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Case Report

Successful Treatment of Refractory Graft-Versus-Host Disease with Ruxolitinib in a Child after Autologous Stem Cell Transplantation

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ABSTRACT

Autologous hematopoietic stem cell transplantation (AHSCT) is an increasingly used curative treatment for some solid tumors in children. Instead of allogeneic transplantation, the risk of developing graft-versus-host disease (GvHD) is much lower after AHSCT. Although the clinical findings of auto-GVHD are mild and self-limited in most cases, rare cases may be severe and need intensive immunosuppressive treatment. Here, we present a case who underwent autologous HSCT due to relapsed neuroblastoma, developed steroid-refractory GvHD after AHSCT, and achieved remission using ruxolitinib. A 12 years old female patient was diagnosed with relapsed neuroblastoma. After metaiodobenzylguanidine treatment, AHSCT was performed, and the status of the disease was a very good partial response at the time of transplantation. Our patient was diagnosed with severe and steroid-refractory GvHD with skin involvement after AHSCT. We used ruxolitinib with extracorporeal photopheresis because of the essential side effects of the other drugs and got a very good response. Over the following five months, there was no recurrence of GvHD. She was in complete remission of neuroblastoma after two years of AHSCT. It is crucial to keep in mind that GvHD may develop after AHSCT. Ruxolitinib is an effective treatment for GvHD also after AHSCT. Further studies and case reports are needed to understand the disease's pathogenesis and regulate appropriate treatment.

Keywords: Autologous stem cell transplantation, children, graft versus host disease, ruxolitinib, steroid-resistant

Introduction

Hematopoietic stem cell transplantation (HSCT) is an increasingly used curative treatment for many benign/malignant hematological diseases, some solid tumors, immunodeficiencies, and various metabolic and autoimmune diseases in childhood. One of the major complications of this curative treatment is graft-versus-host disease (GvHD). GvHD is an immune dysregulation condition caused by inflammatory cytokines resulting from the activation of donor T-cells (1). This complication, which can be fatal, is often expected after allogeneic HSCT. While it occurs in 50% of patients after allogenic transplantation (2), the risk of developing GvHD after autologous HSCT (AHSCT) is much lower. In the literature, AHSCT has been reported in adults, especially with multiple myeloma (1) and a few cases in pediatric patients who underwent autologous transplantation. Disruption of thymic-dependent immune reconstitution and failure of peripheral self-tolerance are considered in its pathophysiology (2). The main therapy of GvHD is immunosuppressive treatment.

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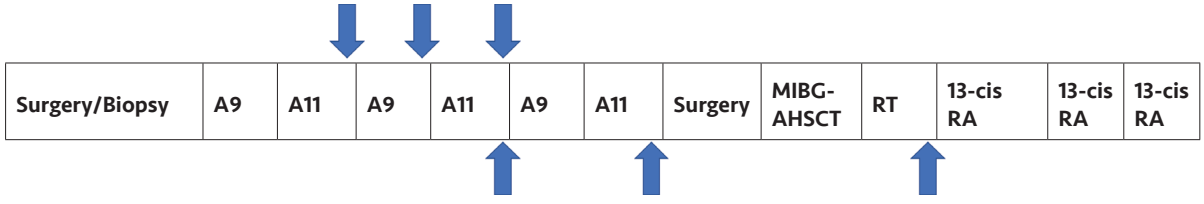
Although steroid is the first line therapy, cyclosporine A, tacrolimus, mycophenolate mofetil, photopheresis, and other immunosuppressive treatments can be used in steroid refractory cases. Another agent currently used in the treatment of steroid refractory GvHD after allogeneic HSCT is Ruxolitinib, which is an inhibitor of Janus kinases 1/2. Ruxolitinib was developed for the treatment of myeloproliferative disease, however, it has also been used successfully in the treatment of GvHD (3).

Here, we present a case who underwent AHSCT due to relapsed neuroblastoma, developed steroid refractory GvHD after AHSCT and achieved remission using Ruxolitinib. Written consent was obtained from patient's family for this case.

Case Report

A 12-year-old female was diagnosed with stage 1, low-risk neuroblastoma after total excision of a right suprarenal gland mass and was followed up without treatment according to our national treatment protocol; Turkish Pediatric Oncology Group Neuroblastoma 2009 (TPOG 2009). Eight months after diagnosis, she had a relapse due to multiple bone involvement of stage IV, high-risk group. Chemotherapy protocol was started according to the TPOG-2009 protocol (Table I), AHSCT was planned. During the treatment, the patient complained of a painless, immobile mass in the right parietal area. Cranial imaging showed bilateral, new bone metastasis. Her chemotherapy protocol was changed to ICE (Ifosfamide, Carboplatin, Etoposide). After metaiodobenzylguanidine treatment, AHSCT was performed (cell dose of $5.14x10^6$ CD34+ cells/kg), the status of the disease was very good partial response at the time of transplantation. The conditioning regimen for AHSCT were melphalan (140 mg/m^2), and busulfan (3.2 mg/kg/days-IV). Prophylactic defibrotide (25 mg/kg/g) for sinusoidal obstruction syndrome was used and prophylactic fluconazole, acyclovir, and ciprofloxacin were used. The patient was monitored weekly for Epstein-Barr virus (EBV) polymerase chain reaction, cytomegalovirus (CMV) pp65 antigen, and galactomannan antigen. She had neutrophil engraftment at day +12, platelet engraftment on day +13. On day 30, widespread, itchy erythematous macules, and lichenoid papular rashes developed in both cheek regions. There was no mucosal involvement or history of using new drugs in the prior two weeks. In laboratory tests, moderate thrombocytopenia was detected. Viral serological tests (EBV, CMV, TORCH, parvovirus, hepatitis markers) were negative. Her prophylactic antibiotics were changed to exclude possible adverse drug interactions at diagnosis, and antihistamine (H1 blocker) was initiated for the symptoms. Punch biopsy was performed because the skin rashes progressed to the hands and feet (Figure 1). Histopathological examination of skin biopsy showed

Table I. High risk neuroblastoma chemotherapy protocol in Turkey, TPOG 2009



Surgery/Biopsy	
A9-A11 (3 cycles chemotherapy)	A9: Vincristine, Dacarbazine, Ifosfamide, Adriamycin A11: Cyclophosphamide, Etoposide, Cisplatin
Surgery	
MIBG	Metaiodobenzylguanidine treatment
AHSCT	Autologous stem cell transplantation
RT	Radiotherapy
13- cis Retinoic acid treatment (3 cycles)	
Stem cell collection	Stem cell collection should be done after 1 cycle of A9- A11 chemotherapy, if necessary after other A9 or A11 chemotherapy
Evaluation	Evaluation should be done after 2 and 3 cycles of A9-A11 chemotherapy, and before the 13- cis retinoik acid treatment

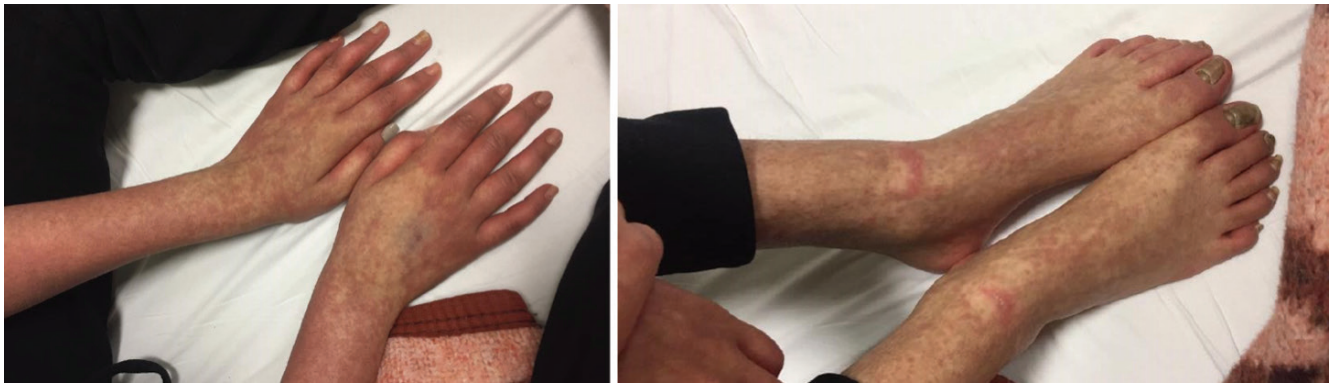


Figure 1. Images of the erythematous and edematous rash on the hands and feet

vacuolar degeneration in the epidermis, lymphocyte exocytosis, necrotic keratinocytes, and superficial perivascular mild-chronic inflammation in the dermis, compatible with acute GvHD. Eosinophil was not detected. Methylprednisolone was started (2 mg/kg/day). While receiving steroid therapy, the skin lesions progressed. The patient was diagnosed with steroid-refractory GvHD, and tacrolimus was added to the treatment. On the 15th day, tacrolimus was discontinued due to elevated liver enzymes and replaced by cyclosporine A. Liver enzyme levels went back to normal. In addition, extracorporeal photopheresis was applied on two consecutive days a week because the reactive skin lesions and sclerosis were compatible with chronic GvHD. The skin findings regressed but were not resolved under cyclosporine-extracorporeal photopheresis. After 8 weeks of photopheresis treatment, it was reduced to two consecutive days, biweekly. Cyclosporine treatment was discontinued due to a high creatinine level, and low glomerular filtration rate. However, we could not discontinue immunosuppressive therapy due to the progressive skin lesions. We added ruxolitinib to the treatment. The skin lesions of our patient regressed under ruxolitinib treatment. There was no severe side effect except for mild hyperlipidemia. The initial dose of ruxolitinib was 5 mg twice a day (B.I.D), and this was increased to 10 mg B.I.D after being well-tolerated. In the 9th month of treatment, the dosage was decreased to 5 mg B.I.D due to hyperlipidemia and it was stopped at the end of the first year. Photopheresis treatment was reduced to two consecutive days monthly after four months, and discontinued after 10 months of the treatment. Over the following 5 months, there was no recurrence of GvHD. She was in complete remission from neuroblastoma after the two years of AHSCT.

Discussion

GvHD is a rare complication of post-AHSCT which especially affects the skin, gastrointestinal tract, and liver (1). It can be spontaneous or induced for antitumor response. There are some reports stating that spontaneous GvHD can be seen after AHSCT, especially in adults with multiple myeloma (1), but only a few reports in children (4). To the best of our knowledge, our case is the third pediatric case in the literature with GvHD after auto-HSCT due to neuroblastoma.

One of the ideas regarding the pathogenesis of GvHD after AHSCT is that some chemotherapeutics, which are used before transplantation, induce changes in regulatory T cell functions, leading to a failure in the development of self-tolerance (4). It has been reported that GvHD can be seen especially after using melphalan in the conditioning regimen (4). Our patient had received melphalan prior to HSCT, and so, for our case, this may be one of the causes of auto-GvHD. The other hypothesis for auto-GvHD is the transfer of maternal cells during the fetal development period and the presence of these cells in circulation resulting in microchimerism. Microchimerism can also be caused by blood transfusions (5). Our patient received many blood transfusions but transfusion-related GvHD was not considered as the blood products were transfused after irradiation and leukocyte filter.

The most common involvement in acute GvHD is skin involvement but gastrointestinal and liver involvement can be part of auto-GvHD as well. In our patient, transaminase levels were elevated after tacrolimus treatment. These returned to normal levels after stopping the treatment, so we thought that this was a side effect of tacrolimus, not liver GvHD. In a study by Hood et al. (6), skin involvement was detected in 8% of patients. The majority of these patients

did not require any treatment and the skin lesions were self-limited. Despite being mostly mild and self-limited, auto-GvHD can be severe or life-threatening (1). In our case, GvHD was severe, and refractory to steroid treatment. As she had new skin lesions and sclerosis during the treatment, we opted for tacrolimus/cyclosporine. Photopheresis treatment was started. However, we had to change the treatment because of some side effects due to tacrolimus and cyclosporine. The other effective agent for GvHD is ruxolitinib. There are some reports in the literature. One of these reports described a response rate of 100% in eight patients with GvHD (7). In another study evaluating its effect on childhood GvHD, the overall response rate was found to be 77% in acute, and 89% in chronic GvHD (7). Uygun et al. (8) reported on 29 pediatric patients with steroid refractory acute or chronic GvHD treated with Ruxolitinib, resulting in 82% and 80% response rates respectively. In May 2019, the FDA approved Ruxolitinib for the treatment of adult patients and pediatric patients aged 12 years or older with steroid refractory acute GvHD (9). However, there were no reports associated with Ruxolitinib treatment of autologous GvHD in children. We used Ruxolitinib with extracorporeal photopheresis due to significant side effects from other drugs. A good response was achieved.

In terms of treatment response, our patient was the first pediatric patient who received Ruxolitinib treatment in addition to photopheresis for auto-GvHD. Ruxolitinib can be preferred, especially in steroid-resistant cases, and it shows a good treatment response. Although our patient had severe GvHD, we think that the graft versus tumor effect also contributed to the remission of her primary disease.

Conclusion

It is important to keep in mind that GvHD may develop after AHSCT. Although the clinical findings of auto-GVHD are mild, and self-limited in most of cases, they can be severe and require intensive immunosuppressive treatment in rare cases. Ruxolitinib is an effective treatment for GvHD after AHSCT. Further studies and case reports are needed to understand the pathogenesis of this disease and to determine appropriate treatment.

Ethics

Informed Consent: Written consent was obtained from patient's family for this case.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.E., B.T.T., Ö.D., E.Ş., A.G.T., A.K., Design: N.E., B.T.T., Ö.D., E.Ş., A.G.T., A.K., Data Collection and/or Processing: N.E., B.T.T., Ö.D., E.Ş., A.G.T., A.K., Analysis and/or Interpretation: N.E., B.T.T., Ö.D., E.Ş., A.G.T., A.K., Writing: N.E., B.T.T., E.Ş.

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