Chronic Graft Versus Host Disease: An Update on the Clinical Characterization and Diagnostic Assessment of Cutaneous and Articular Sclerotic Forms

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Keywords:
Chronic GVHD; Scleroderma; Fasciitis; Fibrosis

1. Abstract

1.1. Background: Chronic graft-versus-host disease (cGVHD) is a late immune-mediated, and sometimes a severe complication of patients undergoing allogeneic hematopoietic cell transplantation. It is a multisystemic inflammatory disease with variable degree of fibrosis, mainly at cutaneous and often-overlooked musculoskeletal level, which entails a negative impact on the quality of life and physical function of these patients.

1.2. Objective: The aim of this review is to provide an update on the clinical characteristics of skin and joint sclerotic variants that develop within the spectrum of cGVHD, and to describe the recommended assessment scales for its diagnosis.

1.3. Methods: We have carried out a systematic literature research in Medline, Web of Science, Embase and Scopus, selecting articles with information on scleroderma-tous GVHD up to June 2021. We excluded those articles not addressing the sclerotic joint and skin clinical involvement characterization and assessment of cGVHD activity.

1.4. Results: Sclerotic cutaneous cGVHD represents a distinctive phenotype of cGVHD, often associated with varying degrees of disability and increased morbidity. It usually begins in the superficial layers and then spreads to deep planes. Fibrous skin lesions are usually symmetrical in distribution and often mixed in pattern, with different types of sclerotic cutaneous coexisting in the same patient. The National Institute of Health (NIH) working group's recommended scales for diagnostic assessment and skin stratification in patients with cGVHD reflect the need to assess both the extent of involvement (by total body surface area on a scale of 0-3) and the type of involvement (superficial or deep scleroderma).

The musculoskeletal manifestations such as arthralgias, myalgias, joint stiffness, oedemas or cramps are very unspecific. In contrast, joint contractures secondary to scleroderma/or fasciitis are considered sufficient diagnostic criteria for cGVHD. The assessment of musculoskeletal involvement, especially fascial/joint, validated in patients with cGVHD are the joint/fascial scale and the P-ROM (Photographic range of motion), both proposed by the NIH working group and also the Hopkins fascia scale that evaluates tightness. The Photographic Range of Motion (P-ROM) scale captures the range of mobility separately for shoulders, elbows, wrists/fingers, and ankles, the more common affected sites.

1.5. Conclusion: The sclerotic affection in patients with cutaneous and articular cGVHD is not infrequent, being able to present a wide range of manifestations, sometimes over-looked, that impact in a negative way in the quality of life of the large survivors patients after allo-HCT.
2. Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) is a highly specialized and complex medical procedure. Allo-HCT is the only curative treatment for many malignant and non-malignant hematologic diseases; its use is steadily increasing [1, 2]. The goal of allo-HCT is twofold: to replace the patient's hemopoiesis that is totally or partially defective, insufficient or neoplastic, with a normal one from a healthy donor; and to benefit, in the case of neoplastic pathology, from the anti-tumor activity of the graft's immunocompetent cellularity, the so-called graft-versus-tumor (GVT) effect [3]. Despite the advances made in recent decades, both in the field of supportive care and in conditioning strategies, the morbidity and mortality of the procedure remains high. The main cause of mortality after allo-HCT is relapse of the disease due to failure of GVT effect. In addition, there are a high percentage of patients who will develop transplant-related morbidity and mortality due to the inherent toxicity of the procedure. In this sense, the most important complications are Graft-versus-Host Disease (GVHD) and infections [4]. GVHD is the resulting reaction from the recognition as foreign of antigens from the recipient by the donor's T-lymphocytes, leading to an immunological, allo-immune, inflammatory and in some cases fibrotic dysregulation, responsible for the characteristic clinical manifestations of the disease [5]. Classically, GVHD has been divided into acute and chronic, according to the time of appearance of the symptoms - before or after the day + 100 after the transplant -, although currently it is considered that it is the clinical manifestations that allow the diagnosis of acute (aGVHD) or chronic GVHD (cGVHD) to be established [6]. Although GVHD in its severe forms are the main cause of morbidity and mortality not related to relapse, the development of GVHD, especially its chronic forms, has been associated in several studies with a reduction in the relapse of the underlying disease and an increase in survival, since GVHD is usually linked to this complication [3].

The aim of this paper is to describe the clinical characteristics of sclerotic variants, both cutaneous and articular, that develop within the spectrum of multisystemic manifestations of cGVHD, characterizing their different clinical forms and emphasizing the recommended scales of systematic evaluation to establish their diagnosis, prior to therapeutic management.

3. Methods

We conducted a systematic review according to PRISMA guidelines. We searched Pubmed, Web of Science, Embase and Scopus, selecting articles with information on sclerodermatous graft-versus-host disease up to June 2021. We used the following search strategy: "graft versus host" OR "sclerodermatous graft-versus-host") AND ("systemic sclerosis" OR scleroderma OR scler-oro* sclerodermatous OR morphea) AND (fascia* OR tendon* OR contractures OR articular OR fasciitis OR tenosynovitis). In order to confirm, that we did not miss any cGVHD induced cutaneuos or joint sclerosis, we performed a manual search to identify other relevant articles, specially, in the National Institutes of Health (NIH) consensus documents in cGVHD. We included studies published from 1978 onward and we excluded articles not addressing the sclerotic joint and skin clinical involvement characterization and assessment, specifically, those articles on another systemic fibrosis, imaging techniques or a therapeutic intervention in cGVH.

Also, by reviewing the references in the most relevant articles we identified additional articles of interest. We limited our search to English language publications.

4. Results

We identified 119 potentially eligible studies, of which we included 49 articles related to sclerotic clinical manifestations and finally, we only reviewed 28 papers deeply. We found a total of 28 articles, which include case series, case reports and review articles. We read all abstracts and we retrieved a full study report of most of them. (Figure 1 shows the study selection process).

Chronic GVHD (cGVHD) is the most common late complication after allo-HCT. It has a highly variable incidence (25-55%) [7] depending on a number of risk factors, such as previous development of aGVHD, advanced age, unrelated donors, HLA disparity, use of female donor for male recipient or of peripheral blood versus bone marrow or umbilical cord. In the last decade, there has been an increase in the incidence of cGVHD, due to both the increase in long term survivors and the change in the allogeneic PH procedure, which increases the risk of its development (increasing patient and donors, increased use of unrelated donors, predominant use of progenitor cells obtained from peripheral blood, strategies such as infusion of donor lymphocytes in certain complications, etc.) [8,9].

Chronic GVHD has a very wide range of clinical manifestations, consisting mainly of characteristic symptoms of auto/alloimmune disease with evidence of chronic and fibrous inflammation. The median onset is around 6 months after the allo-HCT and in approximately half of the patients, the involvement will be multisystemic. Patients with cGVHD have persistent immunodeficiency and recurrent infections, both because treatment of GVHD usually includes immunosuppressants (especially glucocorticoids) for prolonged periods of time, and because of the immune system alteration associated with this entity, causing a marked deterioration in the quality of life of these patients [10].

One of the greatest challenges in the management of cGVHD is the establishment of a correct and early diagnosis. In recognition of these difficulties, in 2005 the National Institutes of Health (NIH) promoted the creation of a group of experts to develop an international consensus on cGVHD, developing guidelines for the correct clinical and histological diagnosis, response criteria and
supportive treatment [11], which have been revised in 2015 [12]. These guidelines establish that in order to make a correct diagnostic approach of cGVHD, three steps are required: establish the diagnosis of cGVHD, score the severity of each affected organ and classify the GVHD as mild, moderate or severe. The diagnosis of cGVHD is established in the presence of 1 diagnostic criteria or 1 distinguishing criteria + biopsy/confirmatory test (Table 1).

Sometimes, patients with cGVHD also have symptoms and/or signs of aGVHD; this is the so-called overlap syndrome. On the other hand, it is called de novo cGVHD when cGVHD appears in a subject with no history of aGVHD, quiescent when it develops in a patient who had aGVHD and it resolved before he or she had symptoms of cGVHD and progressive in those patients who develop cGVHD without having previously resolved the symptoms of aGVHD.

Although the skin is the most frequently affected organ, it is common to involve other locations such as the joints and fascias, these manifestations being the ones we will develop in detail. The oral, ocular and genital mucosa, the liver, the gastrointestinal tract and the lungs are other affected territories. These varied manifestations can occur successively or simultaneously, causing a negative impact on the quality of life of patients [13].

Table 1: Diagnostic criteria and distinguishing features of chronic cutaneous and musculoskeletal GVHD (adapted from Filipovich 2005, Jagasia 2015)

<table>
<thead>
<tr>
<th>ORGAN OR SITE</th>
<th>DIAGNOSTIC (Sufficient to establish the diagnosis of chronic GVHD)</th>
<th>DISTINCTIVE (See in chronic GVHD, but insufficient alone to establish a diagnosis)</th>
<th>OTHER FEATURES OR UNCLASSIFIED ENTITIES</th>
<th>COMMON (Seen with both acute and chronic GVHD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKIN</td>
<td>Poikilodermat-like features</td>
<td>Depigmentation</td>
<td>Sweat imprrtment</td>
<td>Erythema</td>
</tr>
<tr>
<td></td>
<td>Lichen planus-like features</td>
<td>Papulosquamous lesions</td>
<td>Ichthiosis</td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td></td>
<td>Sclerotic features Morphea-like features</td>
<td></td>
<td>Queratosis pilaris</td>
<td>Pruritus</td>
</tr>
<tr>
<td></td>
<td>Lichen sclerosis-like features</td>
<td></td>
<td>Hypopigmentation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperpigmentation</td>
<td></td>
</tr>
<tr>
<td>MUSCLE, JOINTS AND FASCIA</td>
<td>Fasciitis Joint stiffness or contractures due to sclerosis</td>
<td>Myositis</td>
<td>Oedema</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polymiositis</td>
<td>Muscle cramps</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Arthralgia</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Arthritis</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Flowchart of the selection of studies for inclusion in the review.
4.1. Sclerotic cutaneous chronic GVHD

The skin is the most frequently affected organ in cGVHD, reaching up to 75% of patients in some series, and is often the initial manifestation of the disease. Cutaneous cGVHD has been classically divided into two major categories: lichen lesions of earlier appearance and scleroderma manifestations of later development [14]. In many studies it has been noted that sclerotic changes always begin on acute or lichenogenic lesions [15]. However, other studies maintain that they can present simultaneously or even occur independently of each other [16] and that periorbital hypopigmentation could suggest the later appearance of the sclerodermitform form.

Sclerotic cutaneous cGVHD represents a distinctive phenotype of cGVHD first described in 1977, often associated with varying degrees of disability and increased morbidity [17], and may mimic chronic inflammatory and autoimmune diseases well known as systemic sclerosis. The sclerodermitform clinical form is the least frequent among the manifestations of cutaneous cGVHD, with a prevalence of 3% [15]. Unlike systemic sclerosis, internal organ involvement with pulmonary hypertension, altered renal function and cardiac dysfunction is infrequent; the same occurs with the presence of vasculopathy and Raynaud's phenomenon, almost absent in sclerotic cGVHD, although endothelial dysfunction associated with cGVHD has been observed in some studies [18]. Skin involvement in systemic sclerosis begins in the deep layers of the skin and then extends to superficial areas, whereas in fibrotic cGVHD it usually begins in superficial layers and then spreads to deep planes. In a cohort of 977 patients undergoing allogeneic HCT, 20% developed sclerotic changes within 3 years of the onset of cGVHD (17), a percentage slightly higher than that reported in previous studies (10-15%) [19, 20].

Skin tightness, without any evidence of detectable skin injury, may be the first symptom observed. The scleroderma lesions in cGVHD are often localized and superficial in early stages; they appear as indurated, sclerosed, shiny, yellow-white plaques with poorly defined contours (Figure 2). Initially, these lesions may present as inflammatory plaques, both in the form of non-indexed "guttate" and in morphoid plaques without liliaceous ring, with location in the trunk and in the proximal region of the limbs. The deep and often diffuse sclerodermitform form affects both the dermis and the subcutaneous tissues, causing anexal loss, alopecia and ulcers, especially when the lesions are located in the distal areas of the legs. Deep sclerosis can also lead to limitations of mouth opening without facial skin fibrotic involvement, vaginal stenosis, restriction of chest wall expansion, and an inability to move or pinch the skin due to thickening and hardening. Schaffer et al, in similar fashion to what was previously described by Borda, propose a clinical dermatological spectrum of the sclerodermitform form, classified according to the anatomical level of affection, from superficial to deep, which would include sclerosing cutaneous lichen-like lesions, morpheaform-like lesions (Figure 1) and eosinophilic-like fasciitis (Figure 3) forming the different cutaneous sclerosis variants of fibrotic cutaneous cGVHD, [21, 22].

Figure 2: Morpheiform GVHD: Deep scleroderma-like lesion on the front of the legs and back of both feet. There are yellowish, indurated, non-pinachable plates attached to deep planes, extending even to the backs of toes.

The *lichen sclerosus lesions* are mainly located in the neck and upper region of the trunk, with a certain predilection for scar areas (catheter removal, in scars secondary to infections or suction blisters as an isomorphic sclerotic phenomenon) [23]. The *morpheiform lesions* are located in the lower part of the trunk (the belt area), while the *eosinophilic fasciitis lesions* generally develop in the proximal areas of the limbs, respecting hands and feet. Peñas et al add, within this sclerodermitform spectrum, another subtype of localized scleroderma called paniculitis-like (subcutaneous fat tissue), placing it between morpheaform lesions and eosinophilic fasciitis [24]. Exceptionally, cases of pansclerotic Morphia type cGVHD have been described. In addition, Italian authors have reported an infrequent localized sclerodermitform picture similar to nodular/cicatricial scleroderma in patients with cGVHD, increasing the clinical sclerotic skin spectrum of the disease [25]. Vascular proliferations within the area of scleroderma that mimic lesions of Kaposi's sarcoma - particularly in the extremities - have also been described recently, proposing the term for this sclerotic variant of cGVHD-associated angiomatosis due to its specificity of cutaneous cGVHD compared to other fibrotic entities [26].

Fibrous skin lesions are usually symmetrical in distribution and often mixed in pattern, with different types of scleroderma coexisting in the same patient [27].

The diagnosis and stratification of skin involvement in cGVHD is complex due to the heterogeneity of its manifestations, having undergone several modifications over time. Currently, only poikiloderma, lichen plano-like rash, superficial sclerotic changes of the Morpho-like type (localized areas of indurated plaques that can be displaced, often with depigmentation) or lesions of the lichen-sclerosis-like type and deep sclerodermitform changes (induration, thickening, tightness due to deep and diffuse sclerosis over a wide area, usually causing limited joint mobility) are included as diagnostic clinical features of cutaneous GVHD (for which biopsy confirmation is not necessary) are included as diagnostic clini-
cal features of cutaneous GVHD (for which biopsy confirmation is not necessary) [12]. Vitiligo and papulosquamous lesions are "hallmark" symptoms/signs that are not sufficient for the diagnosis of cGVHD without additional confirmatory diagnostic test (biopsy or blood test) (Table 1).

The National Institute of Health (NIH) working group's recommended scales for diagnostic assessment and skin stratification in patients with cGVHD reflect the need to assess both the extent of involvement (by total body surface area on a scale of 0-3) and the type of involvement; if sclerotic, it is divided into superficial and deep involvement (Table 2). In the recommendations published in 2005 by the NIH group, they incorporated the performance of the modified Rodnan scale (17 areas with a score of 0-51) for the assessment of superficial scleroderma [11], but in the last consensus published in 2015 [12], they obviated its performance, probably because of the heterogeneity and variability of its performance in not specifically trained hands, classifying superficial scleroderma with a score of 2 (moderate) and deep scleroderma with a score of 3 (severe). Thus, the existence of scleroderma changes confers worse stratification.

Figure 3: Eosinophilic fasciitis type chronic GVHD: skin rippling on the anterior aspect of the thighs (a) and on the abdomen (b). In (c) rippling and sign of the groove on the inner arm of eosinophilic-like fasciitis can be seen.

Table 2: NIH 2015 Skin assessment score

<table>
<thead>
<tr>
<th>SKIN†</th>
<th>Score % BSA*</th>
<th>GVHD features to be scored by BSA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Check all that apply:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maculopapular rash/erythema</td>
<td>No BSA involved</td>
<td>1-18% BSA</td>
</tr>
<tr>
<td>Lichen planus-like features</td>
<td>Superficial sclerotic features &quot;not hidebound&quot; (able to pinch)</td>
<td></td>
</tr>
<tr>
<td>Sclerotic features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papulosquamous lesions or ichthyosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratosis pilaris-like GVHD</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>SKIN FEATURES SCORE:</th>
<th>No sclerotic features</th>
<th>Superficial sclerotic features &quot;not hidebound&quot; (able to pinch)</th>
<th><strong>Check all that apply:</strong> Deep sclerotic features &quot;Hidebound&quot; (unable to pinch) Impaired mobility Ulceration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other skin CVHD features (NOT scored by BSA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Check all that apply:</strong></td>
<td>Hyperpigmentation</td>
<td>Hypopigmentation</td>
<td>Poikiloderma</td>
</tr>
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</table>

*BSA: Body superficial area
4.2. Sclerotic fascial/joint chronic GVHD

The musculoskeletal manifestations of patients subjected to allo-HCT such as arthralgias, myalgias, joint stiffness, oedemas or cramps are very unspecific, frequent and difficult to attribute to a single cause. In contrast, joint contractures secondary to sclerosis are considered sufficient diagnostic criteria for cGVHD, not requiring biopsy [11] [Table 1]. These manifestations can be detected clinically when the inflammation or fibrosis reaches deep soft tissue (deep sclerosis/fasciitis) or affects the skin surrounding the joints (superficial scleroderma); it should be noted that the former can occur with or without superficial scleroderma. One of the most controversial aspects of cGVHD is when it presents as isolated fasciitis. This condition is often detected by limitation of the range of joint mobility or by inducing sometimes irreversible joint contractures that cause great disability. As we have pointed out in the previous section, within deep fibrotic skin involvement there are sclerotic manifestations that simulate the eosinophilic fasciitis described by Shulman often triggered after strenuous physical activity [28]. Eosinophilic-like fasciitis in the context of GVHD has the appearance of cellulitis due to subcutaneous septal and fascial fibrosis. It usually presents with skin induration, with the appearance of typical "orange peel", peripheral eosinophilia, arthromyalgias and arthritis, tending to joint contractures in the most severe cases (sign of prayer or de Buddha) [29]. Moreover, multiple studies have presented strong correlation between joint and skin symptoms during the course of GVHD (15). According to Vukić, joints change appeared in 83,3% of subjects with coexisting erythematous lesions, superficial o deep sclerosis [30].

Unfortunately, it is not known what clinical, genetic and biological factors are specifically involved in the musculoskeletal and joint involvement of GVHD patients [31-33]. The search for serum biomarkers in this fibrous entity, such as specific autoantibodies, has so far proved unsuccessful. Similarly, there are few studies that analyze the usefulness of advanced imaging techniques, such as magnetic resonance imaging or high resolution ultrasound of soft tissue, in patients with cGVHD with distinctive symptoms such as arthralgias, joint stiffness or tendon rubbing, which could help to make a diagnosis in the early stages of fibrotic disease before joint contractures are established, most of the time irreversible [34,35].

The stratification scales for the assessment of musculoskeletal involvement, especially fascial/joint, validated in patients with cGVHD are the joint/fascial scale and the P-ROM (Photographic range of motion), both proposed by the NIH working group (Tables 3 and 4) [11,12] and also the Hopkins fascia scale than uses a 0–3-point scale but scores only tightness. The NIH joint/fascial scale takes into account three components: composite score for tightness, ROM (range of motion), and activities of daily living (ADL). The Photographic Range of Motion (P-ROM) scale is a series of images that captures ROM separately for shoulders, elbows, wrists/fingers, and ankles. They were initially applied in the evaluation of the severity of the basal manifestations or in cross-sectional studies. However, their application has subsequently been extended, showing their usefulness in detecting longitudinal changes by measuring the response to treatment, in the same way as the scales used to evaluate the clinical response to skin and eye disease [36, 37]. The use of the P-ROM scale has been a great advance in terms of its simplicity and objectivity. Assessing active joint mobility as an objective measure to evaluate the response to treatment has the limitation of requiring an adequately trained professional capable of performing standardized and reproducible measurements with great time consumption. In this sense, the P-ROM scale provides an alternative for clinical use, since any physician can complete the evaluation adequately in 1-2 minutes. However, this scale detects PROs (Patients Report Outcome) less well, probably because it does not take into account rigidity or limitations in performing activities of daily living (ADLs) as the NIH joint/fascial scale does. Incorporating a measure of musculoskeletal symptoms similar to the Lee subscale (0-10) into the photographic scale (P-ROM) would allow changes in PROs to be captured as well as detecting the global cGVHD assessment scale [38].

In some works, such as that of Pidalal et al, it’s recommended to complete the joint/facial assessment by performing the grip strength of the dominant hand through a dynamometer (sphingometer) and the 2-minute gait test [39]. These measurement indices have not been reproduced subsequently and the NIH consensus group does not recommend this in clinical practice, although it is required in some clinical trials [39]. Recently, Inamoto and Lee refined NIH algorithm for chronic GVHD in joints and fascia, and recommend that the NIH joint/fascial score and total P-ROM score should be used for assessing therapeutic response in joint/fascial cGVHD [40].

<table>
<thead>
<tr>
<th>Table 3: NIH joint/fascial scale for cGVHD</th>
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<tr>
<td>0</td>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
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<td>3</td>
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5. Discussion

Chronic GVHD remains of allo-HCT, reportedly occurring in 30-70% of patients surviving more than 100 days. It is also the leading cause of non-relapsed mortality occurring more than 2 years after HCT for malignant disease. Manifestations of cGVHD may be restricted to a single organ or site or may be widespread, with profound impact on quality of life, specially when sclerotic disease is developed.

Diagnosing and scoring the severity of cGVHD is challenging for several reasons: limited understanding of the pathophysiology, coexisting acute GVHD manifestations, pathology samples may be difficult to obtain, previously poorly measurement tools and scoring system, and lack of biomarkers for the diagnosis and assessment of disease activity. The NIH consensus criteria provide standardized tools for reporting cGVHD, although many aspects of the 2005 NIH consensus criteria including organ scoring, global severity, and GVHD categories have been validated by several retrospective and prospective studies, daily practice has raised questions about the clinical scoring of organs and also identified areas of controversy based on experience with the criteria in clinical practice [41]. For example, experts thought that active disease and irreversible “fixed” deficits should be distinguished, and organ dysfunction entirely attributed to a non chronic cGVHD etiology should be excluded from severity and response scoring. According to that, pathognomonic musculoskeletal symptoms, which are sufficient to diagnose cGVHD, include fasciitis, stiffness of the joints or secondary contracture of scleroderma, but fasciitis is classified by some authors, even in the NIH scales, as the deep cutaneous fibrotic variant. However, there is controversy about its inclusion within the skin score, since the fascia is anatomically part of the musculoskeletal system, especially in cases where there is fascia/tendon sclerotic involvement that causes limited joint mobility (carpals, shoulders, elbows and knees) without detectable skin hardening (scleroderma), but causing a decline in physical function in these patients (Figure 4) [32]. Further, the knowledge of clinicians on the correlation between changes in the musculoskeletal system and the probability of diagnosing GVHD is still relatively low.

Figure 4: Score P-ROM=1 in wrist joints (sign of Buddha or prayer) In B she improves joint stiffness with the fingers flexed, reflecting probably the fibrotic involvement of the flexor tendons of the fingers.

Most practitioners view using the NIH cGVHD recommendations in their entirety as too burdensome for use in routine clinical practice. Although these criteria represent advancement in this field, many questions remain, including their role in clinical practice, biomarkers discovery, and regulatory review of the new drugs or devices seeking FDA approval. For certain organs and sites, the minimal criteria to diagnose chronic GVHD have not been clearly defined. Other unresolved issues of the 2005 Consensus criteria include confusion about the chronic GVHD subcategories (specially overlap GVHD), the rules for scoring abnormalities (symptoms, signs, diagnostic testing) not due to GVHD most of them resolves in the 2015 NIH Consensus criteria, but there is still a lack of distinction between active disease and a fixed deficit resulting from prior tissue damage in some cases, specially, in joint contractures [36].

Further, the lack of distinction between active disease (for example, erythematous rash) and fixed deficits or sequelae (for example, hyperpigmentation as a consequence form prior rash or irreversible contractures secondary to sclerosis) provides additional controversies. In clinical condition, where physical exam may be insufficient to distinguish active disease and fixed deficits, identification of biomarkers, certain imaging techniques such an elastog-
raphy or magnetic resonance or molecular studies of biopsies may potentially be useful in differentiating these processes.

The sclerotic affectation in patients with cutaneous and articular cGVHD is not infrequent, being able to present a wide range of manifestations that impact in a negative way in the quality of life of the patients after allo-HCT. The approach to these patients requires multidisciplinary units in which hematologists, dermatologists and rheumatologists collaborate in the diagnosis and stratification of the damage, in order to properly evaluate its progress. The search for new biomarkers associated with fibrosis and the use of advanced imaging techniques to establish its extent could help improve the prognosis of patients with cGVHD.

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References


