Hematopoietic stem cell transplantation (HSCT) – key issues

- Within few decades from an experimental undertaking to an established therapy
- Many severe congenital or acquired disorders of the hematopoietic system, as well as for chemo-, radio- or immunosensitive malignancies
- Over 60’000 procedures worldwide annually, with more than 30’000 of them from an allogeneic donor
- Increasingly be used in older patients with preexisting diseases and comorbidities
- Long term sequelae of HSCT impact quality of live and costs
EBMT Activity survey on HSCT 1973 - 2008

The European Group for Blood and Marrow Transplantation
Cellular reconstitution

![Graph showing immune cell counts over time post-transplant](image)

**Delayed immune recovery**

**Sequence of events in HSCT – eventual dermatologic manifestations**

- Basic disease
- Conditioning
- Transplant procedure (infusion of cells)
- Time to engraftment
- Early post-transplant period (up to day 100)
- Delayed post-transplant period (up to 2 years)
- Late post-transplant period (up to 10 years)
- Very late post-transplant period (more than 10 years)

Dermatologic manifestations of HSCT

- Conditioning
- Pancytopenia
- Immunologic (GvHD)
- Drug reactions
- Underlying disease (preexisting, relapse)
- Organ failure
- Late complications
- Infections (timetable)

**GvHD-Initiation**

Donor CD8 T-cell

Recipient APC

Endogeneous miHA

**GvHD-Evolution**

Donor CD4 T-cell

Donor APC

Apoptotic recipient cell

Exogeneous (recipient) miHA
Macrophages in GvHD

- Recipient macrophages contribute to acute GvHD by antigen presenting and secreting cytokines causing activation and proliferation of CD8+ T cells
  - Recipient dermal macrophages survive conditioning and cutaneous GvHD and are replaced late after HSCT
- Macrophage infiltration of skin is a predictive factor for refractory GvHD and a negative prognostic factor for overall survival (Nishiwaki S. et al. Blood 2009)
The morbilliform eruption in the HCT patient

- Morbilliform drug exanthem
- Morbilliform chemotherapy exanthem
- Morbilliform viral exanthem
- Acute cutaneous GvHD
- Engraftment syndrome
- Eruption of lymphocyte recovery
- Bacterial infections, eg, secondary syphilis


Acute GvHD

Skin involvement in about 90%

Incidence stable over years (well known risk factors)

Clinical stage (I – IV) impacts prognosis (grade 0-IV)

Systemic standard treatment if stage III (only skin, ≥ grade II)
GvHD - acute

Dermatology 2008

Cutaneous Graft-versus-Host Disease
A Guide for the dermatologist
Involvement of genitalia, mouth and appendages in chronic cutaneous GvHD

Eczematoid GvHD

A novel form of aggressive chronic cutaneous disease

Donor and recipient without history for atopic dermatitis

Small study (10 patients)

Creamer D et al. Arch Dermatol 2007;143:1157-1162
Sclerotic-type chronic GvHD to sites of skin injury

- Isomorphic and isotopic responses
- 3 of 4 patients had other skin GvHD involvement

Martines KI et al. Arch Dermatol 2011;147:1081-1086

Categories of acute and chronic GvHD from the NIH consensus development project

<table>
<thead>
<tr>
<th>Category</th>
<th>Timing of symptoms after HSCT or DLI</th>
<th>Presence of acute GvHD features</th>
<th>Presence of chronic GvHD features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute GvHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic</td>
<td>≤ 100 days</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Persistent, recurrent or late-onset</td>
<td>&gt; 100 days</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Chronic GvHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic</td>
<td>no time limit</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Overlap syndrom</td>
<td>no time limit</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>
Chronic GVHD: “Diagnostic” mucocutaneous manifestations

1) Lichen planus-like lesions
2) Lichen sclerosus-like lesions
3) Morphea-like lesions
4) Sclerotic lesions including or fasciitis
5) Poikiloderma
6) Oral hyperkeratotic plaques
7) Oral lichen-type features
8) Restriktion of mouth opening due to sclerosis

Filipovich et al. Biol Blood Marrow Transplant. 2005;11;945-955

Chronic GVHD: “Distinctive” mucocutaneous manifestations

1) Depigmentation
2) New-onset scarring and nonscarring scalp alopecia or papulosquamous lesions or scaling of the scalp
3) Nail dystrophy, longitudinal ridging, splitting, or brittle features, onycholysis, Pterygium unguis and nail loss
4) Xerostomia, mucoceles, oral mucosal atrophy oral ulcers and pseudomembranes

Filipovich et al. Biol Blood Marrow Transplant. 2005;11;945-955
Diagnostic criteria for chronic GvHD of the skin, nails, scalp/hairs and mouth (Filipovich et al.)

- A diagnosis of chronic GvHD requires
  - at least 1 diagnostic manifestation or
  - at least 1 distinctive manifestation plus confirmation of the GvHD diagnosis by biopsy/laboratory tests/imaging in the same or another organ

- In the absence of clinical or histological signs/symptoms of chronic GvHD, the persistence, recurrence or new onset of characteristic manifestations of acute GvHD should be classified as acute GvHD, regardless of the time after the transplantation.

Filipovich et al. Biol Blood Marrow Transplant. 2005;11;945-955

Other features that can be acknowledged as part of the chronic GvHD symptomatology if the diagnosis is confirmed

<table>
<thead>
<tr>
<th>skin</th>
<th>Scalp and body hair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweat impairment</td>
<td>Thinning scalp hair (not explained by endocrine or other causes)</td>
</tr>
<tr>
<td>Ichthyosis</td>
<td></td>
</tr>
<tr>
<td>Keratosis pilaris</td>
<td>premature gray hair</td>
</tr>
<tr>
<td>Hypo- and hyperpigmentation</td>
<td></td>
</tr>
</tbody>
</table>

Filipovich et al. Biol Blood Marrow Transplant. 2005;11;945-955
Male genital skin changes including chronic GVHD and their implication in sexual life after allogeneic hematopoietic stem cell transplantation

Preliminary results of a single-center cross-sectional analysis of 155 patients

Simon Mueller, Peter Häusermann
Alicia Rovo, Joerg Halter, Jakob Passweg, André Tichelli
Department of Dermatology, University Hospital Basel
Department of Hematology, University Hospital Basel
Switzerland

Genital chronic GVHD“ = „female genital chronic GVHD“

- Female genital chronic GVHD is reported in 25-49% of allo-HSCT survivors1-3.
- Impairs quality of life, sexual function and relationship dynamics2.
- Is often associated with cGVHD of other organs, especially skin and oral mucosa1-3.
- Can be the initial presentation of cGVHD in up to 27%1.
- Severity scoring1-3,6 and surveillance/treatment recommendations exist2,4,5.

1. Spinelli, Haematologica. 2003;88:1163-8
2. Zantomio, Bone Marrow Transplant. 2006;38:567-7
6. Filipovich, 2005 Dec;11(12):945-56
### Posttransplant Genital Skin Changes in Males

<table>
<thead>
<tr>
<th>Genital Changes</th>
<th>124 (81%)</th>
<th>31 (20%)</th>
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<tr>
<td>1. Non-inflamatory genital skin changes</td>
<td>10 (6%)</td>
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<tr>
<td>2. Inflammatory genital skin changes, possible GvHD</td>
<td>21 (14%)</td>
<td>12 (8%)</td>
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<tr>
<td>- Zoon’s balanoposthitis-like</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Lichen sclerosus-like</td>
<td>6 (4%)</td>
<td></td>
</tr>
<tr>
<td>- Phimosis</td>
<td>3 (3%)</td>
<td></td>
</tr>
<tr>
<td>- More than one feature</td>
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</tr>
</tbody>
</table>

**Lichen sclerosus-like skin change**

Nylander, Acta Derm Venereol 2007

**Phimosis**

Au, Br J Dermatol 2008
Zoon`s balanoposthitis
Balanoposthitis chronica circumscripta plasmacellularis, Johannes Zoon (Utrecht, NL) 1950

- Unspecific inflammatory reactive pattern due to trauma, heat, poor hygiene
- Usually occurs in uncircumcised elderly men.
- No histological pattern of cGVHD.

- 8/12 patients (66%) had also oral mucosal cGVHD
- Can lead to adhesions/phimosis → `genital cGVHD`
- In rare cases transformation to:
  - carcinoma in situ (Davis-Daneshfar 2000; Starrit 2008)
  - squamous cell carcinoma (Joshi 1999; Bunker 2001; Balato 2009)

### Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>without inflammatory genital skin changes</th>
<th>with inflammatory genital skin changes (possible cGVHD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>134</td>
<td>21</td>
<td>-</td>
</tr>
<tr>
<td>TBI</td>
<td>71 (53%)</td>
<td>10 (48%)</td>
<td>0.599</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Acute leukemia</td>
<td>56 (42%)</td>
<td>8 (38%)</td>
<td>0.958</td>
</tr>
<tr>
<td>- Chronic myeloid leukemia</td>
<td>20 (15%)</td>
<td>3 (14%)</td>
<td></td>
</tr>
<tr>
<td>- Myelodysplastic syndrome, myeloproliferative neoplasms</td>
<td>14 (10%)</td>
<td>3 (14%)</td>
<td></td>
</tr>
<tr>
<td>- Myeloma</td>
<td>7 (5%)</td>
<td>2 (9%)</td>
<td></td>
</tr>
<tr>
<td>- Chronic lymphocytic leukemia, (non-) Hodgkin’s disease</td>
<td>19 (14%)</td>
<td>3 (14%)</td>
<td></td>
</tr>
<tr>
<td>- Others</td>
<td>18 (13%)</td>
<td>2 (9%)</td>
<td></td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Standard</td>
<td>92 (73%)</td>
<td>14 (70%)</td>
<td>0.779</td>
</tr>
<tr>
<td>- High risk</td>
<td>34 (27%)</td>
<td>6 (30%)</td>
<td></td>
</tr>
<tr>
<td>Acute GVHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Grade 0-I</td>
<td>68 (57%)</td>
<td>9 (56%)</td>
<td>0.946</td>
</tr>
<tr>
<td>- Grade II-IV</td>
<td>55 (43%)</td>
<td>7 (44%)</td>
<td></td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>85 (68%)</td>
<td>18 (95%)</td>
<td>0.018</td>
</tr>
<tr>
<td>Oral mucosal chronic GVHD</td>
<td>23 (17%)</td>
<td>14 (67%)</td>
<td>-0.0001</td>
</tr>
<tr>
<td>Ocular chronic GVHD</td>
<td>9 (8%)</td>
<td>5 (36%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Non-mucosal skin chronic GVHD</td>
<td>7 (5%)</td>
<td>6 (28%)</td>
<td>0.026</td>
</tr>
</tbody>
</table>
Increased risk for malignant transformation

1. Immunosuppression/TBI after HSCT
2. Potential malignant transformation of the inflammatory genital skin changes
   - Lichen sclerosus: 4-8% lifetime risk Clouston, BJU Int, 2011
   - Zoon’s balanoposthitis: anecdotal evidence
3. Topical calcineurin inhibitors
   - black box warning. FDA 2006

Elafin is a biomarker of GvHD of the skin

Elafin is an epidermal proteinase inhibitor that is induced by TNF-α and found in inflamed epidermis in such diseases as Psoriasis.

Paczesny S. et al. Sci Transl Med 2010
Elafin is a biomarker of GvHD of the skin

Elafin plasma levels – diagnostic value

Elafin plasma levels – prognostic value

Telomere attrition in allogeneic HSCT: «premature ageing of recipients»

Premature cellular senescence of donor-derived hematopoiesis:
- Late marrow failure?
- Late complications such as:
  - Secondary malignancy?
  - Endocrine dysfunction?
- Aging (skin)?
- Accelerated ageing process?

Graft-versus-host disease
Part I. Pathogenesis and clinical manifestations of graft-versus-host disease
Sharon R. Hymes, MD,1 Amin M. Alousi, MD,2 and Edward W. Cowen, MD, MHS,3
Houston, Texas, and Bethesda, Maryland

Graft-versus-host disease
Part II. Management of cutaneous graft-versus-host disease
Sharon R. Hymes, MD,1 Amin M. Alousi, MD,2 and Edward W. Cowen, MD, MHS,3
Houston, Texas, and Bethesda, Maryland

Graft versus Host Disease
Skin, appendages and genital tract

EBMT Severe Aplastic Anaemia and Complications QoL WP | Budapest, Hungary | 1-3 Nov 2012