What is Chronic Graft-Versus-Host Disease?

Chronic GVHD affects multiple organs with inflammation and fibrosis, leading to significant symptoms, patient burden, and mortality[1-3]

Chronic GVHD is a common long-term complication of allo-HSCT[4]

30-50%

of allo-HSCT recipients experience chronic GVHD[4]

Chronic GVHD leads to a significantly lower health-related QoL, including[5-10]

- Decreased functional status
- Inability to work or resume social roles

Chronic GVHD is associated with significant morbidity[11-14]

Chronic GVHD is associated with severe and frequent infections[11-13]

Chronic GVHD leads to debilitating fibrotic organ damage that can be irreversible[14]

Chronic GVHD is a leading cause of non-relapse mortality following allo-HSCT[15]

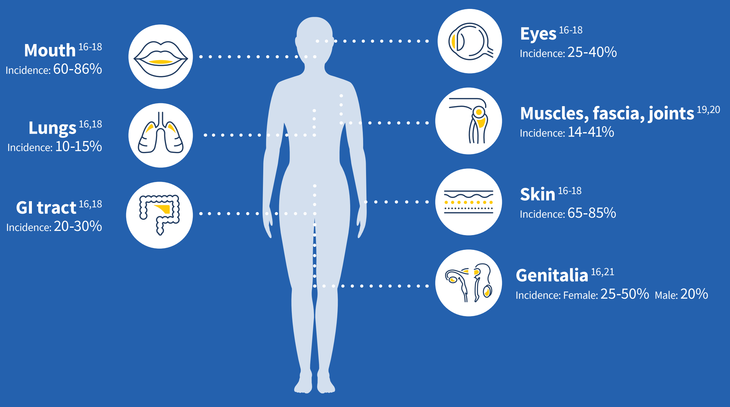
38%

of NRM is associated with chronic GVHD

NRM from chronic GVHD is frequently associated with organ failure and infection

Clinical Presentation of Chronic GVHD

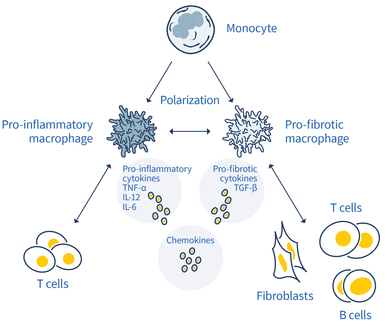
- Chronic GVHD is associated with chronic inflammation and subsequent tissue fibrosis that affects multiple organs[16]
- It most commonly manifests in the eyes, mouth, skin, and joints/fascia[16]



Monocytes and Macrophages in Chronic GVHD

Inflammation[22]

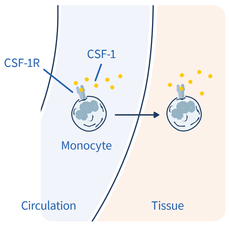
- Monocytes and macrophages are present in chronic GVHD and secrete chemokines and pro-inflammatory cytokines
- Activated macrophages can induce donor T cells to polarize and differentiate, impacting immune homeostasis and leading to chronic inflammation
- Chronic inflammation can lead to dysregulated tissue repair and fibrosis



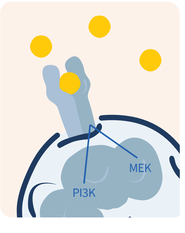
Fibrosis[22]

- Pro-fibrotic macrophages can interact with T cells, B cells, and fibroblasts to drive chronic GVHD
- Pro-fibrotic macrophages secrete cytokines that lead to fibroblast activation and collagen deposition, promoting aberrant tissue repair and fibrosis

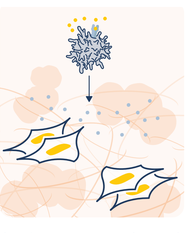
CSF-1R Signaling in Chronic GVHD



CSF-1R signaling promotes the infiltration of monocytes from circulation into tissue[23,24]



CSF-1R signaling activates intracellular pathways associated with the survival, proliferation, migration, and differentiation of monocytes and macrophages[25]



In the tissue, CSF-1R-dependent macrophages promote fibrosis during chronic GVHD[23,24,26]

Allo-HSCT, allogeneic HSCT; CSF-1, colony-stimulating factor 1; CSF-1R, colony-stimulating factor 1 receptor; GI, gastrointestinal; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; IL, interleukin; MEK, mitogen-activated protein kinase kinase; PI3K, phosphatidylinositol 3-kinase; QoL, quality of life; NRM, non-relapse mortality; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha.

1. Blazar BR, et al. *Nat Rev Immunol*. 2012;12:443-458. 2. Cutler CS, et al. *Blood*. 2017;129(1):22-29. 3. Cooke KR, et al. *Biol Blood Marrow Transplant*. 2017;23:211-234. 4. Lee SJ. *Best Pract Res Clin Haematol*. 2010;4:529-535. 5. Kitko CL, et al. *Transplant Cell Ther*. 2021;27:545-557. 6. Lee SJ, et al. *Haematologica*. 2018;103:1535-1541. 7. Wong FL, et al. *Blood*. 2010;115:2508-2519. 8. Bevans M, et al. *Biol Blood Marrow Transplant*. 2017;23:538-551. 9. Yu J, et al. *Cancer Med*. 2023;12:3623-3633. 10. Kurosawa S, et al. *Biol Blood Marrow Transplant*. 2019;25:1851-1858. 11. Arai S, et al. *Biol Blood Marrow Transplant*. 2015;21:266-74. 12. Socié G, Ritz J. *Blood*. 2014;124:374-384. 13. Blau O, et al. *Int J Transplant Red Med*. 2017;3:033. 14. Hill GR, et al. *Annu Rev Immunol*. 2021 Apr 26;39:19-49. 15. deFilipp Z, et al. *Blood Adv*. 2021;5:4278-4284. 16. Jagasia MH, et al. *Biol Blood Marrow Transplant*. 2015;21(3):389-401. 17. Vigorito AC, et al. *Blood*. 2009;114(3):702-708. 18. Lee SJ, et al. *Blood*. 2002;100(2):406-414. 19. Vukic T, et al. *Croat Med J*. 2016;57(3):266-275. 20. Inamoto Y, et al. *Arthritis Rheumatol*. 2014;66(4):1044-1052. 21. Hamilton BK, et al. *Bone Marrow Transplant*. 2017;52(6):803-810. 22. Hong Y et al. *World J Clin Cases*. 2020 May 26; 8(10): 1793–1805. 23. Alexander KA, et al. *J Clin Invest*. 2014;124(10):4266-4280. 24. MacDonald KPA, et al. *Blood*. 2017 Jan 5;129(1):13-21. 25. Hume DA, MacDonald KP. *Blood*. 2012;119(8):1810-1820. 26. Banovic T, et al. *Blood*. 2005; 106(6):2206-2214.

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