Role of Hypogammaglobulinemia in Invasive Fungal Infections in Children May Be Overlooked

Çocuklarda Görülen İnvaziv Fungal Enfeksiyonlarda Hipogamaglobülineminin Rolü Gözden Kaçırılabilir

Jingnan Zhu[1#], Fuping Shen[2#], Yun Cheng[3], Jinlin Liu[4]

[1]*Shangyu People's Hospital of Shaoxing, Department of Clinical Laboratory, Shaoxing, China*
[2]*Zhejiang Chinese Medical University, School of Medical Technology and Information Engineering, Hangzhou, Zhejiang, China*
[3]*Yan'an Hospital of Kunming City, Department of Laboratory Medicine, Kunming, China*
[4]*South China Hospital, Health Science Center, Department of Clinical Laboratory, Shenzhen University, Shenzhen, China*
[#]*These authors contributed equally to this work.*

To the Editor,

We attentively read the paper by Sezgin Evim et al. [1] recently published in Turkish Journal of Hematology. They investigated the clinical features and prognosis of invasive fungal infections (IFIs) in children with leukemia and found that IFIs significantly increased mortality and were poor prognostic factors in children with hematologic malignancies [1]. Therefore, physicians must be aware of these rare but potentially lethal infections. Furthermore, Sezgin Evim et al. [1] also revealed that prolonged severe neutropenia was one of the major risk factors for the incidence of IFI, and this conclusion was reached based on data from 307 children with acute lymphoblastic leukemia (ALL, n=238), acute myeloid leukemia (AML, n=51), and relapsed leukemia (n=18).

However, in this letter, we highlight another important factor that may be overlooked regarding the prognosis of IFIs in children with leukemia, which is hypogammaglobulinemia. Importantly, patients with ALL have lymphocyte deficits, resulting in hypogammaglobulinemia and impaired cell-mediated immunity predisposing them to bacterial, viral, and fungal infections [2]. Chemotherapy often aggravates those deficits, resulting in prolonged periods of severe neutropenia that further increase the risk of infection [2]. Recently, Jowik et al. [3] found that a majority of ALL patients required immunoglobulin replacement during chemotherapy. Moreover, Lange et al. [4] found that hypogammaglobulinemia is a poorly described complication of chemotherapy in young adults and adolescents with ALL. The majority of treated ALL patients had hypogammaglobulinemia, and infectious events during maintenance and febrile neutropenia episodes during the course of treatment occurred more frequently in patients with hypogammaglobulinemia compared to patients with normal immunoglobulin G (IgG) levels [4].

However, hypogammaglobulinemia (e.g., IgG of <5 g/L) or dynamic polyclonal Ig levels before or during the IFIs were not documented or investigated in the study by Sezgin Evim et al. [1], which may mean that the role of hypogammaglobulinemia in the risk of IFIs was overlooked for these childhood leukemia patients. Hypogammaglobulinemia is the hallmark of secondary immunodeficiency and increased infection risk [2]. Therefore, monitoring the polyclonal Ig levels before or during IFIs and calculating the cutoff Ig values for IFI risk could further enhance the surveillance of IFI risk in childhood leukemia patients. Furthermore, using Ig replacement therapy for these potential cases of hypogammaglobulinemia with IFI risk factors could be a feasible method for the prevention of IFIs, significantly reducing the mortality of these children with leukemia [2]. Such supportive care is critical for the quality of life and longer survival of children with acute leukemia [5,6]. However, these hypotheses should be more broadly discussed and more large studies are warranted to validate the effects of hypogammaglobulinemia or other polyclonal Ig levels on IFIs among childhood leukemia patients.

Keywords: Hypogammaglobulinemia, Invasive fungal infections, Leukemia

Anahtar Sözcükler: Hipogamaglobülinemi, İnvaziv fungal enfeksiyon, Lösemi

Authorship Contributions

Concept: J.Z., F.S., Y.C., J.L.; Design: J.Z., F.S., Y.C., J.L.; Data Collection or Processing: J.Z., F.S., Y.C., J.L.; Analysis or Interpretation: J.Z., F.S., Y.C., J.L.; Literature Search: J.Z., F.S., Y.C., J.L.; Writing: J.Z., F.S., Y.C., J.L.

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. Sezgin Evim M, Tüfekçi Ö, Baytan B, Ören H, Çelebi S, Ener B, Üstün Elmas K, Yılmaz Ş, Erdem M, Hacımustafaoğlu MK, Güneş AM. Invasive fungal infections in children with leukemia: clinical features and prognosis. Turk J Hematol 2022;39:94-102.
2. Logan C, Koura D, Taplitz R. Updates in infection risk and management in acute leukemia. Hematology Am Soc Hematol Educ Program 2020;2020:135-139.
3. Jowik K, Marciniak-Stępak P, Derwich K. Clinical use of polyvalent intravenous immunoglobulins during intensive polichemotherapy in children with acute lymphoblastic leukemia. Retrospective single-centre study. Minerva Pediatr (in press). doi: 10.23736/S0026-4946.19.05494-X.
4. Lange CS, Rahrig A, Althouse SK, Nelson RP, Batra S. Hypogammaglobulinemia in adolescents and young adults with acute lymphoblastic leukemia. J Adolesc Young Adult Oncol 2020;9:687-692.
5. Srivastava S, Wood P. Secondary antibody deficiency - causes and approach to diagnosis. Clin Med (Lond) 2016;16:571-576.
6. Patel SY, Carbone J, Jolles S. The expanding field of secondary antibody deficiency: causes, diagnosis, and management. Front Immunol 2019;10:33.

Reply to Letter to the Editor

We thank Zhu et al. for their interest in our article.

Intravenous immunoglobulin therapy and screening for hypogammaglobulinemia are routinely performed for patients undergoing hematopoietic stem cell transplantation and receiving targeted therapy such as CAR-T-cells, rituximab, or blinatumomab. However, the effect of routine Ig screening and its impact on mortality and morbidity in ALL and AML treatment has not been shown in any evidence-based studies and it has been found to be costly. It is not routinely recommended by the ECIL or EORTC/MSG guidelines. Patients with frequent infections can be screened and treated appropriately if their IgG levels are found to be low. In our series, we appropriately treated our patients who had frequent infections and low IgG levels (<500 mg/dL).

Best regards,

Melike Sezgin Evim, Özlem Tüfekçi, Birol Baytan, Hale Ören, Solmaz Çelebi, Beyza Ener, Kevser Üstün Elmas, Şebnem Yılmaz, Melek Erdem, Mustafa Kemal Hacımustafaoğlu, Adalet Meral Güneş

Address for Correspondence/Yazışma Adresi: Yun Cheng, M.D., Yan'an Hospital of Kunming City, Department of Laboratory Medicine, Kunming, China
Jinlin Liu, MD, PhD., South China Hospital, Health Science Center, Department of Clinical Laboratory, Shenzhen University, Shenzhen, China
E-mail : 625619184@qq.com / liujinlinhz@163.com ORCID: orcid.org/0000-0002-9408-0368

Received/Geliş tarihi: October 29, 2022
Accepted/Kabul tarihi: November 10, 2022

DOI: 10.4274/tjh.galenos.2022.2022.0468