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CLINICAL CASE

Vitiligo type cutaneous manifestation of chronic graft-versus-host disease. Case report

Enfermedad injerto contra huésped cutánea crónica tipo vitiligo. Caso clínico

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Abstract

Introduction: Graft-versus-host disease (GVHD) is caused by a pathologic and destructive response of the organism as a result of the interaction between donor immunocompetent T lymphocytes and the recipient tisular antigens. It´s considered the most serious complication of hematopoietic stem cell transplantation, most frequently described after bone marrow transplantation (BMT). The skin is usually the first and most commonly affected organ, in both acute and chronic, with a variable clinical spectrum of presentation. **Objective:** To report a case of vitiligo as a manifestation of cutaneous chronic GVHD, a low prevalence sign, which recognition could help to suspect this severe complication. **Case report:** 8 years old male, diagnosed with acute lymphoblastic leukemia (ALL) at 3 years old, had a combined medullary and central nervous system (NCS) relapse with minimal positive disease 3 years afterwards. After 4 years ALL was diagnosed, he received an allogeneic bone marrow transplant. Seven months after the BMT he presented multiple melanocytic nevi with peripheral hypopigmentation, and some isolated asymptomatic, confluent achromic macules on the face, trunk and limbs. The skin biopsy was compatible with chronic vitiligo and sclerodermiform type GVHD. He received topical treatment with Tacrolimus, achieving clinical stabilization. **Conclusions:** GVHD leads to the appearance of autoantibodies that could act as a trigger in the onset of autoimmune diseases, such as vitiligo. Consequently it could explain this poorly described manifestation in the literature of chronic cutaneous GVHD.

Keywords:
Chronic cutaneous graft-versus-host disease,
Hematopoietic stem cell transplantation,
Vitiligo

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Introduction

Graft-versus-host disease (GVHD) is one of the main complications in hematopoietic stem cells transplantation, its incidence varies from 25 to 80%[1]. It is responsible for most of the post-therapeutic morbidity,mortality and decrease in the quality of life of those patients[2].

Hematopoietic stem cells can be obtained from the bone marrow, peripheral blood or umbilical cord. These cells are transplanted to patients through peripheral venous blood, accommodating in the bone marrow and producing new blood cells able to attack tumor cells. The allogenic bone marrow transplantation, i.e. peripheral blood progenitor cells from a genetically similar donor, is the most common cause of GVDH[3].

Conventionally GVDH has been divided into acute and chronic forms, where the symptoms can appear during or after 100 days of the hematopoietic stem cells transplantation, respectively[3]. However, the use of previous immunosuppressive therapies can change the timeline of the disease, resulting in a late acute disease that could appear after the 100th day of transplantation, and there might also be overlapped syndromes[3]. The spectrum of clinical presentation and severity index of GVDH have been recently classified by the National Institute of EEUU workgroup. These criteria differentiate the acute GVDH from the chronic GVHD form due to mucocutaneous characteristics, regardless of the onset of the disease after the hematopoietic stem cells transplantation[4]. Some of the diagnostic features of chronic cutaneous GVHD include poikiloderma, lichen planus-like eruption, sclerodermiform lesions either morphea or lichen sclerous. On the other hand, distinctive characteristics include achromic and hypopigmented lesions due to vitiligo[4]. However, the literature describes it as an uncommon manifestation with a 5% incidence rate[5].

The objective of this report is to describe a case of vitiligo as a symptom of chronic cutaneous GVHD, which is a symptom of low prevalence and its identification might help in the diagnosis of this severe complication.

Clinical Case

Male patient, eight years and eight months old, with history of acute lymphoblastic leukemia diagnosed at three years old. He had a medullary and central nervous system (CNS) relapse with minimal residual disease at the three and a half years of progression; therefore, after one year he received bone marrow transplantation (BMT) from a family donor (sister). Prior surgery, the patient received CNS and total irradiation, etoposide chemotherapy, and GVHD prophylaxis with cyclosporine. There was no personal or family history of vitiligo.

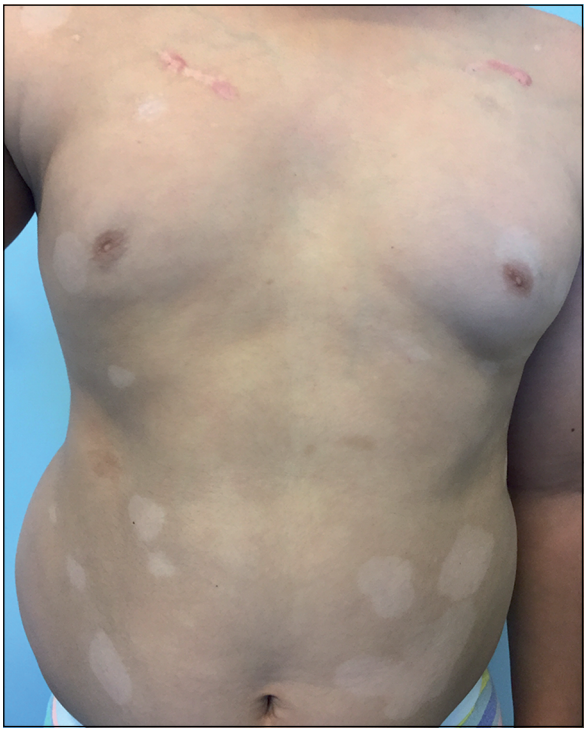

Figure 1. Multiple hypopigmented and acromic macules in the anterior thorax.

The patient consulted seven months after the BMT, due to symptoms which were characterized by multiple melanocytic nevi associated with peripheral hypopigmentation and achromic macules in the face, trunk, and limbs, asymptomatic. The patient was treated with topical fluticasone 0.05% cream (once every night, for a month), resulting in attenuation of some of the lesions. Then, the patient was referred to a dermatologist for an evaluation.

In the physical test, the patient showed a phenotype IV (light brown skin, brown hair and brown eyes), multiple hypopigmented macules in the border of the upper lip and in the left labial commissure. There were approximately 30 macules, and hypopigmented and achromic patches in the anterior and posterior site of trunk, arms, forearms, and legs. They had different sizes but had well-defined borders. Some of them were associated with a nevus in their inside, but there were no signs of atypia (figure 1 and 2). The exam showed a unique sclerodermiform achromic patch, in the posterior site of the right leg (figure 3). The patient did not have lesions on hands, mucosa or scalp.

The exams showed a normal TSH, negative thyroid antibodies and anti-nuclear antibodies 1/160 (mottled

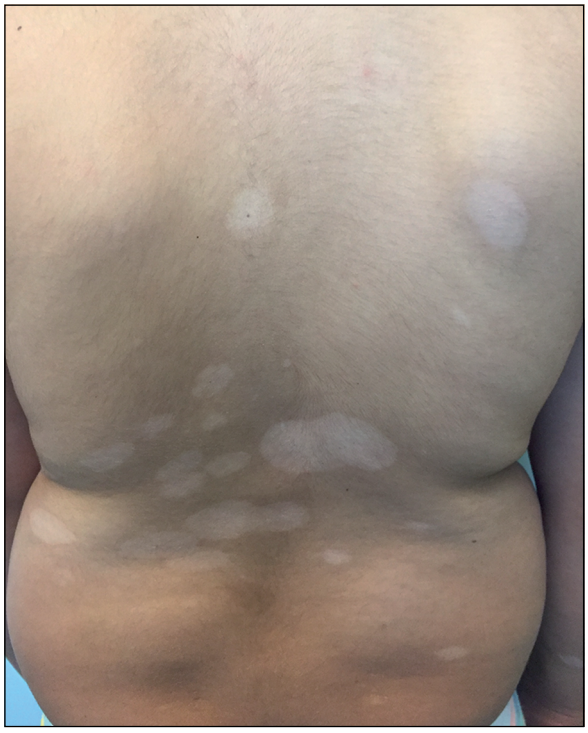

Figure 2. Multiple hypopigmented and acromic macules in posterior thorax.

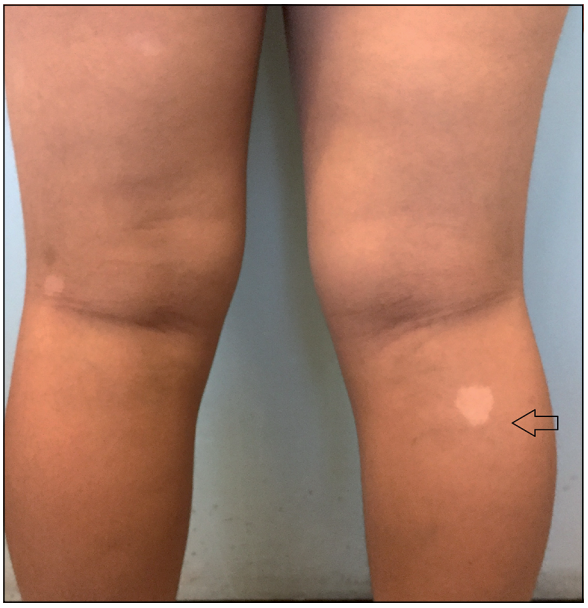

Figure 3. Hypopigmented macules on lower extremities and sclerodermiform plaque on the posterior site of the right leg (arrow).

pattern). A biopsy of the sclerodermiform lesion was performed, which showed findings compatible with sclerodermiform GVHD. The type of lesion, localization, and progression after the BMT suggested chronic vitiligo and sclerodermiform type GVHD.

The treatment started with topical Tacrolimus 0.03% for a month, which led to a reduction of some macules and no new lesions appeared. Then, topical Tacrolimus 0.1% was indicated for six months; the symptoms stabilized and did not progress in the six months of follow-up.

Discussion

Vitiligo is an acquired disorder where the loss of melanocytes results in achromic macules. The main hypothesis regarding its etiology considers it as an autoimmune disease due to the destruction of melanocytes as a dependent response of cytotoxic T-lymphocytes[6]. Chronic cutaneous GVHD implies the appearance of antibodies that could act as a triggering factor to develop autoimmune diseases, and in this case, to start an autoimmune response focused on the destruction of melanocytes, which is manifested as vitiligo[6]. The association of GVHD with multiple autoinmune diseases, such as Sjögren syndrome, systemic scleroderma, Hashimoto's thyroiditis and Grave's disease support this theory[7].

In this case, the laboratory tests of thyroid function were normal, however, the patient presented anti-nuclear antibodies 1/160 (mottled pattern) without lupus manifestations, thus, symptoms must be re-evaluated in each control. The early dermatologic evaluation allowed an opportune diagnosis, despite being an uncommon clinical presentation.

In a prospective cohort study in Croatia, 2016, 50 adults and pediatric patients with chronic cutaneous GVHD were monitored[8]; after applying the criteria of the consensus of the National Institute of Health of EE.UU., it was concluded that 8% of the patients had vitiligo, a higher percentage than the one reported in previous studies[5,7]. Considering that the diagnosis of chronic cutaneous GVHD is mainly clinic, it is essential to carry out a dermatological evaluation after the suspicion in order to confirm the diagnosis. More studies are required to determine the real prevalence of vitiligo in these patients.

Regarding the histopathology in GVHD, its usefulness is discussed since there are no pathognomonic findings[2], and according to the consensus published in 2015 about the cutaneous biopsy in cutaneous GVHD, it is recommended in chronic cutaneous GVHD when there are no diagnostic features and to exclude other

differential diagnoses, especially in acute cutaneous GVHD[9]. In this case, a biopsy of the sclerodermiform lesion was made, which was compatible with sclerodermiform GVHD.

Once the diagnosis of chronic cutaneous GVHD is established, the therapeutic management of achromic and hypopigmented lesions include topical steroids, topical calcineurin inhibitors, and phototherapy[10]. Our patient received a topical treatment with Tacrolimus 0.03% for a month, with a partial response. Then, he was given Tacrolimus 0.1% for 6 months, with stabilization of the symptoms.

Conclusion

The skin is the most commonly affected organ in GVHD. Sometimes it has hypopigmented and achromic lesions caused by vitiligo. According to the consensus of the National Institute of Health about chronic GVHD, although these lesions are a distinctive characteristic of chronic cutaneous GVHD, they are insufficient by themselves to establish a diagnosis. It is required to perform a dermatologic evaluation and biopsy to confirm the diagnosis, in order to dismiss other diseases.

Ethical responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Financial Disclosure

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Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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