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– CASE REPORT –

# Cutaneous Complications after Autologous Stem Cell Transplantation

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***Abstract***

*Autologous stem cell transplantation (ASCT) has become more prevalent for high-grade non-Hodgkin's lymphoma (NHL) over the past decade. ASCT serves as a salvage treatment for high-risk or relapsed patients, offering potential long-term remission. Cutaneous modifications post-ASCT can be classified as early (within 100 days) and late (after 100 days). Understanding these changes is crucial for timely diagnosis and management. Early modifications typically include transient erythema, hyperpigmentation, and acute dermatitis, often linked to the conditioning regimen. Late modifications, occurring months to years post-transplantation, can encompass chronic skin changes such as scleroderma-like features and persistent pigmentary alterations. Emerging evidence challenges the notion that ASCT is free of graft-versus-host disease (GVHD), with incidences of auto-GVHD reported. However, cutaneous GVHD post-ASCT, though uncommon, poses significant diagnostic challenges. Cutaneous GVHD manifestations range from mild eruptions to severe, systemic involvement. The role of skin biopsy in these cases is invaluable, providing histopathological confirmation and distinguishing GVHD from other dermatoses. Recognizing the early and late cutaneous modifications following ASCT is essential for clinicians. Despite the rarity of skin GVHD in ASCT, awareness and prompt biopsy can facilitate accurate diagnosis and appropriate management, improving patient outcomes.*

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## Introduction

Autologous hematopoietic stem cell transplantation (ASCT), developed in the early 1980s, represents a major advancement in treating aggressive lymphoproliferative disorders. The procedure involves administering chemotherapy to induce remission and mobilize autologous stem cells into the peripheral blood, followed by stem cell collection. Patients then receive high-dose chemotherapy to eradicate residual malignant cells, and finally, the autologous stem cells are infused to "rescue" or restore hematopoiesis.

The use of ASCT to treat high grade non-Hodgkin's lymphoma (NHL) has increased over the past decade. While intensive chemotherapy can achieve disease free survival (DFS) rates of up to 50% at five years in certain subtypes of aggressive lymphoma, the likelihood of a favorable response is significantly reduced in high-risk patients and those with relapsed or refractory disease.

ASCT can serve as a salvage treatment option in these scenarios. Retrospective analyses suggest that it can lead to long-term progression-free survival and even cure in a proportion of patients. This evidence, combined with increased availability and experience with ASCT, has led to changes in standard medical practice. More hematologists are now referring patients for transplant, and patient eligibility criteria are gradually broadening.

The Paradigm study conducted by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) and the Cancer and Leukemia Group B (CALGB) is currently the largest randomized study comparing ASCT with chemoimmunotherapy in any NHL subtype. Preliminary results indicate that ASCT consolidation is particularly beneficial for individuals with high-risk or relapsed disease. Therefore, with this study as well as other recent studies showing that transplantation in first remission is superior to that performed at a later time, ASCT looks to become increasingly utilized in the treatment of diffuse large B cell lymphoma (DLBCL).

The ASCT procedure carries significant risks and is generally reserved for fit, relatively young patients. Although transplant-related mortality has decreased in recent years, it remains at approximately 5-10% for patients undergoing ASCT for lymphoma. A substantial portion of this risk is due to infection, disease relapse or progression, secondary primary malignancies, organ failure, and treatment-related toxicity.

## Cutaneous complications in ASCT

Cutaneous complications following ASCT can vary from mild to life-threatening, with a wide range of skin issues reported. These complications are categorized into early and late, depending on their onset relative to the transplantation. Early complications occur within the first 100 days post-transplant, while late complications arise after 100 days. The underlying mechanisms differ between these two categories, which will be discussed in further detail.

## Clinical scenario

A 40-year-old patient was diagnosed with stage IIIA DLBCL not otherwise specified (NOS), germinal center B cell-like (GCB) subtype. The patient was initially treated with R-CHOP immunochemotherapy. Upon disease relapse, he received radiotherapy and R-DHAP, followed by ASCT in partial remission. The pre-transplant conditioning regimen included Lomustine, Etoposide, Cytarabine, and Melphalan. The hole graft, consisting of 37.06 x 106 CD34+ cells, was administered. Grafting occurred on the 12th day. The post-transplant period was complicated by persistent fever of unknown origin and vasovagal syncope.

On day +27 post-transplantation, the patient presented to the Emergency Department with altered general status, loss of appetite, nausea, persistent high fever, and generalized pruritic maculopapular exanthema (Figure 1). Laboratory investigations showed elevated liver enzymes and a positive cytomegalovirus (CMV) PCR (viral load 172.01 copies/ml). Broad-spectrum antibiotics, Valganciclovir, and corticosteroid pulse-therapy were initiated. The patient's clinical condition promptly improved, with resolution of fever and disappearance of the rash.

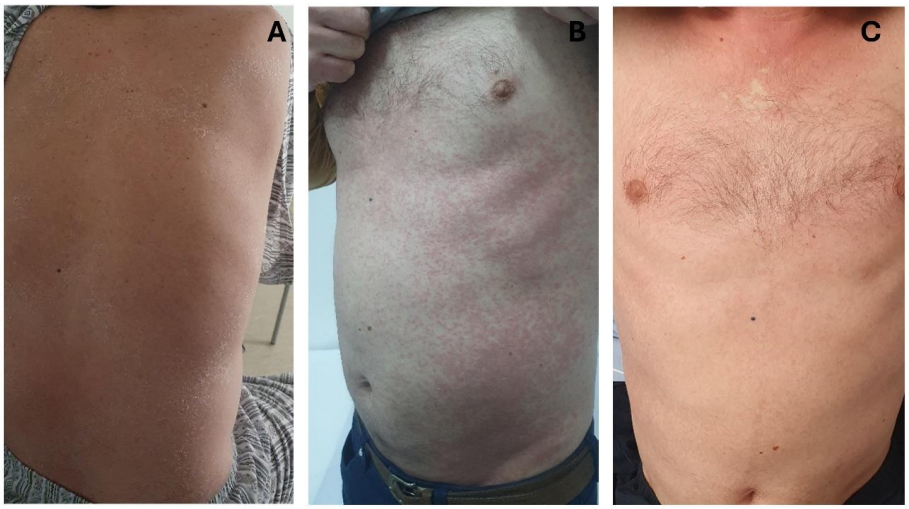


***Figure 1***. *Evolution of the generalised maculo-papular exanthema following ASCT at three time points: A. Day +27; B. Day +49; C. Day +62*

## Early cutaneous complications following ASCT

The timeline for symptoms onset is further divided into two periods: the pre-engraftment period (the first 30 days) and the post-engraftment period (30 days or more). During the pre-engraftment period, high-dose chemotherapy causes mucosal damage and immunosuppression, leading to numerous infectious cutaneous complications. In the post-engraftment period, characterized by immune system reconstitution, the patients can suffer from acute graft-versus-host disease (GVHD) and treatment-related cutaneous complications.

The differential diagnosis is often challenging and typically requires a skin biopsy for accurate identification. Our patient developed early cutaneous complications following ASCT, occurring around the borderline of the two time periods (before/after day +30). The primary challenge was establishing a differential diagnosis. We considered acute GVHD, cutaneous complications due to CMV reactivation, and engraftment syndrome as potential causes.

## Differential diagnosis

The pathologies that should be considered in the differential diagnosis of cutaneous complications are presented in Table 1.

| ***Pathology*** | ***Clinical presentation*** | ***Histological findings*** |
|---|---|---|
| *Acute GVHD* | *Grade 0-4*<br>*Head, neck, acral sites*<br>*(described below in detail)* | *(described below in detail)* |
| *Drug reaction* | *Morbilliform erythema*<br>*Onset 1-2 or 7-10 days after exposure to new drug*<br>*Begins on torso and spreads the next days* | *May not involve hair follicles.*<br>*Fewer eosinophils* |
| *Viral infections (HHV6, HHV7, CMV)* | *Morbilliform or maculopapular eruptions* | *Rare perivascular lymphocytic infiltrates*<br>*Intranuclear inclusions – CMV* |
| *Acral erythema* | *Secondary to chemotherapy*<br>*Affects extremities (palms, soles)*<br>*Edema, blistering, desquamation, pain* | *Dermatitis, necrotic and dyskeratotic keratinocytes, edema of dermis, lymphocytes infiltrate in perivascular space, with vacuolar degeneration* |
| *Toxic epidermal necrolysis* | *Involves more than 30% body surface area*<br>*Appears after 1-3 weeks after exposure to new drug*<br>*Prodrome of flu-like symptoms*<br>*Skin eruption: macular rash, bullae, blisters;*<br>*Nikolsky sign*<br>*Affect face and torso* | *Necrosis and epidermis detachment*<br>*Few mononuclear cells*<br>*Satellitosis*<br>*High eosinophilic necrosis* |
| *Engraftment syndrome* | *Self-limited skin exanthem*<br>*Transient non-infectious fever, diarrhea, pulmonary infiltration/ edema, impaired renal/ liver function, transient encephalopathy, weight gain* | *Eosinophilic necrosis of epidermal keratinocytes in epidermis*<br>*Vacuolization in the basal layer*<br>*Lymphocytic infiltration of perivascular space* |
| *Radiation dermatitis* | *Erythema, desquamation, blisters, necrosis* | *Dermal sclerosis, elastosis, vascular ectasia, hyperkeratosis, epidermal spongiosis, vacuolization of basal layer, hyperchromasia of stroma fibroblasts and endothelial cells, enlargement and atypia, inflammatory infiltrate* |
| *Lupus erythematosus* | *Malar rash on cheeks and nose*<br>*Rash of the forehead, neck with sparring of nasolabial folds*<br>*Edema, papules*<br>*Lasting days-weeks, may appear after sun exposure*<br>*Telangiectasis, erosion, dyspigmentation, poikiloderma* | *Fibrinoid necrosis, liquefactive degenerations and atrophy of the epidermis, edema, hemorrhages, lymphocytic infiltrate in dermis* |

***Table 1****. Differential diagnosis between acute GVHD and other skin conditions after ASCT*
***Abbreviations:*** *GVHD=graft-versus-host disease, HHV=human herpesvirus, CMV=Cytomegalovirus*

## Graft-versus-host disease

While GVHD is traditionally associated with allogeneic stem cell transplantation, its occurrence after ASCT is becoming more recognized. GVHD involves an immune-mediated process where donor T lymphocytes attack recipient tissues, leading to a multisystem disorder. In allogeneic transplantation, GVHD has been associated with a graft-versus-lymphoma effect, contributing to improved disease control. However, GVHD also correlates with increased morbidity and mortality. Studies involving mixed patient population have indicated poorer survival outcomes in those experiencing GVHD complication.

Although ASCT has generally been considered to be free of GVHD due to the absence of donor immune cells, emerging evidence suggests otherwise. In the ASCT, the GVHD is a form of "auto-aggression syndrome" (auto-GVHD). Auto-GVHD has been reported to arise unpredictably or after immunomodulation therapy. A growing number of case reports have highlighted the occurrence of a chronic form of GVHD following ASCT, even in the absence of donor cells.

A comprehensive study conducted by Copelan et al. sheds light on the incidence rate of GVHD following ASCT in DLBCL patients. This study included 402 DLBCL patients. The overall GVHD incidence rate was 39%, with 27% experiencing acute GVHD and 20% chronic GVHD,These results align with findings from other smaller studies. A retrospective analysis by the Center for International Blood and Marrow Transplant Research reported a 36% GVHD incidence rate , while another single-center study reported a rate of 28%.

The clinical manifestation of cutaneous GVHD ranges from erythematous maculopapular morbilliform eruption and follicular erythema, to erythroderma and epidermolysis.40 It may impact areas like the face, ears, palms, soles, extending to the trunk, or even the entire body surface area. Patients may be asymptomatic or report itching or dysesthesia. Additionally, atypical presentations such as pityriasis rubra pilaris, acquired ichthyosis, and psoriasis vulgaris-like eruptions are also possible.

The most common changes encountered in cutaneous GVHD are:

- Poikiloderma: atrophy, hypopigmentation, hyperpigmentation as patches, telangiectasias
- Lichen planus-like features: erythematous or violaceous papules/ plaques on dorsal hands and feet, forearms, trunk; scaling is possible
- Sclerosis: wavy aspect and thickening of fibrous septa in fat, on medial arms and thighs; fascial affliction – contractures determining impaired function of limb
- Morphea-like features: plaques of various colors; shiny appearance of skin; hair loss
- Lichen sclerosis-like features

Depending on the clinical features of the rash and its spread, skin GVHD can be classified into the following grades:

0.Without active rash

1. Maculopapular rash involving less than 25% body surface area
2. Maculopapular rash involving 25-50% body surface area
3. Maculopapular rash involving more than 25% body surface area
4. Generalized erythema involving >50% body surface area, bullae/ desquamation involving more than 5% body surface area

The positive diagnosis relies on several factors, including the affected sites (such as the face, palms, and soles) , dermoscopic changes (pink or red background and telangiectasias). Additionally, the emergence of rashes following sun exposure is a distinct indicator of skin GVHD. Performing a skin biopsy is essential for the positive diagnosis.

The histological changes found in acute cutaneous GVHD are heterogeneous. The most common findings, according to the National Institute of Health Consensus , are:

ducts, and/or lichenoid inflammation, vacuolar change, or lymphocytic satellitosis;

- Lichen planus-like features: epidermal orthohyperparakeratosis, hypergranulosis, acanthosis, lichenoid inflammation, and/or vacuolar changes of eccrine units;
- Lichen sclerosus-like features: uniformity and/or sclerosis of collagen in papillary dermis, melanophages in papillary dermis, rare lymphocytic infiltration;
- Morphea-like features: thickening and homogenization of collagen clumps in reticular dermis and/or pandermal sclerosis;
- Fasciitis: thickened fascial septa, inflammation, and/or subcutis sclerosis.[51]

In our scenario, to confirm the diagnosis, we conducted a skin biopsy. Due to logistical constraints, the biopsy was performed five days after initiating corticosteroid therapy. Histopathological analysis indicated nonspecific changes, including orthokeratosis with areas of parakeratosis,

occasional necrotic keratinocytes, thickened dermis, and perivascular inflammatory infiltrates. Immunohistochemical assessment demonstrated negativity for CD20 and CD79a. These nonspecific changes could potentially be interpreted as GVHD-related, considering the high-dose steroids administered before the biopsy. Furthermore, the changes resolved with steroids treatment.

## Evolution and management

The management approach for GVHD is dictated by its classification, grading, extent of involvement, and symptoms. The treatment options vary, ranging from oral antihistamines and moisturizers, to short-time topical steroids and topical calcineurin inhibitors in grade I GVHD. For grades II-IV, methylprednisolone and calcineurin inhibitors are commonly used. Second-line therapies may include extracorporeal photopheresis , mycophenolate mofetil, TNF-antagonists (such as infliximab and etanercept) particularly for cases with gastrointestinal involvement, IL2 receptor monoclonal antibodies (daclizumab), and anti-thymocyte globulins.

In our specific case, despite initially responding well to corticosteroid treatment, the patient returned to the Emergency Department on day +49 with deteriorating clinical condition and high fever. Laboratory tests indicated elevated liver enzymes, although this time the PCR for CMV was negative. Corticosteroid therapy and broad-spectrum antibiotics were restarted. However, the patient experienced complications stemming from corticosteroid treatment, including corticosteroid-induced diabetes mellitus and depressive disorder with suicidal thoughts. No organic causes for the psychiatric symptoms were identified. Managing these complications involved insulin therapy, antidepressants, antipsychotics, and anxiolytics. Corticosteroid therapy continued for one month. During this period, the rash and itching subsided, and the patient's overall health notably improved.

## Conclusion

Diagnosing cutaneous complications following ASCT is challenging due to similar clinical manifestations from various causes. However, since treatment options often vary, establishing an accurate diagnosis is preferable. Skin biopsy is the most valuable tool for this purpose; however, in some cases, including ours, the findings may be nonspecific. Understanding the various causes of skin changes can help guide physicians towards appropriate treatment, even in the absence of definitive data.

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**Conflicts of interest**

I undersign, certificate that I do not have any financial or personal relationships that might bias the content of this work. The authors declare no conflict of interest.

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient included in the study.

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