LETTER TO THE EDITOR

Turk J Hematol 2025;42:324-326

Engraftment Syndrome Following Autologous Stem Cell Transplantation in a Patient Receiving Nivolumab as Salvage Therapy

Nivolumab ile Kurtarma Tedavisi Uygulanan Bir Hastada Otolog Kök Hücre Nakli Sonrasında Gelişen Engrafman Sendromu

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To the Editor,

Engraftment syndrome (ES) is a clinical entity characterized by fever, rash, diarrhea, pulmonary infiltrates, edema, weight gain, and organ dysfunction, typically occurring within 96 hours before or after neutrophil recovery following autologous hematopoietic stem cell transplantation (ASCT). While ES is more frequently observed after ASCT in patients with multiple myeloma or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes), its incidence remains relatively low among patients with lymphoma [1,2,3]. The reported incidence of ES has varied considerably across studies, largely depending on the diagnostic criteria employed. ES rates range from 7% to 21% based on classical definitions, whereas some studies reported rates as high as 59% when only fever and rash were considered [1]. Maiolino et al. [2] later proposed the broader criteria of non-infectious fever plus any of rash, pulmonary infiltrates, or diarrhea and reported an incidence rate of 20%, with higher risk among patients diagnosed with conditions other than Hodgkin lymphoma (HL). Recent data have further highlighted the variation in ES incidence across different hematological malignancies. In a 2024 cohort, ES was diagnosed by expert consensus in 50.9% of patients with multiple myeloma compared to only 23.9% of those with lymphoma, underscoring a substantially lower risk of ES among patients with lymphoma [4].

Emerging evidence suggests that the expanding use of immune checkpoint inhibitors (ICIs), particularly PD-1/PD-L1 inhibitors, may alter the post-transplant immune milieu and contribute to an increased incidence of ES in patients with classical HL. Several studies have reported a notably higher incidence of ES in ICI-exposed HL patients undergoing ASCT, with rates ranging from approximately 27% to 48% across single- and multi-center cohorts [5,6]. This evolving therapeutic landscape comes with new clinical challenges, including the development of ES or ES-like inflammatory manifestations following ASCT.

We report the case of a 60-year-old man with classical HL refractory after three lines of chemotherapy, who achieved complete remission with nivolumab, a PD-1 inhibitor, before undergoing ASCT. ASCT was performed 15 days after the last dose of nivolumab. On post-transplant day 5, the patient developed a diffuse, completely blanchable, pink-to-red erythematous rash initially involving the face and arms, which subsequently spread to the trunk and lower extremities. The lesions coalesced into broad patches and plaques (Figure 1) and were accompanied by a high-grade fever reaching 40 °C. Within 24 hours, the patient experienced rapid weight gain of approximately 6 kg, along with generalized subcutaneous edema and ascites, without any clinical evidence of cardiac dysfunction or hypoxemia. The onset of rash and fever coincided with neutrophil engraftment (Figure 2). At the onset of fever, empirical piperacillin-tazobactam was initiated according to the institutional febrile neutropenia protocol. A posteroanterior chest radiograph revealed no evidence of pulmonary infiltrates or consolidation. Although C-reactive protein levels were elevated, serum procalcitonin remained within normal limits and all microbiological cultures were negative, supporting a non-infectious inflammatory etiology. Veno-occlusive disease/sinusoidal obstruction syndrome was also excluded based on normal liver function tests and the absence of hepatomegaly or right upper quadrant tenderness. No alternative causes, such as infection, drug reaction, or disease relapse, were identified. Given the constellation of clinical findings, ES was strongly suspected and corticosteroid therapy was initiated as the primary treatment. Diuretics were co-administered for a short duration to manage fluid overload. Rapid clinical improvement

was observed following corticosteroid administration, with resolution of skin lesions and generalized edema. The clinical presentation fulfilled both the Spitzer and the Maiolino criteria for the diagnosis of ES [1,2]. Methylprednisolone was continued for approximately 15 days, resulting in complete resolution of the patient's symptoms. He was subsequently discharged in good clinical condition.

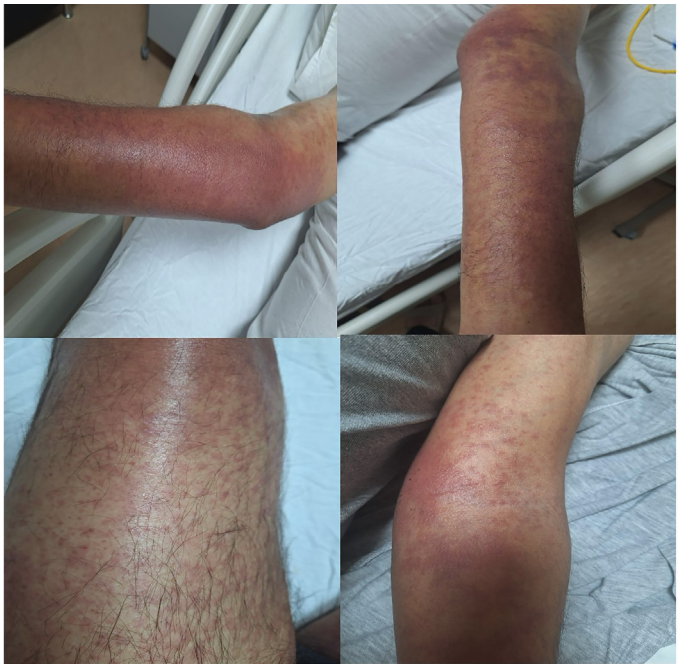

Figure 1. On day 5 following the transplant, the patient developed a diffuse, completely blanchable, pink-to-red erythematous rash initially involving the face and arms, which subsequently spread to the trunk and lower extremities. The lesions coalesced into broad patches and plaques.

The increasing use of ICIs, particularly anti-PD-1 agents, in HL has raised concerns regarding immune-related complications following ASCT. Several studies have demonstrated that prior ICI therapy may predispose patients to ES or engraftment-like inflammatory events. In a single-center study, patients receiving ICIs before ASCT had significantly higher rates of late-onset non-infectious fever or hypotension requiring fluid resuscitation [7]. Other analyses have confirmed the occurrence of ES with high frequency among HL patients treated with ICIs prior to ASCT, with fever, rash, pulmonary infiltrates, and diarrhea being common features [5,6,8]. Although only a minority of cases fulfilled the traditional ES diagnostic criteria, non-infectious inflammatory findings were prevalent [4,5]. Early administration of corticosteroids has been associated with symptom resolution and favorable outcomes [5,6,8,9]. ICIs may stimulate an exaggerated cytokine-mediated inflammatory response during neutrophil recovery, underscoring the need for vigilant monitoring and early intervention following ASCT. Our case underscores the importance of maintaining high clinical suspicion for ES in ICI-treated patients undergoing ASCT. Timely corticosteroid intervention is critical to prevent complications. As the use of ICIs becomes more widespread in HL and other hematologic malignancies, it is imperative to better understand their impact on transplant-related outcomes and immune-mediated complications such as ES.

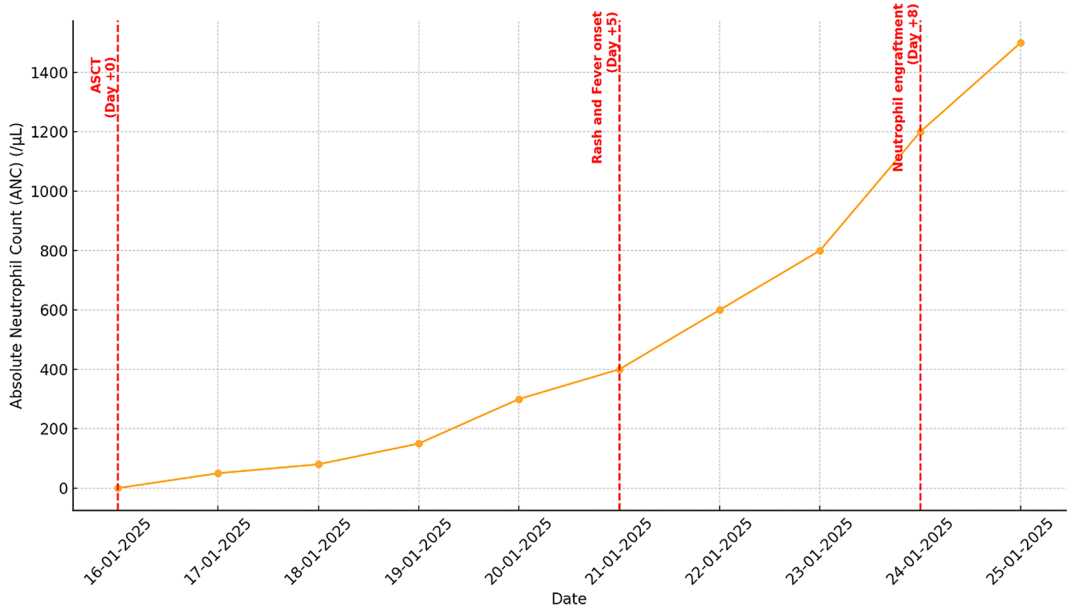

Figure 2. The onset of the patient's rash and fever coincided with neutrophil engraftment.

ASCT: Autologous hematopoietic stem cell transplantation.

Keywords: Engraftment syndrome, Autologous stem cell transplantation, Immune checkpoint inhibitors

Anahtar Sözcükler: Engrafman sendromu, Otolog kök hücre nakli, İmmün kontrol noktası inhibitörleri

Ethics

Informed Consent: The patient provided written informed consent for the publication of all clinical details and images related to this case.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.T.D., P.T., A.G., A.H., Ö.M.; Concept: E.T.D., P.T., A.G., A.H., Ö.M.; Design: E.T.D., P.T., A.G., A.H., Ö.M.; Data Collection and Processing: E.T.D., P.T.; Analysis or Interpretation: E.T.D.; Literature Search: E.T.D.; Writing: E.T.D., Ö.M.

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

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

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Received/Geliş tarihi: April 29, 2025
Accepted/Kabul tarihi: June 11, 2025
Epub: June 11, 2025
DOI: 10.4274/tjh.galenos.2025.2025.0166