Skin Signs of Graft Versus Host Disease

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Abstract

Graft-versus-host disease is a common complication of allogenic hematopoietic cell transplantation and less frequently of solid organ transplantation. The skin is one of the initial and main organs affected, and as such, recognizing the dermatologic manifestations allows early diagnosis and treatment. In this article we aim to describe the cutaneous manifestations of graft-versus-host disease so that non-dermatologist is able to recognize the early signs of this complication.

Keywords: Graft-versus-host disease; Acute graft-versus-host disease; Chronic graft-versus-host disease; Scleromatous graft-versus-host disease; Lichen planus-like graft-versus-host disease

Introduction

Graft-Versus-Host Disease (GVHD) is a common complication associated with high mortality that results from the immunologic insult of introducing immunologically competent cells into an immunoincompetent host, which allows these grafted cells to mount a destructive immune response against the recipient tissues [1-9].

The main cause of GVHD is allogenic Hematopoietic Cell Transplantation (HCT) [10,11] although it can also be seen secondary to solid organ transplantation [11-14].

The skin is one of the initial and main organs affected by GVHD in up to 94.2% of patients [1,7,8,10,11,15], and as such, recognizing these dermatologic manifestations represents an important tool for early diagnosis allowing prompt installation of treatment, although an early start to therapy is not always determinant of outcome [16].

Historically, GVHD has been divided into acute GVHD (aGVHD) and chronic GVHD (cGVHD) [3,10]. Acute GVHD describes a distinctive syndrome of dermatitis, bilirubin elevation, and diarrhea developing within 100 days of transplantation [1,3,10] Chronic GVHD describes a more diverse syndrome developing after day 100 [2-4,10]. However, this definition falls short, and in 2005 the National Institutes of Health classification included late-onset acute GVHD (after day 100) and an overlap syndrome with features of both acute and chronic GVHD [17].

In this article we aim to describe the cutaneous manifestations of GVHD so that non-dermatologist are able to recognize the early signs of this complication.

Risk Factors

Because GVHD results from the recognition of host tissues as foreign by immunocompetent donor cells, the risk of GVHD increases with greater HLA disparity between the donor and recipient [1,18,19]. However, it is important to mention that despite HLA matching between donor and receiver, 40% of patients still develop GVHD due to the genetic differences of minor histocompatibility antigens [1].

Another recognized risk factor is the recipient’s age because the risk of GVHD seems to rise with increasing age [1,16].

Human herpesvirus type 6 reactivation is significantly associated with the occurrence of GVHD, as is coinfection with Epstein-Barr virus [20].

Acute Graft Versus Host Disease

The incidence of acute GVHD varies between 20% and 70%, based on histocompatibility differences between the donor and recipient, the age of the recipient, the type of immunosuppression regimen, and the stage of primary disease [3,10].

Acute GVHD usually starts as pruritic and sometimes painful erythematous-purpuric maculopapular exanthema [16] on the palms, soles, cheeks, neck, ears and upper trunk, preferentially around the hair follicles [10,16]. The scalp is usually spared [1]. As the severity of the GVHD increases, the exantema progresses and can affect the total body surface area [10]. Erythroderma, vesicles, bullae and a positive Nikolsky’s sign define the most severe form of acute GVHD [1,10,21].

Based on the cutaneous involvement in aGVHD a staging system has been proposed to determine the severity of the disease, where Grade 0 represents the absence of rash related to GVHD, Grade 1 represents a maculopapular rash affecting less than 25% of total body surface area, Grade 2 represents a maculopapular rash that affects 25-50% of total body surface area, Grade 3 represents a macular, papular or vesicular eruption affecting between 50% to 100% of total body surface area and Grade 4 represents a generalized exfoliative dermatitis, ulcerative dermatitis or bullae [22].

After the skin, the next most frequently involved organs in acute GVHD are the liver and the gastrointestinal tract, where the disease causes asymptomatic elevation of bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, nausea, vomiting and diarrhea [22].

Chronic Graft Versus Host Disease

Chronic GVHD may occur as either a late phase of acute GVHD or as a distinct entity and it may affect up to 30-80% of patients after
The skin is the primary organ involved in chronic GVHD followed by the oral mucosa, the liver and the eye [10,24].

The cutaneous lesions have been classically divided into two categories: lichen planus-like and scleroderma-like [7]. However, the clinical spectrum of cGVHD is broad [25,26] and it can include poikilodermatous lesions, xerosis, anular scleroderma-like lesions, keratosis pilaris-like lesions, psoriasisform lesions, deep sclerotic features, eccema-like lesions, acral erythema, fasciitis, morphea-like superficial sclerotic features, and/or lichen sclerosus-like [1,7,10,24,27].

The first indication of cGVHD is the appearance of focal, folliculocentric, confluent or linear violaceous lichenified papules, vesicles and plaques that arise with a predilection for flexural surfaces [28]. White lacy patches, indistinguishable from those present in oral lichen planus, can appear on the oral mucosal [10]. Other oral symptoms include xerostomia, mucocele, mucosal atrophy and ulcers [17].

Sclerodermatous GVHD is characterized by hypo or hyperpigmented thickened, tight, indurated and fragile skin which is often associated with poor wound-healing, inadequate lymphatic drainage, skin ulcers from minor trauma, contractures and limited joint mobility [10,24,25]. Characteristically, these lesions tend to appear on sites of minor skin trauma or pressure (waistband line, brassiere line) or on sites of previous skin damage (such as old scars or site of a previous herpes zoster infection) [10].

Extensive skin involvement (>50% of body surface area) [28] is associated with poor prognosis and an increased risk of transplant-related mortality and as well as non-relapse mortality (NRM) in patients with cGVHD [3,24].

Other mucocutaneous manifestations of cGVHD secondary to dermal sclerosis are scarring and non-scarring alopecia, nail dystrophy (in up to 50% of patients), nail pterygium, onycholysis, loss of adnexal structures such as sweat glands, calcinosis, stenosis of the vagina and vulva and xerostomy similar to those observed in systemic skin sclerosis [10,29]. However, unlike systemic sclerosis, involvement of the face, sclerodactyly and Raynaud phenomenon are uncommon [10].

Histology

Skin biopsy with routine hematoxylin and eosin staining is the primary tool for evaluating skin eruptions in suspected acute and chronic GVHD [30].

Acute GVHD is characterized by an interphase dermatitis with vacuolar degeneration due to apoptosis of the basal layer, dyskeratotic and necrotic keratinocytes, exocytosis of lymphocytes and perivascular infiltration in the dermis [1,26,31,32]. Depending on the histological findings a scaling system has been proposed, where Grade 1 consist of lymphocytic infiltrates in the upper dermis without epidermal changes, Grade 2 presents with vacuolization of the basal layer and dyskeratotic keratinocytes, Grade 3 consist of subepidermal vesicle formation and Grade 4 corresponds to complete dermal and epidermal separation with massive necrosis of keratinocytes [10,32,33].

Chronic GVHD on the other hand has unremarkable epidermal changes or similar changes than those observed in aGVHD, but most importantly it presents with thickened and homogenized collagen bundles that affect the dermis, the adipose tissue and even de fascia [7,26].

Differential Diagnosis

The diagnosis of GVHD is complicated by the complex immune status of the patient and by the fact that other eruptions that are common in immunosuppressed patients can be easily confused with GVHD [34]. An accurate diagnosis can be achieved by using specific histological and immunohistochemical criteria [35-37].

Differential diagnosis of skin symptoms includes engraftment syndrome, toxic epidermal necrolysis, irritant or allergic contact dermatitis, lichen planus, morphea, scleroderma, erythrodema, toxic shock syndrome, stevens-johnson syndrome, staphylococcal scalded skin syndrome and most commonly and importantly drug eruptions and viral exanthemas [34,38]. Drug-induced rashes are very common in post-transplant patients due to the amount of medications that these patients have to take. Alemtuzumab used as a conditioning regimen in a patient treated for chronic lymphocytic leukemia with autologous stem cell transplantation, has been associated with a GVHD-like rash [39].

Prevention and Treatment

The best treatment for graft versus host disease (GVHD) is prevention [40]. The current main measures to prevent and treat GVHD are the application of cytotoxic drugs (such as cyclosporine A), immunosuppressive agents (mainly high-dose steroids), and removal of T cells in graft before and after transplantation [5,41,42]. Anti-T-cell globulin, when added to standard immunosuppressive prophylaxis, can result in decreased incidence of acute and chronic GVHD [43].

Treatment has to be multidisciplinary with many specialists involved in the care of the patient [44].

Topical steroids, such as triamcinolone or clobetasol ointment, can be used as a first line treatment in acute GVHD stages I and II [7,31]. For oral lesions, topical tacrolimus has been used effectively [45].

Systemic therapy is recommended in all cases of grade III-IV acute GVHD and chronic GVHD [46,47]. The percentage of body surface area affected and depth of sclerotic involvement in chronic scleromatous GVHD are key determinants for administration of immunosuppressive therapy, its duration and intensity, treatment response, and impairment of patients’ quality of life [46,48]. The most common first-line treatment is steroids in combination with cyclosporine or another calcineurin inhibitor [49].

For patients with steroid-resistant GVHD, second-line treatment is less well defined due to the lack of clinical studies [1,4,47]. There are numerous single drugs or combination therapies that can be used to treat steroid-resistant GVHD, including methotrexate, calcineurin inhibitors (such as tacrolimus, and sirolimus), pulses of high doses of methylprednisolone, extracorporeal photopheresis, mycophenolate mofetil, immunomodulating agents like thalidomide, azathioprine, rituximab, infliximab, daclizumab, hydroxychloroquine, imatinib, alemtuzumab, etanercept, UV A1 phototherapy, extracorporeal photochemotherapy, denileukin difitox amongst others [4,27,47,50-70].

Broad antibiotic, antifungal and antiviral, prophylaxis is of the utmost importance, because infectious complications are common in GVHD [1,16].

Sclerodermatous changes of chronic GVHD may require surgical release of a contracted joint. Also, nonhealing-ulcers secondary to sclerodermatous GVHD may require wound debridement and skin grafting [50].
Conclusion
The skin is the first organ affected by GVHD and as such, recognizing the early dermatologic manifestations can allow prompt diagnosis and treatment, which may prevent the progression to higher-grade disease and improve the outcome of patients [3].

Patients with significant skin involvement in GVHD have increased risk of infections, impaired functional performance, skin cancer, and psychological distress (depression and struggles with body image) and as such, dermatologists play an important role in the multidisciplinary team needed to treat these patients [50].

Unfortunately, current treatment strategies are still not 100% effective because the pathophysiology of GVHD is still not completely understood. As more research is made in this area, newer treatment options targeting the specific immunological disparities that occur in GVHD will become available.

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