

---

# Summary of the consensus and outlook



Daniel Wolff

Dept. of Hematology and Oncology  
University Hospital Regensburg

## Prerequisites

- Histological confirmation of GVHD plays an important role in clinical routine (GI > skin > oral mucosa > liver > lung > ocular)
- Histological confirmation is of central importance
  - in the presence of treatment relevant differential diagnoses
  - lack of diagnostic signs (within clinical trials)
- Despite of the importance histopathology of GVHD is
  - currently not standardized
  - depends on the experience of the individual pathologist
  - Does not determine clinical grading nor distinction between acute and chronic GVHD
  - role in clinical decisions unclear (impact on grading, impact of negative histology etc.)
  - communication between pathologist and Tx physician crucial

# Pathohistology of Murine GVHD

## Prerequisites

- Histological evaluation of experimental BMT is of central importance
- Histology depends on strain combinations, conditioning, graft composition, breed, and laboratory
- Standardized reproducible histopathological grading is crucial but evaluation is performed in a heterogeneous way and different grading systems are used

## Achievements

- ✓ Platform for exchange of techniques for histopathological evaluation of GVHD in murine models
- ✓ Collaboration between pathologists and “mice clinicians”
- Preparation of a catalogue for standardized grading of GVHD within different organs?

# Pathohistology of Cutaneous GVHD

## Prerequisites

- Histological confirmation is performed by ~50% of transplant centers
- Sensitivity depends on sampling and experience of the physician performing the biopsy (prior to treatment and location) and exchange of information between pathologist and clinician
- Can be used to confirm GVHD, to rule out a DD, to assess severity and activity

## Achievements

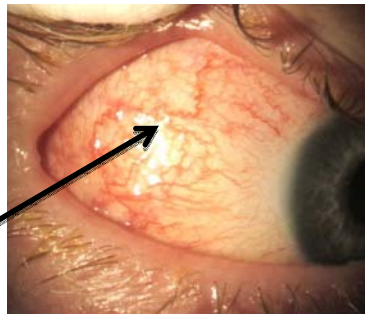
- Agreement on location and time-point of biopsies
- Suggestions for standardized pathology report
- Suggestions for harmonization of clinical and histopathological description of lesions

# Pathohistology of ocular GVHD

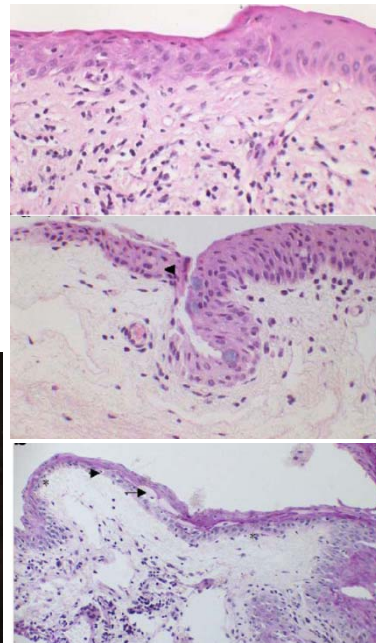
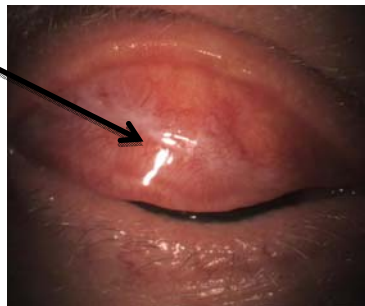
- Lacrimal gland biopsy is not recommended (risk of loss of function)
- Conjunctival biopsy from bulbar (vs. tarsal) conjunctiva
- Routine biopsy is not recommended (absence of pathognomonic markers, collateral damage to the conjunctiva)
- Conjunctival biopsy recommended:
  - a) in uncertain or atypical cases (e.g. symptoms, but normal Schirmer's scores or no other documented GVHD)

b) in clinical studies

biopsy of the bulbar conjunctiva  
(inferotemporal snip biopsy < 3 mm)



biopsy of the tarsal conjunctiva



## Histopathological findings:

- vacuolization of the basal epithelium, spongiosis
- epithelial thinning
- keratinisation
- exocytosis of lymphocytes
- lymphocytic infiltration with variable apoptosis
- epithelial cell necrosis
- reduced goblet cells

# Pathohistology of gastrointestinal GVHD

## Prerequisites

- Lack of diagnostic symptoms
- Histological confirmation is performed by ~90% of transplant centers
- Optimal location of the biopsy and time-point needs to be defined
- Interpretation of follow up biopsies and discrete changes difficult

## Achievements

- ✓Agreement on the need of histopathological confirmation
- ✓Definition of the optimal approach to achieve a diagnostic biopsy
- ✓Critical importance of clinical information to be provided
- Proposed: standards for histopathological reports including a detailed description, definitions for grading applicable in clinical practice

# Pathohistology of liver GVHD

## Prerequisites

Histological confirmation is less frequently performed but considered by ~60% of transplant centers (1/3 of all participating centers upfront, 1/3 of 1st-line treatment fails)

Associated bleeding risk (transcutaneous>transvenous)

Difficult differential diagnosis due to concomitant changes (toxicity, iron overload)

Therapeutic impact of biopsy results ranges between 40-60%

## Achievements

✓ Consensus on indication and minimal requirements incl. clinical information

✓ Consensus on necessary and facultative stains

✓ Progress on standardized reporting of liver results – description is crucial

# Pathohistology of pulmonary GVHD

## Prerequisites

BAL is frequently performed but does not permit diagnosis of BO

BO is diagnosed usually by lung function and Chest-CT

Histological confirmation is rarely performed due to the low diagnostic yield of transbronchiolar biopsies and the associated risks of open lung biopsies

## Achievements

- BO is the only fully accepted manifestation of GVHD (IPS, BOOP)
- In the presence of typical lung function and CT-Chest histology is not required
- required in diffuse or local lung infiltrates if other causes are ruled out atypical clinical or radiological findings (open lung biopsy >> transbronchial biopsy)
- Urgent need for biomarker

## Achievements – Treatment of aGVHD

- 1st-line treatment of aGVHD consists of corticosteroids with a dose of 1.0 – 2.5mg/kg (B II) with the CNI being continued
- additional applied agents are: ECP, MMF, Etanercept, mTOR-inhibitors
- Budesonid is applied by the majority of centers in the presence of GI-manifestations of GVHD
- Additional 1st-line treatment may have a negative impact (Daclizumab (D II))
- Due to the lack of controlled data 2nd-line treatment of aGVHD is extremely heterogenous
- Half of the centers initiate second-line treatment in the presence of no response between 5-8 days on first-line treatment

## Achievements – 1st line treatment of aGVHD

Agent	Recom	Evid.	comments
Steroids	B	II	Of central importance but unspecific
CNI	B	II	In contrast to cGVHD important
Beclomethason	B	II	Survival benefit in GI-GVHD, prevents relapse
Photopheresis			No data yet available
ATG	C-4	II	May be justified in selected cases
PUVA	C-3	III-2	Treatment option in isolated skin GVHD
mTOR –Inh.	C-4	III-2	Increased risk for TAM in combination with CNI
MMF	C-3	III-1	Risk for viral reactivation, best in 4 CTN trial
Infliximab	C-4	II	No improved response rate
Etanercept	C-3	III-1	May speed up and improve response, Failure in CTN-Trial

## Achievements – 2nd line treatment of aGVHD

Agent	Recom	Evid.	comments
Steroids	B	II	Remains important
CNI	B	II	In contrast to cGVHD important
Photopheresis	C-1	II	Important treatment option
ATG			Results improved through the last 10 years
mTOR –Inh.			increased risk for TAM in combination with CNI
MMF			risk for viral reactivation, best in 4 CTN trial
Pentostatin			best results in children
Campath			Effective if low doses are applied
Pulse steroids			May of if use in severe aGVHD

## Achievements – 2nd line treatment of aGVHD

Agent	Recom	Evid.	comments
Infliximab			Infectious risk, risk of relapse of GVHD
Etanercept			Lower infectious risk, most effective in GI-GVHD
PUVA			May be of use in isolated cutaneous GVHD
UVB			does not require photosensitizer
UVA1			does not require photosensitizer
MSC's			best results in GI and Liver GVHD
Denileukin-difitox			Inferior to MMF, may be a treatment option in selected cases
Basilizumab			Appears to be effective, infectious risk
Tregs			Only case reports available

# Outlook I

- ✓ Definition of standards for indication and technique of biopsies in GVHD
- ✓ Definition of standards for essential clinical information for histopathological work-up ([www.gvhd.de](http://www.gvhd.de))
- Definition of standards for histopathological work up
- Establishment of a network of second opinion pathologists for GVHD (analogous to the lymphoma network) including
  - Annual meetings (next in spring in Mainz)
  - Round Robin Tests
  - Scientific Projects
    - Biomarker for Diagnosis
    - Biomarker for Prognosis
    - Evaluation of Pathophysiology of GVHD (Mice – Human)

## Outlook II

- Development of the cGVHD registrar to capture:
  - Organ distribution and risk factors for cGVHD
  - Histopathology? (for evaluation of pathophysiology, biomarker)
  - First-line treatment
  - Follow up (prognostic marker for treatment response, survival)
  - to capture distribution and treatment of acute GVHD?

## Outlook III

- continuation of the work on the manuscripts on histopathology of skin, gastrointestinal, liver and lung GVHD
- submission of the manuscript on gynecological manifestations of cGVHD
- completion of the GI, Endocrinology, Psychology, Nephrology – manuscript
- completion of the manuscript on treatment of acute GVHD
- start of the trial on First-line Treatment of cGVHD with steroids and everolimus next spring
- Application for a grant to establish and run the GVHD Registrar
- Next spring meeting will be in Wiesbaden/Mainz (R. Schwerdtfeger, R.G. Meyer)
- Next fall meeting will be in Basel (J. Halter)

## Acknowledgements

Greifswald, Hamburg-Eppendorf, Münster (adults & children),  
Oldenburg, Rostock, Shreveport, Wien (adults & children), Jena,  
Frankfurt, Würzburg (children), Wiesbaden, Düsseldorf, Erlangen,  
Nürnberg, München-Schwabing (children), Linz, Freiburg, Mannheim,  
München-Großhadern, Tübingen, Ulm, Regensburg (adults & children),  
Göttingen, Düsseldorf, Hannover, Würzburg, Tübingen, Bonn, Stuttgart,  
Mainz, Heidelberg, Basel, Essen, Leipzig, Dresden, Zagreb, Bratislava

Howard Shulman

David Kleiner

Steven Pavletic

Anne Janin

Gerhard Hildebrandt

Diana Cardona

Daniela Massi

