Graft-versus-host Disease After Intestinal or Multivisceral Transplantation: A Scandinavian Single-center Experience

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ABSTRACT

Background. Graft-versus-host disease (GVHD) that develops after intestinal or multivisceral transplantation is difficult to diagnose and is associated with high morbidity and mortality.

Material and Methods. The objectives of this study were to investigate the incidence, clinical picture, risk factors, and outcome of GVHD in a Scandinavian cohort of patients who underwent intestinal or multivisceral transplantation during a period of 16 years (1998–2014). All transplanted patients (n = 26) were retrospectively analyzed with respect to donor- and recipient-derived risk factors. The diagnosis of GVHD was based on clinical signs, chimerism analyses of leukocytes, and histopathologic findings in biopsy specimens.

Results. Five of 26 patients (19%) were diagnosed with GVHD, of which three had skin GVHD, one had skin and bone marrow GVHD, and one had passenger leukocyte syndrome. Only multivisceral-transplanted patients developed GVHD. Risk factors for development of GVHD were an underlying tumor diagnosis and neoadjuvant chemo- or brachytherapy administered before intestinal transplantation. All patients were given high-dose corticosteroids as first line treatment for their GVHD, and all survived their episodes of GVHD.

Conclusions. The risk of GVHD appears to be increased in recipients of multivisceral transplantations who received chemotherapy due to an underlying malignancy. The reasons may be the large amount of lymphoid tissue in these types of grafts, and the cytotoxic effects of the malignancy and chemotherapy on healthy recipient tissues. These patients should be monitored closely for the development of GVHD.

GRAFT-VERSUS-HOST DISEASE (GVHD) occurs in approximately 50% of the patients after allogeneic hematopoietic stem cell transplantation [1]. Among solid organ transplant recipients, GVHD is less frequent. The highest incidence of GVHD is seen after intestinal or multivisceral transplantation, with reported rates of 12% after multivisceral transplantation [2] and 5% in adults after an isolated small bowel graft [3]. The condition is less common after liver transplantation with an incidence of 1.0% [4,5].

GVHD in hematopoietic stem cell transplanted patients was traditionally classified according to the Glucksberg-Seattle criteria from 1972 [6]. According to these criteria, signs of GVHD within 100 days post-transplantation were classified as acute GVHD, whereas later episodes of GVHD were denominated as chronic GVHD. Today, these chronologic diagnostic criteria have been replaced by consensus criteria from the National Institute of Health [7] that put more emphasis on the underlying differences in pathophysiology of

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the acute and chronic forms of GVHD, respectively. Consequently, it is the clinical features that define whether GVHD should be classified as acute or chronic GVHD, or even so-called "overlap GVHD" with features of acute and chronic GVHD. GVHD in organ transplant recipients is sometimes classified as cellular or humoral GVHD. The cellular form occurs when immune competent donor-derived lymphocytes transferred with the transplanted organ(s) undergo activation and clonal expansion in the recipient, resulting in a cellular immune response against healthy tissues. The humoral form is also called passenger leukocyte syndrome and may develop after an AB0-mismatched transplantation, when donor-derived B lymphocytes produce antibodies against erythrocyte antigens of the recipient. There is limited knowledge on how to diagnose GVHD in solid organ transplant recipients, what the risk factors are, and whether GVHD should be treated by increasing or decreasing immune suppressive therapy. The objectives of this retrospective study were to investigate the incidence of GVHD, the clinical picture and risk factors for GVHD, outcome of given therapy, and GVHD-related mortality, in a cohort of 26 adult and pediatric patients who underwent intestinal and/or multivisceral transplantation between February 1998 and September 2014 at Sahlgrenska University Hospital, the only transplantation center to perform intestinal transplantations in Scandinavia during this time period.

MATERIAL AND METHODS

Patients

After approval from the Regional Ethical Review Board of the University of Gothenburg, all patients who underwent isolated intestinal or multivisceral transplantation between February 1998 and September 2014 were retrospectively reviewed for clinical and histopathologic evidence of GVHD. Altogether, 26 patients (18 adults and 8 children) were transplanted at the Sahlgrenska University Hospital and the Queen Silvia Children's Hospital in Gothenburg during this period. The most common cause for transplantation was intestinal failure with life-threatening complications of total parenteral nutrition or neuroendocrine pancreas tumors with unresectable liver metastases. The following two immunosuppressive protocols were used: 1) years 1998–2003: tacrolimus, steroids, and interleukin-2 receptor antagonist daclizumab (Zenapax, Hoffman-La Roche Ltd., Basel, Switzerland); and 2) from 2004 and onwards: antithymocyte globulin induction therapy (ATG-Fresenius, Fresenius Biotech GmbH, Graefelfing, Germany), and tacrolimus monotherapy (Prograf, Astellas, Killorglin, Ireland), a steroid-free protocol described by the Pittsburgh Medical Center [8]. None of the donors received pretreatment with muromonab CD3 (Orthoclone OKT3, Janssen-Cilag, The Netherlands) or similar monoclonal antibodies. A summary of the patient characteristics, type of transplantation, and donor-related data is shown in Table 1. All grafts were from deceased donors. The eligibility criteria and outcome for patients considered for intestinal and multivisceral transplantation at our center have recently been published [9].

Statistics

The Fisher exact test of independence was used to detect differences between groups. A probability of $P < .05$ was used as a threshold value for statistical significance.

Diagnostic Criteria of GVHD

The patients were diagnosed with GVHD after clinical evaluation. The diagnosis was further complemented by a biopsy from the affected tissue (skin n = 3; bone marrow n = 1). All skin biopsy specimens were examined by at least one pathologist with special interest in GVHD and classification was performed according to the Lerner and Horn classification [10,11]. To determine the presence of donor-derived cells in tissues and peripheral blood, DNA chimerism analyses were performed according to Tsutsumi et al [12]. In one case of sex mismatch between donor and recipient, fluorescence in situ hybridization (FISH) for detecting X and Y chromosomes was used to document donor-cell infiltration in tissue [13]. The diagnosis of passenger leukocyte syndrome was confirmed by analysis of donor-derived antibodies as described by Audet et al [14]. A GVHD diagnosis necessitated 1) a clinical picture compatible with GVHD and 2) a positive DNA chimerism analysis and/or histopathologic findings consistent with GVHD.

RESULTS

Incidence of GVHD

Five of 26 patients (19%) developed GVHD. Three patients had skin GVHD, one had skin and bone marrow GVHD, and one had passenger leukocyte syndrome. The incidence of GVHD in the multivisceral transplanted patients was 26% (5/20). None of the patients who received isolated intestinal grafts developed GVHD. Of the patients with GVHD, two were women and three were men. A summary of the patients who developed GVHD is shown in Table 2. Chimerism analyses were evaluated in five patients without a GVHD diagnosis. One of these patients had 27% donor T cells chimerism without a GVHD diagnosis. A more detailed description of the patients with GVHD is provided below, as well as in Fig 1.

Clinical Picture of GVHD

Patient 6. A woman of approximately 60 years old received a multivisceral transplant because of a nonresectable neuroendocrine pancreatic tumor. The patient developed a rash 70 days post-transplantation, located to the thorax, back and both thighs bilaterally down to the knees. There was no pruritus. A skin biopsy collected on day 92 post-transplantation showed necrotic keratinocytes and an inflammatory cell infiltrate, and an additional skin biopsy on day 110 showed progression with a diffuse infiltration of lymphocytes, eosinophils, and histiocytes. The pathologists' interpretation of both biopsy specimens was "unclassified dermatitis." Chimerism analysis of peripheral blood T cells showed a peak level of 40% donor-derived cells on day 70, supporting the diagnosis of GVHD (Fig 1). Because of suspected rejection on day 120 that was confirmed by intestinal biopsy specimens, treatment was administered with systemic steroids and increased basal immunosuppression. Six months after the transplantation, the rash resolved. The patient died 2 years later due to recurrence of the malignancy.

Patient 10. A man in his 40s who received a multivisceral transplant due to a neuroendocrine pancreas tumor developed severe direct antiglobulin–positive hemolytic anemia on day