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CASE REPORT

Central nervous system involvement of chronic lymphocytic leukaemia: A rare case report

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ABSTRACT

Central nervous system (CNS) involvement in chronic lymphocytic leukemia (CLL) is unfamiliar. The diagnosis is delayed commonly, because of underdiagnosis or subclinical symptoms. We describe a 80-year-old woman with a previous diagnosis of CLL who presented to the emergency service with tonic clonic seizure. The new therapies, eg, ibrutinib and venetoclax, can be effective treatment strategies for CLL with CNS involvement. In our case, treatment with ibrutinib led to a resolution of the cerebralspinal fluid (CSF) neoplastic infiltration, but the patient died afterwards.

Keywords: chronic lymphocytic leukemia, central nervous system, cerebralspinal fluid.

INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in adulthood with a frequency 1% of all cancer cases [1]. The disease typically affects elderly patients with an age of diagnosis around 70 years. Generally, CLL is considered as an indolent lymphoma, whereas some cases with a more aggressive disease may associated with lower overall survival [2].

Non-lymphoid tissue is rarely associated with CLL infiltration, and defined as extramedullary CLL. Extramedullary CLL with central nervous system (CNS) infiltration and neurologic complications are reported only in 1% of patients [3,4]. As the diagnosis of CLL with CNS involvement is rare, there are no definitive data on clinical and radiological imaging findings. A wide variety of symptoms have been reported, including headache, convulsions, diplopia, ataxia and facial paralysis. Here, we report a case with CLL presented with tonic clonic epileptic seizure.

CASE PRESENTATION

An 80-year-old woman diagnosed with CLL (Rai, Stage I) in 2017. The patient only had hypertension as a chronic disease. Fluorescence in situ hybridization detected trisomy 12 with a normal karyotype cytogenetic analysis. She had been followed by a wait-and-see approach, until significant disease progression associated with lymphocytosis and axillary lymphadenopathy. In October 2020, the patient was treated with chlorambucil

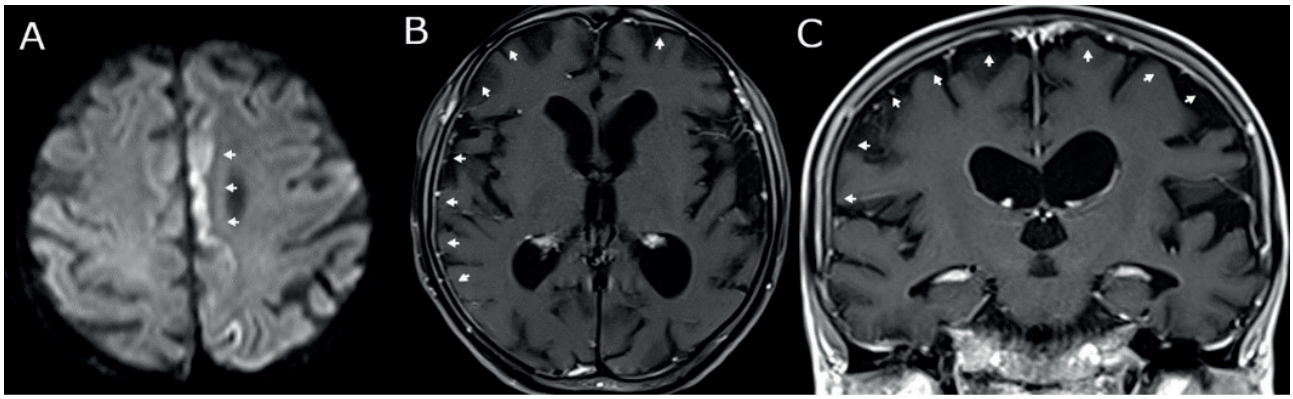
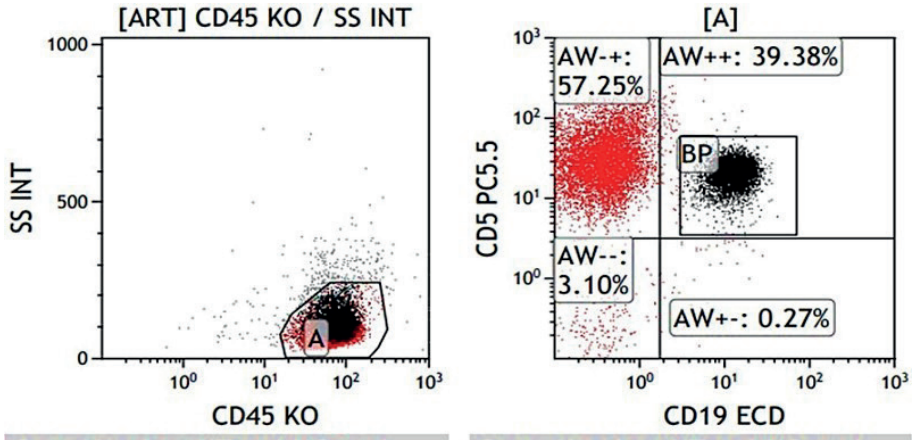


Figure 1. Magnetic resonance imaging of the case. **A)** Axial diffusion-weighted imaging revealing a hyperintensity in the left parasagittal area (arrows), secondary to seizure on the right side. **B)** Axial T1 sequence displays meningeal contrast enhancement (arrows) predominantly on the right side. **C)** Coronal T1 sequence shows contrast enhancement of the meninges on both sides.

monotherapy as first-line treatment. In December 2021, she showed worsening of preexisting lymphocytosis and lymphadenopathy, ascribed to CLL progression. Treatment with Rituximab plus Bendamustine (RB) was commenced.

In the following month, she applied to the emergency service because of a tonic clonic seizure in right arm and leg, unremarkable neurological examination. Magnetic resonance imaging (MRI) revealed restricted diffusion in the left frontal parasagittal area secondary to seizure (Figure-1A). Two weeks later, a secondary MRI with contrast showed contrast-enhancement (lesional enhancement after administration of contrast agents in MRI scans due to impaired blood-brain barrier in CNS pathologies) (Figure-1B,C). A diagnostic lumbar puncture was performed, and the cerebrospinal fluid (CSF) analysis revealed normal glucose, elevated protein (5.13 g/L). It was negative for gram stain and culture, enterovirus PCR, HSV 1 and 2, VZV, EBV, CMV, HHV 6 and 7 PCR. The flow cytometry analysis of the CSF revealed the presence of lymphocytes positive for CD19+/CD5+ (AW++), CD20weak, CD43weak, CD45, CD23, CD3, CD200strong, and findings were consistent with CNS infiltration by CLL cells indicating meningeal carcinomatosis (Figure 2). The CIRS (Cumulative



Gate	Number	%Total	%Gated
All	17,706	96.28	100.00
A	17,285	93.99	97.62

Gate	Number	%Total	%Gated
All	17,285	93.99	100.00
AW--	536	2.91	3.10
AW-+	9,896	53.81	57.25
AW+-	47	0.26	0.27
AW++	6,806	37.01	39.38
BP	6,715	36.51	38.85

Figure 2. Dot plots illustrating cerebral spinal fluid (CSF), (ART) Artefact, (SS) Side Scatter, immunophenotyping CD 45+ (black dots); **(A)** CD19−/ CD5+ (AW− +) cells (red dots) and CD19+ /CD5+ B-CLL (AW+ +) cells (black dots); Fluorochromes (KO) Krome Orange, (ECD) Phycoerythrin-Texas Red-x, (PC5.5) Phycoerythrin-Cyanin 5.5.

Illness Rating Scale) score of the patient was nine. The patient received dexamethasone (intravenous, 40 mg/day, 4 days) followed by intrathecal methotrexate (12 mg/day), cytarabine (40 mg/day), and dexamethasone (4 mg/day), twice a week (6 cycles). Thereafter, because the patient is of advanced age, treatment efficacy and ease of use are known, treatment with ibrutinib monotherapy 420 mg/day was started and her general condition improved with CSF normalisation. Prior to treatment with ibrutinib, the patient underwent electrocardiography, echocardiography and cardiology consultation, and no contraindications were found. She died of an unknown cause at home after one month on ibrutinib treatment.

DISCUSSION

In our case, the patient was diagnosed by CSF flow cytometry analysis that could be predicted malign cells up to 40% [5-7]. The incidence of CNS infiltration in CLL is clearly common in autopsy series than real life [7,8]. This can be the heterogeneity of neurologic symptoms patients with CLL and CNS involvement [9]. The most common symptoms are vision changes (22%), encephalopathy (29%) and weakness with paresthesias (22%) [10]. The clinical presentation of our patient was seizure which Strati et al. reported as the incidence of 7% [7]. The reports revealed that, indeed, neurologic presentations are nonspecific (Table 1). In some reports, it has been suggested that CNS involvement neither related to disease stage (according to Rai or Binet), nor poor prognostic chromosomal factors (e.g. deletion 17p or 11q) [9,11].

There is a lack of consensus on the treatment of patients with CNS involvement in CLL (e.g. intrathecal chemotherapy, chemo-immunotherapy, radiotherapy, combined or alone). Wanquet et al. reported rituximab combined with chemotherapies [RB or RFC (Rituximab, Fludarabine, Cyclophosphamide)] had significantly better progression free survival, and also ibrutinib may be an effective therapy for CNS involvement [12]. In our case, intrathecal chemotherapy with ibrutinib was an option with lower toxicity, and seemed to have led to a decrease in the CLL cells from CNS with flow cytometry analysis. In addition, some reports suggest that venetoclax may be a potent therapeutic option, in patients who progressed under ibrutinib treatment (Table 1) [13,14].

CNS involvement in CLL is uncommon and should be considered in all CLL patients with neurological symptoms.

Author contribution

Study conception and design: DK, RY, and PT; data collection: DK, KUB and NA; analysis and interpretation of results: DK, RY, and PT ; draft manuscript preparation: DK, RY, and PT. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of Ankara University School of Medicine (Protocol no. 11.05.2022; İ05-275-22).

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Conflict of interest

The authors declare that there is no conflict of interest.

Table 1. Patient's characteristics central nervous system (CNS) involvement in CLL

Age/Sex	Symptoms	Stage	Blood lypmhocyte count (×109 /L)	FISH	Treatment	Response	Reference
57/male	Bradypsychia, headaches, nausea, vomiting	Rai-III	85.5	17p	High-dose methotrexate	High-dose methotrexate	4
43/male	Dysphasia, repeated unconsciousness, urinary, incontinence	Rai-IV	23	Normal	Rituximab, fludarabine, cyclophosphamide	Rituximab, fludarabine, cyclophosphamide	4
49/male	Diplopia, bilateral eyelid swelling, and tumors	Rai-IV	86.5	N/A	Cisplatine; cytosine arabinoside; dexamethasone	Cisplatine; cytosine arabinoside; dexamethasone	4
72/male	Dyslexia, lack of fine motor control, diplopia	Rai-IV	103.9	13q14	Cisplatine; cytosine arabinoside; dexamethasone	Cisplatine; cytosine arabinoside; dexamethasone	4
33/male	Diplopia, headaches	Rai low, Binet A	464	Normal	Methotrexate, vincristine, procarbazine; Rituximab subsequent whole-brain radiotherapy; Rituximab, fludarabine, cyclophosphamide; İbrutinib	Methotrexate,vincristine, procarbazine; Rituximab subsequent whole-brain radiotherapy; Rituximab, fludarabine, cyclophosphamide; İbrutinib	9
64/male	Hypoesthesia	Binet B	251	Normal	Rituximab, bendamustin	Rituximab, bendamustin	10
71/male	Transient epileptic seizure, Decreased left upperlimb strength, left hemianopsia, visual hallucinations	Not available	Not available	11q/TP53; IGHV unmutated	Ibrutinib; Methotrexat, rituximab, Venetoclax (relapse); Venetoclax, rituximab, prednisone	Ibrutinib; Methotrexat, rituximab, Venetoclax (relapse); Venetoclax, rituximab,prednisone	14
58/male	Not available	Not available	Not available	Trisomy 12; IGHV unmutated	Ibrutinib; Venetoclax	Ibrutinib; Venetoclax	15

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