

Morphologic Clues to Organ Cross-Reactivity in Transplantation

Tobias Manch*

Departments of Surgical Pathology, University of Bologna, Bologna, Italy

DESCRIPTION

Organ transplantation represents one of the most remarkable achievements in modern medicine, yet its success is intricately tied to the delicate interplay between donor tissues and the recipient immune system. While much attention has focused on direct rejection phenomena, chronic complications, and the role of immunosuppressive therapy, organ cross-reactivity remains a subtle yet significant factor influencing graft outcomes. Cross-reactivity occurs when immune responses directed at one organ or tissue inadvertently affect other organs due to shared antigenic determinants, molecular mimicry, or systemic immune modulation. Recognizing morphologic clues to cross-reactivity is essential for both pathologists and clinicians, as it provides insight into ongoing immune processes, informs therapeutic strategies, and allows early intervention before irreversible tissue injury occurs.

Histopathologic examination of transplanted organs often reveals the first evidence of immune-mediated cross-reactivity. The hallmark feature is the presence of cellular infiltrates that extend beyond the expected targets. Lymphocytes, plasma cells, and macrophages may accumulate in perivascular, interstitial, and parenchymal locations, sometimes in organs not initially associated with donor antigen exposure. The composition of these infiltrates often reflects the nature of the immune response, with predominance of T cells suggesting a cellular-mediated process, while the presence of B cells and plasma cells may indicate humoral involvement. Early morphologic changes include endothelial swelling, perivascular cuffing, and subtle epithelial or parenchymal alterations, which, if unrecognized, can progress to necrosis, fibrosis, or functional compromise.

Parenchymal tissue patterns offer additional clues. In organs experiencing cross-reactive injury, there is often a patchy or multifocal distribution of cellular damage. In the kidney, for instance, glomerular and tubular epithelial changes may appear alongside interstitial inflammation in regions distant from the graft site, suggesting systemic immune activation. Similarly, in the liver, bile duct epithelial cells may display cytoplasmic vacuolation, nuclear irregularities, or apoptotic bodies, often accompanied by portal inflammation and perivenular congestion. Morphologic heterogeneity, with juxtaposition of

relatively preserved tissue and areas of active injury, is a key feature indicating cross-reactivity rather than localized rejection confined to the transplanted organ.

The architecture of lymphoid and immune-related structures is also informative. Secondary lymphoid organs, including lymph nodes and spleen, may undergo reactive hyperplasia in response to cross-reactive immune activity. Follicular expansion, increased germinal center activity, and paracortical lymphocyte proliferation provide indirect evidence of ongoing immune engagement that could influence multiple organs. In some instances, ectopic lymphoid aggregates develop within nonlymphoid organs, forming tertiary lymphoid structures that perpetuate local immune responses. Histologically, these aggregates resemble miniature lymph nodes, with organized T and B cell zones and high endothelial venules facilitating lymphocyte recruitment. Their presence in transplanted or distant tissues underscores the systemic nature of cross-reactive immune events.

Fibrotic remodeling and extracellular matrix alterations frequently accompany chronic cross-reactive injury. Repeated cycles of immune-mediated cell damage and repair induce deposition of collagen, proteoglycans, and other matrix components, leading to architectural distortion. In the kidney, interstitial fibrosis and tubular atrophy may develop, while in the lung, alveolar septa may thicken, and small airways may become obliterated. These fibrotic changes are often disproportionate to the localized injury of the grafted organ, suggesting that systemic immune factors are contributing to widespread tissue remodeling. Histologic evaluation of such fibrosis reveals dense collagen bundles, loss of normal parenchymal organization, and entrapment of residual cellular elements within the matrix, reflecting a maladaptive response to persistent cross-reactive immune signaling.

Apoptotic and necrotic patterns provide further morphologic evidence. Cross-reactive immune processes frequently induce programmed cell death in multiple organ systems. In the heart, myocardial cells may show scattered apoptosis with minimal inflammatory infiltrate, whereas in the pancreas, islet cells may undergo selective necrosis. The distribution of apoptotic bodies or coagulative necrosis, often in organs distant from the primary

Correspondence to: Tobias Manch, Departments of Surgical Pathology, University of Bologna, Bologna, Italy, E-mail: manchtobias@gmail.com

Received: 30-May-2025, Manuscript No. JMSP-25-39080; **Editor assigned:** 02-Jun-2025, PreQC No. JMSP-25-39080 (PQ); **Reviewed:** 16-Jun-2025, QC No. JMSP-25-39080; **Revised:** 23-Jun-2025, Manuscript No. JMSP-25-39080 (R); **Published:** 30-Jun-2025, DOI: 10.35248/2472-4971.25.10.332

Citation: Manch T (2025). Morphologic Clues to Organ Cross-Reactivity in Transplantation. J Med Surg Pathol. 10:332.

Copyright: © 2025 Manch T. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

graft, indicates systemic immune recognition of shared antigens or molecular mimics. Morphologic assessment of these cell death patterns allows pathologists to differentiate cross-reactive phenomena from localized ischemic or toxic injury, particularly when corroborated by the presence of immune infiltrates or vascular alterations.

Immunohistochemical techniques enhance the detection and interpretation of morphologic clues. Staining for T cell markers, B cell markers, complement components, and activation markers provides insight into the type and intensity of the immune response. Patterns of immune deposition along endothelial surfaces, within parenchymal tissue, or in association with apoptotic cells support the diagnosis of cross-reactive injury. Moreover, expression of adhesion molecules, chemokines, and cytokines within affected tissues correlates with histologic evidence of immune recruitment and tissue remodeling. Integrating these immunohistochemical findings

with traditional morphologic assessment strengthens the ability to identify early and subtle cross-reactive events.

CONCLUSION

Morphologic clues to organ cross-reactivity in transplantation encompass a spectrum of vascular, parenchymal, and stromal alterations that reflect systemic immune engagement beyond the primary graft. Key features include endothelial activation, perivascular and interstitial cellular infiltrates, patchy parenchymal injury, tertiary lymphoid aggregates, fibrotic remodeling, apoptotic and necrotic patterns, and immunohistochemical evidence of immune activation. Histologic evaluation of these changes provides valuable insight into the mechanisms of cross-reactivity, facilitates early diagnosis, and guides therapeutic strategies aimed at preserving both graft function and overall organ integrity.