Prevalence and characteristics of central nervous system involvement by chronic lymphocytic leukemia

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ABSTRACT

A broad array of conditions can lead to neurological symptoms in chronic lymphocytic leukemia patients and distinguishing between clinically significant involvement of the central nervous system by chronic lymphocytic leukemia and symptoms due to other etiologies can be challenging. Between January 1999 and November 2014, 172 (4%) of the 4174 patients with chronic lymphocytic leukemia followed at our center had a magnetic resonance imaging of the central nervous system and/or a lumbar puncture to evaluate neurological symptoms. After comprehensive evaluation, the etiology of neurological symptoms was: central nervous system chronic lymphocytic leukemia in 18 patients (10% evaluated by imaging and/or lumbar puncture, 0.4% overall cohort); central nervous system Richter Syndrome in 15 (9% evaluated, 0.3% overall); infection in 40 (23% evaluated, 1% overall); autoimmune/inflammatory conditions in 28 (16% evaluated, 0.7% overall); other cancer in 8 (5% evaluated, 0.2% overall); and another etiology in 63 (37% evaluated, 1.5% overall). Although the sensitivity of cerebrospinal fluid analysis to detect central nervous system disease was 89%, the specificity was only 42% due to the frequent presence of leukemic cells in the cerebrospinal fluid in other conditions. No parameter on cerebrospinal fluid analysis (e.g. total nucleated cells, total lymphocyte count, chronic lymphocytic leukemia cell percentage) were able to offer a reliable discrimination between patients whose neurological symptoms were due to clinically significant central nervous system involvement by chronic lymphocytic leukemia and another etiology. Median overall survival among patients with clinically significant central nervous system chronic lymphocytic leukemia and Richter syndrome was 12 and 11 months, respectively. In conclusion, clinically significant central nervous system involvement by chronic lymphocytic leukemia is a rare condition, and neurological symptoms in patients with chronic lymphocytic leukemia are due to other etiologies in approximately 80% of cases. Analysis of the cerebrospinal fluid has high sensitivity but limited specificity to distinguish clinically significant chronic lymphocytic leukemia involvement from other etiologies.

Introduction

Chronic lymphocytic leukemia (CLL) is a clonal disorder of B lymphocytes, characterized by proliferation and accumulation of small mature-appearing lymphocytes in the blood, bone marrow, and lymphoid tissues.[1] The presence of clinically significant infiltration of CLL lymphocytes outside of these sites is relatively rare and is defined as extramedullary CLL. Although the central nervous system (CNS)

is one of the most commonly observed extramedullary manifestations of CLL,[2] less than 100 cases of CNS involvement by CLL are described in the literature; all are case reports or small case series.[3-16] Despite the low frequency of clinically significant CNS involvement by CLL, post-mortem studies of patients with CLL indicate that occult CNS involvement by CLL is a relatively common finding, with a prevalence of 7%-71%.[17-20] This discrepancy between clinical manifestations and autopsy findings illustrates the fact that, while CLL cells may frequently be present in the CNS, they rarely cause clinically significant manifestations. This makes the evaluation of neurological symptoms in patients with CLL challenging, since the mere identification of CLL cells in CNS does not necessarily indicate that CLL is the etiology of the patients' neurological symptoms. In addition, the spectrum of neurological conditions that occur in patients with CLL is broad and includes infections, other malignancies, autoimmune/inflammatory diseases, and non-CLL-related medical conditions.

Here, we report the first cohort study of patients with CLL undergoing evaluation of neurological symptoms, and describe the prevalence and characteristics of patients diagnosed with clinically significant CNS involvement by CLL or Richter syndrome (RS).

Table 1. Distribution of final diagnosis among patients evaluated for neurological symptoms.

Patients (n=172)	N (%)
Clinically significant CNS involvement by CLL	18 (10)
Richter syndrome involving CNS	15 (9)
Infections	40 (23)
PML	11
Cryptococcus meningitis	9
Aseptic meningitis	7
Sinusitis	5
VZV encephalitis	3
EBV encephalitis	1
WNL encephalitis	1
HHV6 encephalitis	1
Coccidioides meningitis	1
Endophthalmitis	1
Autoimmune/inflammatory	28 (16)
Autoimmune radiculopathy	6
Autoimmune myelopathy	5
CNS vasculitis	5
Autoimmune encephalopathy	4
CIDP	3
Multiple sclerosis	2
Eaton-Lambert	1
Sarcoidosis	1
Uveitis	1
Other cancer	8 (5)
Primary brain tumor	5
Metastatic disease	3
Non-CLL-related	63 (37)
Delirium	19
Non-autoimmune radiculopathy	9
Migraine	9
Epilepsy/seizure	6
Dementia	4
Progressive supranuclear palsy	3
Fibromyalgia	3
Atrophic lateral sclerosis	2
Bell's palsy	2
Arteriovenous malformation	1
Transient ischemic attack	1
Trigeminal pain	1
Refractive eye disorder	1

PML: progressive multifocal leukoencephalopathy; VZV: varicella zoster virus; EBV: Epstein-Barr virus; WNL: West Nile virus; HHV6: human herpesvirus 6; CIDP: chronic inflammatory demyelinating polyneuropathy.

Methods

Study population

This study was reviewed and approved by the Institutional Review Board of the Mayo Clinic and was conducted in accordance with the principles of the Declaration of Helsinki. Between January 1999 [when flow cytometry on cerebrospinal fluid (CSF) was introduced in our institution] and November 2014, 4174 patients with CLL/SLL were cared for and monitored in the Division of Hematology at our institution and consented to be registered on the Mayo Clinic database.

Information regarding base-line evaluation, medical history, laboratory findings, and prognostic factors were obtained from clinical and research records. The latter included fluorescent *in situ* hybridization (FISH) for common CLL chromosome abnormalities, analysis of the mutation status of the immunoglobulin heavy chain variable (*IGHV*) gene, and CD38, ZAP70 and CD49d expression by flow cytometry.

Diagnostic work up for CNS involvement

The present analysis focused on all patients with CLL who underwent evaluation of neurological symptoms (including headache, confusion, and strength or sensitivity deficit) with a magnetic resonance imaging (MRI) of the CNS (e.g. brain, spine) and/or underwent lumbar puncture with CSF analysis. Patients with established active systemic RS at time of neurological symptoms were not included in the study. CSF analysis included: basic chemistry (glucose, protein), total nucleated cells (TNC) quantification, and microbiology/autoimmune studies. CSF studies included cytology and flow cytometry. All CSF and brain biopsies were reviewed by Mayo Clinic pathologists. After comprehensive evaluation, patients in whom the etiology of neurological symptoms was determined to be due to CLL and/or RS, and who required treatment of CLL/RS for their CNS involvement, were considered to have clinically significant involvement of the CNS by CLL. Patients who had an alternative etiology for their neurological symptoms identified on evaluation but who had incidental presence of CLL B cells in the CSF as a bystander were in effect not considered to have clinically significant involvement by CLL.

Statistical analysis

Descriptive statistics were used to summarize base-line characteristics. Categorical and continuous variables were evaluated using the χ^2 or Fisher exact tests and the Mann-Whitney test, as appropriate. Overall survival (OS) was defined as time from CNS diagnosis to death or last follow up. Survival curves were plotted using the Kaplan-Meier method, and comparisons were made using the log rank test. All *P*-values were 2-sided; $P \leq 0.05$ was considered significant. Statistical analysis was performed using SPSS 21.

Results

Diagnostic work up

Of the 4174 patients with CLL cared for at our center

between January 1999 and November 2014, 1115 (28%) underwent MRI of the brain and/or the spine for evaluation of neurological symptoms during the course of their disease. We next focused on the 50 patients who had MRI findings suspicious for possible CNS malignancy (23 with meningeal involvement, 27 with parenchymal brain involvement) and 122 patients whose MRI was not suspicious for CNS malignancy, but who underwent a lumbar puncture with CSF analysis to further evaluate their neurological symptoms. The neurological symptoms that initially prompted evaluation in these 172 were: cognitive-behavioral symptoms in 47 (27%), headache in 34 (20%), cranial nerve deficits in 24 (14%), paresthesia in 21 (12%), weakness in 19 (11%), gait disorder in 15 (9%), and seizure in 12 (7%). A more detailed presentation of the diagnostic work up in these patients is shown in Figure 1.

Final diagnosis

Among the 50 patients whose MRI of the brain/spine was suspicious for CNS involvement by malignancy, 34 underwent a CNS tissue biopsy. Biopsy revealed histological features consistent with a small lymphocytic lymphoma/CLL confirmed by immunostains in 9 cases, RS in 12, progressive multifocal leukoencephalopathy (PML) in 2, vasculitis in 3, other cancers in 6 (3 primary brain tumors, 3 metastatic tumors), and normal brain tissue in 2 patients. Although patients with established systemic RS at the time of CNS evaluation were not included in this series (see Methods), 11 of 12 included patients whose initial manifestation of RS was CNS involvement were later found to have systemic disease. Additional diagnostic work up of CSF and blood for infectious and autoimmune etiologies was based on patients' clinical profile. After comprehensive evaluation in all 172 patients, the etiology of neurological symptoms was determined to be clinically significant CNS involvement by CLL in 18 (10%; 0.4% of overall cohort), CNS involvement by RS in 15 (9% evaluated patients; 0.3% overall), infection in 40 (23% evaluated patients; 1% overall), autoimmune/inflammatory disease in 28 (16% evaluated patients; 0.7% overall), other cancer in 8 (5% evaluated patients; 0.2% overall) and non-CLL-related conditions in 63 (37% evaluated patients; 1.5% overall). Further details regarding non-CLL/RS diagnoses in these patients are provided in Table 1.

Among the 13 patients with clinically significant CNS involvement by CLL, the involvement was parenchymal in 7 patients (Figure 2A) and meningeal in 6 (Figure 2B). Five of the 13 patients ultimately found to have clinically significant CNS involvement by CLL had no evidence of CNS disease on MRI. Diagnosis of clinically significant CNS involvement by CLL was based on both CSF analysis and tissue biopsy in 4 of these patients, on tissue biopsy only (CSF analysis negative or not performed) in 5, on CSF analysis only (tissue biopsy not performed) in 7, and was presumed after exhaustive work up to exclude other causes in 2 patients in whom the location of radiographic disease did not allow a tissue biopsy to be performed.

Among the 15 patients with CNS involvement by RS,

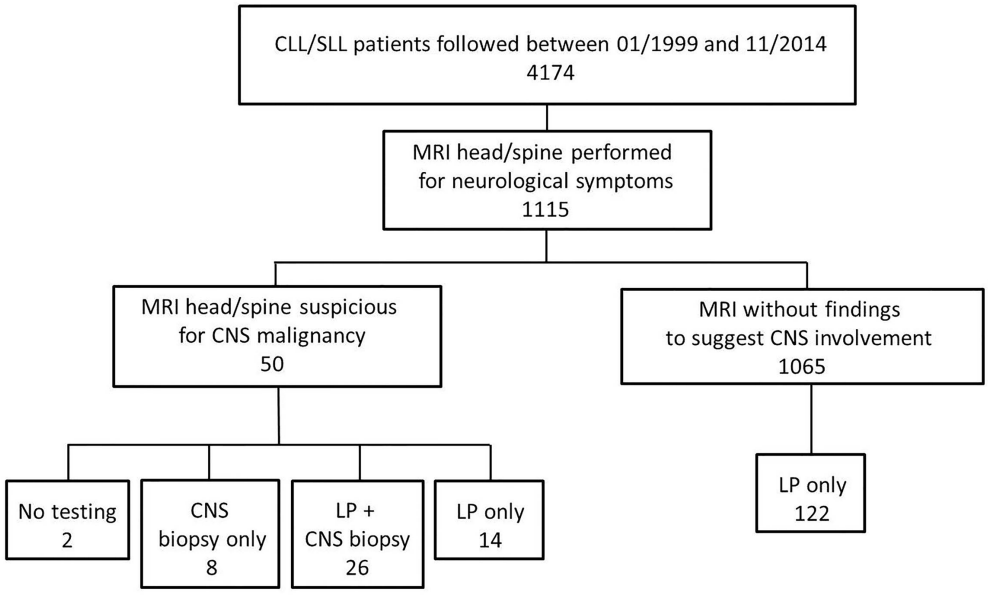

Figure 1. Diagnostic work up performed for neurological symptoms in this cohort of patients with chronic lymphocytic leukemia. CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma; MRI: magnetic resonance imaging; LP: lumbar puncture; CNS: central nervous system.

Table 2. Concordance of lumbar puncture and tissue biopsy for diagnosis of CNS CLL/RS.

Patients (n=162)	N	CNS biopsy positive for CLL	CNS biopsy positive for RS	Final diagnosis of CLL/RS
Negative for CLL/RS by CSF analysis	131	4/19 (21%)	9/19 (47%)	15*/132 (11%)
Positive for CLL/RS by CSF analysis	31	4/7 (57%)	0/7 (0%)	13/31 (42%)

*CNS biopsy was performed in 21 of 145 patients with LP negative for CLL/RS, and in 7 of 31 patients with LP positive for CLL/RS. CNS: central nervous system; LP: lumbar puncture; RS: Richter syndrome; CLL: chronic lymphocytic leukemia. *1 patient with negative LP and CNS lesions not amenable to biopsy was considered to have CNS CLL and treated accordingly; 1 patient had extra-CNS biopsy positive for RS and was considered to have CNS RS.*

the CNS involvement was parenchymal in 8 (Figure 2C) and meningeal in 7 (Figure 2D) patients. Diagnosis of CNS involvement by RS was confirmed by tissue biopsy in 12 patients and by CSF analysis in 3. Tissue biopsy was frequently necessary to confirm the diagnosis of CNS RS. Among the 12 patients with biopsy proven RS, 9 had no findings to suggest RS on CSF analysis while the remaining 3 patients did not undergo CSF analysis.

Lumbar puncture and tissue biopsy concordance in patients with CNS CLL/RS

Overall, 162 patients underwent a CSF analysis: 44 between 1999 and 2004, 54 between 2005 and 2009, and 64 between 2010 and 2015. Of the 131 patients who had no evidence of CLL/RS on CSF analysis, 15 (11%) were ultimately diagnosed with clinically significant CNS involvement by CLL or RS based on tissue biopsy, most of whom had a parenchymal brain lesion on MRI (Table 2). Among the 31 patients with CSF analysis demonstrating the presence of CLL B cells, 18 (58%) had an alternative diagnosis for their neurological symptoms identified after tissue biopsy and/or other work up. This included: infections in 8 patients, an autoimmune/inflammatory process in 5, metastatic cancer in 1, and non-CLL-related etiology in 4.

Factors associated with CNS CLL/RS

Chronic lymphocytic leukemia characteristics of the 33 patients with a final diagnosis of clinically significant involvement of the CNS by CLL or RS are shown in Table 3. CSF characteristics associated with clinically significant CNS involvement by CLL or RS on univariate analysis were: low CSF glucose (53 *vs.* 60 mg/dL; P=0.04), elevated CSF total nucleated cell count (14 *vs.* 2 cells/μL; P=0.007), elevated CSF lymphocyte count (10 *vs.* 2 cells/μL; P=0.02), and elevated CSF CLL cell percentage by flow cytometry (5% *vs.* 0%; P=0.05). Due to substantial overlap in all of these CSF parameters between groups, however, none of these characteristics reliably discriminated between patient's whose neurological symptoms were due to clinically significant CNS involvement by CLL/RS or another etiology.

Treatment and survival of patients with CNS CLL/RS

Of 33 patients with clinically significant CNS involvement by CLL or RS, 30 received therapy for the CNS disease, whereas 3 received best supportive care only. The initial therapy for patients with clinically significant CNS involvement by CLL was a purine nucleoside-analog-based regimen in 8 (42%) patients, radiation therapy in 3 (16%), anthracycline-based regimens in one (5%), high-dose methotrexate (MTX) in 2 (13%), high-intensity regimens (e.g. fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone or ifosfamide, carboplatin, etoposide, variably combined with intrathecal MTX or cytarabine) in 2 (13%), and best supportive care in 2 (11%). Among patients with CNS involvement by RS, the initial therapy was an anthracycline-based regimen in 5 (33%) patients, high-dose MTX in 3 (20%), high-

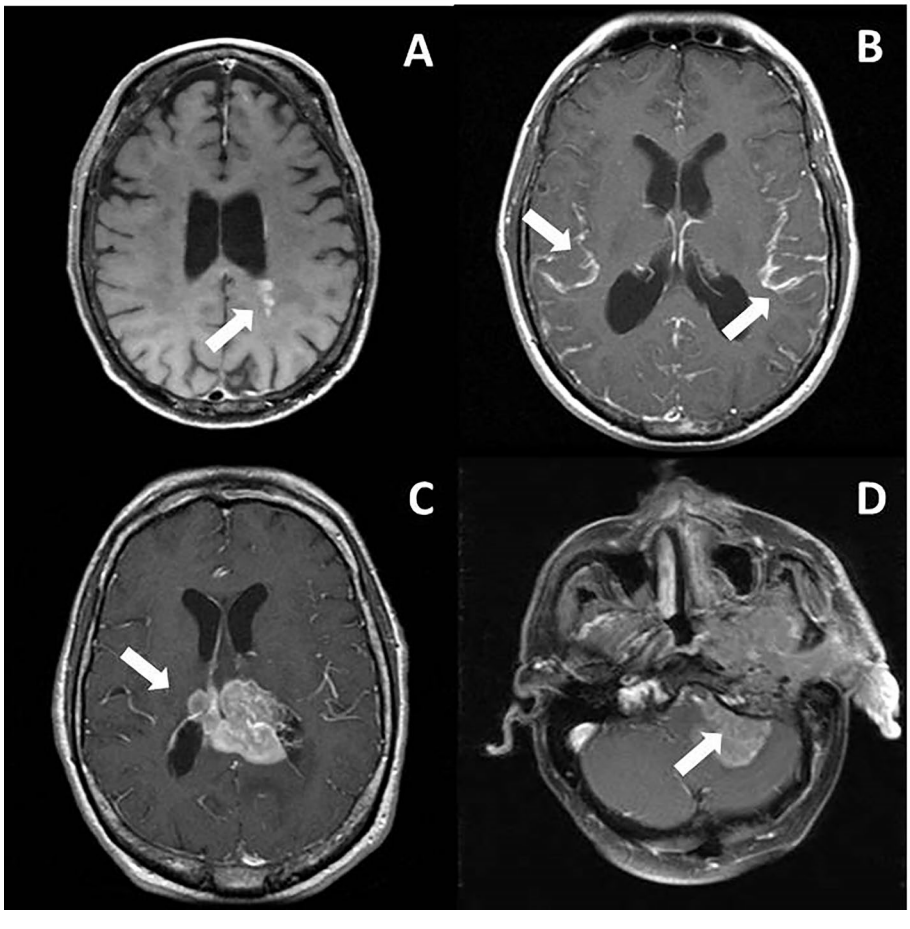

Figure 2. Magnetic resonance findings. (A) Chronic lymphocytic leukemia (CLL) parenchymal. (B) CLL meningeal. (C) Richter syndrome (RS) parenchymal. (D) RS meningeal.

intensity regimens in 6 (40%), and best supportive care in one (7%). After a median follow up of 14 months, the median overall survival (OS) for all 172 CLL patients evaluated for neurological symptoms was 24 months. After a median follow up from diagnosis of CNS involvement by CLL or RS of 12 months (range 1-178 months), 78% of patients with clinically significant CNS involvement by CLL and 80% of patients with CNS RS have died. The median OS of patients with clinically significant CNS involvement by CLL or RS were 12 and 11 months, respectively (Figure 3).

Discussion

Although the CNS is one of the most common extramedullary manifestations of CLL,[2] less than 100 cases have been reported in the world literature to date.[3-16] Among the 4174 CLL patients cared for at our center over a 17-year interval, 33 (19% of evaluated patients; 0.8% overall cohort) developed clinically significant CNS involvement by CLL or RS.

While clinically significant CNS involvement by CLL is rare, neurological symptoms frequently occur in patients with CLL, and distinguishing whether or not these symptoms are due to CLL or other etiologies can be challenging. When a mass lesion is identified on imaging and a tissue biopsy can be performed, the evaluation and diagnosis for CNS involvement by CLL or RS is relatively straightforward. Biopsy is needed in these cases to distinguish between CLL, RS, primary brain tumors, or metastatic malignancy, as illustrated in our series. The evaluation of neurological symptoms becomes far more challenging when no lesion is identified on imaging. In fact, interpret-

Table 3. Clinical characteristics of patients with clinically significant CNS CLL/RS as compared to other etiologies of neurological symptoms.

Patients (n= 172)	N (%), median [range] CNS CLL/RS (33)	No CNS CLL/RS (139)	*P*-uni
Age (years)	63 [48-83]	68 [30-90]	0.44
Males	24 (73)	95 (68)	0.68
Females	9 (27)	44 (32)	
ALC (x10⁹/L)	5 [0-238]	4 [0-325]	0.44
Hemoglobin (mg/dL)	13 [9-16]	12 [7-17]	0.44
Platelets(10⁹/L)	181 [9-431]	163 [22-658]	0.70
Rai stage			
0	12 (36)	53 (38)	
I-II	14 (42)	53 (38)	0.89
III-IV	7 (22)	33 (24)	
CD49d positive	4 (44)	41 (59)	0.49
negative	5 (56)	29 (41)	
CD38 positive	8 (40)	45 (39)	1
negative	12 (60)	69 (61)	
ZAP70 positive	9 (60)	39 (50)	0.58
negative	6 (40)	39 (50)	
IGHV unmutated	3 (30)	43 (67)	0.04
mutated	7 (70)	21 (33)	
FISH			
del13q	3 (33)	6 (14)	0.49
negative	1 (11)	6 (14)	
+12	4 (45)	15 (37)	
del11q	1 (11)	9 (21)	
del17p	0 (0)	6 (14)	
Previously treated	17 (52)	76 (55)	0.85
Untreated	16 (48)	63 (45)	
CSF glucose (mg/dL)	53 [19-90]	60 [15-176]	0.03
CSF protein (mg/dL)	62 [31-161]	60 [11-301]	0.78
CSF TNC (cells/μL)	14 [1-443]	2 [1-11850]	0.007
CSF neutrophils (%)	1 [0-97]	1 [0-96]	0.94
CSF lymphocytes (%)	72 [8-97]	70 [1-100]	0.95
CSF lymphocyte count (cells/μL)	10 [1-97]	2 [1-11731]	0.02
CSF CLL (%)	5 [0-93]	0 [0-74]	0.05

CNS: central nervous system; CLL: chronic lymphocytic leukemia; RS: Richter syndrome; ALC: absolute lymphocyte count; IGHV: immunoglobulin heavy chain variable region gene; FISH: fluorescence in situ *hybridization; CSF: cerebral spinal fluid; TNC: total nucleated cells.*

ing the results of CSF analysis can be particularly difficult. Although flow cytometry is often needed to distinguish between reactive lymphocytes and CLL B cells,[5,12] the presence of CLL B cells in the CSF does not necessarily indicate that CLL is the etiology of the patient's neurological symptoms. In fact, CLL cells traffic to sites of inflammation and can often be present as a bystander in patients with infections or other inflammatory conditions.[21] Contamination of the CSF by peripheral blood (e.g. "bloody tap") can also detect CLL B cells in the CSF. As noted, autopsy series have demonstrated clinically insignificant CNS involvement in up to 70% of patients, indicating asymptomatic CNS involvement by CLL is relatively common.[17-20] This underscores the fact that a complete comprehensive work up is critical to exclude other etiologies of neurological symptoms rather than assuming the mere presence of CLL B cells in the CSF is an indication that CLL is the etiology of the patient's neurological symptoms. Indeed, the specificity of the presence of CLL B cells in the CSF study was relatively poor. As shown in our series, the sensitivity of CSF analysis is also low for those patients with parenchymal brain involvement by CLL/RS. An overview of our approach to the evaluation of neurological symptoms in patients with CLL is provided in Figure 4. As the first step, CLL should be re-staged, and transformation considered. Tests performed on peripheral blood should include cryptococcal antigen, but also erythrocyte sedimentation rate, vasculitis panel and ACE levels; tests performed on CSF should include Gram and fungal staining, bacterial and fungal cultures, and viral studies, including evaluation for all herpetic viruses and JC virus.

It is well recognized that patients with CLL have abnormalities in both cellular and humoral immune function and are at increased risk for infection.[22] Purine nucleoside-analogs, the historical mainstay of treatment of CLL, significantly decrease $CD4^+$ count and also contribute to risk of infection.[23] The most common CNS infection reported in our series was PML, caused by the JC virus. PML occurred in 11 (0.3%) out of the 4174 in our series. The reported incidence of PML in patients with CLL varies from 0.5% to 11.1%. However, most previous reports were heavily weighted toward patients receiving treatment, where advanced age, male sex and use of purine analogs appeared to be the primary risk factors.[8,24-26] In our series, all 11 patients with PML had received treatment, with 8 of 11 having received prior anti-CD20 therapy (e.g. rituximab, ofatumumab, obinutuzumab), 8 of 11 had received purine nucleoside analog-based therapy, and 4 of 11 had received prior alemtuzumab.

Although some statistically significant differences were observed in CSF parameters (e.g. glucose, number of nucleated cells) among patients with clinically significant involvement of the CNS by CLL compared to those with other etiologies for their neurological symptoms there was wide variability, and none reliably distinguished clinically significant involvement of the CNS by CLL from other causes. It is also worth noting that no clinical feature of CLL (e.g. Rai stage, prior CLL therapy) or CLL prognostic parameter (e.g. IGHV, ZAP-70, FISH, CD49d) was clearly associated with CNS involvement. In our series, only 52% of patients had been previously treated at the time of CNS CLL/RS diagnosis, and 78% had early stage disease by physical examination and complete blood count. Interestingly, most cases of CNS involvement by CLL reported in the literature also occurred in early stage and previously untreated patients.[5,14,27,28]

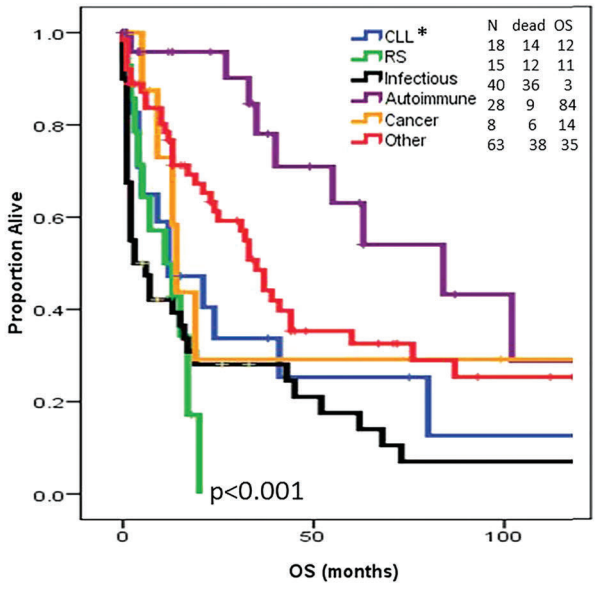

Figure 3. Overall survival (OS) by final diagnosis of etiology of neurological symptoms. *Clinically significant chronic lymphocytic leukemia (see Methods).

While the treatment of other CNS lymphomas has been extensively described and studied, there is no standard initial regimen for CNS CLL/RS due to the rarity of these conditions.[29] Although intrathecal therapy is widely used in the treatment of leptomeningeal diffuse large B-cell lymphoma and some other non-Hodgkin lymphomas, this is primarily because the medications that comprise the definitive treatment for these histologies do not penetrate the CNS. In contrast, a number of case reports have demonstrated the activity of systemic fludarabine-based therapy for CLL patients with CNS disease, which is typically our initial treatment approach.[30-32] Despite treatment, the prognosis for patients with clinically significant CNS involvement by CLL or RS in our series was dismal, with a median OS of 12 and 11 months, respectively, concordant with other published data.[2] The role of newer agents, inhibiting the B-cell receptor pathway and potentially altering the migration of CLL cells in extramedullary tissue, as a treatment for CNS involvement by CLL is unknown. Both lenalidomide and ibrutinib have shown promising CNS penetration in lymphoma, and further studies in patients with CNS involvement are warranted.[34,35]

Our study has some major limitations that need to be highlighted. First of all, this is a retrospective study; the diagnostic work up was not standardized but was based on physician's judgement, with consequent variability and missing values. Although, in our series, more biologically aggressive CLL characteristics were not associated with clinically significant CNS involvement by CLL, the sample size is limited for this analysis and may not have adequate power to detect a modest increase in risk. In addition, the diagnostic tools used have technical limitations; for example, MRI has limited sensitivity in the detection of leptomeningeal disease,[36-38] while the sensitivity of flow cytometry has improved over the 16-year period of our study.

In conclusion, although neurological symptoms occur

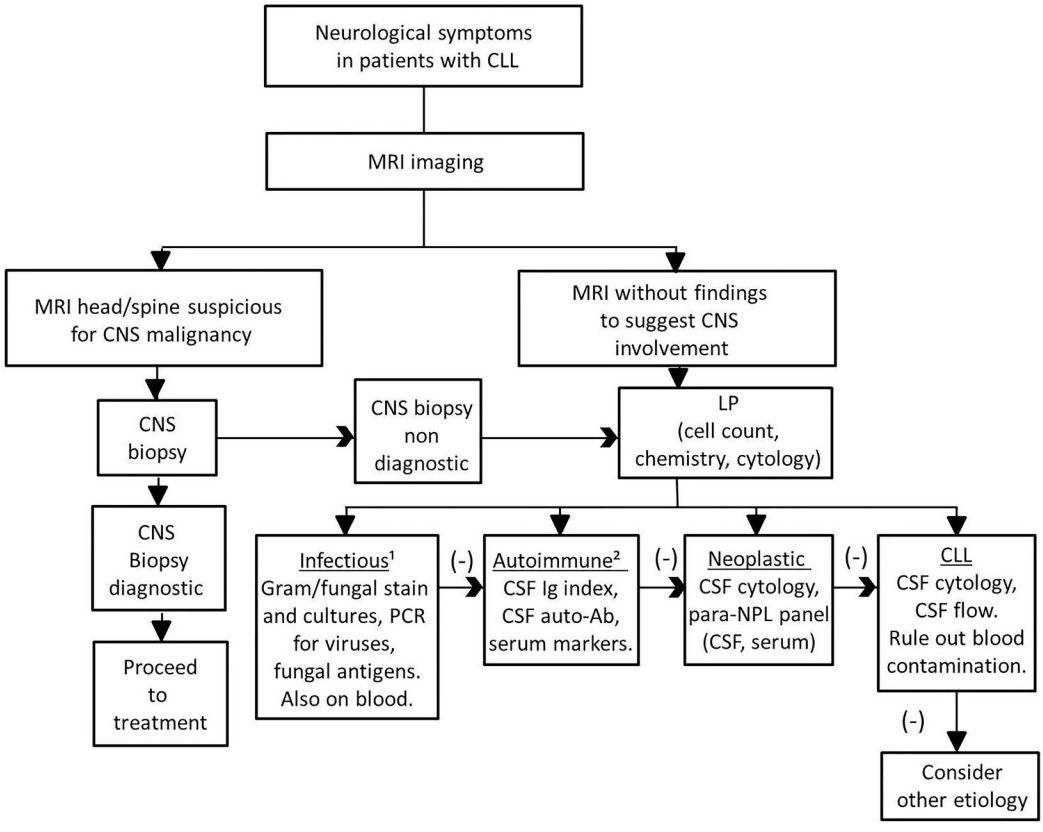

Figure 4. Diagnostic work up of neurological symptoms in patients with chronic lymphocytic leukemia. CNS: central nervous system; LP: lumbar puncture; PCR: polymerase chain reaction; CSF: cerebrospinal fluid; Ab: antibodies; NLP: neoplastic.¹PCR for viruses to include JC, WNL, HHV-6, EBV, VZV and CMV. Fungal antigens (both on CSF and blood) to include cryptococcus and coccidioides. ²CSF evaluation to include oligoclonal bands; serum markers to include p-ANCA, c-ANCA, anti-acetylcholine receptor and ACE.

relatively frequently in patients with CLL, clinically significant CNS involvement by CLL or RS is a rare condition.

The presence of CLL B cells in the CSF has reasonable sensitivity but low specificity and is insufficient to establish CLL as the etiology of patients' neurological symptoms. A comprehensive neurological evaluation including imaging, CSF analysis, and evaluation for a wide range of infectious and inflammatory conditions is needed to determine the etiology of neurological symptoms in these patients.

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