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Case Report

Chronic Lymphocytic Leukemia Presenting with Concurrent Isolated CNS Parenchymal and Leptomeningeal Large B-Cell Lymphoma

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Abstract

A previously well 59-year-old man presented with two weeks of progressive vertigo, ataxia, vomiting and diplopia. Computed tomography (CT) revealed multifocal areas of cerebral and cerebellar edema with contrast enhancement and magnetic resonance imaging with gadolinium also showed diffuse leptomeningeal enhancement with evidence of parenchymal invasion. Cerebrospinal fluid analysis identified malignant lymphocytes consistent with a large B-cell lymphoma. CT of the neck, chest and abdomen did not demonstrate hepatosplenomegaly or lymphadenopathy and peripheral blood counts showed a mild lymphocytosis. Bone marrow biopsy was consistent with chronic lymphocytic leukemia (CLL). Symptoms initially improved with corticosteroids, but the patient declined active therapy and died one month later of progressive central nervous system (CNS) disease. Patients with CLL may rarely develop CNS involvement. Even more rarely, some of these patients can present with aggressive histology lymphoma in the CNS. There is no standard treatment for CNS CLL or large B-cell lymphoma in these patients; although agents that cross the blood-brain barrier and intrathecal chemotherapy are most commonly used. The presence of large B-cell lymphoma involving the CNS appears to double six-month mortality compared to secondary CNS involvement by CLL.

Keywords: Chronic lymphocytic leukemia; CNS lymphoma; Richter syndrome; Transformation

Abbreviations

CT: Computed Tomography; CLL: Chronic Lymphocytic Leukemia; CNS: Central Nervous System; RS: Richter Syndrome; DBLCL: Diffuse Large B-cell Lymphoma; MRI: Magnetic Resonance Imaging; CSF: Cerebrospinal Fluid

Introduction

The natural history of chronic lymphocytic leukemia (CLL) is variable: approximately one third of patients experience long-term survival without need for treatment, one third are initially asymptomatic but eventually experience disease progression requiring therapy and one third have symptomatic disease requiring immediate treatment [1]. Approximately 2-10% patients may experience transformation to an aggressive lymphoma, commonly known as Richter's syndrome (RS) [2]. RS is a rare and fatal complication of CLL with an average survival of 8-12 months [3]. The most common aggressive histology is diffuse large B cell lymphoma (DLBCL) [3].

Symptomatic central nervous system (CNS) involvement in CLL is known to be rare, with only 92 cases described in a recent review of the literature [4]. Asymptomatic CNS involvement identified on autopsy is much more common, between 6-50% [5-7]. In most cases, CNS involvement in CLL occurs within five years of diagnosis, although in a very small subset CNS symptoms are the first presentation of CLL [8-16]. RS can rarely present in the CNS with parenchymal invasion causing encephalopathy, seizures and hemiparesis, or with lymphomatous meningitis [17-32]. Regardless of histology, leptomeningeal infiltration is associated with a median overall survival of 4-6 weeks if untreated [33].

It is exceptionally uncommon for patients to present with newly-diagnosed CLL together with DLBCL involving exclusively the CNS [34-36]. Here we present a case of CLL presenting concurrently with large B-cell parenchymal and leptomeningeal involvement and review the clinical characteristics, treatment and prognosis of this uncommon disease presentation.

Case Presentation

A 59 year-old right-handed man of Chinese ancestry presented with a two-week history of worsening vertigo, ataxia, vomiting and diplopia. His past medical history was only significant for mild hypertension and remote smoking.

Temperature was 37 degrees Celsius, blood pressure estimated by an automatic blood pressure monitor was 153/90 mmHg, heart rate was 72 beats per minute and respiratory rate was 16 breaths per minute. There was no peripheral lymphadenopathy or hepatosplenomegaly. Mental status and language were normal. The pupils were equal and reactive to light and funduscopic examination was normal. There was right beating nystagmus upon right, upward and downward gaze. Saccades were hypometric to the right. There was decreased auditory perception in the left ear. The remainder of the cranial nerve exam was normal. In all four limbs, power was intact (grade 5/5), with

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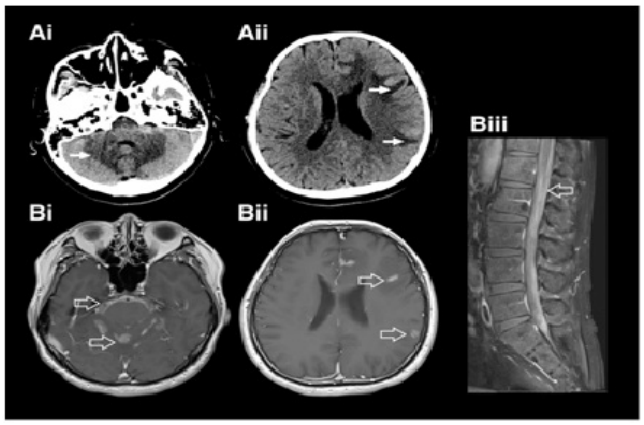

Figure 1: A: Computed Tomography (CT) head (axial) demonstrating vasogenic edema (filled arrows) in the cerebellum (i) and cortex (ii). B: Magnetic resonance imaging with gadolinium (axial) demonstrating diffuse leptomeningeal enhancement (open arrows) in the posterior fossa (i) cortex (ii) and sagital lumbar spine (iii).

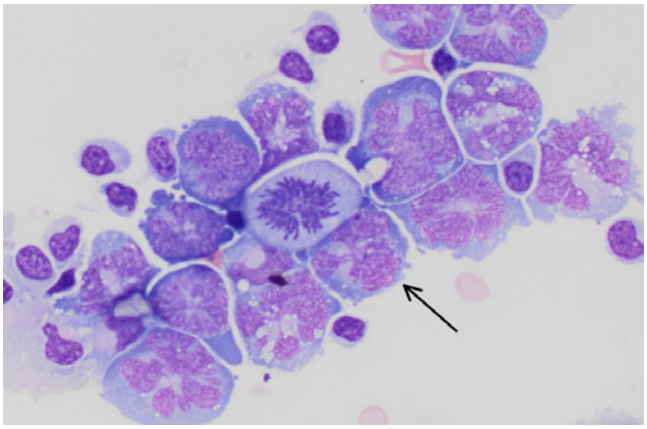

Figure 2: Cerebrospinal fluid cytospin preparation showing large atypical lymphocytes with multilobulated nuclei, prominent nucleoli, and moderate amounts of basophilic cytoplasm (arrow). A mitotic figure is present in the center of the field. (Wright stain, 40x).

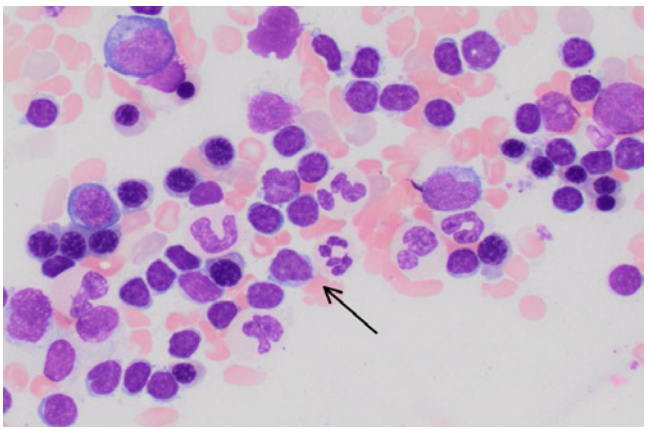

Figure 3: Bone marrow aspirates showing increased lymphocytes, which are small and mature in appearance (arrow). (Wright stain, 40x).

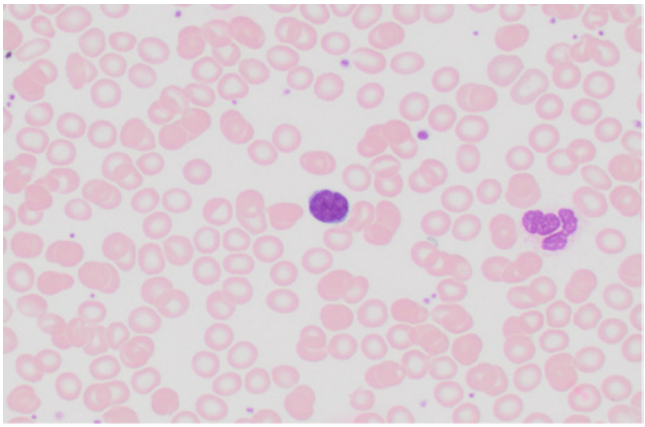

Figure 4: Peripheral blood smears showing small and mature lymphocytes similar in appearance to those in the bone marrow aspirate. (Wright stain, 40x).

decreased tone and reduced reflexes. There was bilateral dysmetria, left greater than right, as well as slow rapid alternating movements in the upper extremities. There was marked ataxia in both legs and gait was ataxic and right-veering.

Peripheral blood cell counts showed white blood cells 13.5x10^9/L (absolute lymphocyte count 4.7x10^9/L), hemoglobin 134 g/L, platelets 215x10^9/L. Serum sodium was 140 mmol/L, potassium 3.9 mmol/L, urea 6.7 mmol/L, creatinine 99 mmol/L, alanine aminotransferase 21 U/L, aspartate aminotransferase 10 U/L, lactate dehydrogenase 125 U/L. Hepatitis B, Hepatitis C and Human Immunodeficiency Virus serologies were negative. Computed tomography (CT) of the neck, chest, abdomen and pelvis did not reveal hepatosplenomegaly or lymphadenopathy. CT head demonstrated bilateral multifocal cerebral and cerebellar areas of vasogenic edema with nodular cortical and cerebellar enhancement and increased vascularity on the CT angiogram (Figure 1A). Caudal images of the head/neck CT identified possible paralysis of the left vocal cord. Magnetic resonance imaging (MRI) with gadolinium demonstrated diffuse contrast enhancement throughout the entire subarachnoid space of the brain and spinal canal. There were multiple leptomeningeal foci along the left cerebral hemisphere and superior cerebellum with marked intraparenchymal edema and restricted diffusion suspicious for parenchymal invasion (Figure 1B).

Cerebrospinal fluid (CSF) analysis via lumbar puncture demonstrated white blood cells 341x10^6/L, red blood cells <500 x10^6/L, glucose 6.3 mmol/L, protein 12,202 mg/L. CSF was thick and straw coloured and flow cytometry identified an abnormal B-cell population positive for CD19, CD20 (bright), CD10, FMC-7 with monotypic expression of kappa surface immunoglobulin light chain. CD5 and CD23 were negative. CSF cytology revealed the presence of malignant lymphocytes with large multilobulated nuclei consistent with large B-cell lymphoma (Figure 2). Bone marrow biopsy showed 30-40% cellularity with an infiltrate of small atypical lymphocytes (Figure 3). They exhibited a different immunophenotype by flow cytometry: positive for CD19, CD20 (dim), CD5 and CD23 with excess surface kappa immunoglobulin light chain expression; but negative for CD10, FMC-7 and CD38. Immunoglobulin V_H mutation status, ZAP-70 and cytogenetics (including TP53) were not performed. Peripheral blood smear showed small, atypical lymphocytes similar in appearance to those in the bone marrow (Figure 4), although peripheral blood flow cytometry was not performed. The findings

were consistent with discordant involvement of the bone marrow with chronic lymphocytic leukemia. Polymerase chain reaction for B-cell receptor clonality was not performed on either specimen.

He was initially treated with oral dexamethasone 8 mg twice daily, with significant improvement of the ataxia and diplopia. Given the aggressive presentation of the leptomeningeal disease, systemic and intrathecal chemotherapy was recommended, including methotrexate, cytarabine, fludarabine and rituximab. Craniospinal radiotherapy was also presented as an alternative. The patient understood the treatment options and given the poor long-term prognosis afforded by the extent of CNS involvement, after a comprehensive informed consent discussion, he opted not to undergo active therapy for CLL or CNS lymphoma. He experienced progressive worsening of neurologic deficits despite dexamethasone and had a tonic-clonic seizure 38 days after his initial presentation. He did not regain consciousness and died a few days later.

Discussion

This case describes a previously healthy man with a sub acute history of cerebellar and cranial nerve deficits secondary to lymphomatous meningitis by aggressive histology B-cell lymphoma. In secondary CNS malignancies, leptomeningeal involvement is the third most common complication in the CNS, after parenchymal masses and epidural spinal cord compression [33]. The hematologic malignancies most likely to present with neoplastic meningitis are lymphoblastic leukemia/lymphoma, Burkitt lymphoma, acute myelomonocytic leukemia and primary CNS lymphoma [37,38].

Because immunoglobulin heavy chain rearrangement studies were not performed on the CSF or bone marrow specimens, we cannot determine whether the CNS disease was a true Richter transformation of systemic CLL or whether it was coincidental, *de novo* primary CNS lymphoma. The disparity between CD10, FMC7 and kappa light chain expression between CSF and bone marrow samples suggests there was no clonal connection between both lymphomas. In a separate report of a case with a very similar presentation, authors clearly demonstrated clonality between the CNS tumor and CLL, indicating that in some instances both histologies are indeed related [39]. Ultimately, this question did not turn out to be significant clinically in our patient, as it did not alter treatment or prognosis.

A MEDLINE search was performed to identify case reports, case series, or cohort studies in English or French of patients with CLL presenting with neurologic involvement. A total of 23 patients with CLL involving the CNS between 1982-2013 were identified from 22 reports [8-17,39-50]. In a separate search to identify cases of CNS DLBCL, there were 15 cases of CNS DLBCL in known CLL from 12 reports [17,19,21,25,26,28-32,51] and two review papers each briefly described 5 additional cases [22,24]. In addition, 4 cases in whom CLL was diagnosed simultaneously with CNS DLBCL were identified from 3 reports [18,23,52]. These findings suggest that involvement of the CNS in patients with CLL is exceedingly uncommon and is more likely to occur in patients with a pre-existing history of CLL. Our patient's presentation with CNS large B-cell lymphoma concurrently with CLL is therefore the least frequent and constitutes the fifth reported case in the literature.

There is no standard of care for the treatment of CNS CLL or RS. Primary and secondary CNS lymphomas are known to be poorly responsive to a variety of agents alone or in combination, presumably due to the genetic abnormalities acquired during its evolution [3,53-56]. The most frequently used therapy across groups in this review was intrathecal methotrexate (47% of those with RS and pre-existing CLL, 40% of those with RS without pre-existing CLL and 26% of those with CNS CLL). Treatment of CNS involvement in CLL has been most successful with IT methotrexate and cranial radiation, which in one retrospective series resulted in symptom improvement in 83% of cases [17]. Due to the enormous variability of treatments, small number of cases and the high mortality, no strong conclusions can be made from this review regarding the success of any particular treatment type or combination.

Despite the apparently favorable prognosis based on Rai staging for a majority of patients, the overall survival of patients with CNS involvement is poor. Of the 43 patients reviewed, 19 (44%) were reported to die in the year after CNS diagnosis, 17 of whom died within the first six months. There was a trend towards better survival in those with CNS CLL compared to CNS DLBCL. In those with untransformed CLL presenting in the CNS, 14 of 23 (58%) were alive at the time of follow up, median 12 months, compared to only 6 of 15 (33%) with RS and prior CLL alive at the time of follow up, median 3 months. In the 5 patients with CNS DLBCL and simultaneous CLL diagnosis, two died within 6 weeks of presentation, two were alive at one year and one was known to be alive at 3 month follow up, though with recurrent lymphoma. The two who survived to one year presented with parenchymal tumors and one received radiation, the other systemic and IT chemotherapy.

This case report and literature review demonstrates that patients with CLL may rarely present with CNS involvement in the form of CNS CLL or aggressive histology B-cell lymphoma. Prognosis appears most influenced by the presence of DLBCL, with a high mortality rate at 6 months. There is no gold standard therapy, though intrathecal methotrexate was most commonly used in the reported cases. Treatment can be effective for symptom relief, but is rarely curative. In the very rare case of CLL presenting in the CNS with DLBCL, death occurs within six weeks if untreated, but survival may be improved by several months with treatment.

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