Turk J Hematol 2025;42:158-160

Successful Treatment of Childhood Hodgkin Lymphoma and Secondary Myelofibrosis Resistant to Intensive Therapy, Including Allogeneic Transplantation

Tedaviye Dirençli Hodgkin Lenfoma ve Sekonder Miyelofibrozisin Allojenik Transplantasyonu İçeren Başarılı Tedavisi

Deniz Koçak Göl[1], Veysel Gök[1], Alper Özcan[1], Ebru Yılmaz[1], Ekrem Ünal[1,2], Ümmühan Abdülrezzak[3], Özlem Canöz[4], Musa Karakükcü[1]

[1]*Erciyes University Faculty of Medicine, Department of Pediatrics, Division of Hematology and Oncology, Kayseri, Türkiye*
[2]*Hasan Kalyoncu University and Medical Point Hospital, Faculty of Health Sciences, Department of Nursing, Gaziantep, Türkiye*
[3]*Erciyes University Faculty of Medicine, Department of Nuclear Medicine, Kayseri, Türkiye*
[4]*Erciyes University Faculty of Medicine, Department of Pathology, Kayseri, Türkiye*

To the Editor,

Myelofibrosis is a rare complication in children with Hodgkin lymphoma (HL) and presents significant treatment challenges due to the disease's low tolerance to chemotherapy. This condition often necessitates dose reductions, which can negatively impact patient outcomes and prognosis [1,2].

An 8-year-old boy was admitted to the Pediatric Hematology and Oncology Outpatient Clinic at Erciyes University with a 6-month history of malaise, anorexia, weight loss, and nocturnal leg pain. Physical examination revealed dyspnea, tachycardia, supraclavicular lymphadenopathy of 3 cm, and hepatosplenomegaly. Laboratory tests showed leukopenia (white blood cell count: 1940/mm^3), neutropenia (absolute neutrophil count: 950/mm^3), lymphopenia (absolute lymphocyte count: 740/mm^3), thrombocytopenia (platelet count: 85,000/mm^3), and severe anemia (hemoglobin: 4.9 g/dL). His erythrocyte sedimentation rate was elevated at 83 mm/h. Thoracic computed tomography revealed multiple mediastinal lymph nodes.

Axillary lymph node excision and bone marrow biopsy were performed based on clinical findings. Histopathological examination of the excised axillary lymph node and bone marrow biopsy specimen confirmed a diagnosis of the mixed-cell type of classical HL. Additionally, the bone marrow biopsy revealed the presence of myelofibrosis (Figure 1). A positron emission tomography-computed tomography (PET-CT) scan showed diffuse conglomerate lesions with hypermetabolic activity in the mediastinal lymph nodes as well as osteosclerotic lesions in cortical bones. Screening results indicated diffuse nodal and extranodal involvement of lymphoma as the primary disease, affecting the liver, spleen, bones, and bone marrow (Figure 2).

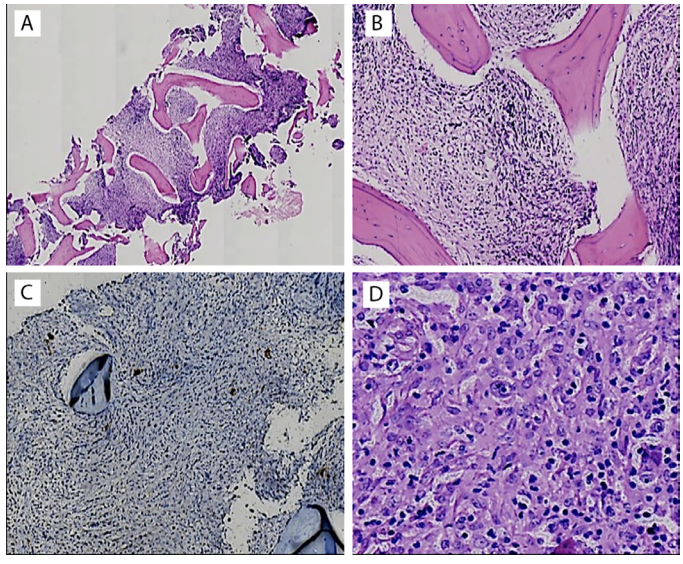

Figure 1. A) Bone marrow biopsy showing extensive fibrosis and hypercellularity (H&E stain, 100^x). B) Higher magnification of the bone marrow biopsy material revealed fibroblastic proliferation in infiltration areas together with rare atypical cells (H&E stain, 200^x). C) Lymph node biopsy showing CD30-positive transformed cells (immunoperoxidase stain, 200^x). D) Lymph node biopsy depicting a mixed inflammatory milieu with single-celled inflammatory cells, including Reed-Sternberg and mononuclear Hodgkin cells (H&E stain, 200^x).

H&E: Hematoxylin and eosin.

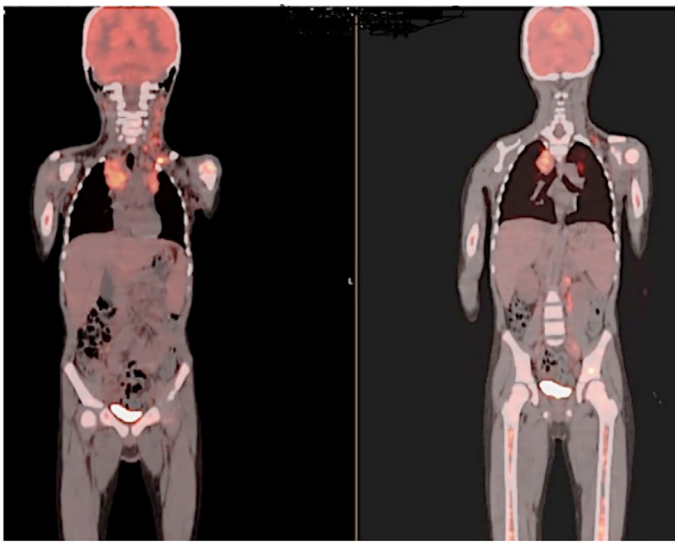

Figure 2. Illustration of the correlation between the clinical manifestations of lymphoma and the distribution of affected lymph nodes within the lymphatic system and other organs.

Whole-exome analysis performed on a peripheral blood sample and *JAK2*, *CALR*, and *MPL* pathological variant studies performed on a bone marrow aspiration sample yielded normal results. The patient was diagnosed with HL of stage IVB and secondary myelofibrosis. Treatment included eight cycles of chemotherapy, with four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine followed by four cycles of cyclophosphamide, vincristine, procarbazine, and prednisone. Post-treatment bone marrow analysis was normal.

Four months after completing chemotherapy, the patient presented with persistent fever and lymph node swelling. A biopsy of a suspected cervical lymph node confirmed the recurrence of HL. The patient received two cycles of a combination regimen comprising brentuximab and etoposide, carboplatin, and ifosfamide. However, PET-CT imaging showed no response to treatment. Consequently, an alternative two-cycle regimen containing brentuximab, prednisolone, ifosfamide, vinorelbine, and gemcitabine was initiated.

Given the diagnosis of relapsed/refractory HL and the impossibility of collecting autologous stem cells, the patient underwent haploidentical transplantation from his healthy mother. The procedure involved cyclophosphamide after the transplant following whole-body irradiation and a conditioning regimen with fludarabine and rituximab. On day 54 after the transplant, PET-CT revealed lymphoma progression despite the achievement of complete chimerism.

Progression was confirmed and four cycles of dexamethasone, gemcitabine, and vinorelbine were administered. Post-treatment PET-CT demonstrated a complete metabolic response and the follow-up bone marrow biopsy showed normal findings. At 10 months after the transplant, the patient remains in remission with complete chimerism.

A literature review indicates that cases of HL associated with myelofibrosis are relatively rare. The first documented case in a pediatric patient was reported in 1900, involving a patient who developed myelofibrosis following pancytopenia treatment [3]. Among 10 patients with a follow-up duration of approximately 16 years, Arya et al. [1] reported that 2 patients had primary myelofibrosis and 8 had secondary myelofibrosis. Notably, only 4 of those 8 patients had HL, with Reed-Sternberg cells (RSCs) detected in the biopsy of just one case. No RSCs were observed in the bone marrow of the other patients [1].

In the present case of HL with secondary myelofibrosis, RSCs were detected by bone marrow biopsy. Another study reported that median survival was 9-11 years in patients without bone marrow involvement but it was reduced to 3-4 years in those with bone marrow involvement [4]. The present case involved pancytopenia, bone marrow myelofibrosis, and RSC invasion of the bone marrow.

Although the relationship between HL and myelofibrosis is not fully understood, HL is recognized as a rare cause of myelofibrosis [5]. The pathogenesis of fibrotic changes in the bone marrow of patients with HL is a subject of increasing medical interest. Fibroblasts play a critical role in stromal proliferation, primarily driven by platelet-derived growth factor (PDGF), which is converted into transforming growth factor-beta (TGF-β). Additionally, fibroblasts are stimulated by essential fibroblast growth factors and other cytokines [6]. PDGF promotes fibroblast proliferation, while TGF-β, fibronectin, and type I and III collagen proteins contribute to the synthesis and accumulation of extracellular matrix components [7]. Elevated plasma TGF-β levels have also been reported in patients with malignant fibrous histiocytoma, correlating with peripheral T-cells, cytotoxic T-cells, and periductal lymphoma infiltrates [8,9].

A literature review suggests that the co-occurrence of HL and myelofibrosis in our patient is a unique clinical scenario. Notably, this is the first documented instance of pediatric bone marrow transplantation in such a context.

In conclusion, pediatric myelofibrosis should be considered as a differential diagnosis in children with HL. Further research is needed to better understand the pathogenesis of myelofibrosis and to identify the immunological abnormalities associated with lymphomas. Such studies will be crucial for developing more effective and targeted therapeutic strategies for these coexisting conditions.

Keywords: Allogeneic transplantation, Hodgkin lymphoma, Myelofibrosis

Anahtar Sözcükler: Allojenik transplantasyon, Hodgkin lenfoma, Miyelofibrozis

Ethics

Informed Consent: Informed consent was obtained from all individual participants included in the study or their parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.K.G., V.G., A.Ö., E.Y., E.Ü., M.K.; Concept: D.K.G., A.Ö., E.Ü., Ü.A., Ö.C.; Design: D.K.G., A.Ö., Ü.A., Ö.C., M.K.; Data Collection or Processing: D.K.G., V.G., Ö.C., Ü.A.; Analysis or Interpretation: D.K.G., V.G., A.Ö., E.Y., E.Ü., Ü.A., Ö.C., M.K.; Literature Search: D.K.G., V.G., A.Ö., E.Y., M.K.; Writing: D.K.G., V.G., A.Ö., E.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Arya LS, Thavraj V, Chandra D, Kulkarni KP, Kumar R, Dawar R. Myelofibrosis in children: experience at a single tertiary care center in India. Pediatr Hematol Oncol. 2010;27:355-362.

2. Flerlage JE, Hiniker SM, Armenian S, Benya EC, Bobbey AJ, Chang V, Cooper S, Coulter DW, Cuglievan B, Hoppe BS, Isenalumhe L, Kelly K, Kersun L, Lamble AJ, Larrier NA, Magee J, Oduro K, Pacheco M, Price AP, Roberts KB, Smith CM, Sohani AR, Trovillion EM, Walling E, Xavier AC, Burns JL, Campbell M. Pediatric Hodgkin lymphoma, version 3.2021. J Natl Compr Canc Netw. 2021;19:733-754.

3. Carroll WL, Berberich FR, Glader BE. Pancytopenia with myelofibrosis. An unusual presentation of childhood Hodgkin's disease. Clin Pediatr (Phila). 1986;25:106-108.

4. Fu R, Yu H, Wu YH, Liu H, Shao ZH. Hodgkin's lymphoma associated with myelofibrosis: a case report. Oncol Lett. 2015;10:1551-1554.

5. Gabali AM, Jazaerly T, Chang CC, Cleveland R, Kass L. Simultaneous hepatosplenic T-cell lymphoma and myelofibrosis. Avicenna J Med. 2014;4:34-36.

6. Tefferi A. Myelofibrosis with myeloid metaplasia. N Engl J Med. 2000;342:1255-1265.

7. Charni Chaabane S, Coomans de Brachène A, Essaghir A, Velghe A, Lo Re S, Stockis J, Lucas S, Khachigian LM, Huaux F, Demoulin JB. PDGF-D expression is down-regulated by TGFB in fibroblasts. PLoS One. 2014;9:e108656.

8. Kadin ME, Agnarsson BA, Ellingsworth LR, Newcom SR. Immunohistochemical evidence of a role for transforming growth factor beta in the pathogenesis of nodular sclerosing Hodgkin's disease. Am J Pathol. 1990;136:1209-1214.

9. Newcom SR, Tagra KK. High molecular weight transforming growth factor beta is excreted in the urine in active nodular sclerosing Hodgkin's disease. Cancer Res. 1992;52:6768-6773.

Address for Correspondence/Yazışma Adresi: Deniz Koçak Göl, M.D., Erciyes University Faculty of Medicine, Department of Pediatrics, Division of Hematology and Oncology, Kayseri, Türkiye
E-mail: deniz_3858@hotmail.com **ORCID:** orcid.org/0000-0003-1853-3780

Received/Geliş tarihi: February 4, 2025
Accepted/Kabul tarihi: April 7, 2025
DOI: 10.4274/tjh.galenos.2025.2025.0044