Review Article

Overview of Graft-Versus-Host Disease with Emphasis on the Pathogenesis of Autologous Graft-Versus-Host Disease

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Abstract

Graft-versus-host disease is a common complication following allogeneic hematopoietic stem cell transplantation that manifests with injury to the gastrointestinal mucosa, skin, and liver. A clinically and histologically indistinguishable graft-versus-host-disease-like syndrome has been described following autologous stem cell transplantation. The current pathogenesis is attributed to the lymphoablative preparative regimen. This regimen compromises thymic function, eliminates the T lymphocyte-dependent regulatory system, and provides a permissive environment for the activation of autoreactive T lymphocytes with subsequent tissue damage. Although the clinical and histological features are practically indistinguishable from allogeneic graft-versus-host disease, the role of eosinophils and neutrophils in the gastrointestinal histopathology has initiated some discussion. These features can be mimicked by other etiologies in the differential diagnosis. Autologous graft-versus-host disease is typically mild and responds well to corticosteroid treatment, but severe cases showing resistance to corticosteroid treatment have been described in patients receiving autologous stem cell transplantation for plasma cell myeloma. This controversial type of graft-versus-host disease is an active area of investigation.

Keywords: Hematopoietic Stem Cell Transplantation; Autologous Graft-Versus-Host Disease; Eosinophils

Abbreviations

GVHD: Graft-Versus-Host Disease;
HSCT: Hematopoietic Stem Cell Transplantation;
CsA: Cyclosporine;
MHC: Major Histocompatibility Complex;
CLIP: Class II Invariant Chain Peptide;
IL-2: Interleukin-2;
IL-4: Interleukin-4;
IL-5: Interleukin-5;
IL-10: Interleukin-10;
IFN-γ: Interferon-γ;
TNF-α: Tumor Necrosis Factor-α;
TGF-β: Transforming Growth Factor-β;
TCR: T-Cell Receptor;
SEB: Staphylococcal Enterotoxin B;
Vβ: Variable β;
HPF: High-Powered-Field

Introduction

Graft-versus-host disease [GVHD] is a common complication following hematopoietic stem cell transplantation [HSCT] that serves as a leading cause of morbidity and mortality in the transplant patient population and often involves the gastrointestinal tract, skin, and liver [1]. GVHD is a frequent complication that has typically been seen following allogeneic HSCT; however, in the more recent literature, a clinically and histologically indistinguishable GVHD-like syndrome has been described following autologous stem cell transplantation [2,3]. Patients who receive allogeneic HSCT develop GVHD about 50%-70% of the time [4]. Autologous GVHD of spontaneous onset has been described to affect only 5%-20% of patients. The rate increases to 30%-80% in autologous HSCT patients who have received induction with cyclosporine-based therapies or interleukin-2 [IL-2] [2-4].

Autologous GVHD is a paradox that mainly involves the skin with only about 4%-13% of autologous GVHD patients' developing gastrointestinal GVHD, which predominantly involves the upper gastrointestinal tract [1,5-7]. Most cases of autologous GVHD develop in patients who have undergone an intensive bone marrow transplant conditioning regimen because this intensive conditioning is necessary for the induction of thymic dysfunction, a key component in the initiation of autologous GVHD. Autologous GVHD is due to an imbalance between the autoreactive and autoregulatory lymphocyte subsets [5]. Autologous GVHD can have liver involvement; however, liver involvement in this entity is very rare [4,7]. The classical histological features involve apoptotic crypt epithelium, lymphocytic aggregates, crypt dropout, and focal lymphocytic infiltration of crypt epithelium [2]. Some studies have discussed the role and predictive value of eosinophils in autologous GVHD of the gastrointestinal tract [8]. Most cases of autologous GVHD are successfully treated with corticosteroids and have a good prognosis, but some cases are more severe with the development of resistance to corticosteroid therapy [2,6,7].

This review discusses an overview of the clinical features, pathogenesis, histopathology, differential diagnoses, known treatments, and prognosis of GVHD. Emphasis is placed on autologous GVHD and its pathogenesis, since this is a fairly recent addition to conventional GVHD and an active area of investigation. This entity has been a subject of controversy and has encountered a considerable amount of skepticism, since it challenges a universally accepted concept that the donor and host must have histocompatibility differences to induce GVHD. Several human and animal studies have been conducted to evaluate the pathogenesis of autologous GVHD [9].

Clinical Features

Since being reported in 1987, autologous GVHD has been described as a self-limited syndrome that follows a milder clinical course than in the setting of acute GVHD in allogeneic HSCT [4,5,7,10]. When comparing the various patient populations who undergo autologous HSCT, a higher incidence of autologous GVHD has been noted in patients with plasma cell myeloma than in patients with other hematopoietic malignancies. Studies show the risk of developing autologous GVHD increases in plasma cell myeloma patients who receive tandem autologous HSCT (12%) compared to those undergoing single autologous HSCT (0.9%) [4,8].

Autologous GVHD can affect the three target organ systems of the skin, gastrointestinal tract, and liver. Acute cutaneous GVHD is the most common clinical manifestation and presents as a maculopapular or pruritic rash. The second most common clinical manifestation is as gastrointestinal GVHD, and this presents with profuse, watery diarrhea; nausea and vomiting; abdominal cramping; and mucosal

bleeding [1,4,7]. Involvement of the liver is uncommon; however, when autologous GVHD affects the liver, then the clinical manifestations are an elevated bilirubin, a mildly elevated alanine aminotransferase and aspartate aminotransferase, and an elevated alkaline phosphatase that is typically greater than two times the upper limit of normal [4,7].

There are two common clinical scenarios surrounding the development of autologous GVHD in HSCT recipients. One is when the disease is intentionally induced by withdrawing cyclosporine in attempts to stimulate a graft-versus-leukemia response to develop an environment of autoimmunity. In this instance, the pathological mechanism, which has been extensively studied, is attributable to the presence of self-reactive, CD8+ T lymphocytes. The second scenario occurs when autologous GVHD develops spontaneously in the absence of any previous immunosuppressive therapies. The pathophysiology of spontaneous autologous GVHD is not as well studied and is less well understood [7].

Pathogenesis

Over the past 15-20 years, several human and animal studies have evaluated the complex immunobiology of autologous GVHD [11]. In the initial studies, there are two major factors in the induction of autologous GVHD. These factors are "thymic-dependent immune reconstitution and the failure to re-establish peripheral self-tolerance," which lead to a dysregulation of the reactivity to self by both central and peripheral mechanisms [11]. Once thymic function is compromised, then the body fails to delete autoreactive T-cells. The autoreactive T-cells then are transported to the periphery where they can become activated, if a "permissive environment" exists. Due to the lymphoablative preparative regimen that is used prior to autologous HSCT, the T-cell-dependent peripheral regulatory system is eliminated, which allows the autoreactive T-cells to undergo activation in the periphery. Thus, autologous GVHD can ensue and cause tissue damage (Figure 1) [11].
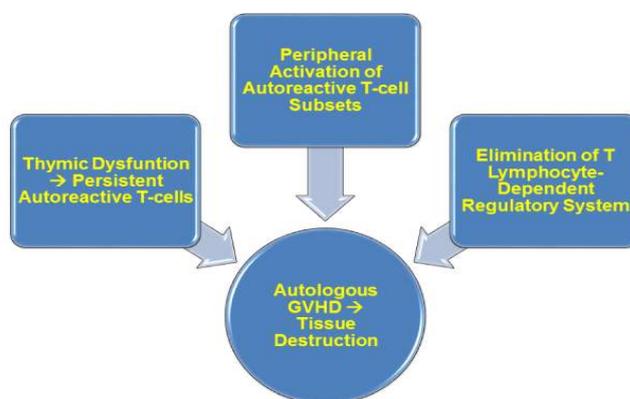

Figure 1. Broad summary of the pathogenesis of autologous GVHD following the effects of a cyclosporine-dependent preparative

regimen – data derived from [11]

A principle component behind autologous GVHD is the failure of thymic mechanisms in the clonal deletion of autoreactive T-cells, which is a central mechanism for the prevention of autoaggression [11]. Initial studies discuss how the preparative regimen for autologous bone marrow transplantation can damage the thymic epithelium, which compromises the thymic mechanisms for deleting autoreactive T-cells [11]. Following autologous HSCT, an immunosuppressive drug known as cyclosporine [CsA] is administered. Studies demonstrate that this drug directly inhibits the thymic-dependent, clonal deletion of autoreactive T lymphocytes. The key role of the thymus in the induction of autologous GVHD is established after animal studies reveal that HSCT recipients that have been thymectomized prior to transplantation do not develop autologous GVHD. Thus, when the thymus fails to delete autoreactive T lymphocytes, these T-cells are exported to the periphery where they undergo activation and lead to autoaggression [11].

Later animal studies evaluate antigen-specific, autoreactive T lymphocytes during both the acute and chronic phases of autologous GVHD [13]. These studies identify two major subsets with overlapping specificity for the MHC class II-binding domain of CLIP. The autoreactive T lymphocyte subsets are differentially dependent on the CLIP N-terminal and C-terminal flanking domains that extend beyond the MHC class II peptide-binding groove. These subsets of the autoreactive T lymphocytes also have distinct cytokine profiles [13]. The N-terminal, CLIP-autoreactive T-cells are associated with the predominant expression of type I cytokines: interferon-γ [IFN-γ], interleukin-2 [IL-2], and tumor necrosis factor-α [TNF-α]. The C-terminal, CLIP-autoreactive T-cells are associated with the predominant expression of type II cytokines: interleukin-4 [IL-4], interleukin-10 [IL-10], and transforming growth factor-β [TGF-β] [11,13]. The N-terminal T-cell subset is primarily increased in acute autologous GVHD while the C-terminal T-cell subset is the predominant subset in chronic autologous GVHD (Table 1) [12].

Table 1. Summary of autoreactive T-cell subsets and cytokine profiles noted in acute and chronic autologous graft-versus-host disease – data derived from [13].

Autologous GVHD Type	Predominant CLIP–Autoreactive T–Lymphocyte Subset	Predominant Cytokine Type Expressed	IFN–γ and TNF–α Expression T-cell Subsets	IL-2 Expression T-cell Subsets	IL-4 Expression and TGF-β T-cell Subsets	IL–10 Expression T-cell Subsets
Acute	N-terminal restricted	Type I	**N-terminal** Increased **C-terminal** Low Expression	**N-terminal** Increased **C-terminal** Low Expression	**N-terminal** No Expression **C-terminal** No Expression	**N-terminal** Low Expression **C-terminal** Low Expression
Chronic	C-terminal restricted	Type II	**N-terminal** Low Expression **C-terminal** No Expression	**N-terminal** Low Expression **C-terminal** Low expression	**N-terminal** No Expression **C-terminal** Increased	**N-terminal** Low Expression **C-terminal** Increased

Note: GVHD = Graft-versus-host disease; IFN = interferon; IL = interleukin; TNF-α = Tumor Necrosis Factor-α; TGF-β-Transforming Growth Factor-β

Autoaggression in autologous GVHD is primarily mediated by a restricted group of autoreactive T-cells that recognize antigens on the major histocompatibility complex [MHC] class II. Animal and human studies reveal that "promiscuous" recognition of MHC class II antigens by the autoreactive T-cells is dependent upon the presentation of the class II invariant chain peptide [CLIP] [11,12]. The biosynthesis of MHC class II is shepherded by the invariant chain. When the MHC class II molecule is transported to the surface of the cell, the invariant chain undergoes enzymatic degradation and leaves CLIP in the peptide-binding domain. The broad specificity of the autoreactive effector T-cells seems to be governed by the functional interaction of the N-terminal domain of CLIP with the variable β [Vβ] chain of the α/β T-cell receptor [TCR] in close proximity to the Staphylococcal enterotoxin B [SEB] super antigen binding site on the Vβ chain [11,12].

Additional studies evaluate the changes in the cytokine expression levels of the N-terminal and C-terminal, CLIP-autoreactive T-cell subsets during acute and chronic autologous GVHD. During acute autologous GVHD, the N-terminal T-cell subset has significant expression levels of IFN-γ and IL-2 with lower-level expression of IL-10; however, during chronic autologous GVHD, expression of IFN-γ and IL-2 is decreased. In contrast, during acute autologous GVHD, the C-terminal T-cell subset only has low-level expression of IFN-γ and IL-2. During chronic autologous GVHD, the cytokine profile of the C-terminal T-cell subset shows no expression of IFN-γ with marked expression of IL-10 and interleukin-4 [IL-4] [12] (Table 1). Additional studies have shown that the N-terminal-restricted T-cell subset can induce histological changes of acute autologous GVHD while the C-terminal-restricted T-cell subset can downregulate type 1 cytokine expression and

induce pathological changes such as fibrosis, which can be seen in chronic autologous GVHD [13]. Based on the cytokine profile and histological studies of the autoreactive T-cell subsets, acute autologous GVHD is associated with N-terminal-restricted, CLIP-autoreactive T lymphocytes, which are type 1 (e.g. IL-2, IFN-γ, TNF-α) cytokine-producing cells. The C-terminal-restricted, CLIP-autoreactive T lymphocytes, which are type 2 (e.g. IL-4, IL-10, TGF-β) cytokine-producing cells are involved in the down regulation of the type 1 cytokines and lead to the progression and development of chronic autologous GVHD [13]. These studies provide insights into the network of effector mechanisms involving the CLIP-autoreactive T-cell subsets and their association with autologous GVHD, which is still an active area of research [13].

Although the inhibition of clonal deletion within the thymus and the export of autoreactive T lymphocytes to the peripheral tissues are critical initial events in the pathogenesis of autologous GVHD, the activation of the autoreactive T-cell subsets cannot occur and lead to manifestation of autoaggression without a "permissive environment" [11]. This is true because healthy organisms have a T-cell-dependent peripheral regulatory mechanism that controls development of autologous GVHD, and the T-cell-dependent regulatory system is in place to control the activity of potentially autoreactive T lymphocytes that escape central deletion by the thymus [11]. When the T-cell-dependent regulatory system is eliminated by the lymphoablative preparative regimen, a "permissive environment" for autoreactive T-cell activation and subsequent target tissue damage is created. Autologous GVHD cannot resolve without the reconstitution of the peripheral regulatory system, which is necessary for downregulating the autoreactive T-cells, and the recovery of the regulatory T-cell system can only occur once cyclosporine is discontinued [11].

Histopathology

The target organ damage of autologous GVHD has mainly affected the skin with only about 4%-13% of autologous GVHD patients developing gastrointestinal GVHD, which predominantly has affected the upper gastrointestinal tract [1,5-7]. Autologous GVHD can also manifest with liver involvement, but significant liver injury rarely occurs [4,7]. The histological features of autologous GVHD have been well documented. However, when autologous GVHD is suspected at an earlier stage of development, the morphological features can be very subtle, particularly in the setting of autologous gastrointestinal GVHD [1].

Classically, epithelial cell apoptosis, which is also known as "crypt cell degeneration," has emerged as the histopathological hallmark of acute autologous GVHD of the gastrointestinal tract [1]. These apoptotic cells demonstrate karyorrhectic debris within intracytoplasmic

vacuoles and are known as "exploding crypt cells" (Figure 2A) [1]. When looking at the surrounding lamina propria, a sparse inflammatory infiltrate composed predominantly of lymphocytes is seen. Neutrophils and eosinophils can be noted as well [1]. Apoptotic bodies may be the only notable feature in mild cases of gastrointestinal autologous GVHD. In severe cases, glandular or cryptic cystic dilatation with regenerative epithelium, obvious epithelial destruction, and crypt abscesses with neutrophils and eosinophils can be seen [1]. In the Cogbill et al. [3] study, most of the autologous GVHD gastrointestinal biopsies show similar histopathology to that seen in allogeneic GVHD. Therefore, many pathologists grade autologous GVHD using the following grading system for allogeneic GVHD: "Grade 1 = isolated apoptotic epithelial cells without crypt loss; Grade 2 = individual crypt loss; Grade 3 = contiguous area of multiple crypt loss; Grade 4 = extensive crypt dropout with denudation of epithelium" [3]. However, the Cogbill et al. [3] group mentions that autologous GVHD has subtle histological differences from allogeneic GVHD. These subtle changes are "dilated, damaged crypts and mucosal hemorrhage" [3]. More studies are needed to decide whether or not the commonly accepted allogeneic GVHD histological grading scheme can be used interchangeably in cases of autologous GVHD [3].

There has been recent discussion in the literature about the importance of the myeloid lineage cells in gastrointestinal autologous GVHD, particularly eosinophils and neutrophils [14-18]. In the Daneshpouy et al. [16] study, tissue eosinophilic infiltration is noted in 52.9% of upper gastrointestinal tract autologous GVHD cases in a study series of duodenal biopsies [16]. The eosinophils are within the lamina propria, as well as invading into the crypt epithelium. The Daneshpouy et al. [16] group also discusses that there is a direct correlation between the density of eosinophils within the lamina propria and the severity of gastrointestinal autologous GVHD (Figure 2B) and [1,8, 15-17]. This group claims that the density of tissue eosinophils has the potential to be useful as markers of inflammatory activity present within gastrointestinal autologous GVHD [16]. A study by Socié et al. [17] looks at the number of lymphocytes and inflammatory cells infiltrating the lamina propria, and the study demonstrates an association with an increase in early transplant-related mortality when greater than 20 neutrophils per high-powered-field [hpf] are present [17]. Chen and Olson [18] propose that an early manifestation of autologous colonic GVHD may be a peripheral blood eosinophilia with an associated eosinophilic infiltrate within the gastrointestinal tract secondary to increased levels of IL-2, IL-4, and interleukin-5 [Il-5] [18]. These studies and observations in the literature support that the myeloid lineage probably has an important role in the pathogenesis of autologous GVHD, [14-18] but this needs to be further studied.
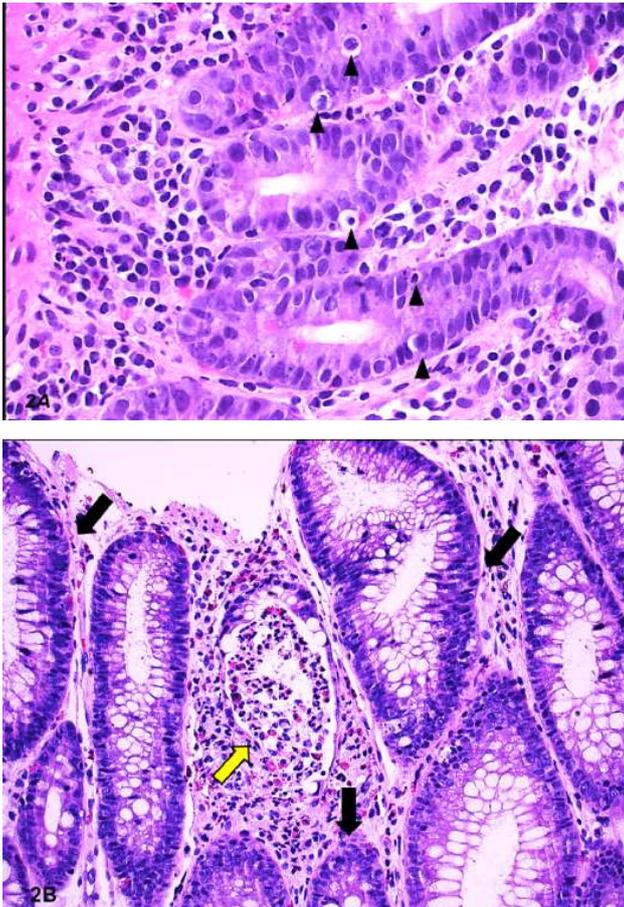
Figure 2. Histologic changes of acute graft-versus-host disease [GVHD] in the gastrointestinal tract. A. Apoptotic bodies (black arrowheads) are present in the crypt epithelium (Hematoxylin and Eosin; 400x magnification). B. Several crypts are present with marked damage and reactive epithelial changes (black arrows), as well as eosinophils and neutrophils in the lumen of the central crypt (cryptitis) (yellow arrow) (Hematoxylin and Eosin; 200x magnification). (Original Images: Benjamin H. Durham, M.D. and Mingyi Chen, M.D., Ph.D)

There are histological differences to autologous GVHD seen in various portions of the tubular gastrointestinal tract. The apoptotic cells within the stomach tend to be smaller and less conspicuous than within the large intestine, and the gastric body typically shows apoptotic bodies within the glandular neck regions. The antrum shows the apoptotic bodies within the deeper glands. Regarding the duodenum or small intestinal sites, subtle villous blunting can be noted with apoptotic bodies within the neck and deep crypts [1]. Also, pericapillary hemorrhage within the small intestine has been associated with severe autologous GVHD. When evaluating the large intestine, many do not embrace isolated, epithelial surface apoptotic bodies as diagnostic of GVHD due to the mimicry of these features by bowel preparatory regimens [1].

Autologous GVHD can also initiate histopathological changes to the liver; however, hepatic GVHD following autologous stem cell transplant is very uncommon. The Saunders *et al.* [19] group reviewed 116 autologous HSCT cases. Out of these 116 patients, only 2 patients develop hepatic GVHD. The study authors consider the liver biopsy histology typical for hepatic GVHD when the biopsy demonstrates a cholestatic injury pattern with apoptosis and dysmorphic changes to the small bile ducts. The enlarged portal tracts contain a predominance of lymphocytes and fibrous connective tissue with ductule proliferation [19]. Dyspolarity, compressed lumina, and nuclear dropout are also noted within the damaged ductules. Damaged ductules can have many intraepithelial lymphocytes (Figures 3A and 3B). Small bile duct epithelium can demonstrate cytoplasmic vacuolization and cytolysis [19]. Ductopenia and lobular acidophil bodies have also been described in cases with worsening jaundice and persistent hepatic autologous GVHD [19].
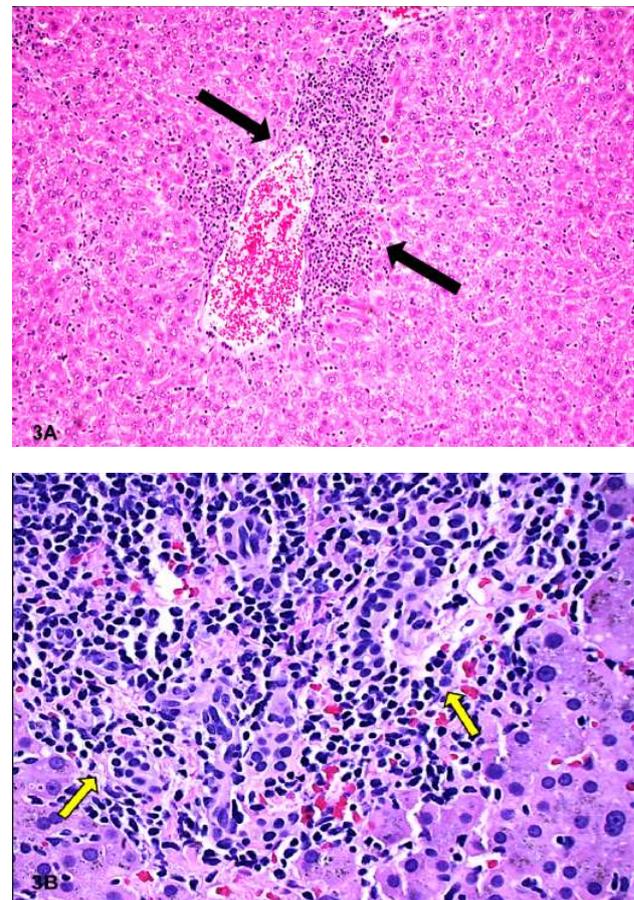

Figure 3A. Liver core biopsy with lymphocytic infiltration of the portal tract following hematopoietic stem cell transplantation (black arrows) (Hematoxylin and Eosin; 40x magnification). B. Liver core biopsy with lymphocytic infiltration of the portal tract and bile duct epithelial injury with intra-epithelial lymphocytes (yellow arrows) following hematopoietic stem cell transplantation (Hematoxylin and Eosin; 400x magnification). (Original Images: Benjamin H. Durham, M.D. and Mingyi Chen, M.D., Ph.D)

Cutaneous GVHD has been reported to occur more often than either gastrointestinal or hepatic GVHD following autologous HSCT [5]. In cutaneous autologous GVHD, the typical histological features demonstrate a lichenoid and

vacuolar reaction at the epidermal-dermal junction, and necrotic keratinocytes are commonly seen (Figures 4A and 4B) [20]. Other features of cutaneous GVHD can be satellitosis and necrotic cells in the dermal appendages. In a case series by Marra *et al.* [21], some of the skin biopsy specimens in cutaneous GVHD demonstrate vacuolar interface dermatitis with scattered eosinophils [21]. In more severe cases, lichenoid and interface dermatitis can appear with an eosinophil-rich, superficial and perivascular inflammatory infiltrate [21].
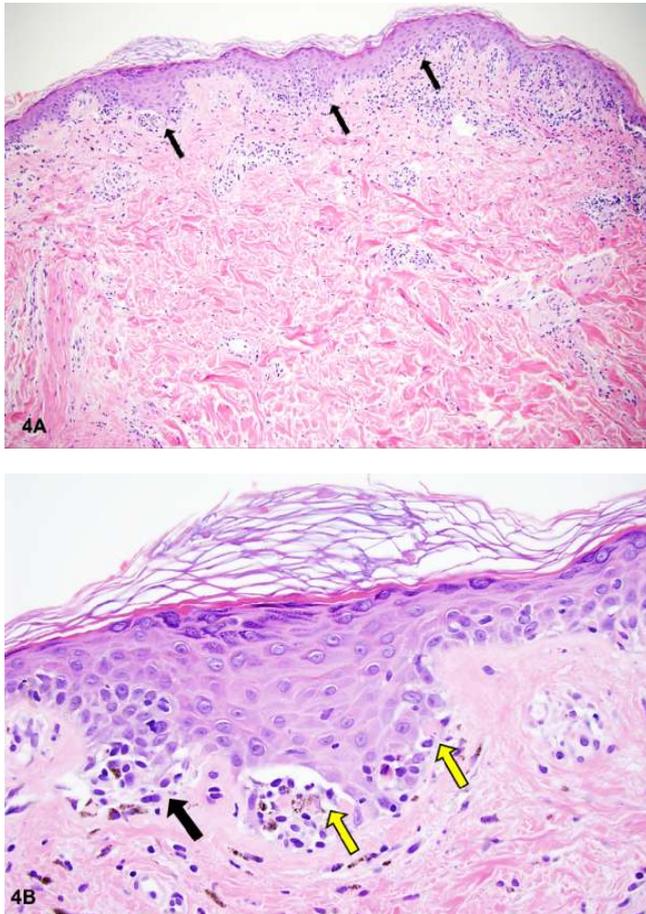

Figure 4. The skin biopsy shows interface dermatitis with basal vacuolization (black arrows) and satellite-cell necrosis with scattered, apoptotic, eosinophilic keratinocytes located at the epidermal-dermal junction (yellow arrows). These features are compatible with GVHD A. (Hematoxylin and Eosin stain; 40x magnification) B. (Hematoxylin and Eosin stain; 400x magnification). (Original Images: Courtesy of Thomas Konia, M.D.)

Differential Diagnosis

Gastrointestinal symptoms in a HSCT patient typically require endoscopic biopsy because the clinical differential diagnosis is very broad [4]. Within the gastrointestinal tract, chemotherapeutic conditioning regimens; infection; proton pump inhibitors; and other drugs such as mycophenolate mofetil can lead to false-positive histopathological interpretations of acute autologous GVHD. For example, when biopsy specimens are acquired within the twenty

days following bone marrow ablation, diffuse apoptosis can be noted, which can cause difficulty in the diagnosis of acute GVHD. If severe injury is present at day twenty or later, this feature is highly suggestive of gastrointestinal GVHD. When the gastrointestinal biopsy shows severe mucosal injury with epithelial apoptosis, careful histological evaluation for cytomegalovirus and cryptosporidium are important because both of these microorganisms can lead to apoptosis within the gastrointestinal epithelium [1]. Proton pump inhibitors lead to increased epithelial cell apoptosis in the gastric antral mucosa in the absence of an inflammatory cell infiltrate [1]; however, the oxyntic mucosa of the gastric body does not demonstrate these histopathological features, which helps distinguish the effects of proton pump inhibitors from autologous GVHD [1]. Mycophenolate mofetil is notorious for causing a colitis picture with increased apoptosis of crypt epithelium, focal mucosal ulcers, and a mixed inflammatory cell infiltration within the lamina propria. However, the discovery of apoptotic bodies in gastrointestinal sites outside the large intestine suggests autologous GVHD [1]. Although tissue eosinophilia has been affiliated with acute gastrointestinal GVHD and tissue eosinophil density within the upper gastrointestinal tract is proposed to correlate with GVHD severity, similar eosinophil infiltration can be seen in hypereosinophilic syndrome; eosinophilic gastroenteritis; acute flares of Crohn's disease; and acute flares of celiac disease. Allergic reactions to medications or foods can manifest with tissue eosinophilia too [16]. Tissue eosinophilia may be a feature of acute autologous GVHD in the gastrointestinal tract, but tissue eosinophilia is not specific for acute gastrointestinal GVHD. Therefore, the patient's clinical history, clinical presentation, and other laboratory testing must be considered with the histological features prior to diagnosing autologous gastrointestinal GVHD.

Hepatobiliary signs and symptoms in a HSCT recipient with autologous GVHD also have a broad differential diagnosis. Similar clinical signs, symptoms, and liver biopsy histopathology can be seen in viral hepatitis and other infectious etiologies; drug and toxin effects; primary biliary cirrhosis; iron overload; or a recurrent lymphoma. Some common drugs in the post-transplant setting that have caused liver injury and have mimicked a clinical and histological presentation of GVHD are cyclosporine, trimethoprim-sulfamethoxazole, itraconazole, voriconazole, fluconazole, and posaconazole. Thus, a thorough clinical history, laboratory work up, and microbiology evaluation are required before making a diagnosis of autologous GVHD of the liver. Whenever a clinical suspicion of autologous GVHD is in the differential diagnosis, the final diagnosis is based on liver biopsy with combined morphological, immunophenotypical, and clinical laboratory evaluation in HSCT patients [19].

Cutaneous autologous GVHD presents as a rash, which

can have several different patterns. In the post-transplant setting, a diagnosis of cutaneous autologous GVHD is difficult to distinguish from rashes secondary to drug reactions or viral infections. Cutaneous autologous GVHD is likely unrecognized in many patients who are first believed to have a drug reaction or a viral infection. In the Marra *et al.* [21] case series, three patients have skin biopsies with eosinophils, and these biopsies lead to erroneous diagnoses of cutaneous drug eruptions because eosinophils in dermatological specimens are classically associated with drug-induced dermatitis [21]. The patients actually have acute cutaneous GVHD. The study authors conclude that there is no single or combined histological feature that is very useful in distinguishing acute cutaneous GVHD or drug eruptions in HSCT patients on skin biopsy. The authors state that evidence of extracutaneous involvement is one of the most helpful features in highlighting GVHD as the etiology of an acute exanthem in HSCT patients because the gastrointestinal tract or liver can be examined histologically to help confirm the presence of GVHD [21]. The Marra *et al.* [21] authors propose that the etiology of a new-onset exanthem in a HSCT patient is most accurately determined through close examination and follow up of the clinical features without the performance of a skin biopsy [21]. Therefore, post-transplant patients need a thorough infectious disease work up, a detailed drug history, and close clinical follow up [22].

There are many challenges in distinguishing autologous GVHD from many of its mimickers or detecting early GVHD based on clinical and histopathological features alone. The recent evolution of proteomics technologies has identified and validated plasma biomarkers as diagnostic and prognostic tools in allogeneic acute and chronic GVHD; however, these promising studies have not yet occurred in the autologous GVHD setting [23,24]. In the future, biomarkers may become useful in autologous GVHD, but specific proteomic studies in autologous GVHD must be pursued for this to become a reality.

Treatment

The typical treatment for autologous GVHD is corticosteroids. Autologous GVHD is usually described as a self-limited syndrome with favorable results to corticosteroid treatment alone. Unless immunosuppressive therapy is being utilized to try to gain a graft-versus-tumor response in a patient with an autologous HSCT, immunosuppression is typically not seen in the autologous GVHD treatment regimens [4,25]. However, the Drobyski *et al.* [7] group discusses a study where patients undergoing autologous GVHD for plasma cell myeloma demonstrate unsuccessful treatment responses to an initial course of corticosteroids and develop severe, steroid-refractory autologous GVHD, which requires the addition of immunosuppressive thearpies [6,7].

Prognosis

In most cases, GVHD occurrence in patients undergoing autologous HSCT is mild with almost all patients responding well to corticosteroids. Therefore, autologous GVHD is usually believed to be self-limited with minimal morbidity or mortality [1,4].

There are exceptions to the typically good prognosis of autologous GVHD. The Drobyski *et al.* [7] group reports a case series of five patients that develop severe gastrointestinal GVHD following autologous HSCT for plasma cell myeloma [7]. The study patients respond very poorly to corticosteroids and have a high mortality rate. This complication is noted to be much higher in patients receiving a second autologous HSCT. This suggests that the repeat exposure to high-dose chemotherapy can compromise regulatory networks important for the maintenance of self-tolerance. This study shows that all cases of severe autologous GVHD occur in plasma cell myeloma patients and not in the other study patients undergoing autologous HSCT for other hematopoietic malignancies [6,7]. Thus, this study's interesting observation warrants further investigation to elucidate why severe autologous GVHD only occurs in the plasma cell myeloma transplant patients.

Conclusions

GVHD disease is a frequent complication that has typically been seen following allogeneic HSCT; however, in the more recent literature, a clinically and histologically indistinguishable GVHD-like syndrome has been described following autologous HSCT. Clinically, this disease entity produces nausea, vomiting, diarrhea, cutaneous changes, and a wasting syndrome with damage to the gastrointestinal tract, skin, and the liver that are essentially indistinguishable from allogeneic GVHD [1]. A few studies have discussed the role of eosinophils and neutrophils in autologous GVHD, and further studies are required to better unravel the role of myeloid cells in the pathogenesis of autologous GVHD [1,8,15-17]. Continued investigation of the effector T-cell subsets in the pathogenesis of autologous GVHD is also required [11-13]. The evaluation of biomarkers by proteomics in autologous GVHD needs to be investigated as well, and maybe the findings can offer benefit in narrowing the differential diagnoses of autologous GVHD as biomarkers have helped in allogeneic GVHD [23,24].

Autologous GVHD usually is a self-limited disease with a good response to corticosteroid therapy alone [4,6,9]. Nonetheless, studies have discussed the development of severe autologous gastrointestinal GVHD in plasma cell myeloma patients that are refractory to corticosteroid treatment, which has not been observed in autologous HSCT for other hematological entities [6,7]. This raises

the clinical and research question of why plasma cell myeloma patients who undergo autologous HSCT are more susceptible to severe, corticosteroid-refractory, autologous GVHD than those patients undergoing autologous HSCT for other hematopoietic malignancies [6,7]. The body of evidence regarding this newer entity of autologous GVHD is definitely growing, but much more clinical and investigative work is necessary to better define autologous graft-versus-host disease in the pathology and gastroenterology literature.

Acknowledgements

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