[14] Nance MA, Neglia JP, Talwar D, et al. Neuroblastoma in a patient with Sotos' syndrome. J Med Genet 1990;27:130–2.
[15] Kulkarni K, Stobart K, Noga M. A case of Sotos syndrome with neuroblastoma. J Pediatr Hematol Oncol 2013;35:238–9.
[16] Deardorff MA, Maisenbacher M, Zackai EH. Ganglioglioma in a Sotos syndrome patient with an NSD1 deletion. Am J Med Genet A 2004;130A:393–4.
[17] Berdasco M, Ropero S, Setien F, et al. Epigenetic inactivation of the Sotos overgrowth syndrome gene histone methyltransferase NSD1 in human neuroblastoma and glioma. Proc Natl Acad Sci U S A 2009;106:21830–5.
[18] Berdasco M, Esteller M. Genetic syndromes caused by mutations in epigenetic genes. Hum Genet 2013;132:359–83.
[19] Tatton-Brown K, Rahman N. The NSD1 and EZH2 overgrowth genes, similarities and differences. Am J Med Genet C Semin Med Genet 2013;163C:86–91.

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Brainstem lymphoma in a myasthenia gravis patient on azathioprine

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ABSTRACT

Azathioprine is used for immunosuppression in myasthenia gravis (MG). We report a patient with seropositive MG who developed a brainstem lymphoma 4 years after being treated with azathioprine and review the literature on the occurrence of lymphoma in this patient population. An 82-year-old man with ocular MG who had been on azathioprine for 4 years developed subacute worsening of bulbar symptoms including diplopia, dysarthria and dysphagia mimicking MG exacerbation. Neuroimaging followed by biopsy showed brainstem diffuse large B-cell lymphoma (DLBCL). To our knowledge this is the first reported patient with brainstem DLBCL after azathioprine treatment in MG. Lymphoma has been reported in MG patients treated with azathioprine, although the incidence is unknown. We suggest reduction of azathioprine dose and subsequent discontinuation, if possible, in MG patients who are in remission. Special caution should be taken with elderly patients and Epstein-Barr virus serology prior to initiation may be useful in this population, but this requires further study.

1. Introduction

Azathioprine has long been indicated in the prevention of organ transplant rejection, severe rheumatoid arthritis and inflammatory bowel diseases. Azathioprine is a frequently used oral immunosuppressive agent for myasthenia gravis (MG), based on two randomized-controlled trials [1,2]. Azathioprine may increase the risk of developing cancer, particularly squamous cell carcinoma and lymphoma. Similarly, mycophenolate mofetil, another immunosuppressive agent used in MG, may be associated with lymphoid malignancy, particularly primary central nervous system lymphoma [3], and opportunistic infections such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV) diseases [4].

We performed a medical record review and report a patient with seropositive MG who developed a brainstem lymphoma 4 years after being treated with azathioprine. We also review the literature on the occurrence of lymphoma in this patient population.

2. Case report

An 82-year-old man was diagnosed with seropositive ocular MG at age 78 when he presented with diplopia and bilateral fatigable ptosis. He did not have limb weakness, dyspnea, dysphagia or dysarthria. Edrophonium (Tensilon) test was positive and acetylcholine receptor antibody was strongly positive at 47 nmol/L (normal < 0.4). CT scan of chest was normal with no evidence of thymoma. He responded partially to pyridostigmine 60 mg six times a day. Prednisone was then added and titrated up to 60 mg/day. Azathioprine was started and titrated up to 150 mg/day. Prednisone was then tapered off slowly and completely withdrawn about 2 years after initial presentation. He was maintained on azathioprine with normal blood count and liver function tests obtained at regular intervals.

At the age of 82 years, 4 years after diagnosis and initiation of immunosuppression, he presented with worsening diplopia, dysarthria, dysphagia, drooling, fatigue, poor appetite and weight loss of 15 lbs (6.8 kg) in 1 month. He was thought initially to have an MG exacerbation, but careful neurological examination revealed left Horner's syndrome without fatigable ptosis of the right eyelid, vertical and left beating horizontal nystagmus, uvula deviation to the right due to left palatal weakness, nasal speech and drooling. Extraocular movements were intact. There was no limb weakness and deep tendon reflexes were normal. MRI of the brain with contrast revealed an enhancing lesion in the left medulla, lower pons and middle cerebellar peduncle. Positron emission tomography scan and CT scan of the chest, abdomen and pelvis did not show evidence of a systemic malignancy. Cerebrospinal fluid (CSF) profile revealed protein 78 mg/dL (normal 15–45), glucose 67 mg/dL (normal 40–70), white blood cells 10/μL (normal 0–5) with lymphocytosis (lymphocyte 93%), and red blood cells 28/μL (normal 0–5). CSF cryptococcal antigen and Listeria antibody were negative. Toxoplasma immunoglobulin (Ig) G was 36.4 IU/ml (normal < 6.5), but Toxoplasma IgM and polymerase chain reaction were all negative, indicating a remote exposure to Toxoplasma. CSF cytology revealed numerous lymphocytes but flow cytometry did not show

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Table 1
Review of the literature published between 1988 and 2014 on the occurrence of lymphoma in myasthenia gravis patients on azathioprine

Author	Year	Type of study	Number of patients	Age	Sex	Type of MG	Thymectomy	Dose of AZA (mg/day)	Length of AZA (years)	Other immune-suppressants	Type of lymphoma	Location	Immuno-phenotype	EBV profile	Intervention	Outcome
Kleinschmidt-DeMasters BK, Damek DM, Lillehei KO, et al. [16]	2008	Case report	1	80	M	Ocular	Yes	200	Unknown	No	DLBCL (PCNSL)	CNS: right parieto-occipital, left parietal	B-cell	Positive	N/A	Did well initially, no further detail available. Died 8 months later. Cause of death was listed as thrombophlebitis
Finelli PF [15]	2005	Case report	1	54	F	N/A	Yes	200	13	MMF 2000 mg/day, prednisone 7.5 mg every other day	DLBCL (PCNSL)	CNS: left parieto-occipital	B-cell	Positive	High-dose methotrexate	Asymptomatic at 3 months and after 10 treatments, reduction of lesion size from 1.5 to 1 cm with reduced signal on DWI and FLAIR. Decreased but persistent rim of enhancement on MRI
Barthelmes L, Thomas KJ and Seale JRC [18]	2002	Case report	1	59	M	Ocular	N/A	N/A	8	None	DLBCL	Right testis extending to prostate and right bladder wall	B-cell	N/A	CHOP regimen	Pain improved, initial reduction in the size of the mass felt per rectum but then developed progression of pelvic disease. Developed bilateral ureteric obstruction and renal failure. Died 2 months after the initial presentation of lymphoma
Herrlinger U, Klingel K, Meyermann R, et al. [17]	2000	Case report	1	66	F	Ocular	Yes	100	12	None	HL (mixed-cell type)	CNS: left fronto-parieatl	CD30-positive, LMP-positive polymorphic cells (Reed-Sternberg cells) the majority; only a small minority were B-cell	N/A	PCV regimen with one additional application of CCNU	Complete clinical and radiological remission at 18 months after the diagnosis of lymphoma
Herrlinger U, Weller M, Dichgans J and Melms A [13]	2000	Case series (retrospective)	2 out of 159 who were on AZA	60 and 66	N/A	N/A	N/A	Initially 2 mg/kg/day	6 and 12 years	No cyclosporine	PCNSL	CNS	N/A	Positive in both	N/A	N/A
Kuks JBM, Djojoatmodjo S, Oosterhuis HJHG [19]	1992	Case series (retrospective)	1 out of 41	37	F	Generalized	N/A	Initially 1.5–2 mg/kg/day	Unknown (median value in female group 5 years)	Unknown (30 patients on prednisone)	NHL (no information on subtype)	Colon	N/A	N/A	N/A	N/A
Hohlfeld R, Michels M, Heininger K, et al. [14]	1988	Case series (retrospective)	1 out of 104	68	F	Generalized	N/A	2.1–2.9 mg/kg	6	N/A	NHL (no information on subtype)	Kidney	N/A	N/A	N/A	N/A
Current case	2014	Case report	1	82	M	Ocular	No	150 mg/day	4	Prednisone 60 mg/day, then tapered off and discontinued after 2 years (age 80)	DLBCL (PCNSL)	CNS: brainstem	B-cell	N/A	None	N/A

AZA = azathioprine, CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone, CNS = central nervous system, DLBCL = diffuse large B-cell lymphoma, DWI = diffusion weighted imaging, EBV = Epstein-Barr virus, F = female, FLAIR = fluid attenuated inversion recovery, HL = Hodgkin's lymphoma, LMP = latent membrane protein, M = male, MG = myasthenia gravis, MMF = mycophenolate mofetil, N/A = not applicable (data not available), NHL = non-Hodgkin's lymphoma, PCNSL = primary central nervous system lymphoma, PCV = procarbazine, CCNU, vincristine.