



## Autologous Graft Versus Host Disease: An Updated Review

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### Abstract

Graft versus host disease is an increasingly recognized complication of autologous hematopoietic stem cell transplantation. It may occur spontaneously, but can be induced by a number of immunosuppressive agents. There are specific risk factors for the evolution of this complication. Clinically and histologically, it resembles graft versus host disease occurring after allografting. It varies in severity from mild and self limited illness to severe forms that may become life-threatening. Early recognition and prompt institution of immunosuppressive therapy are essential to prevent further complications.

**Keywords:** Graft versus host disease; Hematopoietic stem cell transplantation; Graft versus tumor effect; Engraftment syndrome; Immunosuppressive therapy

### Introduction

Graft Versus Host Disease (GVHD), that has Graft Versus Tumor (GVT) effect, is a major complication of allogeneic Hematopoietic Stem Cell Transplantation (HSCT) which is associated with significant morbidity and mortality [1-5]. GVHD in allogeneic HSCT is attributed to donor T cell recognition of recipient alloantigens which results in the generation of cytotoxic effector cells and the production of proinflammatory cytokines [1,4]. The higher relapse rates encountered after autologous HSCT compared with allogeneic HSCT were previously attributed to the lack of GVT effect following autologous HSCT [6,7]. However, recent as well as old studies argue in favor of the existence of autologous GVT effect without the detrimental complications of GVHD that follow allogeneic HSCT [6,8,9-11].

GVHD is an autoimmune complication of HSCT [12]. The recent increase in the number of studies reporting the clinical manifestations and the histological appearances as well as the responses to immunosuppressive therapies prove the existence of GVHD in the setting of autologous HSCT [1,3,4,13-22].

### Landmarks in the history of autologous GVHD

Autologous GVHD has also been called: secondary disease, Omenn syndrome and autoaggression syndrome [13,19,23-26]. In 1951, Lorenz first described secondary disease; manifested by diarrhea, weight loss and coat changes; in lethally-irradiated mice receiving Bone Marrow (BM) and spleen cell transplants [13]. In 1955, Main and Prehn reported secondary disease in mice, when BM and spleen cells from a parent were injected into unirradiated F1 hybrid but not in the converse [13]. In the late 1970s, Rapoport reported the occurrence of GVHD in humans following syngeneic BM transplantation which prompted exploration of the biological mechanisms underlying this phenomenon [2].

In 1987, Hood retrospectively noted the onset of spontaneous autologous GVHD in 7 out of 96 recipients of autologous HSCT between 1977 and 1984 [2,27]. Most of the cases reported were mild, self-limited and all were confined to the skin. A minority of patients required treatment with topical or systemic corticosteroids [2]. Glazier in 1983 and Geller in 1989 developed preclinical transplantation models of autologous HSCT using cyclosporine-A to induce GVHD in the autologous HSCT setting [2,12]. In 1988, Jenkins and Gao demonstrated that while cyclosporine-A greatly reduced the number of mature CD4+ and CD8+ T cells, cyclosporine-treated mice harbored CD8+ T cells with T cell receptor specific for Human Leukocyte Antigen (HLA) class II antigens concluding that cyclosporine therapy impaired central tolerance [2]. In the year 2000, Borrello demonstrated that additional tumor specific antigens may play a role in the development of autologous GVT mechanisms using a syngeneic transplantation model [2]. In 2009, Paczesny described a biomarker panel associated with the clinical and pathological diagnosis of acute GVHD in the setting of allogeneic HSCT that included elevation of serum concentrations of: interleukin

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(IL)-2R $\alpha$ , interferon-R1, hepatocyte growth factor and IL-8 [13]. Lastly in 2011, Brandon found that antibiotic therapy of mice before syngeneic transplants with cyclosporine prevented the development of clinical and pathological features of acute GVHD that occurred when antibiotics were administered [13].

### Epidemiology and incidence of autologous GVHD

Studies have shown that: (1) the incidences of spontaneous and induced GVHD following autologous HSCT are 5%-20% and 20%-100% respectively, (2) the incidences of spontaneous intestinal and skin autologous GVHD are 13% and 5%-10% respectively, and (3) the frequency of autologous GVHD induced by cyclosporine or IL-2 ranges between 30% and 80% [2,3,14]. The incidence of autologous GVHD following peripheral stem cell transplantation is lower than that following BM transplantation and this lower incidence may be attributed to peripheral regulatory cells that are transferred to the stem cell inoculum [26].

### Etiology and pathophysiology of autologous GVHD

After syngeneic or autologous HSCT, a GVHD-like syndrome which is clinically and histologically indistinguishable from allogeneic GVHD has been described in the skin, liver and gastrointestinal tract (GIT) [3]. Autologous GVHD is an autoimmune syndrome initiated by auto-reactive T cells that recognize self-major histocompatibility complex (MHC) class II antigens [5,28-30]. In autologous GVHD, autoreactive CD8 $^+$  T cells recognize MHC class II determinants in association with a peptide from the invariant chain [31]. Also, the discrete antigen-driven expansion of T cells is involved in autologous GVHD [32].

The etiology of syngeneic and autologous GVHD is not well understood, but there are two hypotheses: (1) dominance of autoreactive T cells post-transplantation, and (2) presence of microchimeric or allogeneic T cells [3]. However, microchimerism can be established in two ways: (1) women have higher frequency of microchimerism than men as a result of passage fetal cells into maternal circulation during pregnancy, and (2) blood transfusion [3]. Recent studies have indicated that 2 major factors are necessary for the induction of autologous GVHD: (1) disruption of thymic-dependent immune reconstitution, and (2) failure to reestablish peripheral self-tolerance [19].

In Multiple Myeloma (MM), the predisposing factors for autologous GVHD may include dysregulation of immune response resulting from either the disease, or the immunomodulatory drugs that are used in the treatment of MM or the HSCT conditioning therapy [33]. Polymorphisms in the IL-10 promoter region may explain differences in the susceptibility of patients to autologous GVHD. Additionally, IL-10 and interferon- $\gamma$  may be critical mediators for the development of autologous GVHD [31]. The association between autograft absolute lymphocytic count (ALC) on day 15 following autologous HSCT and survival further supports the existence of GVHD following autologous HSCT [6]. Induction of autologous GVHD may also be beneficial to recipients of autologous HSCT by providing GVT effect thus aiding the elimination of minimal residual disease after autologous HSCT [30,34,35].

### Types of Autologous GVHD

There are three types of autologous GVHD: (1) spontaneous autologous GVHD [15,16,36-38], (2) induced autologous GVHD; using cyclosporine, tacrolimus, interferon- $\alpha$ , interferon- $\gamma$  and alemtuzumab; in order to induce GVT effect in diseases such as:

Hodgkin lymphoma, Non-Hodgkin Lymphoma (NHL), chronic lymphocytic leukemia and acute myeloid leukemia [14,23,26,28-31,34,36,39-41], and (3) GVHD induced by transfusion of unirradiated blood products [36].

### Risk factors for spontaneous autologous GVHD

The following factors predispose to the development of spontaneous GVHD following autologous HSCT: (1) primary disease such as MM, NHL and breast cancer, (2) second autologous HSCT, (3) heavily pre-treated patients, (4) female gender, (5) high CD34 $^+$  stem cell dose infused, (6) achievement of high levels of ALC after autologous HSCT, and (7) the use of bortezomib, lenalidomide, pomalidomide and alemtuzumab in the pre-transplantation therapies of hematological malignancies [1,3,4,8,9,15-18,20,24,27,33,35-38,42-44].

### Clinical manifestations of autologous GVHD

Autologous GVHD may present with: fever, erythematous skin eruption, liver dysfunction, nausea, vomiting, diarrhea, non-cardiogenic pulmonary edema and clinical features consistent with bronchiolitis obliterans organizing pneumonia (BOOP) [9,15,16,27,36,42]. The clinical manifestations of autologous GVHD are very variable. They may be mild and self-limited, moderate requiring immunosuppressive therapies or severe and life-threatening with partial or total unresponsiveness to treatment leading ultimately to organ failure and death. Also, autologous GVHD can be limited to one organ or it may involve multiple organs in either a subsequent or simultaneous manner [8,16-18,24,43-45].

In autologous GVHD, the following body organs are particularly involved: skin, GIT, liver, lungs and kidneys [1,3,15,19,20,22,23,27,34,36,37,42,43]. Autologous GVHD may be acute, chronic or recurrent, thus all forms of GVHD can occur following autografting [4,15,21,22,37,38,42,46]. Studies have shown that autologous GVHD may be: (1) limited to one body organ or can involve multiple organs simultaneously [1,8,16-18,22,38,42,43,47] and (2) variable in severity from mild and self-limited that requires no treatment or local therapy to severe, steroid-refractory and life-threatening forms [1,3,4,15-17,24,36,37,42,43,47].

Skin involvement can be in the form of maculopapular eruption, diffuse erythema, desquamation, sclerodermatous changes or chronic lichenoid eruptions [1,16,21,46,47]. The following histological changes have been reported: dermatitis, cell necrosis, intra-epidermal pustules, proliferation of collagen bundles in the dermis, infiltration by lymphocytes and eosinophils in addition to lichenoid skin changes [1,16,21,46,47]. The clinical manifestations of GIT involvement include: anorexia, nausea, vomiting, heartburn, dysphagia, abdominal pain and diarrhea [1,3,4,16-18,20,22,45]. Histologically, the following findings have been encountered in autologous GVHD: mucosal inflammation, ulcerations and hemorrhage; apoptotic crypt cells and crypt abscesses; infiltration by lymphocytes, eosinophils and mononuclear cells; and fibrotic changes [1,3,4,16-18,20,22].

Autologous GVHD of the liver causes liver dysfunction and abnormal hepatic profile with biochemical evidence of elevation of serum levels of alkaline phosphatase, gamma glutamyl transferase, alanine aminotransferase and bilirubin and histological evidence of non-specific infiltration by lymphocytes and neutrophils in the portal areas [1,16,17]. Although lung involvement is rare in autologous GVHD, clinical manifestations such as dyspnea, productive cough, increasing respiratory distress and even respiratory failure have

been reported [27,42]. The following radiological abnormalities have been encountered: bilateral interstitial pulmonary infiltrates, multiple nodular lesions, bronchiolitis, bronchiectasis and tree in bud radiological appearances. In patients with BOOP syndrome, pulmonary function tests usually show mixed obstructive and restrictive ventilator defects [27,42]. Lung biopsies in patients with autologous GVHD have shown: apoptosis, perivasculitis, T cell infiltration, perivascular lymphocytic cuffing and bronchiolar lymphocytic infiltration [27]. Kidney involvement by autologous GVHD may present with proteinuria and renal dysfunction. Histologically the following changes have been reported: immune-mediated glomerulonephritis, deposition of immune complexes and membranous nephropathy [19]. Other rare clinical and laboratory features that have been reported in patients with autologous GVHD include: fever, variable degrees of BM suppression, thinning and ridging of nails in addition to onycholysis [17,45].

### Biomarkers of autologous GVHD

The following laboratory abnormalities, which can be used as biomarkers, have been reported in patients with autologous GVHD: (1) lower CD3 and CD8 cell counts, (2) peripheral eosinophilia associated with eosinophilic GIT involvement secondary to elevated serum levels of IL-2, IL-4 and IL-5, (3) enhanced expression of GATA-2, CD130 and CXCR4 on CD34+ hematopoietic progenitor cells on flow cytometry, (4) profound FOXP3 regulatory T cell defect coinciding with hyper inflammatory T cell responses that are reversible by rapamycin administration, and (5) expression of HLA-B55 [15,20,25,33].

### Diagnosis and differential diagnosis of autologous GVHD

The diagnosis of autologous GVHD of the GIT can be established when the following criteria are met: (1) ongoing GIT symptoms consistent with GVHD, (2) macroscopic evidence of abnormal mucosa of stomach, duodenum or colon on upper or lower endoscopy, (3) histological evidence of apoptosis or lymphocytic infiltration, and (4) negative viral, bacterial and fungal cultures for pathogens in stools, mucosal brushings or tissue biopsies [3]. The differential diagnosis of autologous GVHD includes: (1) infections such as cytomegalovirus, herpes simplex virus, adenovirus and enteroviruses, (2) medications such as chemotherapeutic agents; immunosuppressive therapies such as cyclosporine, tacrolimus and mycophenolate mofetil; non-steroidal anti-inflammatory drugs and laxatives, (3) engraftment syndrome, (4) transfusion-associated GVHD, and (5) pre-existing inflammatory bowel disease or coeliac disease in patients with GIT manifestations [4,36]. Thus, the diagnosis of autologous GVHD requires: (1) clinical suspicion, (2) ruling out other differentials such as infections, drug effect and engraftment syndrome, (3) performance of biopsies of skin, liver, GIT and lungs, and (5) having biomarkers of GVHD [1,4,13,48].

### Management of autologous GVHD

The main lines of therapy of autologous GVHD are: (1) symptomatic treatment, (2) corticosteroids, and (3) other immunosuppressive therapies [1,4,15,20]. However, autologous GVHD can occasionally be severe and refractory to steroid treatment and may eventually cause death [1,4].

In most cases of autologous GVHD, spontaneous resolution occurs as the condition is mostly mild and self-limited [14,17,46]. In some cases topical or local therapy such as topical steroids for skin involvement or non-absorbable steroids for lower GIT involvement

may be required [15,36,37,42]. In moderately severe cases, systemic corticosteroids in the form of oral prednisolone 1 mg/kilogram (kg) body weight/day or intravenous methylprednisolone 2 mg/kg/day in 2 divided doses may be needed for one week or even longer period of time then steroid therapy can be gradually tapered once clinical improvement is encountered [15,22,28,42-44,47]. Occasionally, prolonged corticosteroid therapy may be needed for patients who are not totally refractory to steroid therapy [24]. Also, autologous GVHD in some patients may be refractory to corticosteroids and such patients may develop organ dysfunction or failure and may eventually die [1,4,16,17]. However, other lines of therapy have been reported and these include: infliximab, alemtuzumab, rituximab, etanercept, rapamycin and hemicolectomy for refractory GIT forms of autologous GVHD [4,19,25].

### Course and prognosis of autologous GVHD

The course of the disease is very variable and ranges from mild and self-limiting illness to severe forms which may require prolonged corticosteroid therapy or other more aggressive lines of treatment and the illness may even become life-threatening [1,4,14-17,19,22,24,25,28,36,37,42-44,46,47]. So, the prognosis largely depends on the: (1) severity of the illness, (2) grade of the GVHD, (3) number of organs involved, and (4) rapidity of initiation of therapy [1,4,20,45]. Prompt recognition of autologous GVHD is essential in order to prevent further complications [15,20,22,45].

### Conclusions and Future Directions

GVHD is a well established complication of autologous HSCT. It resembles GVHD which is encountered following allogeneic HSCT clinically, biochemically, radiologically and even histologically. Also, it responds to corticosteroids and other immunosuppressive therapies. It is essential to establish its existence clinically and histologically, have biomarker panels taken at presentation, and to document not only its severity scores but also its response criteria.

As this complication has certain risk factors and favorable response to immunosuppressive therapies, it is vital to have early recognition of autologous GVHD and prompt institution of treatment in order to prevent further complications.

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