ECHO Program

Atypical Manifestations of Chronic GVHD

Moderator: **Kirk Schultz, MD, FCAHS**

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Presenter: **Geoffrey Cuvelier, MD, FRCPC**
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Winnipeg, CA

Case Presenter: **Iskra Pusic, MD**
Associate Professor
Washington University St. Louis
St. Louis, MO

ECHO Program

Welcome to the Fifth ECHO Program of the GVHD Interactive Provider Network

- The goal of the GVHD Interactive Provider Network ECHO is to connect GVHD specialists with community providers to share expertise, discuss cases, and improve patient care.
- The network is based on the ECHO Model™ (Extension for Community Healthcare Outcomes) which uses proven adult learning techniques and interactive video technology to connect community providers with specialists in collaborative sessions.
- The sessions, designed around case-based learning and mentorship, will help primary care and community-based practitioners gain the practical expertise required to care for GVHD patients. Questions and comments from the learners will be encouraged to facilitate discussion.

ECHO Program

Target Audience

This CE activity is intended for physicians of all specialties, nurse practitioners, physician assistants, and other healthcare professionals who treat patients with chronic GVHD.

Educational Objectives

After completing this CE activity, the participant should be better able to:

- Explain how chronic GvHD can present with atypical manifestations in organ systems not classically described by the NIH consensus criteria.
- Discuss what is known (and what is not known) about chronic GvHD involving the hematopoietic system, peripheral and central nervous system, kidneys, MSK, and serosal membranes.
- Review how to integrate the assessment of atypical chronic GVHD into patient care, including some of the limitations in doing so.

ECHO Program

Program Agenda

- Welcome and Introductions – Kirk Schultz, MD, FCAHS
- Didactic presentation – Geoffrey Cuvelier, MD, FRCPC
- Case presentation – Iskra Pusic, MD
- Q & A and Panel Discussion
- Closing Announcements

Accreditation, Support, and Credit

In support of improving patient care, this activity has been planned and implemented by Medical Learning Institute, Inc., and Aplastic Anemia and MDS International Foundation. Medical Learning Institute, Inc. is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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This CE activity is supported by an educational grant from Incyte Corporation.

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Successful completion of this nursing continuing professional development activity will be awarded 1.0 contact hour and 1.0 contact hour in the area of pharmacology.

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This activity was planned by and for the healthcare team, and learners will receive 1.0 Interprofessional Continuing Education (IPCE) credit for learning and change.

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All relevant financial relationships of individuals for this activity have been mitigated.

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ECHO Program

The GVHD Interactive Provider Network is administered by

the Aplastic Anemia and MDS International Foundation

Partner Organizations of the GVHD Interactive Provider Network:

ECHO Program

For educational and quality improvement purposes,
we will be recording this video-session

By participating in this program you are consenting to be recorded –
we appreciate and value your participation

If you have questions or concerns, please email gvhdnetwork@aamds.org

ECHO Program

Some helpful tips for participating in this ECHO program:

- We encourage you to keep your camera on during the program
- Please mute your microphone when not speaking (left bottom corner of your screen)
- To ask a question or make a comment, raise your hand on camera or use the raised hand icon in the Reaction section at the bottom of your screen
- Speak clearly and state your name and institution or practice before stating your question or comment
- You may also use the chat function to submit comments or questions

Atypical Chronic Graft-Versus-Host Disease:
Challenges in chronic GVHD diagnosis

Geoff Cuvelier MD, FRCPC

Director, Pediatric Blood and Marrow Transplant Program

CancerCare Manitoba

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Winnipeg, Manitoba, Canada

Disclosures

- Consultancy honorarium Miltenyi Biotech
- None related to this talk.

Objectives

After participating in the session that will include a presentation, case examples, and interactive discussion, the learner should be able to:

1. Explain how chronic GvHD can present with atypical manifestations in organ systems not classically described by the NIH consensus criteria.

2. Discuss what is known (and what is not known) about chronic GvHD involving the hematopoietic system, peripheral and central nervous system, musculoskeletal system, kidneys.

3. Review how to integrate the assessment of atypical chronic GVHD into patient care, including some of the limitations in doing so.

National Institutes of Health Consensus Projects on Chronic GvHD

- Three iterations to date: 2005, 2014, 2020
- Represent the most up to date knowledge and expert perspectives on chronic GVHD (diagnosis, pathology, supportive care, biology, biomarkers, response, clinical trials).

- 2005 [1] and 2014 [2] Diagnostic and Staging Working Groups:
- NIH consensus criteria for the diagnosis of chronic GvHD, severity scoring by organ system, and global severity scoring of chronic GvHD.

- Aid for improving the clinical evaluation of patients, while providing standardized and minimal diagnostic criteria for entrance into clinical trials.

1. Filipovich et al. *Biol Blood Marrow Transplant* (2005) 11: 945-56.
2. Jagasia et al. *Biol Blood and Marrow Transplant* (2015) 21: 389-401

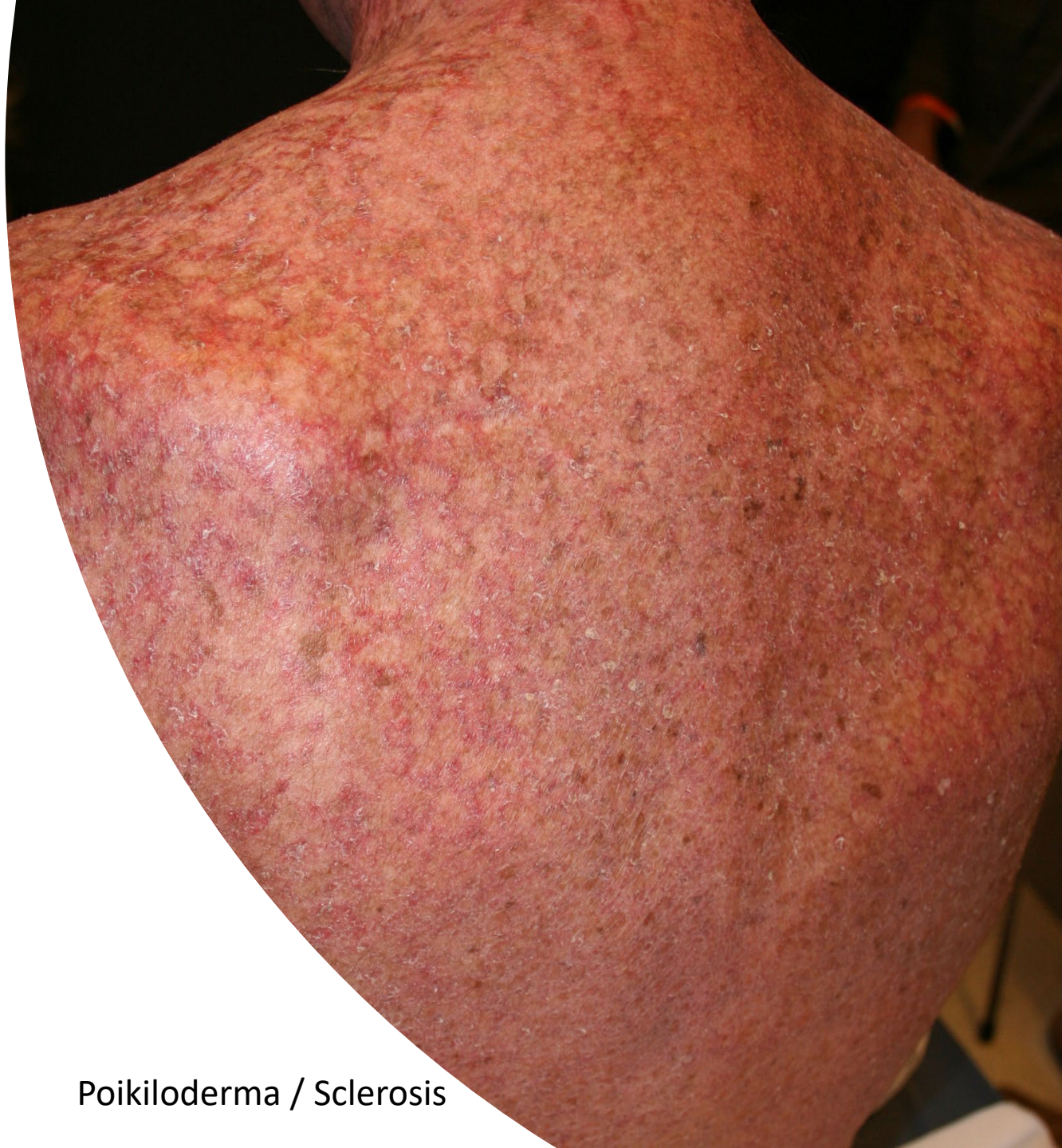
The 2005 and 2014 NIH Consensus Criteria Introduced Important Concepts About Graft-Versus-Host Disease

Chronic Graft-Versus-Host Disease:

- Is a distinct syndrome from acute GvHD.
- Occurs at any time after transplant (time-independent).
- Eight organ systems (+ others? Seems likely)
- Variety of clinical manifestations and severities.

Manifestations Divided Into:

- Diagnostic
- Distinctive
- Common
- Other



Poikiloderma / Sclerosis

ELSEVIER

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT
American Society for Transplantation and Cellular Therapy

Full Length Article
Report

National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. The 2020 Highly morbid forms report

Recognition that Chronic GVHD may:

- Manifest in atypical ways in classical organ systems.
- Impact non-classical organ systems.
- “Atypical” chronic GVHD features may contribute significantly to patient morbidity and mortality.
- Poorly characterized by current NIH consensus criteria.

Wolff et al. *Transplantation and Cellular Therapy* (2021) 27: 817-835.

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Report

Toward a Better Understanding of the Atypical Features of Chronic Graft-Versus-Host Disease: A Report from the 2020 National Institutes of Health Consensus Project Task Force

Check for updates

Objectives:

- Define what is known (and not known) about the atypical features of chronic GvHD.
- Provide clinicians and researchers with provisional diagnostic criteria for atypical features.
- Develop a research agenda for next 3-7 years to help understand atypical features better.

Cuvelier et al. *Transplantation and Cellular Therapy* (2022) 28: 426-445.

Atypical Chronic GVHD Organs and Manifestations

CNS Cognitive Deficits, Meningoencephalitis, Demyelinating diseases, CNS vasculitis*

PNS Neuropathy, Myasthenia gravis

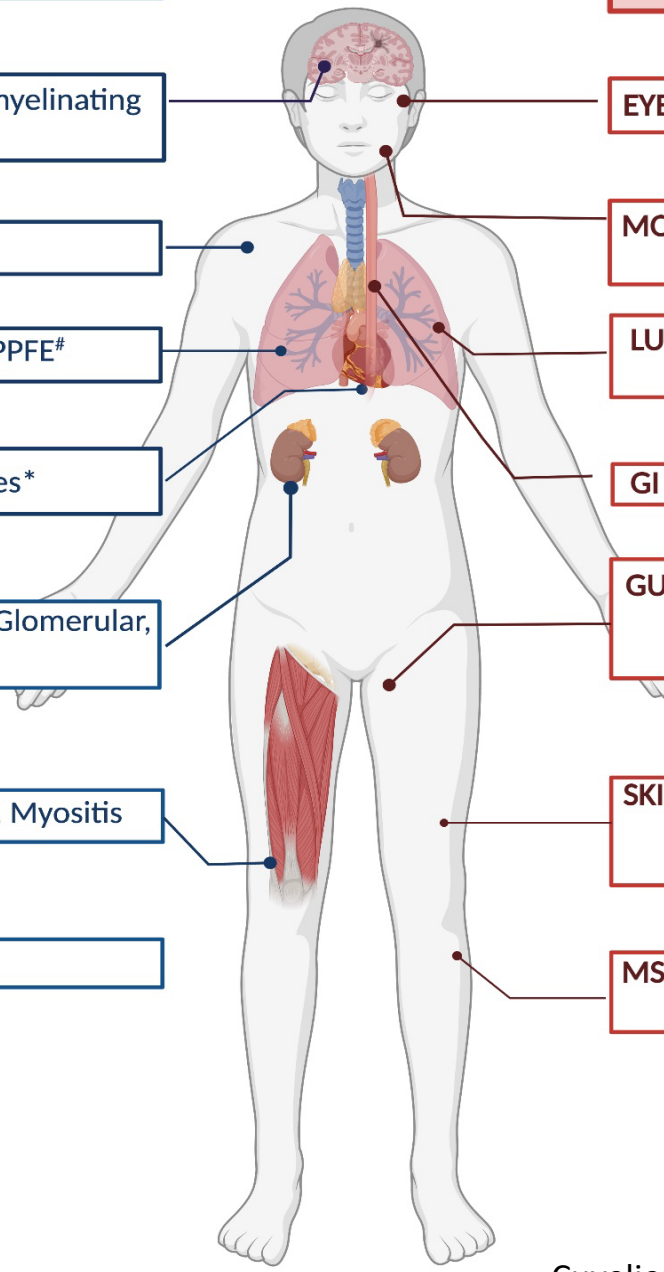
LUNGS COP#, Non-specific Interstitial Pneumonia#, PPFE#

SEROSITIS Percardial effusion*, Pleural effusion*, Ascites*

RENAL Proteinuria*, Nephrotic Syndrome*, Tubular, Glomerular, or Interstitial disease*, Vascular disease*

MSK Edema, Muscle cramps, Arthralgia, Arthritis, Myositis

IMMUNE MEDIATED CYTOPENIAS AIHA, ITP, AIN



NIH Defined Chronic GVHD Target Organs and Manifestations

EYES Dry eyes, Keratoconjunctivitis Sicca, Punctate Keratopathy

MOUTH **Lichen Planus-Like Features**
Ulcers, Xerostomia

LUNGS **Bronchiolitis Obliterans or Bronchiolitis Obliterans Syndrome**

GI **Esophageal web, stricuture or stenosis**

GU **Lichen Planus** or **Lichen Sclerosus-Like Features**
Females: **Vaginal Scarring** or **Clitoral/Labial Agglutination**
Males: **Phimosis** or **Urethral/Meatus Scarring** or **Stenosis**

SKIN **Poikiloderma, Sclerotic Features, Lichen-Planus, Morphea,** or **Lichen-Sclerosus-like Features**
Depigmentation, Papulosquamous Lesions

MSK **Fasciitis, Joint Stiffness, or Contractures due to fasciitis or sclerosis**

Cuvelier et al. *Transplantation and Cellular Therapy* (2022) 28: 426-445.

Atypical Chronic GVHD Manifestations

- Relation to chronic GVHD (pathophysiology) may be uncertain.
  - Level of evidence as features of chronic GVHD may not be high.
- Closer to autoimmune counterpart *vs*. part of chronic GVHD?
  - Therapies are poorly defined.
- Many confounding factors hinder assessment of causality –e.g., medications, infections.
- Particularly challenging for clinicians when atypical manifestations occur in isolation without other diagnostic chronic GVHD.

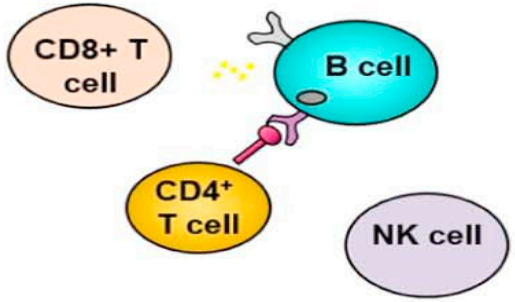
Phase I
Acute inflammation & Tissue injury

Innate immunity

- Cytokines
- TLR agonists
- Neutrophils
- Platelets
- Vascular inflammation

Phase 2
Chronic inflammation & dysregulated immunity

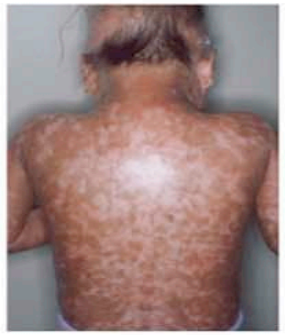
Adaptive immunity



- Thymic Injury and dysfunction
- T cells
- B cells
- NK cells
- Antigen presenting cells
- Regulatory Cells
  - Treg, Breg
  - IL-10 producing regulatory T cells (Tr1)

Phase 3
Aberrant tissue repair & fibrosis

Innate & adaptive



- TGFβ
- PDGFα
- TNFα
- IL-17
- Macrophages
- Fibroblasts

Cooke et al. *Biology of Blood and Marrow Transplant* (2017) 23:211-234.

Provisional Diagnostic Criteria for Atypical Chronic GVHD Manifestations Suggested By NIH Consensus Project

- **Immune Mediated Cytopenias**
  - AIHA, ITP, AIN, Evans Syndrome
- **Pulmonary**
  - Organizing Pneumonia, Interstitial Pneumonitis, Pleuropulmonary Fibroelastosis.
- **Endocrine**
  - Hashimoto's Thyroiditis, Grave's Disease
- **Central Nervous System**
  - Neurocognitive Deficits, Meningoencephalitis, Multiple-Sclerosis-like Encephalitis, CNS vasculitis-like disorders.
- **Peripheral Nervous System**
  - Chronic Inflammatory Demyelinating Polyneuropathy, Myasthenia Gravis, Guillain-Barre syndrome, Small Fiber Polyneuropathy.
- **Renal**
  - Nephrotic syndrome
  - Renal Thrombotic Microangiopathy
- **Musculoskeletal**
  - Myalgias / Myositis, Muscle Cramps, Arthralgias, Arthritis
- **Others**
  - Cardiac conduction abnormalities
  - Polyserositis
  - Raynaud's phenomenon

Cuvelier et al. *Transplantation and Cellular Therapy* (2022) 28: 426-445.

Immune Mediated Cytopenias and Chronic GvHD

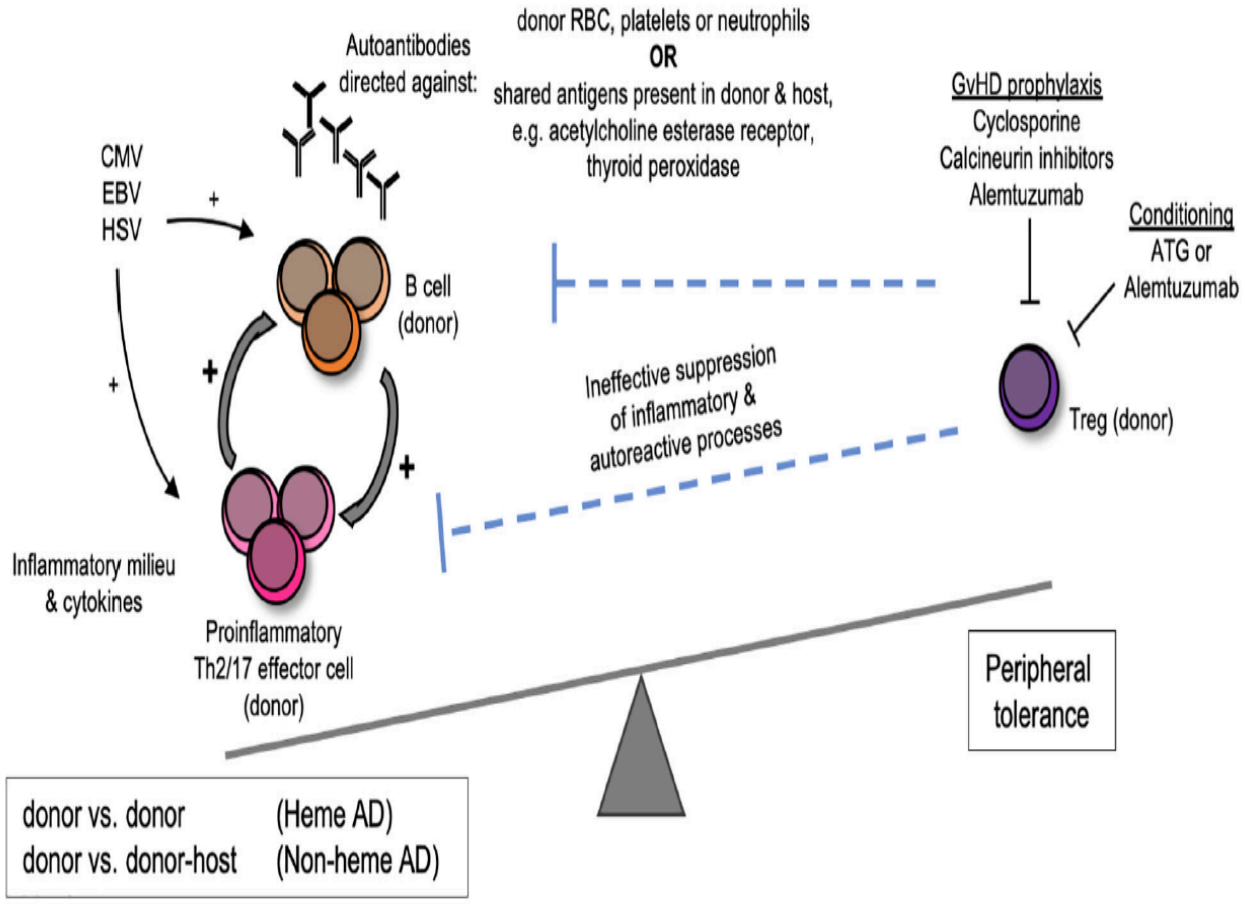
- IMCs (ITP, AIHA, AIN, Evan Syndrome) occur in 2-8% of patients after allo HCT.
- Many reasons for cytopenias after transplant – IMC under-recognized?
- Risk factors for IMC after allo HCT include chronic GvHD in studies.[1,2,3]

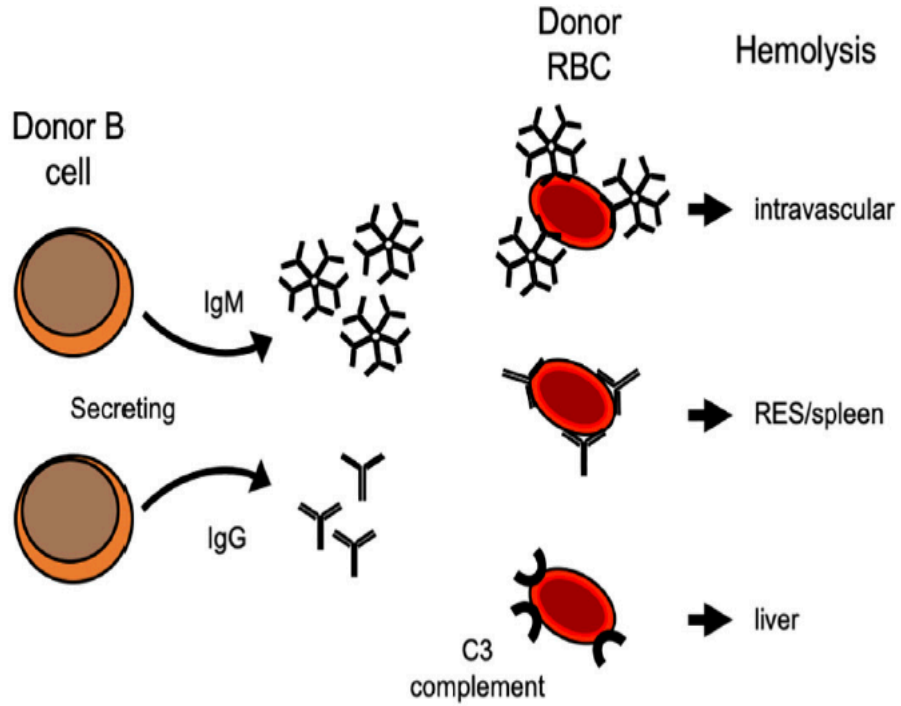
- Higher rates observed in children transplanted with cord blood and non-malignant disorders.

- We do not have a true understanding if IMC are *donor vs donor* (i.e. donor immune system reaction against donor hematopoietic cells) or *donor vs recipient* (true GvHD).

1. Neunert et al. *Pediatr Blood Cancer* (2019) 66: e27569.
2. Sanz et al. *Bone Marrow Transplant* (2014) 49: 1084-0189
3. Sanz et al. *Bone Marrow Transplant* (2007) 39: 555-561

Impaired Peripheral Immune Tolerance / Regulatory T Cells Underlies Immune Mediated Cytopenias After Allo HCT



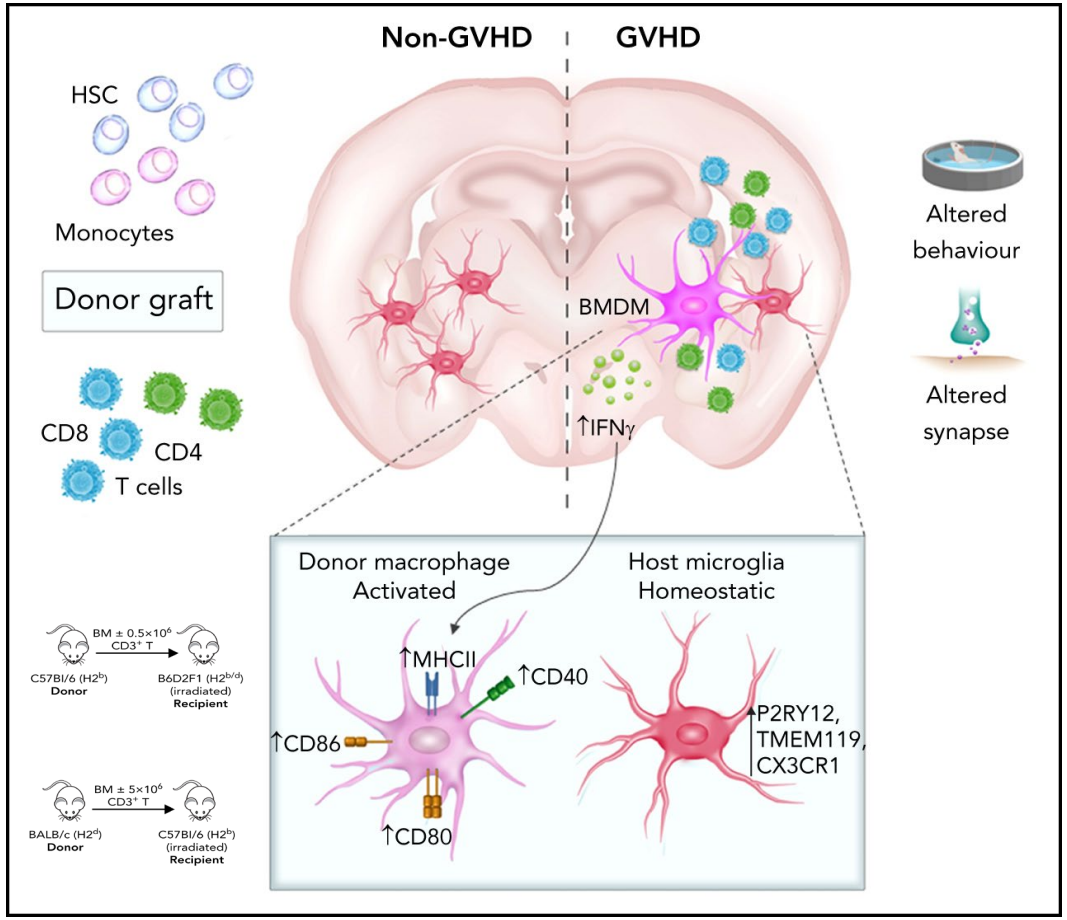


Buxbaum and Pavletic. *Frontiers Immunology* (2020) 11. Ecollection.

Central Nervous System and Chronic GvHD

- Wide variety of clinical syndromes suspected of being due to chronic GvHD of CNS:
  - Non-specific neurocognitive dysfunction (attention, memory, executive functioning, anxiety, depression). Occurs in up to 60% of adults undergoing HCT.
  - Acute Disseminated Encephalomyelitis (ADEM)
  - Multiple Sclerosis-like presentation
  - CNS vasculitis with T-cell infiltration

Donor Bone Marrow-Derived Activated Macrophages Expressing MHCII Drive Neuroinflammation and Mediate Chronic GvHD of the CNS



- Initially high CD8+ T cell infiltration in brain (d+14) then decline in CD8+ T cells (d+70), with increase in CD4+ T cell infiltration and donor bone marrow derived macrophages.
- High IFNγ induces generalized neuroinflammation, defects in spatial learning and memory.
- Suggests ruxolitinib which blocks downstream JAK/STAT could reduce neuroinflammation and improve cognitive function in chronic GVHD.

Adams et al. *Blood* (2022) 139: 1389-1408

Peripheral Nervous System and Chronic GvHD

- Appears to rarely impacted – chronic alloreactivity impacting PNS estimated 0.7 – 6.1% of allo HCT patients.

- Chronic Inflammatory Demyelinating Polyneuropathy
- Myasthenia Gravis – Anti-acetylcholine receptor antibodies.
- Guillain-Barre Syndrome
- Radiculoplexus neuropathies
- Mononeuropathies

Evaluation of PNS Chronic GvHD – Good Neurologic Exam and Nerve Conduction Studies

- Do not forget to rule out nutritional deficiencies, paraneoplastic events, infections, neurotoxic drugs.

Evaluation of Peripheral Neuropathy in Chronic GVHD Patients

Neuropathy in GVHD	Clinical Entity	Nerve Fibers/Structure Affected	Clinical Signs	Diagnostic Tools
Small fiber neuropathy	Neuropathic pain syndrome Dry mouth/eyes Gastrointestinal motility alteration	C- fibers	Warmth, pain, pinprick sensation (paresthesia), NeP allodynia Autonomic dysfunction	Needle, QST (warm thermal input), NeP questionnaires Autonomic testing
		A-delta fibers	Cold sensation	Cold metal, QST (cold thermal input)
		A-beta fibers	Altered position sense, vibratory sensation	Vibration fork
Large fiber neuropathy	GBS CIDP	Axons	Motor deficit, muscle weakness, atrophy, sensory deficit	NCV (sensory and motor fibers analyses)
		Myelin		

NeP indicates neuropathic pain; QST, quantitative sensory testing; NCV, nerve conduction studies.

Cuvelier et al. *Transplantation and Cellular Therapy* (2022) 28: 426-445.

Musculoskeletal Chronic GvHD - Myositis

- Muscle cramps can be a prominent cause of poor quality of life in individuals with chronic GvHD.
  - Non-specific symptom – multiple causes – including peripheral neuropathy
- Proximal muscle weakness.
- Chronic GvHD myositis affecting 1-3% of allo HCT patients.
- Likely under diagnosed.
- Muscle biopsy is the gold standard but invasive.
- Creatine Kinase, Aldolase, Electomyography, Nerve Conduction Studies, MRI may be helpful.

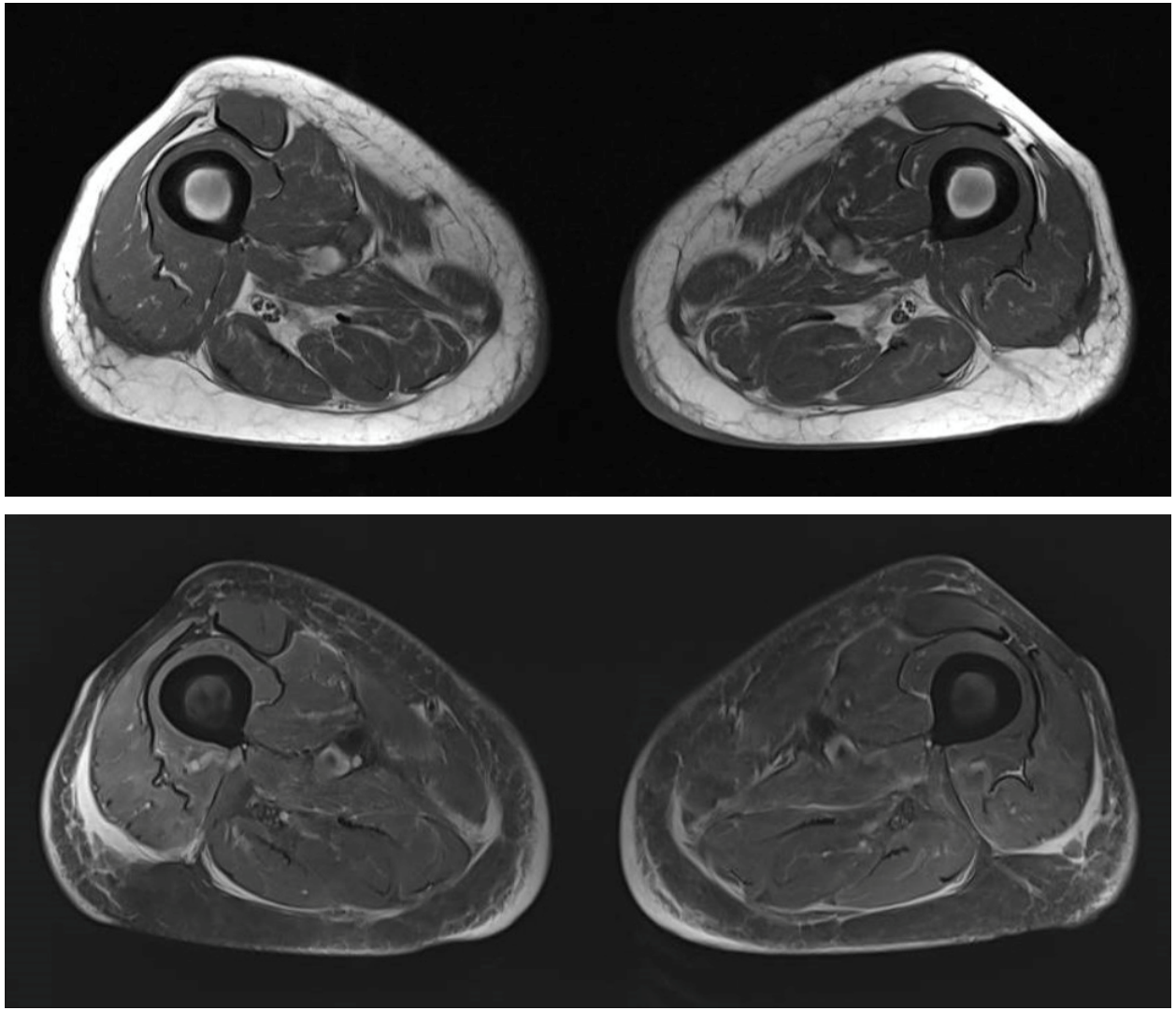
Features of Chronic GVHD Myofasciitis Compared to Spontaneous Autoimmune Myositis, Steroid Myopathy, and Peripheral Neuropathy

	Chronic GVHD Myofasciitis	Spontaneous Autoimmune Myositis	Steroid Myopathy	Chronic GVHD Peripheral Neuropathy
Myositis-specific autoantibodies	Negative	Often positive	Negative	Negative
Creatine kinase	Normal-moderate increase	High	Normal	Normal-mild increase
Aldolase	Mild-moderate increase	High	Normal	Normal-mild increase
EMG	Myopathic pattern	Myopathic pattern	Normal	Neuropathic pattern
MRI	Fasciitis and edema-like signal in the muscle	Fasciitis and edema-like signal in the muscle	No edema-like signal	Usually no edema-like signal
Muscle biopsy	Myopathic pattern: Inflammatory infiltrate, de/regeneration, necrosis	Myopathic pattern: Inflammatory infiltrate, de/regeneration, necrosis	No inflammatory infiltrate, type IIb fiber atrophy	Neurogenic pattern: polygonal shape of the muscle fiber, fiber-type grouping

EMG indicates electromyography.

Cuvelier et al. *Transplantation and Cellular Therapy* (2022) 28: 426-445.

MRI Muscles in Chronic GvHD Myositis



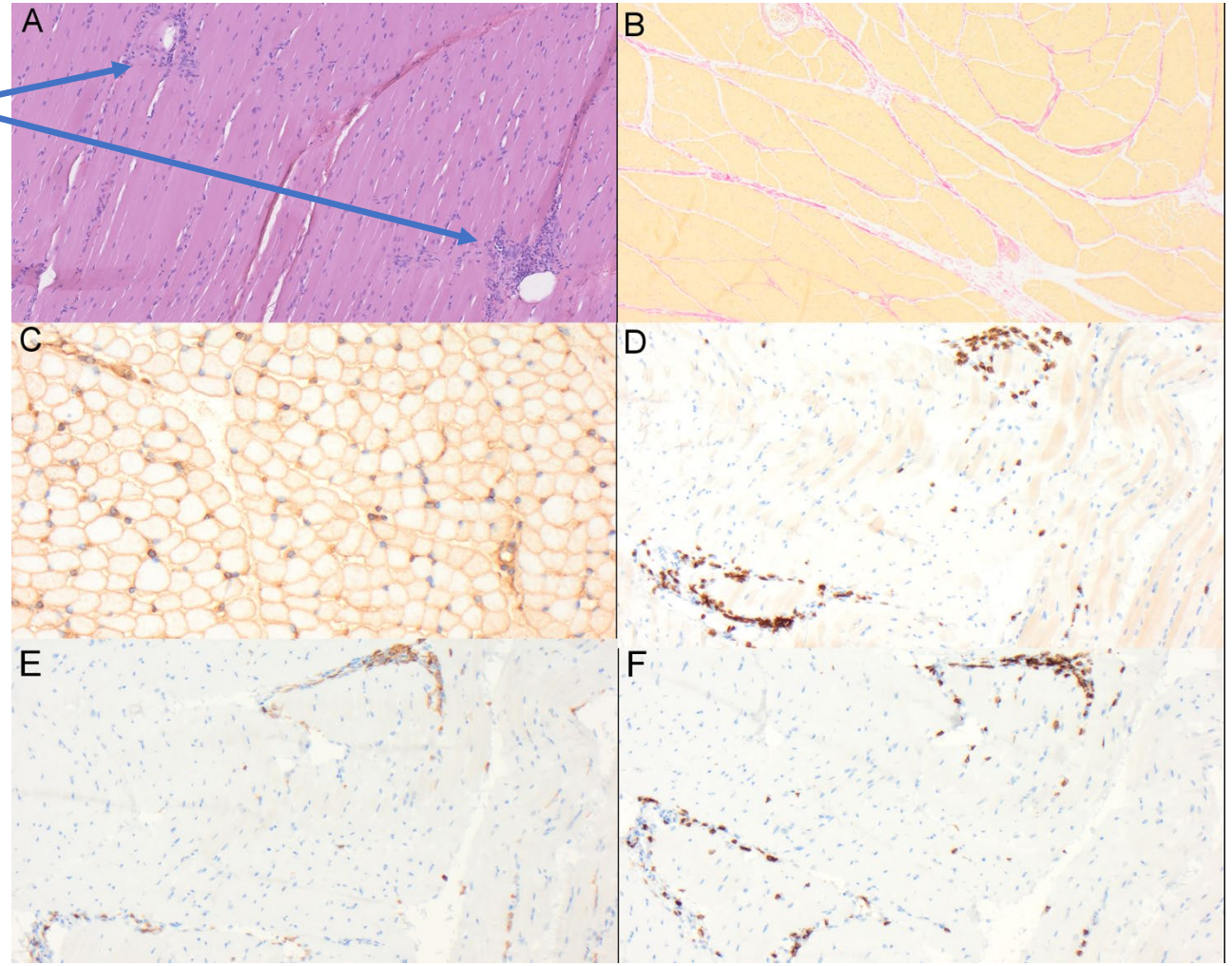
MRI T1 and STIR showing mild fatty infiltration, patchy STIR hyperintense signal, and superficial and subcutaneous edema.

Creatine Kinase: 425 U/L (N: 22-198 U/L)

Courtesy Dr. Iago Pinal-Fernandez

Muscle Biopsy is Ultimately Required to Diagnose Chronic GvHD Myositis

Perimysial perivascular inflammatory infiltrates (H+E stain 100X)



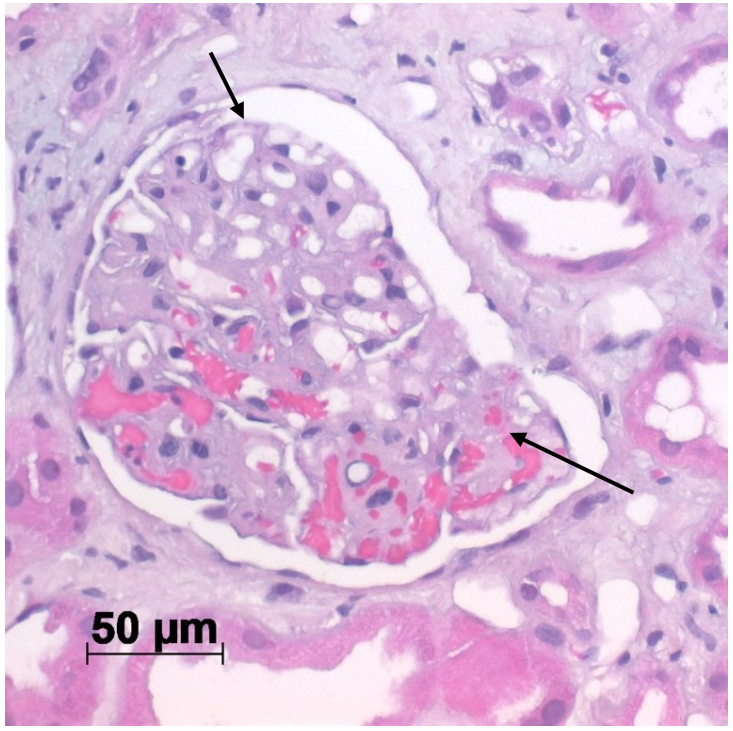
Endomysial Fibrosis (Weigert-Van Gieson stain 100X)

Myositis – distinctive chronic GVHD manifestation requiring biopsy

CD4+ and CD8+ T-Cell Infiltrates (200X)

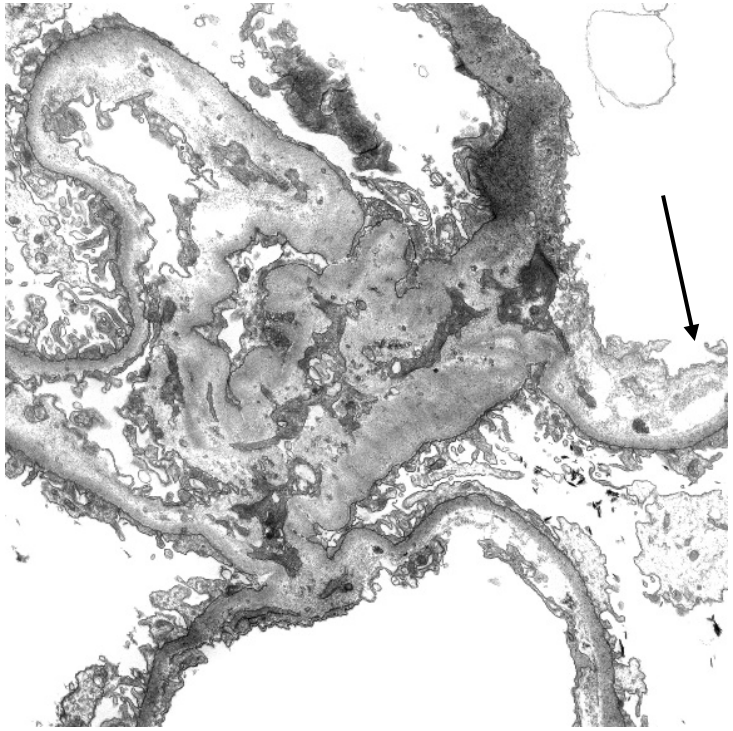
Courtesy Dr. Namita Sinha

Atypical Chronic GvHD – Renal Involvement



Renal Thrombotic Microangiopathy

- Mesangiolysis
- Fragmented RBCs
- Double contours of glomerular basement membrane



Detachment and loss of endothelial cells

Endothelial cell dysfunction – increasing evidence
Endothelial Cells are damaged in chronic alloreactive responses.

Many renal pathologies described in relation to suspected renal chronic GVHD.

Atypical Manifestations Manuscript Suggests:

Every 1-3 months post HSCT – review of nephrotoxic meds, BPs, creatinine, urinalysis and urine albumin:cr and urine protein:cr ratios

Courtesy of Dr. Maike Buettner-Herold

How Should Clinicians Determine if a Clinical Manifestation is due to an Atypical Chronic GvHD Manifestation?

- NIH consensus paper acknowledges the profound difficulty.

- Suggests good clinical description of the problem, association with other chronic GvHD features, extensive investigation (may include biopsy), and ruling out non-alloreactive causes.

- Ascribe the cause of a suspected atypical manifestation to chronic GVHD when:
  - Other chronic GvHD features are present (concurrently or in the past).
  - Alternative causes have been reasonably ruled out.

- Expert opinion – many of the purported atypical chronic GvHD manifestations:
  - Occur in relative isolation
  - Develop as immune suppression is weaned.

Associated Chronic GVHD Manifestation	Initial Evaluations	Additional Secondary Evaluations	Research Evaluations
Immune-mediated Cytopenias	• Markers of hemolysis (LDH, Total and Direct Bilirubin) • Direct Antiglobulin Test • Anti-platelet antibodies (if available) • Anti-neutrophil antibodies (if available)	• Anti-platelet antibodies • Anti-neutrophil antibodies • Bone marrow aspirate and biopsy (if diagnosis is unclear and other causes for cytopenias need to be ruled out)	• Extended immune phenotyping of T and B cell subsets, regulatory T cells, dendritic cells, monocytes including single cell omics • Plasma cytokines and chemokines • Glycosylation patterns of immunoglobulins • Trilineage assessment of chimerism
Musculoskeletal Manifestations Joints / Fascia / Muscles	• Creatine kinase • Aldolase • Aspartate aminotransferase • Alanine aminotransferase • Ultrasound (joints) • MRI (all three components)	• Electromyography • Joint aspiration (to rule out other non-chronic GVHD causes of arthralgia, e.g., septic arthritis, crystals) • Muscle biopsy	• RNASeq • Proteomics • Metabolomics • Single cell CyTOF
Endothelial Dysfunction	• Endothelial activation and stress index (EASIX): LDH x Creatinine/Platelets	• Organ Biopsy	• Non-standardized biomarkers (e.g., vWF, ST2, Angiopoietin 2) • Pathways of endothelial dysfunction in animal models and

Cuvelier et al. *Transplantation and Cellular Therapy* (2022) 28: 426-445.

Addressing Gaps in Knowledge About Atypical Chronic GVHD Manifestations - Research

- Call to action – next 3-7 years need to develop:

- Multi-institution, prospective, observational studies that capture all purported atypical chronic GVHD manifestations.
  - Excellence in clinical description.
  - Description of confounding factors.
  - Laboratory correlates.
  - Timed and event driven biomarker assessments of atypical manifestations.

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- Bernhard Banas
- Maike Buettner-Herold
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- Yoshihiro Inamoto
- Corey Cutler
- Linda Griffith
- Stephanie Lee
- Stefanie Sarantopoulos

Atypical Chronic GvHD:
Challenges for Chronic GvHD Diagnosis

Case Presentation

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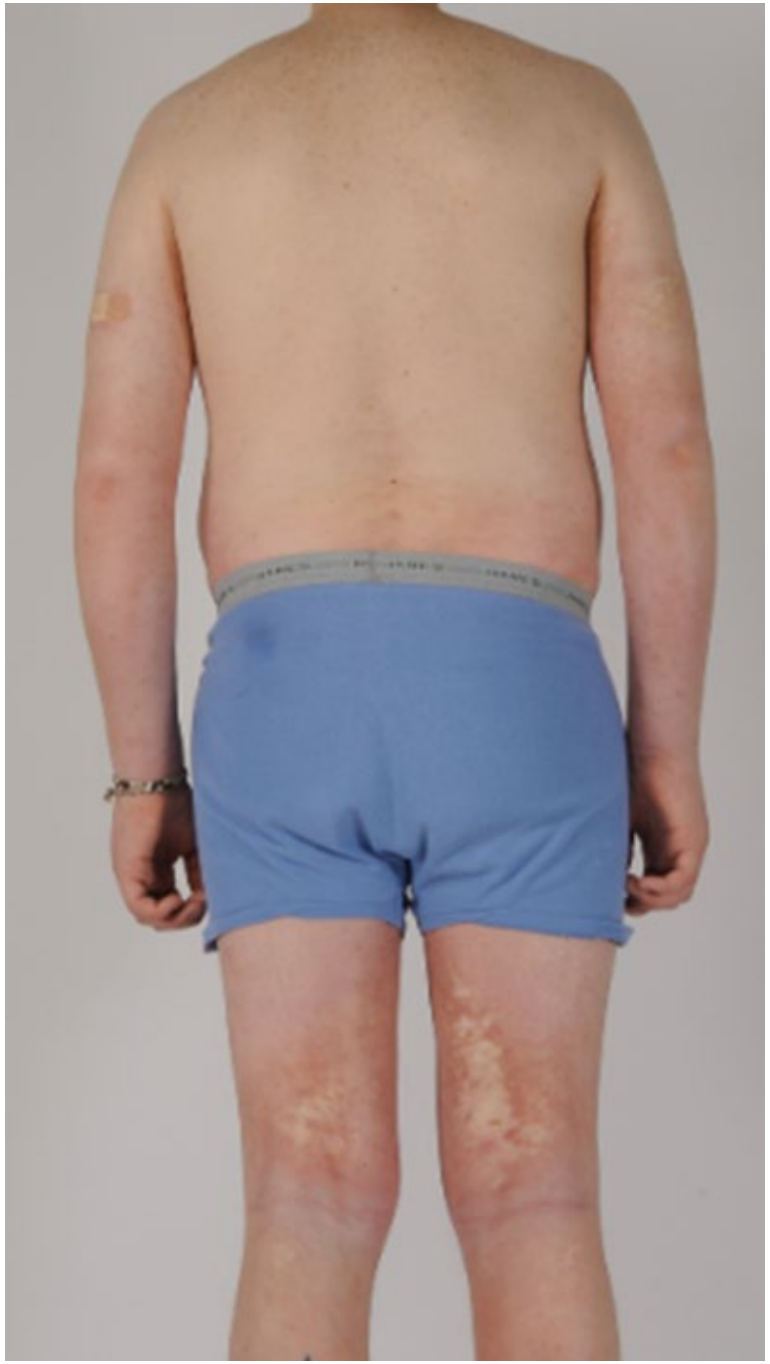
Washington University School of Medicine in St. Louis, MO, USA

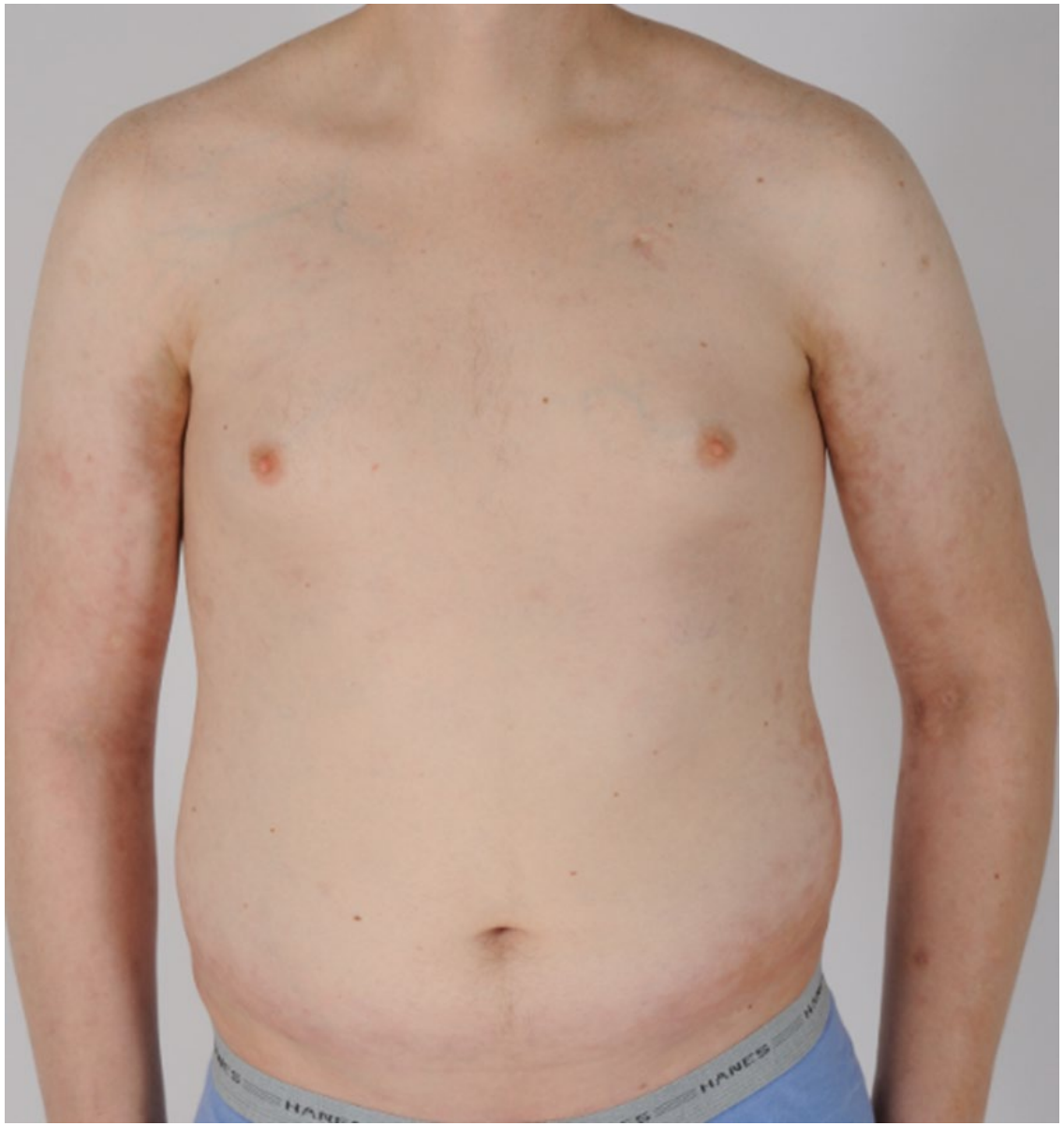
Case 1 (2007-2012):

- 31 y/o man with Hx of ALL with t(4;11), transplanted with persistent disease
  - **Donor:** 10/10 MUD donor
  - **Graft source:** PBSC
  - **Conditioning:** Cy/FxTBI
  - **GVHD PPx:** Tacrolimus/Methotrexate
  - Received **prophylactic DLI**
- A month after DLI → acute GvHD of skin stage 3; resolved with tacrolimus and prednisone
- 4 months later, as tacrolimus was tapered off → oral lichenoid GvHD, lichenoid and hyperpigmented skin changes, dry eyes
- **Prednisone, tacrolimus, … sirolimus added → initial improvement, but then worsening; stopped sirolimus, added mycophenolate, ….continued to progress**

Case 1 , chronic GvHD organ involvement:

- **Skin:** some sclerdoermatous changes; pruritus, allodynia
- **MSK system:**
  - Edema progressing to generalized anasarca, profound interstitial pitting edema unresponsive to diuretics
    - (2D-ECHO, PFTs, chest CT, Dopplers, liver function, creatinine, albumin – all normal);
  - Intense muscle cramps, myalgia, myositis, arthralgia, joints swelling, muscle weakness
    - CK: 136, 240 (30-200)
    - Aldolase: 9.8, 12.8 (0-8.0)
    - All autoantibodies negative (anti- Jo1, ENA, dsDNA, cardiolipin, neutrophil, centromere, myeloperoxidase, proteinase 3, CCP, mitochondrial, liver kidney, parietal, ANA, ANCA)
    - ESR, RF - normal
    - No evidence of avascular necrosis or infection
- **Serositis:** small pleural effusions

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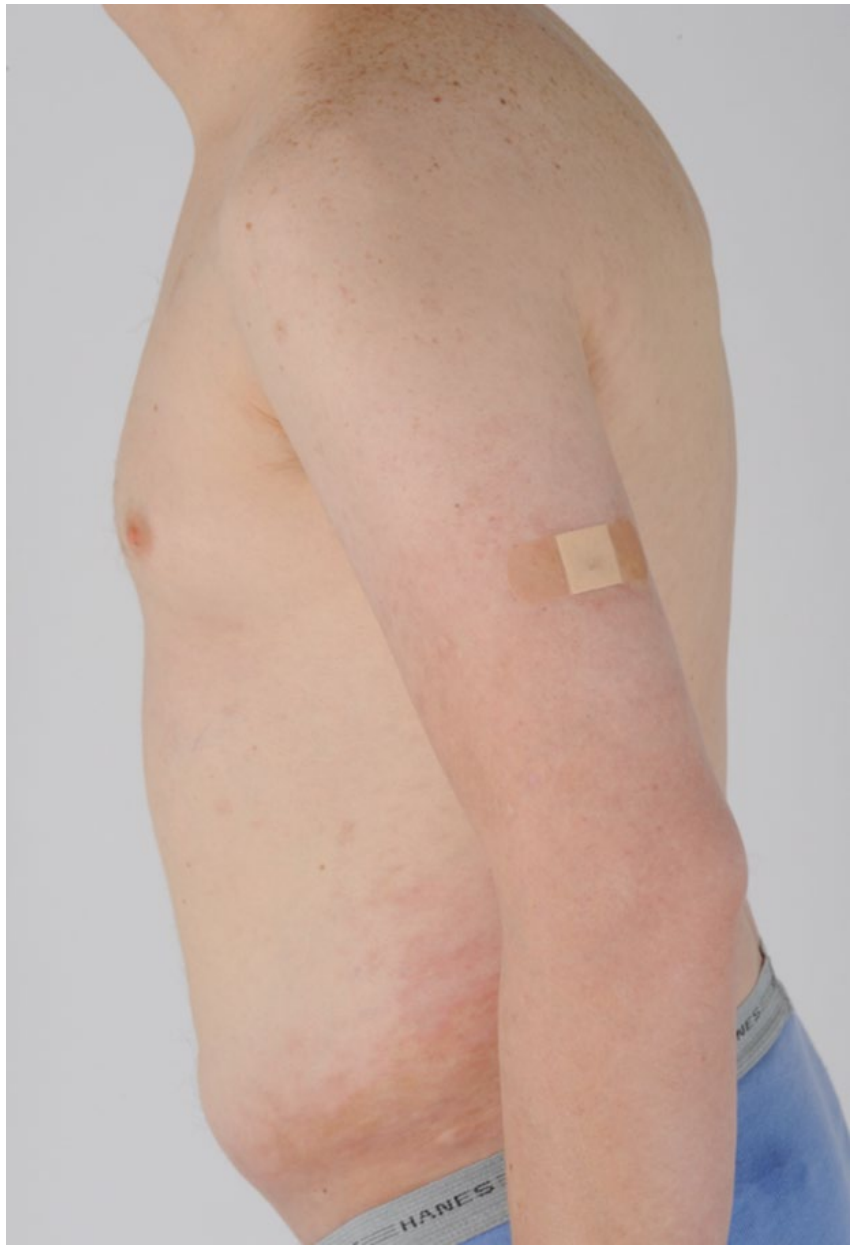
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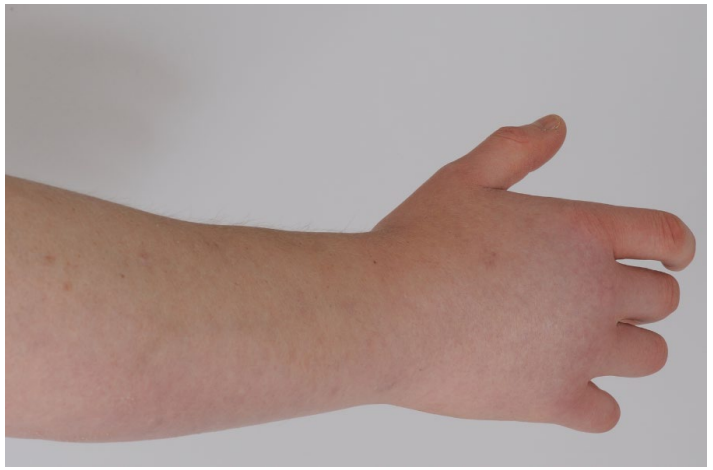

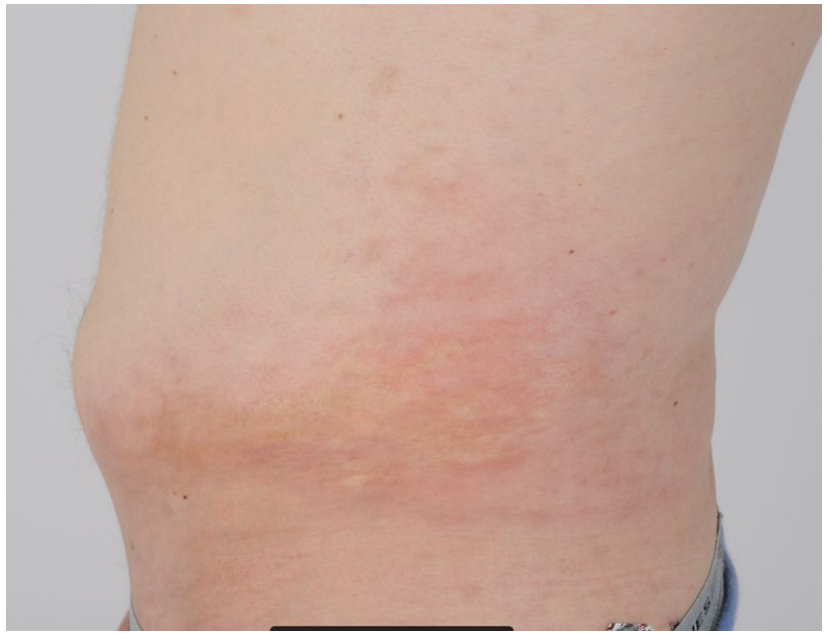

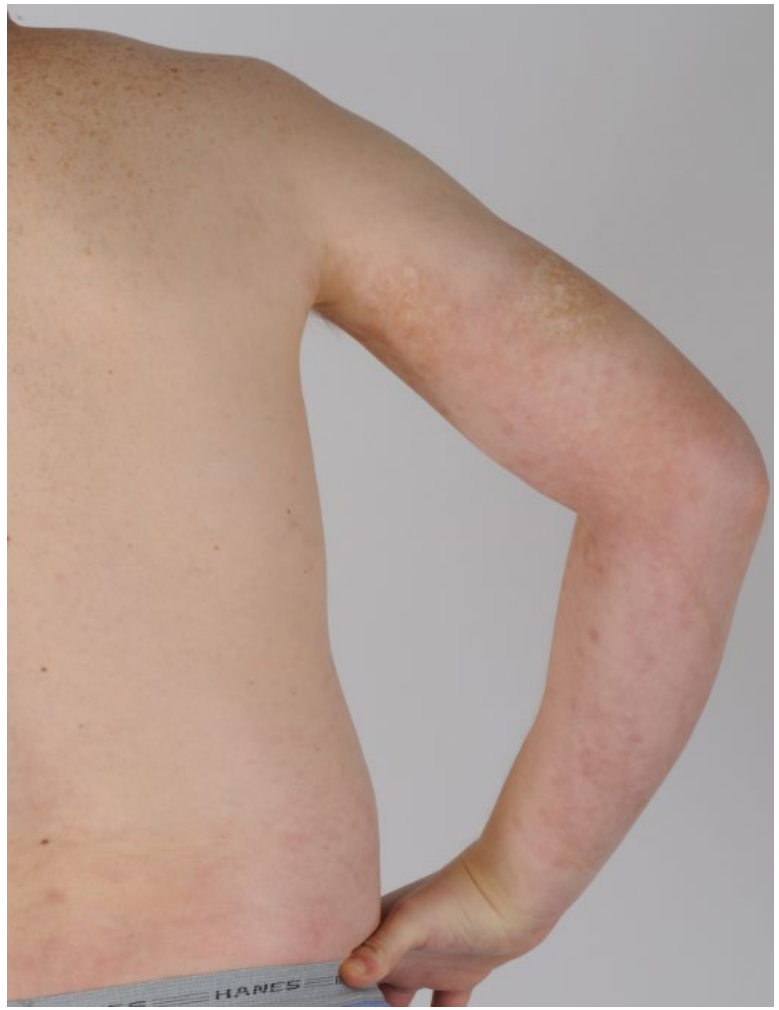
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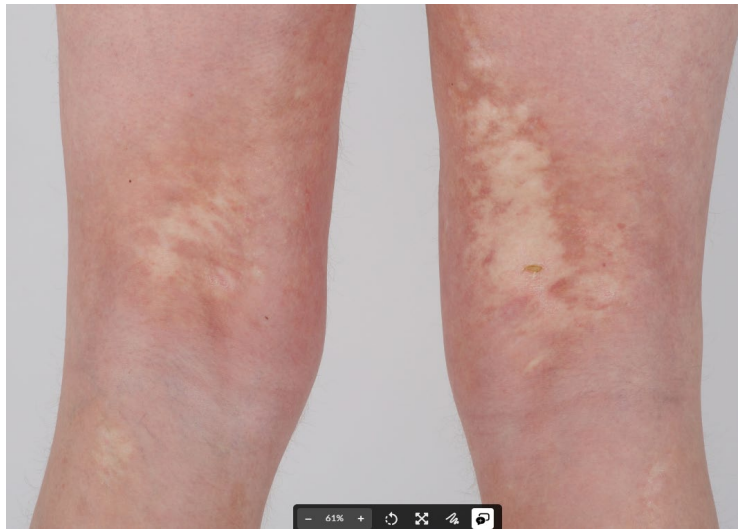
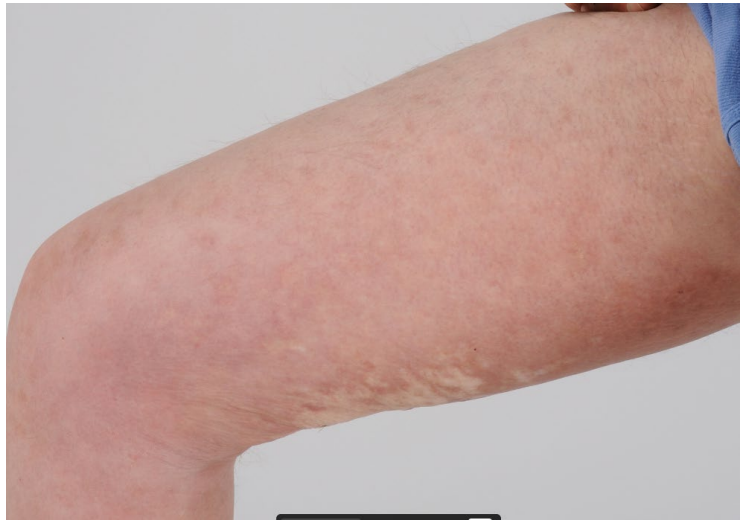
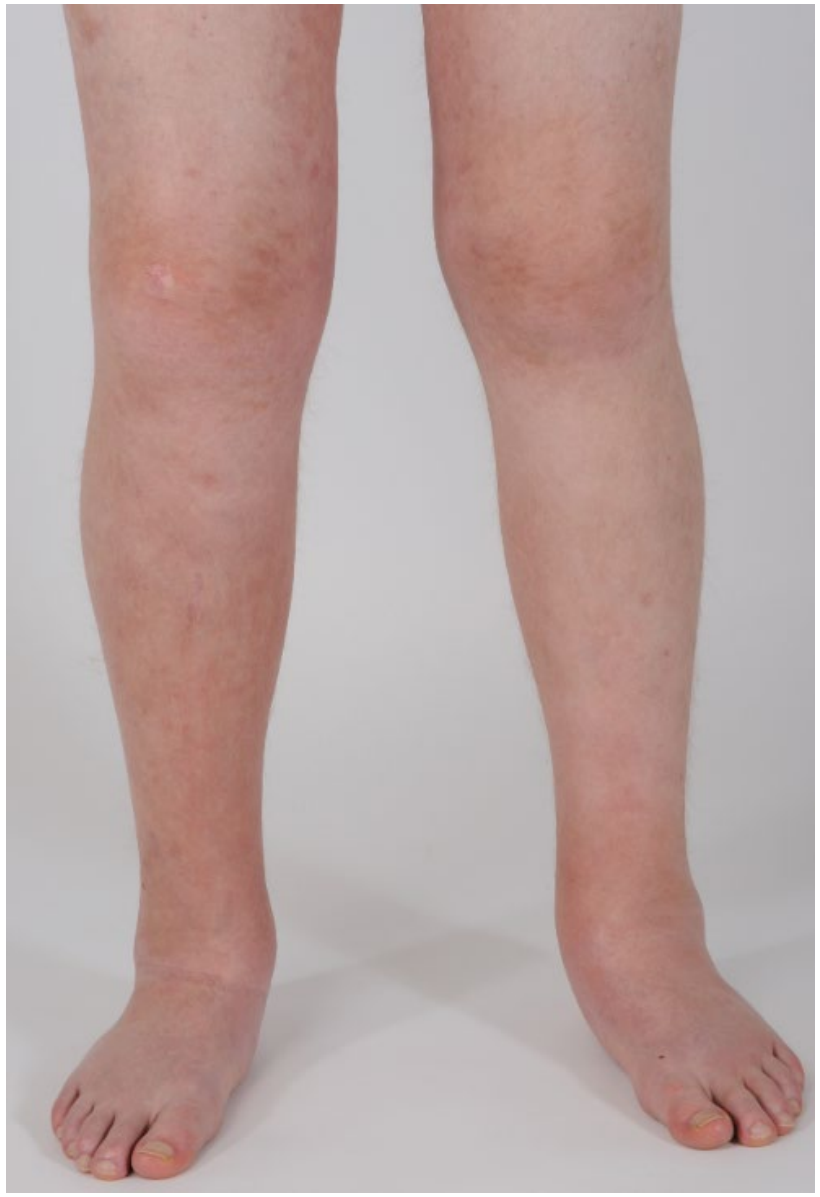
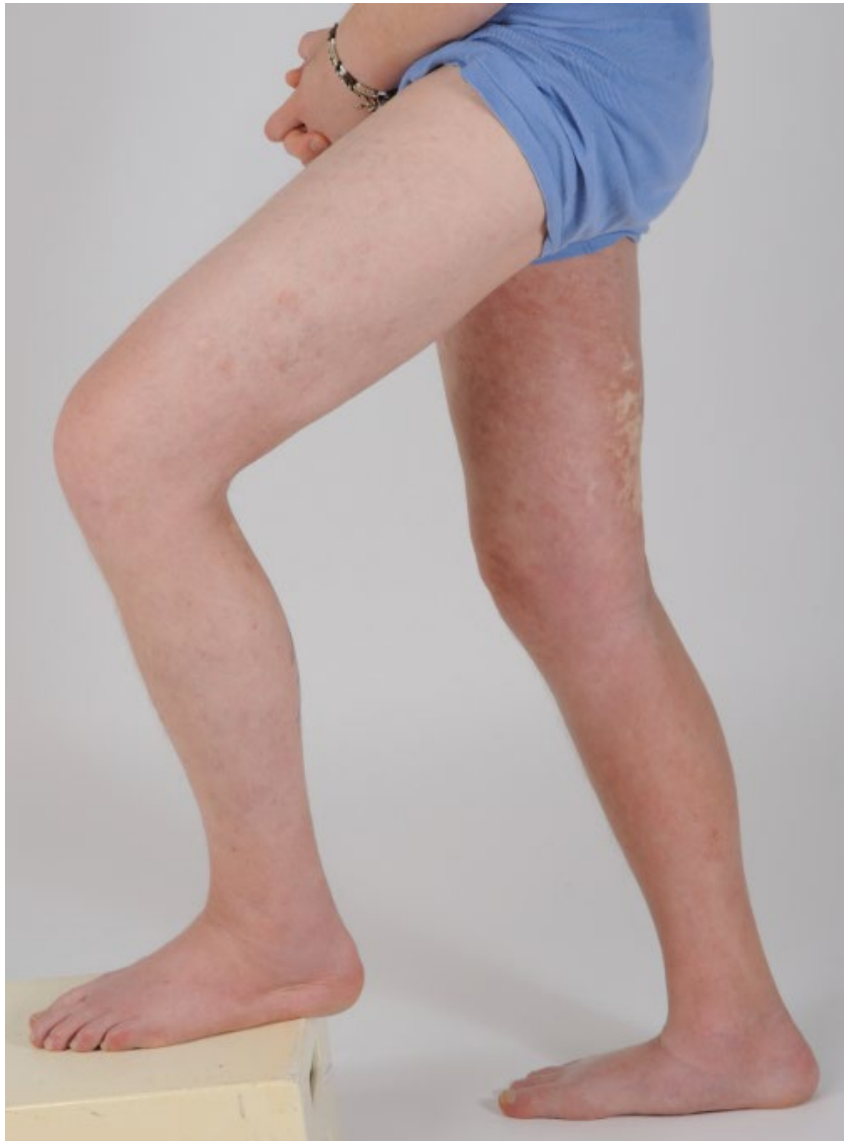
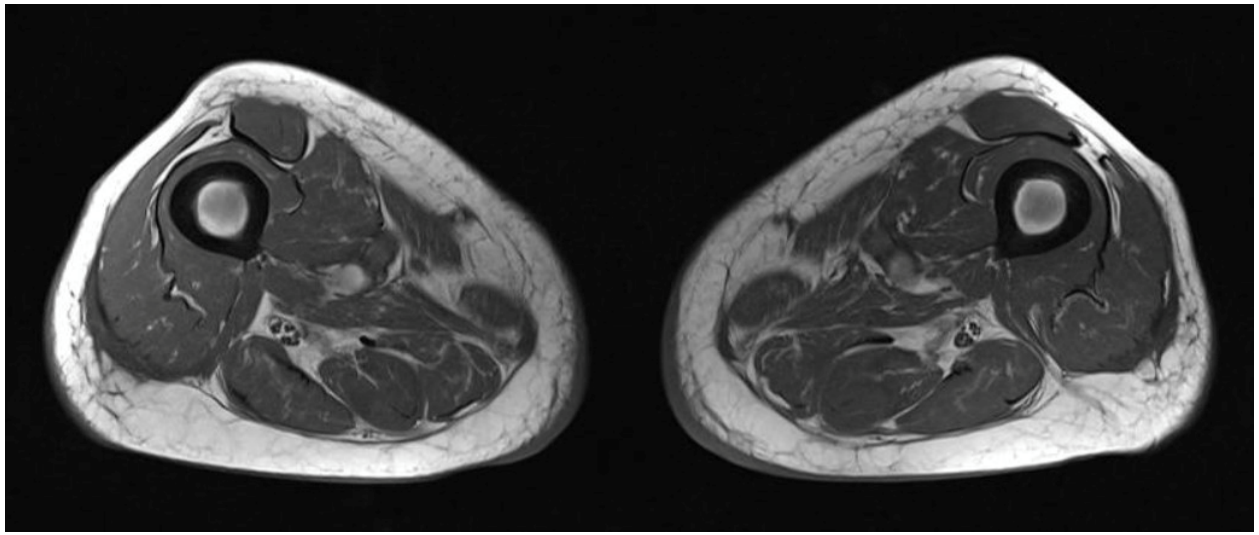
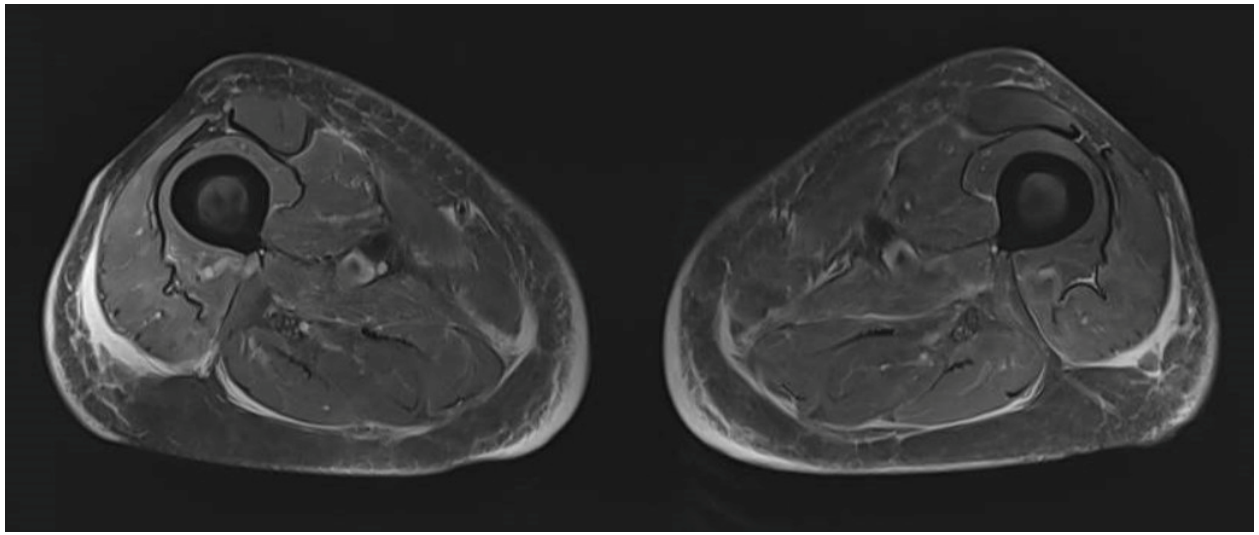












MRI thigh imaging of chronic GvHD myofasciitis

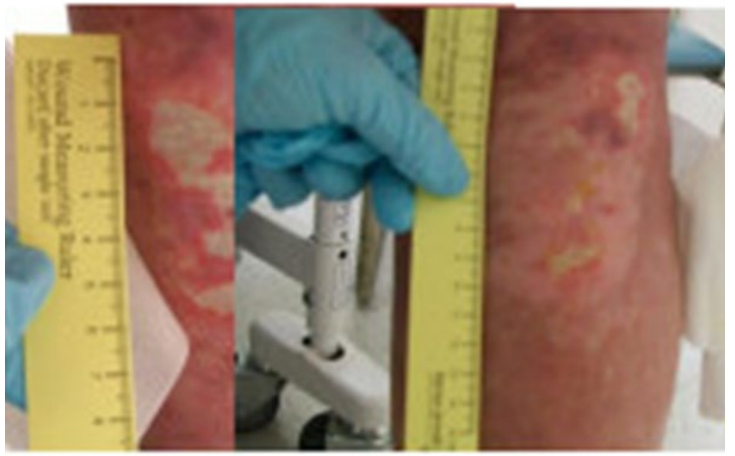
- Mild fatty infiltration, superficial fascial fluid with associated skin thickening and subcutaneous fat edema

Case 1, chronic GvHD organ involvement:

- **Eyes:** dry; keratoconjuctivitis sicca, Schirmer 0
- **Mouth:** dry, mild erythema, tongue atrophy
- **Lung:** initially normal, then combined obstructive and restrictive ventilatory defect, later severe restrictive ventilatory defect
- **Peripheral nervous system:** peripheral neuropathy
- **Hypogammaglobulinemia**
- Fatigue, anxiety, depression

Case 1, treatment history:

- Prednisone, tacrolimus, sirolimus, mycophenolate
- Pomaidomide study x 3 months (2008) → did not tolerate well, worsening cramps and fatigue
- Daclizumab (MoAb against IL-2R, CD25) x 3
- ECP
- Rituximab, imatinib (2009)
- NIH Chronic GvHD Natural History Protocol
- High-dose methylprednisolone, cyclosporine



- Danna Farber study of Low-dose IL-2 (2010) → no response, severe infection, skin ulcers, weaker
- Methotrexate + bortezomib
- 2nd AlloHCT, different MUD, RIC conditioning with post-HCT Cy; patient expired during HCT

Case 2:

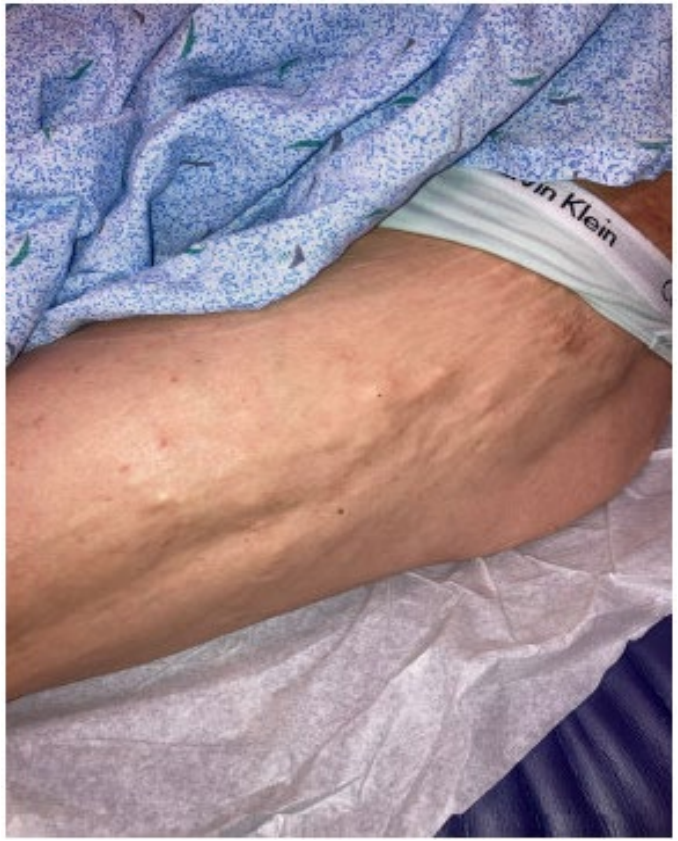
- 45 y/o woman with Hx of MDS→ AML, s/p HCT in 2006
  - **Donor:** 10/10 MUD
  - **Graft source:** PBSC
  - **Conditioning:** Cy/sd-TBI,
  - **GvHD PPx:** Tacro/MTX
- No significant acute GVHD
- **Severe, steroid-refractory cGVHD**
- **NIH-defined chronic GvHD manifestations:**
  - **Skin:** sclerotic changes, SQ thickening, hypepigmentation
  - **Eyes:** keratoconjuctivitis sicca, dry eyes
  - **Oral:** lichenoid changes, erythema, xerostomia
  - **Musculoskeletal:** moderate joint stiffness

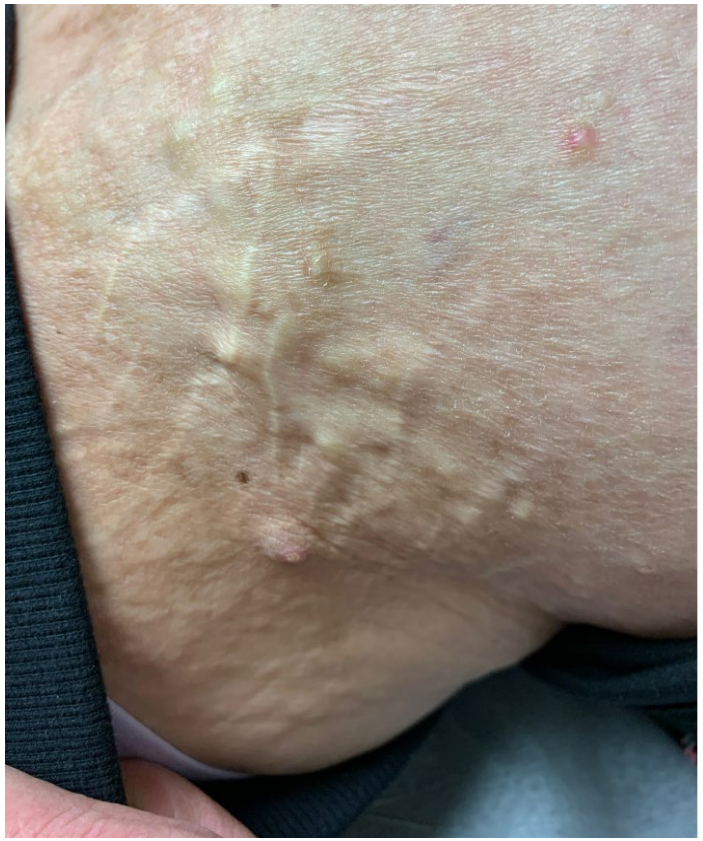
Case 2:

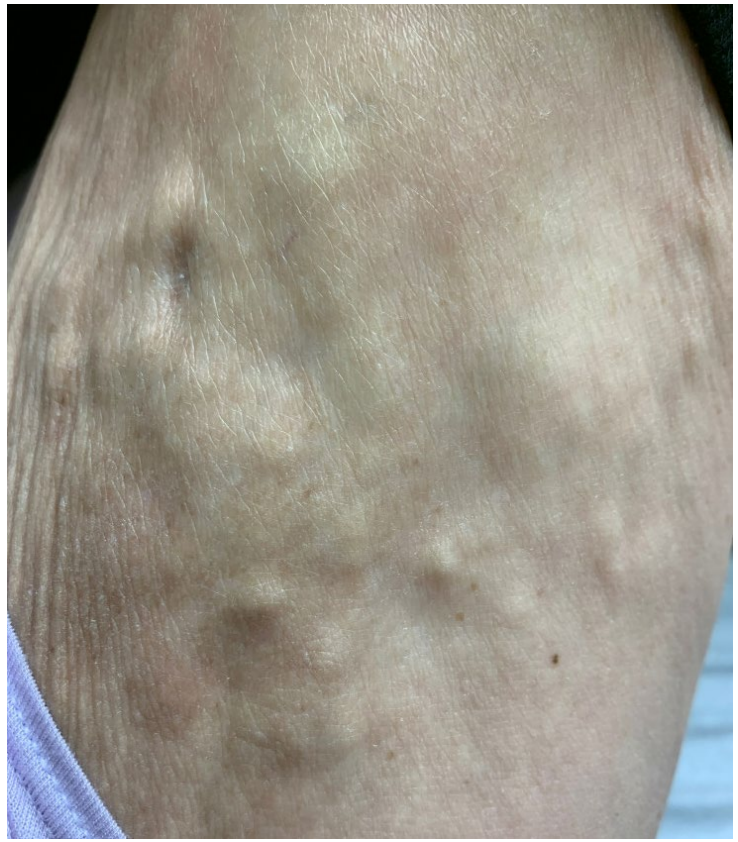
- **Atypical chronic GvHD manifestations:**
  - **Musculoskeletal:** diffuse edema on/off
  - **Central Nervous System:** cognitive deficits – "fogginess"', word-finding difficulties, poor memory, gait disturbance
    - MRI normal (no PRESS)
  - **Peripheral Nervous System:** neuropathy
  - **Lipoid dystrophy:** acquired, secondary to chronic GVHD, associated with insulin resistance
  - **Renal involvement:** Nephrotic Syndrome, nephrotic range proteinuria, membranous nephropathy
    - unable to do kidney Bx due to severe skin pain after lidocaine injection, other causes excluded
    - responded to cyclosporine
  - **Serosits:** edema, moderate pleural effusion

Case 2:

- **Skin:** subcutaneous calcium deposits
  - punch Bx: Morphea profunda with DYSTROPHIC CALCIFICATION







Case 2, treatment history:

- **Multiple therapies over time including:**
  - Prednisone
  - Tacrolimus, cyclosporine, mycophenolate, sirolimus
  - ECP, PUVA
  - Ruxolitinib (in 2016-2017 through patient assistance trial)
  - Ixazomib trial (2017-2018)
  - Ibrutinib (2018)
  - *Baricitinib denied (2019)*
  - *Not eligible for belumosudil trial due to too many prior therapies (2019)*
  - Ruxolitinib, re-chalange (2019-2020)
  - Belumosudil (2021-2022)
  - Compassionate use axatilimab (October 2022)

Case 3:

- 74 y/o man; Hx of MDS→AML, s/p HCT in 2011;
  - **Donor:** 9/10 MUD
  - **Conditioning:** Bu/Cy
  - **GvHD PPx:** Tacro, MTX, MMF
- Acute skin GvHD grade 2 → resolved with prednisone and topical therapy
- Decitabine maintenance study (q 8 weeks, started 12/2011)

Case 3, symptoms:

- Neuropathy
- Sensation that **skin feels sunburn**, but no redness (neuropathy ??)
- Further **skin tingling and sensitivity**, new macular rash (lichenoid) - skin chronic GvHD
- Severe skin **burning and pruritus**, sensation like “rough wool rubbing his skin”
- Intense pain in the skin all over his body (**allodynia**), **hyperalgesia**, unable to wear regular clothes
- **Proximal muscle weakness**
- Eye chronic GvHD

Aldolase, CK, uric acid, CRP, ESR, RF– all normal
All antibodies negative
Testosterone normal
Lipid panel normal

Case 3, cont:

- **Skin Bx:** H&E shows no inflammation. Anti-CD3 staining shows no increased cellularity; superficial and deep perivascular and interstitial dermatitis with eosinophils; lichenoid chronic GvHD

- **Small fiber neuropathy:**

  "The intraepidermal nerve fiber density is decreased at the distal leg and at the distal thigh. Therefore, this biopsy shows evidence for a small fiber neuropathy. There is no increased cellularity or inflammation noted within the dermis."

INTRAEPIDERMAL NERVE FIBER DENSITY (IENFD):

Biopsy Site	Patient Value	Normal (>5th percentile)
Distal Leg	0.3 fibers/mm	>2.8 fibers/mm
Distal Thigh	5.5 fibers/mm	>6.7 fibers/mm

- MRI of L/S spine - normal
- EMG and nerve conduction studies – normal (no large fiber neuropathy)
- Q-sweat study – normal (function of sympathetic sweat response)

Case 3, treatment history:

- Topical steroids → lichenoid chronic GvHD responded
- Prednisone, mycophenolate, tacrolimus, cyclosporine, sirolimus
- Pregabalin, duloxetine, amitriptyline, lidocaine
- ECP
- NIH chronic GVHD Natural History Protocol (seen by Dr. Jay Shah)
- Vitamin E (anti-oxidant properties)
- Ruxolitnib: unable to obtain ruxolitinib in 2015; finally started in 12/2017 → slight improvement in skin GVHD, still allodynia
- Belumosudil added to ruxolitinib in 2022, but no additional response; stable

Questions ?

Announcements

Future GVHD Interactive Provider Network ECHO Programs

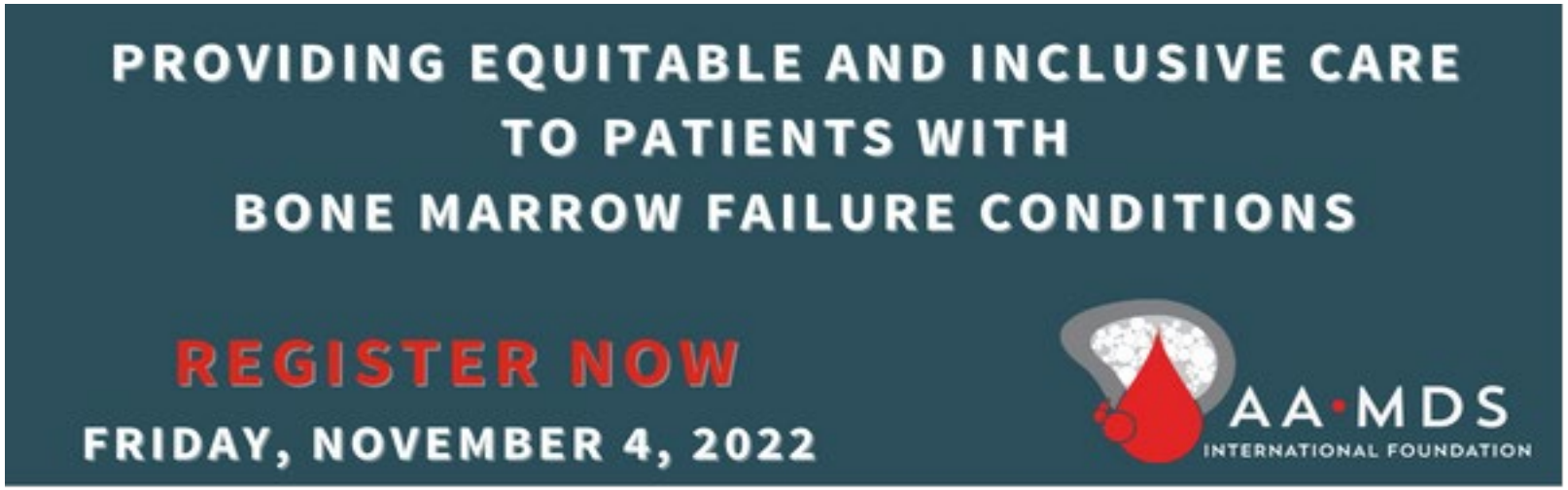
January: Chronic GVHD supportive care: infection, cardiovascular, chronic fatigue, lipid abnormalities, psychosocial

Visit www.gvhdnetwork.org to submit a case related to the above topics for discussion during the session.

Past GVHD Interactive Provider Network ECHO Programs Available on Demand at *www.gvhdnetwork.org*

- Treatment Decisions in cGVHD
- Mucocutaneaous GVHD
- Sclerotic GVHD
- Bronchiolitis Obliterans

Announcements



All Sessions Now Available for On-Demand Viewing

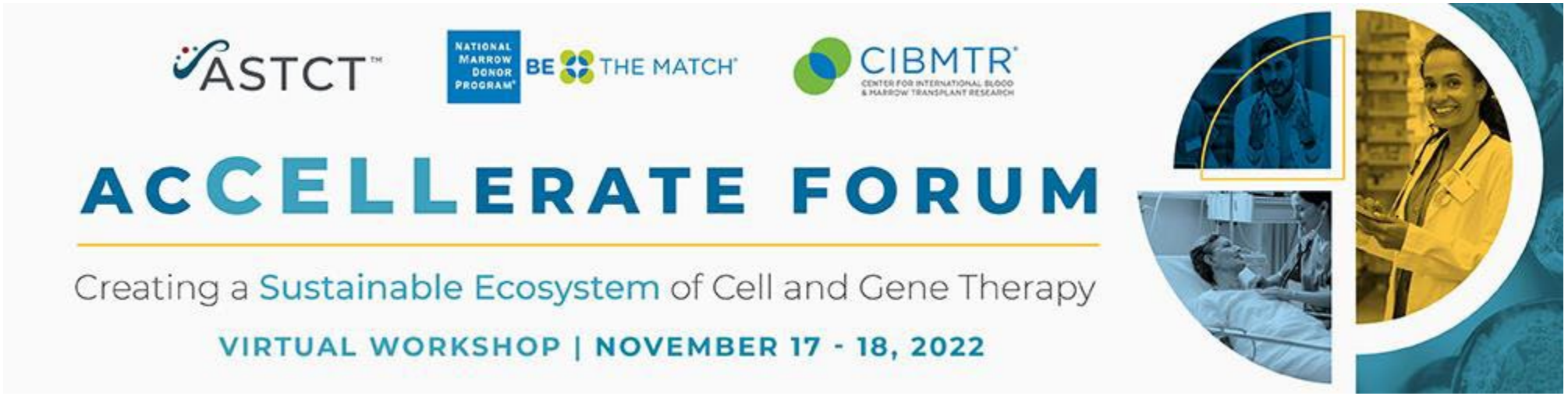
- **Clinical updates on MDS, aplastic anemia and PNH, and transplantation**
- **Panel discussions on addressing gaps in patient care**

GVHD Interactive PROVIDER NETWORK

Project ECHO®

Announcements

Announcements



This two-day virtual workshop co-hosted by the NMDP/Be The Match, the CIBMTR and ASTCT offers providers, payers, government agencies and industry members involved in the field of cell and gene therapy access to educational sessions and robust discussions designed to bring key stakeholders together.

Attendees and speakers will work together to identify ongoing needs and opportunities in the field for advocacy, measurement of value and impact, and sustainability.

Register here: https://www.astct.org/attend/accellerate-forum

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Announcements

Meredith A. Cowden Foundation GvHD 2022-23 National Symposium Series

Friday, January 27 – 10:00 am to 12:00 pm EST
"How to Choose Drugs for cGvHD" – Dr. Joseph Pidala, MD, PhD, Moffitt Cancer Center

Spring 2023 – Patient Advocacy

For more information, contact lynhaselton@cowdenfoundation.org