CASE REPORT

UDC: 616.155.392-06::616-006.44
DOI: https://doi.org/10.2298/VSP210118073M

Successful treatment of synchronous hairy cell leukemia and diffuse large B-cell lymphoma in a patient with severe hypercalcemia and extensive osteolytic lesions

Uspešno lečenje bolesnika istovremeno obolelog od leukemije vlasastih ćelija i difuznog B krupnoćelijskog limfoma sa teškom hiperkalcemijom i ekstenzivnim osteolitičkim lezijama

Olivera Marković*†, Mirjana Gotić†‡, Vesna Čemerikić§, Anica Divac*, Dragomir Marisavljević*

***University Hospital Medical Center "Bežanijska Kosa", Belgrade, Serbia; †University of Belgrade, Faculty of Medicine, Belgrade, Serbia; ‡University Clinical Center of Serbia, Clinic for Hematology, Belgrade, Serbia; §Beolab, Belgrade, Serbia;**

Abstract

Introduction. Although secondary malignancies usually occur at different times after hairy cell leukemia (HCL) treatment, the occurrence of HCL and other malignancies at the same time is very rare. Synchronous HCL and diffuse large B-cell lymphoma (DLBCL) have not been described so far. **Case report.** The report presents a 62-year-old female patient with intense constitutional symptoms, hypercalcemia, pancytopenia, and osteolytic destruction of the left shoulder joint. Immunohistochemical analysis of the bone marrow revealed the presence of two cell populations: a population of HCL cells and a population of DLBCL cells with the expression of CMYC and BCL-2 proteins ("double expressor" DLBCL) and high proliferative activity (Ki-67+cells > 90%). Fluorescence *in situ* hybridization (FISH) analysis showed amplification of the *BCL-2* gene. In addition, *BRAF* gene V600E mutation was detected. After intensive treatment with immunochemotherapy, radiotherapy, and bisphosphonates, the patient achieved complete remission, lasting for more than two years. **Conclusion.** As the association of HCL and lymphoma is very rare, diagnosis of synchronous occurrence of two lymphoproliferative diseases is a diagnostic and therapeutic challenge. It remains unclear whether DLBC and HCL originated from two different malignant clones or DLBCL developed by the transformation of HCL as the result of clonal evolution of the B-cell clone.

Key words:
lymphoma, large b-cell, diffuse; drug therapy; gene expression; leukemia, hairy cell; hypercalcemia; immunotherapy; magnetic resonance imaging; mutation; tomography, emission-computed.

Apstrakt

Uvod. Iako se sekundarni maligniteti obično javljaju u različito vreme nakon lečenja leukemije vlasastih ćelija (LVĆ), istovremena pojava LVĆ i drugih maligniteta je veoma retka. Istovremeno pojavljivanje LVĆ i difuznog krupnoćelijskog B limfoma (DKBL) do sada nisu opisani. **Prikaz bolesnika.** U radu je prikazana bolesnica stara 62 godine koja je imala intenzivne konstitucijske simptome, hiperkalciemiju, pancitopeniju i osteolitičku destrukciju levog ramenog zgloba. Imunohistohemijska analiza koštane srži otkrila je prisustvo dve ćelijske populacije: populaciju LVĆ i populaciju DKBL ćelija sa ekspresijom CMYC i BCL-2 proteina („dvostruki ekspresor" DKBL) i visokom proliferativnom aktivnošću (Ki-67+ ćelije > 90%). *Fluorescence in situ hybridization* (FISH) analiza je pokazala amplifikaciju *BCL-2* gena. Pored toga, otkrivena je mutacija V600E kod *BRAF* gena. Nakon intenzivnog lečenja imunohemoterapijom, radioterapijom i bifosfonatima, bolesnica je postigla potpunu remisiju, koja je trajala više od dve godine. **Zaključak**. Kako je povezanost LVĆ i limfoma veoma retko, istovremena dijagnoza dve limfoproliferativne bolesti predstavlja dijagnostički i terapijski izazov. Ostaje nejasno da li su DKBL i LVĆ vodile poreklo od dva različita maligna klona ili se DKBL razvio transformacijom LVĆ kao rezultat klonalne evolucije B-ćelijskog klona.

Ključne reči:
limfomi, b-krupnoćelijski, difuzni; lečenje lekovima; geni, ekspresija; leukemija vlasastih ćelija; hiperkalciemija; imunoterapija; magnetska rezonanca, snimanje; mutacija; tomografija, kompjuterizovana, emisiona.

Correspondence to: Olivera Marković, University Hospital Medical Center "Bežanijska Kosa", Dr Žorža Matea bb, 11 000 Belgrade, Serbia. E-mail: markovic.olivera@bkosa.edu.rs

Introduction

Hairy cell leukemia (HCL) is an uncommon type of hematological malignancy which constitutes 2% of all leukemias. The prognosis of HCL has considerably improved thanks to new effective chemotherapeutic agents. However, literature data showed that HCL patients have a higher risk of developing second malignancies than the general population. In some studies, second malignancies were the primary cause of death in patients with HCL [1]. Although secondary malignancies usually occur at different times after HCL treatment, the occurrence of HCL and other malignancies at the same time is very rare. Simultaneous occurrence of HCL and several other lymphoproliferative diseases (follicular lymphoma [2], T cell lymphoma [3], B-cell chronic lymphocytic leukemia [4], multiple myeloma [5]) has already been reported. However, no one has described simultaneous HCL and diffuse large B-cell lymphoma (DLBCL) so far.

Case report

A 62-year-old female patient was admitted to our hospital in August 2018 with fatigue, fever, weight loss (15 kg/two months), and left shoulder pain. Physical examination showed poor general condition [Eastern Cooperative Oncology Group (ECOG) 3], fever (38 °C), pallor of the skin, and weakness of the left hand. Skeletal radiography showed osteolytic lesions in the glenoid region of the scapula, whilst chest X-ray showed consolidation in the area of the left lower lobe of the lung. Computed tomography of the thorax showed non-homogeneous consolidation in the S3 zone of the left lung with a negative bronchogram and hilar lymphadenopathy. Blood counts showed pancytopenia [hemoglobin 74g/L (normal range 115–160 g/L); platelets 84×10^9/L (normal range 150–450 $\times 10^9$/L); white blood cells 3.8×10^9/L (normal range 4.0–10.0 10^9/L), with 48% neutrophils (normal range 44–72%); 44% lymphocytes (normal range 20–46%); 6% monocytes (normal range 2–12%); 2% eosinophils (normal value < 7%) and 3 erythroblasts/100 leukocytes] in differential count. Biochemistry analysis showed hypercalcemia (3.3 mmol/L, normal value < 2.35 mmol/L), elevated potassium (5.42 mmol/L, normal value < 4.4 mmol/L), C- reactive protein (147.2 mg/L, normal value < 1.5 mg/L), lactate dehydrogenase (4,008 U/L, normal value < 343 U/L) and β_2-microglobulin (4.48 mg/L, normal range 0.8–2.2 mg/L). The erythrocyte sedimentation rate was significantly accelerated (140 mm/hr, first hour). Needle biopsy of lung and shoulder was unsuccessful several times. However, morphological and immunohistochemical analysis of the bone marrow revealed the presence of two cell populations: a population of HCL cells ($CD103^+$, $TRAP^+$, $annexin^+$) and a population of DLBCL cells with the expression of CMYC and BCL-2 proteins ("double expressor" DLBCL), expression of MUM1 and BCL-6 antigens, and high proliferative activity ($Ki\text{-}67^+$cells > 90%) (Figure 1). Flow cytometry immunophenotyping of bone marrow cells revealed a clonal population of atypical mature B-cells (16% of cells) with immunoglobulin-kappa light chain expression in combination with heavy immunoglobulin D or immunoglobulin M chains and high expression of CD19, CD103, CD11c, CD305, and FMC7 antigen. The same population was detected by flow cytometry in the peripheral blood (6% of cells). Fluorescence *in situ* hybridization (FISH) analysis showed amplification of the *BCL-2* gene, whereas *CMYC* gene amplification was not detected. In addition, *BRAF* gene V600E mutation was detected. Nuclear magnetic resonance of the left shoulder showed complete destruction of the left shoulder joint, with an osteolytic lesion of the left scapula in the glenoid and coracoid region and focal infiltration of surrounding soft tissue (Figure 2). Positron emission

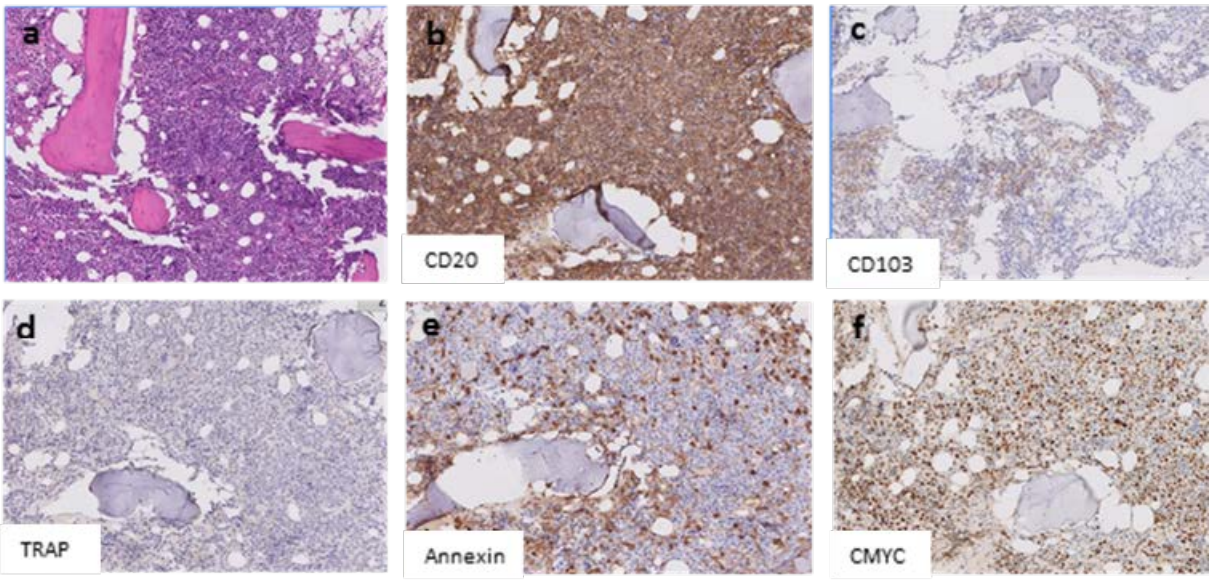

Fig. 1 − Presence of two populations of cells in bone marrow: a population of hairy cell leukemia cells and a population of diffuse large B-cell lymphoma cells (a − hematoxylin eosin, ×40). Immunohistochemical stains of formalin-fixed, paraffin-embedded sections for: b) CD20 (x40), c) CD103 (x40), d) TRAP (x40), e) annexin (x40), f) CMYC (×40).

tomography-computed tomography (PET-CT) scan showed hypermetabolic lesions on left axillary and retroperitoneal lymphadenopathy and multiple bone lesions (highest metabolic activity of SUV 25.52 noted in left scapula). We concluded that the patient has synchronous HCL and "double expressor" DLBCL in IVB clinical stage with a high international prognostic index (IPI) and high national comprehensive cancer network (NCCN)-IPI score. Treatment consisted of immunochemotherapy and bisphosphonates (zoledronic acid). Although lymphoid cells were not detected in cerebrospinal fluid using flow cytometry, because of the high central nervous system (CNS)-IPI score, CNS prophylaxis with intrathecal methotrexate injections was applied. After eight cycles of rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride (doxorubicin hydrochloride), vincristine (Oncovin), and prednisone (R-CHOP) chemotherapy, local irradiation of residual area with PET positivity (left shoulder soft tissue) was applied. Therapy resulted in complete hematological remission, lasting almost two years after completion of the treatment (last follow-up, December 2020).

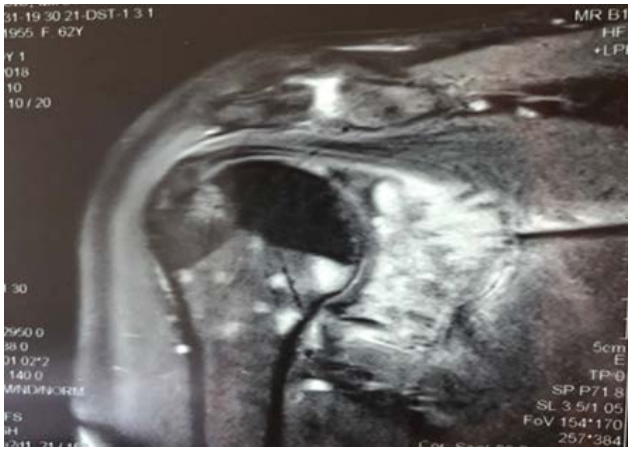

Fig. 2 – Nuclear magnetic resonance (NMR) of the left shoulder showing complete destruction of the left shoulder joint, with an osteolytic lesion of the left scapula.

Discussion

The presented patient is the first reported case of synchronous occurrence of HCL and DLBCL. The patient also had a very uncommon clinical presentation since the association of osteolytic lesions and hypercalcemia are extremely rare initial symptoms of lymphoma (approximately 2%) [6]. Hypercalcemia in malignancies can be mediated by several different mechanisms. Parathyroid hormone (PTH)-like substances [PTH-related protein (PTHrP)] secreted by malignant cells, secreting other cytokines that activate osteoclasts, the ectopic activity of 1-alpha-hydroxylase and the production of 1,25-dihydroxycholecalciferol as well as the excessive production of PTH are some of the well-characterized mechanisms of hypercalcemia [7]. Hypercalcemia caused by malignancy is most often related to PTHrP [8] but, in some cases, is associated with extensive bone metastases, which was the case in our patient. It was previously considered that hypercalcemia is a result of the direct destruction of bone by metastases. However, it was found that hypercalcemia was a consequence of the local release of cytokines from the tumor cells, which activate osteoclasts and stimulate bone resorption, usually through receptor activator of NF-kB/ ligand (RANK/RANKL) [9]. Patients with malignancy hypercalcemia have limited survival of several months, thus it is considered a marker of poor prognosis [7]. It is unclear whether this poor prognosis is related to the advanced stage of malignancy-associated hypercalcemia or is it just a simple marker of underlying cancer. Our patient had numerous osteolytic lesions and advanced disease, however, a complete therapeutic response was achieved owing to optimal therapy.

Nevertheless, it remains unclear whether DLBC and HCL emerged from two different malignant clones or DLBCL developed by the transformation of HCL as the result of clonal evolution of the B-cell clone. Based on phenotype and molecular features of HCL cells, malignant transformation occurs at the level of germinal or post-germinal center cells [10]. That is confirmed by the presence of somatic mutations of variable regions of the immunoglobulin genes, which are the hallmark of a germinal center origin [11]. Lymphoma cells of DLBCL in our patient originated from transformed germinal center B-cells (i.e., GBC type). That altogether supports a thesis of the common origin of synchronous HCL and DLBCL in this case. On the other hand, the hypothesis on the existence of two different malignant clones can be supported by common findings of amplification of the *BCL-2* gene in DLBCL patients and V600E mutation of the *BRAF* gene, a genetic alteration invariably associated with hairy cell leukemia [12].

As the association of HCL and lymphoma is very rare, diagnosis of synchronous occurrence of two lymphoproliferative diseases is a diagnostic and therapeutic challenge. Establishing an adequate diagnosis in cases of double malignancies is particularly important because it allows the implementation of an optimal therapeutic approach which is usually directed to more aggressive diseases. Such an approach resulted in the complete remission of disease in our patient. It is important to emphasize that our patient achieved complete clinical remission after immuno-chemotherapy treatment (i.e., rituximab-CHOP protocol), which can be explained by the responsiveness of malignant B-cell clone of HCL to monoclonal anti-CD20 antibody [13].

Conclusion

As the association of HCL and lymphoma is very rare, diagnosis of synchronous occurrence of two lymphoproliferative diseases is a diagnostic and therapeutic challenge. It remains unclear whether DLBC and HCL originated from two different malignant clones or DLBCL developed by the transformation of HCL as the result of clonal evolution of the B-cell clone.

Conflict of interest

The authors declare no conflict of interest.

R E F E R E N C E S

1. *Hisada M, Chen BE, Jaffe ES, Travis LB*. Second cancer incidence and cause-specific mortality among 3104 patients with hairy cell leukemia: a population-based study. J Natl Cancer Inst 2007; 99(3): 215–22.
2. *McDonald L, Fadalla K*. Synchronous follicular non-Hodgkin's lymphoma and hairy cell leukaemia: a case report. Ann Hematol 2019, 98(6): 1517–8.
3. *Gasljevic G, Kloboves-Prevodnik V, Gazic B, Vovk M*. Coexistent hairy cell leukaemia and hepatosplenic T-cell lymphoma: a case report. Diagn Pathol 2014; 9: 58.
4. *Rastogi P, Jeyaraman P, Sachdeva MU, Malhotra P, Ahluwalia J*. Synchronous hairy cell leukemia and chronic lymphocytic leukemia: a case report with a brief review of literature. Blood Res 2018; 53(2): 160–3.
5. *Zhao X, Maric I*. Chance identification of synchronous hairy cell leukemia and plasma cell myeloma in a potential HSC donor. Blood 2014; 123(24): 3694.
6. *Matsuhashi Y, Tasaka T, Uehara E, Fujimoto M, Fujita M, Tamura T,* et al. Diffuse large B-cell lymphoma presenting with hypercalcemia and multiple osteolysis. Leuk Lymphoma 2004; 45(2): 397–400.
7. *Goldner W*. Cancer-Related Hypercalcemia. J Oncol Practice 2016; 12(5): 426–32.
8. *Stewart AF*. Clinical practice. Hypercalcemia associated with cancer. N Engl J Med 2005; 352(4): 373–9.
9. *Sternlicht H, Glezerman IG*. Hypercalcemia of malignancy and new treatment options. Ther Clin Risk Manag 2015; 11: 1779–88
10. *Burthem J, Zuzel M, Cawley JC*. What is the nature of the hairy cell and why should we be interested? Br J Haematol 1997; 97(3): 511–4.
11. *Küppers R, Klein U, Hansmann ML, Rajewsky K*. Cellular origin of human B-cell lymphomas. N Engl J Med 1999; 341(20): 1520–9.
12. *Tiacci E, Trifonov V, Schiavoni G, Holmes A, Kern W, Martelli MP*, et al. BRAF mutations in hairy-cell leukemia. N Engl J Med 2011; 364(24): 2305–15.
13. *Ravandi F*. Chemo-immunotherapy for hairy cell leukemia. Leuk Lymphoma 2011; 52 Suppl 2: 72–4.

Received on January 18, 2021
Revised on May 26, 2021
Accepted on July 13, 2021
Online First July 2021