Chapter 19
Vascularized Bone Marrow Transplantation: Pathology of Composite Tissue Transplantation-Induced Graft-Versus-Host-Disease

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19.1 Background

Composite tissue allografts (CTAs) represent the transplantation of several tissue types including integumentary, musculoskeletal, cutaneous, and hematopoietic elements. The rat hindlimb CTA using a parental limb to an F₁ hybrid host actually represents a vascularized bone marrow transplant model.¹ The hindlimb CTA provides transplantation of precursor hematolymphoid (bone marrow) and mature (blood and lymph nodes) elements by a surgical approach along with transfer of their syngeneic/supportive microenvironments. Immediate engraftment with and without immune modulation has been previously shown.²⁻⁷

By comparison, other bone marrow transplant models have a finite rate of engraftment failures of which none have been reported with the hindlimb CTA/vascularized bone marrow transplant. There are significant advantages to the transplantation of composite tissues when considering bone marrow transplantation. Compared with other methods of bone marrow transplantation,⁸⁻¹⁰ CTAs allow immediate engraftment of donor lymphoid cells with development of donor-specific lymphoid chimerism.⁴,⁵,⁷

Chimerism produces two profound effects in the hybrid recipient of a parental limb. These are the development of donor-specific immune tolerance and graft-versus-host-disease (GVHD). The tolerant animals showed significantly lower levels of donor-specific T-cell chimerism.¹ The mechanisms of host-specific tolerance are associated with the fate of the chimeric T-cell populations. A curious phenomenon occurs during the first 30 days postvascularized bone marrow transplantation (VBMT). These animals become polyclonal, self-, and host-specifically responsive in in vitro studies.¹¹ These results are similar to the immune reactivity associated with GVHD in other models.¹²⁻¹⁴ This initial dysregulated immune response is later replaced by polyclonal unresponsiveness at 100 days and host-specific unresponsiveness at 200 days.¹¹ Thus, this initial immune dysregulation in the tolerant animals is associated with a stable low-level mixed chimerism. It appears as though the chimeric environment supports the development of suppressor circuits and thus host-specific tolerance.

Unfortunately, the converse of tolerance, when considering VBMT, is GVHD. This undesired outcome is associated with unstable higher levels of donor

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chimerism. In the recipient animal, these chimeric T cells become effector cells that lead to the development of GVHD. In murine studies, evidence of GVHD correlates with the presence of increased levels of donor CD8+ lymphocytes. Thus it follows that the depletion of the CD8+ cells would decrease the chance of developing GVHD, but there is an increased risk of graft failure.

19.2 Gross Clinical Aspects of VBMT

The majority of recipients (60–70%) of parental to F1 hybrid rat hindlimbs are tolerant. They thrive after allograft transplantation. Weight gain is at the usual rate and they remain in excellent health.18 The minority develops GVHD. GVHD is best described as a cachectic wasting syndrome of dermatitis, enteritis, and hepatitis. The dermatitis takes on the form of a macular erythematous rash that can involve any part of the body. In the rat hindlimb model, though, the most affected areas include the ears, nose, and genitalia (Fig. 19.1). In the initial stages of the disease, there is an erythematous appearance to the skin. There is concomitant alopecia. In the later stages, the rash changes to a lichen planus-like rash that eventually becomes sclerotic.

The enteritis is manifested clinically as profound diarrhea and weight loss with loss of appetite. In the rat hindlimb CTA/VBMT, average weight loss ranges from 25 to 40% of original weight at the time of transplantation.

Fig. 19.1 Graft-versus-host-disease in a LEW to LBN CTA/VBMT recipient. LEW to LBN composite tissue allograft/vascularized bone marrow transplant undergoing one-way donor antihost graft-versus-host disease day 41 posttransplant (See Color Plates)