Primary dural lymphomas: a review

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✓Primary dural lymphoma (PDL) is a rare subtype of primary central nervous system lymphoma (PCNSL) that arises from the dura mater and differs biologically from other CNS lymphomas. The PDL is usually a low-grade marginal zone lymphoma (MZL), whereas other types of PCNSLs are usually high-grade, diffuse, large B-cell lymphomas. A PDL usually presents with single or multiple extraaxial masses that enhance diffusely with addition of contrast material and can be confused with meningioma. The MZLs respond well to local therapy such as surgery and radiation treatment. Most patients attain complete response and have good local disease control. Nevertheless, the risk of systemic relapse appears to be high, probably because the dura mater is outside of the blood-brain barrier.

KEY WORDS • primary central nervous system lymphoma • dura mater • non-Hodgkin lymphoma

Primary CNS lymphoma is an extranodal non-Hodgkin lymphoma that arises from the brain parenchyma, eyes, meninges, or spinal cord in the absence of systemic disease.⁴ The most common type of PCNSL presents as a space-occupying lesion in the brain parenchyma. Lymphoma arising primarily from the meninges without brain or systemic involvement is rare. Primary leptomeningeal lymphoma arises within the leptomeningeal space and usually presents with headache, meningeal signs, and cranial nerve involvement.²⁵ Primary dural lymphoma arises from the dura mater and differs biologically from other CNS lymphomas.^{9,24} It is usually a low-grade B-cell MZL, whereas other types of PCNSL are usually high-grade, diffuse, large B-cell lymphomas. Marginal zone lymphoma is an indolent non-Hodgkin lymphoma that occurs more frequently in the gastrointestinal tract, where it has been called the “mucosa-associated lymphoid tissue (MALT) lymphoma.”¹⁷ This specific pathological subtype of the non-Hodgkin lymphoma has important therapeutic and prognostic implications, making PDL a distinct subtype of PCNSL.

Epidemiology

The incidence of PDL is unknown, but it is a rare form of primary intracranial lymphoma. This lesion accounted for 2.4% of 335 patients with PCNSL in our institution.¹⁸ Most published cases of PDL are single-patient reports, and of the two largest series of PDL, one had only 15³⁸ and one had eight¹⁸ patients. This lesion occurs more often in middle-aged women, in contrast to brain parenchyma PCNSL, which has a slight male predilection. In the two series of PDL mentioned earlier, the female/male ratio was 4:1 in one and 3:1 in the other. In contrast with par-

enchymal PCNSL, there has been no clear association between acquired and congenital immunosuppression and the development of PDL.

Pathogenesis

The pathogenesis of PDL is not well understood because the dura is devoid of any lymphoid tissue. One hypothesis is that a benign inflammatory condition of the dura could attract polyclonal lymphocytes from which a monoclonal lymphoma could arise. Chronic infections and autoimmune diseases have been associated with MZL. The most common type of MZL occurs in the stomach and is associated with chronic infection with *Helicobacter pylori*.¹⁷ *Campylobacter jejuni*²⁶ and *Chlamydia psittaci*¹³ probably play a similar role in the pathogenesis of small bowel and ocular adnexal MZL, respectively. Chronic hepatitis C has been associated with nodal and splenic MZL.⁷ Primary MZL of the dura has not been definitively associated with any infectious or autoimmune disease, but patients with hepatitis C,¹² scleroderma,²⁹ Graves disease,³³ and Sjögren disease²² have been reported.

Clinical Presentation

Symptoms are usually dependent on the location of the tumor. The most common clinical presentations are headaches, seizures, focal sensory or motor deficits, and visual disturbances.¹⁸ Other described symptoms include nausea, vomiting, and ataxia.³⁸ More rarely reported presentations include progressive cranial nerve dysfunction causing bilateral visual and hearing loss due to progressive dural involvement by MZL.¹² Another unusual presentation was reported in a patient who had headaches and acute hemiparesis mimicking an acute subdural hematoma.¹⁵ In patients with PDL arising in the spinal cord dura, radicular pain and paraparesis are the most common presenting symptoms.³⁰

Abbreviations used in this paper: MR = magnetic resonance; MZL = marginal zone lymphoma; PCNSL = primary central nervous system lymphoma; PDL = primary dural lymphoma.

FIG. 1. Brain MR images demonstrating a left frontal hypointense extraaxial mass on a T₁-weighted sagittal view (A); the tumor enhances diffusely after gadolinium injection (B). On a coronal T₁-weighted MR image obtained after injection of gadolinium (C), a dural tail tumor is evident.

Neuroimaging

Magnetic resonance imaging reveals single or multiple extraaxial masses that enhanced diffusely after administration of gadolinium contrast (Fig. 1). Up to 50% of patients in one series had more than one mass.¹⁸ The cerebral convexities are the most common site, but the falx, tentorium, and sellar/parasellar regions can also be involved.³⁸ More rarely, intraventricular^{18,23} and spine³⁰ masses can occur. Other MR imaging findings include en plaque thickening of the meninges, dural tail sign, underlying parenchymal vasogenic edema, early invasion of the underlying brain, calvarial hyperostosis, and bone erosion.

Differential Diagnosis

Unquestionably, the most important differential diagnosis is meningioma. In a series of 15 patients with PDL, a clinical and radiographic diagnosis of meningioma was made in 14 prior to the pathological diagnosis.³⁸ The PDLs and meningiomas share many features, including higher incidence in women, similar age of onset (Table 1), and frequent occurrence of more than one extraaxial lesion. Neuroimaging findings are also similar; both tumors present with extraaxial lesions that appear iso- or hypointense on T₁-weighted MR images and diffusely enhance with administration of gadolinium. Moreover, a dural tail is a frequent finding in both meningiomas and PDL.³⁸ On the other hand, underlying vasogenic edema appears to be more common in PDL.

Other differential diagnoses include dural metastasis, solitary fibrous tumors, gliosarcomas, leiomyosarcomas, hemangiopericytomas, melanocytomas, plasmacytomas, inflammatory pseudotumors, neurosarcooidosis, plasma cell granulomas, Rosai–Dorfman disease, Castleman disease, xanthomas, rheumatoid nodules, and tuberculomas.²¹

Pathological Findings

In patients with PDL, the most frequent histopathological diagnosis is MZL (Table 1). Very rarely, cases of high-grade non-Hodgkin lymphoma,^{2,30} low-grade follicular lymphoma,¹⁰ and Hodgkin disease²⁰ have been reported.

The pathological features of MZL arising in the dura

are similar to MZL in other extranodal sites.^{39,40} This tumor has a predominance of small B-cell lymphocytes, but plasma cells, monocytoid-appearing lymphocytes, and scattered large lymphocytes can also be present.¹⁷ The B cells of this type of lymphoma share the cytological features and immunophenotype of marginal zone B cells, and MZL is also characterized by negative markers for CD10, CD5, and CD23.¹⁷

Staging Evaluation

Neurological staging is of primary importance. This includes an MR image of the brain and/or spine (depending on the symptoms and signs) with gadolinium or, if MR imaging is contraindicated, a computed tomography scan with contrast material. Involvement of the leptomeningeal space due to direct tumor contiguity is common and occurred in 63% of patients with PDL in one series.¹⁸ Consequently, all patients should undergo a lumbar puncture for cytological evaluation of the cerebrospinal fluid unless it is contraindicated. Other cerebrospinal fluid studies that may be helpful include protein, cell count, β_2 -microglobulin, *immunoglobulin H* gene rearrangement, and flow cytometry.³

Patients with presumed PDL need to undergo an evaluation to exclude systemic involvement. Although it is typically considered a localized tumor, more than 25% of patients with nongastric MZL presented with Stage IV disease.⁴⁰ A computed tomography scan of the chest, abdomen, and pelvis, and a bone marrow biopsy sampling with aspirate are the recommended staging procedures.

Prognosis

A PDL is more indolent and has a better prognosis than parenchymal PCNSL or systemic lymphoma with CNS metastasis. However, further studies with longer clinical follow up are necessary to assess the final outcome in these patients. In general, patients with MZL have a favorable outcome, with a 5-year overall survival rate greater than 86%, without significant differences between gastrointestinal and nongastrointestinal and between localized and disseminated disease.^{35,36,40}

Primary dural lymphomas

TABLE 1
Literature review of 56 reported cases of PDL*

Authors & Year	Age (yrs), Sex	Lymphoma Histology	Treatment	Outcome
Jazy, et al., 1980	59, M	diffuse lymphocytic	resection, RT	NED, 1.3 yrs
Nguyen & Nathwani, 1989	74, M	small lymphocytic	resection, RT	NED, 1.2 yrs
Scott, et al., 1990	21, F	NA	IT MTX, RT	NED, 1.8 yrs
Miranda, et al., 1996	36, F	DLBCL	laminectomy, RT	alive, 3.3 yrs
	51, F	small lymphocytic	resection, RT	alive, 1.2 yrs
	46, F	DLBCL	laminectomy, RT, CHOP, MTX	alive, 1.1 yrs
	53, M	small lymphocytic	laminectomy, RT, IT MTX, cytarabine	alive, 1 yr
	67, F	large cell immunoblastic	resection, laminectomy	dead, 10 days
Kumar, et al., 1997	40, F	MZL	RT	NED, 5.3 yrs
	62, F	MZL	fludarabine	NED, 1.8 yrs
	52, F	MZL	cytarabine, MTX, IT MTX, RT	NED, 0.6 yr
	43, F	MZL	RT	NED, 0.7 yr
	57, F	MZL	RT	NED, 1.2 yrs
Kambham, et al., 1998	39, F	MZL	resection	NA
	62, F	MZL	resection, RT	NA
Abdel Aziz & van Loveren, 1999	40, F	unspecified B-cell lymphoma	resection, CHOP, RT	NA
Hodgson, et al., 1999	57, F	follicular	resection	NED, 0.5 yr
Altundag, et al., 2000	66, F	MZL	resection, RT	NED, 1 yr
Amaker, et al., 2000	49, F	T-cell-rich large B-cell lymphoma	resection, CHOP, IT MTX, RT	NED, 1.2 yrs
Freudenstein, et al., 2000	50, F	centroblastic/centrocytic	resection, MTX, RT	NED, 3 yrs
Johnson, et al., 2000	55, F	Hodgkin disease	resection, RT	NED, 0.7 yr
Sanjeevi, et al., 2001	46, F	MZL	resection, RT	NED, 1.3 yrs
Estevez, et al., 2002	70, F	MZL	RT	NA
Goetz, et al., 2002	64, F	MZL	resection, RT	NA
Lehman, et al., 2002	63, F	MZL	RT	stable disease
Benouaich, et al., 2003	38, F	MZL	resection, IT MTX, RT	NED, 2 yrs
	45, F	MZL	ifosfamide, doxorubicin, MTX	NED, 1 yr
Beriwal, et al., 2003	67, F	follicular	resection, RT	NED, 1.5 yrs
Bodi, et al., 2003	56, F	MZL	resection	NED, 1.5 yrs
Miller, et al., 2004	49, F	MZL	resection, CHOP, RT	NED, 0.5 yr
Rottnek, et al., 2004†	47, M	MZL	resection, RT	NED, 2.3 yrs
Abdullah, et al., 2005	33, M	lymphoblastic	resection, hyper-CVAD, MTX, cytarabine, IT MTX, IT cytarabine	NED, 2.2 yrs
Assaf, et al., 2005	24, M	MZL	resection, RT	NED, 11 yrs
Kelley, et al., 2005	53, M	MZL	resection, IT cytarabine	NED, 1.2 yrs
Tu, et al., 2005	56, F	MZL	NA	NA
	49, M	MZL	MTX, fludarabine	NED, 7.6 yrs
	66, M	MZL	RT	NED, 1.1 yrs
	55, F	MZL	NA	NA
	45, F	MZL	NA	NA
	68, F	MZL	NA	NA
	29, F	MZL	RT	NED, 3 yrs
	61, F	MZL	NA	NED, 1.7 yrs
	62, F	MZL	RT	NED, 2.1 yrs
	47, M	MZL	NA	NA
	57, F	MZL	MTX, vincristine, procarbazine, cytarabine, RT	NED, 5.5 yrs
	70, F	MZL	RT	NED, 3.9 yrs
	59, F	MZL	RT	NED, 2.8 yrs
	53, F	MZL	RT	NED, 0.9 yr
	48, F	MZL	MTX, RT	NED, 1.7 yrs
Iwamoto, et al., 2006	64, F	MZL	resection, MTX, vincristine procarbazine, IT MTX & cytarabine, RT	NED, 6.6 yrs
	33, F	MZL	IT MTX, IT cytarabine, RT	NED, 7.2 yrs
	35, M	MZL	MTX, vincristine, temozolomide, rituximab, RT	NED, 4.5 yrs
	39, F	MZL	resection, RT	NED, 0.5 yr
	49, F	MZL	resection, RT	NED, 0.7 yr
	51, F	MZL	RT	NED, 0.8 yr
	50, F	MZL	RT	NED, 0.5 yr

* CHOP = cyclophosphamide/doxorubicin/vincristine/prednisolone; DLBCL = diffuse large B-cell lymphoma; hyper-CVAD = fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; IT = intrathecal; MTX = methotrexate; NA = not available; NED = no evidence of disease; RT = radiation therapy.

† This case was also reported in the series published by Iwamoto, et al.

Treatment

Because of the paucity of cases described in the literature, no standard treatment is available for PDL. Clinical Stage I_e MZL (extranodal disease limited to a single site) responds favorably to local treatments such as surgery or focal radiation.^{35,37,40} Complete resection of MZL in the dura can be difficult due to multiple tumors, infiltrative behavior, or en plaque presentation. If complete resection is achieved, clinical and radiological follow up with no additional treatment is appropriate. However, for most cases, adjuvant treatment with either radio- or chemotherapy is necessary. Radiotherapy is preferable because MZL is very radiosensitive and requires relatively low doses of radiation; doses as low as 20 Gy have excellent results and minimize the risk of late neurotoxicity.¹⁸ The radiotherapy port is determined by the extent of the dural lesions and the presence of leptomeningeal involvement.

High-dose methotrexate is the most effective drug for parenchymal PCNSL, but it is unclear if it has a role in PDL, because most patients respond to radiotherapy alone. Furthermore, high-dose methotrexate in conjunction with cranial irradiation can be neurotoxic, leading to progressive leukoencephalopathy, especially in older patients. For patients with disease that was localized to the dura and responded to radiotherapy, chemotherapy is unnecessary. Standard chemotherapy regimens for non-Hodgkin lymphoma and anti-CD20 monoclonal antibodies²⁸ are effective therapies for systemic MZL, but these regimens have not been studied in dural MZL. Moreover, limited data from a retrospective study of patients with nongastric MZL showed no clear advantage of systemic chemotherapy over radiotherapy or surgery.⁴⁰ If the leptomeninges are involved, intrathecal chemotherapy or whole-brain radiotherapy is required.

Conclusions

Complete response is achieved in most patients, even in those with leptomeningeal spread of the disease,^{18,38} although nongastrointestinal MZL has a lower cure and higher relapse rate than gastrointestinal MZL.³⁵ In one study, relapses were found in three of eight patients with PDL; all of the tumors were outside the CNS.¹⁸ Systemic recurrences can occur several years after the initial diagnosis of PDL.⁸ The dura is outside the blood-brain barrier, which may explain the increased risk of systemic relapse compared with other types of PCNSL. Therefore, continued follow up and clinical surveillance are recommended for all patients.

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Primary dural lymphomas

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