Graft Versus Host Disease GVHD

BHS transplantation course - 2022

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Disclosure

HS reports having received personal fees from Incyte, Janssen, Novartis, Jazz Parmaceuticals, Takeda and from the Belgian Hematological Society (BHS), as well as research grants from Novartis and the BHS.

She has also received non-financial support from Incyte, Novartis, Gilead, the EBMT (European Society for Blood and Marrow transplantation) and the CIBMTR (Center for International Bone Marrow Transplantation Research).

- A patient develops a red rash on her whole body around day 125, whilst still receiving prophylactic doses of tacrolimus.
- An infection or drug reaction is excluded.
- What’s the most likely diagnose?

Acute GvHD

- How would you confirm your diagnosis?

By doing a biopsy

- What else do you need to know to properly evaluate the situation?

Bilirubine levels

Upper GI symptoms

Lower GI symptoms

+ EXCLUDE ANY SIGNS OF CHRONIC GVHD

Acute GVHD

Damage associated molecular patterns (DAMPs)
&
Pathogen associated molecular patterns (PAMs)

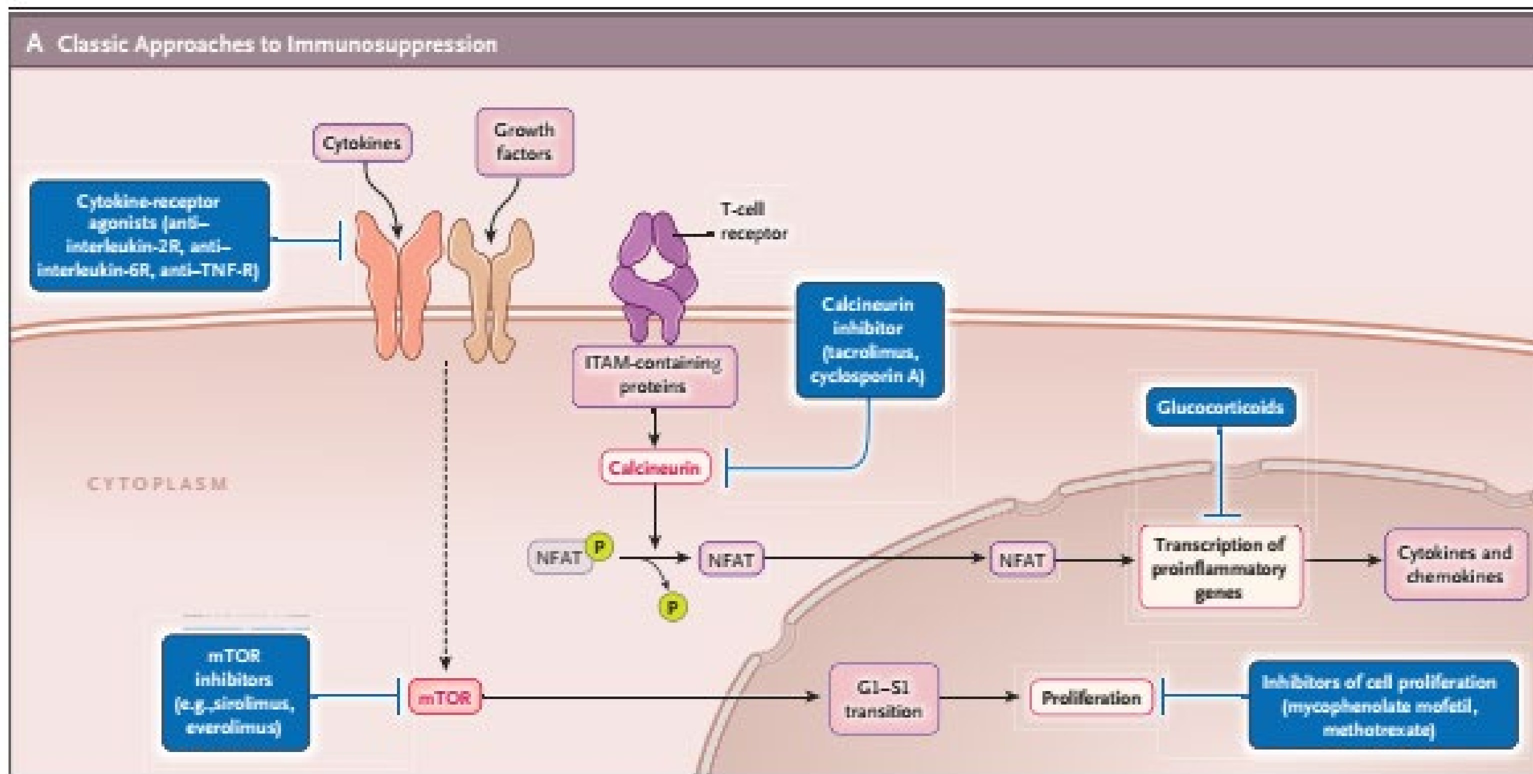
inflammatory cascade

activation of neutrophiles, monocytes, dendritic cells & T cells

Organ damage

Zeiser R et al. Blood, 2021.

GVHD – prevention



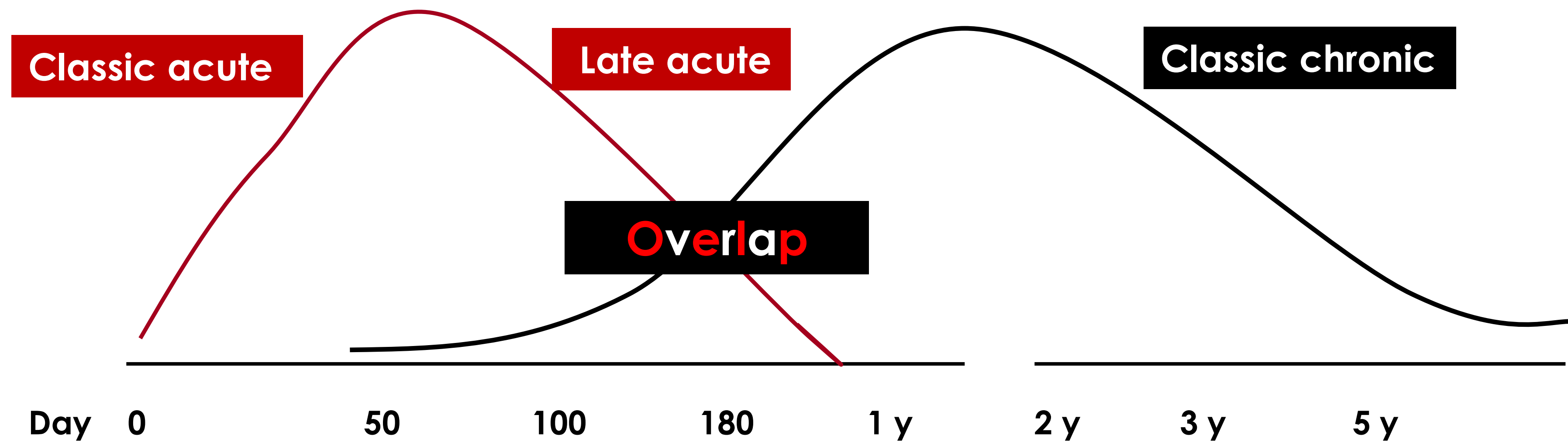
Prevention of GVHD typically relies on a combination of a calcineurine inhibitor with either MTX or MMF (during 3-6 months).

High dosis post transplant Cyclophosphamide and anti-thymoglobiuline (ATG) can also be used in addition.

Depletion of T cells is also an option.

Zeiser R et al. Blood, 2021.

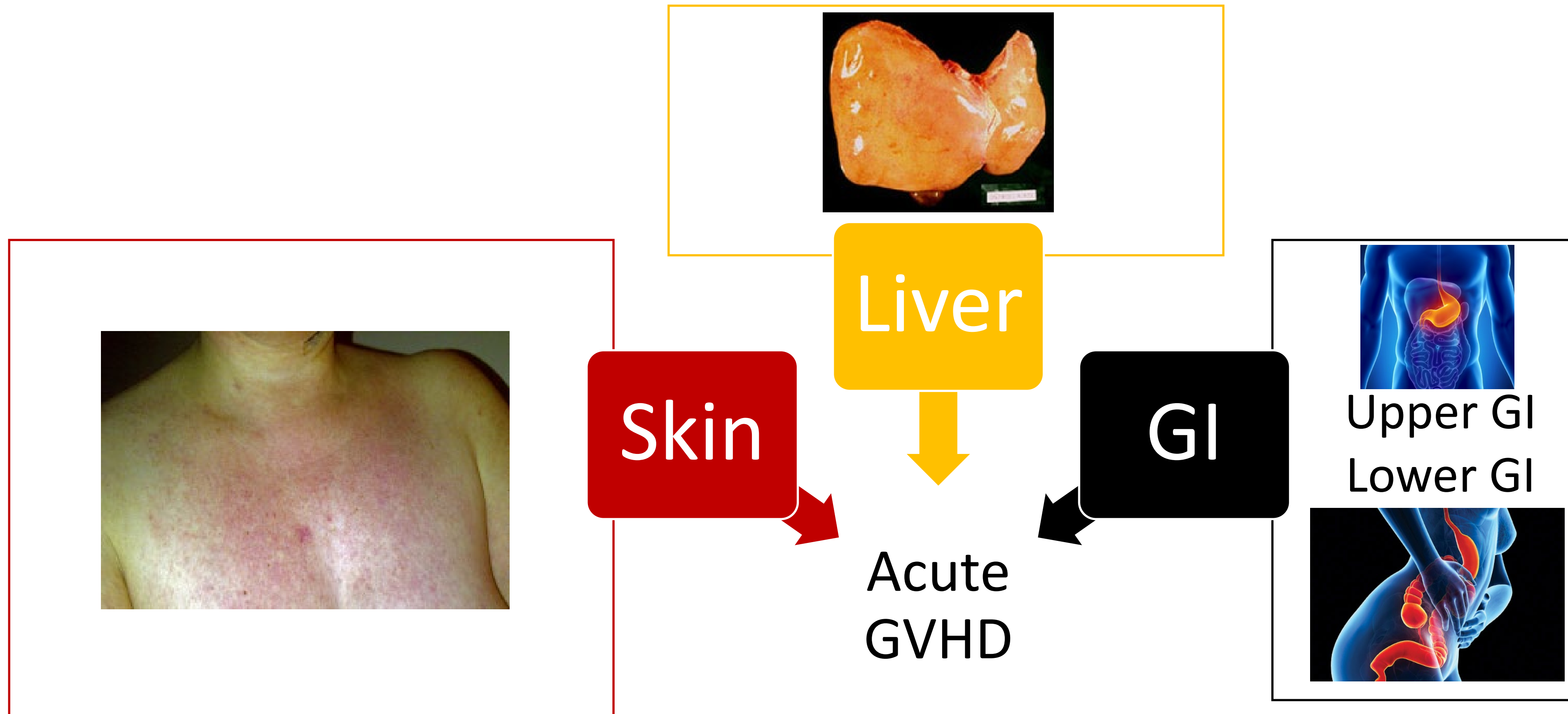
GVHD – detection



Activity (inflammation) → Damage (fibrosis)

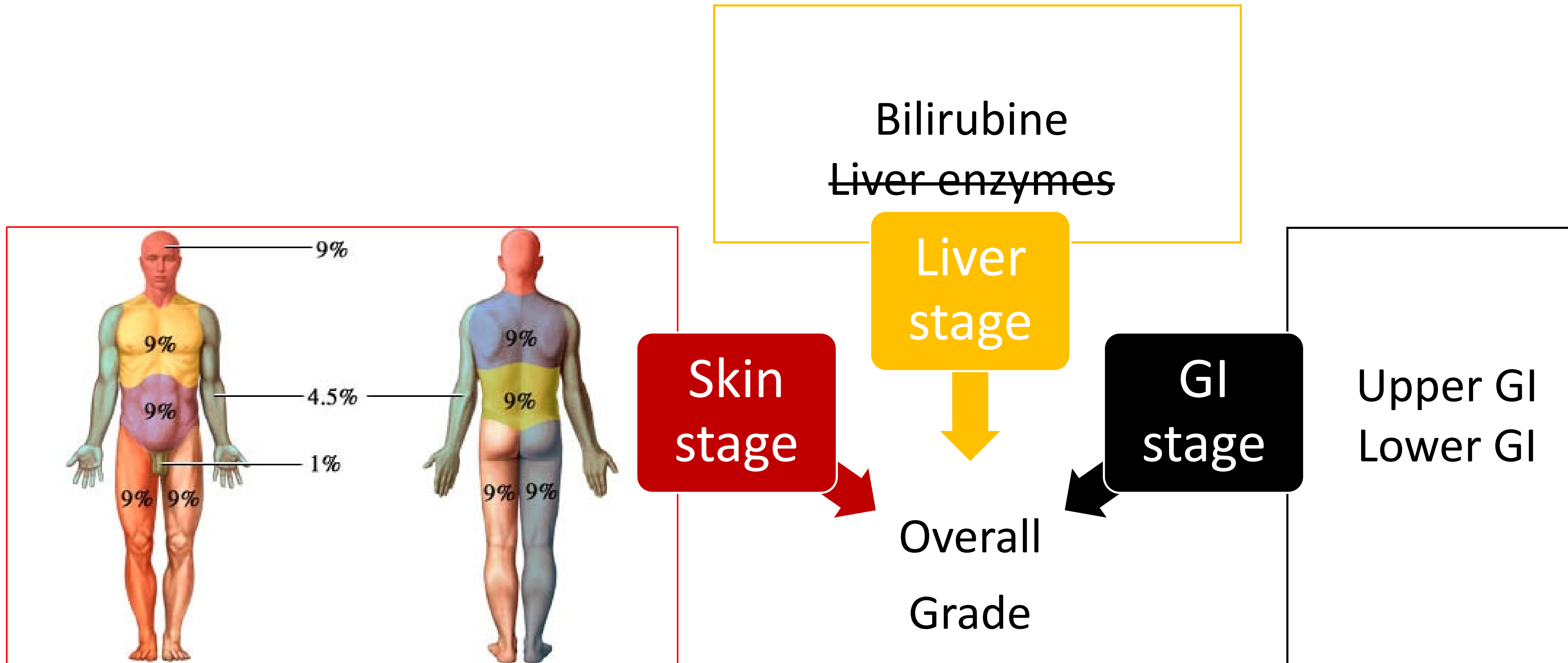
injury   repair

Acute GvHD diagnosis and staging



! A positive biopsy is not strictly required - a clinical suspicion is sufficient!

Acute GvHD diagnosis and staging



Acute GvHD staging per organ (1-4)

Stage	SKIN	LIVER	GI	Lower GI
0	No rash	Bili <2 mg/dL	-	<500ml (3 episodes)
1	Rash <25% BSA	Bili 2,1-3 mg/dL	Perisistent nausea/anorexie/vomiting	500-999ml (3-4 episodes)
2	Rash 25-50% BSA	Bili 3,1-6 mg/dL	-	1000-1500ml (5-7 episodes)
3	Rash >50% BSA	Bili 6,1-15 mg/dL	-	>1500 ml (>7 episodes)
4	Rash >50% BSA + 5% ulcerations	Bili >15 mg/dL	-	Severe abdominal pain / ileus / RBPA

Gluckberg, 1974 revised by Thomas, 1975
Rowlings, Br J Hem 1997
MAGIC (Mount Sinai Acute GvHD International Consortium) consensus : Harris et al, BBMT 2016

Acute overall GvHD scoring (I-IV) – MAGIC

GRADE		SKIN	LIVER	GI
0	NONE	0	0	0
I	Mild	1 or 2	0	0
II	Moderate	3	1	1
III	Severe	-	2 or 3	2 or 3
IV	Life threatening	4	4	4

Harris et al, BBMT 2016

- What's your first line treatment of choice?

Corticosteroids
1 to 2 mg/kg/d

First-line Therapy of Acute GvHD

- **Steroids at 2 mg/kg/day standard**

- **Lower steroid doses**
  - In grade IIa (*not VISCERAL*) 0.5 mg/kg/d are effective.
  - In grades $\geq$IIb (*VISCERAL*) 1 mg/kg/d increased need for secondary IS therapy.

- Start **steroid taper** when GvHD manifestations show major improvement.

- Gradual dose reduction of 0.2 mg/kg/d every 3-5 days, slower taper when prednisone below 20-30 mg/d

- By when does she need to answer to your treatment to avoid being considered to be refractory?

Progession w/i 3 days

No improvement by Day 5-7

No CR by D 28

Steroid refractory acute GVHD treatment

Ruxolitinib (Zeiser et al NEJM 2020)

Alemtuzumab
Alpha-1antitrypsin (AAT)
Anti-Thymoglobulin (ATG)
Basiliximab
Calcineurine inhibitors
Etanercept
Extracorporeal photopheresis (ACP)
Infliximab
mTor inhibitors (sirolimus, …)
Mycophenolate mofetil
Pentostatin
Tocilizumab

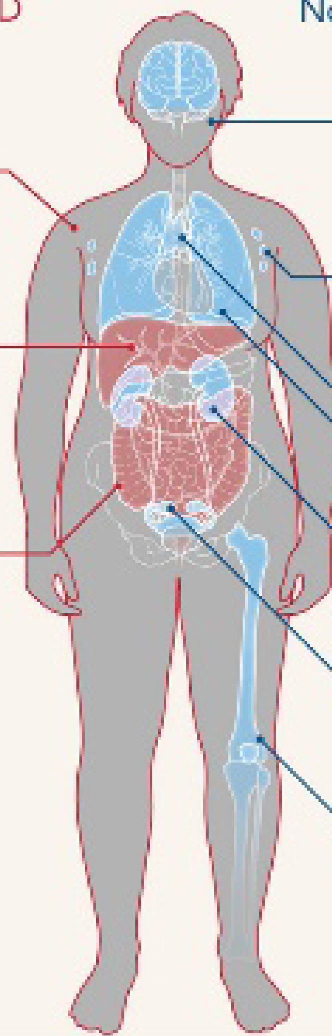
Selection of agent based on:

Institutional preference
Physician experience
Toxicity profile
Effect of prior treatment
Drug interactions
Accessibility
Patient tolerability

!!! consider a clinical Trial !!!!

NCCN guidelines, 2021.

- Emerging evidence indicates that non-classical target organs can be targeted in acute GVHD.
- There is a need to develop a consensus for their diagnosis and treatment.



Zeiser R et al. Blood, 2021.

Chronic GVHD

Damage associated molecular patterns (DAMPs)

&

Pathogen associated molecular patterns (PAMs)

inflammatory cascade

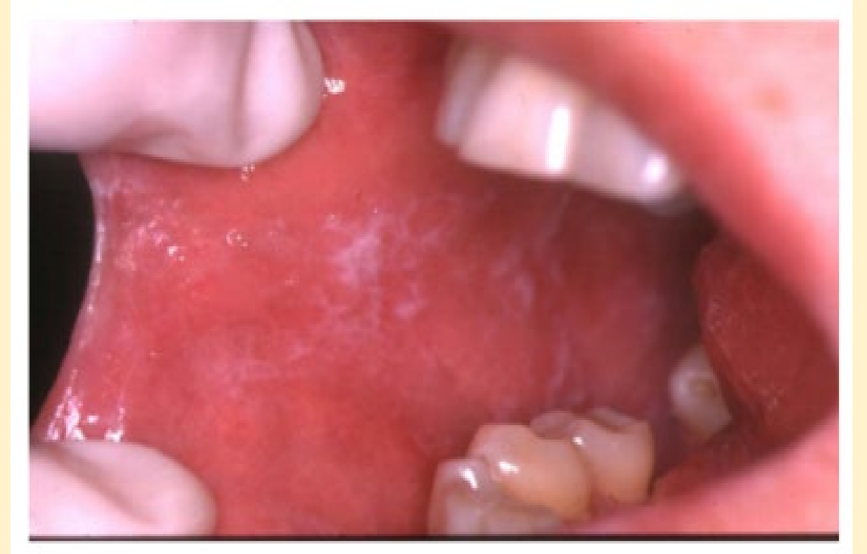
activation B & T cells

fibrotic cascade

Zeiser R et al. NEJM, 2017

- Samy has a pretty uneventful post-tx follow up, but presents to his 9 months follow up visit with slight pain in the mouth.

- This is what you see – what's your diagnosis?

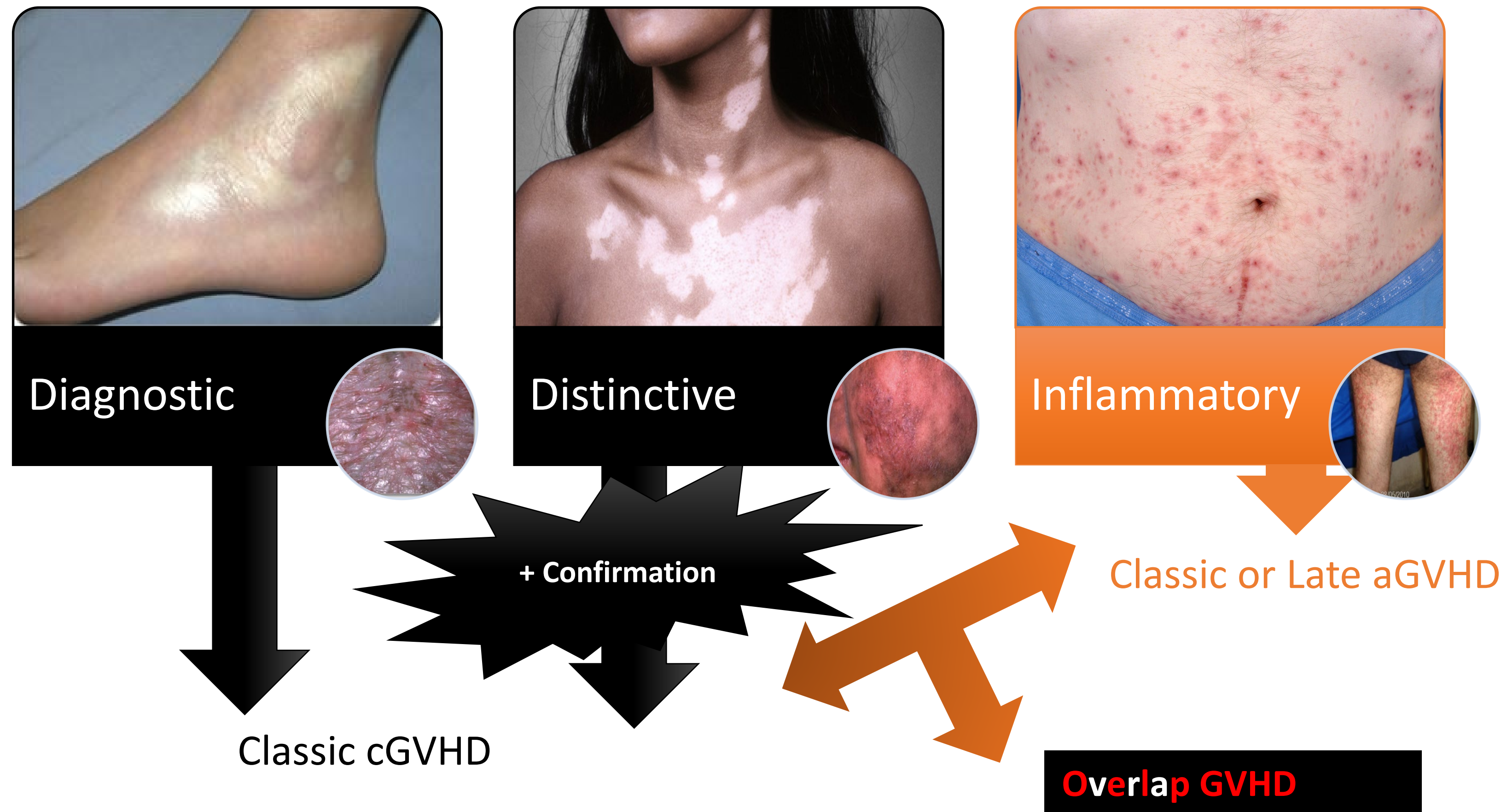


Lichen planus

- Which other organs do you need to evaluate?

All !

A Diagnosis of cGVHD is based on distinct criteria

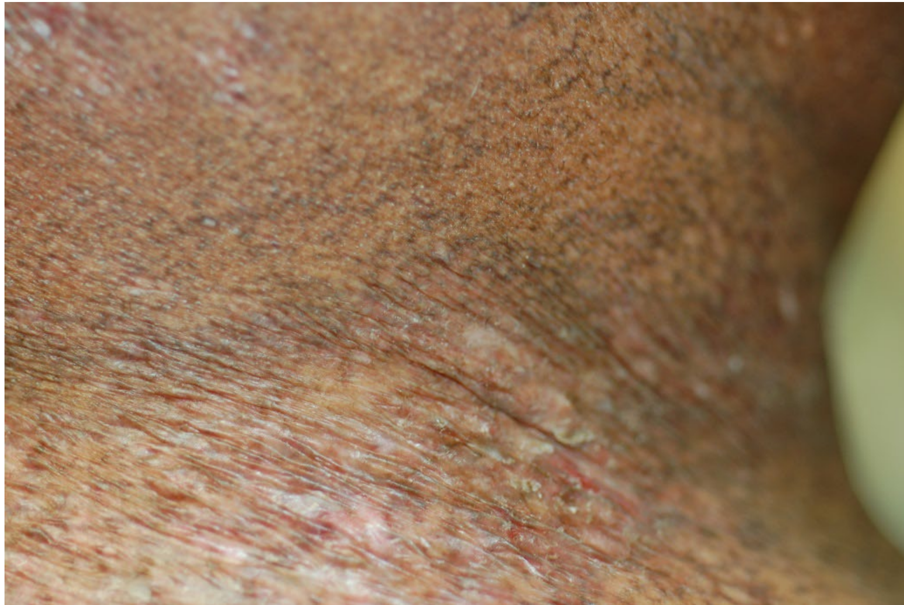


Diagnostic Signs of chronic GvHD

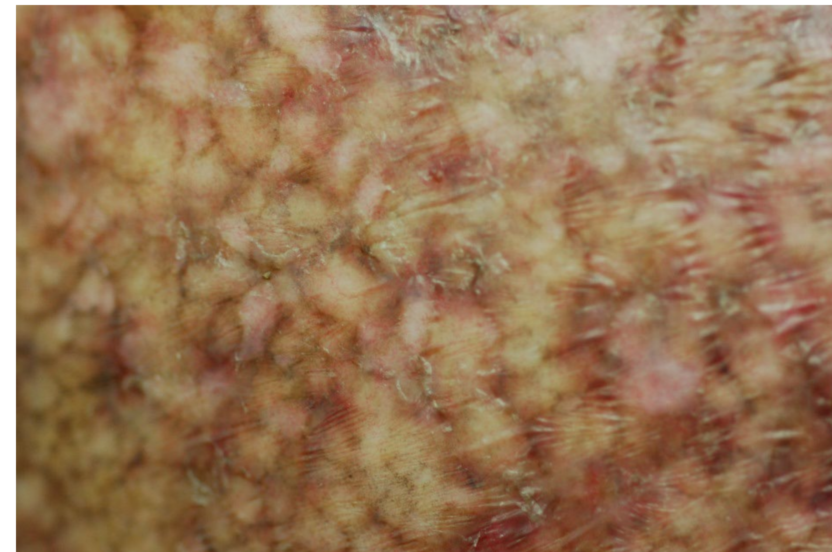
Organ	Feature
Skin	Poikiloderma, lichen planus-like, morphea-like, lichen sclerosus-like, sclerotic features
Mouth	Lichen planus-like
Eyes	-
Genitalia	Lichen planus-like, lichen sclerosus-like
GI Tract	Esophageal web, strictures or stenosis in esophagus
Liver	-
Lung	Bronchiolitis obliterans (BOS) with positive lung biopsy
Muscles, fascia, joints	Fasciitis, joint stiffness or contractures sec. to fasciitis or sclerosis

Jagasia MH, Greinix H et al, BBMT 2015;21:389-401

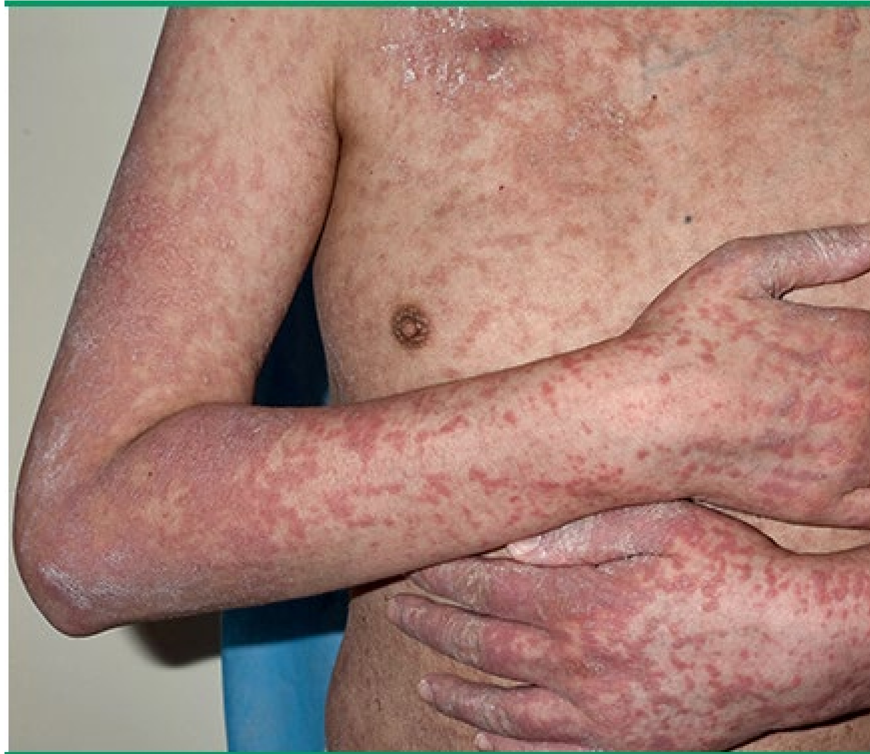
Skin Chronic GvHD: Poikiloderma

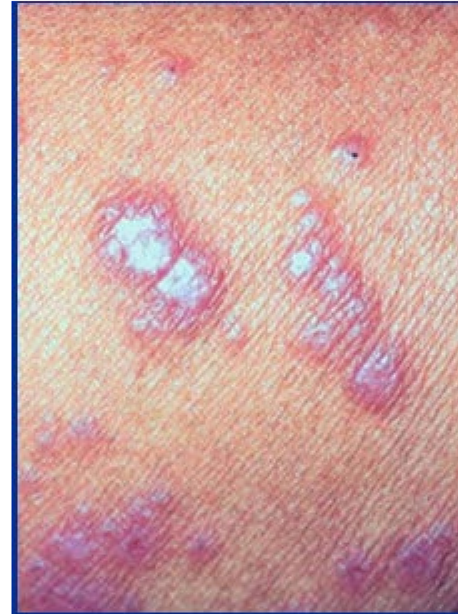


Increased and decreased pigmentation,
Prominent blood vessels, thinning of skin



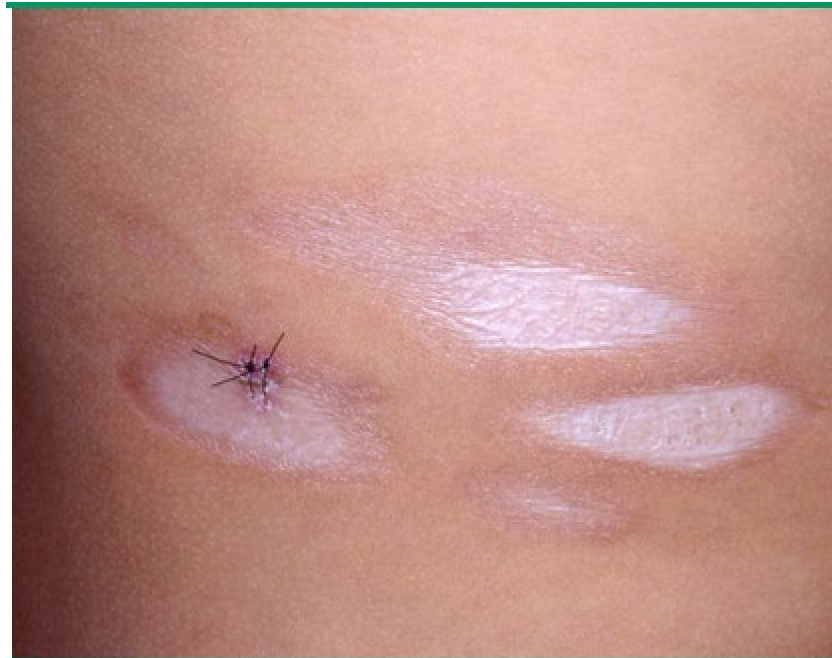
Skin Chronic GvHD: Lichen Planus





NO BIOPSY needed

Skin Chronic GvHD: Lichen Sclerosus



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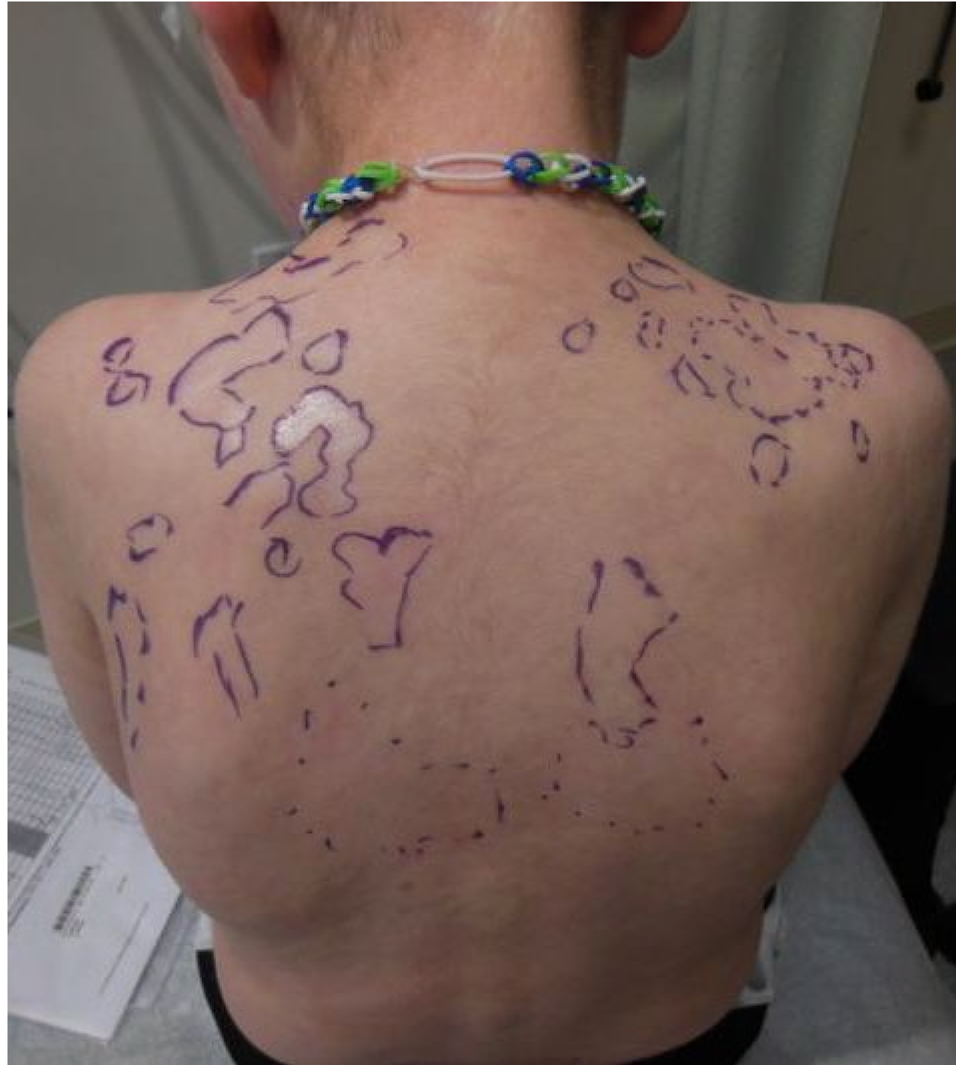
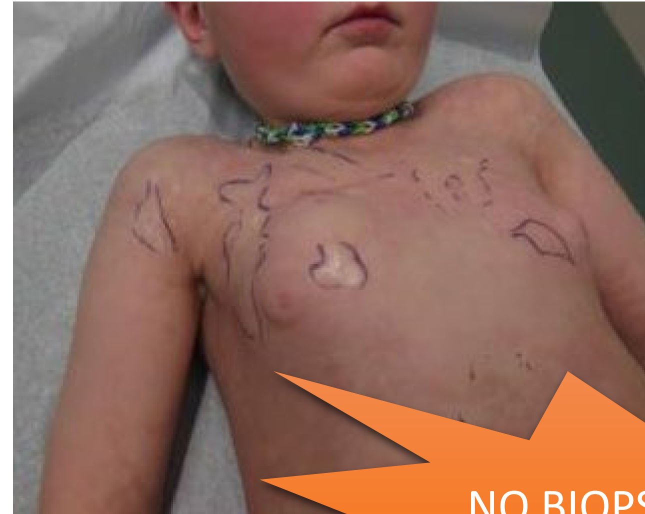
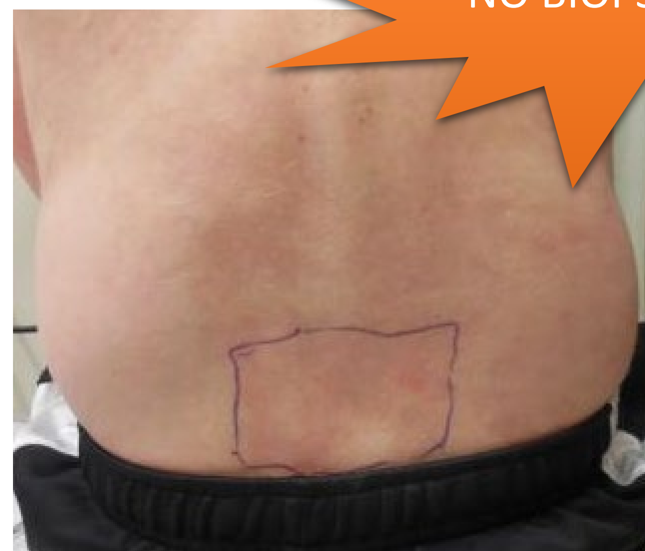
Skin Chronic GvHD: Morphea







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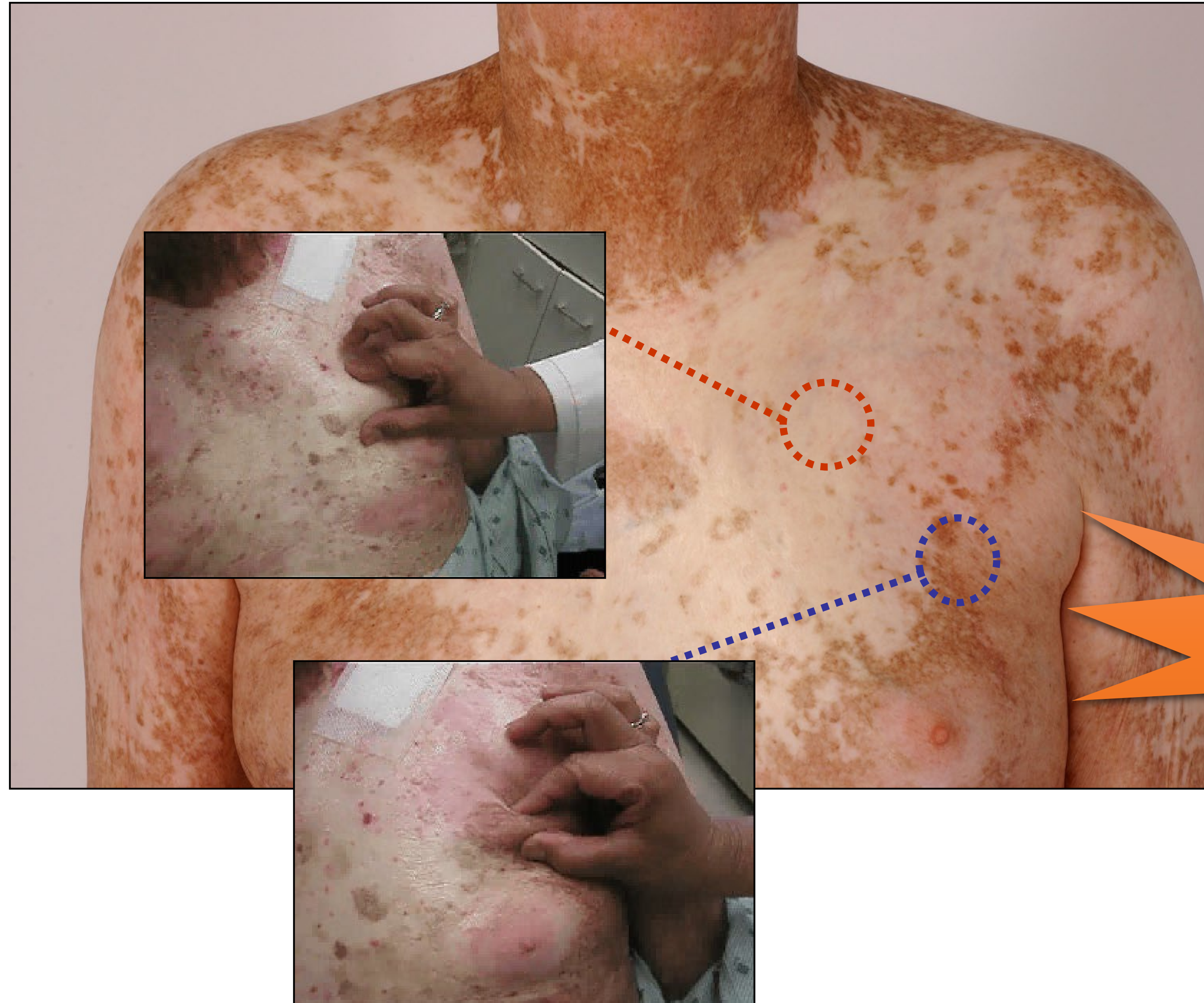
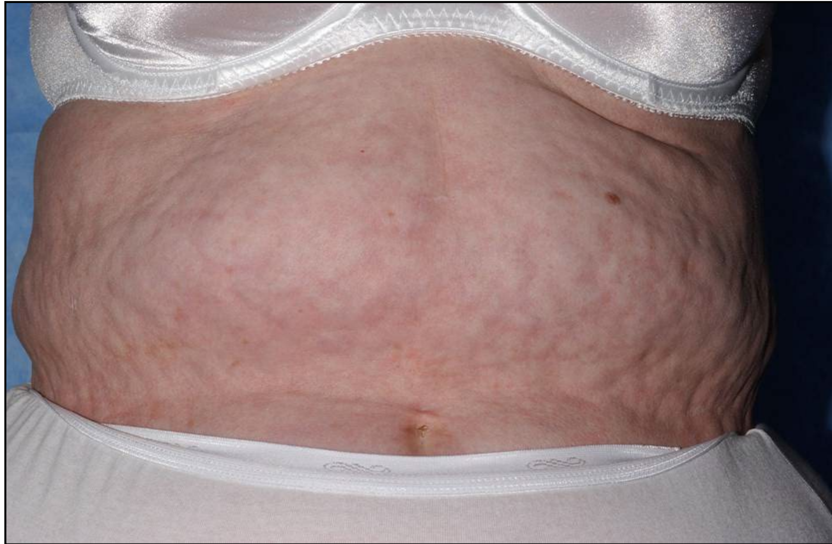
Skin Chronic GvHD: Sclerosis

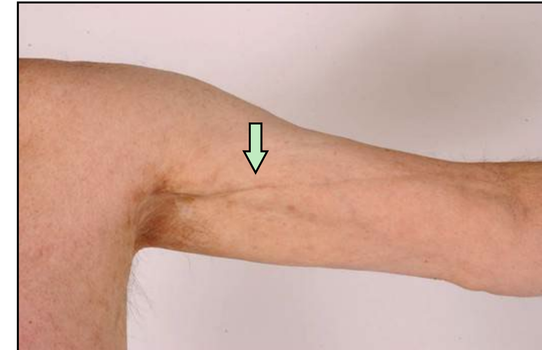


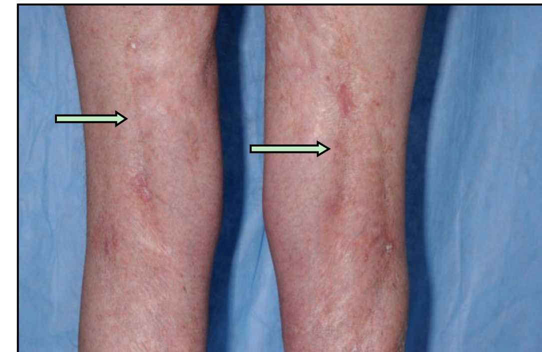
NO BIOPSY needed

Skin Chronic GvHD: Sclerosis

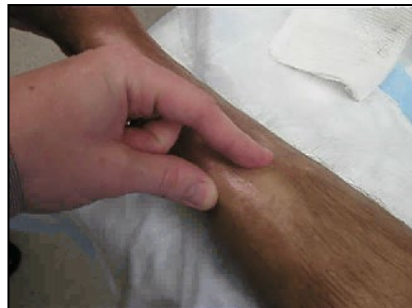


Sub cutaneous sclerosis
'Rippling'





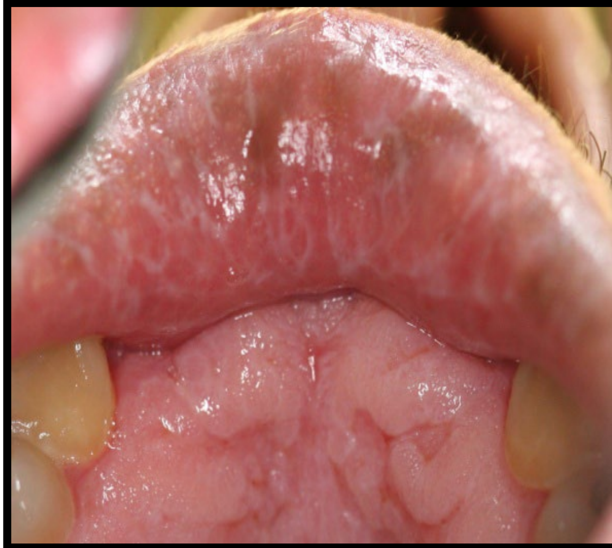
Fasciitis
Groove sign



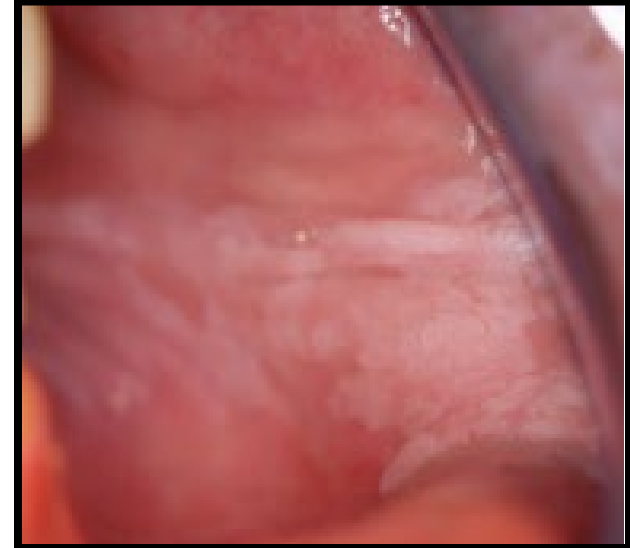
Hindbound skin

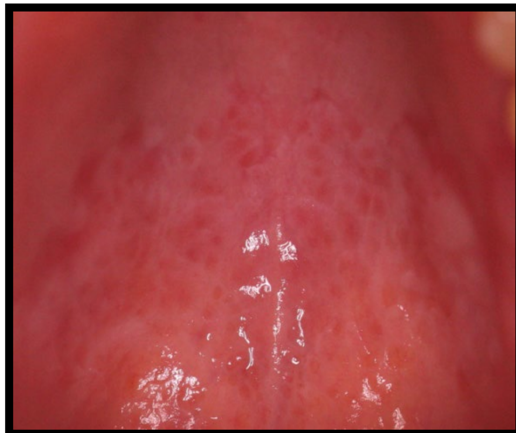
NO BIOPSY needed

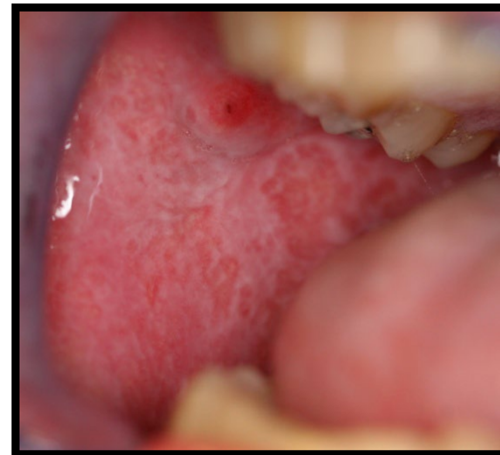
Diagnostic: Lichen-Type Features



Erosive Lichenoid Lesion

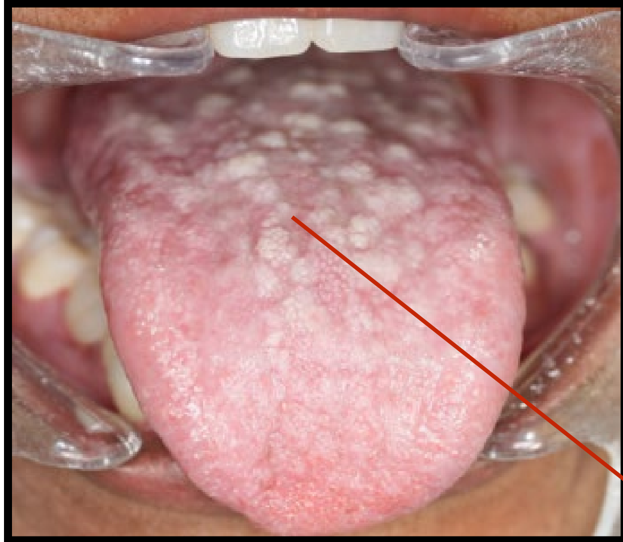


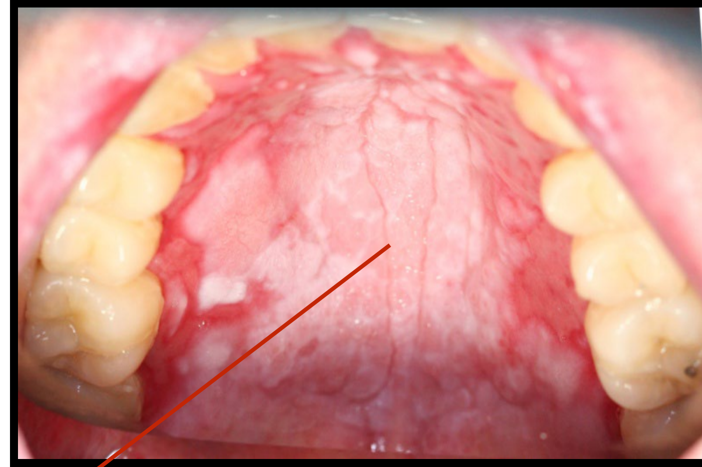


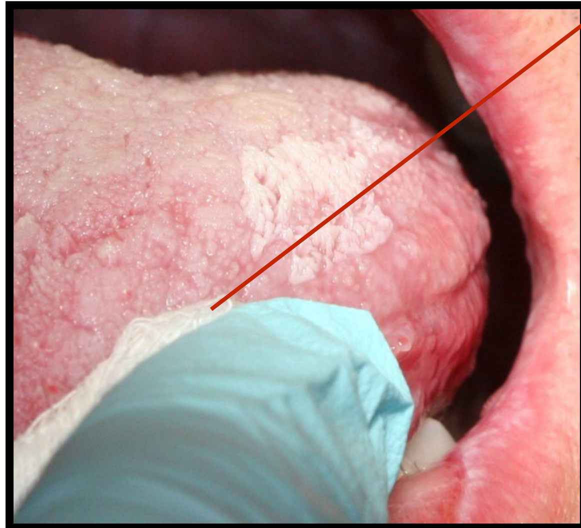


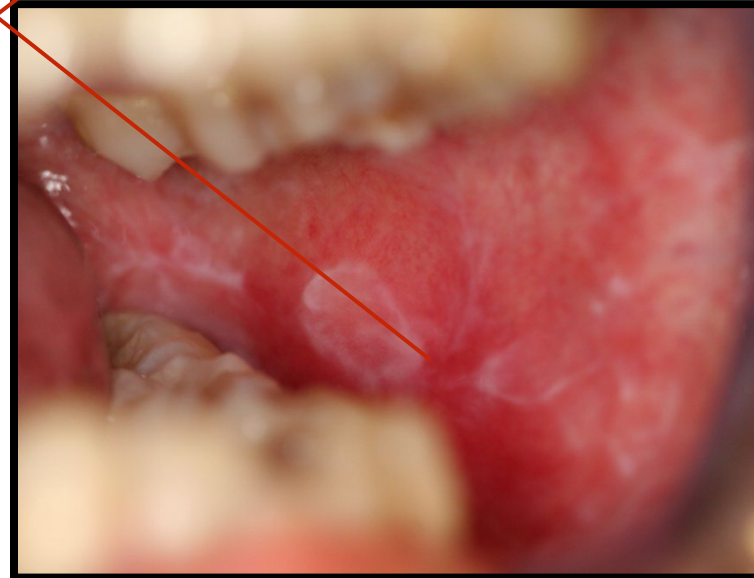
NO BIOPSY needed

NOT Hyperkeratotic Plaques

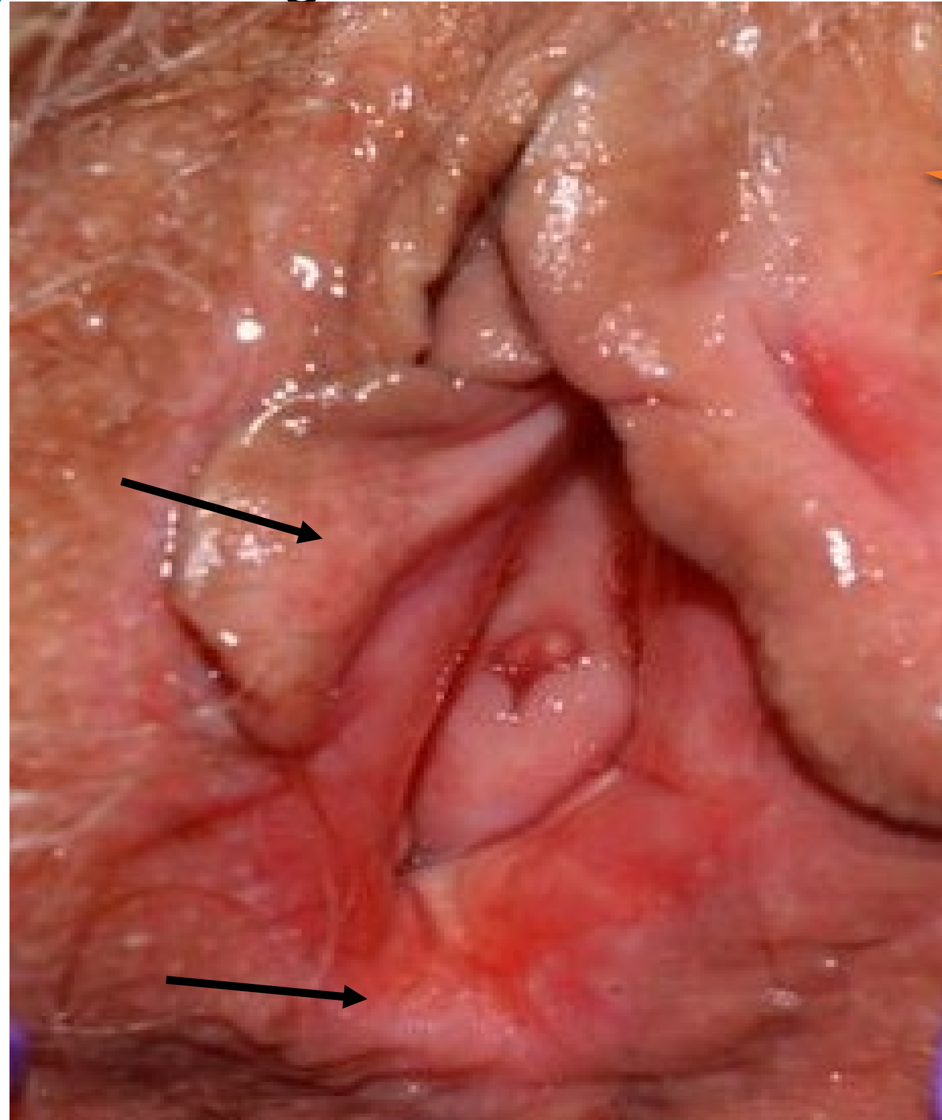






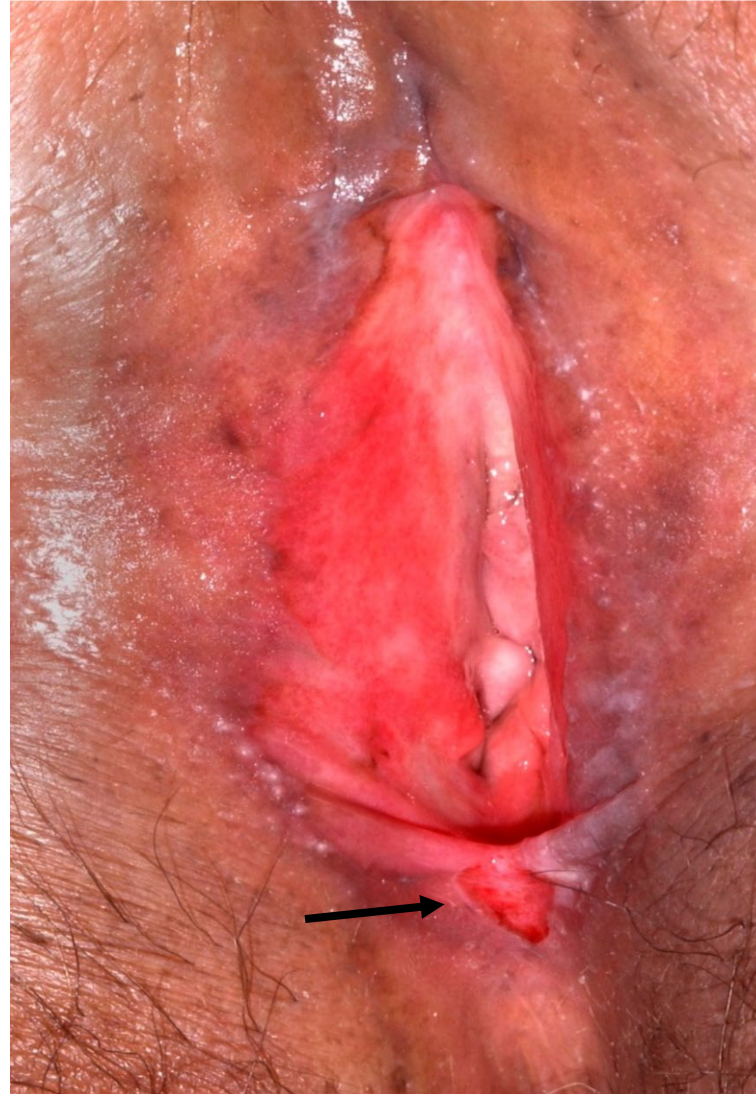


Diagnostic: Reticulated leukokeratosis (lichen-planus like) of the right labia minora and posterior forchette



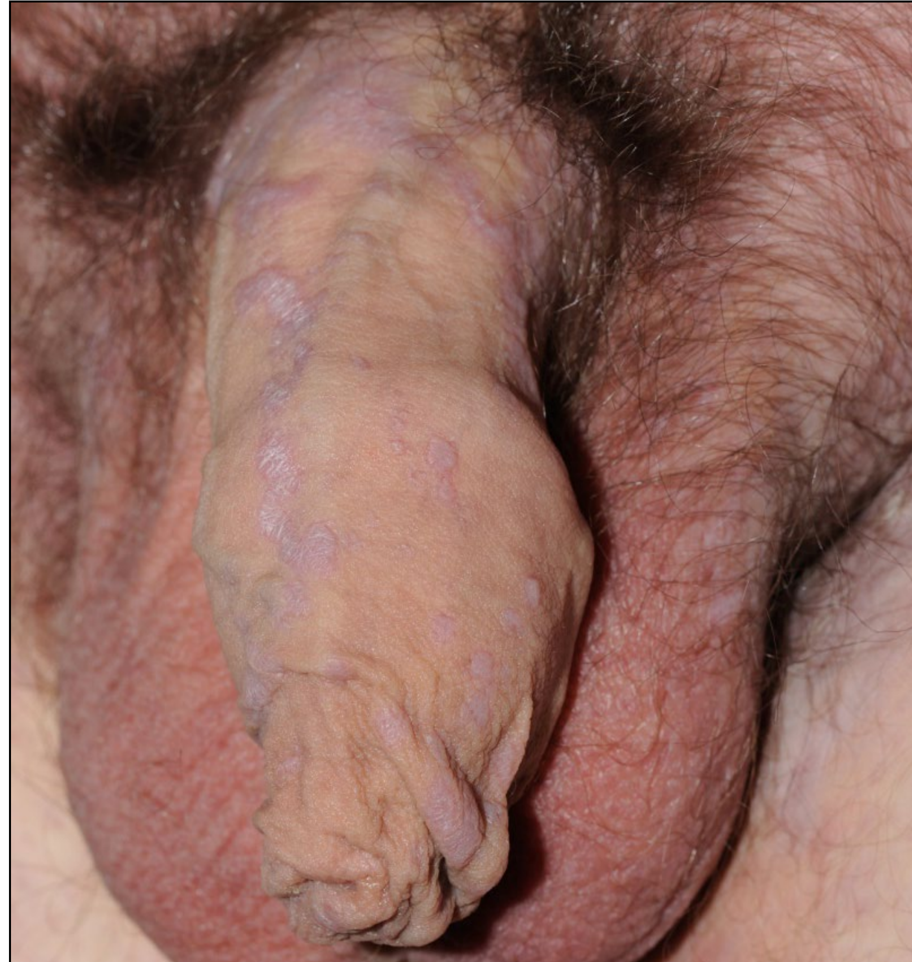
NO BIOPSY needed

Diagnostic: sclerosis (scarring) of the labia; note tear/fissure at posterior commissure (distinctive)



NO BIOPSY needed

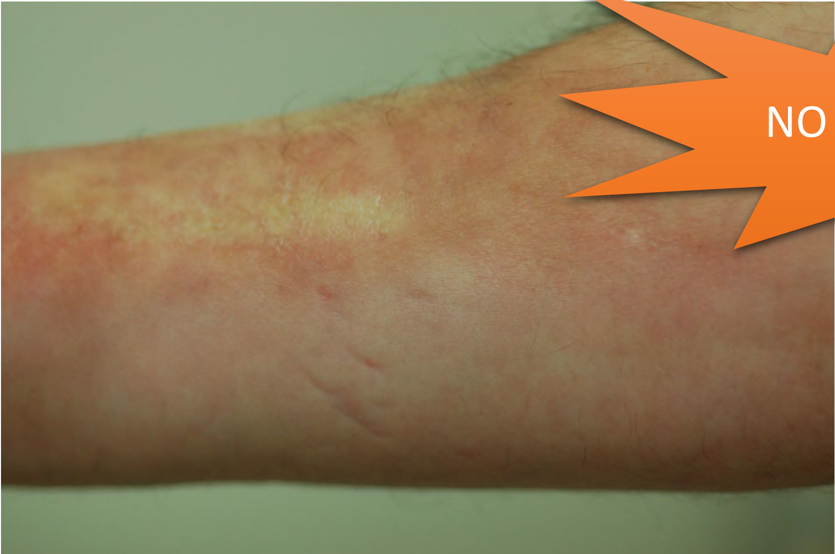
Diagnostic: Lichen planus-like, violaceous papules which may coalesce into ring-like small plaques

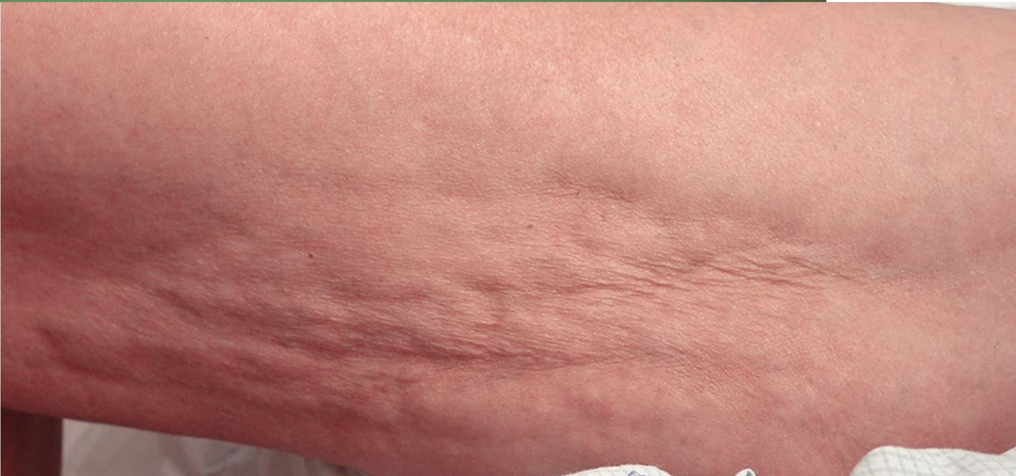


NO BIOPSY needed

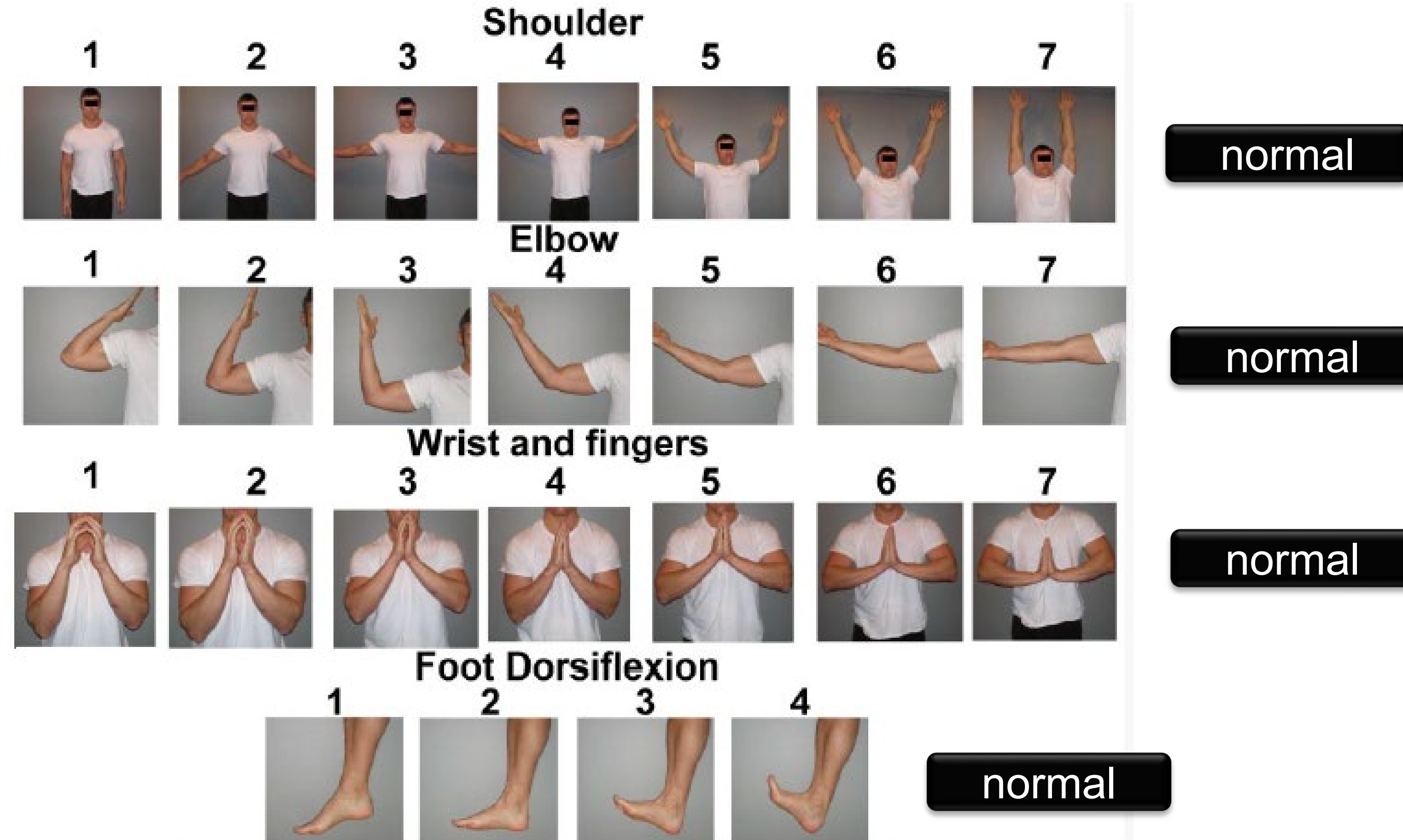
Chronic GvHD: Sclerosis and Fasciitis

NO BIOPSY needed





Chronic GvHD: Sclerotic or Fasciitis and Photographic Range of Movement (P-ROM)



normal

normal

normal

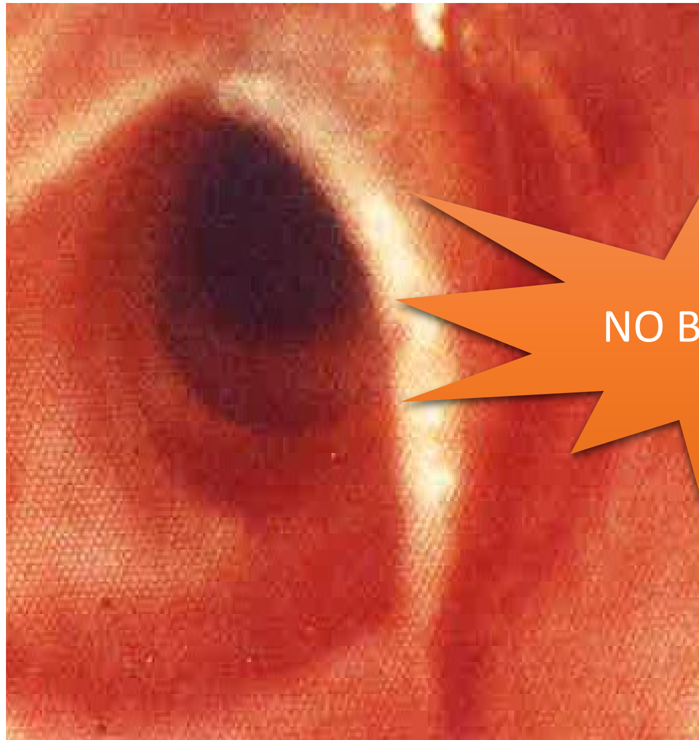
normal

Jagasia MH, Greinix H et al, BBMT 2015;21:389-401

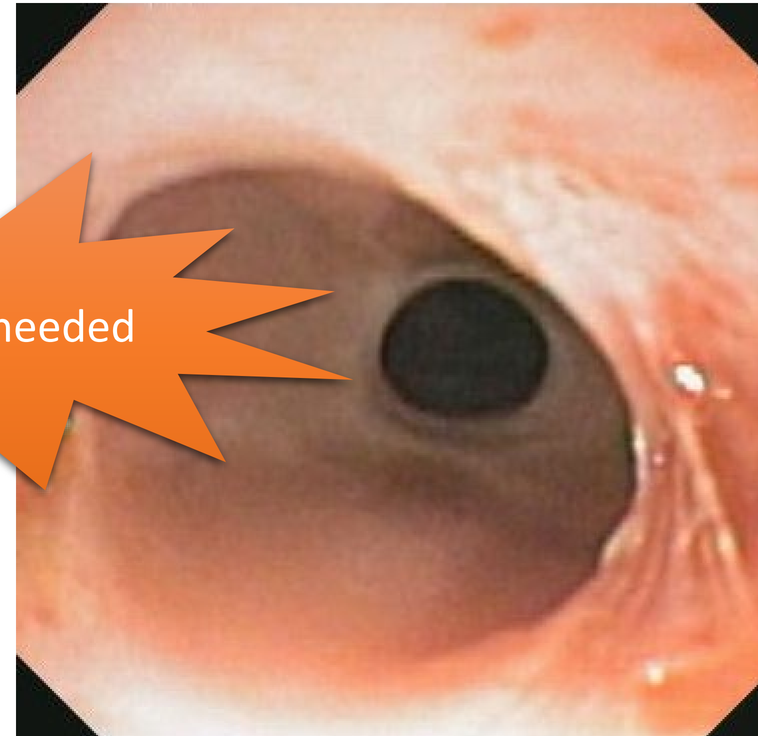
Carpenter P et al, Blood 2011; 118 (13): 2679-2687

Diagnostic Signs - esophagus

Esophageal web



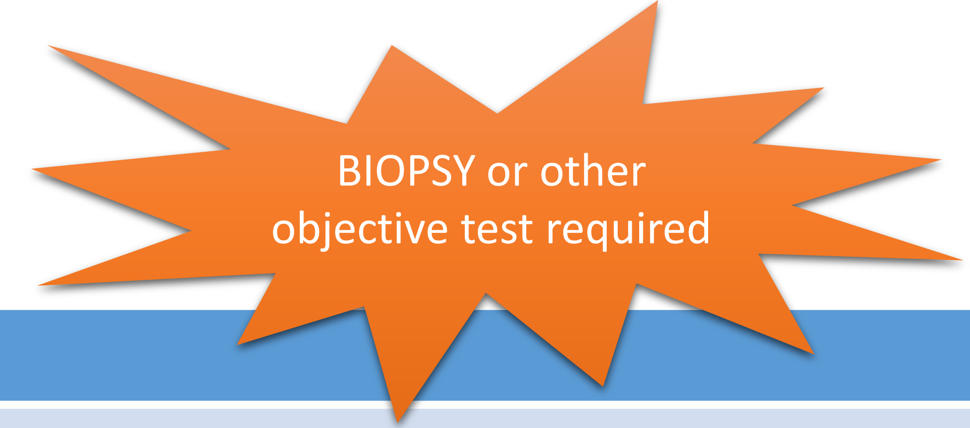
Esophageal stricture



post dilation

NO BIOPSY needed

Distinctive Signs of chronic GvHD



Organ	Example
Skin	Hypo/Hyper pigmentation, alopecia …
Mouth	Hyper keratosis, Sicca, …
Eyes	Sicca, …
Genitalia	Ulcerations, …
GI Tract	-
Liver	Increased liver enzymes (AP and/or ALT) or bilirubine, …
Lung	Impaired lung function with signs of BOS, …
Muscles, fascia, joints	Myositis, …

Jagasia MH, Greinix H et al, BBMT 2015;21:389-401

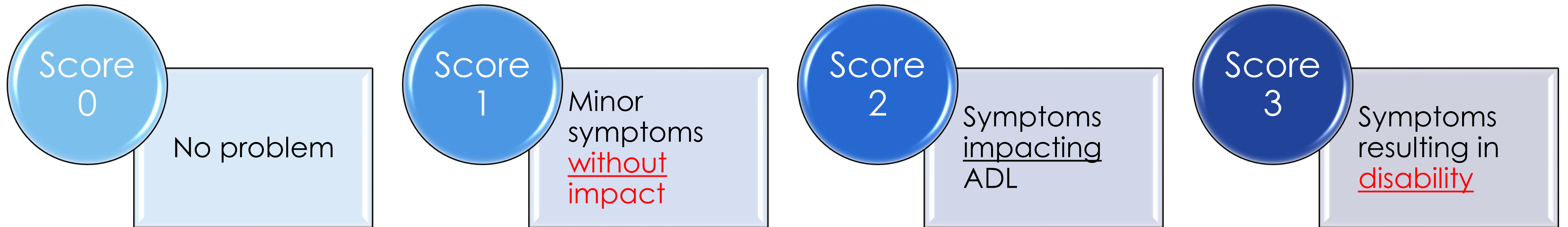
- So let’s pretend there are no other GvHD related symptoms/signs: only slight pain in the mouth because of lichen planus. What’s his diagnosis and score?

Classic Chronic GvHD

Mouth score 1 = mild

cGvHD scores according to NIH 2014

Eight organs : skin, mouth, eyes, GI, liver, lung, genitalia and joints/muscles



Jagasia MH, Greinix H et al, BBMT 2015;21:389-401

cGvHD scores according to NIH 2014

# OF ORGANS	MILD
1	Score 1
2	Score 1
3	

MILD = 1 or 2 organs (but not lung) with maximum Score 1

MODERATE = Lung Score 1 **or** ≥ three organs at Score 1 **or** at least one organ at Score 2

SEVERE = Lung Score 2 **or** Score 3 in any organ

Jagasia MH, Greinix H et al, BBMT 2015;21:389-401

- So let's pretend there are no other GvHD related symptoms/signs: only slight pain in the mouth because of lichen planus. What's his diagnosis and score?

Classic Chronic GvHD

Mouth score 1 = mild

- But... Don't forget to check the lungs!!!

- the lung function tests show an obstructive pattern with increased RV (140%), FVC/FEV1 0.65 and FEV_1 is 59% of normal.

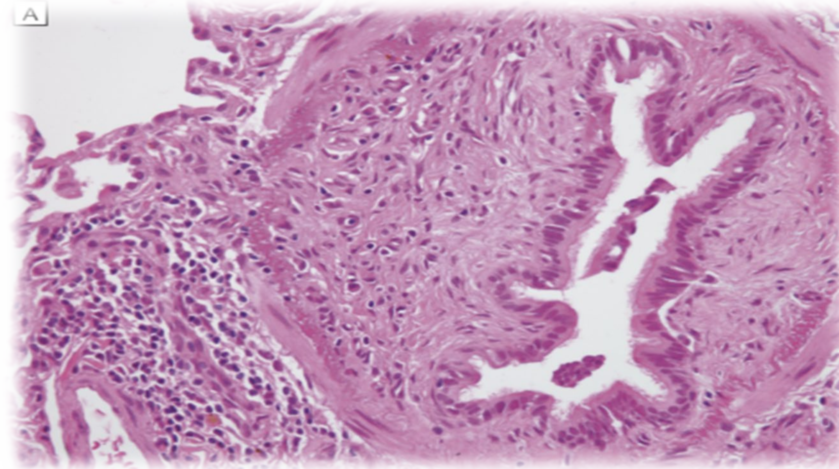
- What's your next step?

Exclude an infection !

GVHD of the lungs

BOS

Bronchiolitis Obliterans Syndrome



Peribronchial proliferation between the epithelium and smooth muscle

Airtrapping ➔ Obstruction

AJR 2012;199:581-587.

Diagnostic – Lung – Bronchiolitis obliterans (BOS)

- FEV1<75% of predicted with ≥10% decline over less than 2 years.
- FEV1/FVC < 0.7 or the fifth percentile of predicted.
- Absence of respiratory tract infection.

ALL THREE

Jagasia MH, Greinix H et al, BBMT 2015;21:389-401

- The lung function tests show an obstructive pattern with increased RV (140%), FVC/FEV1 0.65 and FEV_1 is 59% of normal.

- What's the impact on the GVHD score? Yes

Mouth 1

overall 'MILD'

Mouth 1 + Lung 2

overall 'SEVERE'

cGvHD scores according to NIH 2014

# OF ORGANS	MILD
1	Score 1
2	Score 1
3	

MILD = 1 or 2 organs (but not lung) with maximum Score 1

MODERATE = Lung Score 1 **or** ≥ three organs at Score 1 **or** at least one organ at Score 2

SEVERE = Lung Score 2 **or** Score 3 in any organ

Jagasia MH, Greinix H et al, BBMT 2015;21:389-401

Indications for Systemic Treatment of cGvHD

- **Symptomatic mild cGvHD**
  - Only manifestations not accessible to topical therapy e.g. hepatic, fasciitis
- **Moderate cGvHD**
  - Requires systemic treatment
- **Severe cGvHD**
  - Requires systemic treatment

Wolff D et al. BBMT 2010

Systemic Treatment of cGvHD

FIRST-LINE THERAPY

ADDITIONAL THERAPY

Chronic GVHD[q] →

Clinical trial[i]
or
Continue or consider restarting original immunosuppressive agent
and/or
Systemic corticosteroids 0.5–1 mg/kg/day[r] **methylprednisolone (or prednisone dose equivalent)**
±
Topical steroids as clinically indicated[s]
and/or
Inhaled steroid[t] **± azithromycin**[u] **for lung involvement**[v,w] **(eg, FAM [fluticasone, azithromycin, and montelukast])**

Response[i] → **Taper steroids as clinically feasible**[p]

No response[i] **(steroid-refractory disease)** →

Clinical trial[j]
or
Addition of systemic agent to corticosteroids with steroid taper as clinically feasible[p]
See Suggested Systemic Agents for Steroid-Refractory GVHD (GVHD-E)

NCCN guidelines, 2021.

Steroid refractory chronic GVHD treatment

!!! consider a clinical Trial !!!!

Ruxolitinib (Zeiser et al NEJM 2021)

Alemtuzumab
Abatercept
Alemtuzumab
Belumosudil
Calcineurine inhibitors
Etanercept
Extracorporeal photopheresis (ECP)
Hydroxychloroquine
Ibrutinib
Imatinib
Interleukin-2
Methotrexat
mTor inhibitors
Pentostatin
Rituximab

Selection of agent based on:

Institutional preference
Physician experience
Toxicity profile
Effect of prior treatment
Drug interactions
Accessibility
Patient tolerability

Penack, Lancet Hematology 2020
NCCN guidelines, 2021.

The best way not to miss GVHD is to think about it early…

Recommended baseline evaluation

Organ System	Required Clinical Documentatoin
Skin (including nails and hair)	Baseline skin abnormalities (scars, vitiligo, etc) with photo-documentation, if possible.
Mouth	Presence of linea alba, lichen-planus like changes and mucosal abnormalities.
Eye	Presence of dry eyes and other eye symptoms, use of prescribed or over-the-counter eye drops
Lung	Pulmonary function tests including: spirometry (FEV_1, FVC, FEV_1/FVC ratio, $FEF_{25-75\%}$), lung volumes (VC, TLC, RV), and DLCO.^
Liver	Bilirubin, AST, ALT, Alk phosphatase
GI tract	Presence of anorexia, nausea, vomiting, diarrhea, dysphagia, food allergies/intolerance etc.
Fascia/joints	Baseline limb mobility issues and photographic range of motion (P-ROM)[63] For the pediatric adaption of P-ROM see EBMT handbook/chronic GVHD[32]
Genital	Evidence of lichen-planus like lesions, erythema, ulcers, fibrosis or phimosis in males (ideally women will be evaluated by a gynecologist)

^PFTs may not be feasible in patients <7 years of age.

Repeated every 1-3 months until immunosuppression has been discontinued for at least 6 months

Teach patients how to recognize it themselves

Referral to TX team
if any item is suggestive for cGVHD

https://ncifrederick.cancer.gov/events/conferences/2020ChronicGVHDConsensus/gvhd

Kitko et al, Transplant Cell Ther 2021

Allogeneic Tx or DLI

GVHD ?

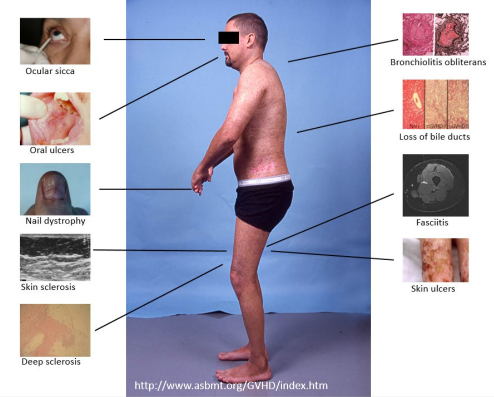
Acute
Classic (<D100) or Late (> D100)

Severity Score
Keystone – MAGIC – (IBMTR)

Grade I (A)

Grade II – IV (B-D)

Chronic
Classic or Overlap or Undefined



Severity Score
(NIH)

Moderate - Severe

Mild

GVHD – Treatment

GVHD – Response

eGVHD App – free for use

www.uzleuven.be/egvhd

Thank you !