New ISHLT nomenclature and diagnostic criteria: Antibody-mediated rejection in heart transplantation

Antibody-mediated rejection of the transplanted heart is a recognized clinical complication and a major limitation to survival of patients who have undergone heart transplantation. Experts have now developed a new working formulation for the pathologic diagnosis, grading, and reporting of cardiac antibody-mediated rejection. Their consensus statement is published in the December issue of *The Journal of Heart and Lung Transplantation*.

Heart transplantation is the definitive therapy for eligible patients with end-stage heart failure. However, antibody-mediated rejection (AMR) of a cardiac allograft—a heart from a genetically non-identical donor— is a recognized clinical complication in the management of heart transplant patients and can develop more than a year after transplantation has occurred.

Over the past 25 years experts have wrestled to establish practical working definitions to guide the diagnosis, grading, and reporting of AMR. In the initial 1990 International Society for Heart Transplantation (ISHLT) working formulation, "positive immunofluorescence, vasculitis, or severe edema in the absence of cellular infiltrates" were proposed as the key diagnostic hallmarks. This working formulation included the qualified recommendation that "centers routinely performing immunofluorescence should consider staining all endomyocardial biopsy specimens obtained in the first six weeks following transplantation."
More detailed histopathologic features and immunopathologic criteria were proposed in the follow-up 2005 ISHLT revision of nomenclature and diagnostic criteria.

In 2010 the increasing awareness of asymptomatic AMR and its association with accelerated cardiac allograft vasculopathy and increased mortality, together with the need to define a therapeutic strategy, led an international multidisciplinary group to recommend the removal of the clinical and serologic components specified in the 2005 working formulation as requirements for the diagnosis of AMR. The biopsy tissue diagnosis of cardiac AMR has since been established by using agreed reproducible histopathologic and immunopathologic criteria akin to the diagnosis of acute cellular rejection (ACR).

In this statement, members of the Pathology Council of ISHLT led by Gerald J. Berry, MD, Professor of Pathology, Stanford University School of Medicine, and Director, Cardiac and Pulmonary Pathology, Stanford University Hospital and Clinics and Lucile Packard Children's Hospital at Stanford, reports the consensus findings from a series of meetings held between 2010 and 2012 to develop a new working formulation for the pathologic diagnosis, grading, and reporting of cardiac AMR.

"Tremendous progress has been achieved over the last decade in recognizing, diagnosing and grading AMR, but its recognition and diagnosis by histopathology, even among experienced transplant pathologists, is challenging," says Berry. "With the rapid changes that occur in medicine, new and more specific antibodies—or even new technologies—may provide more accurate and reproducible results for the diagnosis of AMR. Until then, there remain numerous challenges and unresolved clinical, immunologic, and pathologic questions. It is our distinct intention and hope that the diagnostic criteria and grading scheme presented in this working formulation will aid in the resolution
of these and other issues."

The report covers:

- Histopathologic features of AMR
- Interstitial edema
- Hemorrhage, necrosis, and vascular thrombosis
- Immunopathologic findings in cardiac AMR
- Antibody panels for paraffin immunohistochemistry
- Antibody panels for frozen-tissue immunofluorescence
- Summary of the ISHLT 2012 pAMR biopsy specimen validation study
- Pathologic grading and reporting of cardiac AMR
- Indications, frequency, and follow-up of immunostaining
- Initial and surveillance immunophenotypic studies
- Follow-up of immunophenotypic studies after a positive result
- Surveillance and immunostaining for late-onset AMR
- Mixed ACR and AMR

The Working Group points out that this document reflects the current state of knowledge and experience of transplant pathologists, and also serves as a framework for the organization of future multicenter studies. Areas pinpointed as needing further evaluation include AMR in children and the threshold for therapeutic intervention in patients with "asymptomatic AMR."

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