Late Relapse of Diffuse Large B-Cell Lymphoma in a Patient with Minor Thalassemia: A Diagnostic Challenge

Stephanie Marisca[1,2], Jennifer Jesse Limanto[1,2]

[1] *Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia*
[2] *Siloam Hospital Lippo Village, Tangerang, Indonesia*

Citation: Marisca, S., & Limanto, J. J. 2026. Late Relapse of Diffuse Large B-Cell Lymphoma in a Patient with Minor Thalassemia: A Diagnostic Challenge. Medicinus, 15(3), 79–85.
Keywords: DLBCL; diagnostic challenge; late relapse; minor thalassemia
Correspondance: Stephanie Marisca
E-mail: stephanie.marisca@uph.edu
Online First: 23 June 2026

Abstract

Background:
Diffuse large B-cell lymphoma (DLBCL) commonly responds to chemoimmunotherapy, and relapse risk usually decreases after prolonged remission. Thalassemia has been associated with increased risk of hematologic malignancy, although its relationship with late DLBCL relapse remains unclear.

Case Description:
A 68-year-old woman with minor thalassemia and a history of primary mediastinal B-cell lymphoma in complete remission for 15 years presented with fever and fatigue. Laboratory findings showed pancytopenia and elevated lactate dehydrogenase. FDG-PET/CT demonstrated increased uptake in the spleen and bone marrow. Bone marrow biopsy showed large B-lymphoid cells positive for CD20 and MUM1, establishing relapsed DLBCL with extranodal involvement. Complete remission was achieved after two cycles of R-COP chemotherapy, but the patient later died from severe infection, metabolic complications, and cardiomyopathy during the fourth cycle.

Conclusions:
Late relapse of DLBCL in patients with thalassemia is diagnostically challenging because cytopenia and systemic symptoms may overlap with hematologic complications. Long-term surveillance and prompt evaluation of new pancytopenia, splenomegaly, or systemic symptoms are essential in lymphoma survivors with thalassemia.

Introduction

Lymphoma is a hematological malignancy arising from the lymphoid system.[1] It is classified into Hodgkin lymphoma and non-Hodgkin lymphoma (NHL), with NHL accounting for approximately 80% of lymphoma cases. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL.[2] DLBCL may occur de novo or arise through transformation from a pre-existing low-grade B-cell lymphoma.[3]

DLBCL usually responds well to standard chemoimmunotherapy; however, relapse can occur, most often within two years after initial treatment. Late relapse is uncommon and remains diagnostically challenging, particularly when systemic symptoms and cytopenias overlap with other hematological conditions.[3,15]

Thalassemia is a genetic blood disorder caused by decreased or abnormal synthesis of alpha or beta globin chains.[4] It has been associated with increased risk of malignancy, particularly hematologic cancers, although the mechanism remains unclear. This case report describes

late relapse of DLBCL in a patient with minor thalassemia after a 15-year remission period.

Case Description

A 68-year-old woman presented with a two-week history of recurrent fever and fatigue. She had a history of primary mediastinal B-cell lymphoma diagnosed 15 years earlier and achieved complete remission after six cycles of R-CHOP chemotherapy followed by local radiotherapy. She had undergone annual surveillance without evidence of recurrence, including the most recent follow-up four months before admission. The patient also had minor thalassemia. She denied respiratory symptoms, diarrhea, bleeding, trauma, or reduced food intake.

On physical examination, the patient appeared pale and weak with anemic conjunctivae. Her body temperature was 38°C, while other vital signs were within normal limits. Laboratory investigations revealed pancytopenia with hemoglobin of 5.9 g/dL, white blood cell count of 3.34 x 10^9/L, and platelet count of 84 x 10^9/L, accompanied by elevated lactate dehydrogenase and slightly increased reticulocyte count. Iron studies, liver function tests, renal function tests, and other laboratory markers were unremarkable. The patient was hospitalized for blood transfusion and further evaluation.

Serum protein electrophoresis showed increased kappa light chain, suggesting monoclonal gammopathy potentially related to a lymphoproliferative process. Abdominal CT scan revealed hepatosplenomegaly without detectable masses or lymphadenopathy. FDG-PET/CT demonstrated increased metabolic activity in the spleen, with SUV 8.2, and bone marrow, with SUV 9.46, suggestive of possible extranodal lymphoma involvement.

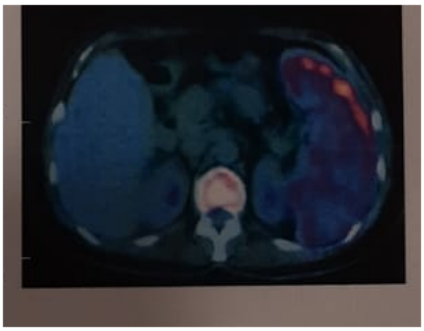

Figure 1. Increased FDG uptake in the spleen.

Bone marrow biopsy revealed hypercellular marrow with focal infiltration of large, atypical B-lymphoid cells in the para-trabecular area. Fibrosis was also observed in the specimen.

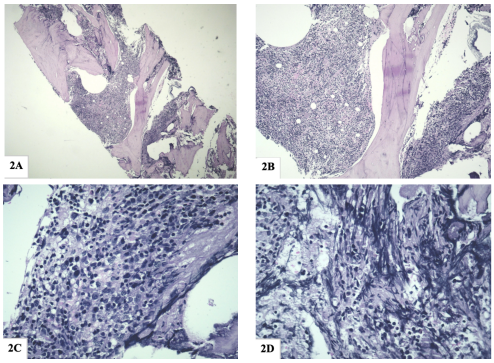

Figure 2. Bone marrow biopsy (HE staining): 2A-2B hypercellular marrow; 2C focal large B-lymphoid infiltration; 2D fibrosis.

Immunohistochemical staining was positive for CD20 and MUM1, supporting a diagnosis of DLBCL. Considering the previous history of large B-cell lymphoma, these findings were consistent with relapsed DLBCL involving extranodal sites. The patient was started on the R-COP chemotherapy regimen. After two cycles, PET evaluation demonstrated

complete remission. Unfortunately, the patient subsequently developed metabolic complications, severe infection, and cardiomyopathy during the fourth cycle of chemotherapy, which ultimately led to death.

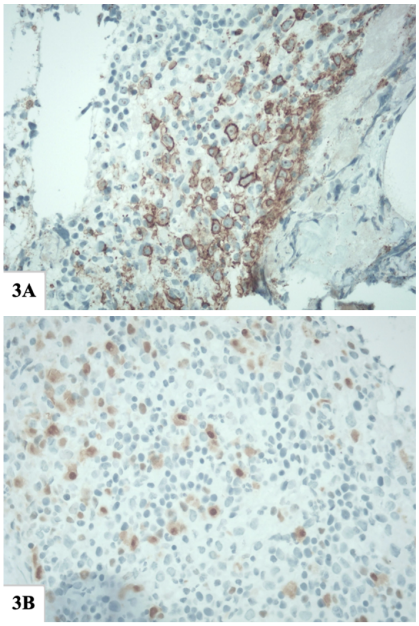

Figure 3. Immunohistochemistry: 3A CD20-positive large B-lymphoid cells; 3B positive MUM1 staining.

Discussion

Diffuse large B-cell lymphoma is the most common subtype of NHL, followed by follicular lymphoma.[2] The incidence has been reported at approximately 5.6 cases per 100,000 population in 2018-2022, with the highest rates among male patients, and DLBCL is most frequently diagnosed in the sixth decade of life.[3,5] The mechanism of tumor development depends on the cell of origin and reflects the stage of B-cell differentiation. DLBCL may be classified into germinal center B-cell-like, activated B-cell-like, or unclassified subtypes.[7,12]

Clinical manifestations of DLBCL include systemic symptoms such as fever, weight loss, and night sweats, which are related to cytokine production. Extranodal involvement occurs in approximately 30% of cases, most commonly in the gastrointestinal tract, followed by bone, spleen, testes, and central nervous system.[9] Diagnostic evaluation requires complete blood examination, lactate dehydrogenase measurement, biopsy with immunohistochemical staining, and imaging using CT or PET-CT to confirm diagnosis and determine disease stage.[10,11,13]

Standard treatment for DLBCL commonly consists of R-CHOP and has a cure rate of approximately 60% to 70%.[14] Despite favorable initial responses, relapse can occur. Early relapse is associated with poorer outcomes, whereas relapse after 24 months is considered late relapse and is relatively rare.[15] Molecular mechanisms proposed in relapsed or refractory DLBCL include aberrant B-cell receptor signaling, PI3K/AKT/mTOR pathway activation, NF-kB activation, BCL2 overexpression, XPO1 dysregulation, and immune checkpoint alterations.[16]

In this case, the patient had minor thalassemia without regular transfusion and a previous history of primary mediastinal large B-cell lymphoma. Thalassemia has been linked with increased risk of malignancy, particularly hematologic cancers. In transfusion-dependent disease, iron overload may promote DNA damage, oxidative stress, and immune dysfunction.[17,18] In non-transfusion-dependent thalassemia, iron accumulation may still occur because of increased intestinal iron absorption and altered hepcidin regulation.[19,20] Chronic marrow stimulation, ineffective erythropoiesis, and tissue hypoxia may also contribute to a pro-proliferative microenvironment.

Pancytopenia in thalassemia can obscure recognition of malignancy, making diagnostic evaluation more difficult. Thalassemic patients who develop new pancytopenia, splenomegaly, lymphadenopathy, or systemic symptoms should be evaluated for possible malignancy until proven otherwise.[23] In suspected relapse, repeat biopsy and PET-CT are important to exclude other causes and to determine whether the presentation represents true relapse or de novo lymphoma.[24]

There are no standardized international guidelines for all cases of relapsed DLBCL. Autologous stem-cell transplantation remains a preferred option for eligible patients, while other options include CAR T-cell therapy, high-dose chemotherapy, and salvage regimens.[25] In the present case, R-COP was selected considering the prolonged remission period and clinical status. Complete remission after two cycles suggested chemosensitive disease; however, the patient later developed severe treatment-related complications and died.

Conclusion

DLBCL is an aggressive but potentially curable lymphoma with standard chemotherapy. Late relapse remains a diagnostic and therapeutic challenge, especially in patients with coexisting thalassemia, where cytopenia and systemic symptoms may overlap with hematologic complications. Thalassemia may contribute to malignant transformation or relapse through chronic anemia, ineffective erythropoiesis, iron overload, oxidative stress, and immune dysregulation. Long-term surveillance and careful evaluation of lymphoma survivors with thalassemia are essential even after prolonged remission.

Acknowledgement

None.

References

1. Padala SA, Kallam A. Diffuse large B-cell lymphoma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.

2. Berhan A, Almaw A, Damtie S, et al. Diffuse large B cell lymphoma (DLBCL): epidemiology, pathophysiology, risk stratification, advancement in diagnostic approaches and prospects: narrative review. Discov Onc. 2025;16:184. doi:10.1007/s12672-025-01958-w.

3. Sehn LH, Salles G. Diffuse large B-cell lymphoma. N Engl J Med. 2021;384(9):842-858. doi:10.1056/NEJMra2027612.

4. Bajwa H, Basit H. Thalassemia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.

5. National Cancer Institute. SEER Cancer Stat Facts: Diffuse Large B-Cell Lymphoma (DLBCL). Bethesda (MD): U.S. National Institutes of Health; cited 2025 Oct 21.

6. Basso K. Biology of germinal center B cells relating to lymphomagenesis. HemaSphere. 2021;5(6):e582. doi:10.1097/HS9.0000000000000582.

7. Vodicka P, Klener P, Trneny M. Diffuse large B-cell lymphoma (DLBCL): early patient management and emerging treatment options. Onco Targets Ther. 2022;15:1481-1501. doi:10.2147/OTT.S326632.

8. Cerhan JR, Kricker A, Paltiel O, et al. Medical history, lifestyle, family history, and occupational risk factors for diffuse large B-cell lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr. 2014;2014(48):15-25.

9. Liu Y, Barta SK. Diffuse large B-cell lymphoma: 2019 update on diagnosis, risk stratification, and treatment. Am J Hematol. 2019;94(5):604-616.

10. Jaffe ES, Arber DA, Campo E, Harris NL, Quintanilla-Fend L, editors. Hematopathology. 4th ed. Philadelphia: Elsevier; 2016.

11. Sehn LH, Salles G. Diffuse large B-cell lymphoma. Nat Rev Clin Oncol. 2021;18(11):727-747. doi:10.1038/s41571-021-00538-4.

12. Schmitz R, Wright GW, Huang DW, et al. Genetic subtypes of diffuse large B-cell lymphoma determined by gene expression and mutations. N Engl J Med. 2018;378(15):1396-1407. doi:10.1056/NEJMoa1801445.

13. Armitage JO. Staging non-Hodgkin lymphoma. CA Cancer J Clin. 2005;55(6):368-376.

14. Jin J, Ji D, Xia Z, Xue K, Zhang Q, Liu Y, et al. Four cycles of R-CHOP followed by two applications of rituximab based on negative interim PET/CT: an analysis of a prospective trial. BMC Cancer. 2022;22:403. doi:10.1186/s12885-022-09486-4.

15. Nowakowski GS, Johnston PB, Cerhan JR, Habermann TM, Witzig TE, Ansell SM, et al. Outcomes in patients with late relapse of diffuse large B-cell lymphoma: a systematic review and meta-analysis. Transplant Cell Ther. 2025. doi:10.1016/j.jtct.2025.06.041.

16. Weiss J, Carty SA, Karimi YH. Molecular pathways and targeted therapies in relapsed/refractory diffuse large B-cell lymphoma (DLBCL). Cancers (Basel). 2025;17(14):2314. doi:10.3390/cancers17142314.

17. Shaw J, Chakraborty A, Nag A, Chattopadhyay A, Dasgupta AK, Bhattacharyya M. Intracellular iron overload leading to DNA damage of lymphocytes and immune dysfunction in thalassemia major patients. Eur J Haematol. 2017;99(4):399-408. doi:10.1111/ejh.12936.

18. Palomo-Colli MA, Zapata-Tarres M, Castelán-Martínez OD, Juárez-Villegas LE, Córdova-Hurtado LP. A strategy for the clinical remission of acute lymphoblastic leukemia elicited by treatment of beta-thalassemia major: a case report. Mol Clin Oncol. 2018;8(2):375-377. doi:10.3892/mco.2017.1533.

19. Hodroj MH, Bou-Fakhredin R, Nour-Eldine W, Noureldine HA, Noureldine MHA, Taher AT. Thalassemia and malignancy: an emerging concern? Blood Rev. 2019;37:100585. doi:10.1016/j.blre.2019.06.002.

20. Cappellini MD, Motta I. New therapeutic targets in transfusion-dependent and non-transfusion-dependent thalassemia. Hematology Am Soc Hematol Educ Program. 2017;2017(1):278-285. doi:10.1182/asheducation-2017.1.278.

21. Goh SC, Ngai S. The clinical challenge of relapsed diffuse large B-cell lymphoma with disseminated infection. Radiol Case Rep. 2023;18(9):3046-3053. doi:10.1016/j.radcr.2023.05.068.

22. Abdel-Hakeem SS, Ahmed AM, Amine MAF, Farouk BR, Yassin EH, Badary FAM. Clinicopathological features of relapsed diffuse large B-cell lymphoma: South Egypt Cancer Institute experience. SECI Oncology Journal. 2021;9(4):192-197. doi:10.21608/secioj.2021.194488.

23. Alavi S, Safari A, Sadeghi E, Amiri S. Hematological malignancies complicating beta-thalassemia syndromes: a single-center experience. Blood Res. 2013;48(2):149-151. doi:10.5045/br.2013.48.2.149.

24. Garcia-Sancho AM, Cabero A, Gutierrez NC. Treatment of relapsed or refractory diffuse large B-cell lymphoma: new approved options. J Clin Med. 2023;13(1):70. doi:10.3390/jcm13010070.

25. Shi Y, Xu Y, Shen H, Jin J, Tong H, Xie W. Advances in biology, diagnosis and treatment of DLBCL. Ann Hematol. 2024;103(9):3315-3333. doi:10.1007/s00277-024-05880-z.

Author's Statement

The authors declared that all the images and figures in this manuscript is/are author's own work and/or has obtained necessary permission to re-use the content from the authors and publisher of respective materials.

(Stephanie Marisca)