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Sclerodermatous manifestation of chronic graft-versus-host disease: therapy challenges

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Abstract

Chronic graft-versus-host disease (cGvHD) is one of the most serious complications after allogeneic hematopoietic cell transplantation (allo-HCT). It varies between patients, often leading to systemic and functional limitations. It can be challenging considering the heterogeneity of patients. The aim of this paper was to present clinical aspects of sclerodermatous manifestation of cGvHD as a complication of allo-HCT in pediatric patients. We diagnosed three patients with different sclerodermatous skin involvement and cGvHD features. The treatment applied varied among the patients, and was based on currently available standards of care. We analyzed the effectiveness of systemic steroid therapy, extracorporeal photopheresis, and ruxolitinib.

All patients achieved an improvement in skin lesions and quality of life, based on an individualized treatment approach.

Key words: graft-versus-host disease, transplantation, scleroderma

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Introduction

Hematopoietic stem cell transplantation (HCT) is a highly important procedure included in the treatment protocols of many diseases, and in most cases forms the final part of treatment. This procedure is associated with the risk of many complications, one of which is graft-versus-host disease (GvHD). Chronic GvHD (cGvHD) is the main cause of non-relapse related mortality in patients after allogeneic hematopoietic cell transplantation (allo-HCT) [1]. Although GvHD can have many clinical manifestations, the most common is skin involvement, with a variety of skin lesions which can simulate autoimmune and inflammatory diseases, often leading to systemic and functional complications [2, 3]. A sclerodermatous manifestation of GvHD, especially a steroid-refractory one, can be challenging considering the heterogeneity of the patients.

The aim of this study was to analyze the clinical course and treatment of sclerodermatous manifestation of cGvHD as a complication of allo-HCT in pediatric patients.

Material and methods

All patients treated in the Transplant Unit were analyzed for cGvHD. Patients with a sclerodermatous manifestation were selected for detailed clinical analysis.

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Results

Demographics

Between 2015 and 2022, a total of 193 patients were transplanted from matched family donors, matched unrelated donors, or haploidentical donors. Overall, three patients (1.5%) were diagnosed for sclerodermatous manifestation of GvHD with different clinical features and stages of the disease (Tables I, II).

Patient 1

A 16-year-old boy was diagnosed with T-cell lymphoblastic lymphoma (T-LBL) CD117+, CD33+ with significant bone marrow involvement. He was treated according to the EURO-LB-02 protocol. The treatment was complicated with toxic meningitis, sepsis caused by staphylococci and blastomycetes, and intestinal perforation with peritoneal abscess which required surgical treatment (intestine resection). After the patient achieved full remission, he was qualified to allo-HCT procedure. Total body irradiation, etoposide and thymoglobulin were used as a conditioning regimen, while GvHD prophylaxis was based on cyclosporine and a short course of methotrexate. Bone marrow from a matched sibling donor [sister, human leukocyte antigen (HLA) 10/10, ABO-matching] was used for transplantation. On day +6, the patient received one dose (150 mg/m^2) of rituximab as a prophylaxis of Epstein-Bárr virus [EBV] reactivation. The early post-transplant period was complicated by bacteremia (*Staphylococcus epidermis*) and mucositis. The patient was discharged on day +28 after transplantation. No signs of GvHD were observed in the early post-transplant period, and cyclosporine prophylaxis ended three months after transplantation.

On day +128, he was diagnosed with chronic GvHD (cGvHD) limited to oral cavity with xerophthalmia manifestation. Topical steroids were introduced (flucinolon). He was admitted to hospital on day +135 because of fever and face erythema. Laboratory tests showed thrombocytopenia, elevated C-reactive protein, hypogammaglobulinemia and elevated transaminases [5 × upper limit of normal (ULN)] and ferritin. A relapse of T-LBL and reactivations of viral infections were excluded. All the above symptoms were recognized as manifestations of cGvHD with oral cavity, skin, liver and eye involvement. The treatment included methylprednisolone (1 mg/kg/day), intravenous gammaglobulins in supplementary doses, antibiotics and subcutaneous deferoxamine injections. After the implemented therapy, the patient achieved clinical and laboratory improvement, and steroids were discontinued.

On day +413, during a scheduled medical examination, thickening of the skin on the lateral sites of the abdomen, upper and lower limbs was identified. A biopsy revealed scleroderma. As a consequence of this, the treatment for cGvHD was intensified and consisted of mycophenolate mofetil, cyclosporine and methylprednisolone. After methylprednisolone taper, hydrocortisone was implemented due to chronic adrenal insufficiency. Gradually, cyclosporine and mycophenolate mofetil were discontinued. The patient responded well to the treatment, and on day +574 his skin was free of sclerodermatous signs. No other signs of chronic GvHD were observed.

Patient 2

A 16-year-old boy diagnosed with myelodysplastic syndrome (MDS RAEB-1) was qualified to allo-HCT. The patient received conditioning according to the European Working Group (EWOG)-MDS protocol based on busulfan, cyclophosphamide, melphalan and thymoglobulin. Peripheral blood allo-HCT from a matched unrelated donor (HLA 10/10, ABO mismatch) was used. GvHD prophylaxis was based on cyclosporine and a short course of methotrexate. On day +5, the patient received one dose (150 mg/m^2) of rituximab as a prophylaxis of EBV reactivation. The early post-transplantation period was complicated by multiple reactivations of cytomegalovirus (CMV) infection, hypogammaglobulinemia and aGvHD with skin and gastrointestinal tract involvement. On day +179, he developed an erythematous rash covering 63% of his body surface. Treatment of GvHD consisted of prednisone 1mg/kg and extracorporeal photopheresis (ECP), two procedures every two weeks.

A month later, the patient presented reduced mobility in the shoulder, elbow and hip- joints, local swelling of the hands and feet, as well as hardening and thickening of the skin of the forearms and lower limbs. A biopsy confirmed GvHD in the lesions with signs of dyskeratosis, satellite cell necrosis, and lymphocyte apoptosis in histopathological assessment. Due to the rapid progression of symptoms, the patient started treatment with ruxolitinib at a dose of 2 × 5 mg. Despite clinical improvement, the drug was discontinued due to severe and symptomatic thrombocytopenia which appeared as a side effect of therapy. Rapidly as a consequence of ruxolitinib discontinuation the patient underwent cytokine release syndrome, and therefore the drug was reintroduced. At this point, sclerodermatous lesions were observed on 95% of his body surface, significantly reducing active and passive mobility in the joints and mobility of the chest. Slowly escalating doses of ruxolitinib (to the maximal dose 2 × 10 mg) with combination of cyclosporine, steroids and ECP were implemented. Due to multiple CMV reactivations, cyclosporine was substituted with sirolimus. Finally, steroids were discontinued on day +420 and rehabilitation was implemented, resulting in a significant improvement in the boy's condition. No signs of GvHD are present at the moment. Sirolimus was ended around two years after allo-HCT, while ruxolitinib at a dose of 2 × 10 mg is still being administered.

Table I. Patient characteristics

Characteristic	Patient 1	Patient 2	Patient 3
Age	16	16	14
Sex (M/F)	M	M	M
Diagnosis	T-LBL	MDS	HV-LPD
Type of transplant	allo-PB-HCT	allo-PB-HCT	allo-PB-HCT
Donor	MUD	MUD	MUD
Conditioning	Myeloablative: VP + TBI	Myeloablative: BU, CY, MEL	Myeloablative: VP, Ara-C, FLU, MEL
GvHD prophylaxis	Thymoglobulin, CsA, MTX	Thymoglobulin, CsA, MTX	Thymoglobulin, CsA, MTX
aGVHD manifestation	None	None	None
cGVHD manifestation (site/NIH score [5])			
Skin	2	4	3
Liver	2	0	2
GI tract	0	3	0
Hematological	3	0	0
Eyes	0	0	1
Lungs	1	2	3

aGvHD — acute graft-versus-host disease; allo-PB-HCT — allogeneic peripheral blood hematopoietic cells transplantation; Ara-C — cytosine arabinoside; BU — busulfan; cGvHD — chronic graft-versus-host disease; CsA — cyclosporine; CY — cyclophosphamide; F — female; FLU — fludarabine; GI — gastrointestinal; HV-LPD — hydroa vacciniforme-like lymphoproliferative disorder; M — male; MDS — myelodysplastic syndrome; MEL — melphalan; MTX — methotrexate; MUD — matched unrelated donor; NIH — National Institutes of Health; TBI — total body irradiation; T-LBL — T-cell lymphoblastic lymphoma; VP — etoposide

Table II. Clinical manifestations of scleroderma, according to Rodnan scale [19]

Scleroderma/clinical assessment	Patient 1	Patient 2	Patient 3
Skin involvement (points)	10	50	13
Skin thickness	Moderate	Severe	Moderate
Joints:			
• swelling	Mild	Moderate	None
• movement limitations	None	Severe	Mild
• walking problems	None	Advanced/wheel chair	None

Patient 3

A 14-year-old boy diagnosed with common variable immunodeficiency (CVID) had been treated with intravenous immunoglobulin since the age of 5. The boy underwent numerous severe infections, including CMV and EBV disease. At age 13, a maculopapular rash appeared on the skin of his lower limbs, feet and abdomen. After two months, the patient developed similar lesions on his head. The viremia of EBV was constantly increasing over the months. Finally, he was diagnosed with hydroa vacciniforme-like lymphoproliferative disorder (HV-LPD), as was described previously [4]. The patient was treated with rituximab, bortezomib and gancyclovir. After two courses of tabelecleucel, EBV-DNA load significantly decreased. As a conditioning regimen, the patient received etoposide, cytarabine, fludarabine, melphalan, and thymoglobulin. A peripheral blood allo-HCT was performed from a matched unrelated donor (HLA 10/10, ABO mismatch). GvHD prophylaxis was based on cyclosporine and a short course of methotrexate. The treatment was complicated with mucositis of gastrointestinal tract in the early post-transplantation period. There were no signs of acute GvHD. The patient received rituximab (150 mg/m^2) as a prophylaxis of EBV reactivation on days +5 and +24 due to the appearance of EBV viremia. On day +31, a third series of therapy with tabelecleucel was started. In total, the boy completed four cycles of immunotherapy and no reactivations of EBV infection were observed afterwards.

Ten months after allo-HCT, the boy was urgently admitted to hospital because of diarrhea and reduced mobility in his elbow, shoulder and knee joints. Moreover, detailed examination showed thickening and hardening of the skin and subcutaneous tissue of his forearms and back. A skin biopsy confirmed sclerodermatous chronic GvHD. According to the National Institute of Health Consensus, the severity of GvHD was determined as moderate. Oral prednisone

1 mg/kg/day, low dose oral methotrexate (20 mg/week), and regular ECP (two procedures every three weeks) were implemented. During immunosuppressive treatment, CMV reactivation which required gancyclovir treatment was observed. Also, EBV-DNA blips with spontaneous negativization were observed. This is why there was no possibility to intensify GvHD treatment with new drugs such as ruxolitinib. Currently, the patient is still receiving low dose prednisolone (5 mg/day) and methotrexate (20 mg/ /week) with two ECP procedures every six weeks. He also receives sirolimus due to new scleroid changes that have appeared in the meantime. Moreover, new signs of bronchiolitis obliterans syndrome in spirometry and CT-scans led to the introduction of FAM (fluticasone, azithromicin, montelukast) therapy. Thus far, a very slow improvement is being observed.

Discussion

We here present three cases of scleroderma as cGvHD manifestation in pediatric patients after allo-HCT. These patients were diagnosed over the last seven years, and so the treatment possibilities and approaches have varied and changed. To date, the standard first line cGvHD therapy consists of systemic steroid regimens. However, in almost 50% of patients, GvHD is recognized as steroid-refractory or steroid-dependent [2, 6]. The second line treatment of cGvHD is not yet standardized and has been changing over the last few years according to novel treatment modalities [6, 7]. Most transplant centers rely on their local standards of care, and so evaluation or comparison of the efficacy of the different strategies is impossible.

In 2020, the European Society for Blood and Marrow Transplantation (EBMT) published updated recommendations indicating the second line cGvHD treatment options to be: extracorporeal photopheresis, calcineurin inhibitors, ibrutinib, mycophenolate mofetil, rituximab or mammalian target of rapamycin (mTOR) inhibitors. Moreover, the role of ruxolitinib as a novel available treatment option has been suggested [7]. Many recent studies have shown that ruxolitinib, a selective Janus kinase (JAK) 1 and 2 inhibitor, is an effective treatment option for patients with cGvHD [8–12]. Ruxolitinib, by its immunomodulatory activity, inhibits donor T-cell expansion and cytokine production. In cohort studies on heavily pretreated patients with a sclerodermatous GvHD manifestation, ruxolitinib led to at least partial improvement [13]. There are some safety concerns about the increased risk of severe infections or cytopenias caused by the use of ruxolitinib. However, in real life observations ruxolitinib's safety profile has proved satisfactory [14], so it is strongly recommended as an alternative treatment option. Extracorporeal photopheresis used in systemic scleroderma [15] also plays an important role in cGvHD treatment. Sclerodermatous manifestation of cGvHD is one of the most likely to improve, while ECP does not increase the risk of infections, does not induce general immunosuppression, and compared to other therapies importantly changes the quality of life and response assessment [16]. Moreover, recently published data confirms that the combined administration of ECP and ruxolitinib is highly encouraged in patients with other risk factors who are not resolving [17–20].

Conclusions

The treatment landscape of GvHD has evolved in recent years, allowing a great many patients to achieve clinical improvement. Yet there remain many patients whose treatment is challenging for clinicians. Therefore, individual needs and risk factors should be addressed regarding the therapeutic choice and combination.

Authors' contributions

MRP, KC — design of study. MRP, RD, JC, KC — provision of clinical data. MRP, MM, KC — analysis of clinical data. MRP, MM — writing manuscript. MRP, KC — editorial preparation of manuscript. All authors — critical revision and final approval.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

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