Hidalgo Calleja *et al.*
Advances in Rheumatology (2022) 62:33
https://doi.org/10.1186/s42358-022-00262-3

Advances in Rheumatology

RESEARCH

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Graft versus host disease-related eosinophilic fasciitis: cohort description and literature review

Cristina Hidalgo Calleja[1*], Daniel Martín Hidalgo[2], Concepción Román Curto[3], Lourdes Vázquez López[4], Estefanía Pérez López[4], Mónica Cabrero Calvo[4], Ana África Martín López[4], María Dolores Caballero Barrigón[4] and Lucía Lopez-Corral[4]

Abstract

Background: Chronic graft versus host disease (cGVHD) simulating eosinophilic fasciitis (EF) is an underdiagnosed and challenging complication due to the lack of knowledge about its pathogenesis, refractoriness to traditional immunosuppressive agents and their negative impact on the physical function and quality of life. The aim of this study is to describe the clinical-biological characteristics and response to treatment of a case series and to provide a comprehensive literature review on cGVHD related EF involvement.

Methods: Prospective observational study to describe the clinical and diagnostic evaluation characteristics of patients with EF-like follow-up as part of our multidisciplinary cGVHD consultations. In addition, the literature on joint and/or fascial musculoskeletal manifestations due to cGVHD was comprehensively reviewed.

Results: 118 patients were evaluated in multidisciplinary cGVHD consultations, 39 of whom (33%) developed fasciitis. Notably, 11 patients had isolated joint contractures without sclerotic skin. After a median of three lines of treatment, the vast majority of patients achieved some degree of response. 94 potentially eligible articles were identified by the search strategy, with 17 of them, the majority isolated case reports, making the final selection. The validated staging scales used for the assessment were the Joint and Fascial Score and the Photographic Range of Motion.

Conclusion: Fascial/articular involvement needs to be recognized and evaluated early. To our knowledge, our cohort is the second largest series to have been reported. Literature addressing fascial/joints complications related to cGVHD is scarce. The search for new biomarkers, the use of advanced imaging techniques and multidisciplinary approach may help improve the prognosis of patients with cGVHD.

Keywords: Chronic graft versus host disease, Fasciitis, Sclerosis, Joint contracture, Allogeneic stem cell transplantation

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HCT) is the only curative therapy for many hematological disorders. Its use has increased markedly over the past two decades. Despite its high efficacy, allo-HCT is associated with significant morbidity and mortality, which are mainly secondary to the development of Graft Versus Host Disease (GVHD) [1, 2].

*Correspondence: chidalgoc15@gmail.com

[1] Rheumatology Department, Complejo Asistencial Universitario de Salamanca-IBSAL, Paseo de San Vicente 58-182, 37007 Salamanca, Spain
Full list of author information is available at the end of the article

In this regard, chronic GVHD (cGVHD) is the leading cause of late morbidity and non- relapse mortality after allo-HCT, and has a highly negative effect on quality of life and performance status [3, 4]. cGVHD development is associated with changes in immune cell populations and immunoregulatory mediators and can be divided into three phases: early inflammation caused by tissue injury (Phase1); thymic injury, dysregulated B-cell and T-cell immunity (Phase 2); and, as a culmination, tissue repair with fibrosis (Phase 3) [5]. Its incidence is highly variable (25–55%) [6, 7] and depends on a number of risk factors, such as previous development of acute GVHD, advanced age, unrelated donors, HLA disparity, use of female donor for male recipient, and 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 the increase in long-term survivors and the change in the allo-HCT procedure [2, 8].

cGVHD has a very wide range of clinical manifestations, consisting mainly of symptoms characteristic of auto/alloimmune disease, with evidence of chronic inflammation, and of debilitating tissue injury leading to irreversible fibrosis. The median onset is around 6 months after allo-HCT and multi-organ involvement occurs in approximately half of patients [9, 10]. One of the major challenges in managing cGVHD is to establish a correct and early diagnosis. In this setting, there are patients who are diagnosed late, and whose treatment is delayed, possibly with irreversible sequelae, and other patients classified with cGVHD in a no longer active phase, who are end up being overtreated and thereby exposed to unnecessary toxicity. The US National Institutes of Health (NIH) promoted an international consensus group on cGVHD that proposed guidelines for the clinical diagnosis, grading and response to treatment criteria in 2005 [11]. These have been revised twice, most recently in 2020 [12–14]. However, NIH diagnostic and response criteria were developed mainly for research purposes and not all transplant providers use them in daily practice.

The skin is the organ most frequently affected in cGVHD. It is involved in 75% of patients in some series, and is often the site of the initial manifestation of the disease [15]. Joint and fascia involvement has been considered to be infrequent and complex to assess, delaying diagnosis and treatment in the early stages. Musculoskeletal symptoms and signs such as arthralgias, myalgias, joint stiffness, edema, and cramps are nonspecific, very frequent, and difficult to attribute to a single cause, but only joint contractures secondary to sclerosis or fasciitis are considered sufficient diagnostic criteria for cGVHD, and these do not require biopsy [12]. Widespread sclerosis may result in joint contractures and severe limitation of function, and common sites of involvement include the hands/wrists, shoulders, elbows, and ankles [16, 17]. Fasciitis caused by inflammation of the fascia, including an eosinophilic component, may manifest as joint stiffness, erythema, edema, arthralgia, restricted range of motion (ROM), and, rarely, as synovitis. Despite the functional impairment of joint and fascia cGVHD involvement, research into this complication has been limited, and little is known about the correlation of joint and fascial cGVHD with other clinical and laboratory manifestations of cGVHD [18–22]. In addition, the therapeutic response is not always measured, and even when it is, the subjective outcome measures make the results difficult to interpret. Finally, there is a lack of complementary examinations to differentiate active disease from residual fibrosis, leading to overtreatment in some cases [23].

The aim of this study is to describe the clinical and biological characteristics, diagnostic evaluation and response to treatment, applying NIH criteria, of 39 patients with fascial involvement after allo-HCT. Our series is one of the longest reported to date and it is important to emphasize that all the patients included were closely followed up by the same team, who systematically used the recommended scales by NIH [11, 12] as part of multidisciplinary GVHD consultations, which were carried out in an allo-HCT referral clinic of a University Hospital. In addition, a narrative review of the literature on all reported cases of fasciitis in the course of cGVHD in patients undergoing allo-HCT was carried out, in order to obtain the best available evidence about the unmet needs in the clinical and diagnostic management of this complex multisystemic pathology.

Material and methods

Chronic GVHD cohort

Study design and participants

We conducted an ambispective, longitudinal, observational study to describe the clinical characteristics and diagnostic assessment of 82 patients with joint and/or fascial cGVHD noted initially and/or during follow-up. All data were prospectively collected in the database of multidisciplinary cGVHD consultations of the University Hospital of Salamanca, covering the period since its initiation in March 2014 to August 2021.

Inclusion and exclusion criteria

Patients who were at least 6 years of age were eligible for the cGVHD Cohort Study. 82 patients from 118 systematically assessment at the multidisciplinary clinic have sclerotic phenotype cGVHD with joint and/or fascial impairment. The diagnosis of sclerodermiform and fasciitis is established with clinical symptoms and signs as

Table 1 Joints and fascia score in cGVHD (adapted from Filipovich 2005, Jagasia 2015)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score Shoulder (1–7): Elbow (1–7): Wrist/finger (1–7): Ankle (1–4):	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND ADL* not affected	Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease of ROM AND mild-to-moderate limitation of ADL*	Contractures WITH significant decrease of ROM AND significant limitation of ADL* (unable to tie shoes, button shirts, dress self, etc.)

Abnormality present but explained entirely by documented non-GVHD cause (specify): **ADL* activities of daily living

required by NIH consortium without the need for histopathological confirmation.

Joint/fascial cGVHD was diagnosed if the patient had NIH joint/fascia score > or = 1 (Table 1). Patients without fascial involvement were excluded if only stiffness without any limited joint mobility in range of motion (ROM) was present at baseline or during follow up.

Follow-up and assessment scales

At enrollment and every 3 months thereafter, clinicians and patients reported standardized information on chronic GVHD organ involvement and manifestations. Patients were treated according to institutional practice in compliance with the NIH chronic GVHD consensus guidelines [24]. In a more detailed way, the clinical, biological, and treatment response of the 39 patients with EF-like manifestation was characterized.

Clinical variables analyzed in the entire cohort were the baseline and transplant-related characteristics and clinical assessment of cGVHD, including time from all-HCT to enrollment, cGVHD type, organs affected, and NIH global score. In addition, and also in the fasciitis group, complementary laboratory and imaging tests, the therapeutic approach and response were reported.

The NIH joint/ fascia scale uses a 0–3-point scale to calculate a composite score for tightness, ROM, and activities of daily living (ADL) (Table 1). The Hopkins fascia scale uses a 0–3-point scale but scores only tightness. The Photographic Range of Motion (P-ROM) scale is a series of images that captures ROM separately for shoulders, elbows, wrists/fingers, and ankles with lower scores indicating more limited ROM. The P-ROM total score is the sum of scores in all 4 joints, with a maximum possible score of 25 (Fig. 1). Patients and physicians reported their overall chronic GVHD symptoms on a 10-point scale of peak severity during the past week (PGA, PhGA) in each visit.

Diagnosis, classification, and evaluation of response to treatment were performed according to 2015 NIH criteria [11, 12, 25]. Patients with joint involvement were also evaluated according to the response criteria redefined by Inamoto 2020 (> 1 point for joint /fascia scores; > 2 points for skin/join tightening and P-ROM scores) [26].

The study protocol was approved by the Salamanca University Hospital Drug Research Ethics Committee and all patients or their guardians were informed and gave written consent in accordance with the Declaration of Helsinki.

Statistical analysis

A descriptive analysis of frequencies was summarized and nonparametric tests were used for group comparisons (χ^2 or Fisher's exact test for categorical variables; Mann–Whitney test for continuous variables). Analyses were performed using IBM SPSS Statistics for Windows v 25.0 (IBM Corp., Armonk, NY, USA).

Narrative literature review

A thorough yet concise and comprehensive review of the literature on joint and/or fascial musculoskeletal manifestations due to cGVHD in patients undergoing allo-HCT was carried out. The PubMed and Embase databases were consulted, using the electronic search strategy "Fasciitis and/or eosinophilic fasciitis and/or contracture and/or joint and graft versus host disease". Articles with clinical and diagnostic information on fascial/articular sclerotic cGVHD published up to August 2021 were selected, specifically those describing clinical cases of fascial phenotype of cGVHD. To avoid missing information, a manual search was performed to identify other relevant articles, especially those in the American National Institute of Health (NIH) consensus documents on the assessment of cGVHD. Articles that did not address fascial clinical involvement and characterization were excluded, so that papers on other types of systemic and nephrogenic fibrosis, imaging techniques, or therapeutic interventions in cGVHD were discarded. Reviewing the references cited in the most relevant publications identified additional articles of interest. The search was limited to publications concerned with research on humans and those written in the English language.

Results

Chronic graft versus host disease: cohort description

Baseline and transplant-related characteristics

The entire cohort of joint/fascial cGVHD (n = 82) was divided in two groups based on the absence (Group 1, n = 43) or presence (Group 2, n = 39) of fascial involvement. Baseline and transplant-related characteristics are summarized in Table 2. The patients' median ages were 52 (range 18–74) and 56 (range 6–78) years for the respective groups. 72% of patients in group 1 and 56% in group 2 were male. Most patients were transplanted due to AML (25.6% in group 1; 43.6% in group 2) and the majority (81% in group 1; 79% in group 2) were in complete remission prior to allo-HCT. With respect to the donor-related characteristics, our series had a very high percentage of unrelated donor transplantation (35% in group 1; 46% in group 2), mainly without mismatched HLA. The conditioning regimen was myeloablative in 37% and 46% of patients, respectively, and almost all patients received mobilized blood cells as the stem cell graft source. It is of note that 76% in group 1 and 69% in group 2 developed prior acute GVHD, highlighting the fact that more severe grades were more common among patients in whom fascial involvement was absent.

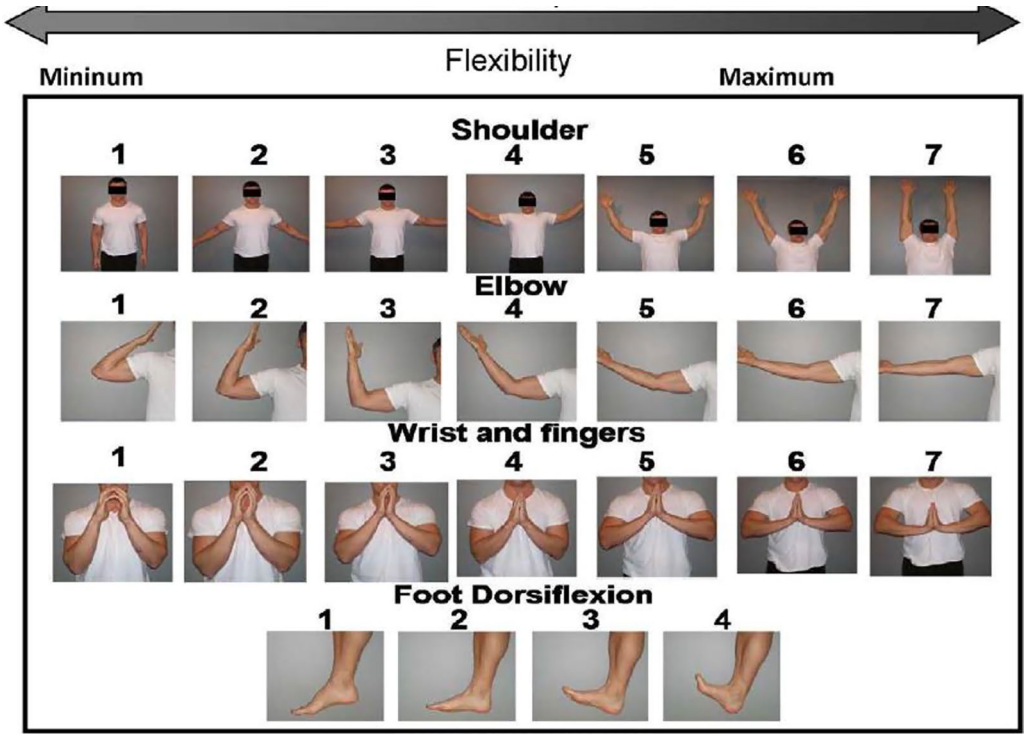

Fig. 1 Photographic range of motion: P-ROM scale. Series of images that captures ROM separately for shoulders, elbows, wrists/fingers, and ankles. Lower scores indicate more limited ROM. The P-ROM total score is the sum of scores in all 4 joints for a maximum of 25 points

Patients with previous acute GVHD have a higher risk of developing chronic GVHD. And indeed, although it does not reach the value of $p < 0.05$ but it is noted that there is a clear trend towards significance.

None of the variables considered showed statistically significant differences between the groups.

Chronic GVHD-related characteristics

Patients were referred for multidisciplinary cGVHD consultation after 20 (range 4–175) and 17 (range, 6–66) months in the non-fasciitis and fasciitis groups, respectively. Most of the patients who developed sclerotic cGVHD had a history of resolved aGVHD, but nearly 20% presented with progressive onset and concomitant acute and chronic GVHD. According to the NIH Global Severity scale, 60.5% of patients in the non- fasciitis group had moderate cGVHD, and 39.5% had severe cGVHD. The most frequently affected organs, in addition to the skin and joints/fascia, were the oral and ocular mucosa. Notably, 11 patients (13% of the total) had isolated joint involvement (joint contractures probably secondary to sclerosis) without detectable scleroderma or fascial involvement (Table 3, Fig. 2), while 16 patients (37.2%) in group 1 developed joint contractures secondary to deep scleroderma. 7% of patients developed bone complications such as avascular necrosis and vertebral fractures as a probable consequence of the treatments (mainly corticosteroids). We also found no significant differences in terms of the type of cGVHD, the type of organ affected and the overall staging of the disease by NIH, taking into account that the presence of fasciitis scores 3 (severe) on the NIH 2015 skin scale [12].

Clinical-biological characteristics and therapies administered to patients with fasciitis

The characteristics of patients with cGVHD-related EF are specified below (Table 4). It is worth noting that non-specific musculoskeletal manifestations appeared in up to 80% of patients who subsequently developed the diagnostic fascial involvement of the disease (Figs. 3, 4), with an impact on physical function in the form of joint contractures in up to 35% of them. In addition, sclerodermiform involvement was present in almost 90% of patients. Two of the patients in our series presented monoarticular arthritis during follow-up, so arthrocentesis was performed, which revealed inflammatory fluid without the presence of crystals.

There was a median of three treatment lines. All but two patients (who were considered cortico-intolerant) received steroids as first-line treatment. Twenty-eight

Table 2 Baseline and transplant-related characteristics

	GROUP 1 fasciitis absent	GROUP 2 fasciitis present	*p*
Characteristics	N (%)/median (range)	N (%)/median (range)	
Total, n	43	39	
Patient age at enrollment, years (range)	52 (18–74)	56 (6–78)	ns
Patient gender			
Male/female	31 (72.1%)/12 (27.9%)	22 (56.4%)/17 (43.6%)	0.138
Diagnosis			
AML/NHL/ALL	11 (25.6%)/8 (18.6%)/9 (20.9%)	17 (43.6%)/9 (23.1%)/4 (10.3%)	
MDS/MPS	8 (18.6%)/1 (2.3%)	5 (12.8%)/2 (5.1%)	0.341
Others (HL, MM, CML, LLC)	6 (13.9%)	2 (5.1%)	
HCT type			
Related	28 (65.1%)	21 (53.8%)	
Unrelated	15 (34.9%)	18 (46.2%)	0.326
HLA matching			
Identical	39 (90.7%)	37 (94.9%)	
1 Mismatched	3 (7.0%)	1 (2.6%)	0.651
Haploidentical	1 (2.3%)	1 (2.6%)	
Conditioning regimen			
Reduced intensity	27 (62.8%)	21 (53.8%)	0.157
Myeloablative	16 (37.2%)	18 (46.2%)	
Stem cell graft source			
Mobilized blood cells	42 (97.7%)	38 (97.4%)	
Bone marrow	0 (0%)	1 (2.8%)	0.366
Umbilical cord blood	1 (2.3%)	0 (0%)	
GVHD prophylaxis			
TACRO + RAPA ± MMF	22 (51.1%)	17 (43.5%)	
TACRO/CSA + MTX	6 (14.0%)	6 (15.4%)	
TACRO + MTX + ATG	11 (25.6%)	15 (38.4%)	0.214
TACRO + MMF + Cy	4 (9.3%)	1 (2.6%)	
Prior acute GVHD	33 (76.7%)	27 (69.2%)	
Grade 2–4	25 (58.1%)	22 (56.4%)	0.053
Grade 3–4	8 (18.6%)	5 (12.8%)	

AML acute myeloid leukemia, *NHL* non-Hodgkin lymphoma, *ALL* acute lymphoblastic leukemia, *MDS* myelodysplastic syndrome, *MPS* myeloproliferative syndrome, *HL* Hodgkin lymphoma, *MM* multiple myeloma, *CML* chronic myeloid leukemia, *LLC* chronic lymphocytic leukemia

cortico- refractory or cortico-dependent patients required additional treatment as salvage therapy: 25 (64%) patients received extracorporeal photopheresis (ECP), eight (20%) received ruxolitinib and 10 (25%) received imatinib. Improvement in the P-ROM and Hopkins scales were achieved in 13, six, and six patients after ECP, ruxolitinib and imatinib, respectively. Almost all patients (n = 36, 92%) achieved some degree of response; 41% of them achieved a complete response rate (resolution of signs and symptoms) (Table 4).

Chronic graft versus host disease-related eosinophilic fasciitis (cGVHD-EF): literature review

The literature search strategy identified 128 potentially eligible articles. Title screening identified twelve duplicate articles, which were discarded, and 104 articles that focused on sclerotic clinical manifestations. A review of the titles and abstracts led to 78 articles being eliminated because they were not relevant to the current study. Reading the full text led us to include only 17 articles reporting EF as the main manifestation of cGVHD (Fig. 5). This included 10 individual case reports [21, 27–35], five retrospective case series [19, 20, 36–38] and one extension of a single prospective observational study [26].

EF-like cGVHD was first reported in 1987 by van den Bergh et al. [34] and later in 1990by Markusse et al. [34]. The four largest case series published to date report a variable incidence of 0.5% to 41% [19, 20, 37, 38],. Similar to classic EF, its clinical features include pain, edema, and stiffness of the extremities, with

Table 3 Clinical assessment of chronic GVHD

	GROUP 1 fasciitis absent	GROUP 2 fasciitis present	*p*
Variables	N (%)/media (DS)	N (%)/media (DS)	
Total, n	43	39	
Time in months from allo-HCT to enrollment (range)	20 (4–175)	17 (6–66)	0.480
cGVHD type			
Progressive/quiescent/de novo	8 (18.6%)/22 (51.2%) /13 (30.2%)	7 (18.0%)/20 (51.2%) /12 (30.8%)	Ns
Involvement site			
ECOG: 1/2/3	14 (32.6%)/6 (14.0%)/2 (4.7%)	16 (41.0%)/6 (15.4%)/0	0.500
Mouth	15 (34.8%)	18 (46.2%)	0.415
Eye	21 (48.8%)	18 (46.2%)	0.466
Genital tract	3 (6.9%)	4 (10.3%)	0.405
Gastrointestinal	3 (6.9%)	2 (5.2%)	0.382
Liver	10 (23.2%)	7 (18.0%)	0.384
Lung	3 (6.9%)	5 (12.8%)	0.640
Skin	32 (74.4%)	35 (89.7%)	0.000
NIH global score			
Moderate/severe	26 (60.5%)/17 (39.5%)	0/39 (100%)	0.000
Bone complications			
Avascular osteonecrosis/bone fracture	3 (6.9%)	3 (7.8%)	ns

Fig. 2 Isolated joint contracture due to sclerosis: P-ROM score of 1 in wrist joints (Buddha prayer posture). Joint stiffness improves with the fingers flexed, probably reflecting the fibrotic involvement of the flexor tendons of the fingers

tightness of the overlying skin and associated arthralgia/arthritis [39]. The disease often results in woody induration of the overlying skin, which initially manifests as the "groove sign" (Fig. 3). The groove sign is due to indentations that develop along the course of superficial veins and later evolve into small depressed areas, resulting in rippling with the typical "peau d'orange" or "pseudo-cellulite appearance" due to subcutaneous fascial and septal fibrosis (Fig. 4) and, in the most severe cases, a tendency towards joint contractures (e.g., the inability to adopt the Buddha's prayer posture). Fasciitis lesions are usually located in the proximal areas of the extremities and abdomen, but sparing the hands and feet. The staging scales for the assessment of fascial-articular involvement, validated in patients with cGVHD, proposed by the NIH task force are: the Joint and Fascia Score (JFS ROM), with values ranging from 0 to 3, and the Photographic Range of Motion (P-ROM) (Fig. 1). However, in most of the literature articles the diagnosis was based on the indistinguishable histopathology findings similar to classic EF in deep skin biopsy [34–38], and on alterations in the fascia revealed by magnetic resonance imaging [30, 36]. The natural history of fasciitis in cGVHD is often progressive, leading to joint contractures [21] and chronic ulcers, making prompt diagnosis and therapy crucial.

The information obtained from the articles reviewed is summarized in Table 5.

Discussion

In the current study, we have reported the second largest series of patients with fascial/articular related cGVHD and performed a narrative review focused on cGVHD related fasciitis. Although literature addressing this complication is scarce, one out of 3 patients evaluated in our multidisciplinary cGVHD consultation developed fasciitis, 13% had isolated joint contractures and 7% severe bone complications. As a result of these events, 35% of patients showed negative impact on physical function.

Studies and reviews specifically of cGVHD-related fasciitis are limited. Most of them are descriptions of isolated cases [21, 27–35] or case series with small sample sizes [19, 20, 36–38], or uncontrolled series [19, 26]. For this reason, the cohort of our hospital is the second largest series to be reported in the literature after that of the Seattle group [26], whose publication extended the data

Table 4 Clinical-biological characteristics and therapies administered in patients with fasciitis (n = 39)

Variables	N (%)
Nonspecific prodromal symptoms	
Absent	8 (20.5%)
Stiffness	33 (84.6%)
Arthromyalgias	24 (61.3%)
Edemas	11 (28.2%)
Cramps	9 (23.0%)
Skin tightness	29 (74.4%)
Joint contracture	14 (35.8%)
Affected range of motion (ROM)	
Mild/moderate/severe	23 (59.0%)/10 (25.6%)/1 (2.6%)
Limitation of upper limb mobility	
P-ROM shoulders	23 (58.9%)
P-ROM elbows	13 (33.4%)
P-ROM wrists/fingers	19 (50.0%)
Limitation of mobility of lower limbs	
P-ROM ankles	14 (35.9%)
Concomitant skin sclerosis	35 (89.7%)
Superficial scleroderma	2 (5.1%)
Deep scleroderma	33 (84.6%)
Mixed (scleroderma/lichenoid)	13 (33.3%)
Combined scleroderma	18 (46.2%)
Biopsy information	22 (56.4%)
Lichenoid	7 (18%)
Deep Sclerodermiform	10 (25.6%)
Mixed (scleroderm/lichenoid)	4 (10.2%)
Fasciitis	1 (2.5%)
Thrombopenia at diagnosis (< 100,000/µL)	1 (2.6%)
Eosinophilia at diagnosis (> 500/mm^3)	21 (53.8%)
Positive autoantibodies	10 (25.7%)
Synovial fluid study (inflammatory)	2 (5.1%)
Imaging tests performed:	
Rx/MRI/Echo	2 (5.1%)/2 (5.1%)/3 (7.7%)
Median number of treatment lines (range)	3 (1–7)
First-line treatment	
Corticosteroids	37 (94.9%)
Rescue treatment	
Extracorporeal photopheresis	25 (64.1%)
Ruxolitinib	8 (20.5%)
Imatinib	10 (25.6%)
Others	11 (28.2%)
Physiotherapy program	15 (38.5%)
Best response achieved	
Complete response	16 (41.0%)
Partial response	20 (51.3%)
Refractoriness	2 (5.1%)
PGA* < 4	22 (56.4%)
PhGA$^{\$}$ < 4	22 (56.4%)
Exitus	7 (17.9%)
Relapse	2
cGVHD progression	1
Infection	2
Other	2

**PGA* patient global assessment

$^{\$}$ *PhGA* physician global assessment

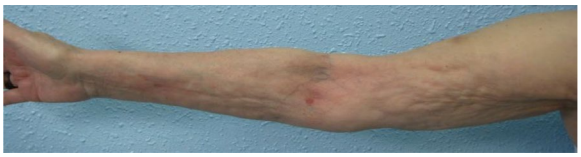

Fig. 3 Rippling and groove sign on the innerarm of EF-like associated to skin sclerosis

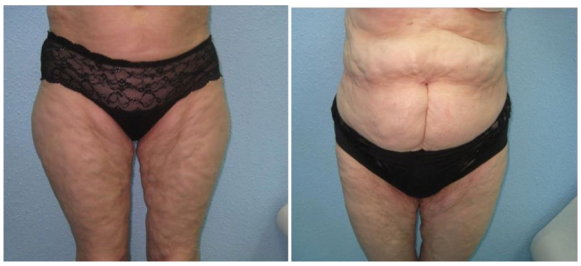

Fig. 4 Chronic GVHD-related EF: skin rippling on the anterior aspect of the thighs and on the abdomen. Skin is not involvement

they published in 2014 [19]. Similar to our series, Inamoto et al. also compared two groups based on the presence or absence of joint/fascia manifestations at the time of enrollment and mainly highlights the need to systematically, objectively, reliably, and simply assess fascia and joint involvement in a clinically meaningful way. However, in contrast to our study, the Inamoto study did not specify how many patients in the cohort presented with EF-like disease.

More than 80% of the patients with fasciitis in our series had some nonspecific symptom before they developed fascial sclerosis. None of these manifestations is considered a diagnostic criterion for GVHD [11, 12] In this regard, our hospital's series, reported here, reflects a much higher incidence of nonspecific musculoskeletal symptoms. This is probably due to recruitment bias, since these are patients with established cGVHD, most of whom were refractory to first-line treatment, followed in a multidisciplinary consultation that also considered dermatology and rheumatology. On the other hand,

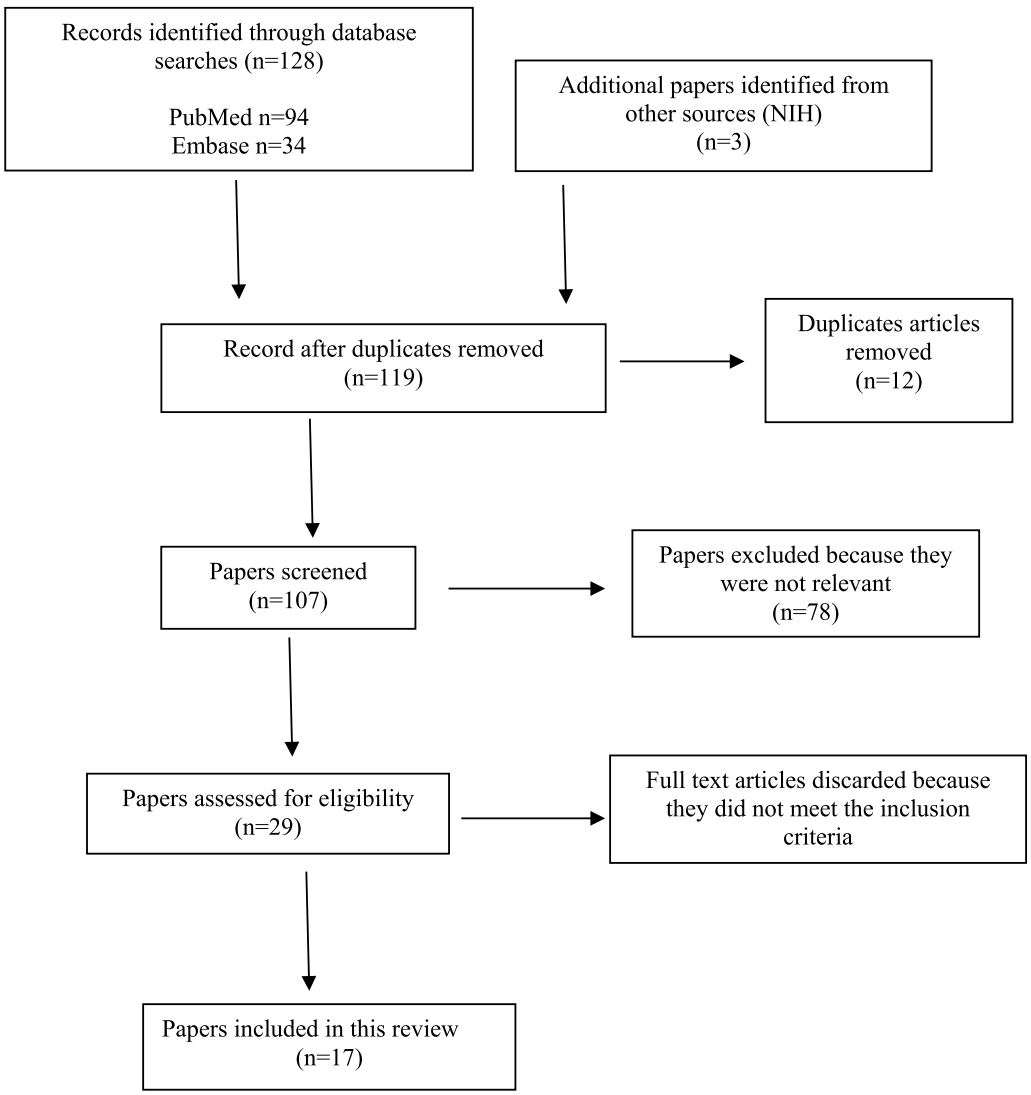

Fig. 5 Flow-chart of selection articles

inflammatory joint involvement is a very rare, and only exceptionally described entity [40]. Accordingly, only two patients in our series developed arthritis. Sclerotic cGVHD at onset of disease occurs infrequently but long-standing cGVHD is likely to advance to sclerotic so it is necessary that allo-transplanted patients who start with non- specific musculoskeletal symptoms must be evaluated by rheumatologist in order to make an early diagnosis and treatment to prevent irreversible damage and bone complications induced by high dose steroid treatment. Although infrequent at the cGVHD onset, sclerotic manifestation including fasciitis may be developed during the follow-up. Hematologist, rheumatologist and dermatologist should become aware of this post-transplant condition, in order to stablish an early approach to identify and treat this aspect of cGVHD. Allo-HPT transplanted patients with nonspecific and persistent musculoskeletal symptoms such as arthralgias, joint-stiffness, and tendon-rubbing or decrease of joint mobility should be thoroughly evaluated to rule out incipient fibrous disease. Early recognition of chronic GVHD may offer an opportunity to prevent evolution to more severe disease with irreversible damage.

In our cohort, 47% of patients developed fascia involvement during follow-up. The NIH consensus criteria joint/fascia score does not distinguish the contributions to cGVHD severity made by isolated joint involvement compared with joint restriction associated with skin sclerosis [11–13]. Although joint/fascia involvement is common in cGVHD, the incidence of

Table 5 Reported cases of EF-like chronic GVHD

References	Participants	Interventions scales/scores assessed	Outcomes and conclusions
Chalopin et al. [27] Case report	46-year-old male + 227 days post-allo-HCT	Clinical features	Importance of MRI to guide biopsy
Inamoto et al [26] Multicenter, longitudinal, prospective observational study Case series (extension of 2014 report) [22]	Group 1 (n = 209): fascial/articular sclerotic cGVHD > 18 years according to NIH 2005 evaluation criteria (2007–2012) Group 2 (n = 191): Fascial/articular sclerotic cGVHD > 18 years according to NIH 2014 evaluation criteria (2013–2017)	Evaluation every 6 months except initially at 3 months in incident cases: NIH joint/fascial (ROM) score (range 0–3) P-ROM (range 4–25) PRO Lee Symptom score Quality of life Physical function	Redefine therapeutic response criteria
Orzechowska et al. [21] Case report	17-year-old male with overlap GVHD	Clinical features	Multiple joint contractures Disability
Vukić et al. [20] Retrospective observational study October 2013–October 2015	n = 17 cGVHD without fascial/articular involvement n = 12 with fascial/articular cGVHD	Comparison of clinical and functional features, laboratory parameters and scales (ROM; P-ROM, gait test and grip strength)	41% fascial/articular sclerosis High correlation with skin involvement Elevated C3 levels
Ganta et al. [28] Case report and literature review of reported case	n = 13 3 small case series (2, 8 and 14) and 7 isolated case reports	Clinical features Treatment	Update of therapeutic approach
Chu et al. [29] Case report	51-year-old male, 3 years post-allo-HCT	Differential features with scleroderma-miform cGVHD	Need for deep biopsy
Inamoto et al. [19] Retrospective observational study	n = 977 cGVHD Recruited May 2000-December 2009	Development of skin, fascial or joint sclerosis	20% sclerosis (70 (33%) only joint/fascial) Factors associated with sclerosis
Oda et al. [36] Retrospective observational study Case series January 1994–March 2005	n = 8	Incidence Risk factors Clinical features	Early diagnosis and treatment to avoid disability Biopsy and MRI
Patel et al. [30] Case report	41-year-old male + 671 days post-allo-HCT	Development of deep cutaneous sclerosis and fasciitis with joint contractures Treatment: photopheresis	Early diagnosis MRI
Schaffer et al. [37] Case series	n = 2	Clinical and histological features	No cutaneous sclerosis
Sbano et al. [31] Case report	54-year-old woman + 15 months post-allo-HCT	ANA + nucleolar ultrasonography	Photopheresis treatment
Ustun et al. [32] Case report	35-year-old male + 1 year post-allo-HCT	Myositis and fasciitis	Importance of the biopsy
Kim et al. [33] Case report	33-year-old woman + 20 months post-allo-HCT	Skin stiffness and arthralgias Subsequent proximal fasciitis of upper and lower limbs	Distinctive entity
Janin et al. [38] Retrospective observational study Case series 01/1974–01/1991	Total n = 475 n = 14 with fasciitis	Clinical features Biopsy	Onset with edema Similarity to eosinophilic myalgia syndrome
Markusse 1990 [35] Case report	49-year-old woman + 8 months post-allo-HCT	Isolated fasciitis without cutaneous involvement Biopsy	Supra-adjacent skin without affectation
Van den Bergh et al. [34] Case report	30-year-old woman + 365 days post-allo-HCT	Clinical, laboratory and histological features	First case of fasciitis with cGVHD entity

isolated joint involvement contracture in the absence of detectable superficial or subcutaneous skin sclerosis is low [41]. It is likely to go unnoticed and be underdiagnosed unless thorough clinical examination of the range of joint mobility is performed as a matter of course (Fig. 1). This entity is considered by some authors, even in the NIH scales, to be the deep

cutaneous fibrotic variant. However, there is controversy about its inclusion as part of the skin staging [38, 42].

Additional studies are needed to determine whether joint involvement in the absence of sclerotic skin changes represents involvement of the deep tissues below the limit of clinical detection or if it is a separate clinical process. Several studies have shown a strong correlation between joint and skin symptoms during the course of GVHD [12, 19, 38] According to Vukiç et al [20], joint changes appeared in 83.3% of subjects with superficial/erythematous cutaneous sclerosis and deep sclerosis. These data are consistent with those obtained in our series, in which 89.7% of patients with fascial involvement also had concomitant sclerotic skin involvement.

There is a gap in knowledge and unmet needs regarding sclerotic GVHD, including the need of improving the sclerotic patient's assessment as reflects NIH 2020 reports [13, 14]. We lack of prognostic biomarkers, we need new approaches for early identification and treatment of fibrotic changes and new tools to objective assess skin sclerosis in cGVHD. Time of intervention (early versus late) is very important to avoid progression and improvement in physical functioning and quality of life.

Janin et al. [38] published a retrospective study in 1994 of a series of 14 patients diagnosed with cGVHD who developed fasciitis during their follow-up. They presented with sudden painful swelling of the skin on their extremities and some on their flanks. Seven of these 14 patients (50%) had a history of strenuous or unusual physical exertion, as in the case described by Ustun et al [32]. In our series, we documented in only one patient the presence of exertion as a trigger for fascial involvement in the abdomen and proximal region of the upper limbs.

Patients with sclerotic cGVHD experience negative effects on their physical function, due to decreased joint mobility, and a reduced quality of life [3]. In our series, more than 15% of the patients studied had an ECOG score greater than 1, and up to 70% of those with fasciitis had some limitation on their joint mobility.

Unfortunately, the clinical, genetic, and biological factors that are specifically linked to musculoskeletal and joint involvement in patients with GVHD are unknown [18, 19, 42]. The search for serum biomarkers in this fibrosing entity, such as specific autoantibodies (anti-sclerosis) has so far proved unsuccessful [43]. In our series of patients with fasciitis, positive antinuclear antibodies were detected in 25% of patients, with the nucleolar pattern being the most frequent.

Chu et al [29] concluded in their work that patients with clinical manifestations suggestive of EF-like cGVHD should undergo a full-thickness biopsy consisting of skin, muscle and fascia and, in some cases, an additional MRI study to detect the pattern of involvement and monitor the response to treatment. Fasciitis in the NIH consensus is included as a diagnostic entity of cGVHD, and biopsy confirmation is not necessary [11, 12], which is why neither biopsy nor advanced imaging tests were routinely requested for patients in our cohort. Few studies have analyzed the usefulness of advanced imaging techniques, such as magnetic resonance imaging or high-resolution soft-tissue ultrasound [44, 45], in patients with cGVHD with nonspecific prodromal musculoskeletal symptoms such as arthralgias, joint-stiffness, and tendon-rubbing. In our patients, imaging tests were occasionally performed, because they had an established diagnosis of cGVHD and the information that such tests could provide was considered unlikely to change any aspect of their therapeutic management. Nevertheless, it would undoubtedly be worthwhile designing a study that included imaging tests in the initial stages of the disease, to try to detect the inflammatory phases in the initial stages, and to analyze whether early treatment improves the functional prognosis of this fibrosing entity, such as the development of sclerosis joint contracture.

The assessment of active joint mobility as an objective measure to evaluate response to treatment has the limitations of requiring time and a properly trained professional who can carry out standardized, reproducible measurements. In this setting, the P-ROM scale offers an alternative for clinical use, since any clinician can complete the assessment adequately in 1–2 min. However, this scale does not detect patient-related outcomes (PROs) as well, probably because it does not take stiffness or limitations in performing activities of daily living into account, as does the NIH joint/fascial scale. Incorporating a measure of musculoskeletal symptoms similar to Lee's subscale (0–10) into the P- ROM scale would capture changes in PROs and would carry weight in the overall GVHD assessment score [9]. In addition, some studies have recommended that the dominant hand grip strength be measured with a dynamometer or sphygmomanometer and a 2-min gait test carried out [46]. These measurement indices have not been subsequently replicated and the NIH consensus group does not recommend their use in clinical practice, although they are required in some clinical trials.

This disease entity remains a therapeutic challenge due to the lack of knowledge about its pathogenesis and the need to use rescue therapy due to corticorefractoriness and the frequent adverse effects, such as bone complication morbidities (7% in our series), related to steroid treatment. Since the patients treated in our multidisciplinary cGVHD clinic are mainly corticosteroid-refractory or corticosteroid-intolerant,

most of them required several lines of treatment. Although no clear conclusion can be drawn about specific agent response due to the limitations of our study, it is important to emphasize that the majority of them experienced improvement, and 41% of them achieved complete resolution of their signs and symptoms. The usefulness of non- pharmacological measures such as physiotherapy and other physical therapies to prevent disease progression is also extensively reported [16, 47].

Conclusion

GVHD-related fasciitis and joint involvement are frequent manifestations after allo-transplants but are usually detected at late stages and when already impairing function Fascial and joint sclerotic involvement needs to be recognized and evaluated early with validated scales. We need to extend our knowledge about the pathogenesis of this fibrosing entity so that we can improve early diagnosis and treatment of patients with cGVHD. The search for new biomarkers associated with fibrosis, the use of advanced imaging techniques and a multidisciplinary approach may help improve their prognosis.

Acknowledgements
Lucía Pantoja Zarza and María Dolores Sánchez González for narrative review Phil Mason for English editing.

Author contributions
CHC, DMH, CFC, LLP performed the systematic evaluation of the disease and were responsible for its treatment and assessment of the response. CHC and DMH performed the narrative review. LVL, ELP, MCC,AAML and MDCB analyzed and interpreted the patient data regarding the hematological disease and the transplant. CHCDMH and LLC were the major contributor in writing the manuscript. All authors read and approved the final manuscript.

Funding
This work was partially supported by the Education Council and Health Council of the Junta de Castilla y León (GRS 2183/A/20), Spain.

Availability of data and materials
The datasets generated and/or analysed during the current study are available at University Hospital of Salamanca (Spain) and from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Salamanca University Hospital Drug Research Ethics Committee (code: 2020 10 586).

Consent for publication
All patients or their guardians were informed and gave written consent in accordance with the Declaration of Helsinki.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Rheumatology Department, Complejo Asistencial Universitario de Salamanca-IBSAL, Paseo de San Vicente 58-182, 37007 Salamanca, Spain. [2]Family and Community Medicine Training Programme, Hospital Universitario Río Hortega, Valladolid, Spain. [3]Dermatology Department, Complejo Asistencial Universitario de Salamanca-IBSAL, Salamanca, Spain. [4]Haematology Department, University Hospital of Salamanca (HUS/IBSAL), CIBERONC and Cancer Research Institute of Salamanca-IBMCC (USAL-CSIC), 37007 Salamanca, Spain.

Received: 28 January 2022 Accepted: 29 July 2022
Published online: 23 August 2022

References

1. Kurosawa S, Oshima K, Yamaguchi T, et al. Quality of life after allogeneic hematopoietic cell transplantation according to affected organ and severity of chronic graft-versus-host disease. Biol Blood Marrow Transpl. 2017;23(10):1749–58. https://doi.org/10.1016/j.bbmt.2017.06.011.
2. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. Lancet. 2009;373(9674):1550–61. https://doi.org/10.1016/S0140-6736(09)60237-3.
3. Hamilton BK, Storer BE, Wood WA, et al. Disability related to chronic graft-versus-host disease. Biol Blood Marrow Transpl. 2019;S1083–S8791(19):30676–7. https://doi.org/10.1016/j.bbmt.2019.10.019.
4. Andrews C, Smith S, Kennel M, Schilling S, Kalpakjian C. The association of performance status and disease severity in patients with chronic graft-vs-host disease. Arch Phys Med Rehabil. 2019;100(4):606–12. https://doi.org/10.1016/j.apmr.2018.04.034.
5. Zeiser R, Blazar BR. Pathophysiology of chronic graft-versus-host disease and therapeutic targets. N Engl J Med. 2017;377(26):2565–79. https://doi.org/10.1056/nejmra1703472.
6. Lee SJ, Vogelsang G, Flowers MED. Chronic graft-versus-host disease. Biol Blood Marrow Transpl. 2003;9(4):215–33. https://doi.org/10.1053/bbmt.2003.50026.
7. Arai S, Arora M, Wang T, et al. Increasing Incidence of chronic graft-versus-host disease inallogeneic transplantation: a report from the center for international blood and marrow transplant research. Biol Blood Marrow Transpl. 2015;21(2):266–74. https://doi.org/10.1016/j.bbmt.2014.10.021.
8. Grube M, Holler E, Weber D, Holler B, Herr W, Wolff D. Risk factors and outcome of chronic graft-versus-host disease after allogeneic stem cell transplantation—results from a single-center observational study. Biol Blood Marrow Transpl. 2016;22(10):1781–91. https://doi.org/10.1016/j.bbmt.2016.06.020.
9. Lee SJ. Classification systems for chronic graft-versus-host disease. Blood. 2017;129(1):30–7. https://doi.org/10.1182/blood-2016-07-686642.
10. Carpenter PA. How I conduct a comprehensive chronic graft-versus-host disease assessment. Blood. 2011;118(10):2679–87. https://doi.org/10.1182/blood-2011-04-314815.
11. Filipovich AH, Weisdorf D, Pavletic S, et al. 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 Transpl. 2005;11(12):945–56. https://doi.org/10.1016/j.bbmt.2005.09.004.
12. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in chronic graft-versus-host disease: I. The 2014 diagnosis and staging working group report. Biol Blood Marrow Transpl. 2015;21(3):389–401. https://doi.org/10.1016/j.bbmt.2014.12.001.
13. Wolff D, Radojcic V, Lafyatis R, et al. 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. Transpl Cell Ther. 2021;27(10):817–35. https://doi.org/10.1016/j.jtct.2021.06.001.
14. Williams KM, Inamoto Y, Im A, et al. National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2020 etiology and prevention working group report. Transplant Cell Ther. 2021;27(6):452–66. https://doi.org/10.1016/j.jtct.2021.02.035.
15. Gandelman JS, Zic J, Dewan AK, et al. The anatomic distribution of skin involvement in patients with incident chronic graft versus host disease. Biol Blood Marrow Transpl. 2018. https://doi.org/10.1016/j.bbmt.2018.09.007.
16. Choi I-S, Jang I-S, Han J-Y, Kim J-H, Lee S-G. Therapeutic experience on multiple contractures in sclerodermoid chronic graft versus host

disease. Support Care Cancer. 2009;17(7):851–5. https://doi.org/10.1007/s00520-009-0602-x.
17. Jung M, Sung IY, Ko EJ. Rehabilitation in children with sclerodermoid chronic graft-versus-host disease: case series. Ann Rehabil Med. 2019;43(3):347–51. https://doi.org/10.5535/arm.2019.43.3.347.
18. Inamoto Y, Martin PJ, Flowers MED, et al. Genetic risk factors for sclerotic graft-versus-host disease. Blood. 2016;128(11):1516–24. https://doi.org/10.1182/blood-2016-05-715342.
19. Inamoto Y, Storer BE, Petersdorf EW, et al. Incidence, risk factors, and outcomes of sclerosis in patients with chronic graft-versus-host disease. Blood. 2013;121(25):5098–103. https://doi.org/10.1182/blood-2012-10-464198.
20. Vukić T, Smith SR, Kelečić DL, et al. Joint and fascial chronic graftvs- host disease: correlations with clinical and laboratory parameters. Croat Med J. 2016;57(3):266–75. https://doi.org/10.3325/cmj.2016.57.266.
21. Orzechowska Z, Strojny M, Komisarek O, Krasuska-Sławińska E, Pawłowska J. Joint and fascia manifestations in the course of graft-versus-host disease (GVHD) as a diagnostic trail for doctors of various specialties—case report. Issue Rehabil Orthop Neurophysiol Sport Promot. 2018;22:55–62. https://doi.org/10.19271/IRONS-00054-2018-23.
22. Inamoto Y, Pidala J, Chai X, et al. Assessment of joint and fascia manifestations in chronic graft-versus-host disease. Arthritis Rheumatol (Hoboken, NJ). 2014;66(4):1044–52. https://doi.org/10.1002/art.38293.
23. Inamoto Y, Jagasia M, Wood WA, et al. Investigator feedback about the 2005 NIH diagnostic and scoring criteria for chronic GVHD. Bone Marrow Transpl. 2014;49(4):532–8. https://doi.org/10.1038/bmt.2013.225.
24. Sarantopoulos S, Cardones AR, Sullivan KM. How I treat refractory chronic graft-versus-host disease. Blood. 2019. https://doi.org/10.1182/blood-2018-04-785899.
25. Lee SJ, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in chronic graft-versus-host disease: IV. The 2014 response criteria working group report. Biol Blood Marrow Transpl. 2015;21(6):984–99. https://doi.org/10.1016/j.bbmt.2015.02.025.
26. Inamoto Y, Lee SJ, Onstad LE, et al. Refined National Institutes of Health response algorithm for chronic graft-versus-host disease in joints and fascia. Blood Adv. 2020;4(1):40–6. https://doi.org/10.1182/bloodadvances.2019000918.
27. Chalopin T, Vallet N, Morel M, et al. Eosinophilic fasciitis (Shulman syndrome), a rare entity and diagnostic challenge, as a manifestation of severe chronic graft-versus-host disease: a case report. J Med Case Rep. 2021;15(1):1–5. https://doi.org/10.1186/s13256-021-02735-3.
28. Ganta CC, Chatterjee S, Pohlman B, Hojjati M. Chronic graft-versus-host disease presenting as eosinophilic fasciitis: therapeutic challenges and an additional case. J Clin Rheumatol. 2015;21(2):86–94. https://doi.org/10.1097/RHU.0000000000000212.
29. Chu G-Y, Lin H-L, Chen G-S, Wu C-Y. Eosinophilic fasciitis following allogeneic bone marrow transplantation in a patient with acute myeloid leukaemia. Acta Derm Venereol. 2014;94(2):221–2. https://doi.org/10.2340/00015555-1669.
30. Patel AR, Avila D, Malech HL, Pavletic SZ, Yao L, Cowen EW. Rippled skin, fasciitis, and joint contractures. J Am Acad Dermatol. 2008;59(6):1070–4. https://doi.org/10.1016/j.jaad.2008.08.023.
31. Sbano P, Rubegni P, De Aloe GB, Guidi S, Fimiani M. Extracorporeal photochemotherapy for treatment of fasciitis in chronic graft-versus-host disease [2]. Bone Marrow Transpl. 2004;33(8):869–70. https://doi.org/10.1038/sj.bmt.1704436.
32. Ustun C, Ho G. Eosinophilic fasciitis after allogeneic stem cell transplantation: a case report and review of the literature. Leuk Lymphoma. 2004;45(8):1707–9. https://doi.org/10.1080/10428190410001683787.
33. Kim KW, Yoon CH, Kay CS, Kim HJ, Lee EH, Park SY. Fasciitis after allogeneic peripheral blood stem cell transplantation in a patient with chronic myelogenous leukemia. J Clin Rheumatol. 2003;9(1):33–6. https://doi.org/10.1097/01.RHU.0000037772.99917.86.
34. Van Den Bergh V, Tricot G, Fonteyn G, Dom R, Bulcke J. Diffuse fasciitis after bone marrow transplantation. Am J Med. 1987;83(1):139–43. https://doi.org/10.1016/0002-9343(87)90509-2.
35. Markusse HM, Dijkmans BA, Fibbe WE. Eosinophilic dasciitis after allogeneic bone marrow transplantation. J Rheumatol. 1990;17(5):692–4.
36. Oda K, Nakaseko C, Ozawa S, et al. Fasciitis and myositis: an analysis of muscle-related complications caused by chronic GVHD after allo-SCT. Bone Marrow Transpl. 2009;43(2):159–67. https://doi.org/10.1038/bmt.2008.297.
37. Schaffer JV, McNiff JM, Seropian S, Cooper DL, Bolognia JL. Lichen sclerosus and eosinophilic fasciitis as manifestations of chronic graft-versus-host disease: expanding the sclerodermoid spectrum. J Am Acad Dermatol. 2005;53(4):591–601. https://doi.org/10.1016/j.jaad.2005.06.015.
38. Janin A, Socie G, Devergie A, et al. Fasciitis in chronic graft-versus-host disease: a clinicopathologic study of 14 cases. Ann Intern Med. 1994;120(12):993–8. https://doi.org/10.7326/0003-4819-120-12-199406150-00004.
39. Shulman LE. Diffuse fasciitis with eosinophilia: a new syndrome? Trans Assoc Am Phys. 1975;88:70–86.
40. García-López A, Fernández-Delgado C, Hernández-Sánchez R, Uceda J, Parody R. Manifestaciones osteomusculares en pacientes sometidos a trasplante alogénico de progenitores hematopoyéticos. Reumatol Clin. 2005;1(2):112–5. https://doi.org/10.1016/S1699-258X(05)72723-6.
41. Kuzmina Z, Joe GO, Baird K, et al. Prevalence of isolated joint involvement in chronic graft-versus-host disease Comment on the article by Inamoto et al. Arthritis Rheumatol. 2014;66(9):2646–8. https://doi.org/10.1002/art.38697.
42. Martires KJ, Baird K, Steinberg SM, et al. Sclerotic-type chronic GVHD of the skin: clinical risk factors, laboratory markers, and burden of disease. Blood. 2011;118(15):4250–7. https://doi.org/10.1182/blood-2011-04-350249.
43. Yu J, Storer BE, Kushekhar K, et al. Biomarker panel for chronic graft-versus-host disease. J Clin Oncol. 2016;34(22):2583–90. https://doi.org/10.1200/JCO.2015.65.9615.
44. Polańska A, Dańczak-Pazdrowska A, Silny W, Sadowska A, Jenerowicz D, Osmola-Mańkowska A, Olek-Hrab K. High-frequency ultrasonography in monitoring the effects of treatment of selected dermatoses. Postep Dermatologii i Alergol. 2011;28(4):255–60.
45. Clark J, Yao L, Pavletic SZ, et al. Magnetic resonance imaging in sclerotic-type chronic graft-vs-host disease. Arch Dermatol. 2009;145(8):918–22. https://doi.org/10.1001/archdermatol.2009.78.
46. Pidala J, Chai X, Martin P, et al. Hand grip strength and 2-minute walk test in chronic graft-versus-host disease assessment: analysis from the chronic GVHD consortium. Biol Blood Marrow Transpl. 2013;19(6):967–72. https://doi.org/10.1016/j.bbmt.2013.03.014.
47. Smith SR, Asher A. Rehabilitation in chronic graft-versus-host disease. Phys Med Rehabil Clin N Am. 2017;28(1):143–51. https://doi.org/10.1016/j.pmr.2016.08.009.

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