman AJ, Lai M, Zhou L, Tsou R, et al. Cellular and Synaptic Mechanisms of Anti-NMDA Receptor Encephalitis. *J Neurosci*. 2010; 30(17): 5866-5875.
5. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical Experience and Laboratory Investigations in Patients with Anti-NMDAR Encephalitis. *Lancet Neurol*. 2011;10(1):63-74.
6. Day GS, High SM, Cot B, Tang-Wai DF. Anti-NMDA-Receptor Encephalitis: Case Report and Literature Review of an Under-Recognized Condition. *J Gen Intern Med*. 2011; 26(7): 811-816.
7. Luca N, Daengsuwan T, Dalmau J, Jones K, Deveber G, Kobayashi J, et al. Anti-N-methyl-D-aspartate Receptor Encephalitis: A Newly Recognized Inflammatory Brain Disease in Children. *Arthritis Rheum*. 2011; 63(8): 2516-2522.
8. Gable MS, Gavali S, Radner A, Tilley DH, Lee B, Dynner L, et al. Anti-NMDA Receptor Encephalitis: Report of Ten Cases and Comparison with Viral Encephalitis. *Eur J Clin Microbiol Infect Dis*. 2009; 28(12): 1421-1429.
9. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor Encephalitis: Case Series and Analysis of the Effects of Antibodies. *Lancet Neurol*. 2008;7(12):1091-1098.
10. Graus F, Saiz A, Lai M, Bruna J, Lopez F, Sabater L, et al. Neuronal Surface Antigen Antibodies in Limbic Encephalitis: Clinical-immunologic Associations. *Neurology*. 2008; 71(12): 930-936.
11. Lebas A, Husson B, Didelot A, Honnorat J, Tardieu M. Expanding Spectrum of Encephalitis With NMDA Receptor Antibodies in Young Children. *J Child Neurol*. 2010; 25(6): 742-745.
12. Tuzun E, Dalmau J. Limbic Encephalitis and Variants: Classification, Diagnosis and Treatment. *Neurologist*. 2007; 13(5): 261-271.
13. Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-methyl-D-aspartate Receptor (NMDAR) Encephalitis in Children and Adolescents. *Ann Neurol*. 2009; 66(1): 11-18.
14. Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. N-methyl-D-aspartate Antibody Encephalitis: Temporal Progression of Clinical and Paraclinical Observations in a Predominantly Non-paraneoplastic Disorder of Both Sexes. *Brain*. 2010;133(6):1655-1667.
15. Gabilondo I, Saiz A, Galan L, Gonzalez V, Jadraque R, Sabater L, et al. Analysis of Relapses in Anti-NMDAR Encephalitis. *Neurology*. 2011; 77(10): 996-999.

Manuscript Information: Received: May 07, 2015; Accepted: June 15, 2015; Published: June 19, 2015

Authors Information: Benjamin W Hoyt BS¹, Clifton Mo MD², Sarah M Heaton MD³, Andrew J Senchak DO^{1,4}

¹Department of Surgery, Uniformed Services University

²Department of Hematology/Oncology, Walter Reed National Military Medical Center

³Department of Pathology, Walter Reed National Military Medical Center

⁴Department of Otolaryngology, Walter Reed National Military Medical Center

Citation: Benjamin W Hoyt, Clifton Mo, Sarah M Heaton, Andrew J Senchak. Hodgkin lymphoma presenting with anti-n-methyl-d-aspartate receptor encephalitis. Open J Clin Med Case Rep. 2015; 1015

Copy right Statement: Content published in the journal follows Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>). © Hoyt BW 2015

Journal: Open Journal of Clinical and Medical Case Reports is an international, open access, peer reviewed Journal focusing exclusively on the medical and clinical case reports.

Visit the journal website at www.jclinmedcasereports.com

For reprints & other information, contact editorial office at info@jclinmedcasereports.com