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Case Report

Long-term effect of venetoclax therapy in a patient with the transformation of chronic lymphocytic leukemia into Richter's syndrome

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Abstract

Richter's syndrome (RS) is the next step in the progression of chronic lymphocytic leukemia (CLL) progression. It leads to reduced overall patient survival, the necessity of aggressive chemotherapy and a decline in the quality of life. The first line of RS treatment includes traditional chemotherapy such as rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone. However, during the past decade, novel targeted agents added to the therapy dramatically changed the treatment outcome for patients with RS. In our case, we describe a patient with CLL that had progressed to RS and achieved complete remission that lasted > 15 months with venetoclax monotherapy.

INTRODUCTION

Richter's syndrome (RS) is described as the transformation of chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia into a more aggressive form of lymphoma [1], most commonly, it is a diffuse large B-cell lymphoma (DLBCL). The frequency of RS among CLL patients is ∼2–10% [2]. Clinically, RS is characterized by the onset of B symptoms, rapid growth of lymphadenopathy, elevation of lactate dehydrogenase and multi-organ dysfunction from invasive or obstructive processes [1], [3]. Because of RS's dismal prognosis, aggressive nature and treatment difficulty, every patient with RS requires an individual approach. Here we describe a patient with RS who was successfully treated with venetoclax monotherapy and achieved complete remission (CR) lasting more than a year.

CASE REPORT

A male patient, 73 years old, was admitted to the hospital because of high white blood cell (WBC) levels. There was no pain, night sweats or weight loss. Physical examination did not show enlarged lymph nodes. Complete peripheral blood count revealed a white cell count of 11×10^9/L with lymphocyte count of 6×10^9/L, normal platelet (PLT) count of 220×10^9/L and hemoglobin (Hb) level of 140 g/L. Chest and abdominal computed tomography (CT) scans showed no enlargement of the liver, spleen or lymph nodes. Based on immunophenotyping of peripheral blood lymphocytes (CD19+/CD5+/CD23+/Ig lambda+), the patient was diagnosed with CLL (stage 0 according to Rai classification). Results of fluorescence *in situ* hybridization (FISH) for del (17p), del (13q) and del (11q) were negative. There was no indication for treatment, and the patient was under observation. In May 2018, he was admitted to the hospital for the second time. The full blood count showed a Hb level of 120 g/L, a WBC count of 60.1×10^9/L, a lymphocyte count of 56.4×10^9/L and a PLT count of 189×10^9/L. Physical examination revealed peripheral lymphadenopathy, and an abdominal CT scan showed an increased size of the lymph nodes in the abdominal cavity without signs of organomegaly. Treatment was started (4 cycles of rituximab and bendamustine), resulting in CR. In June 2020, the patient was admitted to the hospital because of the fast enlargement of lymph nodes in the neck, supraclavicular, axillary and inguinal areas. A CT scan revealed a larger liver and spleen and numerous larger lymph nodes in the abdominal cavity and retroperitoneum. A core biopsy of a neck lymph node was performed. The diagnosis of CLL was obtained based on the histopathological examination of the lymph node. After treatment (4 cycles of rituximab and bendamustine), the patient achieved partial remission. The patient had deep secondary immunodeficiency, leading to an increased incidence of upper respiratory tract infections. Therefore, the frequency of chemotherapy cycles was disrupted, and the intervals between cycles were increased. In December 2020, he was presented to the emergency department with shortness of breath and fever. The patient tested positive for coronavirus disease (COVID)-19 using reverse transcription-polymerase chain reaction analysis of material from nasopharyngeal and throat swabs. A chest CT scan was performed. According to the World Health Organization case definition, the patient was classified as having moderate COVID-19 disease and was hospitalized. After 10 days, the fever and shortness of breath completely resolved. One month after discharge, the patient presented for a follow-up appointment.

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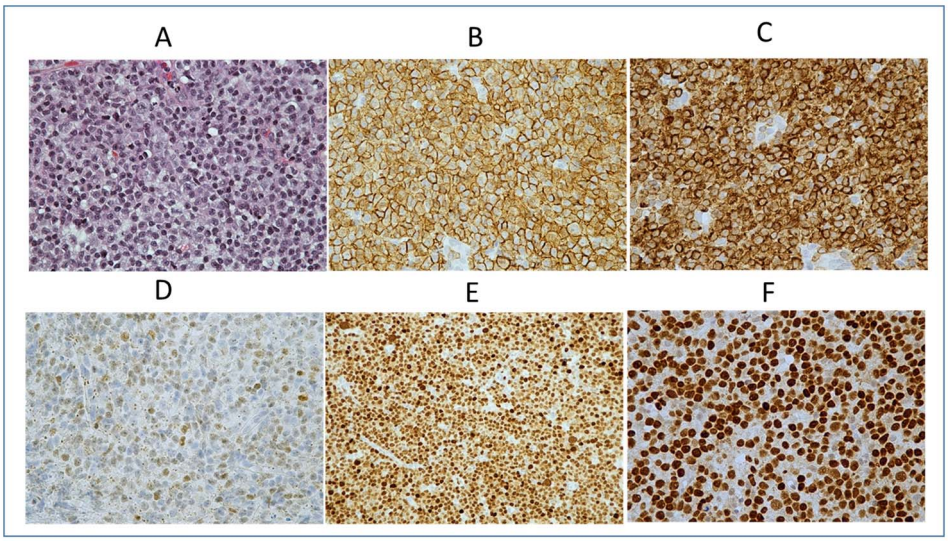

Figure 1. Transformation of CLL in DLBCL (Richter syndrome) in the lymph node (**A**—hematoxylin–eosin staining, ×40, the cells have large, irregularly shaped nuclei with fine nuclear chromatin and prominent nuclei) and immunohistochemical reaction positive for CD 20 (**B**), Bcl2 (**C**), Bcl6 (**D**), MUM1 (**E**), PAX5 (**F**)—objective imagine ×40).

A physical exam indicated that the patient had fast-growing lymph nodes (maximal size 5 × 6 cm). In January 2021, a core biopsy of an axillary lymph node was performed. The biopsy revealed large lymphoid cells with the morphology of centroblasts and immunoblasts (CD20+/BCL-2+/BCL-6+/MUM+/PAX5+) (Fig. 1). The results of the immunohistochemical examination led to the diagnosis of the progression of CLL into DLBCL-RS. The results of FISH for del (17p) were negative. Based on the patient's age, comorbid disorders, intolerance to the chemotherapy, deep immunodeficiency and post-COVID-19 asthenic syndrome, we decided to start monotherapy with venetoclax. The drug was administered according to a weekly ramp-up schedule over 5 weeks to the recommended daily dose of 400 mg. There were no adverse effects during or after the initiation of the treatment. After the first 5 weeks of the treatment, all groups of peripheral lymph nodes decreased in size by > 50%, and after 8 weeks, all lymph nodes were of normal size. In the blood, WBCs, PLT and Hb were all normal. After 16 weeks of treatment, a CT scan of the chest, abdomen and pelvis revealed no enlarged lymph nodes or internal organs. During the next 12 months, the patient continued the treatment with 400 mg venetoclax per day. His condition is good as of 02 April 2022, he remains in CR as determined by a CT scan.

DISCUSSION

RS is a complication affecting up to 3–20% of patients with CLL and has a poor prognosis with a median survival of only 1–2 years [4]. For most cases, anthracycline-based chemotherapy remains the first line of choice for RS treatment, which results in CR in only 5–15% of patients. Higher intensity chemotherapy does not improve outcomes. The treatment of CLL and RS dramatically changed with the emergence of several novel targeted agents, such as ibrutinib, acalabrutinib, idelalisib, duvelisib and venetoclax [1, 2, 3, 5–8]. In our case, the disease progression associated with transformation into DLCDL determined the necessity of decision regarding further treatment. Combined targeted therapy was deemed to be the best choice for our patient. However, considering the possibility of severe side effects of the combined agents, we decided to proceed with venetoclax monotherapy [9], [10].

Several studies have shown that venetoclax, in combination with other targeted inhibitors, is recommended to treat RS. Venetoclax is safe and highly effective, and the most common serious side effect is neutropenia [11]. Partial remission was achieved after 1 month of treatment with venetoclax. CT scans at 4 and 16 months after the start of the therapy indicated CR (with the size of all lymph nodes > 10 mm). We did not notice any side effects during the treatment. Thus, monotherapy of RS with venetoclax demonstrated high efficiency and safety in our case.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest declared.

ETHICAL APPROVAL

This work was approved by the ethical committee of the Main Military Clinical Hospital named after N.N. Burdenko.

CONSENT

All consent forms were signed by the patient.

GUARANTOR

Victoria Tutaeva MD, PhD.

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