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Review

Sclerodermatous GVHD after Allogeneic Bone Marrow Transplant: a Review

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Abstract: Chronic graft versus host disease (cGVHD) is the leading cause of non-relapse mortality after allogeneic hematopoietic bone marrow transplantation (HCT) for blood malignancy in patients who survive for more than two years. cGVHD can significantly affect quality of life and cause decreased mobility amongst other grave consequences such as end-organ damage, contributing to morbidity and mortality rates for recipients of HCT. Unlike acute GVHD (aGVHD), the chronic variant of graft versus host disease (GVHD) has complex immunopathology involving both humoral and cell immunity. It typically affects the integumentary system, though is known to also affect myofascial, mucocutaneous tissues as well as cause end organ damage ultimately resulting in death. Sclerodermatous cGVHD is a type of cGVHD characterized by involvement of the skin, subcutaneous tissue and fascia without evidence of disease in the viscera. Manifestations of this disease are often evocative of autoimmune disease, which is a self-directed inflammatory reaction to the innate and adaptive immune system in various tissues or multiple organ systems. This inflammatory reaction gives rise to autoantibodies as well as B-cell and T-cell mediated direct toxicity which can cause chronic inflammatory changes of tissues ultimately resulting in tissue scarring and end organ dysfunction. We aim to review the literature on this grave disease and elucidate aspects of the immunopathology of chronic sclerodermatous GVHD in hopes that it may lead to revelations inspiring novel therapies after its diagnosis or preventative measures before stem cell transplantation for malignancy.

Keywords: allogeneic bone marrow transplant; GVHD, graft versus host disease; sclerodermatous GVHD; chronic GVHD; HCT

1. Sclerodermatous Chronic Graft Versus Host Disease

Chronic graft versus host disease (cGVHD) remains the predominant cause of non-relapse mortality in patients who receive allogeneic hematopoietic bone marrow transplantation (HCT) for blood malignancy and survive for more than two years [1]. The risk of cGVHD is increased with older HCT recipient age, transplant from an unrelated donor, use of peripheral blood as the HCT source as well as treatment with donor-lymphocyte infusion [2,3]. cGVHD can greatly impact quality of life and mobility for those afflicted with it, contributing to morbidity and mortality for recipients of HCT. Unlike its acute counterpart, the chronic variant of graft versus host disease (GVHD) has complex immunopathology and most commonly affects the integumentary system, though is known to also affect myofascial, mucocutaneous tissues as well as cause end organ damage [1]. Sclerodermatous cGVHD is characterized by involvement of the skin, subcutaneous tissue and fascia without evidence of disease in the viscera [4]. Recipients of HCT who present with sclerodermatous skin changes have been demonstrated to have elevated levels of antibodies to TGF-B and PDGF [4]. Many manifestations of this disease are evocative of autoimmune pathology, which is a self-directed inflammatory reaction to the innate and adaptive immune system in various tissues or multiple organ systems. This inflammatory reaction gives rise to autoantibodies which can cause chronic inflammatory changes of tissues ultimately resulting in tissue scarring and end organ dysfunction [5]. The most characteristic histopathological feature of acute GVHD is dyskeratotic epidermal keratinocytes surrounded by lymphocytes called "satellitosis" [6,7]. cGVHD in the skin begins with an appearance of lichenoid tissue inflammation which progresses to a condition with scleroderma-like features [6,7]. On histology, sclerodermatous cGVHD features thickened collagen bundles in the dermis [6,8].

2. Clinical Features

Most cases of cGVHD occur in months or years after HCT, even when not preceded by acute GVHD (aGVGD). cGHVD symptoms are reminiscent of a variety of autoimmune diseases such as systemic sclerosis, Sjögren syndrome, systemic lupus erythematosus, primary biliary cirrhosis, bronchiolitis obliterans, and immune cytopenias [8]. Pathognomic characteristics include sclerosis, lichen-planus-like lesions, poikiloderma, esophageal webs, fasciitis, and bronchiolitis obliterans. Skin is the most common site involved in cGVHD at the initial diagnosis in about 75% of subjects [8]. Clinical

manifestations of immune-mediated fibrosis are observed in ocular, oral, esophageal, integumentary, joint, fascial, pericardial and pleural and genital tissues with varying degrees of severity which can ultimately result in renal failure and premature cardiovascular and endocrine disease. We aim to focus on integumentary manifestation of cCVHD in this review. Patients afflicted with cutaneous manifestations of cGVHD are at risk of joint contractures secondary to sclerodermatous skin changes, skin atrophy with ulceration, esophageal strictures, lichen planus-like lesions of mucosa and skin and keratoconjunctivitis sicca [8]. Severity of cutaneous fibrotic disease can be measured noninvasively in terms of skin thickness and density by 20 MHz high-frequency ultrasonography as well as skin elasticity via non-invasive suction skin elasticity meter, Cutometer MPA 480. These two noninvasive parameters are an imperfect measurement and gold standard diagnostic testing is skin biopsy, but they can be employed to assess disease severity, though they are typically not used outside of the purposes of research [9].

3. Immunopathology

cGVHD is a complex disease process which involves interaction between alloreactive and dysregulated T and B cells as well as innate immune defenses—namely, macrophages, dendritic cells, toll-like receptors (TLRs) and neutrophils which ultimately incite profibrotic pathways and disease manifestation.The immunological pathology of autoimmune disease generally is a failure of correct identification of self-antigens when they are presented. It was previously believed that cross-reactions with antigens carried by foreign particles such as microbes were responsible for inciting auto-aggressive phenomena. Studies have now shifted to investigating the microenvironment of the presentation process to identify self [5,10]. This may contribute to understanding of pathology of cGVHD after hematopoietic stem cell transplantation in context of a cytotoxic environment affected by immune-depleting chemotherapeutics necessary in pre-transplantation protocols.

Our basic understanding of chronic GVHD from study of experimental animal models is that it is a 3-step process. First, there is an activation of host antigen-presenting cells (APCs) which are induced by the HCT preconditioning protocols in an acute inflammation and tissue injurious phase [1]. This has been described as a reaction of innate immunity which is mediated by cytokines, toll like receptor agonists, neutrophils, platelets which are released in response to cytotoxic agents, infections and acute GVHD [1]. This is followed by a phase of chronic inflammation and dysregulated adaptive immunity which is distinguished by proliferation and migration of effector T cells, B cells, antigen-presenting cells and NK cells [11,12]. It is during the final “effector phase”, that involvement of the innate and adaptive immunity is observed in a process directed dysregulated donor lymphocyte populations via transforming growth factor-β (TGFβ), PDGFα, TNFα, IL-17, macrophages and fibroblasts which ultimately cause organ damage and fibrotic skin changes [11,13]. The release of these profibrotic mediators causes

macrophage and fibroblast activation, collagen deposition, fibrosis and irreversible end organ damage. In cGVHD, TGFβhas been shown to be central for the development of skin fibrosis via Th2/Th17 pathways. Monocyte-produced TGF-β1, a potent stimulus for collagen synthesis, is thought to drive the fibrosis which causes eventually debilitating sclerodermatous skin changes and skin contractures [6,14].

Highly cytotoxic ablative chemotherapy may predispose an auto-aggressive innate immunity response via release of cytotoxic agents which directly trigger toward the Th1 and Th17 as well as TGF-b and IL-6 pathways, inciting adaptive regulatory lymphocyte production [10,15,16]. CD4+ CD25+ regulatory T cells (Tregs) are thought to influence the size of peripherally activated CD4 count in the arsenal prepared to identify and attack exogenous systems or develop auto-inflammatory reactions and subsequent tissue damage [17]. A balance between memory and activated peripheral CD4 cells exists on account of direction by the Treg pool and disruption of this balance in the healthy individual can result in derangements in the peripheral lymphocyte population and thereby incite immune deficiencies or clonal expansions resulting in autoimmune disease and its manifestations [11].

The role of humoral immunity in GVHD immunopathology has also been examined in great detail, of late. New roles for B cell- mediated immunostimulation though antigen presentation and immunoregulation have been recognized by Shimabukuro-Vornhagen, et al [18]. B cell- mediated immune responses are carried out by antibody-mediated and antibody-independent mechanisms. Antibodies produced by B cells after activation can effect complement activation, antibody-mediated direct cytotoxicity and Fc-receptor antigen uptake resulting in phagocytosis [19]. B cells can subsequently secrete a large number of pro-inflammatory cytokines including IL-2, TNF-α, IL-6, IL-12, MIF and interferon-γ when consequently activate a large number of immune cells such as T cells (including Th17 cells), macrophages, and natural killer (NK) cells which, as previously recapitulated in this review, have been shown to have direct roles in graft versus host (GVH) reaction and clinical morbidity [18]. It is also understood that antigen presentation by activated B cells that have upregulated major histocompatibility complex and costimulatory molecules such as CD80 and CD86 which leads to CD4+ and CD8+ T-cell activation and differentiation ultimately also shown to effect GVH related skin fibrosis post allogeneic bone marrow transplant [18].

Cytokines in acute versus chronic GVHD are another area of interest, particularly in terms of the role of chemokines as potential therapeutic target. RT-PCR analysis of expression of cytokines in various severities of disease reveals increased expression of interferon-γ (INF-γ) and interleukin (IL) 10 mRNA as well as upregulated IL-4, IL-5, IL-13 in aGVHD [11,14]. This evidence of a Th2 pathway was supported by a finding of enhanced CCL17 and CCL22, which were found to be downregulated in chronic forms of GVHD [20]. In contrast, Th1-mediated immune response was predominant in chronic sclerodermatous GVHD as evidenced by increased expression of INF-γ, CXCL9, CXCL10, CCL5 [11,20].

4. Current Therapeutics in Sclerodermatous cGVHD

Evaluating therapies for csGVHD is a challenge on account of the heterogeneous group of patients who are afflicted with single or multiple organ cGVHD involvement. This heterogeneity makes meta-analysis difficult, though increasing attention has focused on the role of chemokines and their potential as a therapeutic target in both acute and chronic GVHD. The use of agents interfering with these particular molecules has shown promising results in animal models of aGVHD but yielded no significant advantage in human patients [6]. Imatinib (a tyrosine kinase inhibitor, TKI) has been used for steroid-refractory sclerodermatous GVHD with initially promising results involving two cases reported in 2008 by Magro et al. wherein two patients who developed refractory sclerodermatous cGVHD following allogeneic stem cell transplant received Imatinib at the dose of 400 mg/day; in both patients, the sclerodermatous GVHD symptoms resolved within 3 months of initiation of the treatment [21]. In larger studies, however, efficacy of Imatinib for severe sclerodermatous cGVHD was limited [22,23]. Profibrotic cytokines (such as TGFβ and PDGF) have key roles in the pathogenesis of the autoimmune disease scleroderma as well as sclerodermatous cGVHD [14]. Both of these cytokines are upregulated in the skin of idiopathic scleroderma patients and strongly stimulate matrix synthesis by fibroblasts in the dermis; this phenomenon is also seen histologically in skin samples of patients with sclerodermatous cGVHD [8]. In accordance with these findings, blockade of TGFβ or PDGF signaling has been found to reduce the development of skin fibrosis in various experimental models but only inconsistently in human trials [21]. Long wavelength UVA treatment as well as administration of bone marrow-derived mesenchymal stem cells have been sparsely studied and yield somewhat promising results, though they have not been studied in large scale to assess their true efficacy as of yet [23–25]. Impact of these modalities on development of chronic GVHD or skin malignancies is also unknown. Similarly, no clear differences in the incidence of cGVHD or sclerodermatous cGVHD between TKI-exposed and unexposed patients was observed in retrospective studies with Imatinib and Dasatinib [4,26].

Therapies directed toward B cell mediated GVH have been an attractive target in sclerodermatous GVHD as well as other forms of cGVHD. B cell depletion was considered a potential therapeutic route after the discovery that rituximab (a chimeric human-murine monoclonal IgG antibody targeted at the B cell CD20 receptor) treatment for immune thrombocytopenia actually improved a patient's sclerodermatous GVHD symptoms [27]. Rituximab depletes B cells by various mechanisms resulting in a concomitant decline in T call activation and increase in Treg population [18]. A meta-analysis and systematic review of the efficacy of rituximab in cGVHD in which seven studies were included (three of which were prospective trials), was recently published and revealed a broad range of response rates from 13–100% [27]. Due to the heterogeneity of disease type and burden, very few meta-analyses exist in the literature at this time and this compilation is of utility to the scientific and clinical community. This meta-analysis data show that rituximab is a treatment option for patients with extensive

steroid-refractory cGVHD as well as patients with steroid-refractory cGVHD manifesting as thrombocytopenia or with sclerodermatous, other cutaneous or rheumatologic symptoms [27]. Yet another multi-center phase II clinical study performed by Kim, SJ et al found a cutaneous response rate of 77% among a cohort of 22 patients with sclerodermatous GVHD receiving weekly rituximab followed by monthly rituximab administration [28].

5. Future Therapeutic Investigations

While the incidence and severity of cGVHD has not decreased, several randomized trials are hoping to show a lower rate of cGVHD. Current therapies are not more effective or less toxic, but some promising therapies are in clinical trials, and there appear to be others still in development to improve outcomes of HCT as well as attempt to prevent occurrence of cGVHD [29,30]. New therapies may target the specific pathophysiologies of cGVHD, as opposed to the pan-immunosuppressive agents currently available [29]. Specifically, the described role of Th1 cytokines in cGVHD, especially of the skin and liver is a potentially targetable in therapeutics for cGVHD or Th2 cytokines and mediators in efforts to prevent preceding acute GVHD [14,31]. In addition to targeting fibrosis with imatinib and B cell-mediated antibody depletion to prevent downsteam activation of pro-fibrotic pathways, biologics are continuously studied and developed in attempts to stabilize or improve debilitating and deforming cutaneous manifestations of cGVHD. One such biologic is tocilizumab, an anti-IL-6 receptor antibody therapy which revealed mixed cutaneous response rates and concern for worsening hyperbilirubinemia in a cohort of 8 patients with both aGVHD and cGVHD [32]. Pravastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, was investigated for a potential role it may have in cGVHD, though the results of it were promising in murine disease and disappointing in human subjects [33]. Abl kinase and PDGF receptor inhibitors (dasatinib and nilotinib) are also under investigation for a role in cGVHD treatment. A phase II open-label trial specific to cutaneous GVHD is underway at the National cancer Centre which is expected to elucidate useful data in current GVHD therapeutics [34]. Among the emerging therapies for sclerodermatous GVHD, imatinib and rituximab are most convincing. Though sclerodermatous cGVHD is better understood than it was even 5 or 10 years ago, advancements in therapeutics after its onset are few after high dose steroid therapy is exhausted. For patients and practitioners alike, succumbing to complications of the HCT therapy for malignancy in a state of remission is painfully unfortunate. Future directions of research in the pathogenesis of sclerodermatous cGVHD may reveal crucial novel targetable therapy.

Conflict of Interest

All authors declare no conflicts of interest in this paper.

References

1. Cooke KR, Luznik L, Sarantopoulos S, et al. (2016) The Biology of Chronic Graft-versus-Host Disease: A Task Force Report from the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease. *Biol Blood Marrow Transplant* 23: 211-234.
2. Jacobsohn DA, Kurland BF, Pidala J, et al. (2012) Correlation between NIH composite skin score, patient-reported skin score, and outcome: results from the Chronic GVHD Consortium. *Blood* 120: 2545-2552.
3. Flowers ME, Inamoto Y, Carpenter PA, et al. (2011) Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. *Blood* 117: 3214-3219.
4. Salhotra A, Tsai N, Thomas SH, et al. (2015) Sclerodermatous chronic GVHD in patients receiving tyrosine kinase inhibitors after allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant* 50: 139-141.
5. Tyndall A, Dazzi F (2008) Chronic GVHD as an autoimmune disease. *Best Pract Res Clin Haematol* 21: 281-289.
6. McCormick LL, Zhang Y, Tootell E, et al. (1999) Anti-TGF-β Treatment Prevents Skin and Lung Fibrosis in Murine Sclerodermatous Graft-Versus-Host Disease: A Model for Human Scleroderma. *J Immunol* 163: 5693-5699.
7. Shulman HM, Kleiner D, Lee SJ, et al. (2006) Histopathologic diagnosis of chronic graft-versus-host disease: National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: II. Pathology working group report. *Biol Blood Marrow Transplant* 12: 31-47.
8. Olivieri J, Coluzzi S, Attolico I, et al. (2011) Tirosine Kinase Inhibitors in Chronic Graft versus Host Disease: From Bench to Bedside. *Sci World J* 11: 1908-1931.
9. Osmola-Mańkowska A, Silny W (2013) Assessment of chronic sclerodermoid Graft-versus-Host Disease patients, using 20MHz high-frequency ultrasonography flowersand cutometer methods. *Skin Res Technol* 19: e417-e422.
10. Lang KS, Recher M (2005) Toll-like receptor engagement converts T-cell autoreactivity into overt autoimmune disease. *Nature Med* 11: 138-145.
11. Brüggen M, Klein I, Greinix H, et al. (2014) Diverse T-cell responses characterize the different manifestations of cutaneous graft-versus-host disease. *Blood* 123: 290-299.
12. Hofmeister CC, Quinn A, Cooke KR, et al. (2004) Graft-versus-host disease of the skin: life and death on the epidermal edge. *Biol Blood Marrow Transplant* 10: 366-372.

13. Nikolic B, Lee S, Bronson RT, et al. (2000) Th1 and Th2 mediate acute graft-versus-host disease, each with distinct end-organ targets. *J Clin Invest* 105: 1289.
14. Dander E, Balduzzi A, Zappa G, et al. (2009) Interleukin-17-producing T-helper cells as new potential player mediating graft-versus-host disease in patients undergoing allogeneic stem-cell transplantation. *Transplantation* 88: 1261-1272.
15. Steinman L (2007) A brief history of TH17, the first major revision in the TH1/TH2 hypothesis of T cell-mediated tissue damage. *Nat Med* 13: 139-145.
16. Broady R, Yu J, Chow V, et al. (2010) Cutaneous GVHD is associated with the expansion of tissue-localized Th1 and not Th17 cells. *Blood* 116: 5748-5751.
17. Annacker O, Burlen-Defranoux O, Pimenta-Araujo R, et al. (2000) Regulatory CD4 T Cells Control the Size of the Peripheral Activated/Memory CD4 T Cell Compartment. *Immunol* 164: 3573-3580.
18. Shimabukuro-Vornhagen A, Hallek MJ, Storb RF, et al. (2009). The role of B cells in the pathogenesis of graft-versus-host disease. *Blood* 114: 4919-4927.
19. Robson NC, Donachie AM, Mowat AM (2008) Simultaneous presentation and cross-presentation of immune-stimulating complex-associated cognate antigen by antigen-specific B cells. *Eur J Immunol* 38: 1238-1246.
20. Filipovich AH, Weisdorf D, Pavletic S, et al. (2005) National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant* 11: 945-956.
21. Lee SJ (2010) Have we made progress in the management of chronic graft-vs-host disease? *Best Pract Res* 23: 529-535.
22. Choi SW, Levine JE, Ferrara JLM (2010) Pathogenesis and Management of Graft versus Host Disease. *Immunol Allergy Clin North Am* 30: 75-101.
23. de Masson A, Bouaziz J, de Latour RP, et al. (2012) Limited efficacy and tolerance of imatinib mesylate in steroid-refractory sclerodermatous chronic GVHD. *Blood* 120: 5089-5090.
24. Denton CP, Merkel PA, Furst DE, et al. (2007) Recombinant human anti-transforming growth factor beta1 antibody therapy in systemic sclerosis: a multicenter, randomized, placebo-controlled phase I/II trial of CAT-192. *Arthritis Rheum* 56: 323-333.
25. Schlaak M, Schwind S, Wetzig T, et al. (2010) UVA (UVA-1) therapy for the treatment of acute GVHD of the skin. *Bone Marrow Transplant* 45: 1741-1748.
26. Sanchez-Ortega I, Servitje O, Arnan M, et al. (2012) Dasatinib as salvage therapy for steroid refractory and imatinib resistant or intolerant sclerotic chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 182: 318-323.
27. Ratanatharathorn V, Carson E, Reynolds C, et al. (2000) Anti-CD20 chimeric monoclonal antibody treatment of refractory immune-mediated thrombocytopenia in a patient with chronic graft-versus-host disease. *Ann Intern Med* 133: 275-279.

28. Kim SJ, Lee JW, Jung CW, et al. (2010) Weekly rituximab followed by monthly rituximab treatment for steroid-refractory chronic graft-versus-host disease: results from a prospective, multicenter, phase II study. *Haematologica* 95: 1935-1942.
29. Lee SJ, Flowers ME (2008) Recognizing and managing chronic graft-versus-host disease. *Hematology Am Soc Hematol Educ Program* 134-141.
30. Zhou H, Guo M, Bian C, et al. (2010) Efficacy of Bone Marrow-Derived Mesenchymal Stem Cells in the Treatment of Sclerodermatous Chronic Graft-versus-Host Disease: Clinical Report. *Biol Blood Marrow Transplant* 16: 403-412.
31. Pène J, Chevalier S, Preisser L, et al. (2008) Chronically inflamed human tissues are infiltrated by highly differentiated Th17 lymphocytes. *J Immunol* 180: 7423.
32. Drobyski WR, Pasquini M, Kovatovic K, et al. (2011) Tocilizumab for the Treatment of Steroid Refractory Graft-versus-Host Disease. *Biol Blood Marrow Transplant* 17: 1862-1868.
33. Hori A, Kanda Y, Goyama S, et al. (2005) A prospective trial to evaluate the safety and efficacy of pravastatin for the treatment of refractory chronic graft-versus-host disease. *Transplantation* 79: 372-374.
34. Distler JHW, Distler O (2010) Tyrosine kinase inhibitors for the treatment of fibrotic diseases such as systemic sclerosis: towards molecular targeted therapies. *Ann Rheum Dis* 69: i48-i51.

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