CASE REPORT

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Diffuse Large B-Cell Lymphoma with Second Relapse in Leukemic Phase

İkinci Nüksünde Lösemik Faz ile Başvuran Yaygın Büyük B Hücreli Lenfoma

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ABSTRACT

The leukemic phase of diffuse large B-cell lymphoma (DLBCL) is a rare condition and can be difficult to distinguish from acute leukemia or the leukemic phases of other non-Hodgkin lymphoma subtypes. When intermediate-to-large abnormal lymphoid cells are observed in the peripheral blood, it should be considered as one of the differential diagnoses. Flow cytometry and immunohistochemical staining are helpful for definitive diagnosis. The leukemic phase typically occurs in the progressive phase or stage IV disease and is rare at the time of initial diagnosis in DLBCL. The development of a leukemic phase during the course of the disease is particularly associated with poor prognosis. There are no evidence-based treatment recommendations for this condition. In our case, we presented a patient with DLBCL who developed a leukemic phase upon second relapse.

Keywords: Diffuse large B-cell lymphoma, leukemic phase, prognosis

ÖZ

Yaygın diffüz büyük B hücreli lenfoma (DLBCL) lösemik fazı nadir görülen bir durumdur ve akut lösemiden veya diğer Hodgkin dışı lenfoma türlerinin lösemik fazlarından ayırt edilmesi zor olabilir. Periferik kanda orta ila büyük boyutlarda anormal lenfoid hücreler izlenmesi durumunda ayırıcı tanılardan biri olarak düşünülmelidir. Kesin tanı için flowsitometri ve immünohistokimyasal boyalar yardımcı olur. Lösemik faz genellikle ilerleyici bir faz veya evre IV hastalıkta görülür ve DLBCL tanı anında nadirdir. Özellikle hastalığın seyrinde lösemik faz gelişmesi kötü prognozla ilişkilidir. Tedavisi hakkında kanıta dayalı öneriler yoktur. Bizde DLBCL tanılı hastanın ikinci nüksünde lösemik faz başvurusunu sunduk.

Anahtar Kelimeler: Yaygın büyük B hücreli lenfoma, lösemik faz, prognoz

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphomas (NHLs) and accounts for approximately one-third of all types of NHL[1]. The presence of malignant lymphoma cells in peripheral blood is well recognized in mantle cell lymphoma, follicular lymphoma, anaplastic large cell lymphoma, and the terminal phases of all refractory lymphomas[2-5]. The leukemic phase of DLBCL is a rare condition and may be difficult to distinguish from acute leukemia or other types of NHL[6-9]. The leukemic phase usually occurs as a progressive phase or in stage IV disease and is rare at the time of diagnosis in DLBC[10,11].

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CASE REPORT

A 68-year-old female patient presented with complaints of neck swelling, weight loss, and night sweats. Complete blood count was normal. Superficial ultrasonography revealed multiple lymph nodes in bilateral cervical, inguinal, and axillary regions, the largest of which measured 20 mm in short axis, some with a reticular appearance, some with a compressed hilum, and thick cortex. An excisional biopsy was performed from the cervical region. The biopsy revealed tumor cells positive for immunohistochemical markers CD20, BCL-2, CD79A, and 50% positive for C-MYC, 1-2% positive for MUM-1, and negative for CD3, CD5, CD10, BCL-6, CD23, CD30, and Cyclin D1. The Ki-67 index was 80-90% (Figure 1). Diagnosis of non-germinal center type DLBCL was made. Bone marrow biopsy was also found to be consistent with DLBCL involvement. The patient with Stage 4 high International Prognostic index (IPI) score was given rituximab-gemcitabine-cyclophosphamide-vincristine-prednizon (R-GCVP) due to low ejection fraction. Prophylactic intrathecal (IT) methotrexate was administered as a result of the high probability of central nervous system (CNS) recurrence of lymphoma. After 3 cycles of R-GCVP, a partial metabolic response to treatment was observed with positron emission tomography-computed tomography. Continuation of R-GCVP treatment was planned but the patient developed strabismus during follow-up. Contrast brain magnetic resonance imaging (MRI) was performed to investigate CNS involvement. A mass was detected on contrasted pituitary MRI, which, when evaluated radiologically and clinically together, was considered as lymphoma infiltration. The patient was planned to start MATRix chemotherapy protocol. Three cycles were administered. After 3 cycles of MATRix chemotherapy, a follow-up contrasted pituitary MRI showed significant regression. Thereupon, the patient was planned for autologous hematopoietic stem cell transplantation (AHSCT). Stem cell mobilization was performed. When the patient was admitted for AHSCT one month later, she had complaints of fatigue and abdominal pain. Complete blood count revealed a white blood cell count of 16,760/mm^3, hemoglobin 8.6 g/dL, and platelet count of 169,000/mm^3. Peripheral smear showed leukocytosis and 34% medium- to large-sized atypical lymphoid cells with condensed nuclear chromatin and inconspicuous nucleoli (Figure 2). In the flow cytometry performed on peripheral blood, a lymphoid cell population of approximately 45% was observed, showing positive expression of CD19, CD20, CD22, CD45, CD79a and negative expression of CD3, CD5, CD7, CD23, CD34, CD56, TdT. Indistinct, scattered, slightly hyperintense nodular lesions with the largest measuring 2 cm were observed in the liver. Tru-cut needle biopsy was performed here. Liver biopsy was consistent with non-germinal center type DLBCL. During this period, the patient's leukocyte count rapidly increased to 50,000/mm^3, which was consistent with the leukemic phase of DLBCL. Since she was unfit and refractory to standard chemotherapy, rituximab-ibrutinib-lenalidomide treatment was started. There was no response to this treatment. The patient died due to renal failure and sepsis within a short period of 1 month after the leukemic phase diagnosis. A short survival of 11 months was achieved compared to the time of the first diagnosis.

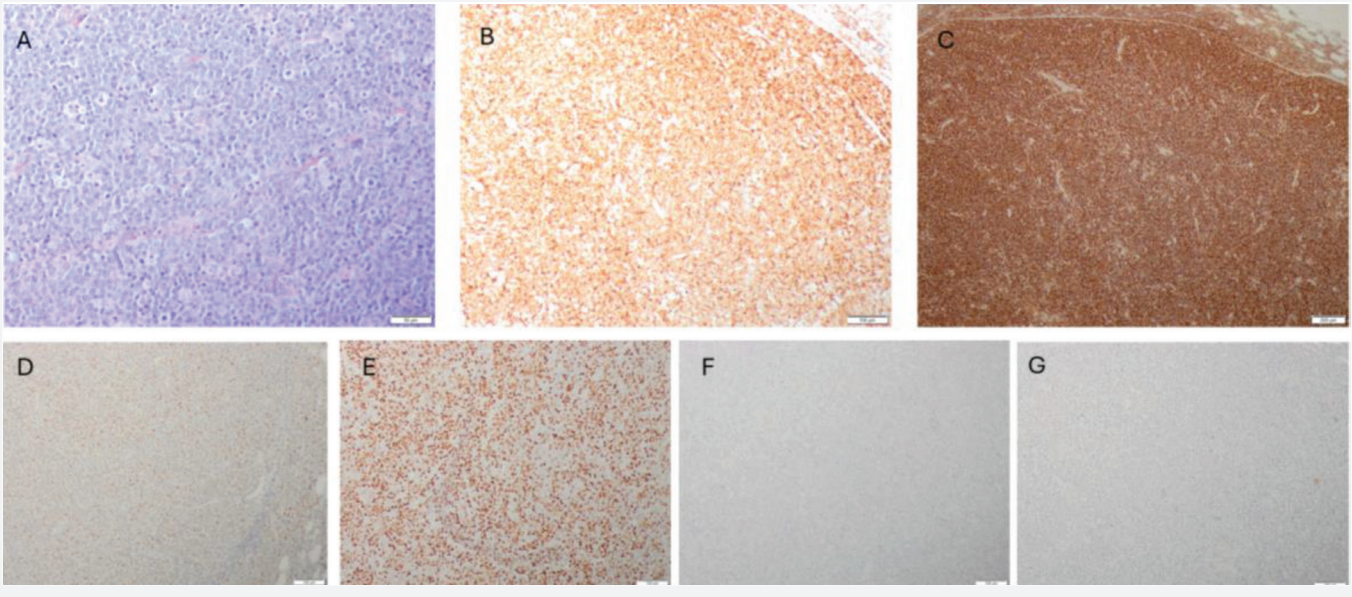

Figure 1. (A) Hematoxylin-eosin (50 µm), (B) BCL2 positive (scale bar: 100 µm), (C) CD20 positive (scale bar: 200 µm), (D) C-MYC 50% positive (scale bar: 100 µm), (E) Kİ-67 80-90% (scale bar: 100 µm) (F) BCL6: Negative (scale bar: 100 µm) (G) CD10 negative (scale bar:100 µm)

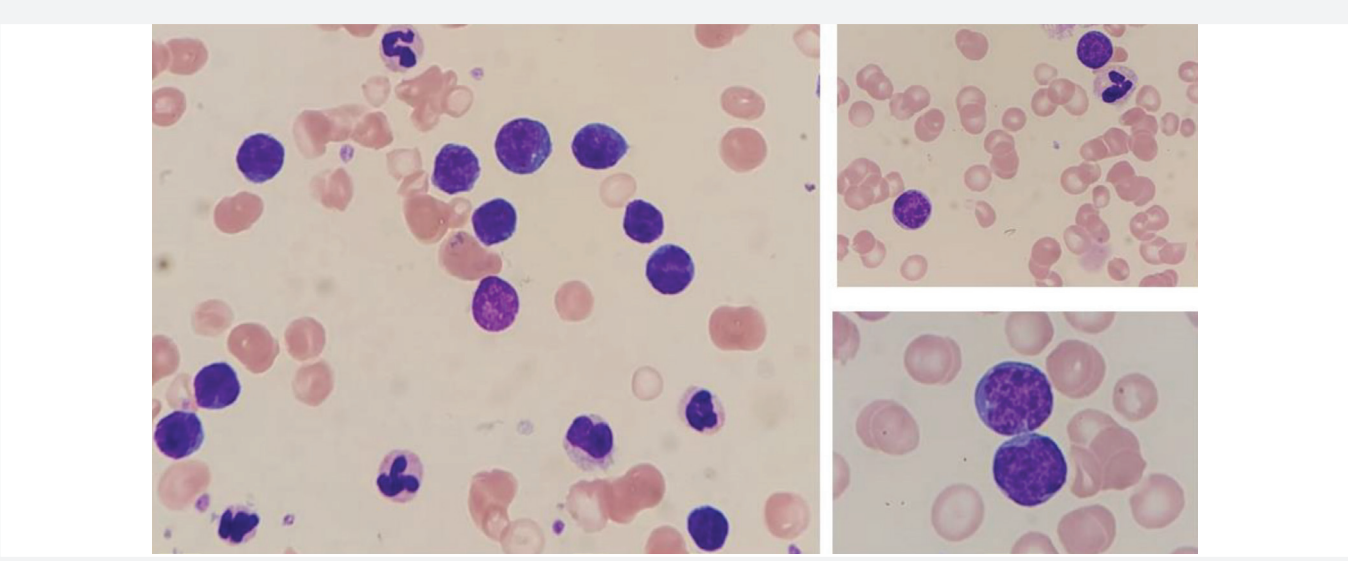

Figure 2. Peripheral smear shows large-sized atypical lymphoid cells with condensed nuclear chromatin and inconspicuous nucleoli

DISCUSSION

Lymphomas are diagnosed primarily based on histologic findings, although dissemination of these lymphoma cells into the circulation (leukemic phase) can be diagnosed based on cellular immunophenotypic analysis by flow cytometry[8]. Immunophenotypically, these cells show strong membrane positivity for B-cell lineage markers such as CD19, CD20 and follicular center markers such as CD10 (40%) and BCL6 (60%). Non-germinal center type DLBCL will show positivity for CD38 and MUM1[11,12].

IPI is the primary prognostic scoring system used for patients with DLBCL. IPI was developed to assess pre-treatment characteristics that predict outcomes in patients with aggressive non-Hodgkin lymphoma, including DLBCL. In patients receiving chemotherapy containing doxorubicin, overall survival and progression-free survival are associated with age, serum lactate dehydrogenase levels, performance status, clinical stage, and extranodal disease[13]. Following the introduction of rituximab, the IPI model was validated in patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) and R-CHOP-like regimens[14,15]. Other studies have investigated prognostic markers such as neutrophil count, lymphocyte count, neutrophil/lymphocyte ratio, mean platelet volume, uric acid, and fibrinogen levels[16,17].

A study of 29 patients with leukemic phase DLBCL showed that all patients had extranodal involvement, high IPI, and poor performance status. Anthracycline and rituximab-based regimens R-CHOP or rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin achieved an overall response of 88% and a complete response (CR) of 54%, with a 4-year survival of approximately 50%[12]. A patient diagnosed with leukemic phase DLBCL at the age of twenty-eight and given 6 cycles of DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) chemotherapy followed by abdominal radiotherapy was reported to have relapsed in a short period of 2.5 months. The patient, who was subsequently given the R-BFM-90 protocol, died due to disease progression[7]. A 74-year-old female patient presented with DLBCL leukemic phase and conventional cytogenetic studies showed a complex karyotype with t (8;14) (q24q32). Although a CR was achieved with the modified hyper CVAD protocol, relapse occurred in a short time and permanent remission could not be achieved with various treatments[18]. One case of DLBCL in the leukemic phase that was CD19 negative was reported[19]. In another case report, a diagnosis of de novo DLBCL in the leukemic phase was made, positive for both CD5 and CD13, and the patient was treated with the recombinant human cartilage oligomeric matrix protein regimen and achieved complete remission but relapsed one month later. This was interpreted by the authors as an indicator of poor prognosis for DLBCL with CD5+ leukemic presentation[20]. A case of DLBCL with complex karyotype including TP53 deletion with leukemic phase and cerebrospinal fluid (CSF) involvement was given R-Hyper-CVAD chemotherapy with twice weekly IT therapy (alternative methotrexate and cytarabine) for two cycles. Due to persistent CSF involvement, his treatment was changed to rituximab and IT thiotepa was added to his regimen. Finally, after more than 2 months of systemic and CT chemotherapy, his CSF cleared. Then, consolidative craniospinal irradiation was performed before proceeding to allogeneic transplantation in the first remission. Unfortunately, despite aggressive measures, CNS relapsed on the 50th day post-allogeneic transplantation[21]. A 54-year-old patient with leukemic phase DLBCL was treated with a combination of rituximab, cyclophosphamide, R-CHOP and lenalidomide because of myelocytomatosis oncogene positivity, and achieved a CR[9].

Forty-five patients with relapsed and refractory DLBCL, who had received at least one prior treatment, were treated with ibrutinib + rituximab + lenalidomide. Of the patients, 51% had non-germinal center B-cell (non-GCB) like DLBCL, 33% had transformed DLBCL, 60% were refractory, and 27% had primary refractory disease. The overall response rate (ORR) was found to be 44% (CR: 28%); among these, in non-GCB patients, the ORR was 65% (CR: 41%), in relapsed patients (n=16), the ORR was 69%, and in secondary refractory patients (n=27), the ORR was 56%[22]. Our patient was relapsed/refractory after receiving two lines of treatment, and their current condition was not suitable for standard chemotherapy. Based on the study mentioned above, and considering the diagnosis of non-GCB DLBCL and performance status, treatment with ibrutinib + rituximab + lenalidomide was initiated.

CONCLUSION

Although the study by Muringampurath-John et. al[12] mentioned above found that the response rates and survival of DLBCL leukemic phase patients were similar to those of non-leukemic phase DLBCL, neither our case nor other cases presented in the literature support this. Our case survived only one month after entering the leukemic phase and the total survival was eleven months. There is insufficient evidence in the literature regarding the treatment of DLBCL leukemic phase. Since most of these patients may be primary refractory, new treatment methods are needed.

Ethics

Informed Consent: Written informed consent was obtained from all participant.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.D., İ.G., N.K., H.H.E., A.T., Concept: S.D., İ.G., Design: S.D., Data Collection or Processing: S.D., N.K., H.H.E., Analysis or Interpretation: S.D., A.T., Literature Search: S.D., İ.G., Writing: S.D., İ.G.

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REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375-90.
2. Morra E, Lazzarino M, Orlandi E, Pagnucco G, Brusamolino E, Castello A, Inverardi D, Bernasconi C. Leukemic phase of non-Hodgkin's lymphomas. Hematological features and prognostic significance. Haematologica 1984;69:15-29.
3. Berinstein NL, Reis MD, Ngan BY, Sawka CA, Jamal HH, Kuzniar B. Detection of occult lymphoma in the peripheral blood and bone marrow of patients with untreated early-stage and advanced-stage follicular lymphoma. J Clin Oncol. 1993;11:1344-52.
4. Criel A, Pittaluga S, Verhoef G, Wlodarska I, Meeus P, Mecucci C, et al. Small B cell NHL and their leukemic counterpart: differences in subtyping and assessment of leukemic spread. Leukemia. 1996;10:848-53.
5. Villamor N, Rozman M, Esteve J, Aymerich M, Colomer D, Aguilar JL, et al. Anaplastic large-cell lymphoma with rapid evolution to leukemic phase. Ann Hematol. 1999;78:478-82.
6. Bain BJ, Catovsky D. The leukaemic phase of non-Hodgkin's lymphoma. J Clin Pathol. 1995;48:189-93.
7. Balasubramanian P, Ramteke P, Mallick S, Kumar L, Tanwar P. Diffuse large B-cell lymphoma relapsing in leukaemic phase presenting as acute leukaemia. Clin Med Insights Blood Disord. 2019;12:1179545X18821160.
8. Suresh PK, Basavaiah SH, Goel M, Dsouza S, Rai S. Diffuse large B-cell lymphoma in blood and bone marrow: a rare presentation of leukemic phase at diagnosis. Hematol Transfus Cell Ther. 2020;42:180-3.
9. Bilgin YM, Castel R. MYC -Positive diffuse large B-cell lymphoma in leukemic phase at presentation: a diagnostic and therapeutic challenge. J Hematol 2021;10:80-2.
10. Wong E, Juneja S. Diffuse large B-cell lymphoma in leukemic phase with flower cell morphology. Blood. 2014;123:3378.
11. Pires PP, Kanegae MY, Rays J, Catania M, Lima FR, Noronha TR, et al. Diffuse large B-cell lymphoma presenting in the leukemic phase. Autops Case Rep. 2016;6:41-5.
12. Muringampurath-John D, Jaye DL, Flowers CR, Saxe D, Chen Z, Lechowicz MJ, et al. Characteristics and outcomes of diffuse large B-cell lymphoma presenting in leukaemic phase. Br J Haematol. 2012;158:608-14.
13. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993;329:987-94.
14. Ziepert M, Hasenclever D, Kuhnt E, Glass B, Schmitz N, Pfreundschuh M, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28:2373-80.
15. Salles G, de Jong D, Xie W, Rosenwald A, Chhanabhai M, Gaulard P, et al. Prognostic significance of immunohistochemical biomarkers in diffuse large B-cell lymphoma: a study from the Lunenburg Lymphoma Biomarker Consortium. Blood. 2011;117:7070-8.
16. Demircioğlu S, Doğan A, Ekinci Ö, Demir C. The association of NLR and MPV with treatment responses, disease stages, and international prognostic ındex scores in DLBCL. Eastern Journal Of Medicine. 2019;24:325-9.
17. Çiftçiler R, Ciftciler AE, Selim C. Evaluation of the association between serum danger molecules at diagnosis and survival outcomes in patients with diffuse large B cell lymphoma. Med Int (Lond). 2025;5:25.
18. Jain P, Sargent RL, Konoplev SN, Benjamini O, Kantarjian H, Kadia T. Multiple recurrent extra-medullary relapses of high-grade diffuse large B-cell lymphoma presenting in acute leukemic phase. Am J Hematol. 2013;88:433-4.
19. Ramalingam TR, Uthayasuriyan R, Prabhakar V, Vaidhyanathan L. CD19 negative diffuse large B-cell lymphoma presenting in leukemic phase. Cytometry B Clin Cytom. 2023;104:331-3.
20. Carulli G, Ciancia EM, Caracciolo F, Sammuri P, Domenichini C, Ferreri MI, et al. A rare case of de novo CD5+ diffuse large B-cell lymphoma in leukemic phase and positive for CD13. Hematol Rep. 2018;9:7437.
21. Sinkoff J, Olteanu H, Peterson JF, Shah NN. Leukemic phase and CSF involvement of diffuse large B-cell lymphoma with a complex karyotype including a TP53 deletion. Clin Case Rep. 2017;6:235-7.
22. Goy A, Ramchandren R, Ghosh N, Munoz J, Morgan DS, Dang NH, et al. Ibrutinib plus lenalidomide and rituximab has promising activity in relapsed/refractory non-germinal center B-cell-like DLBCL. Blood. 2019;134:1024-36.