Original article

Annals of Oncology 16: 450–454, 2005
doi:10.1093/annonc/mdi076
Published online 10 January 2005

Central nervous system involvement in indolent lymphomas

G. Spectre[1]*, A. Gural[1], G. Amir[2], A. Lossos[3], T. Siegal[3] & O. Paltiel[1,4]

Departments of [1]Hematology and [2]Pathology, [3]The Leslie and Michael Gaffin Center for Neuro-Oncology, and [4]School of Public Health, Hadassah-Hebrew University Hospital, Jerusalem, Israel

Received 3 April 2004; revised 29 July 2004; accepted 5 October 2004

Background: Central nervous system (CNS) involvement, a well-recognized complication of aggressive non-Hodgkin's lymphomas (NHL), has rarely been reported in indolent lymphomas. Large series have reported this complication in 3% of indolent NHLs, generally following histological transformation.

Patients and methods: We retrospectively reviewed the disease characteristics and clinical course in seven patients (six females, one male) with indolent B-cell lymphomas who developed CNS involvement during various stages of their illness.

Results: The median ages at diagnosis of systemic and CNS lymphoma were 60 and 63 years, respectively. Histologies were: small lymphocytic lymphoma (two), follicular lymphoma grade I (two), follicular lymphoma grade II (two) and unclear low-grade histology (one). There were diverse neurological symptoms. Two patients had parenchymal involvement, three had leptomeningial involvement and two had both. Systemic lymphoma was found in all patients, all but one having bone marrow involvement. Four patients had a transformation to high-grade histology. Six patients were treated with systemic and intra-cerebrospinal fluid chemotherapy, and two received radiotherapy as well. Five patients achieved CNS response. Survival was 1–9 years for treated patients (median 2 years). Three patients died of CNS disease.

Conclusions: CNS involvement is a rare and unexpected complication of indolent NHL, which should be considered in the differential diagnosis of patients presenting with new neurological signs. This condition is treatable and some patients have a long clinical course.

Key words: central nervous system, clinical course, indolent, non-Hodgkin's lymphoma

Introduction

The central nervous system (CNS) becomes involved in non-Hodgkin's lymphoma (NHL) in ~8% of patients [1, 2]. Factors predictive of this complication are aggressive histologies, especially Burkitt's and lymphoblastic lymphomas [3, 4], certain subtypes such as testicular lymphoma [5, 6] or lymphoma involving the paranasal sinuses [5], and adverse prognostic features such as increased lactate dehydrogenase (LDH) [1, 7, 8], bone marrow involvement [5–7] and involvement of multiple extranodal sites [4, 7, 9]. CNS involvement in indolent lymphoma has rarely been described. It has been estimated that this complication occurs in 3% of low-grade lymphomas [1, 2, 4, 9, 10], mainly after histological transformation to high-grade lymphoma [6, 10, 11]. There are currently no recommendations regarding prophylactic treatment or staging examinations to rule out CNS involvement in indolent lymphoproliferative disorders. Previously published series [4] included mantle cell or 'diffuse small cleaved cell lymphoma' within the category of indolent histologies. However, the latter entity may behave as a relatively aggressive disease and is known to be associated with CNS involvement in 4% to 22% of patients [12–14].

Very little is known about the characteristics of patients with indolent lymphomas, such as follicular lymphoma and small lymphocytic lymphoma, who develop brain or leptomeningeal involvement. There are only a few published reports of this complication and there are no published series exclusively devoted to CNS involvement in indolent lymphoma, except for a few reports on chronic lymphocytic leukemia (CLL) [15–18]. We present a series of patients with indolent B-cell lymphoma, not including mantle cell lymphoma, and CNS involvement who were diagnosed and treated in our hospital between 1993 and 2003. Our goals were to describe their

**Correspondence to*: Dr G. Spectre, Department of Hematology, Hadassah, Jerusalem, Israel 12000. Tel: +972-51-874302; Fax: +972-2-6449145; E-mail: galiaspectre@hotmail.com

Table 1. Clinical characteristics of seven patients with indolent lymphoma and CNS involvement

Patient no.	Sex/age (years)	Systemic disease					CNS disease							Cause of death
		Histology	BM involvement	LDH at presentation	Treatment	Time to CNS involvement (years)	Clinical presentation	Type of CNS involvement	CSF	Biopsy	Therapy	Response to treatment	Survival from CNS disease (years)	
1	M/49	SLL	+	Normal	None	0	Ataxia, dysarthria	P/LM	SLL	–	Sys+IT+RT	PR	9+	
2	F/43	Follicular lymphoma grade II	+	Normal	CC	7	Diplopia, cranial nerve palsy	P/LM	SCC	–	Sys+IT+RT	NR	1	CNS lymphoma
3	F/67	SLL	+	Normal	WW	9	Confusion	LM	SLL	–	Sys+IT	CR	4	Breast carcinoma
4	F/60	Follicular lymphoma grade I	+	Normal	WW	0.5	Dysgraphia, dyscalculia, hemiparesis	P	Normal	DLC	Sys+IT	CR	2.5	CNS lymphoma
5	F/73	Follicular lymphoma grade I	+	Normal	CC, immunotherapy	4	Hemiparesis, dysarthria	P	Normal	DLC	Sys+IT	PR	2+	
6	F/60	Low grade	+	NA	CC	2	Headache	LM	SLL	–	Sys+IT	CR	2	Systemic lymphoma
7	F/78	Follicular lymphoma grade II	–	NA	CC, RT, immunotherapy	4	Confusion, dizziness	LM	–	–	Steroids	NR	0.25	CNS lymphoma

CNS, central nervous system; BM, bone marrow; LDH, lactate dehydrogenase; CSF, cerebrospinal fluid; M, male; F, female; P, parenchymal; LM, leptomeningeal; SLL, small lymphocytic lymphoma; DLC, diffuse large cell lymphoma; Sys, systemic chemotherapy (including blood–brain barrier disruption and intra-arterial chemotherapy in two); IT, intrathecal; RT, radiotherapy; CC, combination chemotherapy; SCC, small cleaved cells; WW, watch and wait; PR, partial response; CR, complete response; NR, no response; NA, not available.

clinical presentations, histologies, pattern of involvement, clinical course and outcome.

Patients and results

Seven patients with indolent lymphoma and CNS involvement were diagnosed and treated in our hospital in between 1993 and 2003.

Data regarding sex, age, histology of the systemic disease, bone marrow involvement, LDH at presentation and type of treatment are listed in Table 1. The time from diagnosis of systemic lymphoma to CNS involvement was between 0 and 9 years, and the clinical presentation of CNS involvement was diverse (Table 1).

Computed tomography (CT) scan was performed in all patients and magnetic resonance imaging (MRI) in four. Four patients had parenchymal brain lesions, which included a single parietal mass (patient 5), bilateral parietal masses (patient 4), multiple small cerebral and brain stem lesions (patient 1) and a large periventricular mass around the third, fourth and lateral ventricles (patient 2). Patient 7 had periventricular enhancement and patient 6 had dural enhancement, both compatible with leptomeningial disease. Patient 3 had a normal CT scan.

Cerebrospinal fluid (CSF) examination was performed in six patients (Table 1). Cytology of the CSF in four patients showed small lymphocytes, which resembled the peripheral indolent lymphoma and confirmed the diagnosis of CNS involvement in those patients. Two patients had a normal CSF examination and underwent a brain biopsy for diagnosis (patients 4 and 5); both patients had transformation to high-grade lymphoma in the CNS. One patient refused further invasive evaluation and treatment, and the diagnosis was based on clinical signs and a brain CT scan that showed strong periventricular enhancement compatible with brain involvement in lymphoma (patient 7).

In four patients, molecular examinations of the original lymphoma and the cells in the CNS were performed. Of these, one patient had evidence of a V3 immunoglobulin gene rearrangement in the CSF and J-H gene rearrangement of bone marrow, one was positive for Bcl-2 and J-H gene rearrangement of bone marrow only, and two were negative for both Bcl-2 and immunoglobulin gene rearrangement in both CSF and bone marrow.

At the time of diagnosis of brain lymphoma, evidence of active systemic indolent lymphoma was found in all the patients and LDH levels were mildly elevated in three patients (patients 3, 6 and 7). Bone marrow involvement on initial diagnosis of lymphoma was seen in all patients except one.

The time from diagnosis of systemic indolent lymphoma to diagnosis of CNS involvement was between 5 months and 9 years in six patients. In patient 1 the diagnosis of CNS involvement was simultaneous with the systemic disease; he initially presented 9 years ago with ataxia and dysarthria and was diagnosed as having parenchymal and leptomeningial involvement by small lymphocytic lymphoma, together with systemic bone marrow disease. He received combination chemotherapy [high-dose methotrexate (HDMTX), procarbazine and intrathecal injections of cytosine arabinoside], and then clinically deteriorated and whole-brain radiotherapy was added. The patient relapsed 2 years later and was retreated with fludarabine and intrathecal methotrexate. Since then he has remained in good partial remission for 7 years with stable lesions on MRI and an unchanged neurological examination. He is currently being followed clinically with no treatment.

Two patients developed symptoms of brain involvement while receiving chemotherapy for systemic lymphoma (patients 2 and 6), one following radiotherapy to a paravertebral mass (patient 7), and three patients were not receiving treatment despite the presence of systemic indolent lymphoma. Four patients had evidence of high-grade histological transformation at the time of CNS involvement; patients 4 and 5 had transformation in the CNS while patients 6 and 7 had systemic transformation.

Treatment received for CNS disease included intrathecal methotraxate and/or cytosine arabinoside in six patients, HDMTX in five patients, blood–brain barrier disruption regimen (HDMTX, VP16, cyclophosphamide) in two patients, and fludarabine in one patient. Cranial irradiation was given in patients 1 and 2 as second-line therapy. Patient 7 refused chemotherapy, received dexamethasone only, and died from brain lymphoma 3 months after the diagnosis. Five patients achieved CNS remission (patients 1, 3, 4, 5 and 6). Patient 3 died 4 years after the diagnosis of brain lymphoma, from metastatic breast cancer; patient 6 had both systemic and leptomeningeal relapse 2 years after diagnosis of brain lymphoma and died of systemic lymphoma and pancytopenia. Patient 4 underwent autologous bone marrow transplantation for systemic relapse of transformed follicular lymphoma, but relapsed in the CNS 7 months after bone marrow transplantation and died of sepsis and active brain disease. Her case history is presented in Figures 1–3. Patients 1 and 5 are alive between 2 and 9 years after the diagnosis of brain involvement.

Patient 2 failed to achieve CNS remission and died from brain lymphoma and liver failure 11 months after the diagnosis of CNS disease.

Discussion

CNS involvement in indolent NHL does exist, although it is a rare complication, and the literature on this complication is scarce. In CLL, however, there are a few published autopsy series reporting an incidence of 15% to 70% invasion of the CNS by CLL lymphocytes, mainly in advanced disease, but neurological symptoms are very rare [18–20].We present a series of patients with indolent lymphoma and symptomatic CNS involvement. We found no clinical series devoted to this pathology and only three case reports describing dural or meningeal involvement in follicular or mucosa-associated lymphoid tissue (MALT) NHLs [21–24], and an abstract

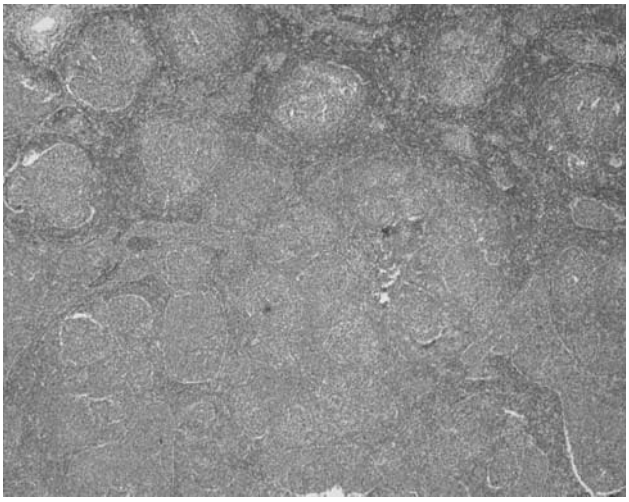

Figure 1. Follicular lymphoma grade I (hematoxylin–eosin, original magnification ×50). A 60-year-old woman (patient 4) presented in March 2001 with asymptomatic lymphadenopathy. A supraclavicular lymph node biopsy revealed the diagnosis of follicular lymphoma grade I, Bcl-2-negative, with bone marrow involvement, and she was followed clinically.

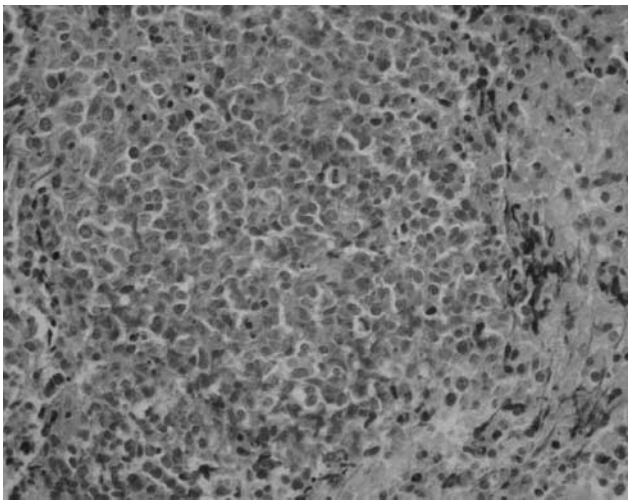

Figure 2. Diffuse large B-cell lymphoma of the brain; focal necrosis is seen on the right (hematoxylin–eosin, original magnification ×400). Five months after presentation, on July 2001, while on vacation, patient 4 suddenly noticed difficulty in concentrating, reading and calculating. A brain magnetic resonance imaging was performed and showed bilateral parietal enhancing masses. Cerebrospinal fluid examination was negative and a brain biopsy showed transformation to diffuse large B-cell lymphoma.

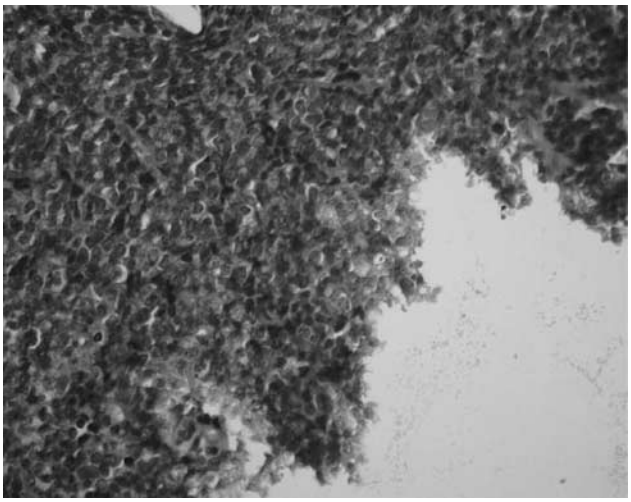

Figure 3. Cervical lymph-node biopsy showing diffuse large B-cell lymphoma (hematoxylin–eosin, original magnification ×400). Patient 4 received six cycles of combination chemotherapy with blood–brain barrier disruption and achieved a complete central nervous system (CNS) remission. However, in April 2002 she developed progressive cervical lymphadenopathy and a biopsy revealed a systemic transformation to high-grade lymphoma. The patient received salvage chemotherapy and underwent autologous bone marrow transplantation, relapsed again in the CNS and died of sepsis and active lymphoma in November 2003.

describing seven patients with chronic B-cell lymphoproliferative disease (which included mantle cell lymphoma) [25]. Interestingly, in the latter study, from the Royal Marsden Hospital, as in our group of patients, four of the seven patients had evidence of disease transformation at the time of CNS transformation. The abstract did not provide information about the site of disease transformation; however, in our group two patients had systemic and two had CNS transformation. In their group all patients had a significant rise in LDH at the time of CNS involvement, while in our group only three patients did. Survival in their group was poor in all but two patients.

The seven patients in our series represent a very small portion of B-cell malignancies treated at our institution (<1%), and <3% of those with indolent histologies. The clinical course was different in each case. For example, one patient presented with neurological symptoms at the time of the original diagnosis and two other patients developed brain lymphoma while receiving treatment for systemic lymphoma. Hollender et al. [4] reported an incidence of 2.8% of CNS involvement in low-grade lymphoma (although their series included mantle cell lymphoma according to the WHO classification). Multivariate analysis revealed that B symptoms, bone marrow involvement and skin involvement were risk factors for developing CNS involvement. These factors together carried a risk of 7% of developing brain lymphoma within 5 years of diagnosis. None of our patients had skin lymphoma, and B symptoms were reported in only one of the seven patients. The only common features we could find in our patients were bone marrow involvement at the time of lymphoma diagnosis (six of seven patients) and systemic or CNS high-grade histological transformation (four of seven patients). However, bone marrow involvement is a very common feature of indolent lymphoma and can be found in at least 70% of patients presenting with advanced-stage follicular lymphoma [26]. Thus, we believe bone marrow involvement is of no predictive value in these patients. In the four patients with samples available for molecular analysis we did not find agreement between the gene rearrangement in the systemic lymphoma and the brain lymphoma. However, the sample size was too small to draw meaningful conclusions.

According to the literature, CNS involvement occurring as a complication of NHL carries a very poor prognosis. The median survival is reported to be $\sim$4 months among agressive histologies [1, 2, 6, 27]. Van Besien et al. [7] described a 1 year survival of 25%. Our patients with indolent lymphoma and CNS involvement had a good response to treatment; the shortest survival of 3 months was documented in the only patient who refused treatment, five out of six patients who received treatment achieved CNS remission and only three patients died of brain lymphoma. The survival of six patients who received treatment was between 11 months and 9 years (median 2 years), and two patients are currently alive at 2 and 9 years after diagnosis of CNS lymphoma. Survival in our patients is relatively low for patients with indolent lymphomas, but is certainly longer compared with survival of patients with CNS relapse of aggressive lymphomas.

Initial treatment of brain lymphoma in our patients was based on chemotherapy and did not include initial radiotherapy. Nevertheless, a good response rate was achieved, and only two patients required radiotherapy as second-line treatment. We assume that this therapeutic approach is reasonable

and can prevent the long-term CNS morbidity, including cognitive dysfunction, that occurs after brain irradiation.

CNS involvement in indolent lymphoma is a rare complication. A significant number of patients presenting with this complication may also present with disease transformation that can be either systemic or confined to the CNS. Considering the rarity of CNS involvement and the limited number of common features in our patients, we presume that this complication will continue to be an unexpected occurrence in indolent lymphoma. Given its rarity there will be no place for prophylactic CNS chemotherapy for patients with these disorders. However, this entity should be considered in the differential diagnosis of new neurological symptoms and signs in patients with indolent lymphoma, especially when disease transformation is diagnosed.

References

1. Tomita N, Kodama F, Sakai R et al. Predictive factors for central nervous system involvement in non-Hodgkin's lymphoma: significance of very high serum LDH concentrations. Leuk Lymphoma 2000; 38: 335–343.
2. Wolf MM, Olver IN, Ding JC et al. Non-Hodgkin's lymphoma involving the central nervous system. Aust N Z Med 1985; 15: 16–21.
3. Mackintosh FR, Colby TV, Podolski WJ et al. Central nervous system involvement in Hodgkin lymphoma: an analysis of 105 cases. Cancer 1982; 49: 586–595.
4. Hollender A, Kvaloy S, Nome O et al. Central nervous system involvement following diagnosis of non-Hodgkin's lymphoma: a risk model. Ann Oncol 2002; 13: 1099–1107.
5. Liang R, Chiu E, Loke SL. Secondary central nervous system involvement by non-Hodgkin's lymphoma: the risk factors. Hematol Oncol 1990; 8: 141–145.
6. Keldsen N, Michalski S, Bentzen S et al. Risk factors for central nervous involvement in non-Hodgkin's lymphoma. Acta Oncol 1996; 35: 703–708.
7. Van Besien K, Ha CS, Murphy S et al. Risk factors, treatment, and outcome of central nervous system recurrence in adults with intermediate grade and immunoblastic lymphoma. Blood 1998; 91: 1178–1184.
8. Zinzani PL, Magagnoli M, Ferezza G et al. Isolated central nervous system relapse in aggressive non-Hodgkin's lymphoma: the Bologna experience. Leuk Lymphoma 1999; 32: 571–576.
9. Litam JP, Cabanillas F, Smith TL et al. Central nervous system relapse in malignant lymphomas: risk factors and implications for prophylaxis. Blood 1979; 54: 1249–1257.
10. Young RC, Howser DM, Anderson T et al. Central nervous system complications of non-Hodgkin's lymphoma. The potential role of prophylactic therapy. Am J Med 1979; 66: 435–443.
11. Bollen EL, Brouwer RE, Hamers S et al. Central nervous system relapse in non Hodgkin lymphoma. A single center study of 532 patients. Arch Neurol 1997; 54: 854–859.
12. Oinonen R, Franssila K, Elonen E. Central nervous system involvement in patients with mantle cell lymphoma. Ann Hematol 1999; 78: 145–149.
13. Montserrat E, Bosch F, Lopez-Guillermo A et al. CNS involvement in mantle cell lymphoma. J Clin Oncol 1996; 14: 941–944.
14. Valdez R, Kroft SH, Ross CW et al. Cerebrospinal fluid involvement in mantle cell lymphoma. Mod Pathol 2002; 15: 1073–1079.
15. Hoffman MA, Valderrama E, Fuchs A et al. Leukemic meningitis in B cell prolymphocytic leukemia. A clinical, pathologic and ultrastructural case study and review of the literature. Cancer 1995; 75: 1100–1103.
16. Miller K, Budke H, Orazi A. Leukemic meningitis complicating early stage chronic lymphocytic leukemia. Arch Pathol Lab Med 1997; 121: 524–527.
17. Brick WG, Majmundar M, Hendricks LK et al. Leukemic leptomeningeal involvement in stage 0 and stage 1 chronc lymphocytic leukemia. Leuk Lymphoma 2002; 43: 199–201.
18. Cramer SC, Glapsy JA, Efird JT et al. Chrnic lymphocytic leukemia and the central nervous system: a clinical and pathological study. Neurology 1996; 46: 19–25.
19. Barcos M, Lane W, Gomez GA et al. An autopsy study of 1206 acute and chronic leukemias (1958 to 1982). Cancer 1987; 60: 827–837.
20. Reske-Nielsen, Petersen JH, Sogaard J et al. Leukemia of the central nervous system. Lancet 1994; 211–212.
21. Beriwal S, Hou JS, Miyamoto C, Gracia-Young JA. Primary dural low grade BCL2 negative follicular lymphoma: a case report. J Neurooncol 2003; 61: 23–25.
22. Altundag MK, Ozsik Y, Yalcin S et al. Primary low grade B cell lymphoma of the dura in an immunocompetent patient. J Exp Clin Cancer Res 2000; 19: 249–251.
23. Subramanian S, Bahceci E, Kanji A. Primary follicular lymphoma of the meninges: a case report. Proc Am Soc Clin Oncol 1995; 14: (Abstr 308).
24. Goetz P, Lafuente J, Revesz T et al. Primary low grade B-cell lymphoma of mucosa associated lymphoid tissue of the dura mimicking the presentation of an acute subdural hematoma. Case report and review of the literature. J Neurosurg 2002; 96: 611–614.
25. Scully MA, Dearden CE, Matutes E et al. Central nervous system relapse in chronic B-cell lymphoproliferative disease. Blood Suppl 2003; 102: 287b (Abstr 4872).
26. Child JA, Jack AS, Morgan GJ. The Lymphoproliferative Disorders. London: Chapman and Hall Medical 1998.
27. Recht L, Straus DJ, Cirrincoine C et al. Central nervous system metastasis from non-Hodgkin's lymphoma: Treatment and prophylaxis. Am J Med 1998; 84: 425–435.