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Case Report

Sclerotic-type chronic graft-versus-host disease - a case report

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Abstract. Graft-versus-host disease (GVHD) is an important complication of hematopoietic stem cell transplantation (HSCT) and the most common clinical manifestation of GVHD is the skin. This article will present the case of a 22 years old patient, diagnosed with leukemia, who developed cutaneous sclerotic lesions 6 years after HSCT. The sclerotic lesions were treated with narrowband UVB phototherapy, with a curbed evolution of disease. In this case report we want to highlight the skin aspects that may occur after a long-time post-transplant, aspects that multidisciplinary health care team need to consider in this category of patients.

Key Words: allogeneic hematopoietic stem cell transplant, graft-versus-host disease, cutaneous sclerotic lesions.

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Introduction

Graft-versus-host disease (GVHD) is an immunologic condition which occurs as a complication of hematopoietic stem cell transplantation (HSCT), being associated with significant morbidity and mortality of life.

The disease is due to interaction between the immunocompetent donor T cells and recipient tissue which is seen as a foreign antigen by donor cells (Kavand et al 2017).

GVHD is classified into acute and chronic types, each of them presenting different clinical features and different prognosis. Traditionally, the classification into acute and chronic GVHD was based on the period of time after the clinical features appear post-transplantation, less than and greater than 100 days, respectively. A recent National Institutes of Health consensus criteria were developed to classify GVHD, including additional subtypes of GVHD with overlapping features or timing of acute and chronic symptoms (Jagasia et al 2015).

The most common clinical manifestation of GVHD is in the skin, both in acute and chronic disease, and the clinical picture is polymorphic. Every organ system may be affected by GVHD, the most frequently involved being hepatic and gastrointestinal (GI) systems, hematopoietic, musculoskeletal systems (Shi et al 2017).

Chronic GVHD is an important complication of allogeneic HSCT, affecting approximately 30-70% of patients (Jagasia et al 2015). The skin is the most commonly involved, followed by the mouth, liver, eye, GI tract, lung, female genital tract and joints (Lee et al 2008).

We report a case of cutaneous GVHD, manifesting with cutaneous sclerotic lesions, appeared 6 years after HSCT in a young patient diagnosed with leukemia with Philadelphia chromosome-positive. The role of the dermatologist is important, in order to recognize and treat the complications of HSCT.

Case report

A 22-year-old patient diagnosed 6 years ago with acute leukemia (mixed phenotype, lymphoblastic with B precursors and myeloblastic), with Philadelphia chromosome-positive, was evaluated in the Department of Medical Oncology for a violaceous, non-pruritic rash, with a progressive expansion. It is mentioned that 6 years ago, the patient followed cytostatic therapy with the ALL IC-BFM 2002 HRG protocol (acute lymphoblastic leukemia, International Berlin-Frankfurt-Münster 2002, high risk group), and after 1 month with Imatinib 400 mg / day p.o. Three months after initiating this treatment, molecular biology tests revealed a decrease in BCR / ABL gene translocation to 0.57% (partial molecular remission). After another 3 months, the patient was transplanted with hematopoietic stem cells, derived from periphery blood, from an identical HLA donor (his sister). Post-transplantation, the patient followed the treatment with Imatinib 500 mg / day for one year, associated with antibiotic and antiviral prophylaxis, and hepatoprotective drugs.

At admission, the patient had a good general condition, was afebrile, and the dermatological examination revealed violet-gray plaques, with hyperpigmented areas, discrete sclerotic atrophies, and well-defined borders, localized on the anterior thorax, abdomen, and axillary left area, without adenopathy or organomegaly (Fig. 1a, b).

Hematological parameters were within normal values, and biochemical parameters revealed cholestasis (gamma-glutamyltransferase: 331 U/l, normal values: <61U/l) and increased values of ferritinemia (1085 ng/ml, normal values: 30-400 ng/ml).

A cutaneous biopsy from a sclerotic lesion was performed, revealing a skin with mild hyperkeratosis and atrophy of the epidermis, basal membrane hyalinization, the presence of thickened collagen bundles, hemorrhage, rare melanophages in the superficial dermis, atrophic and reduced adnexal structures (Fig. 2).

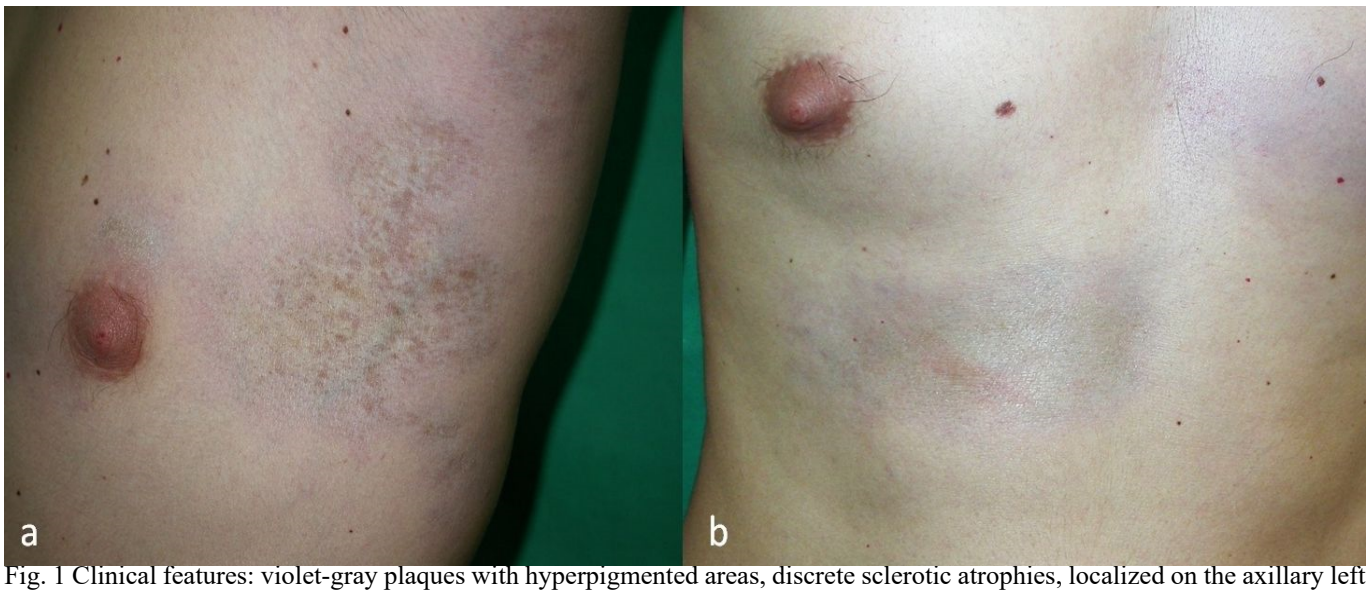

Fig. 1 Clinical features: violet-gray plaques with hyperpigmented areas, discrete sclerotic atrophies, localized on the axillary left area (a); violet plaques, localized on the anterior thorax and abdomen (b)

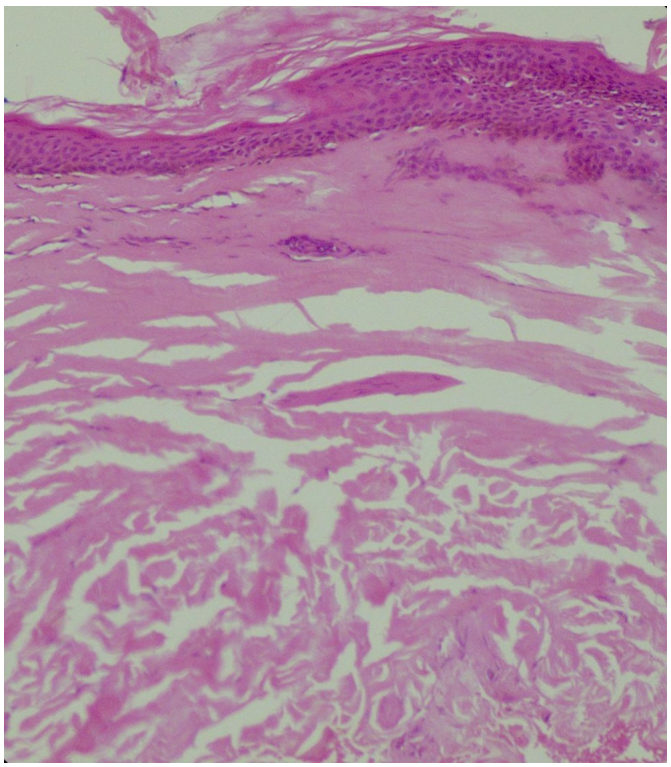

Fig. 2 Histopathology of the skin lesions: mild hyperkeratosis of the epidermis, hyalinization of the collagen throughout the dermis and loss of appendageal structures

The patient (phototype II) was treated with narrowband UVB phototherapy, with a total dose of 10.75 J/cm2. The evolution of disease was kept under control, the existing lesions remained unchanged and no new lesions appeared.

The patient signed an informed consent form, that gives the permission for the use of medical data and pictures.

Discussion

The risk factors associated with the development of GVHD are: HLA-mismatch between donor and recipient, patient age (elderly patients are more frequent affected), female donor/male recipient, stem cell source (peripheral blood more than bone marrow), unrelated donor, interruption or rapid tapering of immunosuppression (Cowen 2012). According to this, in our case the risk factors included female donor/male recipient and the stem cell source (peripheral blood).

The pathogenesis of GVHD is based on the theory that initially there is an acute inflammation mediated by innate immune response, followed by a chronic inflammation due to dysregulation of T and B cells in adaptive immunity, and finally T cells produce pro-fibrotic cytokines capable of stimulating collagen production (Cooke et al 2016).

The diagnostic of chronic GVHD is made on history, cutaneous examination and histology. Time of onset has no more a role in the definition of chronic disease, thus a previous history of acute GVHD is the single greatest risk factor for chronic disease.

The cutaneous lesions in acute GVHD consists of erythematous dusky macules and papules of the volar and plantar surfaces and ears, generalized exanthem, erythema limited to hair follicles, pruritus, bullae, necrosis.

The cutaneous lesions in chronic GVHD may include poikiloderma, a lichen planus-like eruption and sclerotic features, resembling lichen sclerosus, manifesting as porcelain-white atrophic plaques or as patchy sclerotic plaques with hypo- and hyperpigmentation mimicking morphea. Sclerodermatous graft-versus-host-disease is a variant of chronic GVHD characterized by deposition of collagen in the skin and the estimated prevalence is between 3-11% (Skert et al 2006). The clinical features consist of sclerosis, hyper- and hypopigmented macular lesions, atrophy, ulceration and contractures (White et al, 2007).

Sclerotic involvement is less common than lichenoid GVHD and tends to occur later post-HSCT. (Cowen 2012). In our case, cutaneous lesions were initially diagnosed as morphea, unrelated to the HSCT.

Other cutaneous lesions may include: nail involvement, milia formation, porokeratosis, angioma formation at sites of skin sclerosis, nipple hyperkeratosis, vitiligo, alopecia (Filipovich et al 2008).

Patient monitoring is very important because sclerotic GVHD can progress to fibrosis of the dermis and subcutaneous tissue, ulcerations, joint contractures, myalgias and pain. Also, the patients are at increased risk for melanoma and nonmelanoma skin cancers due to GVHD-associated immunodysregulation,

immunosuppressive treatment for GVHD, or after PUVA therapy (Cowen 2012).

The prognostic factors are: a history of progressive involvement from acute to chronic GVHD, thrombocytopenia, elevated bilirubin, older age, gastrointestinal symptoms, and lack of response to therapy at 6 months, extensive (>50%) skin involvement and lichenoid skin histology (Cowen 2012).

Treatment of chronic GVHD remains challenging, consisting of immunosuppressive agents, such as systemic corticosteroids, methotrexate, mycophenolate mofetil, imatinib mesylate, rituximab, and extracorporeal photophoresis. Phototherapy (UVA1, PUVA or UVB-NB) is usually indicated in fibrotic involvement of the skin. The topical treatment includes corticosteroids and calcineurin inhibitors.

Conclusion

The dermatologist should play a role in the multidisciplinary approach to chronic GVHD management, in order to exclude adverse drug reactions or other new skin disease from GVHD, to monitor for possible cutaneous complications, and to monitor the dermatological treatment.

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