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CASE REPORT

Refractory Chronic Lymphocytic Leukemia with Central Nervous System Involvement: A Case Report with Literature Review

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Abstract: There have been few reports on central nervous system (CNS) involvement in chronic lymphocytic leukemia (CLL). This is an extremely rare disease with poor prognosis, owing to resistance to various treatments. We describe a 33-year-old man with intractable CLL with CNS involvement. He was diagnosed with CLL, with diplopia as the first manifestation. Magnetic resonance imaging revealed a contrast-enhancing tumor in the right temporal lobe, which was diagnosed as CNS involvement in CLL on brain biopsy. High-dose methotrexate therapy was ineffective for this lesion, which was also resistant to subsequent whole-brain irradiation, treatment with fludarabine–cyclophosphamide–rituximab chemoimmunotherapy, and ibrutinib administration. Because no standard protocol exists for CLL with CNS involvement, it is important to accumulate case data to verify the choice of new drugs for administration at an early stage. Therefore, we also conducted a literature review of 50 case reports of CNS lesions in the last 10 years to consider the pathophysiology, diagnosis, and treatment of CNS involvement in CLL. The possibility of new therapeutic agents, eg, ibrutinib and venetoclax, or a combination of these agents and methotrexate, can be envisioned as a treatment strategy for CLL with CNS involvement.

Keywords: chronic lymphocytic leukemia, central nervous system involvement, literature review

Introduction

Chronic lymphocytic leukemia (CLL) is the most frequent adult leukemia in the US and Europe, but is a rare disease in Japan, with a frequency 10% that in theUS.[1] The disease typically occurs in older patients, and the median age at diagnosis is 72 years.[2] Generally, CLL progresses slowly, but some cases progress rapidly and aggressively.[3] Furthermore, CLL has a highly variable clinical course, and neurological complications arising from direct leukemic involvement in the central nervous system (CNS) are reported in only 1% of patients with CLL.[4,5] Here, we present a rare case of a young CLL patient with CNS involvement that was resistant to various therapies. CLL treatment has improved considerably in the last decade; however, it remains unclear which the best treatment for CNS involvement in CLL is. Therefore, in this case report, we also conducted a comprehensive literature review of 50 case reports with CNS involvement in the last 10 years in which the clinical course was described.

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Case Presentation

A 33-year-old man with diplopia was referred to our hospital. He had a 9 month history of asymptomatic revised Rai low– and Binet A–stage CLL that had been diagnosed owing to an increase in lymphocyte count at a medical checkup, but he had not come to the hospital at his own discretion. Thereafter, he developed diplopia and was referred to neurosurgery by an ophthalmologist. Except for double vision and intracranial hypertension–related headaches, the neurological examination was unremarkable, and he had no other symptoms or lymph-node swelling. Magnetic resonance imaging (MRI) revealed a 5×3.5 cm nonuniformly contrasted mass in the right temporal lobe that appeared hypointense on T_1-weighted and hyperintense on T_2-weighted images (Figure 1A). In this case, because there was a risk of cerebral hernia owing to a bulky CNS lesion, lumbar puncture could not be performed.

A diagnostic cranioscopic biopsy was performed, which revealed infiltration of small monoclonal lymphocytes with expression of CD5, CD20 (Figure 2), and CD79A, but without CD10, CD23, cyclin D1, or evidence of transformation. Similarly, his blood showed CLL-cell clonality, with expression of CD5, CD19, CD20 (dim), CD22, and cell-surface Ig, but no expression of CD10, CD23, or IgH-BCL1 on fluorescence in situ hybridization. Bone marrow (BM) specimens revealed 96.6% of lymphocytes had the same flow-cytometry appearance as peripheral blood (PB). BM lymphocytes had a normal karyotype without poor prognostic factors, deletion 17p, deletion 11q, or transformation (Figure 3), which was compatible with a diagnosis of CLL. These findings were indicative of leukemic involvement in the CNS, and the patient was eventually transferred to hematology. In this case, Richter's syndrome was initially suspected from the symptoms and course, but CNS-infiltrating cells were small lymphoid cells similar to those of PB and BM, and transformation to a diffuse large-cell type was ruled out by brain biopsy. Therefore, we diagnosed CNS involvement in CLL.

Laboratory data (Table 1) were significant for a white blood–cell count of 464,200/μL (98.5% lymphocytes and 1.5% neutrophils). Hemoglobin level and platelet count were 11.7 g/dL and 305,000/μL, respectively. Lactate dehydrogenase was 262 IU/L (normal range 112–230 IU/L) and soluble IL2R 11,000 IU/L (normal range 124–466 IU/dL).

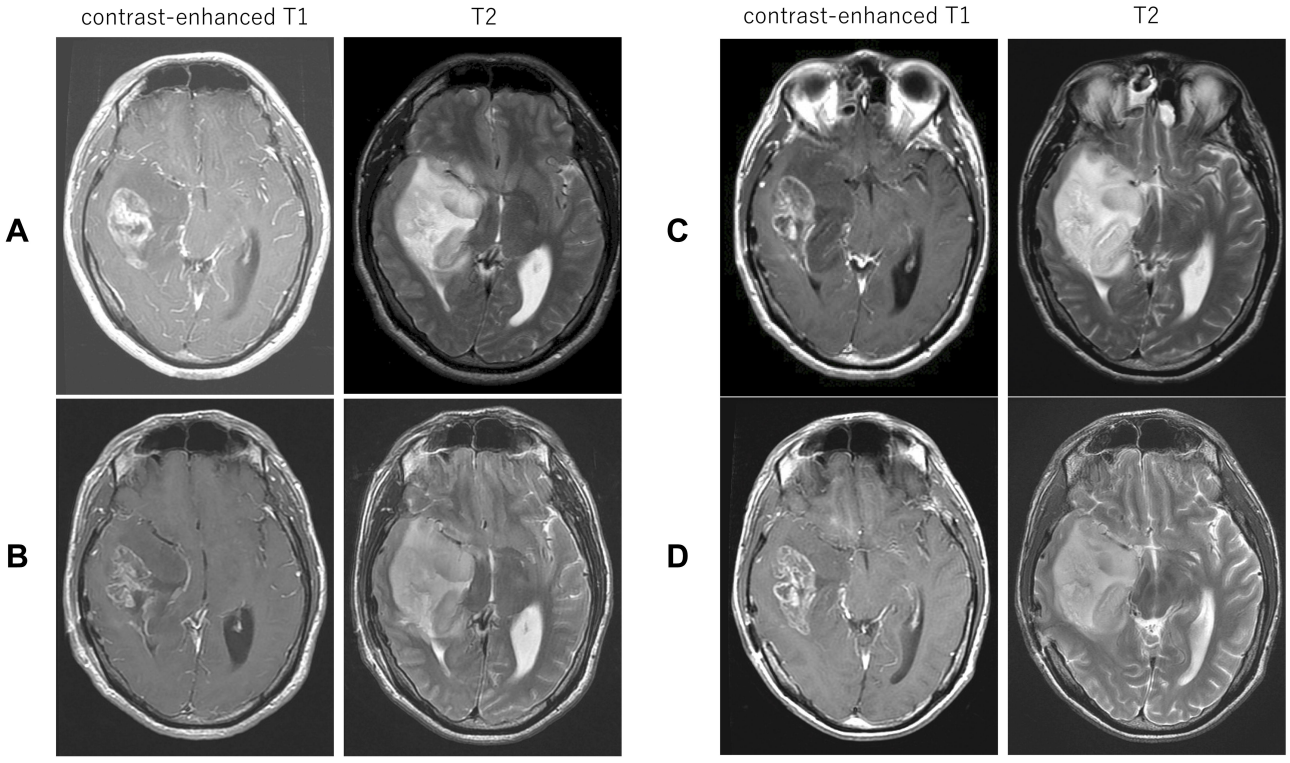

Figure 1 Magnetic resonance imaging (MRI) showing 5×3.5 cm abnormal nonuniformly contrasted mass with hypointensity on T_1-weighted image (left) and with hyperintensity on T_2-weighted image (right) in the right temporal lobe. (**A**) MRI at first consultation; (**B**) MRI after MPV administration (at day 17 after admission); (**C**) MRI after FCR administration (at day 34 after admission); (**D**) MRI after Ibr administration (at day 54 after admission).

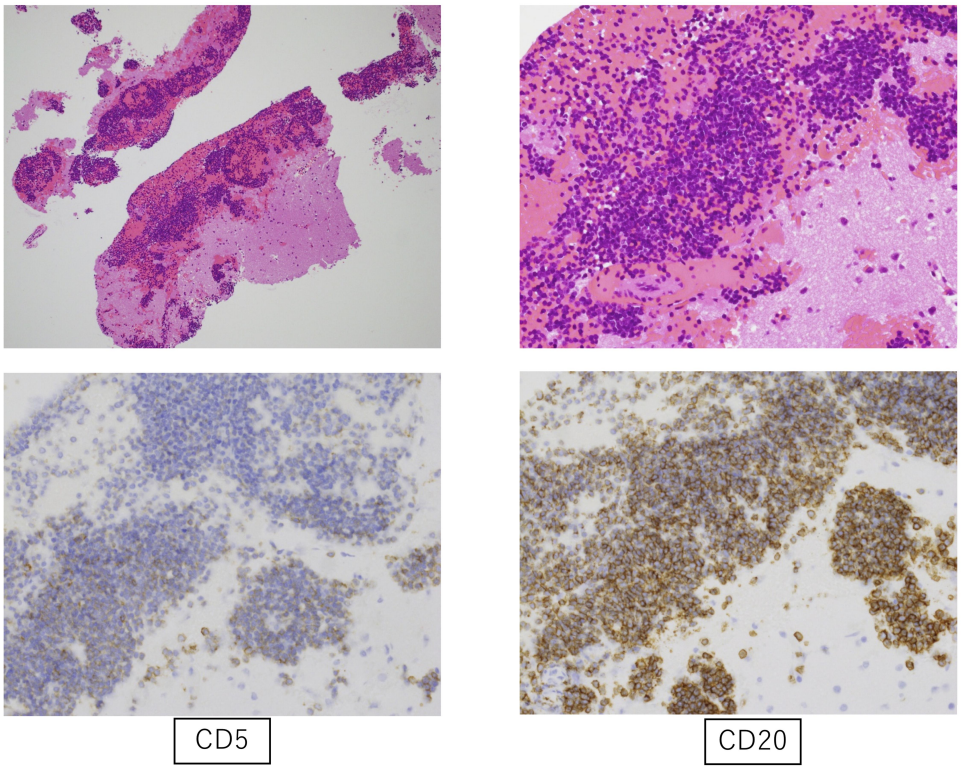

Figure 2 Brain specimens (cranioscopic biopsy) showing infiltration of small monoclonal lymphocytes with expression of CD5 and CD20 (upper left, H&E ×40; upper right, H&E ×100; lowerleft CD5 ×100; lower right, CD20 ×100).

β_2-microglobulin was 2.1 mg/L. Evaluation with thoracoabdominal computed tomography (CT) revealed splenomegaly and mild systemic lymphadenopathy.

Treatment with 2 mg betamethasone for 7 days transiently improved the diplopia and headaches, but tumor size evaluated by CT/MRI remained unchanged. No standard protocol exists for CLL with CNS involvement, because it is an extremely rare disease condition. Therefore, according to the treatment strategy of primary CNS lymphoma, MPV chemotherapy (methotrexate 3.5 mg/m^2 on day 1, vincristine 1.4 mg/m^2 [max 2.8 mg on day 1], and procarbazine 100 mg/m^2 per day on days 1–7) was started. Ten days after treatment, intracranial hypertension–related symptoms, such as diplopia and headaches, recurred and performance status was decreased. MRI showed that the tumor size remained unchanged (Figure 1B) and PB-lymphocyte reduction was poor (Figure 4), indicating resistance to the MPV treatment. Therefore, rituximab (Rtx) 375 mg/m^2 and subsequent whole-brain radiotherapy (30 Gy/15 fr) plus simultaneous in-field boost (10 Gy/5 fr) were administered.

After Rtx administration, the diplopia and headaches improved and lymphocyte reduction was observed. Therefore, treatment with one cycle of FCR chemotherapy (fludarabine 25 mg/m^2 per day and cyclophosphamide 250 mg/m^2 per day for the first 3 days, with addition of Rtx 375 mg/m^2) was started. Although the PB lymphocytes decreased steadily (Figure 4) without recurrence of intracranial hypertension–related symptoms, no reductive effect on the intracranial tumor was observed on contrast-enhanced MRI (Figure 1C). Because the effects of ibrutinib (Ibr) on the CNS have been reported in CLL and mantle-cell lymphoma,[6] we next selected Ibr 420 mg/day for treatment. However, 2 weeks later, contrast-enhanced MRI revealed no reductive effect, and diplopia and headaches had recurred (Figure 1D). Finally, the patient refused subsequent treatment and was self-discharged from the hospital. He died at home 9 weeks after the onset of initial symptoms (48 weeks after the diagnosis of CLL).

Discussion

Diagnostic cranioscopic biopsy was performed in our case, but many cases were diagnosed by cerebrospinal fluid (CSF) analysis in a retrospective cohort of 30 CLL patients with CNS involvement.[7] In that cohort, biopsies

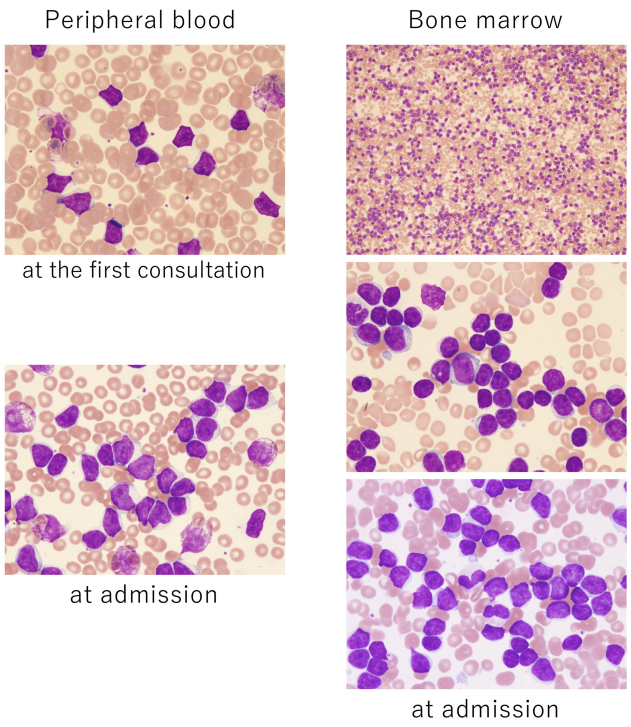

Figure 3 CLL cells from peripheral blood at first consultation and admission and BM at admission showed mature small monoclonal lymphocytes with narrow cytoplasm, concentrated nuclei, and partially aggregated chromatin without transformation to a large cell type (H&E ×40 and ×200).

Table 1 Hematologic Assessment of Patient

White blood Cells/μL	464,200/μL	Na	141 mEq/L
Neutrophils	1.5%	K	4.2 mEq/L
Basophils	0	Cl	103 mEq/L
Eosinophils	0	BUN	12 mg/dL
Lymphocytes	98.5%	Cr	0.83 mg/dL
Monocytes	0	TP	6.5 g/dL
Others	0	Alb	4.1 g/dL
Plt	30.5×10^4/μL	AST	26 U/L
RBC	449×10^4/μL	ALT	37 U/L
Hb	11.7 g/dL	T-Bil	0.4 mg/dL
Ht	42.1%	D-Bil	0 mg/dL
MCV	93.8 fL	ALP	544 U/L
MCH	26.1 pg	γGTP	87 U/L
MCHC	27.8 g/dL	LDH	262 U/L
APTT	25.7 seconds	CRP	0.072 mg/dL
PT	107.4%		
FBG	241 mg/dL	IgG	955 mg/dL
AT-III	109%	IgA	83 mg/dL
HBs-Ag	—	IgM	29 mg/dL
HCV-Ab	—	sIL2R	11,000 U/mL
HTLV-I	—	BMG	2.1 mg/L
HIV	—	ANA	—

were performed in only five cases, of which only one was diagnosed by brain biopsy.[7] Our review of the literature revealed diagnostic biopsies had been performed in 12 of 50 cases (not including surgical resection). Ten of the 50 cases were diagnosed as Richter's syndrome, and 11.3% of Richter's transformation with intracranial involvement was found in an old literature review of CLL (before 2011).[8] By contrast, there were no cases of Richter's syndrome in the 30 cases of the retrospective cohort.[7] It has been reported that Richter's transformation occurs in approximately 5%–10% of the CLL population;[9] therefore, it is still difficult to conclude whether there is an intimate correlation between CNS involvement and Richter's transformation.

The 50 reported cases of CNS involvement in CLL had diverse and uncharacteristic symptoms, such as headaches, convulsions, diplopia, ataxia, facial paralysis, and cognitive dysfunction (Table 2). It is difficult to identify the risk factors for CNS involvement in CLL.[10,11] Our literature review confirmed this, because we could not find a common feature in cases of CNS involvement. There are cases in which CNS involvement develops when the stage is not necessarily progressive (on Rai or Binet staging) or without high-risk chromosomal abnormality, such as del17p or del11q. This suggests clinical and pathophysiological heterogeneity of CNS involvement in CLL.[7]

A report summarizing the literature published before 2011 of CNS involvement in CLL[8] showed average age 63.4 years, average latency between CLL diagnosis and first signs of CNS involvement 2.6 years, average overall survival (OS) from CLL diagnosis 3.8 years, and average OS from time of CNS onset 12 months. Our review of the 50 case reports revealed average age 62.2 years (in 49 cases) and average latency 4.9 years (in 32 cases. OS data could not be extracted. Our case showed a younger and more aggressive disease course of age 33 years, latency 9 months, OS 48 weeks, and OS from time of CNS onset 9 weeks. Our case was resistant to high-dose Mtx and whole-brain radiotherapy as standard treatments for primary CNS lymphoma. As the standard treatment for non–high risk CLL, FCR was effective in reducing the number of PB lymphocytes and improved intracranial hypertension-related symptoms; however, it had less effect on tumor shrinkage, indicating it was ineffective for the CNS lesion. Although the number of reports of CNS involvement in CLL is low, there were reports of successful treatment with FCR in some cases in our

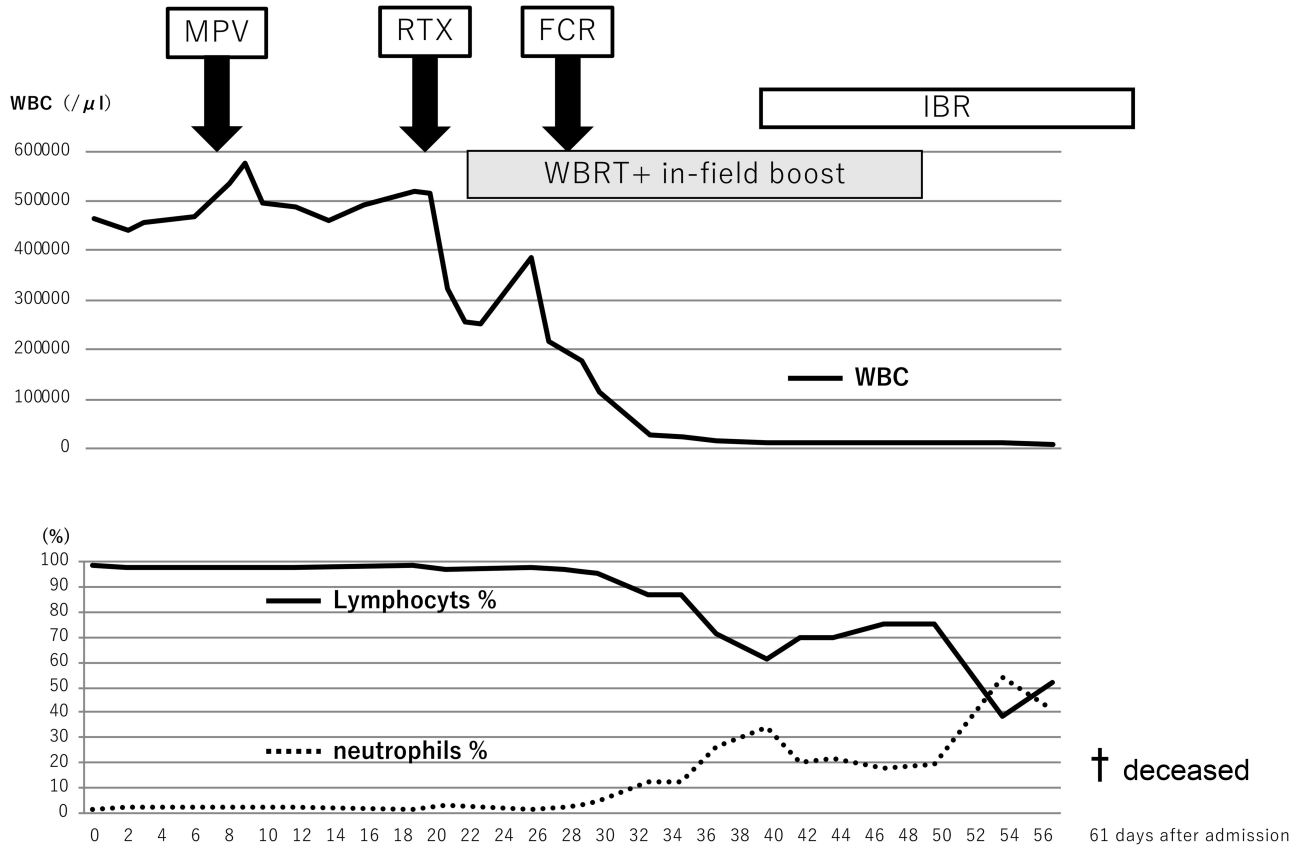

Figure 4 Clinical course of WBC and lymphocyte counts after treatment.
Abbreviations: MPV, methotrexate 3.5 mg/m^2 (day 1), vincristine 1.4 mg/m^2 (max 2.8 mg) (day 1), and procarbazine 100 mg/m^2 per day (days 1–7); Rtx, rituximab (375 mg/m^2; FCR, fludarabine (25 mg/m^2 per day), cyclophosphamide (250 mg/m^2 per day) for the first 3 days, with addition of Rtx 375 mg/m^2; WBRT, whole-brain radiotherapy (30 Gy/15 fr) plus simultaneous in-field boost (10 Gy/5 fr).

literature review (Table 2). However, in general, prognosis was poor, owing to resistance to various treatments, such as high-dose Mtx, intrathecal injection, whole-brain radiotherapy, and FCR. A similar result was obtained in our case

Ibr has been reported to be effective in CNS lesions of mantle-cell lymphoma[6] and Waldenström macroglobulinemia.[12] Effects of Ibr appear 1–2 weeks after administration.[13] Nine successful cases of Ibr treatment for CNS involvement in CLL were found in 50 cases (complete response in eight cases, partial response in one) (Table 2); therefore, Ibr may be a promising drug for CNS involvement. However, this was not found in our case. It is possible that the effective concentration of Ibr in the CNS lesion had not reached sufficient levels in our case. Concentration in CSF was reported to be 2log lower than in the plasma of 18 patients with primary CNS lymphoma treated with Ibr.[14] It has been reported that an increased dose of Ibr escalates CSF concentration without adverse events,[15] and that increasing the dose of Ibr is effective for CNS lesions in CLL.[16] It will be necessary in the future to verify the optimal dose of Ibr for CNS lesions. Bulky disease in CNS lesion might also cause treatment failure. Although ofatumumab and alemtuzumab are alternative treatment options, we did not select them, because they did not show superiority to Ibr in the data or in drug penetration of the CNS. In addition, there have been two reports showing the effectiveness of venetoclax against CNS lesions (Table 2).[17,18] One of those was a case where venetoclax was effective after Ibr resistance, and thus it may be beneficial to test venetoclax against CNS involvement in CLL.

Conclusion

Patients with CNS lesions in lymphoid tumors have a poor prognosis, but the possibility of concomitant use of Mtx and Ibr or venetoclax can be envisioned. Accumulation of

Table 2 Literature on CNS Involvement in CLL

Reference	Age (years), sex	Symptoms	Interval from diagnosis of CLL to first CNS symptoms	Rai/ Binet	Lymphocyte count	FISH (G-band)	Method of diagnosis	Transformation to Richter's syndrome	Treatment (treatment prior to diagnosis of CNS involvement)	Response
Clin Case Rep. 2020.8.269. [17]	71 M	Epileptic seizures	12 years	NA	NA	11q deletion	CSF^{-} Clinical diagnosis		WW/FCR/ Rtx–bendamustine–Ibr HD Mtx Rtx Venetoclax	Venetoclax PR
Mult Scler Relat Disord. 2020.37.101455 [19]	50 M	Fecal incontinence, tetraparesis	NA	NA	131,000 (WBC)	NA	CSF+		Rtx and cyclophosphamide IVIg	CR
Can J Neurol Sci. 2019.46.640. [20]	53 M	Neck pain, adenopathy, urinary retention, monocular vision loss in right eye	5 years	NA	NA	NA	CSF^{+}		WW Dex pulse→ Rtx and cyclophosphamide	CR
Haematologica.2019.104. e222. [18]	58	NA	NA	NA	NA	Trisomy 12	CSF^{+}		Six FCR courses, six Rtx–bendamustine cycles, and four Rtx–DHAP courses Ibr Venetoclax with IT chemotherapy (cytarabine plus methotrexate)	Ibr PD Venetoclax CR

Case Rep Hematol. 2019. 1,825,491; [21]	62 M	Dysmetria, left upper–extremity paresis, apraxia, mild amnesia, and prosopagnosi	NA	NA	5,300 (WBC)	del13q14 (BM)	Craniotomy with resection CSF^{-}		FCR	CR
BMC Neurol. 2019 0.19. 200. [22]	45 F	6-month history of headache	NA	NA	NA	NA	Biopsy CSF^{+}		HD Mtx with IT Mtx and AraC	CR
BMC Neurol. 2019 0.19. 200. [22]	49 M	Headache and dizziness for past 5 years	NA	NA	NA	NA	Biopsy CSF^{+}		Rtx, HD Mtx, Dex, and vincristine with IT Mtx	CR
Neuropathology. 2019.39.54. [23]	61 F	Mental disturbance	14 years	NA	3300 (WBC)	Trisomy 12 (lymph node)	Biopsy CSF^{+}		CHOP/FC HD Mtx	PD
Cureus. 2018. 10. e2176. [16]	61 F	Chronic headaches	14 years	Rai I	NA	NA	CSF^{+}		WW/FCR Ibr 420 mg→560 mg	CR
Case Rep Hematol. 2018. 7,817,918. [24]	65 M	Headache complaints, photophobia, vertigo, and extensive pain (from the cervical spine down to the inferior limbs)	9 years	Rai 0 Binet A	NA	13q deletion	CSF^{+}		Chlorambucil monotherapy IT Mtx + liposomal AraC →Ibr 420 mg →HD Mtx →WBRT	CR
Adv Clin Exp Med. 2018.27. 1683. [25]	54 M	Disturbances of consciousness	71 months	Rai II	NA	NA	CT Autopsy	Yes	CVP, CHOP, FC, F, ofatumumab + idelalisib vs no treatment	PD

(*Continued*)

Table 2 (Continued).

Reference	Age (years), sex	Symptoms	Interval from diagnosis of CLL to first CNS symptoms	Rai/ Binet	Lymphocyte count	FISH (G-band)	Method of diagnosis	Transformation to Richter's syndrome	Treatment (treatment prior to diagnosis of CNS involvement)	Response
Turk J Hematol 2018.35.147. [26]	71 F	Expressive aphasia, memory problems, confusion, and headache	12 years	Binet A	14,652	Normal	Biopsy reject CSF^{-}		WW Rtx Ibr 420 mg	PR
Annals of Hematology. 2018.97. 1627. [27]	81 M	Paralysis of the left oculomotor nerve and left hemianopsia	20 months	Rai 0 Binet A	35,600	NA	CSF^{+}		WW Rtx and chlorambucil with IT Mtx	PR
Annals of Hematology. 2018.97. 1627. [27]	77 M	Apathy, urinary incontinence	9 years	Rai II Binet B	44,500	NA	CSF^{+}		Fludarabine and cyclophosphamide No	PD
Medicine. 2018. 97. e12701 [28]	67 F	Slurred speech, headache, and left-sided hemiparesis	NA	NA	14,500	$p53^{+}$	Surgical resection CSF (DLBCL)	Yes	HD Mtx IT Mtxand AraC	PD
Cureus.2018.10. e3660 [29]	84 F	Mild dysmetria in the upper-left extremity	NA	Rai 0	15,311,000	NA	Tumor resection	Yes	Temozolomide and WBRT	PD
Ann Indian Acad Neurol. 2018. 21. 85. [30]	57 M	Bradypsychia, headaches, nausea, vomiting	6 months	Rai III	85,500 (WBC)	del17p	CSF^{+}		WW HD Mtx	PD

Ann Indian Acad Neurol. 2018. 21. 85. [30]	43 M	Dysphasia, repeated unconsciousness, urinary incontinence	62 months	Rai IV	23,000 (WBC)	Normal	CSF^{+}		FC FCR	SD?
Ann Indian Acad Neurol. 2018. 21. 85. [30]	72 M	Dyslexia, lack of fine motor control, diplopia	9 months	Rai IV	103,900 (WBC)	13q14 nullisomy	CSF^{-}		WW DHAP	PD
Ann Indian Acad Neurol. 2018. 21. 85. [30]	49 M	Diplopia, bilateral eyelid swelling, and tumors	63 months	Rai II	86,500 (WBC)	NA	CSF^{+}		CHOP DHAP	PD
Br J Haematol. 2017.176. 829. [31]	66 M	Tightness, paresthesia, and neuropathic pain in the left hand and left arm	NA	Rai III	94,000	NA	CSF^{+}		Steroids Ibr 420 mg	CR
BMC Hematol. 2017.17.3 [32]	60 F	Progressive lower-extremity weakness and urinary incontinence	NA	Rai 0	13,400	Normal	CSF^{+}		FCR	PR→PD
J Neuroophthalmol. 2016. 36.61. [33]	45 M	Visual loss in the right eye	2 years	NA	2304	NA	Optic nerve–sheath biopsy CSF^{+}		Ibr with IT Mtx	CR
Blood. 2016.127. 2356 [34]	58 M	Dysautonomy	NA	Binet C	NA	del17p	CSF^{+}		Eight prior lines of therapy for CLL Ibr 420 mg	CR
Blood. 2016.127. 2356 [34]	75 M	Headaches and cognitive disturbance	NA	Binet B	NA	del17p	CSF^{+}		Four prior lines of therapy for CLL Ibr 420 mg	CR

(*Continued*)

Table 2 (Continued).

Reference	Age (years), sex	Symptoms	Interval from diagnosis of CLL to first CNS symptoms	Rai/ Binet	Lymphocyte count	FISH (G-band)	Method of diagnosis	Transformation to Richter's syndrome	Treatment (treatment prior to diagnosis of CNS involvement)	Response
Blood. 2016.127. 2356–2358 [34]	63 M	Cerebellar syndrome and aphasia, confusion	NA	Binet C	NA	NA	CSF^+		Two prior lines of therapy for CLL Ibr 420 mg	CR
Blood. 2016.127. 2356 [34]	68 F	Visual loss	NA	Binet A	NA	del17p	CSF^+		No prior lines of therapy for CLL Ibr 420 mg	CR
BMC Res Notes. 2014.7.645. [35]	75 F	Headache, otalgia in the right ear, fever, dizziness, and dysphagia	5 years	Rai I	24,300 (WBC)	NA	CSF^+		Chlorambucil and prednisone IT Mtx FC	CR
Leukemia Lymphoma. 2014. 55.1939 [36]	64 M	Hypoesthesia	2 months	Binet B	251,000	Normal	CSF^+		WW IT Mtx + AraC Rtx–bendamustine	CR
BMJ Case Rep. 2014. Bcr-2013-202,051. [37]	45 F	Seizures, headaches, and vomiting	NA	NA	NA	NA	Biopsy		Surgical excision RT	Relapse
Clin Lymphoma Myeloma Leuk. 2013.13. 338. [38]	44 F	Double vision	3 years	Rai I	98,280	Trisomy 12 and 13q-	Biopsy CSF^+		Rtx mPSL IT AraC FCR	CR

Leuk Lymphoma. 2013.54. 2070. [39]	67 M	Gait disturbance, tremors, slurred speech, marked fatigue, intermittent confusion, and visual impairment	10 years	Rai I	2200 (WBC)	Diploid	CSF^{+}	Yes	Chlorambucil–fludarabine–pentostatin, cyclophosphamide, and Rtx–ofatumumab–lenalidomide IT liposomal AraC IT Rtx HD AraC WBRT	PD
J Clin Exp Hematop. 2013.53. 157 [40]	66 F	Fatigue and difficulty walking	2 years	Rai 0	27,000	NA	Biopsy (CT-guided), non-GCB DLBCL	Yes	WW/ cyclophosphamide + PSL IT Dex RT Rtx	Transient PR→relapse
J Clin Oncol. 2013.31 e280 [41]	75 M	Right-eye pain associated with blurry vision, floaters, and bright halos	I years	Rai 0	34,900	Trisomy12	CSF^{+}		PSL Rtx–fludarabine	CR
Acta Haematol. 2012;127. 93 [42]	56 M	Seizures, psychomotoric deficits, and left-sided hemiparesis	I month	Binet A	NA	NA	Stereotactic biopsy CSF^{-}	Yes	Systemic and intraventricular polychemotherapy regimen WBRT Topotecan	Transient CR→relapse

(*Continued*)

Table 2 (Continued).

Reference	Age (years), sex	Symptoms	Interval from diagnosis of CLL to first CNS symptoms	Rai/ Binet	Lymphocyte count	FISH (G-band)	Method of diagnosis	Transformation to Richter's syndrome	Treatment (treatment prior to diagnosis of CNS involvement)	Response
J Neurooncol 2012.106. 185 [8]	53 F	Vision changes	4 years	Rai I	16,000,000 (WBC)	NA	CSF^+		CVP Rtx–fludarabine Alemtuzumab Rtx IT Mtx Temozolomide RT	PR
J Neurooncol 2012.106. 185 [8]	52 M	Encephalopathy, dementia, seizures	3 years	Rai IV	14,000,000 (WBC)	NA	CSF^+		Fludarabine None	PD
J Neurooncol. 2012.109. 213 [43]	65 F	Difficulty speaking, weakness in the right arm and leg	1 month	Rai IV	600,000 (WBC)	13q14 deletion (biopsy)	Biopsy		Cyclophosphamide + steroids FCR WBRT Rtx–bendamustine	CR
Case Rep Hematol. 2012 589,718 [44]	66 F	Bilateral hearing loss	NA	NA	104,000 (WBC)	del (17p13.1) and del (13q34)	Tympanic membrane biopsy CSF^+		Rtx-CVP Rtx IT liposomal cytarabine Cyclophosphamide, cladribine, and Rtx HyperCVAD	PR
Am J Hematol. 2011.86.783 [45]	73	Bilateral visual loss	NA	Rai II Binet B	NA	NA	Ethmoidectomy		Fludarabine/FCR Steroids RT	PD

J Neurol Neurosurg Psychiatry. 2011.82.943 [46]	late60sM	Bilateral leg weakness, pain, and urinary retention	NA	Rai III	NA	Normal	Brain biopsy	Yes	WW/chlorambucil/ FCR/CHOP HD Mtx	PD
J Clin Oncol. 2010.28.e30 [47]	58 M	Temporary seizures, poor memory, and progressive blindness	10 years	Rai III	36,000 (WBC)	NA	Open-brain biopsy CSF^{-}		Mtx Flu RT	PD 6 months
Blood.2010. 116. 2617 [48]	68 M	Paraparesis of both legs, urinary and stool incontinence, and central right-sided facial nerve palsy	NA	NA	NA	NA	CSF^{+}		HD Mtx + ifosfamide HD AraC + Mit + IT Mtx Dasatinib	CR
Br J Haematol. 2010.150.618 [49]	52 M	Headache, cognitive complaints: slow response and inattentiveness	61 months	Rai I Binet A	NA	NA	CSF^{+}		IT liposomal AraC RT Rtx + VCR + HD Mtx + PCBZ + HD AraC FCR	CR
Br J Haematol. 2010.150.618 [49]	68 F	V cranial pair palsy	34 months	Rai IV Binet B	NA	NA	CSF^{+}	Yes	IT liposomal AraC HD Mtx + HD AraC	Transient CR →relapse
Br J Haematol. 2010.150.618 [49]	44 M	Headache, chin and face dysesthesia, optic neuritis, blurred vision	25 months	Rai IV Binet C	NA	NA	CSF^{+}		IT liposomal AraC Chlorambucil	Transient CR →relapse
Br J Haematol. 2010.150.618 [49]	81 M	Headache, nausea, weakness, somnolence, lethargy, and confusioned state	25 months	Rai 0 Binet A	NA	NA	CSF^{+}		IT liposomal AraC FCR	CR
Br J Haematol. 2010.150.618 [49]	64 F	Headache and diplopia	13 months	Rai IV Binet C	NA	NA	CSF^{+}		IT liposomal AraC R-CHOP	CR

(*Continued*)

Table 2 (Continued).

Reference	Age (years), sex	Symptoms	Interval from diagnosis of CLL to first CNS symptoms	Rai/ Binet	Lymphocyte count	FISH (G-band)	Method of diagnosis	Transformation to Richter's syndrome	Treatment (treatment prior to diagnosis of CNS involvement)	Response
Br J Haematol. 2010.150.618 [49]	79 M	Leg weakness, difficulty walking, upper-back pain, and VII cranial pair palsy	66 months	Rai IV Binet B	NA	NA	CSF^+	Yes	IT Mtx and liposomal AraC HyperCVAD/MA	Transient CR →relapse
Br J Haematol. 2010.150.618 [49]	68 F	Headache	24 months	Rai IV Binet B	NA	NA	CSF^+	Yes	IT Mtx and liposomal AraC AraC	CR

Abbreviations: NA, not available; FISH, fluorescence in situ hybridization; CSF, cerebrospinal fluid; Rtx, rituximab; FCR, fludarabine–cyclophosphamide–Rtx; MPV, methotrexate–procarbazine–vincristine; HD, high dose; Mtx, methotrexate; Mit, mitoxantrone; AraC, cytosine arabinoside (cytarabine); CVP, cyclophosphamide–vincristine–prednisone; IT, intrathecal; RT, radiotherapy; Ibr, ibrutinib; WBRT, whole-brain radiotherapy; hyperCVAD, cyclophosphamide–vincristine–adriamycin–dexamethasone; CHOP, cyclophosphamide–hydroxydaunorubicin (doxorubicin)–oncovin (vincristine)–prednisone; DHAP, dexamethasone–HD AraC (cytarabine)–platinol (cisplatin); WW, watch and wait.

data from cases is important to verify the choice of new or combination drugs for administration from an early stage.

Ethics

Informed consent was provided by the patient on admission to have the case details published. The patient passed away before publication of causes not included in the case report. Institutional approval was not required for publication.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval to the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Chihara D, Ito H, Matsuda T, et al. Differences in incidence and trends of haematological malignancies in Japan and the United States. *Br J Haematol*. 2014;164(4):536–545. doi:10.1111/bjh.12659
2. Hallek M. Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification and treatment. *Am J Hematol*. 2019;94(11):1266–1287. doi:10.1002/ajh.25595
3. Stilgenbauer S, Zenz T. Understanding and managing ultra high-risk chronic lymphocytic leukemia. *Hematology Am Soc Hematol Educ Program*. 2010;2010:481–488. doi:10.1182/asheducation-2010.1.481
4. Hanse MC, Van't Veer MB, van Lom K, et al. Incidence of central nervous system involvement in chronic lymphocytic leukemia and outcome to treatment. *J Neurol*. 2008;255(6):828–830. doi:10.1007/s00415-008-0710-4
5. Lopes da Silva R. Spectrum of neurologic complications in chronic lymphocytic leukemia. *Clin Lymphoma Myeloma Leuk*. 2012;12(3):164–179. doi:10.1016/j.clml.2011.10.005
6. Bernard S, Goldwirt L, Amorim S, et al. Activity of ibrutinib in mantle cell lymphoma patients with central nervous system relapse. *Blood*. 2015;126(14):1695–1698. doi:10.1182/blood-2015-05-647834
7. Wanquet A, Birsen R, Bonnet C, et al. Management of central nervous system involvement in chronic lymphocytic leukaemia: a retrospective cohort of 30 patients. *Br J Haematol*. 2017;176(1):37–49. doi:10.1111/bjh.14387
8. Moazzam AA, Drappatz J, Kim RY, et al. Chronic lymphocytic leukemia with central nervous system involvement: report of two cases with a comprehensive literature review. *J Neurooncol*. 2012;106(1):185–200. doi:10.1007/s11060-011-0636-z
9. Molica S. A systematic review on Richter syndrome: what is the published evidence? *Leuk Lymphoma*. 2010;51(3):415–421. doi:10.3109/10428190903515192
10. Cramer SC, Glaspy JA, Efird JT, et al. Chronic lymphocytic leukemia and the central nervous system: a clinical and pathological study. *Neurology*. 1996;46(1):19–25. doi:10.1212/WNL.46.1.19
11. Brick WG, Majmundar M, Hendricks LK, et al. Leukemic leptomeningeal involvement in stage 0 and stage 1 chronic lymphocytic leukemia. *Leuk Lymphoma*. 2002;43(1):199–201. doi:10.1080/10428190210191
12. Cabannes-Hamy A, Lemal R, Goldwirt L, et al. Efficacy of ibrutinib in the treatment of Bing-Neel syndrome. *Am J Hematol*. 2016;91(3):E17–19. doi:10.1002/ajh.24279
13. Tucker DL, Naylor G, Kruger A, et al. Ibrutinib is a safe and effective therapy for systemic mantle cell lymphoma with central nervous system involvement - a multi-centre case series from the United Kingdom. *Br J Haematol*. 2017;178(2):327–329. doi:10.1111/bjh.14122
14. Lionakis MS, Dunleavy K, Roschewski M, et al. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. *Cancer Cell*. 2017;31(6):833–843.e835. doi:10.1016/j.ccell.2017.04.012
15. Grommes C, Pastore A, Palaskas N, et al. Ibrutinib unmasks critical role of bruton tyrosine kinase in primary CNS lymphoma. *Cancer Discov*. 2017;7(9):1018–1029. doi:10.1158/2159-8290.CD-17-0613
16. Rizvi W, Truong Q. Unusual relapse of chronic lymphocytic leukemia after remission. *Cureus*. 2018;10(2):e2176.
17. Beziat G, Gauthier M, Protin C, et al. Venetoclax with high-dose methotrexate and rituximab seem effective and well-tolerated in the treatment of central nervous system involvement of chronic lymphocytic leukemia: a case report. *Clin Case Rep*. 2020;8(2):269–273. doi:10.1002/ccr3.2580
18. Reda G, Cassin R, Dovrtelova G, et al. Venetoclax penetrates in cerebrospinal fluid and may be effective in chronic lymphocytic leukemia with central nervous system involvement. *Haematologica*. 2019;104(5):e222–e223. doi:10.3324/haematol.2018.213157
19. Akdogan O, Guven T, Altindal S, et al. An uncommon neurological manifestation of chronic lymphocytic leukemia: longitudinally extensive transverse myelitis. *Mult Scler Relat Disord*. 2020;37:101455. doi:10.1016/j.msard.2019.101455
20. Witton LA, Menon S, Perera KS. Central nervous system involvement with chronic lymphocytic leukemia. *Can J Neurol Sci*. 2019;46(5):640–641. doi:10.1017/cjn.2019.75
21. Gallastegui N, Cassidy DP, Heros DO, et al. Central nervous system involvement by small lymphocytic lymphoma after a myxoma-related embolic event. *Case Rep Hematol*. 2019;2019:1825491.
22. Guo R, Zhang X, Niu C, et al. Primary central nervous system small lymphocytic lymphoma in the bilateral ventricles: two case reports. *BMC Neurol*. 2019;19(1):200. doi:10.1186/s12883-019-1430-3
23. Otani R, Uzuka T, Matsuda H, et al. Brain invasion by chronic lymphocytic leukemia. *Neuropathology*. 2019;39(1):54–57. doi:10.1111/neup.12525
24. Mousinho F, Mendes T, Sousa E, et al. Treatment sequencing in a chronic lymphocytic leukemia patient with central nervous system involvement. *Case Rep Hematol*. 2018;2018:7817918.
25. Wąsik-Szczepanek E, Szymczyk A, Szczepanek D, et al. Richter syndrome: a rare complication of chronic lymphocytic leukemia or small lymphocytic lymphoma. *Adv Clin Exp Med*. 2018;27(12):1683–1689. doi:10.17219/acem/75903
26. Christoforidou A, Kapsas G, Bezirgiannidou Z, et al. Successful treatment of chronic lymphocytic leukemia multifocal central nervous system involvement with ibrutinib. *Turk J Haematol*. 2018;35(2):147–149. doi:10.4274/tjh.2017.0313
27. Timmers NKLM, de Maar JS, van Kruijsdijk RCM, et al. Central nervous system localisation of chronic lymphocytic leukaemia, description of two very distinct cases and a review of the literature. *Ann Hematol*. 2018;97(9):1627–1632. doi:10.1007/s00277-018-3329-2
28. Xu L, Song JC, Sun XH, et al. Richter's syndrome of the central nervous system diagnosed concurrently with chronic lymphocytic leukaemia: a case report and literature review. *Medicine (Baltimore)*. 2018;97(41):e12701. doi:10.1097/MD.0000000000012701

29. Albakr A, Alhothali W, Samghabadi P, et al. Central nervous system lymphoma in a patient with chronic lymphocytic leukemia: a case report and literature review. *Cureus*. 2018;10(11):e3660.
30. Mihaljevic B, Smiljanic M, Antic D, et al. Chronic lymphocytic leukemia involvement of central nervous system: clinical diversity, diagnostic algorithm and therapeutic challenges. *Ann Indian Acad Neurol*. 2018;21(1):85–87.
31. Tam CS, Kimber T, Seymour JF. Ibrutinib monotherapy as effective treatment of central nervous system involvement by chronic lymphocytic leukaemia. *Br J Haematol*. 2017;176(5):829–831. doi:10.1111/bjh.14000
32. Rojas-Hernandez CM, Nemunaitis J, Marjon KD, et al. Chronic lymphocytic leukemia with clinical debut as neurological involvement: a rare phenomenon and the need for better predictive markers. *BMC Hematol*. 2017;17:3. doi:10.1186/s12878-017-0073-0
33. Khan K, Malik AI, Almarzouqi SJ, et al. Optic neuropathy due to chronic lymphocytic leukemia proven with optic nerve sheath biopsy. *J Neuroophthalmol*. 2016;36(1):61–66. doi:10.1097/WNO.0000000000000300
34. Wanquet A, Birsen R, Lemal R, et al. Ibrutinib responsive central nervous system involvement in chronic lymphocytic leukemia. *Blood*. 2016;127(19):2356–2358. doi:10.1182/blood-2016-02-697193
35. de Souza SL, Santiago F. Ribeiro-Carvalho, MeM, et al. Leptomeningeal involvement in B-cell chronic lymphocytic leukemia: a case report and review of the literature. *BMC Res Notes*. 2014;7::645.
36. Rossi C, Brisou G, Baseggio L, et al. Central nervous system involvement in chronic lymphocytic leukemia: uncommon manifestation with undefined therapeutic management. *Leuk Lymphoma*. 2014;55(8):1939–1941. doi:10.3109/10428194.2013.858152
37. Aziz M, Chaurasia JK, Khan R, et al. Primary low-grade diffuse small lymphocytic lymphoma of the central nervous system. *BMJ Case Rep*. 2014;2014.
38. Benjamini O, Jain P, Schlette E, et al. Chronic lymphocytic leukemia with central nervous system involvement: a high-risk disease? *Clin Lymphoma Myeloma Leuk*. 2013;13(3):338–341. doi:10.1016/j.clml.2012.12.007
39. Jain P, Benjamini O, Pei L, et al. Central nervous system Richter's transformation and parvovirus B19 infection. *Leuk Lymphoma*. 2013;54(9):2070–2072. doi:10.3109/10428194.2013.765565
40. Ishida F, Nakazawa H, Takezawa Y, et al. Richter transformation in the brain from chronic lymphocytic leukemia. *J Clin Exp Hematop*. 2013;53(2):157–160. doi:10.3960/jslrt.53.157
41. Gonsalves WI, Zent CS, Pulido JS, et al. Visual loss in early-stage chronic lymphocytic leukemia. *J Clin Oncol*. 2013;31(17):e280–282. doi:10.1200/JCO.2012.46.7431
42. Stuplich M, Mayer K, Kim Y, et al. Richter syndrome and brain involvement: low-grade lymphoma relapsing as cerebral high-grade lymphoma. *Acta Haematol*. 2012;127(2):93–95. doi:10.1159/000334068
43. Imitola J, Pitt K, Peoples JL, et al. Multifocal CNS infiltration of chronic lymphocytic leukemia in the form of small-cell solid metastatic lesions. *J Neurooncol*. 2012;109(1):213–215. doi:10.1007/s11060-012-0869-5
44. Cohen JB, Cavaliere R, Byrd JC, et al. Hearing loss due to infiltration of the tympanic membrane by chronic lymphocytic leukemia. *Case Rep Hematol*. 2012;2012:589718.
45. Ackermann KA, Z'Graggen WJ, El-Koussy M, et al. Blindness in a patient with chronic lymphocytic leukemia. *Am J Hematol*. 2011;86(9):783–784. doi:10.1002/ajh.22042
46. Graves TD, Collins GP, Parry A. Richter's syndrome of the brain and the spinal cord. *J Neurol Neurosurg Psychiatry*. 2011;82(8):943–944. doi:10.1136/jnnp.2010.209759
47. Kakimoto T, Nakazato T, Hayashi R, et al. Bilateral occipital lobe invasion in chronic lymphocytic leukemia. *J Clin Oncol*. 2010;28(3):e30–32. doi:10.1200/JCO.2009.23.8436
48. Russwurm G, Heinsch M, Radkowski R, et al. Dasatinib induces complete remission in a patient with primary cerebral involvement of B-cell chronic lymphocytic leukemia failing chemotherapy. *Blood*. 2010;116(14):2617–2618. doi:10.1182/blood-2010-04-279786
49. Calvo-Villas JM, Fernández JA, de la Fuente I, et al. Intrathecal liposomal cytarabine for treatment of leptomeningeal involvement in transformed (Richter's syndrome) and non-transformed B-cell chronic lymphocytic leukaemia in Spain: a report of seven cases. *Br J Haematol*. 2010;150(5):618–620. doi:10.1111/j.1365-2141.2010.08238.x