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 diploia 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.

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 the US.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 T₁-weighted and hyperintense on T₂-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](https://www.dovepress.com/)

**Figure 1** Magnetic resonance imaging (MRI) showing 5×3.5 cm abnormal nonuniformly contrasted mass with hypointensity on T₁-weighted image (left) and with hyperintensity on T₂-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).
β₂-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/m² on day 1, vincristine 1.4 mg/m² [max 2.8 mg on day 1], and procarbazine 100 mg/m² 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/m² 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/m² per day and cyclophosphamide 250 mg/m² per day for the first 3 days, with addition of Rtx 375 mg/m²) 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, 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. In that cohort, biopsies

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**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; lower left CD5 ×100; lower right, CD20 ×100).

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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.\(^7\)

| Table 1 Hematologic Assessment of Patient |
|------------------------------------------|
| White blood cells/µL | 464,200/µL | Na | 141 mEq/L |
| Neutrophils | 15% | 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 × 10^9/µL | AST | 26 U/L |
| RBC | 449 × 10^6/µL | ALT | 37 U/L |
| Hb | 11.7 g/dL | TBil | 0.4 mg/dL |
| Ht | 42.4% | DBil | 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 |
| 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 | — |

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...
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 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
| 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.        | 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. 2020.37.10.1455 | 50 M             | Fecal incontinence, tetraparesis               | NA                                                 | NA         | 131,000 (WBC)    | NA             | CSF+                             |                                      | Rtx and cyclophosphamide IVig                           | CR       |
| Can J Neurol Sci. 2019.46.640.    | 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.     | 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 prosopagnosia | 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) | Treatment (treatment prior to diagnosis of CNS involvement) | Treatment (treatment prior to diagnosis of CNS involvement) | Response |
|----------------------------------|------------------|-----------------------------------------------|-----------------------------------------------------|------------|------------------|----------------|----------------------|--------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|----------|
| Turk J Hematol 2018.35.147.      | 71 F             | Expressive aphasia, memory problems, confusion, and headache | 12 years Binet A                                     | 14,652     | Normal           | Biopsy reject CSF | WW                   | Rtx and chlorambucil with IT Mtx | WW Rtx lbr 420 mg                                    | PR                                              |                                          |          |
| Annals of Hematology. 2018.97.   | 81 M             | Paralysis of the left oculomotor nerve and left hemianopsia | 20 months Rai 0 Binet A                               | 35,600     | NA               | CSF<sup>+</sup>  | WW                   | Rtx and chlorambucil with IT Mtx | WW Rtx lbr 420 mg                                    | PR                                              |                                          |          |
| Annals of Hematology. 2018.97.   | 77 M             | Apathy, urinary incontinence                   | 9 years Rai II Binet B                                | 44,500     | NA               | CSF<sup>+</sup>  | Fludarabine and cyclophosphamide | No                                                  | PD                                              |                                          |          |
| Medicine. 2018. 97. e12701       | 67 F             | Slurred speech, headache, and left-sided hemiparesis | NA                                                  | 14,500     | p53<sup>+</sup>  | Surgical resection CSF (DLBCL) | Yes                                                      | HD Mtx IT Moand AraC | PD                                              |                                          |          |
| Cureus.2018.10. e3660            | 84 F             | Mild dysmetria in the upper-left extremity     | NA                                                  | 15,311,000 | NA               | Tumor resection | Yes                                                      | Temozolomide and WBRT | PD                                              |                                          |          |
| Ann Indian Acad Neurol. 2018. 85. | 57 M             | Bradysychia, headaches, nausea, vomiting       | 6 months Rai III                                      | 85,500     | del17p           | CSF<sup>+</sup>  | WW                   | HD Mtx                                                  | PD                                              |                                          |          |
| Journal                           | Year | Sex | Age | Duration | Rai | WBC                  | Diagnosis                                      | Treatment          | Follow-up |
|----------------------------------|------|-----|-----|----------|-----|----------------------|------------------------------------------------|--------------------|-----------|
| Ann Indian Acad Neurol.          | 2018 | M   | 43  | 62 months| IV  | 23,000 (WBC)         | Dysphasia, repeated unconsciousness, urinary incontinence | FC                 | SD?       |
| Ann Indian Acad Neurol.          | 2018 | M   | 72  | 9 months | IV  | 103,900 (WBC)        | Dyslexia, lack of fine motor control, diplopia   | WW                 | PD        |
| Ann Indian Acad Neurol.          | 2018 | M   | 49  | 63 months| II  | NA                   | Diplopia, bilateral eyelid swelling, and tumors | CHOP               | PD        |
| Br J Haematol.                   | 2017 | M   | 66  | NA       | III | 94,000 (WBC)         | Tightness, paresthesia, and neuropathic pain in the left hand and left arm | Steroids 420 mg | CR        |
| BMC Hematol.                    | 2017 | F   | 60  | NA       | 0   | 13,400               | Progressive lower-extremity weakness and urinary incontinence | FCR               | PR→PD     |
| J Neuroophthalmol.               | 2016 | M   | 45  | 2 years  | NA  | 2304                 | Visual loss in the right eye                     | Ibr with IT Mtx   | CR        |
| Blood.                          | 2016 | M   | 58  | NA       | Binet C | del17p           | Dysautonomony                                   | Eight prior lines of therapy for CLL Ibr 420 mg | CR        |
| Blood.                          | 2016 | M   | 75  | NA       | Binet B | del17p           | Headaches and cognitive disturbance             | 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      | 63 M             | Cerebellar syndrome and aphasia, confusion    | NA                                                   | Binet C    | NA                | NA            | CSF                 |                                       | Two prior lines of therapy for CLL lbr 420 mg               | CR       |
| Blood. 2016.127. 2356            | 68 F             | Visual loss                                   | NA                                                   | Binet A    | NA                | del17p        | CSF                 |                                       | No prior lines of therapy for CLL lbr 420 mg                 | CR       |
| BMC Res Notes. 2014.7.645.       | 75 F             | Headache, otalgia in the right ear, fever, dizziness, and dysphagia | 5 years                                              | Rai 1      | 24,300 (WBC)      | NA            | CSF                 |                                       | Chlorambucil and prednisone IT Mtx FC                       | CR       |
| Leukemia Lymphoma. 2014. 55.1939| 64 M             | Hypoesthesia                                  | 2 months                                             | Binet B    | 251,000           | Normal        | CSF                 |                                       | WWW IT Mtx + AraC Rtx–bendamustine                       | CR       |
| BMJ Case Rep. 2014. Bcr 2013-202,051. | 45 F             | Seizures, headaches, and vomiting             | NA                                                   | NA         | NA                | NA            | Biopsy              |                                       | Surgical excision RT                                      | Relapse  |
| Clin Lymphoma Myeloma Leuk. 2013.13. 338. | 44 F             | Double vision                                 | 3 years                                              | Rai 1      | 98,280            | Trisomy 12 and 13q- | Biopsy              | CSF                 |                                       | RT mPSL IT AraC FCR                                       | CR       |
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|---|
| **Leuk Lymphoma. 2013.54. 2070. 39** |
| **Gait disturbance, tremors, slurred speech, marked fatigue, intermittent confusion, and visual impairment** |
| 67 M |
| 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** |
| **Fatigue and difficulty walking** |
| 66 F |
| 2 years |
| Rai 0 |
| 27,000 |
| NA |
| Biopsy (CT-guided), non-GCB DLBCL |
| Yes |
| WWW/ cyclophosphamide + PSL IT Dex RT Rtx |
| Transient PR→relapse |
| **J Clin Oncol. 2013.31 e280 41** |
| **Right-eye pain associated with blurry vision, floaters, and bright halos** |
| 75 M |
| 1 years |
| Rai 0 |
| 34,900 |
| Trisomy 12 |
| CSF+ |
| Yes |
| PSL Rtx–fludarabine |
| CR |
| **Acta Haematol. 2012.1 27. 93 42** |
| **Seizures, psychomotoric deficits, and left-sided hemiparesis** |
| 56 M |
| 1 month |
| Binet A |
| NA |
| NA |
| Stereotactic biopsy CSF+ |
| Yes |
| Systemic and intraventricular polychemotherapy regimen WBRT Topotecan |
| Transient CR→relapse |
| (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 | 53 F | Vision changes | 4 years | Rai I | 16,000,000 (WBC) | NA | CSF* | | CVP, Rtx-fludarabine, Alemtuzumab, IT Mtx, Temozolomide, RT | PR |
| J Neurooncol 2012.106. 185 | 52 M | Encephalopathy, dementia, seizures | 3 years | Rai IV | 14,000,000 (WBC) | NA | CSF* | | Fludarabine, None | PD |
| J Neurooncol. 2012.109. 213 | 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 | 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 | 73 | Bilateral visual loss | NA | Rai II Binet B | NA | NA | Ethmoidectomy | | Fludarabine/FCR, Steroids, RT | PD |
| J Neurol Neurosurg Psychiatry. 2011.82.943 | late60sM | Bilateral leg weakness, pain, and urinary retention | NA | Rai III | NA | Normal | Brain biopsy | Yes | WWW/chlorambucil/ FCR/CHOP HD Mtx | PD |
|---|---|---|---|---|---|---|---|---|---|---|
| J Clin Oncol. 2010.28.e30 | 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 | 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 | 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 | 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 | 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 | 81 M | Headache, nausea, weakness, somnolence, lethargy, and confused state | 25 months | Rai 0 Binet A | NA | NA | CSF^ | IT liposomal AraC FCR | CR |
| Br J Haematol. 2010.150.618 | 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 | 79 M | Leg weakness, difficulty walking, upper-back pain, and VII cranial pair palsy | 66 months | Rai IV Binet B | NA | NA | CSF<sup>+</sup> | Yes | IT Mtx and liposomal AraC | Transient CR ➔ relapse |
| Br J Haematol. 2010.150.618 | 68 F | Headache | 24 months | Rai IV Binet B | NA | NA | CSF<sup>+</sup> | Yes | IT Mtx and liposomal 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.

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