

Graft-versus-host disease as an unusual complication following autologous stem cell transplantation

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Abstract

Introduction: Graft-versus-host disease (GVHD) is a common and serious complication after allogeneic stem cell transplantation (allo-SCT). However, a similar syndrome has been reported after autologous stem cell transplantation (ASCT) as well. Case report: A 61-year-old female diagnosed with immunoglobulin (Ig) G lambda multiple myeloma completed 10 cycles of bortezomib, thalidomide, and dexamethasone (VTD) and 2 cycles of cyclophosphamide, thalidomide, and dexamethasone (CTD). High-dose of melphalan (200 mg/kg) was given as conditioning, followed by an infusion of 2.5×10^6 CD34+ cells/kg. Three months later, she received her second ASCT. On Day +25 after tandem ASCT, the patient developed a maculopapular, itchy skin rash, which covered her face, trunk, and limbs. A skin biopsy was in line with the diagnosis of GVHD. The other organs were not involved. Treatment with systemic and local corticosteroids (CSs) resulted in the improvement of skin lesions, but the CSs were slowly tapered due to toxicity. In the following weeks, she developed symptoms of liver and gut involvement, which were resistant to steroids. The introduction of other immunosuppressive agents failed to achieve a response. As a consequence, she had cytomegalovirus (CMV) reactivation, as well as pancytopenia, and eventually, she died of infectious complications. Conclusions: GVHD after ASCT remains a rare but life-threatening complication with poor prognosis.

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Introduction

Graft-versus-host disease (GVHD) after autologous stem cell transplantation (ASCT) is a rare complication, but it can have a major impact on disease course and survival. Autologous GVHD is thought to occur in approximately 5% of transplanted patients [1]. Acute GVHD (aGVHD) is usually reported after allogeneic stem cell transplantation (allo-SCT) and is caused by donor T-cell recognition of recipients' minor histocompatibility antigens followed by organ-specific attack [2, 3]. However, in the context of ASCT, the pathomechanism of GVHD remains unclear. Malfunctioning of regulatory T-lymphocytes, leading to the creation of autoreactive T-cells as a result of hematological malignancy itself, remains one reliable explanation [4]. Another hypothesis suggests that some of the maternal cells transmitted during fetal development may persist in adult life, leading to microchimerism, which has been proved to be related to certain types of autoimmune diseases and might trigger GVHD [5]. Auto-GVHD can appear either spontaneously, without any previous immunosuppressive therapy [1, 6, 7], or be triggered by immunomodulatory drugs [8, 9], e.g., by cyclosporin A withdrawal, which is thought to be attributable to self-reactive CD8+ T-cells escaping apoptosis. It can affect only a single organ (e.g., skin or gastrointestinal tract) or may present with multiorgan involvements [1, 7, 10–15]. The differential diagnosis of auto-GVHD is difficult and requires the exclusion of other probable causes of the reported abnormalities. Although this pathology may easily be confused with other conditions, it is potentially curable if promptly and correctly diagnosed [11].

Herein, we report a case of severe acute auto-GVHD in a patient who underwent tandem ASCT for multiple myeloma (MM). In this case, the disease affected the skin, gut, and liver and was unresponsive to corticosteroids (CSs) and other immunosuppressants. No similar case has been reported in the Polish literature so far.

Case report

A 61-year-old female diagnosed with immunoglobulin (Ig) G lambda MM, International Staging System (ISS) = 1, standard cytogenetic risk group, completed 10 cycles of treatment with bortezomib, thalidomide, and dexamethasone (VTD) and 2 cycles of treatment with cyclophosphamide, thalidomide, and dexamethasone (CTD), achieving partial response a year later. Cytomegalovirus (CMV) serological status before the transplant was as follows: CMV IgM negative and CMV IgG positive. A total dose of 350 mg of melphalan (MEL) was given as conditioning, followed by her first ASCT (transplantation dose of 2.5×10^6 CD34+ cells/kg and 9.24×10^8 nucleated cells (NCs)/kg), with no serious complications. The patient regenerated and achieved normal blood count. Three months later, she received tandem ASCT due to the presence of partial response. The conditioning consisted of MEL 200. The total number of transplanted CD34+ and NC cells was 2.76×10^6 /kg and 13.83×10^8 /kg, respectively. On Day +5 post-ASCT, she developed fever. Chest X-ray findings, together with an elevated C-reactive protein (CRP) level, were suggestive of pneumonia. The introduction of empiric antibiotics and antifungal agents resulted in pneumonia resolution; however, the fever did not subside. Of note is

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that blood culture tests were negative. On Day +25 after ASCT, a diffuse, erythematous, maculopapular, and itchy skin rash covered her body. The appearance of skin lesions and physical examination were suggestive of cutaneous aGVHD. A skin biopsy revealed basal vacuolar degeneration and sparse inflammatory infiltration in the dermis, which was in line with the diagnosis of GVHD (Fig. 1, Fig. 2). At that time, the other organs were not involved. Treatment with systemic and local CSs resulted in the improvement of skin lesions, but the CSs were slowly tapered due to the occurrence of side effects. Furthermore, at Day +53 post-ASCT, a polymerase chain reaction (PCR) test revealed CMV reactivation with 77,000 copies/mL; thus, valganciclovir was used at a dose of 900 mg twice daily for 2 weeks. Within 2 weeks, CMV was eradicated, but she remained pancytopenic, probably due to the drug's myelosuppressive effect. At Day +100 following ASCT, the patient was urgently admitted with

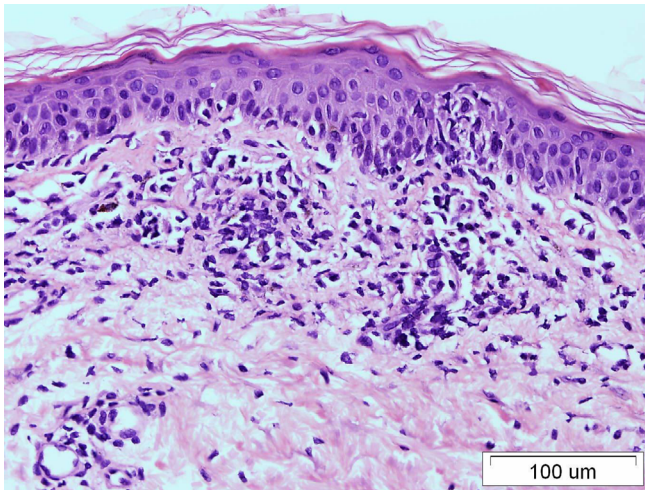


Fig 1. There are infiltrates of T-lymphocytes (CD3+) in the subepithelial layer of the dermis surrounding the extended small vessels. Focal vacuolar degeneration of the basal cell layer is also seen. Single eosinophilic degeneration in the subepidermal layer is seen (hematoxylin and eosin stain)

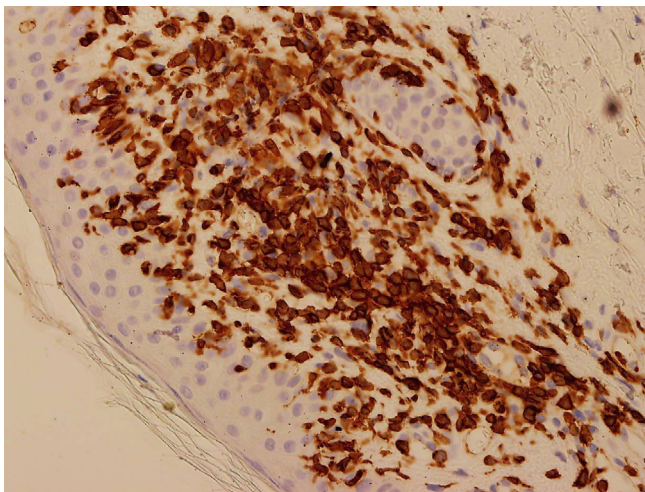


Fig.2. Anti-CD3 antibody immunostaining of the skin revealed the presence of T-cells in the subepithelial layer of the dermis

gastrointestinal symptoms presenting as persistent diarrhea (stools: 7 to 8 times/day), poor appetite, general weakness, and weight loss. Her skin became dry and peeling, with patches of pigmentation on the chest, abdomen, back, and limbs. Colon biopsy was not performed due to the patient's overall bad condition. CMV test by PCR was negative at that time. Immunosuppressive treatment consisting of methylprednisolone, mycophenolate mofetil, and tacrolimus was initiated; however, the disease persisted. A severe variant of steroid-resistant GVHD was diagnosed. As a consequence, second CMV reactivation was demonstrated (Day +110; copy number: 37,000/mL). Treatment with ganciclovir was initiated, but the patient showed deepening of her pancytopenia and became dependent on transfusion. Bone marrow examination revealed mild dysplasia. In the following months, the patient's general condition continued to deteriorate, and she finally expired due to infectious complications. Autopsy was not performed as the patient died in a local hospital.

Discussion

MM represents the most common indication for ASCT. Studies have shown that this procedure, in combination with high-dose chemotherapy, results in an improvement in complete remission (CR) rates and prolongs both progression-free survival (PFS) and overall survival (OS) [16, 17, 18]. Of note is that auto-GVHD occurs usually in patients undergoing transplantation for MM [7]. Interestingly, auto-GVHD was demonstrated in 5 out of 223 transplanted MM patients in the study reported by Drobyski et al. [7] but in none of the 136 patients who underwent ASCT for acute myeloid leukemia (AML), non-Hodgkin lymphoma (NHL), or Hodgkin disease. Batra et al. [15] described eight MM patients who developed auto-GVHD after ASCT. All these patients presented with skin rash; six of them had diarrhea, and three showed elevated levels of transaminases. It has been hypothesized that MM patients can become predisposed to the development of auto-GVHD through the dysregulation of the immune response resulting from the myeloma itself, prior treatment with immunomodulatory agents, or the conditioning regimen. It is postulated that newer drugs used for MM treatment, e.g., bortezomib or lenalidomide, can alter the regulatory T-cell function and trigger the overproduction of autoreactive lymphocytes, which could potentially lead to GVHD [5, 9]. Dhodapkar et al. [19] suggested that a higher percentage of Th17 cells in the bone marrow of MM patients, compared to the figure in patients with other monoclonal gammopathies, may predispose to the development of auto-GVHD in the former group. These Th17 cells participate in the pathogenesis of inflammatory autoimmune diseases and, therefore, may lead to auto-GVHD as a form of autoimmunity among susceptible patients [15, 19]. According to these data, it is of high importance to be aware of the risk of development of auto-GVHD, especially in MM patients. In contrast to allogeneic GVHD, auto-GVHD usually manifests in a milder form, and symptoms in most patients resolve spontaneously or respond to CSs [9, 14]. However, there have been reports suggesting that auto-GVHD can run a more severe course, being unresponsive to CSs particularly in MM patients [1, 6, 7, 15]. Batra et al. [15] reported six patients who did not respond well to CS treatment. In all the five patients mentioned in the study by Drobyski

et al. [7], response to CSs was unsatisfactory, indicating steroid-refractory GVHD. The patients underwent tandem transplantation, and three out of the five eventually died. The frequency of auto-GVHD after ASCT was estimated to be around 12% in patients who had undergone tandem transplantations, whereas it was only 1% in patients after a single procedure. It was speculated that repeated exposure to high-dose conditioning regimen within a short period of time may destabilize endogenous peripheral regulatory mechanisms, predisposing patients to autoimmunity [7]. One study demonstrates the negative impact of MEL on T-cell function and suggests that this effect might be amplified during the second transplant [6]. Hence, it seems that the number of prior autologous transplantations for MM may play a role in the development of this rare complication [7]. Moreover, the low number of CD34+ cells infused each time to the patient might also play an important role in the post-ASCT outcome. It might contribute to the pancytopenia and worsen the patient's immunity. It is well known that the development or exacerbation of GVHD favors the reactivation of CMV, e.g., due to the release of inflammatory mediators and by increasing immunosuppression. CMV reactivation in ASCT recipients remains a rare complication; however, it was seen in 11% of autotransplanted patients [20]. Returning to our case, analysis of CMV serological status by PCR was performed at the early onset of skin lesions; however, the clinical picture was suggestive for GVHD. Of note is that the cutaneous manifestation of CMV is extremely rare, with about 60 cases reported in the English literature so far. It usually presents as ulcers located in the perianal and genital regions, and the histological picture includes nuclear inclusions [21]. Such a manifestation was not demonstrated in our patient. CMV reactivation was also not detected at the time of occurrence of gastrointestinal symptoms, and therefore, CMV enteritis was not taken into consideration. It should be underlined that only PCR and histological examination performed on a colon biopsy would resolve this clinical dilemma. Auto-GVHD can manifest similar to GVHD after allogeneic transplantation [7, 12]. Cutaneous involvement has been reported to be the most frequent manifestation in auto-GVHD, followed by gastrointestinal tract involvement. However, among the nine cases of auto-GVHD reported by Lazarus et al. [9], involvement of the gastrointestinal tract predominated, while only one patient presented skin manifestations. The least frequently targeted organ was the liver [1, 9].

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Some disorders can mimic the pathological and clinical changes of the disease, and, therefore, be misleading, but GVHD cannot easily be distinguished without endoscopy and mucosal biopsy [9]. The differential diagnosis should take into account viral reactivation and side effects of administered drugs. Biopsy of affected organs remains a gold standard in GVHD diagnosis; however, it is not routinely performed.

Conclusions

GVHD is an extremely rare complication after autologous transplantation; the treatment does not differ from that for patients after allo-SCT, and the general prognosis is usually poor when the disease is steroid refractory. Early recognition of auto-GVHD symptoms is of high importance for the prompt initiation of appropriate treatment and the avoidance of potentially life-threatening consequences.

Authors' contributions

MW – collected data and wrote a manuscript. AW, KW – collected data. MT – collected data and provided a microscopic image. AWK, DK – collected data, critical revision. GH – co-wrote a manuscript, critical revision.

Conflict of interest

The authors have no competing interest.

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Not applicable.

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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