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Allogeneic Hematopoietic Stem Cell Transplantation in Hemophagocytic Lymphohistiocytosis: Therapeutic Role and Trigger of Post-Transplant Hyperinflammation

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To the Editor.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has a contradictory role in the treatment course of hemophagocytic lymphohistiocytosis (HLH). Although allo-HSCT represents a curative potential in familial (primary) HLH (pHLH), it may serve as a trigger for life-threatening secondary HLH (sHLH) in the post-transplant setting.[1,2] As a diagnostic and therapeutic challenge, this dualism within the same framework deserves attention to sustain early diagnosis and prompt treatment. Here, we report two cases that exemplify this paradox to elucidate the underlying immunological mechanisms and improve diagnostic and therapeutic approaches.

A 62-year-old male with a diagnosis of post-essential thrombocythemia myelofibrosis underwent haploidentical allo-HSCT with a conditioning regimen consisting of fludarabine, melphalan, and total body irradiation (TBI). Cyclosporine, mycophenolate mofetil, and post-transplant cyclophosphamide were used for graft-versus-host disease (GvHD) prophylaxis. On day +40, he presented with fever, confusion, and rapidly progressive multiorgan dysfunction. Splenomegaly was reported on physical examination. Laboratory evaluation was remarkable with severe pancytopenia, transaminitis [aspartate aminotransferase (AST): 696 U/L, alanine aminotransferase (ALT): 501 U/L], acute renal injury (creatinine: 2.64 mg/dL), elevated lactate level (6.7 mmol/L), and hyperbilirubinemia (total bilirubin: 2.98 mg/dL) along with extremely increased procalcitonin (PCT: 309 ng/mL), ferritin (65,000 ng/mL) and C-reactive protein levels (133 mg/L). The HScore was compatible with a 99% probability of HLH (**Table 1**).[3] Bone marrow examination could not be performed because of his poor clinical condition and concomitant coagulopathy. As microbiological assessments, including throat, sputum, urine, stool, bloodstream, and catheter cultures, were negative, empirical meropenem and teicoplanin were started to provide broad-spectrum antibacterial coverage. Viral tests, including cytomegalovirus, Epstein-Barr virus (EBV), adenovirus, and respiratory viruses, were negative. Serum galactomannan was within normal limits, and chest computed tomography (CT) did not demonstrate any pulmonary infiltration.

The combination of extreme PCT elevation and multiorgan failure generated a compelling but ultimately misleading display of septic shock. Because transplant-associated thrombotic microangiopathy (TA-TMA) should have been considered in the differential diagnosis, cyclosporine was withheld, and empirical therapeutic plasma exchange was initiated while awaiting confirmation of normal ADAMTS13 activity. In addition, dexamethasone, ruxolitinib (10 mg twice daily with dose escalation up to 20 mg twice daily, for 40 days), intravenous immunoglobulin (IVIG), and broad-spectrum antibiotics were initiated on day +41, within 24 hours of presentation, with intensive care support. Hemodynamic stabilization was maintained within 48 hours. Vasopressor support was discontinued on day 2, while ferritin levels declined sharply by day 7. Procalcitonin levels returned to the normal range without an infectious aetiology ever identified (**Figure 1**). Based on the combination of clinical and laboratory features, along with the early and dramatic treatment response, probable post-transplant sHLH was considered the most likely diagnosis in this case.

The second case was a 35-year-old male who presented with recurrent fever, splenomegaly, and pancytopenia (hemoglobin: 10.4 g/dL, platelets: 97,000/μL, leukocytes: 2,200/μL). Laboratory tests yielded hyperferritinemia (4,230 ng/mL), hypertriglyceridemia (403 mg/dL), elevated AST level (209 U/L), and severe hypofibrinogenemia (67 mg/dL).

Table 1. HScore Characteristics.

Parameter	Case 1	Pts	Case 2	Pts
Immunosuppression	Cyclosporine	18	None	0
Fever >38.4°C	Present	33	Present	33
Organomegaly	Preexisting splenomegaly (related to myelofibrosis, not scored)	0	Splenomegaly	23
Cytopenia	3 lineages	34	2 lineages	24
Ferritin (ng/mL)	> 65,000	50	4,230	35
Triglyceride (mg/dL)	155 (1.75 mmol/L)	44	403 (4.55 mmol/L)	64
Fibrinogen (mg/dL)	168 (1.68 g/L)	30	67 (0.67 g/L)	30
Aspartate aminotransferase (U/L)	696	19	209	19
Hemophagocytosis (Bone marrow)	Not assessed	0	Absent	0
Total HScore		228 (~99%)		228 (~99%)

HScore calculated per Fardet et al. (Arthritis Rheumatol. 2014). Pts: points.

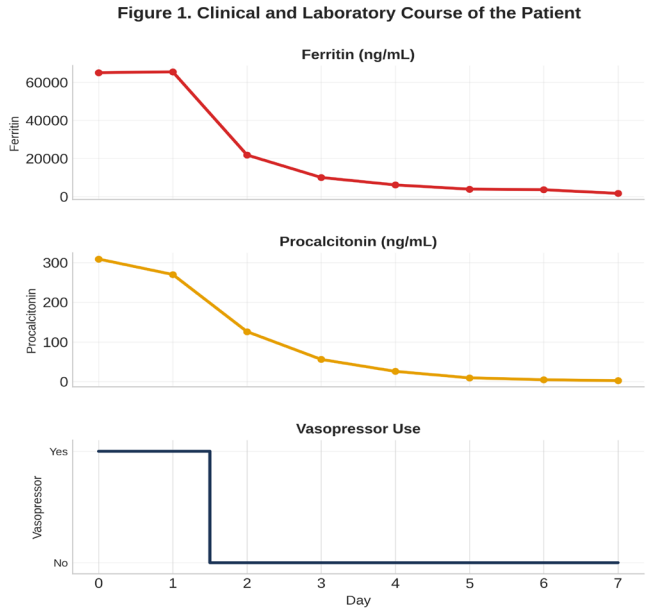

Figure 1. Clinical and laboratory course of Case 1 following the initiation of HLH-directed therapy (dexamethasone, ruxolitinib, IVIG, and plasma exchange). Ferritin (upper panel) declined from greater than 65,000 ng/mL to approximately 1,500 ng/mL over 7 days. Procalcitonin (middle panel) normalized in parallel from 309 ng/mL to less than 10 ng/mL without any microbiological growth identified, supporting a predominantly cytokine-driven hyperinflammatory state. Vasopressor support (lower panel) was discontinued on day 2. IVIG: intravenous immunoglobulin.

Although bone marrow biopsy did not reveal hemophagocytosis features, HScore was calculated to be 228, which was highly compatible with a diagnosis of HLH (**Table 1**).[3] After a comprehensive work-up to exclude secondary causes, a heterozygous UNC13D variant (c.766C>G; p.Arg256Gly, exon 10, classified as variant of uncertain significance per ACMG 2015 criteria) was determined on genetic analysis. The same variant was detected in his asymptomatic sibling, which was consistent with a germline predisposition. A heterozygous variant of uncertain significance does not by itself establish pHLH, since biallelic variants were not identified and a functional NK-cell degranulation assay was not available. Nevertheless, based on the distinctive clinical characteristics including young age, refractory disease course, elevated HScore, and underlying genetic predisposition, the treatment schedule was implemented with etoposide and dexamethasone as HLH-targeted therapy. Due to the delay in donor selection for allo-HSCT, disease control was gradually lost during the treatment course. Consequently, he received ruxolitinib (up to 25 mg twice daily, continued for approximately nine months) in combination with dexamethasone as a bridging strategy to transplantation.[4] Given the absence of a matched sibling or 10/10 matched unrelated donor, haploidentical allo-HSCT from a genetically normal second-degree cousin was performed after conditioning with treosulfan, fludarabine, and TBI. Cyclosporine, mycophenolate mofetil, rabbit antithymocyte globulin (ATG), and post-transplant cyclophosphamide were used for GvHD prophylaxis. Mesenchymal stem cell infusions were administered on days 0 and +7 to prevent graft rejection. Successful hematopoietic engraftment was achieved with full donor chimerism.

On day +48, EBV reactivation was detected (29,000 copies/mL), rising to 51,000 copies/mL by day +76 after four weekly doses of rituximab (375 mg/m²). Positron emission tomography-computed tomography (PET-CT) revealed a focal hypermetabolic splenic lesion [maximum standardized uptake value (SUVmax): 14.8], which was consistent with probable EBV-associated post-transplant lymphoproliferative disorder (PTLD)

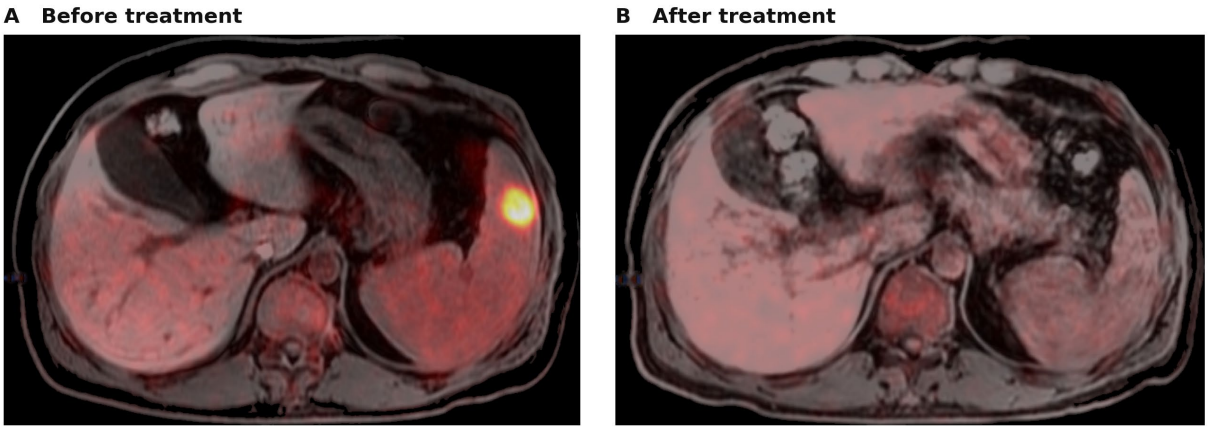

Figure 2. PET-CT images of Case 2. (**A**) Before treatment: focal hypermetabolic splenic lesion (SUVmax 14.8) consistent with EBV-associated post-transplant lymphoproliferative disorder. (**B**) After rituximab and donor lymphocyte infusion: almost complete resolution of splenic FDG uptake, corresponding to EBV clearance and clinical remission. EBV: Epstein-Barr virus; FDG: fluorodeoxyglucose; PET-CT: positron emission tomography-computed tomography; SUVmax: maximum standardized uptake value.

(**Figure 2A**).[5] Splenic biopsy, which showed necrosis on histopathological examination, was performed after two rituximab doses due to refractory thrombocytopenia. Consequently, the diagnosis of PTLD, which could not be confirmed by tissue biopsy, was mainly based on EBV viral load and imaging studies. Additionally, donor lymphocyte infusion (DLI) with a $CD3^+$ cell dose of 5×10^6/kg was administered on day +78. EBV viral load was undetectable within 45 days, and subsequent PET-CT indicated almost complete resolution of splenic fluorodeoxyglucose (FDG) uptake (**Figure 2B**).[5] After DLI, he developed grade 2 steroid-refractory acute skin GvHD on day +114, which was successfully treated by ruxolitinib 10 mg twice daily, continued on a tapering schedule. On day +140, the patient remained in sustained remission regarding HLH and EBV-associated PTLD, with full donor chimerism.

These two cases illustrate the distinct immunological role of allo-HSCT in HLH. In Case 2, allo-HSCT achieved durable disease control in a patient with refractory HLH and a possible genetic predisposition. In contrast, several factors, including immune dysregulation, viral reactivation, and endothelial injury, can trigger sHLH in the course of a post-transplant immunosuppressive setting.[2,6,7] Overlapping mechanisms such as sepsis, TA-TMA, and GvHD may cause difficulties in the differential diagnosis, which may eventually result in high mortality rates.[6,7] Notably, the same post-transplant immune dysregulation may manifest as lymphoproliferative rather than hyperinflammatory complications, as represented by EBV-associated PTLD in Case 2.

Extremely high levels of PCT were observed in Case 1. Although PCT is considered a marker of bacterial infection, the cytokine milieu, including interleukin-6, interleukin-1β, and tumor necrosis factor-α, may induce PCT synthesis in hyperinflammatory states.[8] In our patient, the simultaneous decline of PCT and ferritin levels after immunomodulatory treatment supports the predictive value of PCT in the diagnostic work-up of systemic inflammatory disorders characterized by increased cytokine response. This mechanism has been reported in macrophage activation syndrome and systemic inflammatory states, but remains underestimated in post-transplant sHLH.[8,9] However, PCT elevation does not exclude sHLH and may, paradoxically, reflect the severity of immune dysregulation.

Although HScore has been primarily generated for the diagnosis of reactive sHLH, it was assumed to be the mainstay of HLH diagnosis in both cases. Because several components of the scoring system, such as fever, cytopenia, transaminitis, hyperferritinemia, organomegaly, and immunosuppression, may overlap with common post-transplant complications, it should be interpreted with caution in this setting.[3] Unfortunately, more specific HLH markers, including soluble IL-2 receptor/CD25, NK-cell activity, and CXCL9, could not be evaluated in either case. In general, histopathological examination is difficult in this complicated clinical scenario due to factors such as cytopenias, coagulation abnormalities, and poor performance status. Because histological identification may occur only in later stages of the disease and may not correlate with clinical symptoms and ferritin levels, the role of tissue biopsy should be questioned in the clinical diagnosis of HLH. As the absence of hemophagocytosis does not preclude the diagnosis of HLH, HScore should therefore be assessed earlier in the clinical course, as soon as post-transplant hyperinflammation is encountered.[1,10-12]

Secondary HLH is a state of immune reactivation and hyperinflammation which may result in cytokine-mediated tissue injury and multiorgan failure. A careful and comprehensive clinical approach is mandatory for patients who present with unexplained fever and/or organ dysfunction after allo-HSCT, based on HLH diagnostic and monitoring algorithms.[1] HScore

Table 2. Compact timeline of the two cases: transplant, HLH/fever onset, ferritin and procalcitonin trend, microbiology, virology, HScore, treatment start, and outcome. alloHSCT: allogeneic hematopoietic stem cell transplantation; CMV: cytomegalovirus; DLI: donor lymphocyte infusion; EBV: Epstein-Barr virus; IVIG: intravenous immunoglobulin; TBI: total body irradiation.

Feature	Case 1	Case 2
Transplant (day 0)	Haploidentical alloHSCT (fludarabine/melphalan/TBI)	Haploidentical alloHSCT (treosulfan/fludarabine/TBI)
Fever / HLH onset	Day +40 (fever, confusion, multiorgan dysfunction)	Pre-transplant refractory HLH; post-transplant EBV reactivation day +48
Ferritin / procalcitonin trend	Ferritin 65,000→~1,500 ng/mL and procalcitonin 309→<10 ng/mL over 7 days	Ferritin 4,230 ng/mL at presentation
Microbiology	Blood, urine and throat cultures sterile	Not reported
Virology	CMV and EBV negative; respiratory viral panel negative	EBV positive (reactivation)
HScore (probability)	228 (~99%)	228 (~99%)
Treatment start	Day +41: dexamethasone, ruxolitinib, IVIG, antibiotics, plasma exchange	Ruxolitinib-based bridge; rituximab (day +49); DLI (day +78)
Outcome	Recovery; vasopressors stopped day 2	Remission, full donor chimerism (day +140)

evaluation should be performed when clinically suspected, regardless of PCT levels or microbiological assessments, and repeated within 24 to 48 hours if clinical deterioration is observed despite broad-spectrum antimicrobial therapy. Serial measurements of ferritin and PCT levels may better discriminate HLH from infection, as persistent increases despite infection control may indicate a high probability of HLH. Vasopressor-dependent sepsis and hyperferritinemia were shown to be associated with early mortality in sHLH following allo-HSCT. Secondary HLH should be considered in the differential diagnosis of post-transplant endothelial complications and requires early multidisciplinary evaluation to shorten time to treatment and reduce considerable mortality, with rates up to 80% in previously reported studies.[1,2,12,13]

From a physiopathological point of view, ruxolitinib may represent a common immunomodulatory thread across the distinct poles of this clinical spectrum. As a JAK1/2 inhibitor, ruxolitinib attenuates the cytokine signaling cascade, which has a central role in HLH pathophysiology.[4] In Case 1, ruxolitinib was an essential component of an integrated immunomodulatory strategy including dexamethasone, IVIG, and plasma exchange, which contributed to rapid clinical stabilization consistent with the previously reported overall response rate of 85.7% in newly diagnosed adult HLH patients.[14] In Case 2, ruxolitinib exhibited two distinct roles: as a bridge to transplantation in refractory HLH and as second-line treatment in steroid-refractory acute GvHD.[4,15] This dual efficacy, which may highlight the JAK-STAT pathway's role in inflammatory and alloimmune reactions, warrants further investigation. Nevertheless, the optimal dose and duration of ruxolitinib remain undefined. On the other hand, plasma exchange, which was performed for a possible diagnosis of acquired TTP in Case 1, may have contributed to effective cytokine clearance (**Table 2**).[16-18]

Conclusions. Allo-HSCT may hold a contradictory position between primary and post-transplant sHLH. Clinicians must maintain a high index of suspicion for sHLH in the differential diagnosis of post-transplant hyperinflammatory states, including endothelial syndromes. Because factors such as viral reactivation, infectious complications, conditioning regimen toxicity, PTLD, and GvHD may trigger post-transplant sHLH, management should be individualized and directed at the underlying trigger, which is primarily associated with immunosuppression. There are neither standardized diagnostic criteria nor validated treatment guidelines for sHLH in allo-HSCT recipients. For this reason, established HLH criteria should be evaluated with caution, given their limitations in this patient group. Serial ferritin measurements in culture-negative febrile patients may be feasible for early diagnosis.[12,18,19] Because ruxolitinib may affect distinct poles of this clinical spectrum, future studies should clarify its role via the cytokine network in the immunological microenvironment.

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performed in accordance with the Declaration of Helsinki.

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