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CASE REPORT

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Management of atypical chronic lymphocytic leukemia presenting with extreme leukocytosis

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Abstract

Atypical chronic lymphocytic lymphoma (CLL) with CCND1 translocation is poorly described, particularly in the era of modern inhibitors of the B-cell receptor pathway. We present a patient with atypical CLL who had a significant response to ibrutinib, highlighting the effectiveness of this agent in higher risk CLL subgroups.

KEYWORDS

Atypical chronic lymphocytic leukemia, ibrutinib, leukocytosis

1 | INTRODUCTION

The t(11;14) is typically the hallmark of mantle cell lymphoma (MCL), but can also be present in chronic lymphocytic leukemia (CLL) in 2%-5% of cases and confers a poor prognosis due to an oncogenic IGH/CCND1 translocation leading to the aberrant expression of cyclin D1.[1] The t(11;14) identifies a unique subtype of B-CLL that shares some biological features with MCL.[2] The disease is characterized by aggressive cytologic and cytogenetic evolution, confers a poor prognosis, and frequently requires early treatment at presentation.[3] This subset of CLL also has an atypical morphology consisting of several small lymphocytes and some larger lymphocytes and prolymphocytes. It also has a unique immunophenotype with the expression of FMC7, which is found to be negative in typical CLL. $FMC7^+$ is also found in MCL and is considered to be a marker of aggressive clinical behavior.[4] The optimal management of atypical CLL with t(11;14) is not well studied given the low incidence, despite poorer risk disease.

There is no standard of care for initial treatment of CLL, and treatment decisions are typically guided by the patient's age, fitness, and cytogenetic risk. As CLL is generally considered incurable, the goals of therapy are directed toward relief of symptoms and prevention of disease progression. Historically, clinical trials of chemo-immunotherapy combinations for CLL have used age above 65-70 as being an indicator of decreased benefit and tolerance with these therapies. In addition, superior outcomes can be achieved in patients with poor-risk disease (eg, 17p deletion or *TP53* mutation) with the oral Bruton's tyrosine kinase inhibitor ibrutinib.[5] The recently published phase III A041202 trial randomized patients 65 years or older with untreated CLL to one of three arms: bendamustine plus rituximab, ibrutinib alone, or ibrutinib plus rituximab. The estimated percentage of patients with progression-free survival at 2 years was 74% with bendamustine plus rituximab and was higher with ibrutinib alone at 87% and with ibrutinib plus rituximab at 88%. There was no significant difference between the ibrutinib plus rituximab group and the single-agent ibrutinib group with regard to progression-free survival.[5] A common initial effect of ibrutinib is transient lymphocytosis resulting from the redistribution of CLL cells from lymph nodes into the peripheral blood.[6] Given this phenomenon, there is a theoretical risk of hyperleukostasis with starting ibrutinib in patients with high WBC counts. Leukostasis has been rarely reported in CLL unless WBC exceeds roughly 400 K/μL.[7]

2 | CASE REPORT

A 65-year-old Caucasian male was referred to the hematology clinic for evaluation of leukocytosis, with white blood cell count (WBC) value reported as >100 K/μL. He initially presented to his primary care physician with symptoms of progressive exertional dyspnea 2 months prior. At that time, a work-up llustrated a white blood cell count of >100 K/μL with the differential showing predominantly lymphocytes and anemia with hemoglobin (Hgb) of 10.7 g/dL. A complete blood count (CBC) two years earlier demonstrated a WBC of >100 K/μL without evidence of anemia; however, a work-up was not initiated at the time. He now reported a diminished appetite and fatigue, but denied B symptoms, headaches, dizziness, blurry vision, or chest pain. Past medical history included type 2 diabetes mellitus (DM) and hypertension (HTN). He also denied any family history of hematological disorders. He had no recent travel or infections, and medications included amlodipine, valsartan, metformin, and glimepiride. Vital signs on presentation were pertinent for a blood pressure of 129/76 mm Hg and an oxygen saturation of 95% on room air. Physical examination revealed a well-developed male in no distress with palpable 2 cm bilateral supraclavicular lymphadenopathy and palpable splenomegaly. This patient had no evidence of infection and was not taking any medications that could explain his laboratory findings. Additionally, he was asymptomatic despite a persistently elevated WBC for over 2 years which suggested a chronic process. His presentation with hyperleukocytosis, anemia, and palpable lymphadenopathy and splenomegaly prompted further work-up including repeat peripheral flow cytometry, cytogenetics, and imaging studies.

A CBC performed in the clinic on the day of presentation revealed a WBC of 593 K/μL (3.9-11.0 K/μL), Hgb of 8.5 g/dL (12.4-18.0 g/dL), MCV 103 (80-99), and platelet count of 85 000/μL (160 000-392 000/μL). Chemistry showed a BUN 31 mg/dL (7-25 mg/dL), creatinine 1.0 mg/dL (0.7-1.25 mg/dL), potassium level 6.1 mmol/L (3.5-5.3 mmol/L), and calcium 10.4 mg/dL (8.6-10.3 mg/dL). Other pertinent laboratory results included an elevated uric acid 9.5 mg/dL (4.0-8.0 mg/dL), phosphorus 3.6 mg/dL (2.1-4.3 mg/dL), LDH 301 U/L (120-250 U/L), and beta-2 microglobulin 11.5 mg/L (<2.51 mg/L). The peripheral smear revealed numerous lymphocytes as well as smudge cells, with no evidence of red blood cell agglutination (Figure 1). Flow cytometry revealed a clonal population of CD5+, CD10−, CD19+, CD20+, FMC7+, and CD23+ B-lymphocytes in 81% of the cells analyzed. CT scan of the chest, abdomen, and pelvis showed diffuse bulky (defined as >5 cm) lymphadenopathy (measuring up to 6.2 cm) and hepatosplenomegaly with the spleen measuring 22 cm in greatest diameter (Figure 2).

The work-up was consistent with a diagnosis of CLL which is characterized by a clonal population of CD5+ and CD23+ mature B-lymphocytes. The disease was classified as Rai stage IV based on findings of lymphadenopathy, hepatosplenomegaly, anemia, and thrombocytopenia. Polymerase chain reaction (PCR) amplification and sequencing analysis showed 4.1% mutated immunoglobulin heavy chain (IGHV) which is a marker of good prognosis. Conventional cytogenetics and fluorescence in situ hybridization (FISH) revealed t(11;14) and deletion 13q (Figure 3).

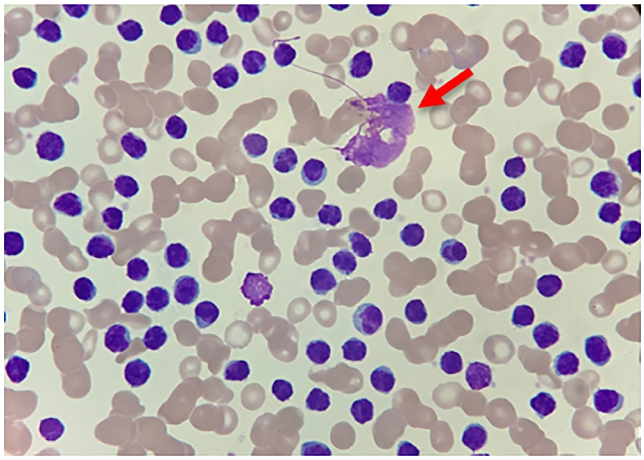

FIGURE 1 Peripheral blood smear illustrating numerous small lymphocytes and a smudge cell (arrow)

Sodium polystyrene sulfonate was used to lower the potassium level to normal. He was also started on allopurinol, intravenous fluids, and received a dose of rasburicase to manage tumor lysis prior to initiating therapy directed at his atypical CLL. The patient's elevated potassium level was likely due in part to pseudohyperkalemia, which has been reported in patients with CLL who present with markedly elevated WBC counts. Pseudohyperkalemia is thought to be due to the increased fragility of leukemic white cells which can lyse during tube transportation, prolonged incubation, and tourniquet use leading to release of intracellular potassium.[8] Given the elevated WBC count, potassium, uric acid, and LDH along with bulky lymphadenopathy, there was concern for potential to augment tumor lysis syndrome (TLS) after initiation of treatment. Patients with CLL are typically considered at low to intermediate risk of developing TLS.[9] However, as the risk of TLS in patients with atypical CLL with markedly elevated WBC count is not well established, he was treated empirically as high risk for TLS.[10]

Treatment options were discussed with aim of both cytoreduction and consolidation of his Rai IV disease. As there is a scarcity of literature to guide the management of patients with markedly elevated WBC counts and the theoretical risk of leukostasis when starting ibrutinib, a decision was made to start chemotherapy with single-agent bendamustine for initial cytoreduction followed by definitive therapy with modern targeted agents. His WBC rapidly downtrended to 90.0 K/μL after one dose of 90 mg/m^2 bendamustine (Figure 4). He

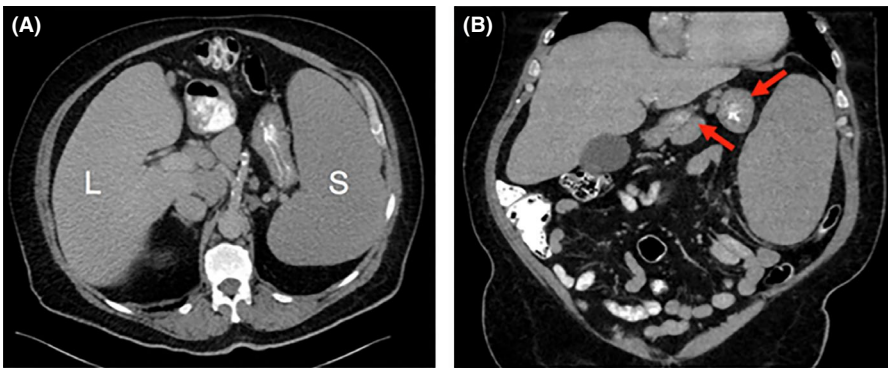

FIGURE 2 CT imaging of the abdomen/pelvis illustrating (A) hepatosplenomegaly (B) bulky portocaval lymphadenopathy (arrows)

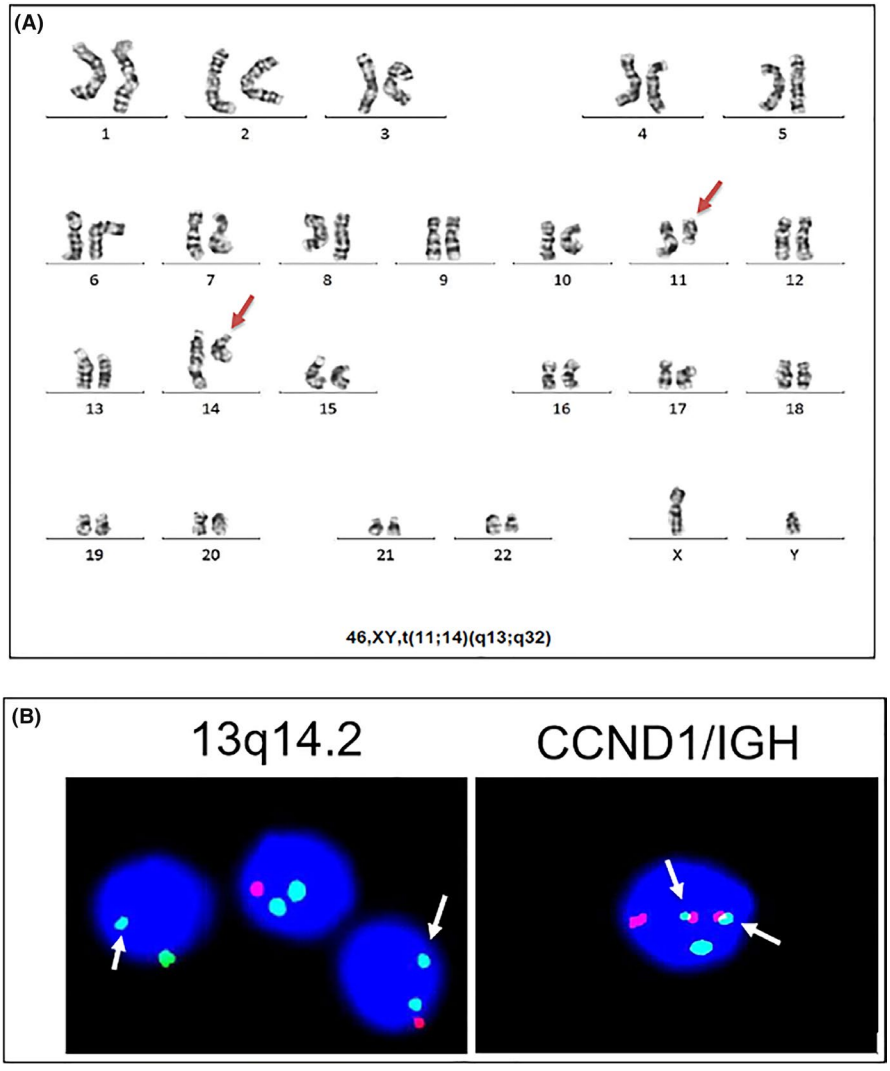

FIGURE 3 A, Karyotype illustrating t(11;14)(q13;q32), a reciprocal translocation between the proximal long arm of chromosome 11 and the distal long arm of chromosome 14, resulting in the placement of CCND1 downstream of IGH. This finding is typically found in mantle cell lymphoma, but can also be seen in atypical chronic lymphocytic lymphoma. B, Interphase FISH results. The image shows hemizygous and homozygous deletion of 13q14.2 (left) and the t(11;14) involving CCND1/IGH (right)

developed hyperkalemia (potassium level of 6.8 mmol/L) and acute kidney injury (creatinine of 1.5 mg/dL) after treatment was initiated. These abnormalities resolved with IVFs and a repeat dose of sodium polystyrene sulfonate. The decision was made to transition the patient to Ibrutinib at this time for further consolidation of his atypical CLL. He continued to respond once started on ibrutinib, with a WBC 92 K/μL after his first month on treatment (Figure 4). His lack of appetite, shortness of breath, and decreased energy improved as well. A repeat CBC after his 5 months on ibrutinib showed WBC 51.6 K/L, Hgb 14.5 mg/dL, and platelets 124 K/μL. In addition, repeat body imaging showed resolution of his lymphadenopathy. Given his partial remission by iwCLL criteria, he continues to be on ibrutinib without adverse effects and

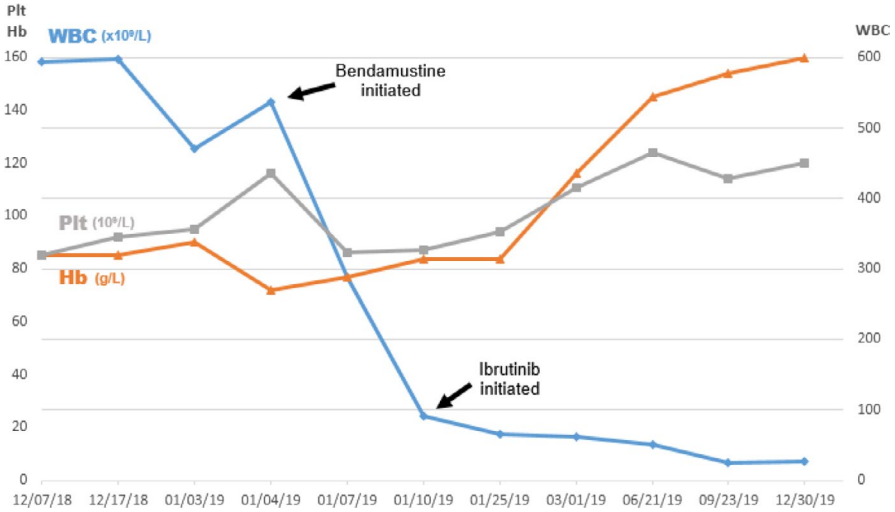

FIGURE 4 Trend of total WBC, platelets, and hemoglobin over time from presentation to most recent follow-up

has follow-up with monitoring every 3 months, with the goal of achieving absence of minimal residual disease.[11]

3 | DISCUSSION

Chronic lymphocytic lymphoma often presents with a laboratory finding of leukocytosis. Hyperleukocytosis with WBC >100 K/μL can result from both benign and malignant conditions (Table S1). The differential diagnosis of markedly elevated WBC count includes leukemoid reaction due to infection or medications such as corticosteroids, lithium, and beta agonists, and primary bone marrow disorders such as myeloproliferative neoplasms or leukemia.[12] Atypical CLL with t(11;14) presenting with the degree of hyperleukocytosis seen in this case has never been reported.

The (11;14)(q13;q32) translocation was previously considered to be the hallmark of mantle cell lymphoma (MCL), but is currently identified 2%-5% of CLL cases.[1] Recognition of this cytogenetic subset of atypical CLL is crucial given its poor prognosis and need for prompt treatment.[13,14] CLL with this translocation is associated with atypical morphology with predominantly small lymphocytes and prolymphocytes and/or large lymphocytes seen on peripheral smear. This subset of CLL also has a distinct immunoexpression with cells that are $CD5^+$, $CD19^+$, $CD23^+$, sIg+, $FMC7^+$, and CD10− which likely accounts for its atypical presentation. This differs from the conventional B-CLL phenotype in which cells are $CD5^+$, $CD19^+$, $CD23^+$, $FMC7^-$, and $CD10^-$ with variable expression of sIg.[13] As with atypical CLL, MCL tends to be $FMC7^+$, but differs in that it is characteristically $CD23^-$.[15]

It is important to distinguish between CLL with t(11;14) and MCL in the leukemic phase as both can present similarly with late-stage disease involving the lymph nodes and spleen.[16] The t(11;14) leads to the overexpression of the CCND1 gene which encodes cyclin D1. This protein belongs to the highly conserved cyclin family and is important for cell cycle regulation. Cyclin D1 typically forms a regulatory complex with cyclin D-dependent kinases (CDK) 4 and 6 which phosphorylate the retinoblastoma 1 (RB1) tumor suppressor protein thereby allowing for G1/S cell cycle transition. The juxtaposition at the IGH locus in t(11;14) causes overexpression of cyclin D1 thereby allowing for the evolution from G1/S phase to become unrestrained.[17] It has been shown that both Bruton's tyrosine Kinase (BTK) and the Bcl-2 family of anti-apoptotic proteins are upregulated in mantle cell lymphomas harboring t(11;14). Ibrutinib acts by two primary mechanisms in CLL: by covalently bonding to the active site of BTK, leading to the irreversible inhibition of its enzymatic activity, and inhibiting the enzyme's ability to autophosphorylate, preventing downstream activation thereby blocking cell growth, proliferation, and survival.[18] Ibrutinib both inhibits the BTK pathway and downregulates the expression of Bcl-2 proteins, which likely accounts for its effectiveness in both MCL and atypical CLL.[19]

Leukostasis has been occasionally reported after the initiation of ibrutinib and is thought to be due to an increase in circulating leukocytes.[20] Therefore, starting ibrutinib immediately could potentially make this patient susceptible to leukostasis and thromboembolic events. As such, chemotherapy was used as initial treatment to reduce this theoretical risk and allow for a transition to ibrutinib with potentially less risk of hyperleukocytosis or TLS. Given this potential risk, bendamustine was started for initial cytoreduction.[21] The patient had an excellent initial response to bendamustine and is enjoying a durable remission since being transitioned to ibrutinib with normalization of his hemoglobin and resolution of his symptoms.

The optimal management of atypical CLL is not well studied given its low incidence. It has been reported that

patients with this high-risk cytogenetic abnormality have a poor response to cytotoxic therapy.[22] However, in this patient, bendamustine appeared to be effective for rapid cytoreduction in this disease. Previous studies have demonstrated that the use of chemotherapy in patients with high-risk cytogenetics such as 17p deletion show poor long-term outcomes.[23] Extrapolating from these data, the decision was made to transition to ibrutinib which has been shown effective and durable in patients with CLL with poor-risk cytogenetics.[24] Additionally, ibrutinib is also approved for the treatment of mantle cell lymphoma in the relapsed and refractory setting providing further evidence for its potential efficacy in patients with t(11;14).[25]

This case illustrates the dilemma of modern management of late-stage CLL in the setting of extreme leukocytosis. Historically, Rai stage IV disease correlated to a poor overall survival compared to earlier stages, but this difference has been largely eliminated with the use of modern agents such as ibrutinib.[5] Additionally, this case suggests that ibrutinib can overcome the poor prognosis associated with an atypical t(11;14), similar to how it has been shown to outcomes poor cytogenetics risk in typical CLL.[24] In this case, a single dose of bendamustine served as effective cytoreduction prior to starting ibrutinib. Further studies are needed to determine whether modern oral agents can improve outcomes in patients with atypical CLL, particularly in those presenting with a markedly elevated WBC.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

RM and NT: wrote the initial draft. MB: edited and submitted the manuscript. All authors were involved in the management of this patient and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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