ACUTE GRAFT-VERSUS-HOST DISEASE

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Keywords Acute lymphoblastic leukemia, transplantation, graft-versus-host disease, child.

Abbreviations **allo-HSCT** = allogeneic hematopoietic stem cell transplantation; **GVHD** = graft-versus-host disease.

Case report. A 9-year-old boy with early relapse of B-cell acute lymphoblastic leukemia was under follow-up in the Oncology unit after allogeneic hematopoietic stem cell ransplantation (allo-HSCT). On day +25 post-transplant, he developed an erythematous, pruritic rash on the cheeks, which spread to the face, upper chest, and arms, eventually becoming generalized and associated with bilateral eye discharge and mild cough. Three days later, fever and bullous lesions on the neck appeared, leading to admission to the Oncology ward.

At admission: hemoglobin 10.4 g/dL (normal 11–14.5), platelets 38,000/μL (normal 150,000–400,000), white blood cells 6,550/μL (normal 3,830–9,840), neutrophils 3,700/μL (normal 1,500–7,000), C-reactive protein 0.34 mg/dL (normal 0–0.5), normal liver function, negative blood cultures, SARS-CoV-2 positive, negative viral loads for EBV, adenovirus, and CMV, and normal chest X-ray.

Treatment with intravenous methylprednisolone 2 mg/kg/day, piperacillin–tazobactam, and hydroxyzine was initiated. Ophthalmologic evaluation revealed mild keratoconjunctivitis, for which lubrication and tobramycin eye drops were prescribed.

On the second day of hospitalization, flaccid bullae appeared on both upper limbs, prompting evaluation by pediatric plastic surgery for suspected early acute cutaneous GVHD. Bedside dressing was attempted but was limited by severe pain, so subsequent procedures were performed under general anesthesia. Two days later, after a platelet transfusion, extensive involvement of the face, trunk, and upper limbs was noted, affecting 40% of the total body surface area, with a positive Nikolsky sign — findings consistent with severe grade IV/D acute cutaneous GVHD (see Table 1) —.

Surgical debridement was performed under general anesthesia, with removal of devitalized tissue and temporary coverage using silver-based absorbent occlusive dressings. The patient was then transferred to the intensive care unit for combined medical and surgical management, requiring invasive mechanical ventilation, deep sedation-analgesia, and vasopressor support.

Due to the severity of the condition and the decrease of serum IgG levels (315 mg/dL; normal 595–1,308 mg/dL), intravenous immunoglobulins 400 mg/kg were administered, along with ruxolitinib 10 mg/day, vancomycin–amikacin, and gradual tapering of methylprednisolone after 10 days.

Follow-up testing revealed an increasing cytomegalovirus viral load (1,470 copies/mL; normal 0), for which ganciclovir was initiated. The patient underwent two additional surgical procedures at 7-day intervals for further debridement, during which stabilization of the skin lesions was observed (Figs. 1, 2). Intraoperative cultures were negative.

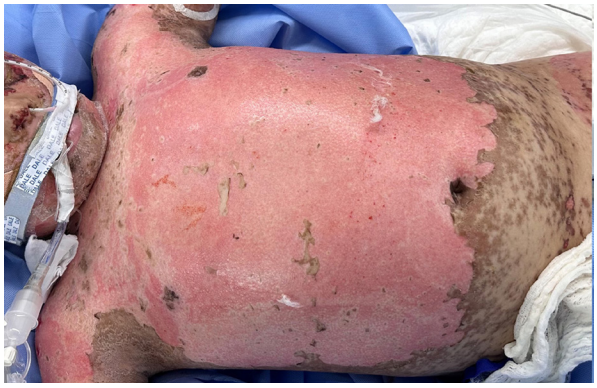

Fig. 1

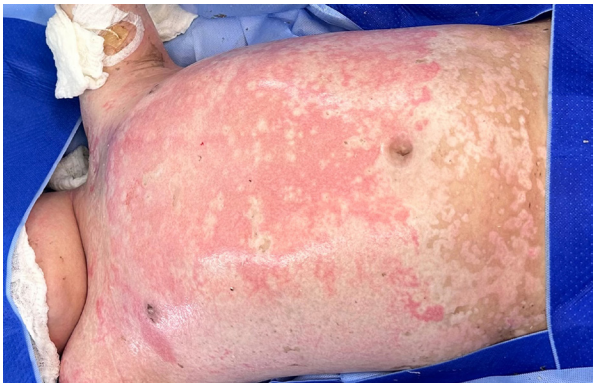

Fig. 2

Fig. 1, 2: Acute graft-versus-host disease on the ninth (Fig. 1) and sixteenth day from onset.

During hospitalization, he was also followed by nutritionists, physical therapists, occupational therapists, and mental health specialists. By day 20 of hospitalization, he was transferred back to the oncology unit with clear symptomatic improvement, discontinuation of deep sedation, and progressive re-epithelialization, showing an overall favorable clinical response.

Table 1. Grading of acute cutaneous graft-versus-host disease.

I	A	Maculopapular rash <25% of body.
II	B	Maculopapular rash 25-50% of body.
III	C	Generalized erythroderma.
IV	D	Generalized erythroderma with bullous formation.

Table adapted from Glucksberg et al. and the International Bone Marrow Trasplant Registry (IBMTR).

Discussion. Acute GVHD is caused by the interaction between the host's antigen-presenting cells and the donor's mature T lymphocytes. This immune dysregulation triggers inflammation and destruction of host cells, leading to multisystem tissue damage (2, 3, 4). GVHD thus results from the donor's immune cells recognizing the host's tissues as foreign (2).

Symptoms typically appear 1 to 3 weeks after hematopoietic stem cell transplantation (HSCT) and include pain and itching, followed by a maculopapular rash involving the face, ears, neck, and palms and soles. The rash may progress to erythroderma, sometimes with blister formation and a positive Nikolsky sign (2).

Differential diagnoses include viral exanthems, drug eruptions, toxic epidermal necrolysis, and acral erythema secondary to chemotherapy. Although histopathologic examination is a useful tool for diagnosing acute GVHD, its specificity is limited, and its diagnostic value has been questioned (5).

When acute cutaneous GVHD is suspected, treatment should be initiated according to severity, using either topical or systemic therapy (1, 2). In localized cases or grade I (A) acute cutaneous GVHD, topical corticosteroids and topical calcineurin inhibitors are used (1). In more extensive or severe cases, systemic therapy is required, with systemic corticosteroids representing the first-line treatment — for example, methylprednisolone 1-2 mg/kg/day for at least 5 days —. If there is no response within

5 days or worsening after 3 days of corticosteroid therapy, second-line treatments are considered, including phototherapy, extracorporeal photopheresis, mTOR inhibitors, Janus kinase inhibitors (JAKi), and intravenous immunoglobulins (1, 2).

In our case, ruxolitinib, a JAK1 and JAK2 inhibitor, was used. It acts by blocking JAK kinase activity and reducing intracellular signaling via the JAK/STAT pathway, which mediates the production of inflammatory cytokines and growth factors. Ruxolitinib was chosen because it offers the highest likelihood of survival and cutaneous recovery in severe, steroid-refractory acute GVHD (1).

The main adverse effects (1) include cytopenia and cytomegalovirus reactivation. Cytomegalovirus reactivation is a known but manageable risk, outweighed by the drug's proven efficacy in controlling the underlying inflammatory process in both adult and pediatric populations. In fact, the current patient was treated with ganciclovir. Intravenous immunoglobulins were also administered to reduce keratinocyte apoptosis mediated by Fas-Fas ligand interaction (2).

Given the extensive skin involvement, the patient required surgical management by the plastic surgery team on three separate occasions.

Conclusion. This case of GVHD was presented to emphasize the importance of a multidisciplinary approach involving dermatologists, plastic surgeons, hemato-oncologists, ophthalmologists, and intensive care specialists to reduce morbidity and mortality in these patients.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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