Cutaneous *graft-versus-host* disease

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Allogenic bone marrow transplantation is currently a frequent therapy for a wide variety of malignant neoplasms. Graft-versus-host disease (GvHD) is a major cause of morbidity and mortality in patients with allogenic bone marrow transplantation. The skin, liver and gut are the main targets of GvHD. Cutaneous GvHD comprises in fact two different diseases: acute and chronic GvHD.

Cutaneous acute GvHD

Acute GvHD may clinically and histologically simulate viral exanthems, adverse drug reactions, cutaneous eruptions of lymphocyte recovery, bacterial and fungal sepsis or cutaneous reactions to the preparatory regimen. Histological signs are classified into four grades: grade I, basal cell vacuolization; grade II, basal cell vacuolization and single necrotic keratinocytes; grade III, subepidermal clefts and numerous necrotic keratinocytes; and grade IV, necrosis of the entire epidermis and complete separation from the dermis. Nonetheless, a major problem in diagnosing acute GvHD arises because histological features are not specific. In fact, absolute criteria for acute GvHD are poor. The presence of extracutaneous involvement can help to support this diagnosis but it is usually a late phenomenon. With regard to the pathogenesis, major and minor histocompatibility antigens of host tissues are recognized by donor cytotoxic T-cells, followed by the development of cutaneous lesions mediated by activated effector cells and secreted cytopathic molecules. This process can be analyzed in three phases.

The endothelial phase is characterized by diapedesis of lymphocytes through postcapillary venules of the superficial dermis and is associated with the initial clinical signs (around 2-3 weeks after transplantation). Mast cell degranulation seems to play an important role, provoking gap formation between adjacent endothehal cells and facilitating, by means of histamine and tumor necrosis factor-cr (TNF-cr), a cascade of cell adhesion molecule expression [p-selectin,E-selectin, vascular cell adhesion molecule-i (VCAM-1), intercellular adhesion molecule-i (lOAM-i), PECAM-1/CD31], which are responsible for leukocyte-endothelial adhesion and migration through the vessel wall. The role of mast cells in acute GvHD is exemplified by the delay of cutaneous GvHD lesions in mast cell-deficient animals.

In the epidermotropic phase, lymphocytes migrate into the epidermis and follicular infundibulum, first within the basal cell layer, without spongiosis or significant damage to basal cells. Expression by epidermotropic cells of cx3fil, an integrin that serves as a receptor for epiligrin (a basement membrane ligand), may play a role in this process. However, in addition, lymphocytes must gain access to suprabasal epidermal layers and this may be mediated by enhanced expression of CAM—i and HLA-DR by keratinocytes (stimulated by interferon-y of lymphocytic origin) or by interaction between keratinocytic E-cadherin and lymphocytic integrin crEj37.

In the target-cell phase, multiple lymphocytes surround necrotic ("dyskeratotic) keratinocytes, a phenomenon called "satellitosis'. Immunohistological studies in this phase reveal numerous CD8+ T-cells within the epidermis, whereas CD4+ cells predominate in the dermis. CD8+ cytotoxic cells kill via recognition of recipient peptides in the context of class I major histocombatibility complex (MHC) molecules. In addition, cytokines produced by activated CD4+ cells activate other cell types (cytotoxic T-cells, natural killer cells and macrophages), induce phenotypic changes in keratinocytes (as previously mentioned) and may damage keratinocytes directly (TNF-cr and interferon-y). Other cell types involved in this phase are natural and cytokine-activated killer cells of donor origin, which can mediate cytotoxicity in the absence of class I or II molecules on target cells. Other molecules produced by cytotoxic lymphocytes implicated in target cell injury include performs (which have similarities with complement components), granzymes (which might access to the intracellular millieu via perform channels), and Fas (APO-1), a member of the TNF-a receptor superfamily, which is involved in apoptosis. Fas ligand is present on the surface of cytotoxic lymphocytes, and Fas receptor is expressed on target epidermal keratinocytes. Fas ligand-receptor binding activates caspases, responsible for enzymatic digestion of their intracellular substrates and cell death. In fact, the TdT-mediated dUDP-biotin nick end labeling (TUNEL) method demonstrates that apoptosis is a major mechanism in keratinocyte death in cutaneous acute GvHD. Therefore, the so-called "dyskeratotic' cells are in fact apoptotic.

Cutaneous chronic GvHD

Chronic GvHD develops in 30-50% of transplant recipients more than 3 months after transplantation. It may appear *de novo* but the risk is 11 times higher if the patient previously had acute GvHD. There are two main types of chronic GvHD: lichenoid and scierodermatous. Lichenoid lesions are early lesions clinically consisting of erythematous or violaceous papules or plaques and are histologically characterized by a band-like lymphocytic infiltrate with melanophages in the papillary dermis, together with necrotic keratinocytes with satellite lymphocytes as well as some degree of epidermal hyperplasia with hyperkeratosis. Scierodermatous lesions are late, clinically indurated, shiny, white-yellow plaques, histologically characterized by epidermal atrophy, destruction of adnexal structures, linearization of the dermoepidermal junction and descending superficial collagen fibrosis. Pericapillary infiltrates are present in the dermis and granular 1gM deposits are found at the dermoepidermal junction in 86% of biopsy specimens. Chronic GvHD seems to be the consequence of a complex interaction between anti-host and autoimmune phenomena. As in acute GvHD, several immunohistochemical studies have shown that CD8±T-cells predominate in the epidermis, whereas CD4+ cells are the most prevalent in the dermis, and Langerhans cells are significantly reduced. Apoptosis, probably Fas-induced, is also a major mechanism of keratinocyte death in chronic GvHD. Interteron-y is constantly present in these lesions but, in contrast to acute GvHD, perform does not seem to play a role. The similar profile of cytokines and adhesion molecules in lichenoid and scierodermatous lesions (with the exception of the expression of VCAM-i in dermal vessels, which seems to be restricted to lichenoid lesions) suggests that the scierodermatous phase is a consequence of the healing process.

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New developments in the pathogenesis of systemic vasculitis

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The vasculitides include a highly heterogeneous group of clinicopathological entities. Ranging from benign, self-limiting disorders to life-threatening conditions, the vasculitides share a common histopathologic substrate; the inflammation of blood vessels, which may involve vessels of any size throughout the vascular system.

Largely unknown etiological agents among which viruses, drugs and other environmental agents can be considered, trigger a cascade of immunopathogenical mechanisms able to damage the vessel wall. In addition to classically recognized immune complex deposition and complement activation, these include the generation of antineutrophil cytoplasmic antibodies, antiendothelial cell antibodies and a T-cell-mediated immune response directed against putative antigens potentially present in the vessel wall. These and other potential immunopathogenic mechanisms are not mutually exclusive and they probably act in concert to sustain and reinforce vessel damage triggered by still elusive and probably heterogeneous agents.

Etiolopical agents

It is well known that lesions caused by fungal and bacterial infections *(i.e.,* aspergillus, tuberculosis) may include vasculitic phenomena. An association between hepatitis B virus infection and the development of classical polyarteritis nodosa has been observed for many years. Recently, a strong association between hepatitis C virus infection and mixed cryoglobulinemia has been recognized. Other viral infections that have been related to the occurrence of vasculitis are HIV, cytomegalovirus and parvovirus B19. Identifying viruses as potential etiological agents in vasculitis may have important therapeutic implications.

Immunonathogenic mechanisms

Immune comolex deposition

Many years ago, experimental animal models, such as the Arthus phenomenon and serum sickness, provided interesting insights into the potential of immune complexes to damage the vessel wall. According to this model, immune complexes would activate the complement cascade with the generation of chemotactic products. These would attract neutrophils which, in turn, would damage the vessel wall by releasing lysosomic enzymes and reactive oxygen species.

Antineutroohil cytoolasmic antibodies

One of the most intriguing discoveries in the field of vasculitis has been the recognition of an association between Wegener's granulomatosis and microscopic polyangiltis and the presence of circulating antineutrophil cytoplasmic antibodies (ANCA). Accumulated experience has revealed that ANCA potentiate neutrophil-mediated vessel damage both *in vitro* and in animal models. ANCA-mediated immunopathogenic mechanisms will be discussed in depth in the next lecture.

Antiendothelial cell antibodies

Antiendothelial cell antibodies (AECA) have been described in a variety of systemic vasculitis, as well as in autoimmune diseases with vascular involvement. AECA exhibit different functional activities on endothelial cells. Some are able to induce an activated phenotype in cultured endothelial cells while others can induce complement-activated endothelial cell lysis. Antigens recognized by AECA seem to be highly heterogeneous and await further characterization.

T-cell-mediated immune response

Immunopathogenic studies have shown that, in several vasculitis syndromes, inflammatory infiltrates are mainly composed by activated T lymphocytes and macrophages. Even in the processes where neutrophils are thought to have a prominent role, such as immune complex-mediated vasculitis or ANCA-associated vasculitis, at some point, inflammatory infiltrates disclose a seemingly high amount of mononuclear cells. The mechanisms through which T lymphocytes and macrophages are activated to produce vessel injury are heterogeneous. In temporal arteritis lesions, the identification of clonal expansion of a minority of infiltrating T lymphocytes suggests a specific immune response directed against antigens present in the vessel wall. In Takayasu arteritis, heat shock protein recognition by 7/6 T lymphocytes may contribute to vessel damage.

Vascular response to inflammation

Vessel wall components, particularly endothelial cells, actively and dynamically react to the products released by infiltrating leukocytes. During the past few years, it has become apparent that endothelial cell response to cytokines and growth factors amplifies the inflammatory response by three main mechanisms: expression of adhesion molecules for leukocytes, additional cytokine and