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LETTER TO THE EDITOR

Extranodal marginal zone lymphoma of the cranial dura mater: report of three cases and systematic review of the literature

Brady E. Beltrán[1], Benjamin Kuritzky[2], Pilar Quiñones[3], Domingo Morales[3], José C. Alva[3], Gary Lu[4], Maitrayee Goswami[4], Roberto N. Miranda[4] & Jorge J. Castillo[2]

[1]*Department of Oncology and Radiotherapy and* [3]*Department of Pathology, Edgardo Rebagliati Martins Hospital, Lima, Peru,* [2]*Division of Hematology and Oncology, Rhode Island Hospital, The Warren Alpert Medical School of Brown University, Providence, RI, USA and* [4]*Department of Hematopathology, M. D. Anderson Cancer Center, Houston, TX, USA*

Marginal zone lymphoma (MZL) comprises three distinct subtypes: nodal MZL, extranodal MZL of mucosa-associated lymphoid tissue (MALT) and splenic MZL [1]. MALT lymphomas account for 5% of non-Hodgkin lymphomas (NHLs), and frequently originate in the stomach; however, MALT lymphomas also arise from other organs [1]. The pathogenesis of MALT lymphoma has been associated with chronic infections or autoimmune diseases [2]. Primary dural lymphomas are rare, and most reported cases are extranodal MALT lymphoma [3]; however, a systematic review of the literature is not available [4–6]. In the present study, we describe the complete features of three cases of MALT lymphoma involving the dura in adult immunocompetent patients, and have performed a systematic review of the literature.

Patients with newly diagnosed primary dural MALT lymphoma were identified from the records of the Hospital Nacional Edgardo Rebagliati Martins in Lima, Peru between 2006 and 2011. This study was approved by the local Institutional Review Board. Pathological samples were evaluated by three hematopathologists. Each case underwent staining for CD20, CD3, CD5, CD10, BCL2, immunoglobulin G (IgG), IgG4, kappa and lambda. Fluorescence *in situ* hybridization (FISH) for the detection of t(14;18)(q32;q21)/*IgH-MALT1* and for centromeric chromosome 3 (Vysis Abbott Laboratories, Des Plaines, IL) was performed following described protocols [7,8]. Clinical data including age, sex, B symptoms, laboratory data, therapy received, response to therapy and overall survival (OS) were gathered. A literature search using the keywords "marginal zone AND MALT AND lymphoma AND (intracranial OR dura OR dural)" was independently performed by two investigators using Pubmed through 30 June 2012, regardless of language. Independently, three investigators retrieved pertinent clinical and pathological data. Cases in which the lymphoma was extracranial or recurrence from a pre-existing lymphoma were excluded. The characteristics are reported using descriptive statistics. Comparisons were made using χ^2 tests. OS was defined as the time elapsed since the date of diagnosis until the date of death or last follow-up. Survival estimates were obtained using the Kaplan–Meier method. All calculations were obtained using MedCalc (Mariakerke, Belgium).

Our first case is a 48-year-old healthy woman who presented with a 2-month course of occipital headache and scotomas without B-symptoms. Physical and neurological examinations were unremarkable. A computed tomography (CT) scan with intravenous (IV) contrast revealed two hyperintense lesions of 4 cm and 6.5 cm with surrounding edema in the right occipital area. A third 7 cm lesion was seen in the left parietal area. No additional lesions were identified. The patient underwent a craniotomy with complete resection of the tumors. The patient received whole brain irradiation (WBI) at a dose of 50 Gy as adjuvant therapy. Twenty-one months later, she developed a pelvic tumor that showed the same characteristics as the dural tumor. Treatment was started with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) for six cycles, obtaining a complete response. She is alive 47 months after the initial diagnosis. Our second case is a healthy 35-year-old man who presented with an 8-month course of occipital headache, fever and night sweats, and one isolated episode of seizures. Neurological examination was unremarkable. CT scan revealed the presence of a mass with surrounding edema in the right frontal convexity. He then had a frontal craniotomy with complete resection of the tumor. After diagnosis, the patient received adjuvant WBI at a dose of 50 Gy. The patient is alive without evidence of disease 36 months from diagnosis. Our third case is a 70-year-old woman with a history of hyperthyroidism who presented with a 2-year history of headache, diplopia and vertigo without B-symptoms. Physical examination was unremarkable. A brain magnetic resonance imaging (MRI) scan revealed a 6×3 cm mass in the interhemispheric cissura. The patient underwent a frontoparietal craniotomy with complete resection of the tumor, which was located in the midline; the tumor infiltrated the

Corresponding author: Jorge J. Castillo, MD, 164 Summit Ave, Providence, RI 02906, USA. Tel: 401-7937151. Fax: 401-793-7132. E-mail: jcastillo@lifespan.org
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falx and superior sagittal sinus. She then received adjuvant WBI at 50 Gy. The patient is alive, free of disease 12 months from initial diagnosis. All three patients had normal blood counts, renal and liver function, lactate dehydrogenase, β_2-microglobulin and serum protein electrophoresis, and were seronegative for human immunodeficiency virus (HIV) and hepatitis B and C. All three cases showed sclerotic dura marrow with a diffuse lymphoid infiltrate [Figure 1(A)]. The infiltrate was composed of small lymphocytes with round to irregular nuclei and an occasional intermediate size lymphocyte with vesicular chromatin. Some lymphocytes displayed clear cytoplasm, with a monocytoid appearance [Figure 1(B)]. No mitotic figures or necrosis was detected. In case 1, a significant number of lymphocytes showed clear cytoplasm [Figure 1(B)] and no plasmacytic differentiation was noted. In cases 2 and 3, the infiltrate was more polymorphic and admixed with numerous small, mature plasma cells [Figure 1(C)]. Immunohistochemical studies showed that most cells in the infiltrate were positive for CD20 [Figure 1(D)] and BCL2. Cases 2 and 3 had monotypic kappa plasma cells [Figure 1(E)]. Testing for IgG was positive in all cases, but IgG4 expression was minimal [Figure 1(F)]. No cells marked with CD10 or cyclin D1. Bone marrow examination was negative in all three patients. FISH for *IgH-MALT1* and trisomy 3 were negative in all three patients.

Our study focuses on 36 studies that included 88 patients. With the addition of our cases, we included a total of 91 patients. The median age at presentation was 52 years (range 18–78 years), with a female predominance (79%). With regard to therapy, 64 patients (70%) had surgery, 67 (73%)

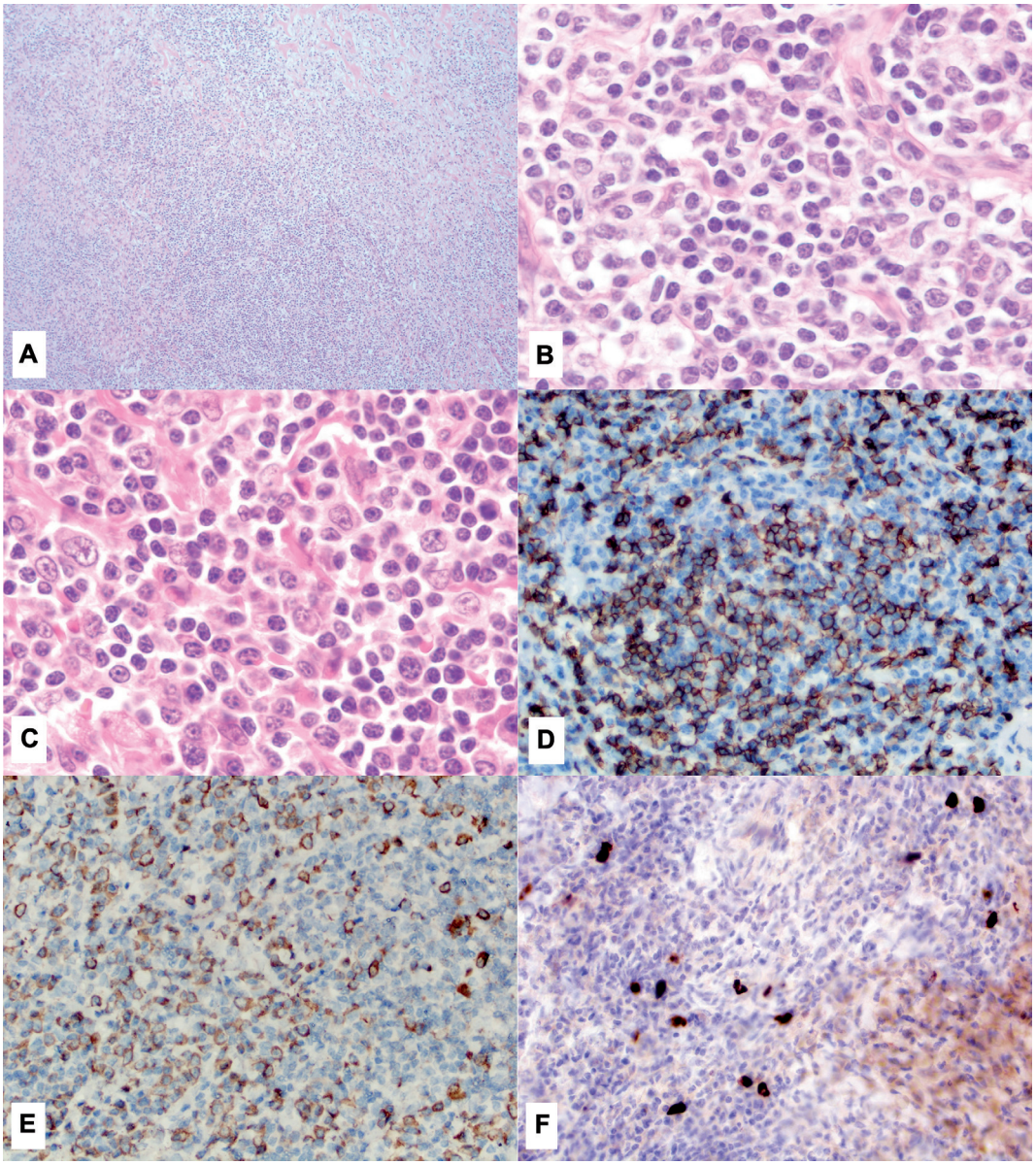

Figure 1. (A) Low magnification shows a dense lymphocytic infiltrate with vague nodularity; there is sclerosis in the background. (B) High magnification shows that the infiltrate is composed predominantly of small round lymphocytes with clear cytoplasm admixed with scattered small mature plasma cells. (C) High magnification shows a mixed infiltrate with small to intermediate and rare large size lymphocytes admixed with numerous plasma cells. (D) Immunohistochemistry for the B-cell marker CD20 highlights small to intermediate size lymphocytes. Many negative cells are likely plasma cells. (E) Immunohistochemistry for immunoglobulin kappa light chain demonstrates that most plasma cells are positive (monotypic kappa). (F) Immunohistochemistry for immunoglobulin G4 (IgG4) demonstrates that scattered plasma cells are positive.

had radiation therapy and 28 (37%) received some form of chemotherapy. Selected clinical features, therapy, response and outcome are shown in Table I. Pathological characteristics are shown in Table II. Of the five patients who relapsed, three (60%) received two modalities and two (40%) received three modalities of therapy, with a median time to relapse of 36 months (range 4–132 months). Of the four patients who died, one (25%) received one modality, one (25%) received two modalities, one (25%) received three modalities and one (25%) was not treated, with a median OS of 91 months (range 2–336 months). There were no specific characteristics associated with higher risk of relapse or death (data not shown). However, of the four patients who died, two had relapsed disease (50%).

Primary dural MALT lymphomas are rare, with no more than 100 cases reported in the literature. Based on our study, there are several points worth discussing. An initial point is that primary dural MALT lymphomas are more commonly seen in middle-aged women. The median age of presentation is 52 years, lower than the age of patients with more common indolent lymphoproliferative disorders such as follicular lymphoma and chronic lymphocytic leukemia [9,10], and also lower than the age of patients with splenic, nodal and extranodal MZL, according to a recent population-based study [1]. There are no clear explanations for the reported female predominance, and there is no evidence of a similar pattern in other lymphoproliferative disorders, with the exception of primary breast lymphomas [11]. One could hypothesize a hormonal role in the pathophysiology of these lymphomas; however, this has not been investigated and remains speculative. The clinical presentation of these lymphomas includes a variety of symptoms associated with a direct mass effect. These findings are not surprising, as primary dural MALT lymphomas can be seen at any intracranial location. What is interesting is that in most of the cases (86%) there was one lesion (unifocal), and only a minority had multifocal lesions. This could be a reflection of the slow-progressing nature of these lymphomas. Interestingly, multifocality did not appear to convey worse response rates or overall survival. However, data are scant and these observations should remain preliminary. Pathologically, primary dural MALT lymphomas have a similar morphology and immunophenotype to MZL affecting other anatomic sites. The tumor infiltrates the dura in a perivascular, interstitial fashion, as well as discrete masses. The neoplastic cells are small, mature lymphocytes with frequent plasmacytic differentiation. The neoplastic cells express CD20 and BCL2 but are negative for CD5, CD10, CD23 and BCL6 [12]. Cases with plasmacytic differentiation show immunoglobulin light chain restriction [6]. Analysis of clonality demonstrates that most cases have clonal rearrangements of the immunoglobulin heavy chain genes [13]. Cytogenetic analyses are rarely carried out in these cases, and when performed are difficult due to the low proliferation rate of these tumors. Venkataraman *et al*. reported trisomy of chromosomes 3 and/or 18 in three out of nine evaluated cases [6]. We did not detect the presence of trisomy 3 in any of our cases. Bhagavathi *et al*. [14] reported one case associated with the *IgH-MALT1* fusion gene. Venkataranam *et al*. tested two of their cases for this abnormality and both cases were negative [6]. Our three cases were tested for *IgH-MALT1*, and failed to demonstrate this abnormality. Venkataraman *et al*. noted that six of 18 cases expressed monotypic IgG4 with light-chain-restricted plasma cells corresponding to IgG4 [6]. They suggested that a subset of dural lymphomas may arise in a background of IgG4-sclerosing disease [15]. None of our cases showed IgG4 expression consistent with underlying IgG4-sclerosing disease. With regard to therapy, >75% of the patients received surgery alone, radiation therapy alone or surgery followed by radiation therapy, while 37% received chemotherapy at

Table I. Clinical characteristics of 91 patients with marginal zone lymphoma of mucosa-associated lymphoid tissue primary of dura mater.

Characteristic	Number	Percentage
Age ($n = 91$)		
>60 years	25	27%
<60 years	66	73%
Sex ($n = 91$)		
Male	19	21%
Female	72	79%
Geographical distribution ($n = 91$)		
North America	67	74%
Europe	14	15%
Latin America	6	7%
Asia	4	4%
Location ($n = 83$)		
Unifocal	70	84%
Multifocal	13	16%
Symptoms ($n = 60$)		
Headache	26	43%
Seizures	23	38%
Visual disturbances	15	25%
Cranial nerve palsy	12	20%
Speech abnormality	7	12%
Dizziness	7	12%
Gait abnormality	6	10%
Therapy ($n = 91$)		
One modality	30	33%
Surgery alone	18	60%
Radiation alone	9	30%
Chemotherapy alone	3	10%
Two modalities	39	43%
Surgery + radiation	23	59%
Chemotherapy + radiation	10	26%
Surgery + chemotherapy	6	15%
Three modalities	7	8%
Unknown therapy	15	16%
Response ($n = 69$)		
Complete response	69	100%
Relapse	5	7%
Outcome ($n = 66$)		
Alive	62	94%
Dead	4	6%

Table II. Immuophenotypic findings of cases with marginal zone lymphoma of mucosa-associated lymphoid tissue primary of dura mater.

Feature	No. positive/no. tested	Percentage
CD20	62/62	100%
BCL2	13/15	87%
Ki67 < 10%	5/6	83%
BCL6	2/5	40%
IgG4	7/21	33%
CD10	1/24	4%
CD5	1/35	3%
CD23	0/11	0%
EBER	0/3	0%

IgG4, immunoglobulin G subclass 4; EBER, Epstein–Barr virus encoded RNA.

some point during their treatment. Only three patients (4%) received chemotherapy alone. Our cases were treated with craniotomy and resection of their tumors followed by 50 Gy of radiation. Although these doses are not standard, they have been effective in patients with primary central nervous system (CNS) lymphoma [16]. We do acknowledge, however, that lower doses of radiation are effective while associated with less toxicity. Based on the good results seen with any treatment modality, it is hard to argue strongly in favor of any approach. However, it is the authors' opinion that surgery should be used in severely symptomatic patients in whom a rapid resolution of the mass effect is needed and/or with an accessible location of the tumor. Radiation therapy should be used as an adjunct in multifocal disease or less accessible tumor locations or alone in patients who are not severely symptomatic or are not good candidates for surgery. The role of systemic or intrathecal chemotherapy alone is currently unclear. We acknowledge that the weaknesses in our study include the retrospective nature of the cases, the heterogeneity of the population and the therapies administered, and the limited extent of pathologic and genetic studies, in particular the evaluation for IgG4 or translocations associated with MALT lymphoma. Despite our shortcomings, we were able to shed additional light on the epidemiology and clinical characteristics of patients with primary dural MALT lymphomas. There are, as expected, several open questions. Why are women predominantly affected? Why does this subset of MZL lymphoma present earlier in life than other MZL subtypes? Would lower doses of radiation be as effective in controlling the disease? How can we decrease the potential morbidity of therapy in such highly controllable disease?

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

References

[1] Olszewski AJ, Castillo JJ. Survival of patients with marginal zone lymphoma: analysis of the Surveillance, Epidemiology, and End Results database. Cancer 2013;119:629–638.

[2] Swerdlow S, Campo E, Harris N, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: IARC; 2008.

[3] Iwamoto FM, Abrey LE. Primary dural lymphomas: a review. Neurosurg Focus 2006;21:E5.

[4] Iwamoto FM, DeAngelis LM, Abrey LE. Primary dural lymphomas: a clinicopathologic study of treatment and outcome in eight patients. Neurology 2006;66:1763–1765.

[5] Tu PH, Giannini C, Judkins AR, et al. Clinicopathologic and genetic profile of intracranial marginal zone lymphoma: a primary low-grade CNS lymphoma that mimics meningioma. J Clin Oncol 2005;23:5718–5727.

[6] Venkataraman G, Rizzo KA, Chavez JJ, et al. Marginal zone lymphomas involving meningeal dura: possible link to IgG4-related diseases. Mod Pathol 2011;24:355–366.

[7] Garcia M, Konoplev S, Morosan C, et al. MALT lymphoma involving the kidney: a report of 10 cases and review of the literature. Am J Clin Pathol 2007;128:464–473.

[8] Jaso J, Chen L, Li S, et al. CD5-positive mucosa-associated lymphoid tissue (MALT) lymphoma: a clinicopathologic study of 14 cases. Hum Pathol 2012;43:1436–1443.

[9] A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909–3918.

[10] Smith A, Howell D, Patmore R, et al. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. Br J Cancer 2011;105:1684–1692.

[11] Jeanneret-Sozzi W, Taghian A, Epelbaum R, et al. Primary breast lymphoma: patient profile, outcome and prognostic factors. A multicentre Rare Cancer Network study. BMC Cancer 2008;8:86.

[12] Cavalli F, Isaacson PG, Gascoyne RD, et al. MALT lymphomas. Hematology Am Soc Hematol Educ Program 2001:241–258.

[13] Miranda RN, Glantz LK, Myint MA, et al. Stage IE non-Hodgkin's lymphoma involving the dura: a clinicopathologic study of five cases. Arch Pathol Lab Med 1996;120:254–260.

[14] Bhagavathi S, Greiner TC, Kazmi SA, et al. Extranodal marginal zone lymphoma of the dura mater with IgH/MALT1 translocation and review of literature. J Hematop 2008;1:131–137.

[15] Cheuk W, Chan JK. IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. Adv Anat Pathol 2010;17:303–332.

[16] Abrey LE, DeAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. J Clin Oncol 1998;16:859–863.