CASE REPORT
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Hodgkin transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma

Hočkinova varijanta transformacije hronične limfocitne leukemije/limfoma malih limfocita

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Abstract

Introduction. In rare cases, chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma may transform into Hodgkin lymphoma, with about a hundred cases reported in the literature so far. We present a case of the Hodgkin variant of Richter transformation. **Case report.** After a one-year watch and wait period, a 60-year-old male with CLL developed B symptoms, generalized lymphadenopathy, and splenomegaly. Upon initial staging (Binet B/Rai 3), he was started on fludarabine, cyclophosphamide, and rituximab (FCR) regimen. After the third cycle of treatment, the right-sided axillary lymphadenopathy persisted and became painful, while the dimensions of the remaining organs affected by the disease decreased. Upon the finalization of the final sixth FCR cycle, the painful right-sided axillary lymphadenopathy persisted (though partially decreasing in size), with the development of local redness and swelling. A biopsy of the residual axillary node was performed, which revealed disease transformation into Hodgkin lymphoma. Upon multislice computed tomography-based staging (IV E clinical stage) and prognostic assessment (unfavorable prognosis), it was decided that the treatment be continued with doxorubicin, vinblastine, dacarbazine (AVD) regimen. The presented patient died two months after the diagnosis of Hodgkin transformation (HT) was established during the initial cycle of AVD. **Conclusion.** Although CLL is an indolent malignancy, in rare cases of HT, the prognosis is largely dismal. The available treatment strategies demonstrate suboptimal results, although novel immunotherapies may change the landscape of HT therapy in the near future.

Key words:
antineoplastic combined chemotherapy protocols; immunohistochemistry; histological techniques; hodgkin disease; leukemia, lymphocytic, chronic, b-cell; multidetector computed tomography; treatment outcome.

Apstrakt

Uvod. Hronična limfocitna leukemija (HLL)/limfom malih limfocita se u retkim slučajevima može transformisati u Hočkinov limfom, a u literaturi je do sada opisano oko sto ovakvih slučajeva. Prikazujemo bolesnika sa Hočkinovom varijantom Rihterove transformacije. **Prikaz bolesnika.** Godinu dana nakon početka kontrolnog praćenja, kod 60-godišnjeg muškarca sa HLL došlo je do razvoja B simptoma, generalizovane limfadenopatije i splenomegalije. Posle početnog određivanja stadijuma bolesti (Binet B/Rai 3), započeto je lečenje prema protokolu fludarabin, ciklofosfamid, rituksimab (FCR). Nakon trećeg ciklusa lečenja i dalje se održavala i postajala bolna, desnostrana pazušna limfadenopatija, dok su se dimenzije preostalih, bolešću zahvaćenih organa, smanjile. Po okončanju poslednjeg, šestog ciklusa FCR terapije, bolna desnostrana pazušna limfadenopatija se održavala (iako se delimično smanjila u veličini), sa razvojem lokalnog crvenila i otoka. Biopsijom zaostalog pazušnog nodusa dokazana je transformacija bolesti u Hočkinov limfom. Nakon određivanja stadijuma bolesti na osnovu nalaza multislajsne kompjuterizovane tomografije (IV E klinički stadijum) i procene prognoze (nepovoljna prognoza), odlučeno je da se lečenje nastavi prema protokolu doksorubicin, vinblastin, dakarbazin (AVD). Bolesnik je preminuo dva meseca nakon potvrde dijagnoze Hočkinove transformacije (HT), u toku sprovođenja prvog AVD. **Zaključak.** Mada je HLL sporo progresivna maligna bolest, u retkim slučajevima sa HT prognoza je nepovoljna. Dostupne terapijske mogućnosti daju suboptimalne rezultate, mada bi u skorijoj budućnosti inovativne imunološke terapije mogle izmeniti tok lečenja bolesnika sa HT.

Ključne reči:
lečenje kombinovanjem antineoplastika, protokoli; imunohistohemija; histološke tehnike; hočkinova bolest; leukemija, b ćelije, hronična; tomografija, kompjuterizovana, multidetektorska; lečenje, ishod.

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Introduction

Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) is an indolent B-cell malignancy and the most common malignant disease in hematology [1].

CLL/SLL complications significantly contribute to both the morbidity and mortality of the affected patients. While infectious complications occur in 80% of CLL/SLL patients, other complications [secondary malignancies, autoimmune cytopenias, and Richter transformation (RT)] are less common [2–5]. An uncommon CLL/SLL complication, which is a result of disease transformation into more aggressive lymphomas or leukemias, is known as RT [5, 6].

We present a case of the Hodgkin transformation of CLL/SLL in a 60-year-old male patient.

Case report

In February 2022, a complete blood count performed on a 59-year-old male prior to eye surgery revealed isolated lymphocytosis. Upon further investigation, a diagnosis of CLL/SLL was established based on morphological and flow cytometric findings of peripheral blood (Matutes CLL score 4). The disease was initially staged as Binet A (Rai 0), requiring only regular follow-up.

The first symptoms developed in March 2023 with the onset of fatigue and night sweats, as well as generalized indolent lymphadenopathy (the largest of which were axillary nodes, ~ 5 cm in size) and splenomegaly (ultrasound bipolar diameter – 175 mm).

The patient was hospitalized and treated at the Hematology, Allergology, and Clinical Immunology Clinic, University Clinical Center Niš, Serbia, once each month between April and December 2023.

Being a fit patient with a symptomatic Binet B (Rai 3) stage CLL [lymphocytes (Ly) 7.7 × 10^9/L, reference range (RR): 1.0–4.0 × 10^9/L; white blood cells (WBC) 13.8 × 10^9/L, RR: 4.0–10.0 × 10^9/L], developing anemia [hemoglobin (Hgb) 104 g/L, RR: 110–170 g/L] (Table 1), with progressive lymphadenopathy, he was started on fludarabine, cyclophosphamide, rituximab (FCR) (six cycles) treatment in April 2023. After the third cycle of therapy, our patient experienced painful right-sided axillary lymphadenopathy (ultrasound: 31 × 9.5 mm, and a conglomerate 42 × 22 mm in size), while other peripheral lymph nodes slightly decreased in size, and the spleen became impalpable.

Upon the fourth cycle of therapy, he developed fever (39.4 °C) and night sweats, in addition to the persistent painful axillary lymphadenopathy (~ 5 cm), which was treated with antibiotics and supportive therapy and did not require surgery.

The sixth cycle of therapy was finalized in September 2023.

The right-sided axillary lymphadenopathy persisted, although partially decreasing in size, with the pain, redness, and swelling spreading to the right arm, causing its weakness. In October 2023, an excisional biopsy of the rest axillary lymph node was performed. Histological (hematoxylin and eosin) (Figure 1) and immunohistochemistry findings (Figure 2) supported the diagnosis of the Hodgkin transformation of CLL/SLL. A whole body computed tomography scan was performed in November 2023, revealing bilateral cervical, right-sided axillary (64 × 22 mm conglomerate), mediastinal, retroperitoneal, and pelvic lymphadenopathy, splenomegaly, focal changes in spleen and liver, as well as pleural, pericardial, and abdominal effusions (Figure 3). Drainage from the biopsy site persisted for 48 hrs, and since the fever developed, a swab was taken. Corynebacterium spp. were isolated, and antibiotic treatment (linezolid) followed.

On the day of the final admission (on December 12, 2023) to the Clinic, the patient brought the latest laboratory results (six days prior, from another laboratory) [Ly 0.31 × 10^9/L, RR: 1.19–3.35 × 10^9/L; WBC 3.83 × 10^9/L, RR: 4.0–10.7 × 10^9/L; Hgb 76 g/L, RR: 130–170 g/L; Platelets 172 × 10^9/L, RR: 150–400 × 10^9/L; C-reactive protein (CRP) 174.08 mg/L, RR: < 5.0 mg/L; erythrocyte sedimentation rate (ESR) 140 mm/1st hr, RR: < 20 mm/1st hr].

Being a fit, 60-year-old patient with an unfavorable advanced (IV E Ann Arbor clinical stage) Hodgkin transformation of CLL/SLL, it was decided that upon the resolution of the febrile syndrome treatment be continued with doxorubicin, vinblastine, dacarbazine (AVD) regimen.

Table 1

The dynamics of hematological and biohumoral parameters throughout treatment (April–December 2023)

Parameter	Type, month/day and cycle (C) of therapy								
	FCR 04/28 C1	FCR 05/28 C2	FCR 06/23 C3	FCR 07/24 C4	FCR 08/24 C5	FCR 09/22 C6	– 10/12 –	– 11/23 –	AVD 12/16 C1
White blood cells (×10^9/L)	13.8	12.7	8.9	10.6	18.4	4.0	5.1	7.7	3.1
Hemoglobin (g/L)	104	108	109	101	119	97	112	82	87
Platelets (×10^9/L)	269	181	259	198	279	202	229	112	27
Lymphocytes (×10^9/L)	7.7	3.4	–	1.4	3.3	0.7	1.3	1.2	1.1
Neutrophils (×10^9/L)	5.3	8.3	4.5	8.0	13.2	2.9	2.4	3.4	0.9
C-reactive protein (mg/L)	–	55.8	–	67.9	–	127.5	14.4	125.4	208.6
Albumin (g/L)	–	39	–	35	–	33	36	24	22
Lactate dehydrogenase (U/L)	–	471	–	574	–	506	503	513	445

FCR – fludarabine, cyclophosphamide, rituximab; AVD – doxorubicin, vinblastine, dacarbazine.
Note: The first line therapy of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) was performed in the period from April–September; Rest axillary lymph node biopsy was performed in October; Diagnosis of Hodgkin lymphoma (HL) transformation of CLL/SLL was made in November; HL therapy was initiated in December.

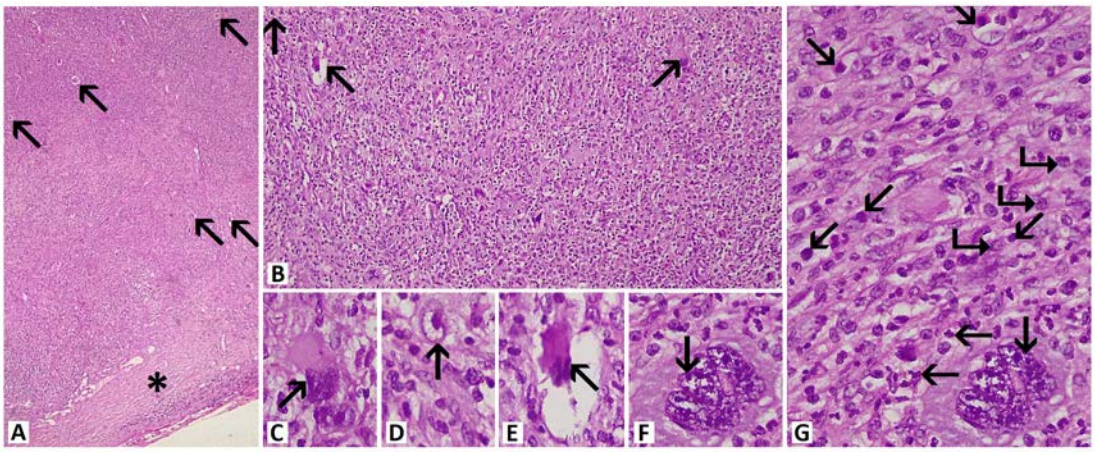

Fig. 1 – Morphological features which support the diagnosis of the Hodgkin transformation (nodular sclerosis) in a patient with prior chronic lymphocytic leukemia/small lymphocytic lymphoma: A) Lacunary Reed-Sternberg cells (RSC) (↖) are visible on low power field inside the parenchyma of an enlarged lymph node, which has a thickened capsule (*). Lymph node parenchyma is separated by irregular gracile bands of fibrous connective tissue [Hematoxylin and Eosin (HE), × 40]; B) Neoplastic tissue is heterogenous, with numerous (5% of total cellularity) large, neoplastic, lacunary (↖), pleiomorphic, mononuclear (↑), and polynuclear (↗) variants of RSC, inside an inflammatory milieu (HE, × 100); C) Polynuclear RSC (↗) – detail; D) Mononuclear Hodgkin cell (↑) – detail; E) Lacunary RSC (↖) – detail; F) Pleiomorphic RSC (↓) – detail; G) The heterogeneous inflammatory milieu consisting of small lymphocytes (↙), eosinophils (↘), neutrophils (←), and histiocytes (↳). C-G (HE, × 200).

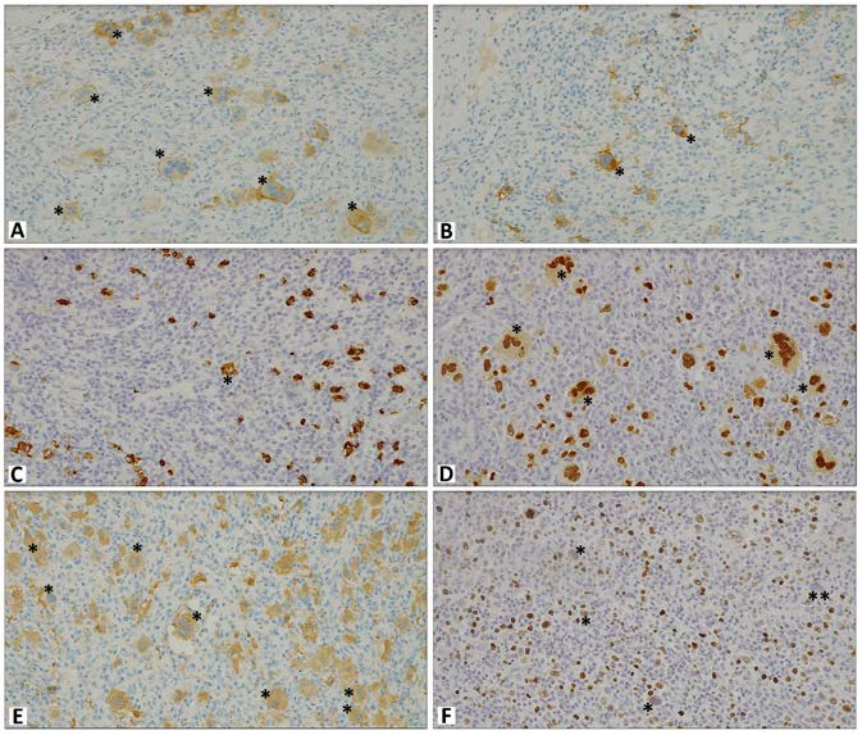

Fig. 2 – Immunohistochemistry (IH) features of the Hodgkin transformation in a patient with prior chronic lymphocytic leukemia/small lymphocytic lymphoma. The immunophenotype of Hodgkin-Reed-Sternberg cells (HRSCs) of the presented patient: $CD30^{+}$, $CD15^{+}$, $MUM1^{+}$, $Pax5^{+}$, $Fascin^{+}$, $EMA^{+/-}$, $LMP1^{-}$, $CD3^{-}$, $CD20^{-}$. A) CD30 membrane positivity of HRSCs (*); B) CD30 positivity of the Golgi zone (*) of HRSCs; C) CD15 positivity of the cytoplasm of a HRSCs (*); D) Weak Pax5 positivity of HRSCs (*); E) Fascin positivity of HRSCs (*); F) The majority of HRSCs demonstrate Ki67 nuclear positivity (indicating proliferation) (*), while other HRSCs are ki67 negative (**). A-F (IH, × 100).

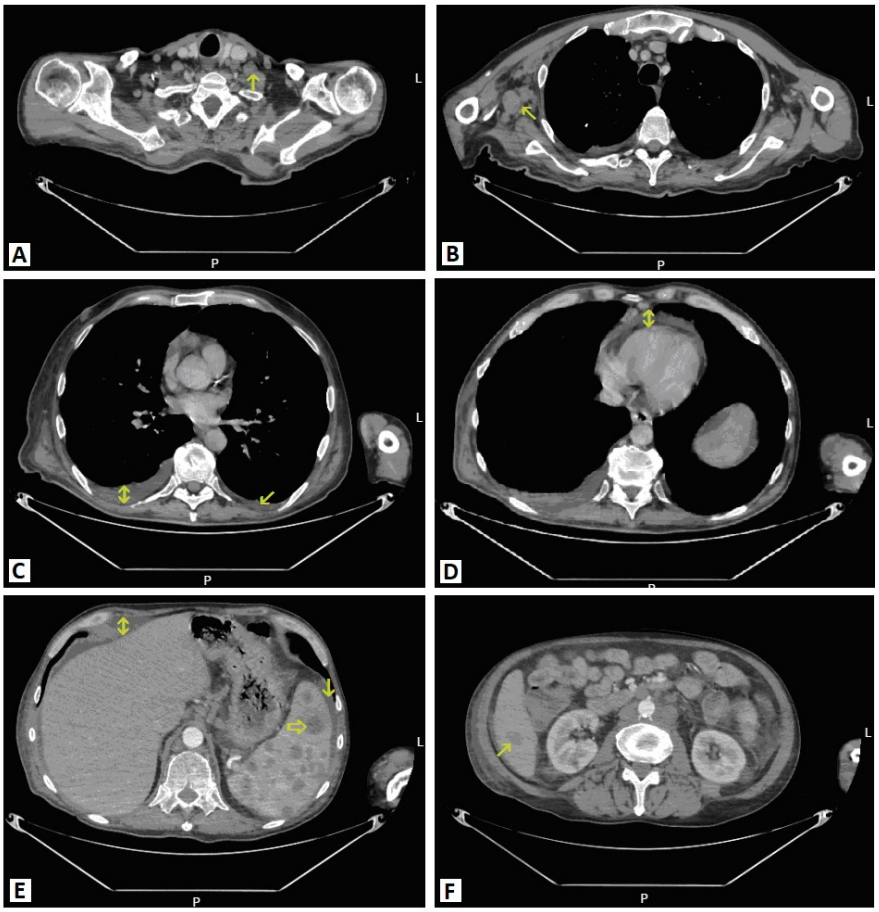

Fig. 3 – Multislice computed tomography of the patient with the Hodgkin transformation of chronic lymphocytic leukemia: A) Bilateral cervical lymphadenopathy, with the largest lymph node on the left (↑); B) Lymph node conglomerate in the right axilla with signs of central necrosis (↖); C) Both right-sided (↕) and left-sided (↙) pleural effusion; D) Pericardial effusion (↕) with the density of simple fluid next to the right ventricle of the heart; E) Perihepatic (↕) and perisplenic (↓) collection of simple fluid (ascites) as well as an enlarged spleen (170 mm) with numerous focal hypodense lesions, the largest of which is located near the lower pole of the spleen (⇨); F) The largest hypodense lesion in the S6 segment of the liver (↗).

Prior to the initiation of the first cycle of AVD treatment, on December 16, 2023, further laboratory analyses were performed [alkaline phosphatase (ALP) 202 U/L, RR: 30–120 U/L; total bilirubin 28.2 μmol/L, RR: 5.0–21.0 μmol/L; direct bilirubin 13.1 μmol/L, RR: 0.0–3.4 μmol/L; cholesterol 1.59 mmol/L, RR: 3.9–5.2 mmol/L; CRP 208.6 mg/L, RR: < 5.0 mg/L; albumin 22 g/L, RR: 35–52 g/L; lactate dehydrogenase (LDH) 445 U/L, RR: 220–450 U/L; aspartate transaminase 31 U/L, RR: 10–37 U/L; alanine transaminase 34 U/L, RR: 10–42 U/L].

Unfortunately, the patient died due to disease progression on December 23, 2023, during the initial cycle of AVD, about two months after the diagnosis of Hodgkin lymphoma (HL) was established.

Discussion

RT develops in about 2–10% of CLL/SLL patients [7, 8]. RT is named after the American pathologist Dr. Maurice Richter, who, in 1928, first published a case report of a male with lymphocytic leukemia who had died in just one month upon rapidly developing progressive lymphadenopathy and organomegaly [5, 6, 9, 10]. However, it was not until 1964 when Dr. Lortholary and colleagues correctly suggested that the disease transformation might be related to the underlying CLL and proposed the term “Richter syndrome” to name this phenomenon [5, 6, 10].

Even though the majority of CLL/SLL transformation cases consist of disease transformation into diffuse large B-cell lymphoma (80–90%), other less frequent variants have also been described, such as transformation into HL (10–20%), however, all other variants (Burkitt lymphoma, multiple myeloma, plasmablastic lymphoma, lymphoblastic lymphoma, T-cell lymphoma, hairy cell leukemia, prolymphocytic leukemia) comprise less than 1% of RT cases [5, 6, 8, 10, 11].

CLL/SLL causes a secondary immunodeficiency (associated with impaired immune surveillance), which, together with specific aberrations (TP53 mutation; 17p deletion) pre-

sent in some CLL/SLL cases, provides a setting for the development of secondary hematological and non-hematological malignancies [1, 12, 13]. Moreover, antineoplastic chemoimmunotherapy (such as FCR) is also a major contributing factor to the development of cancer in CLL/SLL patients [4].

One might imagine it would be appropriate to determine whether a newly diagnosed hematological malignancy in a CLL/SLL patient is a coexisting *de novo* disease (clonally independent) or a result of a true RT, in which an aggressive lymphoproliferative disease is clonally related to the underlying CLL/SLL [11].

However, in the case of the Hodgkin transformation of CLL/SLL, it is impossible to make such a distinction in routine clinical practice.

The malignant Hodgkin-Reed-Sternberg (HRS) cells are scattered throughout the affected lymph nodes, comprising no more than 1–5% of total lymph node cellularity, making microdissection (which would be essential for performing genomic studies) substantially difficult [14, 15].

Another reason for the lack of insight into the genetic mechanisms of Hodgkin transformation of CLL/SLL is the fact that the Hodgkin transformation is a rare clinical entity, with only about a hundred reported cases in the literature so far [8, 16].

This is also the main reason for insufficient studies regarding the efficacy of various treatment options in this group of patients.

Recent studies suggest that the Hodgkin transformation of CLL/SLL might be a two-step process, beginning with isolated HRS cells forming inside an environment containing scarce inflammatory cells (CLL-HRS), which is going to be replaced with mixed inflammatory background later on (CLL-HL) [17].

However, based on the findings of immunohistochemical studies, it seems that there are no major differences between the immunophenotype of HRS cells found in the Hodgkin transformation of CLL/SLL, and those found in classic HL (cHL) [17, 18].

Thus, all HL cases in patients with a previous CLL/SLL diagnosis are considered RT [17].

Excisional lymph node biopsy with subsequent morphological and immunohistochemical microscopic analyses is considered the gold standard for diagnosing the Hodgkin variant of RT [5].

Although LMP1 positivity of HRS cells is found in 60–80% of patients with Hodgkin transformation of CLL/SLL [17], this was not the case with our patient, whereas typical (although not obligatory) CD20 negativity was observed.

Typical clinical manifestations of RT (worsening of B symptoms, rapid enlargement of the lymph nodes, rapid organomegaly, increase in LDH levels) were mostly absent in our patient, with the exception of rapid splenomegaly. On the other hand, the patient had extranodal affection of both the spleen and liver, which may be attributed to the Hodgkin transformation since such findings have been previously reported in the Hodgkin transformation of CLL/SLL [19]. We did not perform biopsies of the affected extranodal sites because we strived to initiate treatment as soon as possible, as we expected to achieve a therapeutic response of affected extranodal sites upon treatment. The mechanisms of hepatic granulomatosis present in HL are not fully understood; however, the results of certain studies suggest the importance of the secretory activity of HRS cells in the development of granulomas and fibrosis (delayed hypersensitivity) [19, 20]. In December 2023, the presented patient had a moderate increase in serum ALP (202 U/L), which could be attributed to the existing hepatic lesions. The increase in serum ALP levels had already been reported in a case of the Hodgkin transformation of CLL/SLL with hepatic involvement, indicating an unfavorable prognosis [19]. Some other hepatic parameters were also abnormal in case of our patient, such as elevated levels of both total and direct bilirubin (28.2 μmol/L and 13.1 μmol/L, respectively), as well as hypocholesterolemia (cholesterol 1.59 mmol/L) and hypoalbuminemia (albumin 22 g/L) causing pericardial, bilateral pleural, and abdominal effusions, indicating impairment of both excretory and synthetic functions of the liver. The levels of both LDH and transaminases were normal. There was an increase in the level of inflammatory markers (CRP 174.08 mg/L, ESR 140 mm/1st hr, prior to the final admission to the Clinic on December 12, 2023), which could have been attributed to both HL and the resolution of a prior postoperative wound infection.

Our patient had hardly any risk factors associated with the development of RT (such as young age, markedly elevated LDH, and multiple CLL relapses) except for anemia [19].

On the contrary, at the moment of establishing the RT diagnosis, our patient had almost all of the established cHL risk factors (age $\geq$ 50 years, elevated ESR, at least four supradiaphragmatic nodal areas, extranodal disease, at least three nodal areas on both sides of the diaphragm) except for a large mediastinal tumor mass [21].

Based on the clear survival benefit, it is justifiable that patients with the Hodgkin transformation of CLL/SLL should be treated with chemotherapy protocols used for cHL since the efficacy of CLL-based regimens is far inferior in these circumstances [1, 16, 17].

Besides being the most commonly used protocol for the treatment of Hodgkin transformation of CLL/SLL, doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) seems to be also the most efficient regimen in this indication, with an estimated median overall survival of 13.2 years [16]. It is not clear whether brentuximab vedotin–AVD is less efficient than ABVD since brentuximab vedotin–AVD was usually the treatment of choice for older, frail patients with a higher International Prognostic Score (IPS), who were more likely to have a poor prognosis regardless of the chosen treatment option (brentuximab vedotin–AVD vs. ABVD), whereas the younger, more fit patients, with a lower IPS, usually received ABVD, being a more aggressive option [16]. Other less used and less efficient therapeutic alternatives include brentuximab vedotin monotherapy, cyclophosphamide, vinblastine, procarbazine, and prednisone (CVPP), nitrogen mustard, vincristine, procarbazine, prednisone (MOPP), rituximab, cyclophosphamide, vincristine, prednisone (R ± CHOP), and

FCR regimens [8, 11, 16]. The strongest predictor of survival of the patients with the Hodgkin variant of RT is achieving complete remission upon ABVD treatment [22]. Unlike for cHL, in the case of Hodgkin transformation of CLL/SLL, most clinicians avoid high-dose chemotherapy (HDT) followed by hematopoietic stem cell transplantation (HSCT) (HDT + HSCT) upon achieving the first complete remission (CR1), since these patients are usually elderly (> 70 years), with significant comorbidities, making them unfit for such aggressive treatment, whereby performing HDT + HSCT after CR1 demonstrated no survival benefit in patients with a Hodgkin variant of RT [16].

Based on the achievements reported in individual cases, there may be reasons to assume that novel immunotherapies (such as brentuximab vedotin or checkpoint inhibitors) could change the treatment paradigm and prognosis of affected patients in due time [18].

Since fluorescence *in situ* hybridization of bone marrow blood was not performed prior to the initiation of FCR, the 17p deletion/TP53 mutation status of our patient remains unknown. Although fludarabine may promote the development of the Hodgkin variant of RT due to immunosuppression, this complication has been reported in CLL/SLL patients on Bruton's tyrosine kinase (BTK) inhibitor treatment as well [16, 19, 23]. Therefore, we could speculate that the Hodgkin variant of RT would have occurred in our patient regardless of the therapeutic option chosen for the first-line treatment of CLL/SLL (FCR vs. BTK inhibitor). According to the indications provided by the Republic Fund of Health Insurance (Belgrade, Serbia), ibrutinib is currently the sole BTK inhibitor available for first-line therapy of CLL/SLL only for patients with a documented 17p deletion/TP53 mutation [24].

The Hodgkin transformation of CLL/SLL was considered to have a more unfavorable prognosis than *de novo* cHL [11, 16]. However, based on the results of the largest retrospective multicentric study performed on a cohort of 94 cases of the Hodgkin transformation of CLL/SLL, it seems that there are no major differences prognostic-wise [16].

IPS [male gender; age $\geq$ 45 years; IV Ann Arbor clinical stage (CS); albumin level < 40 g/L; Hgb < 105 g/L; Ly < 0.6 × 10^9/L and/or Ly < 8%; WBC $\geq$ 15 × 10^9/L; each awarded 1 point] and Richter Syndrome Score (RSS) [Eastern Cooperative Oncology Group performance status (ECOG-PS) > 1; LDH level 1.5 times greater than the upper limit of normal; thrombocytopenia; tumor mass at least 5 cm in size or larger; more than one prior line of therapy – each awarded 1 point] are used for the prognostic assessment of the Hodgkin variant of RT [5, 16, 25, 26].

Our patient had developed several episodes of febrile neutropenia during the course of FCR treatment and was therefore treated with granulocyte colony-stimulating factor (CSF-G) on multiple occasions. He was also a chain-smoker for almost four decades. Since he was an elderly heavy smoker who would potentially require CSF-G support during the course of further treatment, it was decided that bleomycin be omitted from the ABVD in order to avoid lung toxicity [21, 27, 28].

Since our patient had a high IPS = 6 (male, 60 years old, IV Ann Arbor CS, albumin 22 g/L; Hgb 76 g/L; Ly 0.31 × 10^9/L) and an intermediate RSS = 2 (ECOG-PS = 2, lymph node conglomerate in the right axilla 64 × 22 mm in size), even though without markedly elevated LDH, we considered him to be a patient with an unfavorable prognosis.

Although patients with the Hodgkin transformation of CLL/SLL may have similar survival rates compared to the patients with *de novo* cHL, Stephens et al. [16] reported that 5% of patients with the Hodgkin variant of RT die within two months of RT diagnosis, which was the case with our patient as well.

Conclusion

For most cases, CLL currently remains an incurable B-cell malignancy with a generally favorable prognosis, being a slowly progressive disease with an adequate response to the existing therapeutic options. However, in a small portion of patients who develop RT, the prognosis is largely dismal. The treatment of the Hodgkin transformation of CLL remains an unmet need, although novel immunotherapies may potentially alter the outcome of such patients in the near future.

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