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Graft Versus Host Disease

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INTRODUCTION

Allogeneic haemopoeitic stem cell transplantation is an effective therapy for various malignant and non-malignant diseases. The number of allogeneic cell transplantation (HCTs) continues to rise with more than 20,000 allogeneic transplantations being performed annually. Graft versus host disease (GvHD) continues to limit the procedure's success nearly 50 years after it was first described [1]. GvHD results from one of the direct functions of the immune system i.e. the distinction of self from non-self. The donor cells (e.g. graft) recognize patient's cells (e.g. host) cells as foreign and initiate a graft versus host reaction leading to GvHD. This chapter will focus on the pathobiology and classification of acute and chronic GvHD.

PATHOPHYSIOLOGY OF ACUTE GVHD

Billingham in 1966 formulated three essential requirements for the development of GvHD.

These included:

- The graft must contain immunologically competent cells
- The recipient must be incapable of rejecting the transplanted cells

- The recipient must express tissue antigens that are not present in the donor, thus recognizing them as foreign.

Rapid advancements have allowed refinement of this model proposed several decades ago. According to these advances, the classical scheme of GvHD involves 5 steps.

Step1: Priming of the Immune Response

This is the earliest phase of acute GvHD which is caused by conditioning chemotherapy. Damaged host tissues release proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 which contribute to the "cytokine storm". This increases the expression of adhesion molecules, costimulatory molecules, major histocompatibility complex (MHC antigens) and chemokine gradients. The enhanced expression is actually a "red alert" to activate host tissue cells including antigen presenting cells (APCs). During this process, the gastrointestinal tract is also damaged from the conditioning chemotherapy. This development is particularly important because it allows for systemic translocation of lipopolysaccharide (LPS) that further contributes to APC activation [2]. Therefore in some human randomized trials, increased risk of GvHD has been associated with intensive conditioning regimens [3].

Step 2: T Cell Activation and Co-Stimulation

The second step is fundamental part of the graft versus host immune reaction. The donor T cells proliferate and differentiate in response to host APCs [4]. Recently, the presence of a subset of post mitotic, self-renewing CD44lo/CD62Lhi/CD8+ T cells have been indicated that can generate and sustain all allogeneic T-cell subsets in GvHD reactions [5].The "red alert" generated in the first step augments this activation. The incidence of acute GvHD is directly related to the degree of mismatch between HLA antigens [6]. However, recipients of HLA identical grafts can still develop systemic acute GvHD to due genetic differences that lie outside the MHC loci and encode proteins of minor histocompatibility antigens (MiHAs) [7]. A major role for GvHD initiation has been associated with CD28/cytotoxic T-lymphocyte antigen 4 (CTLA-4) (CD152):B7 interactions which consist of both a stimulatory and inhibitory pathway. Another B7 supergene family member, inducible costimulator (ICOS; CD278) binds the ligand B7h (CD275) expressed on host APCs and promoted T effector responses. Blockade of ICOS on donor T cells declines gut and liver GvHD [8]. Members of the TNF receptor family also function as costimulatory molecules and regulate GvHD. When tissue injury ensues in presence of activated T cells, inhibitory pathways are up-regulated in an attempt to protect the host against injury. The immune response is down-regulated by CTLA-4 and programmed death-1 (CD279). These markers are primarily expressed in the cytoplasm of activated T cells and CD4+CD25+ regulatory T cells. In addition to these markers, the tryptophan catabolic pathway, indoleamine 2,3-dioxygenase, induced by IFN-γ in targeted organs, diminishes the T-effector cell destruction through local mechanisms that result in an increased T-cell apoptosis and decreased proliferation [9].

Step 3: Alloreactive T Cell Expansion and Differentiation

Diverse T cell subpopulations are involved in GvHD. Animal studies have shown that T cells can undergo a massive and early expansion in lymph nodes and Peyer patches [10]. CD4+CD25+Foxp3+ regulatory T cells have suppressor activity in vivo and vitro. Infusion of these cells (donor) has shown to block aGvHD. Conversely, depletion of CD25+ T cells from the graft or in recipient immediately after HSCT aids in the development of acute and chronic GvHD in various mouse models while maintaining a graft versus leukemia effect in most of the studies [11,12]. Immunosuppressive therapy also affects the expansion and fuction of these regulatory T cells. Calcinuerin inhibitors e.g. Cyclosporine, decrease IL-2 production, leading to reduction of regulatory T cells. Contrast to this, it has been seen in ex-vivo culture systems that Rapamycin either spares or increases murine and human regulatory T cells depending on the overall cell yield [13]. A second inhibitory population shown to inhibit GvHD is the natural killer T (NKT) cell that co-expresses NK and T cell surface markers [14]. In humans undergoing haematopoietic stem cell transplants, it has been seen recently that the presence of increased number of donor NKT cells in a graft containing high number of mobilized T cells leads to decreased incidence of GvHD [15]. A more recently discovered Th17 cells have been recognized to have a role in GvHD [16]. This T cell subset has been seen in experimental models of inflammatory bowel disease and lung and skin GvHD. Currently, the role of Th17 cells in humans is unknown [17].

Step 4: Activated T Cell Trafficking

The migration of T cells into secondary lymphoid organs during GvHD and other inflammatory responses have been well defined. However, the migration of leukocytes into parenchymal organs is less well understood. Changes in vascular permeability, requirement of specific selectin-ligand, chemokine receptor and integrin ligand interactions have been described. When a GvHD reaction develops, donor T cells initially migrate to spleen and peripheral lymphoid tissue [18]. Naïve donor T cells populate the lymphoid tissues. Whereas the alloreactive T cells receive activation signals from APCs and subsequently migrate to specific GvHD target organ sites [19]. All tissues in the recipient express transplant antigens but acute GvHD is limited to gut, skin, liver, secondary lymphoid organs and Thymus. The combination of CD62L and beta7 integrin expression is required to induce acute colitis and facilitate entry of CD4+ donor T cells in mesenteric nodes to cause GvHD of gut [20]. Alloreactive donor T cells invade specific organs through a combination of signals that bind to corresponding receptors on host tissues and counter receptors expressed on donor T cells, including members of chemokine family e.g. macrophage inflammatory protein 1a and other chemokines (CCL2-CCL5, CXCL2 etc.) [21].

Step 5: Destruction of the Target Tissues by Effector T Cells

Once the effector T cells migrate to the target tissues of GvHD, tissue destruction starts through both cytotoxic activity and the recruitment of other leukocytes. Many studies have postulated acute GvHD to be a Th1/T cytotoxic type (IL-12, IL-2 and IFN-γ) disease on the basis

of the predominance of cytotoxic T cell mediated pathology and increased production of Th1 type cytokines [22]. The amount and timing of cytokine release into target organs is crucial for the development of GvHD. IL-10 promotes Th2 and type 1 regulatory T cell responses which induce tolerance to allografts. Higher production in humans is associated with decreased incidence and severity of GvHD [23]. In contrast, high levels of IL-10 can accelerate GvHD in murine models and has a fatal outcome in patients who develop GvHD post HSCT. T cells demonstrate their effects of GvHD through multiple pathways. The expression of both Fas and Fas ligand is increased on CD8+ and CD4+ donor T cells. With respect to the perforin-granzyme pathway, two-thirds of studies demonstrate its importance in GvHD pathogenesis. Polymorphisms in the TNF-α gene of transplants recipients are associated with increased level of its production and subsequently increased incidence of GvHD [24]. Pathophysiology of aGvHD (Figure 1).

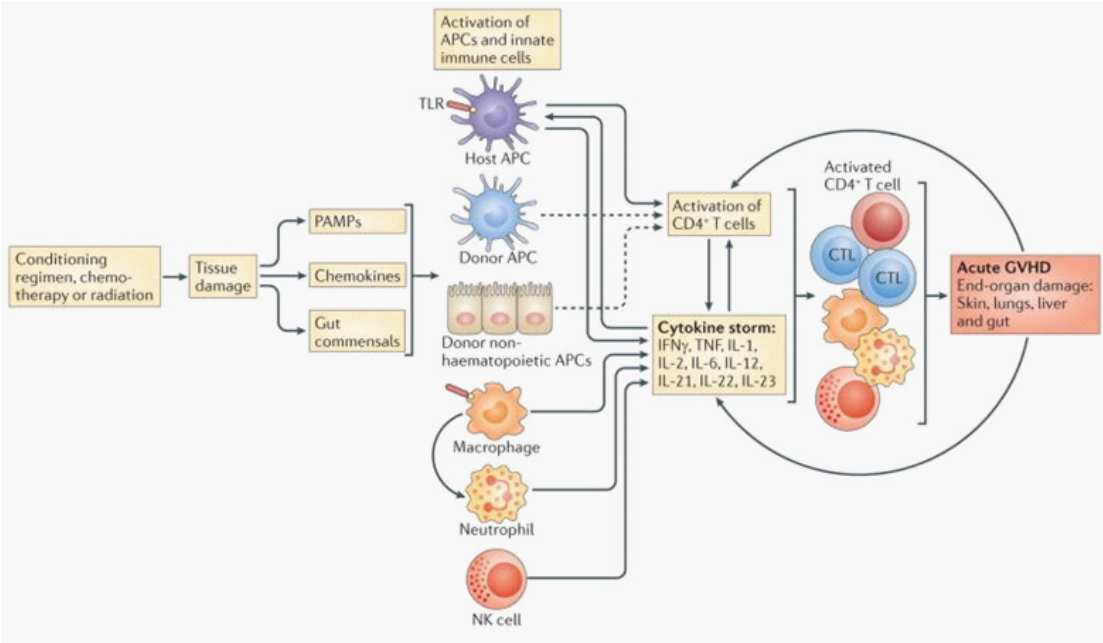

Figure 1: Pathophysiology of aGvHD [25].

DIAGNOSIS OF ACUTE GRAFT VERSUS HOST DISEASE

The diagnosis of acute graft versus host disease (aGvHD) is mainly based on clinical findings and is a diagnosis of exclusion. The most common site of involvement is the skin which presents as a maculopapular rash. The rash usually starts on the palms and soles and then spreads to the rest of the body. In severe forms, it may resemble toxic epidermal necrolysis with widespread skin involvement, mucocutaneous ulceration and bullae [26]. Other diagnosis to consider include drug reactions, viral exanthems, chemotherapy or radiation related side effects and engraftment syndrome. If the distribution of the rash is on the face, palms and soles, accompanied by deranged bilirubin and diarrhoea, aGvHD is the most likely possibility [27]. The diagnosis is made on the

basis of skin biopsy which may reveal apoptosis at the base of epidermal rete pegs, dyskeratosis, exocytosis of lymphocytes and perivascular lymphocytic infiltration in the dermis [28].

Followed by skin, the gastrointestinal tract (GIT) is the next common site of involvement. Patients with GI GvHD present with secretory diarrhoea, nausea, vomiting, anorexia, weight loss and abdominal pain. Diarrhoea is profuse and in severe cases accompanied by bleeding due to mucosal ulceration [29]. Differential diagnosis includes infection including pseudomembranous colitis and side effects of chemotherapy or radiation. Diagnosis is made by biopsy of the gut as well as endoscopic appearance [30]. The histopathological findings may show patchy ulcerations, apoptotic bodies at crypt bases, crypt ulceration and flattening of surface epithelium [31].

Acute GvHD of the liver presents with non-specific symptoms of anorexia, fever and nausea. Patients are clinically jaundiced. Laboratory parameters show elevated conjugated bilirubin, alkaline phosphatase and gamma-glutamyl-transpeptidase. Other clinical signs include painful hepatomegaly, dark urine or pale stools and fluid retention. In some patients with acute and chronic GvHD, hepatitis like picture has been described with elevation of alanine aminotransferase [32]. In children particularly, this pattern varies. Bile acids and serum cholesterol are elevated and in severe cases they may develop coagulopathy and hyperammonaemia. The differential diagnosis includes veno-occlusive disease of the liver, viral infections, drug toxicity and sepsis. Findings in liver biopsy include endolithiasis, lymphocytic infiltration of portal areas, pericholangitis and bile duct destruction [33]. Iron overload if present as a result of previous blood product transfusions, represents an adverse prognostic factor [34].

DIAGNOSTIC CRITERIA

Staging of aGvHD is done by the number and extent of organ involvement. The staging system was devised following a consensus conference in 1994 [35]. Data recently supports the usage of a grading system since it is able to subdivide patients into risk categories for morbidity and mortality. In this system, patients are divided into four grades (I-IV), depending on the degree or stage of involvement in one of the three organs. The skin is staged according to the percentage of body surface area involved, the liver is staged according to the bilirubin level derangement and the GI tract is staged according to the amount of diarrhoea. Using this criterion, (Table 1), a single grade is assigned to each patient.

Table 1: Extent of organ involvement [36].

Stage	Skin	Liver (bilirubin)	Gut (stool output/day)
0	No GVHD rash	< 2 mg/dl	< 500 ml/day or persistent nausea.
1	Maculopapular rash< 25% BSA	2–3 mg/dl	500–999 ml/day
2	Maculopapular rash 25 – 50% BSA	3.1–6 mg/dl	1000–1500 ml/day
3	Maculopapular rash > 50% BSA	6.1–15 mg/dl	Adult: >1500 ml/day
4	Generalized erythroderma plus bullous formation	>15 mg/dl	Severe abdominal pain with or without ileus
Grade			
I	Stage 1–2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	-	Stage 2–3 or	Stage 2–4
IV	Stage 4 or	Stage 4	-

A similar grading system was devised by the International Bone Marrow Transplant Registry (IBMTR) to diminish the interobserver variability in GvHD grading. This system assigned four risk categories (A-D) to each patient with aGvHD [37]. A prospective study was done to compare the Glucksberg criteria with the IBMTR. The study did not show a clear benefit of one system over the other [38]. There was less physician bias in assigning grades with the IBMTR scoring system but the Glucksberg system was better at predicting early survival.

PATHOPHYSIOLOGY OF CHRONIC GVHD

Defining the pathophysiology of chronic GvHD (cGvHD) has been complicated by the absence of animal models that capture the disease process or its clinical setting. This is in contrast with aGvHD, in which murine models of MHC mismatched HSCT provide a comprehensive picture of its pathophysiology as a clinical disease [39]. Chronic GvHD was initially defined as a syndrome that presents at 100 days post-transplant, either as an extension of acute GvHD (progressive onset cGvHD), after a disease free interval (quiescent cGvHD) or without preceding acute GvHD (de novo cGvHD) [40]. At least four theories have been postulated to explain the mechanism of chronic GvHD so far:

Breakage of Immune Tolerance to Self-Antigens

Immune tolerance to self-antigens is disrupted which gives rise to the autoimmune manifestations of the disorder. One hypothesis is that conditioning regimens and/or acute GvHD cause thymic epithelial damage leading to dysregulation of central tolerance mechanisms during reconstitution of immune system [41]. Chronic GvHD is evolved from acute GvHD through CD4+ T cells generated from donor stem cells [42]. Chronic GvHD may occur de novo as well. In 95%-99% of healthy individuals, immature T cells in the cortex of thymus die through apoptosis. Furthermore, in the thymic medulla, single-positive T cells will encounter marrow-derived APCs also bearing self-antigens (sequestered from the blood) and if strongly autoreactive, will die by apoptosis (negative selection). During this process, low-affinity T cells enter the periphery and will receive survival but not activation signals when they encounter the same self-antigen/

MHC complex. In a pro-inflammatory environment and high tissue-specific autoantigen load, this balance maybe absent. Due to this central tolerance failure, cGvHD resembles an autoimmune disease. It has been seen that host thymus is not required for the induction of cGvHD and the dormant autoreactive T and B cells are activated and expanded to cause cGvHD [43].

CD4+ CD25+ Regulatory T Cells and Their Role in cGvHD

In several studies, regulatory T cell numbers have been reported to be decreased in GvHD, though there are contradictory reports [44,45]. The mechanism by which these T regulatory cells suppress cGvHD remains obscure but few reports suggest the interplay of cytokines e.g. TGF-β, IL-10, contact with plasmacytoid dendritic cells through indoleamine 2, 3 dioxygenase [46]. Direct inhibitory influence on target tissues has also been observed [47]. The adoptive transfer of T regulatory cells in animal models of GvHD has demonstrated their efficacy. It has been seen that alloantigen derived expansion rather than homeostatic proliferation is critical for the effectiveness of T regulatory cells in cGvHD.

The role of B Cells and Antibody Production

The initial report of B cells in the pathogenesis of GvHD was highlighted by a case report of a patient with cGvHD who responded to Rituximab based therapy [48]. Ample amount of evidence after this has suggested the role of B and T cell interactions in cGvHD. Many examples have quoted autoantibody formation in patients with cGvHD, but the role of autoantibody formation in the pathogenesis has not been demonstrated [49]. High plasma levels of B cell activating factor (BAFF), a cytokine that appears to drive B cell autoimmunity, has been found in patients with cGvHD [50]. The development of antibodies to minor compatibility antigens (mHA) encoded on Y chromosome in male patients receiving female grafts has been strongly associated with the incidence of cGvHD [51]. A study done by Zhang C et al suggested that donor B cell depletion protected from development of cGvHD [43]. It can therefore be concluded that alloreactive donor CD4+ T cells could be activated by host B cells, and that this, in turn, promotes the activation and expansion of quiescent autoreactive donor B cells in stem cell grafts.

Fibrotic Changes

In the initial phase of chronic skin GvHD, there is an intense mononuclear inflammatory infiltrate and destructive changes at the dermal-epidermal junction accompanied by irregular acanthosis, hyperkeratosis, atrophy, progressing to dermal fibrosis and sclerosis [52]. Other changes include destruction of tubuloalveolar glands ducts in the skin, salivary and lacrimal glands, respiratory epithelium and bile ducts. In addition to this, complement factor 5 (C5) has been found to dose dependently modify liver fibrosis [53]. Gene expression studies have shown that increased TGF-β signaling in CD4 cells and CD8 cells is associated with a reduced risk of cGvHD in man [54]. The association between increased TGF-β activity and a reduced risk of cGvHD might result from a lower risk of acute GvHD, which is a well-recognized risk factor of cGvHD. There is now evidence that expansion of Th2 cells after HSCT is associated with development of cGvHD

in both murine models and humans [55]. CD4+ T cells play an important role in the progression of cGvHD. Although an equally potent inflammatory response develops when Th1 CD4+ T cells, which produce interferon IFN-γ, dominate under these circumstances, the development of tissue fibrosis is almost completely attenuated [56]. These studies show that chronic inflammation does not always induce the deposition of connective-tissue elements and that the magnitude of fibrosis is tightly regulated by the phenotype of the developing Th cell response. Pathophysiology of cGvHD (Figure 2).

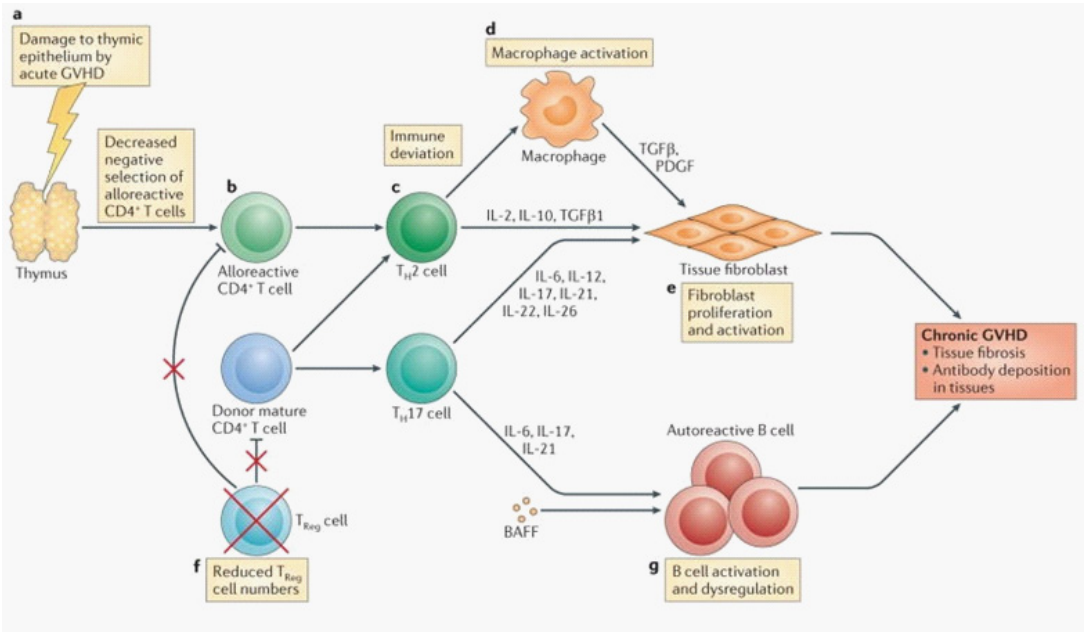

Figure 2: Pathophysiology of cGvHD (25).

DIAGNOSIS OF CHRONIC GRAFT VERSUS HOST DISEASE

Previously cGvHD was defined as occurring more than 100 days after transplant. Based on clinical features rather than the time of onset, the NIH consensus conference provided two subcategories of cGvHD, classic and overlap syndrome. According to this criterion, classical features of cGvHD could occur within 100 days of transplant and features of acute and chronic GvHD could occur together. Furthermore, "diagnostic" and "distinctive" features of cGvHD were identified. Diagnostic signs include clinical features that aid in the diagnosis of cGvHD without the need for further investigations. Distinctive signs include clinical features not associated with acute GvHD but insufficient to make a diagnosis of cGvHD and require histopathological or laboratory findings [57]. In all cases, drug reaction, infection, recurrent or new malignancy and other causes must be excluded. Organ specific "diagnostic" and "distinctive" features are highlighted below [57].

Hair

Distinctive features include new scarring and non-scarring scalp alopecia and loss of body hair. Other characteristics are premature graying, thinning, or brittleness but these findings are not diagnostic.

Eyes

Distinctive features of cGvHD of eyes include new onset of dry, gritty or painful eyes; cicatricial conjunctivitis; keratoconjunctivitis sicca; and confluent areas of punctate keratopathy. Other manifestations include photophobia, periorbital hyperpigmentation, mucoid secretions and blepharitis. New onset of ocular sicca documented by low Schirmer test values with a mean value of both eyes of ≤5 mm at 5 minutes or a new onset of keratoconjunctivitis sicca by slit-lamp examination with mean values of 6 to 10 mm on the Schirmer test is sufficient for the diagnosis of cGvHD if accompanied by distinctive manifestations in at least one other organ.

Mouth

Diagnostic features include lichen planus-like changes, hyperkeratotic plaques (leukoplakia) or decreased oral range of motion. Distinctive features of chronic include xerostomia, mucoceles, mucosal atrophy, pseudomembranes and ulcers.

Lungs

The only diagnostic manifestation in lungs in cGvHD is biopsy proven bronchiolitis obliterans (BO). BO is characterized by new onset of an obstructive lung defect. Clinical manifestations may include dyspnea on exertion, cough, or wheezing. Pneumothorax, pneumomediastinum, and subcutaneous emphysema are rare and often represent advanced disease. BO diagnosed through pulmonary function and radiologic testing requires at least one other distinctive manifestation in a separate organ system to establish the diagnosis.

Gastrointestinal Tract

Diagnostic features include esophageal web, stricture or concentric rings confirmed by endoscopy or barium contrast radiography and pancreatic exocrine insufficiency. Wasting syndrome maybe a part of cGvHD but is often multifactorial in origin. Endoscopically, mucosal edema, erythema or focal erosions with apoptotic epithelial cells may be seen but are not considered diagnostic for cGvHD. Patients with unresolved aGvHD may have more severe intestinal mucosal lesions, including ulcers and mucosal sloughing.

Liver

Hepatic acute and chronic GVHD typically presents as cholestasis, with increased bilirubin or alkaline phosphatase, but it may also present as acute hepatitis [58]. Because of differential diagnosis, liver biopsy is compulsory to confirm involvement of liver by GvHD. Furthermore,

because of the similarity in histopathological findings in liver biopsy for acute and chronic GvHD, distinctive manifestation in at least one other organ is also required.

Skin

Diagnostic manifestations include poikiloderma, lichen planus like eruption, deep sclerotic features (e.g., smooth, waxy, indurated skin—"thickened or tight skin," caused by deep and diffuse sclerosis over a wide area), morphea-like superficial sclerotic features or lichen sclerosis-like lesions. Severe sclerotic features are characterized by thickened, tight, and fragile skin often associated with poor wound healing, inadequate lymphatic drainage, and skin ulcers from minor trauma. A distinctive feature of cGvHD is depigmentation combined with biopsy or laboratory confirmation. Sweat impairment and intolerance to temperature change from loss of sweat glands are also seen in chronic GVHD.

Nails

Dystrophic changes consisting of longitudinal ridging, nail splitting or brittleness, onycholysis, pterygium unguis and nail loss are distinctive signs of chronic GVHD but are not sufficient for diagnosis.

Musculoskeletal System

Diagnostic features include fascial involvement affecting the forearms or legs which may lead to joint stiffness or contractures, fasciitis, edema of the extremities and myositis. Myositis is a non-diagnostic manifestation which may present as proximal myopathy. Evaluation of myositis involves electromyography and measurement of creatinine phosphokinase or aldolase. Arthralgia and arthritis are uncommon and are occasionally associated with the presence of autoantibodies.

Haemopoietic and Immune Systems

Cytopenias may result from stromal damage or autoimmune process Lymphopenia (≤ 0.5 x 109/L), eosinophilia ((≤ 0.5 x 109/L) hypogammaglobulinemia, or hypergammaglobulinemia may be present. Autoantibodies may develop with autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura. Thrombocytopenia (≤100 x 109/L) at the time of cGvHD diagnosis has been associated with a poor prognosis.

Genitalia

Diagnostic manifestations for the genitalia include lichen planus like features and vaginal scarring or stenosis.

DIAGNOSTIC CRITERIA

Chronic GvHD was initially staged as limited or extensive disease previously. The NIH consensus document proposed a new clinical scoring system on a four point scale (0–3) with 0 representing no involvement, 1 mild involvement (no significant impairment of daily living),

2 moderate involvement (significant impairment of daily living) and 3 representing severe impairment (major disability). Chronic GvHD is then classified as mild, moderate or severe. Patients with involvement of one or two organs with a score of 1 and no pulmonary GvHD are classified as having mild cGvHD. Moderate cGvHD is defined as involvement of three organs with a score of 1, at least one organ with a score of 2 or pulmonary GvHD with a score of 1. Patients who have major disability resulting in a score of 3 in any organ or site or patients who have pulmonary GvHD scoring 2 or 3 are classified as having severe cGvHD.

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐	☐ No Symptoms	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
MOUTH	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI TRACT	☐ No symptoms	☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation
LIVER	☐ Normal LFT	☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	☐ Bilirubin or enzymes > 5 x ULN

Table 2: Clinical scoring of organ system [57]. *AP maybe elevated in growing children not reflective of organ dysfunction. Pulmonary scoring should be performed using symptoms and PFT. Scoring using the lung function score is preferred (LFS). FEV1 should be used when DLCO is not available. ECOG (Eastern Cooperative Oncology Group), KPS (Karnofsky performance status), LPS (Lansky performance status), ADL (Activities of daily living), ULN (upper limit of normal).

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