Chronic Lymphocytic Leukemia Involvement of Central Nervous System: Clinical Diversity, Diagnostic Algorithm and Therapeutic Challenges

Sir,

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia, but extranodal involvement is rare, as previously reported in 4 and 30 patients, respectively.[1,2] Neurologic complications are reported in only 1% of patients with CLL.[3] Nevertheless, some previous autopsy studies reported central nervous system (CNS) involvement to be far more frequent, suggesting that it can be underdiagnosed.[3] Diagnostic includes clinical examination, cerebrospinal fluid (CSF) cytology, magnetic resonance imaging, and additional CSF flow cytometric immunophenotyping (FCI) since CSF cytology is of low sensitivity.[4] Here, we present four CLL patients with CNS involvement in which the most common neurological

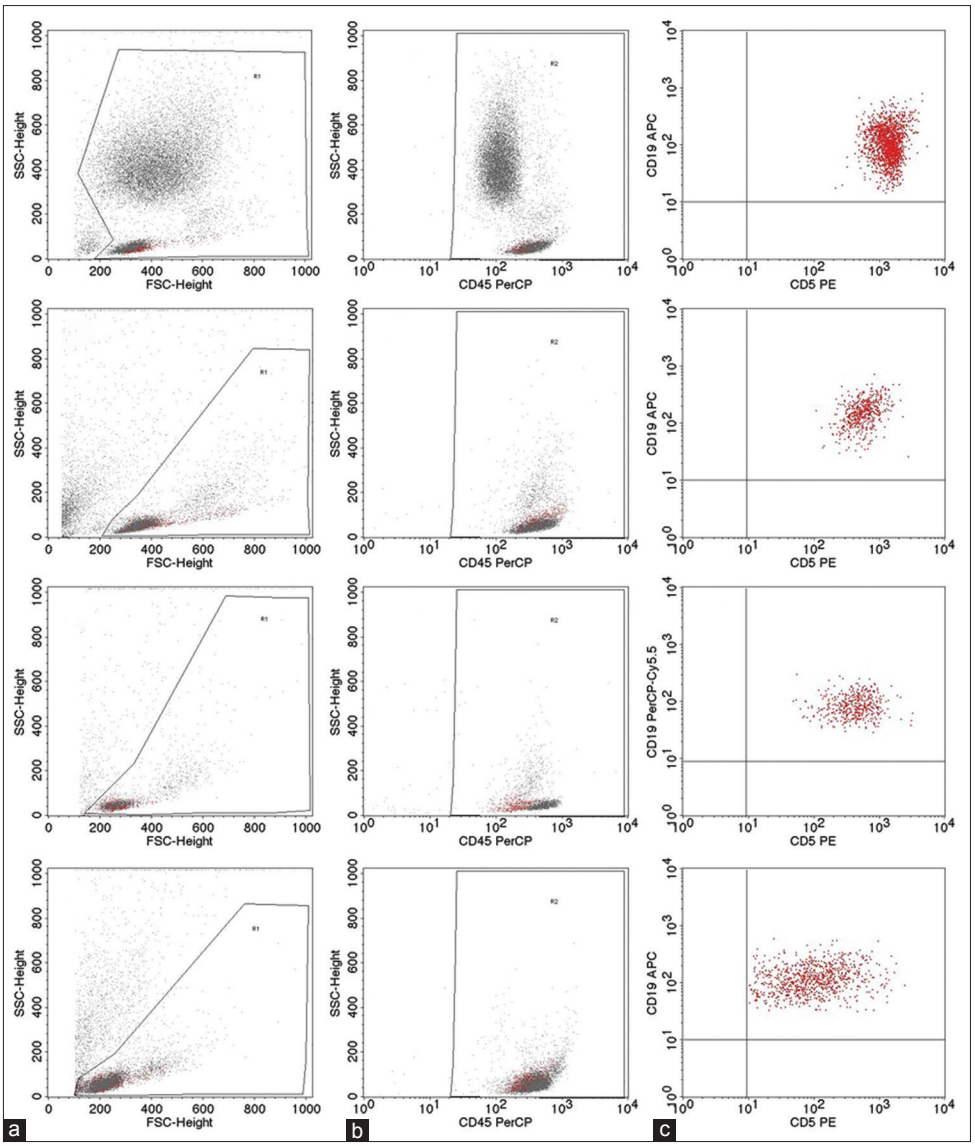

Figure 1: Two-parameter dot blot histograms representing CSF FCI analysis in all patients: a) CSF specimen characteristics according to forvard scatter (FSC) vs. side scatter (SSC); b) CSF specimen characteristics according to CD45 vs. SSC; c) population of CLL cells detected in CSF specimen according to specific immunophenotype and low SSC – $CD19^{+}CD5^{+high}CD45^{+high}/SSC^{low}$

symptoms were headaches, mental status changes, cranial nerve abnormalities, cerebellar symptomatology, lower and upper limbs weakness, and optic neuropathies. All our patients were males with an average age of 55.2 years. Average latency period from diagnosis of CLL to CNS symptomatology onset was 2.9 years. In all cases, CNS involvement was treated with systemic chemotherapeutics plus intrathecal therapy. Radiotherapy was not applied due to either poor general condition or severe thrombocytopenia. Median overall survival from CNS leukemia onset was 3.5 months, with lethal outcome in 75% of patients. General patients characteristics are summarized in Table 1, in which is obvious that all of them had an advanced disease stage at presentation. Moreover, when CNS infiltration in CLL patients was diagnosed, CSF biochemistry and microbiology showed normal findings, despite of the presence of CLL neoplastic cells (3%–17%) in CSF detected by CSF-FCI [Figure 1]. This is consistent with the fact that a diagnostic "gold standard" of CNS involvement in CLL is CSF cytology, with excellent specificity (>95%), but lower sensibility in up to 60% of explored cases.[5] Besides, the correlation between CNS involvement and presence of neurological symptoms in CLL is not always obvious, regarding the fact that many of these patients have never presented with any neurological symptoms. No specific risk factor for CNS involvement has been identified yet, and in that context, the number of leukocytes at diagnosis had no influence on the occurrence of CNS infiltration. Even though the presence of infectious agents can affect destabilization of hematoencephalic barrier, it was not verified in our patients.

Concerning standard therapeutic approaches, no significant difference in long-term outcome was observed with intrathecal therapy versus radiotherapy versus intrathecal plus radiotherapy. Some systemic chemotherapy regimens such as fludarabine, cycplophosphamide, or bendamustine, combined with rituximab with/without intrathecal therapy significantly improved clinical course, especially high effective bruton tyrosine kinase inhibitor-ibrutinib.[2]

In view of the poor prognosis in these patients, prompt recognition of even a slight occurrence of neurological symptoms in CLL is an imperative for appropriate diagnosis

Table 1: General patient's characteristics

Patient's ID	1 - MV	2 - DJA	3 - DR	4 - TR
Age/sex	57/male	43/male	72/male	49/male
CLL onset				
CS (Rai)	III	IV	IV	II
WBC ($\times 10^9$/L)	85.5	23	103.9	86.5
Peripheral blood FCI dg/ matutes CLL score	CLL, $CD38^+$/score 5	CLL, $CD38^+$/score 5	CLL, $CD38^-$/score 5	CLL, $CD38^-$/score 5
Karyotype	Del 17p	Normal	13q14 nullisomy	N/A
CNS involvement on CLL onset	No	No	No	No
CNS onset - CS (Rai)	IV	IV	IV	IV
Neurological symptoms on CNS involvement onset	Bradypsychia, headaches, nausea, vomiting	Dysphasia, repeated unconsciousness, urinary, incontinence	Dyslexia, lack of fine motor control, diplopia	Diplopia, bilateral eyelid swelling, and tumors
Type/localization of CNS lesions	Periventricular, thalamic, insular, basal ganglia, leptomeningeal	Supratentorial white matter, basal ganglia, medulla oblongata	Parietal/frontal subcortex, both cerebelar peduncles	Medulla oblongata
CSF cytology	Positive (2200 c/µl)	Positive (16 c/µl)	Negative (14 c/µl)	Positive (136 c/µl)
CSF FCI	CLL cells - 3%	CLL cells - 9%	CLL cells - 17%	CLL cells - 8%
CD45/SSC differential (%/$CD45^+$ cells)	Σ lymphocytes - 27%	Σ lymphocytes - 88%	Σ lymphocytes - 86%	Σ lymphocytes - 99%
	Neutrophils - 69%	Neutrophils - <1%	Neutrophils - <1%	Neutrophils - <1%
	Monocyte elements - 2%	Monocyte elements - 10%	Monocyte elements - 14%	Monocyte elements <1%
CSF biochemistry	Reference range	Reference range	Reference range	Reference range
CSF microbiological analysis	Normal	Normal	Normal	Normal
Time from CLL onset to CNS onset (months)	6	62	9	63
Intrathecal therapy	Yes	No	No	No
Therapy at CLL diagnosis	"watch and wait"	"watch and wait" FC	"watch and wait"	CHOP
Therapy on CNS onset	HD-MTX	R-FC	DHAP	DHAP
Time from CNS onset to death (months)	4	Still in follow up (7 months from CNS onset)	3	2

CLL: Chronic lymphocytic leukemia, CS: Clinical stadium, WBC: White blood cells, FCI: Flow cytometric immunophenotyping, CNS: Central nervous system, CSF: Cerebrospinal fluid, SSC: Side scatter, N/A: Not available, CHOP: Doxorubicin; cyclophosphamide; vincristine; prednisolone, HD-MTX: High dose methotrexate, FC: Fludarabine; cyclophosphamide, R-FC: Rituximab; fludarabine; cyclophosphamide, DHAP: Cisplatine; cytosine-arabinoside; dexamethasone

of CNS involvement, whereas the implementation of CSF-FCI as a routine diagnostic tool may be of a great importance, due to its high sensitivity.

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Conflicts of interest

There are no conflicts of interest.

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