Coexistence of chronic lymphocytic leukemia and NK/T lymphoma of the nasopharynx in a patient treated with ibrutinib

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ABSTRACT

Extranodal NK/T-nasal cell lymphoma is rare in Europe and North America. This report presents a case of a female chronic lymphocytic leukemia patient who developed an extranodal NK/T lymphoma of the nasopharynx shortly after the withdrawal of ibrutinib therapy.

Keywords: chronic lymphocytic leukemia, ibrutinib, lymphoma

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is characterized by clonal proliferation of B lymphocytes, accumulating in peripheral blood, bone marrow, lymphoid organs, and rarely in extra lymphatic organs [1, 2]. One of CLL's most important prognostic factors are cytogenetic abnormalities identified by fluorescent in situ hybridization, found in more than 80% of patients at the diagnosis [3]. In approximately up to 10% of patients at diagnosis, a 17p deletion (*TP53* gene *locus*) is diagnosed. *TP53* loss or dysfunction leads to resistance to immunochemotherapy comprised of alkylating agents, purine nucleoside analogs, and anti-CD20 antibodies [1, 2]. Besides the 17p deletion and the non-mutated status of the immunoglobulin variable heavy chain (*IGHV*) genes, the mutations of the *TP53* and *NOTCH1* genes are associated with an unfavorable prognosis in patients with CLL [1, 2, 4, 5]. The currently recommended therapeutic options for patients with 17p deletion, *TP53* mutation, as well as in patients with unmutated *IGHV* gene, are inhibitors of the B-cell receptor (BCR) pathway, mainly Bruton kinase inhibitors (BTKi) [1, 2, 6]. BTKi act independently of the *TP53* gene status, making them effective in patients with its inactivation or loss. Nevertheless, the most clinically important side effects of BTKi drugs include cardiac arrhythmias, elevated blood pressure, and increased bleeding risk pose the most potent adverse events of these agents. However, it must be noted that depending on the compound occurrence of the above-mentioned adverse event varies [6–10].

In some CLL cases, especially heavily pretreated, a transformation to aggressive lymphoma [Richter's transformation (RT)] is observed [5, 11, 12]. Transformation into diffuse large B-cell lymphoma (DLBCL) is most frequently observed, much less often into Hodgkin lymphoma (HL) or other aggressive types of lymphoma [13]. Coexistence of T-cell lymphoma occurs extremely rarely.

This report presents a case of a female CLL patient who developed an extranodal NK/T-cell lymphoma of the nasopharynx shortly after the withdrawal of ibrutinib therapy.

CASE DESCRIPTION

In 2003, a 66-year-old woman was observed due to increased leukocytosis [white blood cells (WBC) 14.5 G/L] with

lymphocytosis (70% lymphocytes in the peripheral blood smear) but normal red blood cells (RBC) and platelets (PLT). Lymphadenopathy or organomegaly was not found. In June 2006, a peripheral blood immunophenotypic examination confirmed the diagnosis of B-cell lymphoma (B-CLL).

In September 2007, symptomatic progression of CLL was observed. The patient was qualified for treatment according to the FC (fludarabine, cyclophosphamide) regimen. By January 2008, a total of 4 treatment courses were given, resulting in complete remission (CR). In November 2016, progressive lymphocytosis and worsening of anemia were found. The ultrasonography examination revealed bilaterally enlarged axillary lymph nodes up to 23.5 mm and around the hepatic hilum up to 19.5 mm; no organomegaly was diagnosed. The cytogenetic examination using the fluorescence *in situ* hybridization (FISH) technique showed the presence of 17p13 deletion and the deletion 13q14 in 42% and 86% of the nuclei, respectively. The patient was qualified for second-line treatment according to the BR (bendamustine, rituximab) regimen. Until April 2017, the patient received a total of 6 cycles, achieving partial remission (PR).

In November 2017, the patient was diagnosed with autoimmune hemolytic anemia (AIHA). After administering prednisone at a dose of 60 mg/day (1 mg/kg body weight), the hemolysis has withdrawn, and the patient remained in observation.

In December 2018, another symptomatic CLL progression as a doubling of lymphocytosis within two months (WBC 91.81 G/L), anemia [hemoglobin (Hb) 11.6 g/dL], and thrombocytopenia (PLT 90 G/L) was observed. Ultrasonography studies showed hepatomegaly and splenomegaly, 155 mm and 135 mm, respectively. The patient was treated with ibrutinib and achieved PR as the best response. The treatment was firmly well tolerated. The patient experienced infectious complications grade 3, including bronchitis, urinary tract infections, and soft tissue inflammation. Immunoglobulin supplementation was given.

After eleven months of ibrutinib therapy dark brown, up to 1.5 cm in diameter nodules appeared on the skin of the whole body, especially on the lower limbs. Histopathological examination of the skin revealed abundant infiltrates in the subcutaneous adipose tissue, composed mainly of T lymphocytes (CD3+, CD8–/+, CD4+/–, granzyme B+, TIA+, CD5+/–, Ki-67 in about 5–20% of cell nuclei), with numerous macrophages (CD163+, CD68–, PGM1+), and few small CLL cells — atypical lymphocytic lobular panniculitis was diagnosed. The T-cell receptor (TCR) gene rearrangement clonality was confirmed. Trephine biopsy showed no T-cell lymphoma infiltration, and the B-CLL clone accounted for 3% of all bone marrow cells. Ibrutinib therapy was temporarily withdrawn and prednisone was started at a dose of 0.5 mg/kg body weight with initial clinical improvement. Restarting ibrutinib resulted in the worsening of the skin lesions.

In August 2020, for the first time, the patient was suspected of a tumor located in the paranasal sinus due to local edema and difficulties with nasal breathing; however, the diagnosis of these lesions was temporarily postponed due to logistical difficulties caused by the coronavirus disease 2019 (COVID-19) pandemic and freshly diagnosed pulmonary embolism. A massive infiltrative lesion in the nasal region was found. Computed tomography (CT) showed tissue changes in the nasopharynx and obstruction of the ethmoid cells on the left side, the left maxillary sinus, and the left nasal passage. In December 2020, a surgical biopsy of the tumor was performed. Histopathological examination revealed a nasal NK/T-cell lymphoma infiltration [extranodal NK/T-cell lymphoma, nasal type (ENKTCL)] (Figure 1).

In December 2020, an 83-year-old patient was referred to the Department of Hematology of the Institute of Hematology and Transfusion Medicine in Warsaw. On admission, the patient denied general symptoms. The physical examination revealed a massive infiltrative lesion in the nasal region. The morphology showed WBC 7.33 G/L (manual smear 21% lymphoma cells/prolymphocytes), Hb 9.5 g/dL, and PLT 42 G/L. Elevated lactate dehydrogenase (LDH) activity (1,166 U/L) and a slightly elevated beta$_2$-microglobulin concentration of 6.43 mg/L were found. Bone marrow histopathology showed 70% infiltration of B-CLL/small lymphocytic *lymphoma* (SLL) cells; T-cell lymphoma infiltration was not observed. At the time of ENKTCL diagnosis, the patient had a low number of Epstein-Bárr DNA copies detectable (329 copies/mL). CT confirmed previous infiltration in the nasopharynx. As the patient did not consent to radiotherapy of the tumor in the nasopharynx, she was qualified for mini-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) immunochemotherapy. The rationale for reducing chemotherapy doses was the advanced patient's age, numerous comorbidities (hypertension, dyslipidemia, hypothyroidism), and difficult cooperation with the patient. The patient received two mini-CHOP cycles achieving disease stabilization. Before 3rd cycle, the patient died due to a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

DISCUSSION

In the presented case, two significant but very rare complications of BTKi therapy were observed — skin nodules and secondary malignancy. Skin lesions are one of the most common non-hematological side effects of ibrutinib, occurring in 2–27% of patients. Most often there are petechiae, erythema, or ecchymoses. Advanced changes were observed in patients with a history of hypersensitivity to drugs, e.g., penicillin, cephalosporins, allopurinol, and tricyclic antidepressants. The time of appearance of skin lesions varies, from a few days to several months of treatment with BTKi. Skin lesions in this circumstance should be treated with systemic steroid therapy and antihistamines.

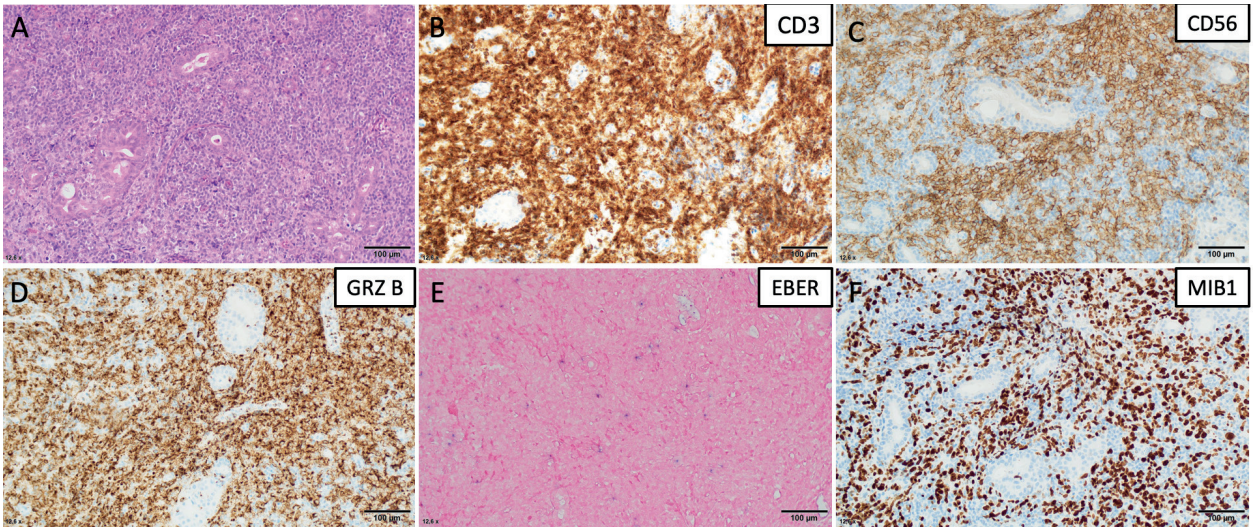

Figure 1. Extranodal NK/T-cell lymphoma, nasal type (ENKTCL) in hematoxylin–eosin section (**A**). ENKTCL cells were positive for CD3 (**B**), CD56 (**C**), granzyme B (**D**), and Epstein-Bárr virus (EBV)-encoded small RNAs (**E**). The MIB-1 (Ki-67) positivity was noted in approximately 70% of tumor cells (**F**)

Following such treatment, recurrence of these lesions after resuming BTKi is rarely observed. However, it should be remembered that the recurrence of such lesions can be rapid. Therefore, an additional maintenance treatment for several weeks with low doses of corticosteroids is recommended in such a clinical scenario. Once skin lesions resolve, return to BTKi therapy at a reduced dose is recommended [14–17]. In the patient described above, the temporal withdrawal of ibrutinib treatment and steroid therapy, unfortunately, did not result in any significant long-term improvement effect. The histopathological examination revealed clonal infiltrates of T lymphocytes of the skin. recognized as atypical lymphocytic cellulitis [14, 15].

Apart from autoimmune cytopenias and immune disorders, leading to frequent and severe infections, the third common complication of CLL is secondary neoplasms. The risk of developing solid lesions (e.g., melanoma, skin squamous cell carcinoma, breast cancer, prostate cancer) and hematological malignancies such as DLBCL, HL, and even acute leukemias and myelodysplastic syndromes is significantly higher in patients with CLL than in the general population [11]. Aggressive lymphomas such as DLBCL, may result from clonal transformation (RT) or may appear *de novo*. Transformation to aggressive lymphoma may result in a rapid deterioration of the patient's general condition, the appearance of general symptoms, or progressive, often asymmetric lymphadenopathy. *De novo* aggressive lymphomas are denoted as non-clonal and characterized by better treatment and survival outcomes as clonally related DLBCL true RT [5, 18].

Patients with CLL and T-cell lymphoma coexistence are the rarest, even casuistic cases. So far, only 27 such cases have been described, and ENKTCL has been reported in only two other patients [19, 20].

The first case concerned a man diagnosed with CLL with 17p deletion which appeared four years after diagnosis. For the next four years, the patient was treated according to various schemes, based primarily on fludarabine and cyclophosphamide, which allowed him to achieve PR. After nine years after the first symptoms of CLL, the diagnosis of ENKTCL CD56+ was made. No T-cell lymphoma cells were found in the bone marrow. The patient received one course of treatment according to the SMILE protocol (methotrexate, dexamethasone, ifosfamide, mesna, etoposide, peg-asparaginase), but died shortly after due to infectious and thrombotic complications [19].

The second case, published in 2020 described a male patient with concurrent diagnosis of CLL/SLL and ENKTCL [20]. The extranodal T-cell lymphoma was treated with radiotherapy at a total dose of 54 Gy. CR was achieved. One year after irradiation, ENKTCL recurred in the oropharynx. Radiotherapy was reintroduced and supplemented successfully with cis-platinum consolidation chemotherapy. During this time, no progression of CLL/SLL was observed. Six years later, a 77-year-old patient was diagnosed with another lymphoproliferative neoplasm — lymphoid granulomatosis (LyG). The clonality of LyG cells in relation to CLL/SLL was confirmed, and the presence of T-cell lymphoma cells was excluded. Due to the appearance of LyG, CLL progression, and deterioration of the patient's general condition, ibrutinib was started as monotherapy. At the time of publication of the article, the patient was in CR eight years after the diagnosis of CLL/SLL and recurrent ENKTCL and two years after the diagnosis of LyG [20]. The present case is the third presented patient with the coexistence of CLL and ENKTCL and the first in which T-cell lymphoma developed after ibrutinib treatment.

ENKTCL is rare in Europe and North America. The endemic areas of this disease are eastern Asia and South America. It is more common in men, with a median age at diagnosis of 53 years. Classically, it occupies the nasopharynx area, leading to obstruction of the upper

respiratory tract, nosebleeds, or perforation of the palate. Its correlation with the Epstein-Bárr virus (EBV) is well proven. Confirming the presence of viral DNA in the patient's body is crucial for making a proper diagnosis and is widely recommended [21]. The pathogenesis of the coexistence of ENKTCL with CLL is not fully understood. The most likely cause is immunosuppression present in CLL patients. The weakening of the immune mechanisms related to the underlying disease and treatment leads to an imbalance between the immune system and the EBV, whose genetic material can be detected in at least 95% of the adult population. This may result in the development of lymphoproliferative diseases based on infection with this herpes virus [19].

The appearance of a second proliferative disease in a patient with CLL significantly worsens the prognosis. Treatment of these patients should be selected individually and depend on the type of secondary neoplasm, its pathogenetic features, clonality concerning CLL, and the general condition of the patient [17]. In the case of ENKTCL, chemotherapy regimens based on asparaginase or its pegylated form, combined with radiotherapy of the affected area, should be the standard of care. However, protocols with anthracyclines, e.g., CHOP, are not recommended due to the overexpression of P-glycoprotein (also known as multidrug resistance protein 1) in neoplastic NK-cells and the associated low effectiveness of cytotoxic compounds [22]. Due to the palliative nature of the procedure in the presented patient, at an advanced age, burdened with numerous comorbidities, it was decided to start treatment with mini-CHOP.

SUMMARY

The presented patient is a rare example of B- and T-cell lymphoma coexistence. ENKTCL developed during treatment with BTKi. Increased oncological vigilance should be maintained in patients with CLL, as secondary malignancies are a statistically frequent complication. In such patients, optimal, aggressive treatment may not be introduced, and due to the persistence of comorbidities and advanced age, it is usually associated with a poor prognosis.

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