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Pathology of Chronic Rejection: An Overview of Common Findings and Observations About Pathogenic Mechanisms and Possible Prevention

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Definition, Clinical Presentation and Suspected Etiology

Very good to excellent one year patient and graft survival rates at most experienced transplant centers has shifted considerable attention in research away from short term complications like acute rejection to chronic rejection (CR), which is the major obstacle to long-term, morbidity-free survival (reviewed in detail[1]). In comparison to acute rejection, chronic rejection is a more indolent, but progressive form of allograft injury, which is largely irreversible and eventually results in allograft failure.

Although the term "chronic" implies a temporally prolonged course, many cases of chronic rejection clearly evolve from severe or inadequately controlled acute rejection episodes because of noncompliance or an inability to maintain immunosuppression, or to monitor the allograft for rejection. Such patients experience a progressive decline in organ function over a period of weeks to months. Another significant cohort of patients slowly develop graft dysfunction and eventual failure over a period of years from chronic rejection. This may be attributable to "clinically silent" rejection episodes that go undetected or to other factors. A third cadre of patients become trapped in a disheartening cycle that alternates between rejection and infection (e.g., CMV, polyoma virus[2]), in which the immunosuppressive therapy is repeatedly increased then decreased. Each turn of the cycle further damages the organ, which eventually fails with features of chronic rejection.

Three lines of evidence best support the contention that alloimmunity is the major etiologic factor, as originally suspected.[3,4] First, isografts rarely, if ever, suffer the same set of changes seen in allografts with chronic rejection, although some isografts do develop chronic arterial lesions, but they are delayed in onset and less severe in comparison to allografts.[5-8] Secondly, patients who are at high risk of severe or persistent acute rejection;[9-16] and those inadequately immunosuppressed have a higher rate of chronic rejection.[17,18] This is likely related to an increased risk of alloreactivity like that seen with donor/recipient racial or ethnic mismatches,[19-23] sex mismatching,[14,24] viral infections[25-32] and in patients treated with immune activating drugs.[33] Finally, greater MHC mismatching results in a higher rate of long term allograft failure, although the data for liver allografts is conflicting.[19,20,22,23,34-39]

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Common Histopathological Features

There are several similar histopathologic and pathophysiologic manifestations of chronic rejection in the various solid organ allografts which enables us to cover the topic from a common perspective. The common features include: a) patchy, organized interstitial inflammation; b) patchy interstitial fibrosis and associated parenchymal atrophy; c) graft vascular disease (GVD) which primarily manifests as fibrointimal hyperplasia of arteries; d) destruction of epithelial-lined conduits; and e) destruction and atrophy of organ-associated lymphoid tissue and lymphatics. Except for widespread GVD, which is rarely detected on biopsy and an uncommon finding in the absence of chronic rejection, none of these features, in isolation, is diagnostic for chronic rejection. Each can be seen with non-chronic rejection related complications. In fact, the usefulness of a biopsy in establishing the diagnosis of chronic rejection is directly related to the ability to sample the target structures.

There are however, certain manifestations of chronic rejection that are accentuated in specific organs because of physioanatomic variations and interactions with the environment. For example, GVD is the primary manifestation of chronic rejection in heart allografts,[40-43] which may be related to the natural tendency of the heart to develop atherosclerosis. In lung transplantation, destruction of the small bronchioles is the major chronic rejection-related insult limiting long-term survival which could be related to bronchial exposure to environmental antigens/infection.[12,42,44-47] GVD is not a significant problem after lung transplantation.[12,42,44-46] In the liver, both bile duct loss and GVD (see below) together contribute to allograft failure.[48-52] It is clear however that these physioanatomic and "environmental factors" clearly exert their influence in the context of severe and/or persistent alloreactivity, a contention based on the experience with isografts mentioned above.

In addition, there are major differences in the incidence of chronic rejection 5 years after transplantation: it affects roughly 25–50% of hearts; 50–60% isolated lungs, 40–60% pancreas

and 30% of kidney allografts, but only 7–20% of liver allografts (reviewed in greater detail in reference[1]). Thus, although there is no accepted generic histopathological definition of chronic rejection equally applicable to all organs, the common features can be used as a general guide for analysis and comparison. Each of these common features is discussed in more detail below.

Patchy, Organized Interstitial Inflammation

A mononuclear interstitial inflammatory infiltrate is a constant feature of chronic rejection, and architecturally organized nodular aggregates of lymphocytes and macrophages often arise from a background of isolated mononuclear cells scattered sparingly throughout the organ.[1,53,54] Overall, the infiltrates consist primarily of $CD4^+$ and $CD8^+$ T cells and macrophages.[53-60] In contrast to acute rejection, B cells and plasma cells are seen in greater numbers,[55,56,61] while eosinophils are less frequently seen.[62]

In all allografts, the organized nodular aggregates are often located near the adventitia of arteries with GVD, near peripheral nerve trunks, and the serosa or capsule of organs.[53,54,63] These are also the site of draining lymphatics. The overall arrangement and the occasional presence of germinal centers[1,53,54] within these nodules is typical of organized lymphoid tissue in the regional lymph nodes, and is indicative of ongoing intra-organ antigen presentation. A similar process occurs in autoimmune diseases, such as Crohn's disease and Hashimoto's thyroiditis.[53,54]

The aggregates and cells individually scattered throughout the interstitium are often seen in close association with damaged parenchymal cells. Cytokine mRNA analysis and immunohistochemical studies for effector molecules showing granzyme B and the presence of Th1-like cytokines IL-2 and IFN-γ.[60]

Patchy Interstitial Fibrosis and Associated Parenchymal Atrophy

Over time, the necro-inflammatory activity discussed above, results in patchy interstitial fibrosis and atrophy of parenchymal cells. This process is accentuated in adventitia of arteries and in sites of ongoing immunological activity near epithelial-lined conduits (discussed in more detail below). The evolving fibrogenesis is likely related to ongoing parenchymal and microvasculature injury (see below) associated with the release of multiple growth factors,[64-68] which results in the deposition of tenascin and other matrix components,[69,70] endothelin[71] and activation of interstitial myofibroblasts.[70] The presence of larger scars is indirect evidence that ischemic injury with healed infarcts also contribute to fibrogenesis.[40]

Graft Vascular Disease

Graft vascular disease (GVD) affects the majority of solid organ allografts with chronic rejection to some degree and accounts for the most serious physiological consequences in heart, kidney, and pancreatic allografts. It is of secondary importance in some liver allografts because destruction of the bile ducts is of more importance and GVD is an uncommon problem for lung allografts. Nevertheless, GVD has become synonymous with chronic rejection and has received the most research attention, even though there are other well-known pathologic aspects of chronic rejection and in some allografts GVD is not a significant problem.

Caveats aside, GVD manifests primarily as concentric arterial intimal thickening and adventitial fibrosis,[40,41,72-74] but occasional mild venous involvement[44,74,75] and focal destruction of the microvasculature (e.g. renal glomeruli and peri-biliary capillary plexus)[48,76,77] are also seen. GVD should be separated from atherosclerosis, which is endemic in the general population, but there are overlapping characteristics that make distinction difficult in some cases. This is particularly true for organs such as the heart that are normally prone to atherosclerosis, but less of a problem in atheroresistant organs, like the liver.

In general, GVD more often involves *both* the extra-organ (e.g., epicardial, hepatic hilar, etc.) and first and second-order branches of medium-sized intra-organ muscular arteries,[40-42,72-74] in contrast to atherosclerosis, which primarily affects the extra-organ portion of the vessels. However, involvement of the intra-organ arterial tree by GVD is not as diffuse as one might expect from a review of the pathology literature[40-42,72-74] and the lesions often begin and evolve more quickly near branch points.[40]

Except for the kidney, arteries commonly affected by GVD are rarely sampled in allograft biopsies routinely used to monitor for rejection. Thus, reconstruction of events preceding the development of GVD depends on examination of many failed allograft and autopsy specimens obtained at serial time points after transplantation. An early phase of GVD with which most investigators are familiar is inflammatory arteritis showing intimal inflammation and/or antibody deposition. This is a histopathological marker of severe acute rejection in all allografts and results in endothelial damage, loss of barrier function and the influx of clotting proteins (including fibrin), platelets, blood cells and lipids,[65,78-80] all of which disrupt intimal homeostasis and trigger a macrophage influx. The media often shows edema and individual myocyte apoptosis. The adventitia is usually edematous and often contains a cuff of lymphocytes and macrophages. The intimal injury leads to a stereotypic repair response that results in fibrointimal hyperplasia and eventual lumenal narrowing.[64,74,81-86] Intimal inflammation is not observed in milder grades of acute rejection, yet some of these patients go on to develop chronic rejection. Instead, the inflammation is often limited to the adventitia. Even so, adventitial inflammation or injury alone can trigger an arterial repair response culminating in fibrointimal hyperplasia.[54,87-91] Thus, GVD may not require intimal inflammation or direct endothelial injury from antibodies or cells.

The preferential localization of leukocytes in the adventitia and intima of arteries suggests that these are the most important antigenic targets or sites of arterial damage.[40,73,83,92-95] That the endothelium is targeted in some reactions is not particularly surprising, since it is well-known to be immunologically active. The adventitia contains a lymphatic plexus which is surrounded by donor dendritic cells making it a site of both peripheral sensitization in acute rejection and a conduit for emigrating leukocytes.[40,54,83,91,93,95] It is easy to envisage that the shoulder region of a pre-existing donor atherosclerotic lesion would also be highly

immunogenic because of the presence of donor hematolymphoid cells and neovascularization.

As GVD progresses, the intimal and/or adventitial inflammation often persist, but the inflammatory cells migrate to the deeper aspects of the thickened intima where they are separated from an intact endothelial layer by a concentric ring of intimal myofibroblasts. Overall, the developing lesion vaguely resembles the shoulder region of an atherosclerotic plaque, discussed above. The deep intimal focus of inflammatory cells often communicates with an adventitial sheath of lymphocytes and macrophages through a focally disrupted media. Thus, from a morphological perspective, the endothelia no longer appears to be the focus of immunologic activity.

Immunophenotypic analyses have shown that the arterial inflammation consists primarily of an admixture of $CD4^+$ and $CD8^+$ T cells, some of which show perforin positivity and macrophages, with occasional dendritic cells (marker of ongoing antigenic presentation), eosinophils and plasma cells.[40,62,83,92,96-98] Mitotic activity within this population occurs at the same time as smooth muscle DNA synthesis, suggesting that the immunological reactions and vessel repair are related.[1,40] In the final stages of GVD, the media of involved arteries becomes thinned and both the intima and the adventitia thickened, fibrotic and hypocellular.

Focal destruction of the microvasculature of allografts is also part of GVD.[48,66,76,77] This process is probably related to direct immunological damage to the immunogenic microvascular endothelium and is best observed in renal and liver allografts. The glomerular characteristically evolve through a sequence of changes that eventually result in global glomerulosclerosis.[77] In the liver, similar changes are seen in the peri-biliary plexus,[48,76] which shares some morphological and functional similarities with the renal glomerulus.

Destruction of Epithelial-lined Conduits

Epithelial cells that line conduits used for exchange of substances with the environment, such as bronchioles, bile ducts, pancreatic ducts, renal tubular epithelium are particularly prone to damage during chronic rejection. There are several possible non-exclusionary explanations for this observation: 1) the presence of a basement membrane, which could potentially play a role in migration, positioning and co-stimulation of T-cells;[99] 2) an immunologically active antigenic profile that is significantly different than other parenchymal cells, including class I and II MHC, and various adhesion and co-stimulatory molecules;[99,100] and 3) the presence of nearby antigen presenting cells and lymphatics that facilitate the functional role of these conduits in processing environmental antigen for local presentation and traffic to the regional lymph nodes.

The bronchioles[31,100] and bile ducts[18,48,50,52,101-106] are good examples of the last possible explanation for "targeting" of epithelial conduits. A bronchiocentric or ductulocentric immune response precipitated by environmental or autoantigens in an allograft, creates inflammatory microenvironment that has the potential to trigger a rejection reaction. Either reaction can compromise the structural integrity of the conduit, and focally destroy the local microvasculature and lymphatic drainage, which in turn can ischemically damage the conduit inhibit efficient antigen clearing. One could easily appreciate how this could lead to a vicious cycle, alternating between a persistent and inadequate response to environmental antigens/infections and allogeneic injury, resulting in a downward spiral of allograft structural integrity and function. In liver and lung allografts, an additional consideration is the exclusive blood supply by the hepatic and bronchial arteries, respectively. Either destruction of these vessels, or failure to revascularize them, can significantly contribute to conduit injury.[48,49,107]

Destruction and Atrophy of Organ-associated Lymphoid Tissue

All organs contains a network of hematolymphoid cells that travel into and out of, and transiently occupy, the interstitium of all vascularized organs. These cells consist of mature T and B lymphocytes, macrophages, hematopoietic stem cells and dendritic cells, primarily derived from progenitors that migrate hematogenously from the bone marrow, although maturation from local precursors can also contribute to this pool. In concert, they monitor the microenvironment and communicate with regional lymph nodes via the circulation and lymphatics. When the organ becomes an allograft, these cells are called "passenger leukocytes" and they are primarily responsible for triggering acute rejection reactions via the ability of mature dendritic cells to directly stimulate allogeneic T cells.

Organs such as the lungs and intestines have a large specialized compartment of organ or mucosal-associated lymphoid tissue (MALT), commensurate with their task of directly dealing with antigens from the external environment. In contrast, the liver is richly endowed with a large macrophage population, consistent with its role as a filter of various opsonized material and other physiological debris. Although not as extensive or well known, the kidney,[108] heart[109,110] and pancreas also have considerable intra-organ immune networks.

It is our opinion, that the significance and eventual functional re-establishment of this network has not received enough attention in either acute or chronic rejection, or tolerance induction. In general, the therapeutic window for avoiding graft failure from rejection and infection from over-immunosuppression is most narrow for those organ with the largest component of mature T cells, such as the intestines and lungs. As soon as an allograft is revascularized, recipient immune cells circulate through the organ, including the organ-associated lymphoid tissues (GALT, BALT, portal lymphoid tissue)[111,115] and regional donor lymph nodes transplanted en bloc, with the organ.[116] Donor cells also leave the allograft and lodge in recipient lymphoid tissues.[117,118] Subsequently a bi-directional "in vivo mixed lymphocyte response" occurs in the recipient lymphoid tissue and in the allograft which manifests as acute rejection.[111-114,116] The greater component of immunogenic cells, the more robust the initial reaction.

Transplantation of an organ also transiently disrupts the efferent lymphatics resulting in organ edema, which contributes to the re-implantation response. The lymphatic channels reconnect within two to three weeks,[119,120] unless disrupted by acute rejection, which increases production of lymph fluid and again disrupts the

lymphatic microvasculature. Both of these insults contribute to the reappearance of graft edema and swelling during acute rejection reactions.[119,121-124]

If immunosuppression is kept high during the early post-transplant period, there is a gradual replacement of donor hematolymphoid cells or immune network with similar recipient cells and the intra-organ network, MALT and regional lymph node architecture is restored.[115] However, if the framework is disrupted during acute rejection, repopulation is prevented and the allografts develop chronic rejection.[115] In chronic rejection, the lung[124,125] and intestine[114] mucosal-associated lymphoid tissue and regional lymph nodes are often destroyed or undergo atrophy. Patchy interstitial fibrosis also focally disrupts intra-organ lymphatics.[54,126] Both of these changes undoubtedly contribute to an inability of chronically rejecting allografts to adequately process infectious agents and antigens that are normally cleared via these pathways.[17,28,31,125,127-129] In fact, it is tempting to speculate that failure to physiologically re-establish these systems after transplantation accounts for the frequent association between infection and chronic rejection. Conversely, one wonders whether this intra-organ immune network also plays a role in maintaining tolerance to the organ.[54,130-132]

Lastly, disruption of lymphatic drainage, which can occur in the adventitia of arteries can produce arterial injury and intimal thickening similar to that seen with GVD.[133] Thus, we[54] and others before us[126] have suggested that this potential mechanism of arterial injury might importantly contribute to the development of OA.

The "Special Case" of Liver Allografts

There are two fascinating aspects of chronic liver allograft rejection: its potential reversibility possibly related to ductal regeneration and liver progenitor cells[1,50,134] and an appreciably lower incidence than other allografts.[1,135] Also pertinent is the observation that a liver allograft can also protect other organs from the same donor from chronic rejection.[54]

Theories explaining the special immunological properties of a liver allograft can be broadly separated into two general categories based on whether emphasis is placed on the parenchymal or non-parenchymal fraction. Release of soluble donor MHC class I antigen from the allograft is cited as evidence supporting the importance of the parenchyma.[136] However, murine liver allografts are routinely accepted between strains of mice that show no difference between the class I loci but are mismatched for class II[137] and fully allogeneic liver allografts from class I or II MHC deficient mice, which do not shed soluble MHC antigens,[137,138] are also accepted. Other organs also secrete soluble MHC antigens[139] but they are routinely rejected. Finally, studies attempting to induce graft acceptance with administration of soluble donor MHC have met with limited success.

Another potential explanation for the importance of the parenchyma relies on the concept that allogeneic hepatocytes provide only one of two signals needed for allogeneic lymphocyte activation,[140] which in turn, could theoretically result in the induction of anergy in the responding lymphocyte populations.[140] Alternatively, loss of passenger leukocytes from the allograft or graft adaptation could result in ignorance of the allograft.[142,144] Such a pathway might be especially true for the liver, which is a sink for effete and highly activated cytotoxic T cells.[143-144]

Our focus has been on the donor hematolymphoid cells within the liver, which might initially mediate activation induced clonal purging or deletion[145-151] which is followed by long term hematolymphoid microchimerism[147,152,153] sustained by donor hematopoietic stem contained within the liver.[154-156] An important aspect of both of these mechanisms is that hematolymphoid cells are capable of potent stimulation and have direct access to the recipient lymphoid tissue. However, it is difficult to understand how the initial purging would provide long term protection since one must account for perpetuation of non-reactivity. Freedom from chronic rejection requires long term unresponsiveness. An attractive explanation might combine the initial clonal purging, followed by "ignorance" of the allograft because of the adaptation and replacement of the passenger leukocytes. The situation could be likened to the expression of alloantigens on parenchymal cells in transgenic mice. Unfortunately, this ignorance can be disrupted by viral infections and other local immune activating events,[142,157,158] which are difficult, if not impossible to avoid in an allograft.

From our perspective, the immunologic mechanisms involved in perpetual graft acceptance and freedom from chronic rejection appear to be active and are probably not different from those required for self-tolerance.[54,159-162] In essence, to permanently avoid chronic rejection, tolerance to the organ must be induced, and this requires transplantation and functioning of the donor immune system.[160,161]

Summary

In summary, there are histopathological features of chronic rejection that are common to all solid organ allografts, and immunological injury seems to play a primary role in the initiation and progression of lesions. However, the final phenotypic expression of chronic rejection is dependent on an interaction between immunologic and physiologic/environmental factors that results in one or another of these features predominating in certain organs. Finally, in addition to traditional clinical studies and experimental models, it will be important to study conditions of resistance to chronic rejection in an effort to prevent or avoid this disorder.

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