Chronic Lymphocytic Leukemia with Central Nervous System Involvement Mimicking a Demyelinating Disease Treated Successfully with Ibrutinib.

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Running head: CLL with CNS involvement treated with ibrutinib

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Abstract:
Chronic lymphocytic leukemia (CLL) is a mature B cell neoplasm characterized by clonal proliferation of B lymphocytes in peripheral blood, bone marrow and lymphoid tissue. Leukemic involvement of the central nervous system (CNS) is rare with incidence less than 1%. In addition to the diagnostic challenge of CLL with CNS involvement (CNSi), no consensus exists about the optimal treatment. Herein, we describe a case of middle-aged male who presented with lymphocytosis and intramedullary lesion mimicking a demyelinating disorder. After comprehensive investigations, our patient is diagnosed with CLL Rai 0 with concurrent leukemic infiltration of the spinal cord. Patient was successfully managed with ibrutinib monotherapy.

INTRODUCTION:

- Chronic lymphocytic leukemia (CLL) is a mature B cell lymphoproliferative disorder characterized by a clonal B cell proliferation in the bone marrow, peripheral blood and the lymphoid tissues. Central nervous system (CNS) infiltration, though is rare, is the most common extramedullary site of CLL [1]. To the current knowledge, no risk factors of CLL with CNS involvement (CNSi) have been identified. Moreover, clinical manifestations are heterogeneous and non-specific [2]. There is no consensus agreement on the optimal treatment for CNSi in CLL patients.
  In this report, we aim to describe the diagnostic dilemma we faced in a case, who was otherwise healthy, presented with concurrent lymphocytosis and an intramedullary lesion and to review the literature on the optimal treatment for CNSi in CLL patients.

CASE PRESENTATION:

- A 55-year-old male referred from neurology department with right hand numbness, weakness and absolute lymphocytosis of 16 x 10^9/L. Physical examination was unremarkable apart from right upper limb weakness (4/5). Complete blood counts (CBC) showed: White blood cells (WBC) 28.5 X10^9/L, absolute lymphocyte counts (ALC) 16 x 10^9/L, hemoglobin level 15.1 g/dL and platelet count 254 x 10^9/L. Blood film morphology showed absolute mature lymphocytosis and few smudge cells. Peripheral blood flow cytometry showed clonal lymphocytosis expressing CD5+, CD23+, CD19+, CD200+, CD38+ and kappa light chain restriction and cytogenetic evaluation using fluorescent in situ hybridization (FISH) revealed 11q and 13q deletions. Magnetic resonance imaging (MRI) of the brain and neck demonstrated an intramedullary cord lesion located at C3 and C4 levels (figure 1A). The radiological findings were suggestive of a demyelinating process or less likely a neoplastic infiltration of the cord. Computed tomography (CT) scan of the abdomen and pelvis demonstrated multiply enlarged small supra and infra diaphragmatic lymph nodes (3.4 x 4.1 cm). The cerebrospinal fluid (CSF) examination showed a clear fluid with normal glucose, lactate dehydrogenase (LDH) and protein levels. Cytological examination of the CSF fluid demonstrated rare red blood cells and many small mature lymphocytes and flow cytometry revealed 15% clonal lymphocytes expressing CD5, CD19, CD23 and CD38 and kappa restriction. He was treated initially with triple intrathecal therapy (TIT) consisting of methotrexate, cytarabine and dexamethasone, however after three TIT the symptoms were persistent. Neuromyelitis optica was ruled out by negative aquaporin 4 membrane protein antibody. Patient was evaluated by neurologist who advised a trial of pulse steroid (1g/day) for five days duration because of the possibility of a demyelinating disorder. However, symptoms were persistent and worsening.

- Clinically, patient symptoms were progressing. Since CNSi by CLL is rare, we sought ruling out RT by PET/CT scan that showed mild FDG cord uptake (SUV Max 2.9) in the cervical area from C2 to C5. This finding decreased the possibility of RT. Final decision was to initiate therapy for CLL that can penetrate the blood-brain barrier (BBB). However, patient was reluctant to receive chemoimmunotherapy (CIT). Ibrutinib as a single agent was initiated in May 2019 at a dose of 420 mg/day. Patient showed clinical and radiological responses (figure 1B) after two months of commencing therapy with no toxicity.

DISCUSSION:

- CNS involvement in CLL (CNSi) is a rare complication. Strati and colleagues have reported 0.4% incidence of CNSi in CLL in 4174 CLL pts with no specific risk factor or clinical feature that can predict the CNSi [2]. CNSi might occur at any time during the course of CLL [1]. No correlation between CNSi and cytogenetic/molecular abnormality or Rai stage has been documented [1]. The clinical manifestations are heterogeneous, which include cranial nerve palsies, headache, cognitive decline, sensory and motor deficits. Lopez Da Silva has nicely reviewed the spectrum of CNS complications in CLL, ranging from infections, hemorrhagic, iatrogenic, other tumors to leukemia involvement [3], therefore careful evaluation of other differential diagnosis is warranted. At present, data is lacking about the prognostic significance of CNSi, however some reports indicating CNSi considered to be a high risk feature [4]. However, study by Strati et al., median overall survival (OS) of patients with CNSi were only 12 months [2] indicating a higher risk disease and shorter OS. On the contrary, the 5-year OS was higher in both treatment naïve and pre-treated patients with CNSi; 72% and 48% respectively (P = .006) as reported in more recent study by Wanquet et al. [5].

- As regard to management, no consensus exists on the optimal therapy [6]. Nevertheless, different treatment approaches reported in the literature in the form of case reports or case series, including CNS radiation, intrathecal chemotherapy, anthracycline based regimens, purine analogue based regimens and new targeted therapy including ibrutinib and venetoclax. It is crucial to diagnose and treat promptly CNSi CLL in order to improve outcomes.

- In a retrospective review of 78 cases of CLL with CNS involvement, intrathecal chemotherapy with or without systemic chemotherapy or CNS radiation was used in the majority of the cases [1]. The commonest intrathecal chemotherapy was methotrexate with or without cytarabine. The majority of the cases, which showed complete neurological remission, had intrathecal methotrexate [3], however responses were not durable.

- Other chemotherapeutic agents that cross the blood brain barrier include high-dose methotrexate and high-dose cytarabine and to a lesser extent fludarabine-based regimens with favorable activity against CLL. Fludarabine monotherapy demonstrated inconsistent outcome when used in CNSi with one report of complete neurological response [1]. Fludarabine has been used in combination with cyclophosphamide and rituximab with and without intrathecal chemotherapy in 9 pts achieving high response rate (9/9 pts, 100%) [5], bendamustine is an alkylating agent with purine analogue component and has been used in CLL.

- Dasatinib, a BCR-ABL and SRC-tyrosine kinase inhibitor, have shown a long-lasting complete remission when used in a case of primary CNS CLL who experienced a relapse after 2 lines of chemotherapy.

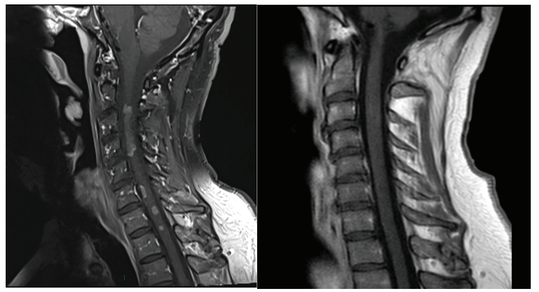
- Although, intrathecal rituximab is found to be safe and modestly effective in treatment of refractory primary CNS lymphoma, no report about its role in CNSi.

- Recently, ibrutinib with or without intrathecal chemotherapy demonstrated complete neurological response in three out of sex patients with CNSi and partial neurological response in the remaining based on a retrospective study. (blood j).

- Finally, venetoclax, a selective BCL2 inhibitor, demonstrated a promising result in CNSi when given with IT chemotherapy for a relapsing patient with CLL, who was heavily pretreated with chemoimmunotherapy and relapsed post-ibrutinib+IT. In the same case, CSF clearance achieved one month only after venetoclax initiation.

KEY CLINICAL MESSAGE:

- Though is extremely rare, leukemic infiltration of the CNS should be considered in the differential diagnosis of any neurological complaint in patients with CLL. Our report supports the previously published data about the efficacy of ibrutinib in treatment of patients with CNSi.



Lopez	1 pt	CNS CLL	IT MTX + arac + CHOP	CR	3 mon	Alive		
Elliot	1 pt	CNSi CLL	Fludarabine single x 6	CR	6 mon	Alive		
popla	1 pt	CNSi CLL	Chemo + IT MTX	Clinical improvement	6 mon	Died	Respi sepsis	Procarbazine CCNU DEXA Kuwa
kuwa	1 pt	CNSi CLL	TIT	Clinical imp	3 mon	Died	Resp sepsis	
hanse	5 pts / 129 pts	CNSi CLL	IT chemo +/- RT or chlorambucil/CHOP	Clinical imp	23+ mons	4 Alive 1 Died	CNSi progression	3 ch 1 CHOP No correlation BW outcome and CNSi : Rai/WBC

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