Central nervous system involvement in indolent lymphomas

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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 leptomeningeal 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
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex/age (years)</th>
<th>Systemic disease</th>
<th>CNS disease</th>
<th>Cause of death</th>
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<tr>
<td></td>
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<td>Histology</td>
<td>Treatment</td>
<td>Time to CNS involvement (years)</td>
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<tr>
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<td>M/49</td>
<td>SLL +</td>
<td>Normal None</td>
<td>0</td>
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<tr>
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<td>F/43</td>
<td>Follicular lymphoma grade II +</td>
<td>Normal CC</td>
<td>7</td>
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<tr>
<td>3</td>
<td>F/67</td>
<td>SLL +</td>
<td>Normal WW</td>
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<td>F/60</td>
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<td>Normal WW</td>
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<td>F/78</td>
<td>Follicular lymphoma grade II –</td>
<td>NA CC, RT, immunotherapy</td>
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</table>

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 brainstem 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 leptomeningeal 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 leptomeningeal 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 methotrexate 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.
describing seven patients with chronic B-cell lymphoprolifera-
tive disease (which included mantle cell lymphoma) [25].

Interestingly, in the latter study, from the Royal Marsden Hos-

total, as in our group of patients, four of the seven patients

disease transformation at the time of CNS

The seven patients in our series represent a very small

portions 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 classi-

fication). Multivariate analysis revealed that B symptoms,

bone marrow involvement and skin involvement were risk fac-

tors 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

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 ~4 months among aggresive 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 remis-

sion 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. Sur-

vival 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 radiothe-

rapy. Nevertheless, a good response rate was achieved, and

only two patients required radiotherapy as second-line treat-

ment. We assume that this therapeutic approach is reasonable

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.
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


