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Views & Reviews

Chronic lymphocytic leukemia and the central nervous system:

A clinical and pathological study

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Article abstract—Chronic lymphocytic leukemia is the most common human leukemia but infrequently causes neurologic symptoms. We have reviewed all previously reported cases of chronic lymphocytic leukemia in the CNS along with three new cases; one patient was diagnosed antemortem and treated with immediate improvement and 4-year survival. In addition, we reviewed all autopsy cases since 1972 and available lumbar puncture data on patients with chronic lymphocytic leukemia admitted to the Massachusetts General Hospital. Invasion of the CNS by chronic lymphocytic leukemia often leads to confusional state, meningitis with cranial nerve abnormalities, optic neuropathy, or cerebellar dysfunction. Lumbar puncture shows a lymphocytosis consisting of monoclonal B cells, but CSF cytology studies are of limited value in establishing the diagnosis. Long-term survival may be related to the stage of chronic lymphocytic leukemia at the time of CNS disease and may be associated with intrathecal chemotherapy. A mild, asymptomatic infiltration of the brain, frequently noted in late-stage chronic lymphocytic leukemia in autopsy series, may explain the CSF lymphocytosis in some patients with late-stage chronic lymphocytic leukemia.

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Chronic lymphocytic leukemia (CLL), the most common human leukemia the United States,[1] is an indolent disease that principally affects the elderly, whose median age at diagnosis is 60[2] and whose average survival is 6 years from the time of diagnosis.[3] Only a small percentage of patients progress to a more malignant phenotype.[4,5] Although there are many reports of CLL involvement of the peripheral nervous system, including peripheral neuropathy,[6-9] facial nerve palsy,[10-13] acoustic neuropathy,[13] femoral neuropathy,[10] and epidural compression of the spinal cord,[8,14,15] symptomatic invasion of the CNS by CLL has only rarely been reported. In autopsy series,[16-19] however, infiltration of the brain or spinal cord is common in CLL, but patients are asymptomatic. Thus, despite the diagnosis of 200,000 cases of CLL in the United States in the last 20 years,[20] there are only 18 reported cases causing CNS manifestations.

In this study, we document a case of successfully treated CNS CLL and review the literature on previously reported cases of CLL infiltration of CNS. In addition, we describe the pathological details of all CLL patients autopsied at the Massachusetts General Hospital (MGH) since 1972. To address the issue raised by autopsy studies of clinically silent infiltration of CNS by CLL, we also reviewed lumbar puncture results from 18 unselected CLL patients.

Methods. *Review of pathology.* Between 1972 and 1994, 83 patients with CLL died at MGH. Review of available charts and autopsy records disclosed 21 autopsies, 16 with CNS examination, which we studied (table 1). CNS CLL was diagnosed whenever abnormal numbers of mature or atypical lymphocytes were seen in the subarachnoid space or brain parenchyma, in the absence of an alternative explanation.[21]

Literature review. We only included cases of CNS CLL that met the following criteria: (1) a diagnosis of CLL; (2) a pleocytosis of predominantly lymphocytes in CSF or in the subarachnoid space on pathologic examination of the CNS; plus either (3a) histopathology highly suggestive of infiltration by CLL in the absence of an alternative explanation, (3b) predominantly B lymphocytes, preferably established as monoclonal, in the CSF, or (3c) a response to intrathecal chemotherapy and/or x-ray therapy, which was immediate and sustained. Use of the term CLL in this paper refers to the B-cell variety, as this accounts for 98% of CLL in the United States.[5] Using these criteria, several patients could not be included (Korsager et al,[22] patient 2; Leidler and Russell,[23] patient 16; Póltorak et al[24]; Diwan et al[25]; Pandolfi et al[26]; and Diamond,[27] patient 12).

Lumbar puncture review. Data on lumbar punctures performed on patients with CLL at MGH were identified during a review of the charts for pathology or from a review of laboratory data since 1988 on MGH patients with CLL.

Table 1 *Neuropathologic findings of 12 autopsy cases with CLL at Massachusetts General Hospital since 1972*

Case no.	Age at death (yr)	Rai stage	Last WBC	Clinical findings	Cause of death	Other CLL (+) organs	Neuropathology
A1	67	III	29,000	Neuro WNL	Renal failure	Spleen, lymph nodes, liver, kidneys	(−)
A2	59	IV	300	Confusion, left toe up, MRI (−)	Sepsis	(−)	Cerebral edema, subdural effusions
A3	81	II	42,000	Left VII palsy, dysmetria, dementia, CT (−); IgG κ paraprotein	Pneumonia	Lymph nodes, liver, spleen, bone marrow	Diffuse Lewy body disease
A4	78	IV	7,000	Neuro WNL	Pneumonia	Bone marrow, spleen, lymph nodes	(−)
A5	77	0	15,000	Ataxia; weak ankles, loss of vibration sense	Pneumonia	(−)	Cortical atrophy, hydrocephalus
A6	59	IV	386,000	Cells blastic in final mos, neuro WNL	CHF and pneumonia	Bone marrow, liver, spleen, kidney, lungs, larynx, heart, adrenals, periosteum	Lymphocytes in brain and Virchow-Robin space; areas of recent ischemic change (see figure 1)
A7	53	II	2,000	Prior x-ray therapy to parotid lymphoma; confused	*Listeria monocytogenes* meningitis	Scalp; CLL and lymphoma in lymph nodes and lungs	Changes of acute meningitis, early cerebral infarcts
A8	63	IV	111,000	Neuro WNL; transformed to lymphoma (Richter's syndrome)	Lymphoma	DWDL and large cell lymphoma in liver and spleen; former also in nodes	Subdural ecchymoses
A9	87	0†	14,000	Agitated; bilateral hygromas on CT	Strangulated hernia	Prostate, lungs, bone marrow, liver, kidneys, spleen	Clusters of subarachnoid lymphocytes (see figure 2), lacunae, subdural hygromas, Alzheimer's disease
A10	69	I	15,000	Neuro WNL	Gastrointestinal bleeding	Lymph nodes, spleen, kidneys	(−)
A11	63	II	13,000	14-mo history of lung cancer; neuro WNL	Sepsis	Bone marrow, spleen, liver; lung cancer in brain/other sites	Large-cell lung cancer metastasis
A12	69	IV	4,000	Cells blastic in final mos; mild, diffuse weakness	Sepsis	Spleen, lymph nodes, bone marrow, liver, kidneys	Some subarachnoid lymphocytes with normal appearance

† Diagnosis of CLL made at autopsy.

WBC = white blood cell count; CLL = chronic lymphocytic leukemia; WNL = examination within normal limits; IgG = immunoglobulin G; CHF = congestive heart failure; DWDL = diffuse well-differentiated lymphocytic.

Statistical analysis. The Kaplan-Meier product-method[28] was used to estimate survival probabilities, with statistical inferences on actuarial curves made using the log-rank test.[29] Six patients who did not die, but who lacked at least 1 year of followup, were excluded from survival analysis.

Case Report. A 62-year-old woman (see table 2, case C21) presented to UCLA Center for Health Sciences with complaints of left ear hearing loss, weakness, poor balance, and unsteady gait. Twelve days before admission, her white blood cell (WBC) count was 35,000 and her physical examination was unremarkable. A diagnosis of CLL had been made 2 years before and she had received no therapy, remaining Rai stage 0.[3] Her past medical history was significant for bilateral myringotomies with tube placement 3 years before, and she had been treated with oral ampicillin for 2 days before admission.

She had a temperature of 37.8°C. A physical examination showed a serous otitis media and a mass on the left auditory canal wall; no lymphadenopathy or hepatosplenomegaly was noted. Neurologic examination disclosed normal mental status. Funduscopy was normal. She had four beats of lateral nystagmus on end-point gaze to the left and to the right and intermittent ptosis. Deep tendon reflexes were 3+ with normal tone and bilateral extensor toe
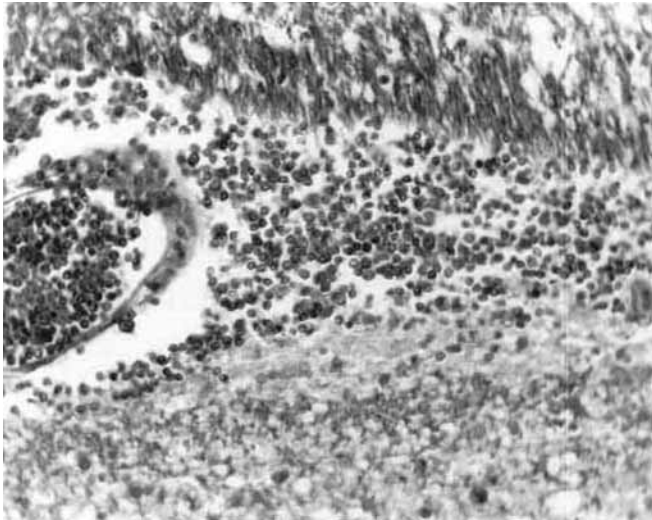
Figure 1. Case A6. In a patient with chronic lymphocytic leukemia who underwent a blastic transformation, lymphocytes with a malignant appearance fill a subcortical blood vessel and the Virchow-Robin space (Luxol fast blue, hematoxylin and eosin, ×250).

responses. Motor and sensory examinations revealed only decreased vibration in her feet. An intention tremor of the upper extremities was more marked on the left, and heel-to-shin testing was normal. Her gait was wide based and ataxic; tandem gait was poor. Bárány's tests were negative. Her laboratory results were significant for a WBC of 98,000, including 91% lymphs, 4% segs, and 3% bands. Peripheral smear lymphocytes were predominantly mature with less than 3% immature forms. Hemoglobin was 12.2 g/dl with platelets of 313,000/mm³. A contrast-enhanced CT scan of the brain was interpreted as diffuse swelling of the cortex and cerebellum with small, enhancing lateral ventricles and a slit-like fourth ventricle. Opacification was noted in the left middle, but not inner, ear.

Intravenous dexamethasone, cefuroxime, and ampicillin were begun, and she quickly defervesced. Myringotomy cultures were negative and the left ear mass/otitis media improved markedly with antibiotics, but before methotrexate. Lumbar puncture performed on hospital day 1 was traumatic. Lumbar punctures on days 3 and 5 showed normal opening pressures, glucose ratios, and protein and a WBC count that fell from 260/mm³ to 135/mm³, all lymphocytes in both cases. Extensive microbiological studies were negative. Atypical lymphocytes were noted on cytology studies. Immunocytochemical studies of CSF and peripheral blood lymphocytes showed a clonal population of immunoglobulin G (+), κ light chain (+) B cells. After the second and third lumbar punctures, 12 mg of methotrexate in 10 ml of Elliot's B solution was given intrathecally. Her neurologic examination became normal over 7 days and the patient was discharged. Her subsequent total intrathecal therapy was six doses of 12 mg of methotrexate and one dose of 100 mg of cytarabine (Ara-C) over an 8-week period. A lumbar puncture done 26 days after admission was normal. She then received 4000 cGy of cranial x-ray therapy.

Two years later, she was placed on chlorambucil for anemia. Four years after her CNS symptoms were treated, her WBC count rose to 225,000 with increased numbers of

immature cells. A bone marrow biopsy showed small, cleaved, follicular center-cell lymphoma with evolution to large-cell lymphoma, and chemotherapy was started. She then presented with a fever and multiple abdominal masses. She could not follow one-stage commands, although her neurologic examination was otherwise unremarkable. A noncontrast head CT scan was normal, and a lumbar puncture was normal with negative cytology. The patient's death was ascribed to transformation of CLL to a malignant large-cell lymphoma (Richter's syndrome). No autopsy was performed.

Results. The neuropathology findings from the 12 autopsied patients with CLL at MGH with available microscopic sections are described in table 1; no gross diagnostic abnormalities were recorded and no microscopic sections were taken in four cases. Infiltration of CNS by CLL cells was noted in two cases: one, Rai stage IV (case A6, figure 1) and the other, Rai stage 0 (case A9, figure 2). The degree of infiltration[21] was grade III/III for case A6 and grade I/III for case A9. An aggressive transformation of the CLL was noted in cases A6, A8, and A12, whereas case A7 was associated with a recurrent lymphoma. The spinal cord was included in only one autopsy (case A12).

Table 2 illustrates the clinical features for the 18 reported patients from the literature and our three cases of CLL in the CNS. CNS involvement occurs across all stages of CLL, with a median age of 63 years (range, 38–87) and
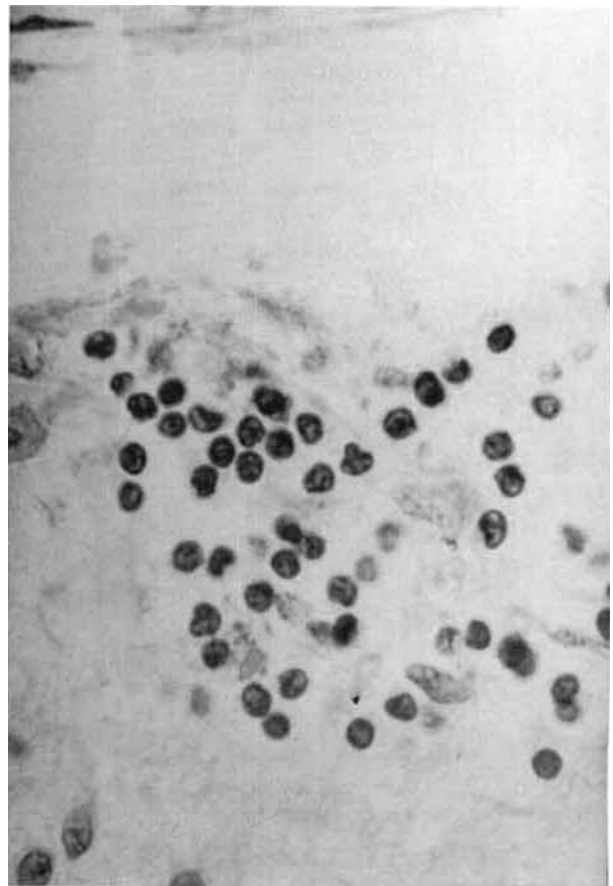

Figure 2. Case A9. This patient was diagnosed with chronic lymphocytic leukemia at autopsy. Scattered clusters of atypical-appearing lymphocytes in Virchow-Robin space (Luxol fast blue, hematoxylin and eosin, ×790).

Table 2 *Clinical characteristics of patients with CLL in the CNS*

Patient no.	Rai stage	Clinical findings	CSF WBC (cells/mm^3)	Treatment	Course
C1[30]	0	Headache, confusion, reverse ocular bobbing; suprasellar lesion on CT	Lymphs; protein 600	VP shunt	Died on postoperative day 10
C2[31]	IV	Headache, fever	253 WBC; 100% lymphs	XRT and it MTX	Died of cardiac causes after 5 asymptomatic mo
C3[31]	IV	Fever, right VI palsy	80 WBC; 100% lymphs	it MTX	Symptom free at 30 mo
C4[22]	II	2 years dementia	257 WBC; 100% lymphs	XRT and it MTX	Transiently improved with XRT, died at 7 mo
C5[32]	II	Fever, infiltrate in sinuses and orbits on CT	170 WBC; 100% lymphs	XRT and it MTX	Disease free at 1 mo; died of sepsis at 1 year
C6[33]	III	10 mo optic neuropathy	25 WBC; 100% lymphs	XRT to optic nerve	Died at 10 mo of trauma
C7[33]	III	2 mo optic neuropathy	21 WBC; 100% lymphs	XRT to optic nerve	Stable at 9 mo
C8[33]	IV	6 mo optic neuropathy	Lymphs	XRT to optic nerve	XRT improved symptoms; died at 13 mo of lung process
C9[34]	0	Sensorimotor symptoms; optic atrophy and central scotomas	117 WBC; 96% lymphs	XRT, it MTX, and Ara-C	No symptoms at 20 mo
C10[34]	0	6 mo sensory and cerebellar symptoms; intention tremor, poor tandem gait, right leg vibration loss	2,500 WBC; most lymphs	XRT, it MTX, and Ara-C	Free of disease at 7 mo
C11[35]	II	6 weeks vomiting, vertigo, tinnitus, unsteady gait	4 WBC; most lymphs	Aspirin	Symptoms continue at 4 mo
C12[36]	0	1 mo loss of OD vision and movement; ataxia, confusion, right face sensory loss; orbital mass on MRI	175 WBC; 98% lymphs	None	Died 3 mo later
C13[37]	II	Ataxia, lower cranial nerve palsies, later coma	71 WBC*	XRT and it MTX	No symptoms at 30 mo
C14[38]	III	Headache, fever, SIADH	334 WBC; 100% lymphs	it MTX	No symptoms; died after 1 year of cardiac disease
C15[39]	II	OS visual loss; pituitary mass	12 WBC; 95% lymphs	Removal of mass	Normal postoperative neurologic assessment
C16[40]	IV	Headache and vomiting	1,100 WBC*	it MTX and Ara-C	No symptoms at 3 mo
C17[41]	0	Headache, right VII and bilateral VI palsies, ataxia, AD deafness	676 WBC; 100% lymphs	XRT and it MTX	No symptoms at 2 mo
C18[42]	IV	Spastic paraparesis	Malignant cytology	XRT and it MTX	Died of cardiac causes days after beginning treatment
C19	IV	No neurologic signs or symptoms	11 WBC; 100% lymphs	None	Died of pneumonia; CNS CLL diagnosed at autopsy
C20	0	Agitated	No lumbar puncture	None	Died of strangulated hernia; CLL diagnosed at autopsy
C21	0	AS deafness, nystagmus, ataxia, hyperreflexia	260 WBC; 100% lymphs	XRT, it MTX, and Ara-C	Died at 4 years of Richter's syndrome sparing CNS

Cases C19 and C20 appear in table 1 as A6 and A9, respectively. Case C21 is the case report.
* The majority of WBCs are prolymphocytic.

CLL = chronic lymphocytic leukemia; WBC = white blood cell count; VP = ventriculoperitoneal; XRT = x-ray therapy; it MTX = intrathecal methotrexate; Ara-C = cytarabine; OD = right eye; SIADH = syndrome of inappropriate antidiuretic hormone secretion; OS = left eye; AD = right ear; AS = left ear.

an even sex distribution. Presenting features include altered mental status (acute and chronic), optic neuropathy, meningitis with cranial nerve deficits, and cerebellar signs. Lumbar puncture was performed in all but one patient and showed a lymphocytic pleocytosis of variable degree, with a range of 4 to 2,500 WBC/mm^3 (median, 172). In 11 cases in which immunostaining was performed, CSF cells were monoclonal and identical to peripheral lymphocytes. Cytologic results were normal in five cases, positive for malignant cells without further details in one case, and only atypical in four cases. CSF glucose was normal in 11 cases and low in one, whereas CSF protein was normal in six cases and high in seven (median for elevated values, 107 mg/dl). Only one patient in this group had a serum paraprotein. Brain imaging was unremarkable in four cases and revealed a mass in three, thickened optic nerves in two, and ventriculomegaly in one. Autopsy was performed in four cases, two of which were detailed.

Survival time, or time to last followup, was calculated from the time of treatment initiation. Survival was correlated with treatment in the 15 patients who received x-ray therapy or intrathecal methotrexate, or both. The dose of x-ray therapy was 3000 cGy in half of the cases in which the dose was reported, with a range of 1000 to 4000 cGy. Those patients who received x-ray therapy did not fare better than those who were not radiated. While support for cranial x-ray therapy may come from the observation that three of the four longest survivors received a dose of 3000 cGy or greater, two of these long-term survivors had isolated optic nerve disease. When reported, the number of intrathecal methotrexate doses ranged from two to seven and the doses ranged from 5 to 12 mg. When maximum survival data were analyzed with regard to the use of intrathecal methotrexate, a significantly improved survival ($p < .005$) was noted when compared with another or no treatment. The combination of intrathecal methotrexate and x-ray therapy, however, did not yield improved survival when compared with the combined group of untreated patients and patients treated with intrathecal methotrexate or x-ray therapy alone. Once CLL in the CNS was eradicated, it tended not to recur and neurologic relapse was not evident in the four longer term survivors in whom the cause of death was reported. These survival results, however, are based on a review of a relatively small and heterogeneous population; larger controlled studies will obviously be needed to address these issues more completely.

A nonsignificant trend between increased survival time and earlier stage of CLL at the time of CNS infiltration was observed. Of the four longest survivors in table 2, two were stage 0 and one was stage II. No significant survival advantage was found as a function of age, gender, WBC count, Rai stage, or duration of disease.

The data from 19 lumbar punctures from 18 patients with CLL at MGH showed a CSF lymphocyte count of less than or equal to 3 cells/mm^3 in all cases, except for four with a mild lymphocytic pleocytosis (range, 6–60 cells/mm^3) and a fifth with Listeria monocytogenes meningitis. Two of the four cases with mild CSF lymphocytic pleocytosis had elevated CSF proteins (68 and 75 mg/dl). Cytologic examination was performed in seven patients, two with a lymphocytic pleocytosis, and was unremarkable in all cases. CSF pleocytosis occurred in patients with stage IV

disease and in the absence of focal neurologic abnormalities; significantly, three of the four cases had systemic infections at the time of lumbar puncture. One of these cases (A6) was autopsied and was found to have infiltration of CNS by CLL.

Discussion. Symptomatic infiltration of the CNS by CLL is uncommon and is usually expressed as confusional state, meningitis with cranial nerve abnormalities, optic neuropathy, or cerebellar signs. Symptomatic CNS involvement occurs at all stages of CLL and is accompanied by a CSF lymphocytosis. Asymptomatic CNS CLL, however, is common, particularly in later stages, with autopsy studies showing frequencies of >8%,[19] 45%,[18] 50%,[17] and 71%.[16] Only 17% of cases in our autopsy series (see table 1) had CNS CLL, but this low frequency may reflect the paucity of available sections of spinal cord, the most commonly involved site.[17] In our lumbar puncture series, 18% of asymptomatic patients had lymphocytic pleocytosis, all of whom died with Rai stage IV disease within days of lumbar puncture. These cases may represent the antemortem analogue of the asymptomatic CNS CLL noted in autopsy series.

Increased risk for symptomatic CNS CLL was not predicted by Rai stage, duration of CLL, gender, age, immunologic phenotype, or peripheral WBC count (see table 2). Symptomatic CNS CLL occurred at all Rai stages and in patients from the time of CLL diagnosis to 12 years after diagnosis. CNS involvement was present in equal numbers of men and women. The median age of the patients was 63 years, approximating the median age of patients diagnosed with CLL—60 years.[2] Immunophenotyping in 13 patients showed immunoglobulin M heavy chains and κ light chains in almost all cases, which are typical of CLL in general.[43,44] Only four of the 21 patients with CNS involvement had a peripheral lymphocyte count greater than 1.5 times the mean number associated with respective stage of the disease.[3]

On the other hand, autopsy comparison of systemic CLL sites between those patients with CNS involvement and those without CNS involvement disclosed four extraneural sites unique to patients with CNS disease: parathyroid, prostate, heart, and larynx. CNS infiltration was also associated with a greater number of affected systemic sites: All four CNS CLL cases with detailed autopsy had CLL in five or more organs at the time of death, whereas only 1 of 10 autopsies without CNS involvement had CLL spread to this many sites. CLL infiltration into CNS may therefore be a random event whereby a fraction of patients with bulky disease, including leukemia in skull bone marrow or peri-CNS tissues, will suffer CNS involvement.

CNS infiltration by CLL may also reflect a biologically more aggressive neoplasm, since some CLL subtypes may be more malignant. For instance, a subset of CLL patients with more diffuse bone marrow infiltration and shortened survival have certain

chromosomal aberrations,[45-47] but karyotypic studies of CNS CLL have not yet been performed. Alternatively, transformation of CLL to a more aggressive variant or association of CLL with an extraneural lymphoma may predispose to CNS involvement. Six of the 21 CNS CLL cases (see table 2) had either lymphomas or transformation. However, this frequency of Richter's syndrome and prolymphocytic transformation is similar to those of other large CLL series.[4,5]

The mechanism by which CLL cells enter the CNS remains unknown. Neuropathologic findings include leukemic meningitis, perivascular CLL cells, and lymphocytes extravasated with hemorrhage. The similarity to descriptions of ALL in the CNS[21] suggests that CLL cells may gain access in an analogous manner, by extending along perforating vessels from the bone marrow through the dura mater and into the subarachnoid space.[48] Other investigators postulated the same mechanism for CNS spread of non-Hodgkin's lymphoma.[49,50] Consistent with these hypotheses is the observation of a peri-CNS focus of CLL in five of the cases (see table 2). ALL may also gain entry to the CNS via hemorrhage into brain parenchyma,[51,52] a mechanism which may underlie some CNS CLL (case A6, table 1).

One case in our lumbar puncture series, with a normal CSF and no serum paraprotein, was diagnosed with amyotrophic lateral sclerosis (ALS). Younger et al[53] reported three patients with CLL and ALS or motor neuron disease who also had normal CSF cell counts and cytology. A monoclonal gammopathy was identified in two of the three patients of Younger et al,[53] but in only one of the 21 patients in table 2. The relationship between CLL, ALS, and monoclonal gammopathies, however, has not been clearly established.[53]

The diagnosis of CNS CLL has a number of potential pitfalls. First, early in the course, CNS symptoms may occur with a normal peripheral lymphocyte count, necessitating immunophenotyping studies of peripheral lymphocytes for diagnosis.[54] Second, routine cytologic evaluation is of limited value given the morphologically mature appearance of CLL lymphocytes,[55] the limited diagnostic value of atypical lymphocytes, and the occurrence of false-positive and false-negative results. For instance, in one series of CLL patients, the only positive CSF cytologies were false-positive.[56] On the other hand, a review of antemortem cytology in patients with autopsy-proven leptomeningeal cancer revealed more than half to be false-negative.[57] Third, many diseases can mimic the clinical and CSF picture of CNS CLL. Apart from lymphoma,[58,59] however, these produce a T-cell–predominant CSF lymphocytosis.[60-63] Lymphoma can arise in the setting of CLL (Richter's syndrome) and may involve the CNS, but can be distinguished clinically from CNS CLL.[64] In systemic Richter's syndrome, the diagnosis is suggested by fever, weight loss, and painful abdominal masses,[4] whereas the rare primary CNS Richter's syndrome

features an intracranial mass lesion.[65-67] Because of such potential pitfalls, the importance of immunophenotyping CSF lymphocytes to reach a diagnosis of CNS CLL should be stressed.[43,54]

Our case illustrates that, with treatment, infiltration of the CNS by CLL need not have a dire prognosis. The treatment of our patient with intrathecal chemotherapy and cranial x-ray therapy resulted in a 4-year, neurologically asymptomatic survival. Analysis of 21 cases showed a significant increase in survival associated with intrathecal chemotherapy alone, but not when intrathecal chemotherapy was combined with x-ray therapy. For patients who received x-ray therapy alone, the only two long-term survivors had disease localized to the optic nerve, which may represent a different disease process. Given the paucity of data, the role of systemic chemotherapy in CNS CLL cannot be ascertained. Subsequently, conclusive recommendations for therapy of symptomatic CNS CLL must await a larger prospective trial. In addition, asymptomatic patients with monoclonal CSF lymphocytosis may also benefit from intrathecal chemotherapy, but this, too, must await further study.

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