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Editorial

# The beat goes on: historical perspectives and future directions of cardiac transplantation
## A summary of the Society for Cardiovascular Pathology's 2019 Companion Meeting

On Sunday, March 17, 2019, the Society for Cardiovascular Pathology held its annual meeting at the United States and Canadian Academy of Pathology's annual meeting in National Harbor, Maryland. The topic of this year's companion society meeting was cardiac transplantation. The session covered both historical landmarks in the field as well as an expert commentary on the future directions of the field. Of course, special attention was paid to the role of pathology in this important area, and a nod was given, more specifically, to those pathologists who played critical roles in the development of the field.

Fifty years have now passed since the first heart transplant. It is currently the third most commonly transplanted solid organ, and there has been a steady increase in the number of transplant surgeries over the last 5 years. This session updated participants on the latest developments in the field including established grading criteria for both cell- and antibody-mediated rejection, and new ancillary studies to monitor for rejection. The highlight lecture of the session was be given by Dr. Gayle Winters, the 2019 recipient of the Society for Cardiovascular Pathology's Distinguished Achievement Award, wherein she put into historical context the role that endomyocardial biopsy has played in heart transplantation.

The session was co-chaired by myself and Dr. Marc K. Halushka of the Johns Hopkins Hospital in Baltimore, Maryland. The objectives set out for the session included the following: (1) describe grading systems used for both cell- and antibody mediated rejection in cardiac allografts; (2) discuss key surgical issues pertaining to cardiac allotransplantation; and (3) identify nonbiopsy methods used to monitor for cardiac allograft rejection, describing both their benefits and shortcomings. This editorial is meant to summarize the contents of the session.

### Cell-mediated rejection

Dr. Annalisa Angelini, from the University of Padua Medical School in Padua, Italy, provided an excellent review of the grading system that is currently in place for acute cell-mediated (cellular) rejection (ACR). She also discussed practical tips for recognizing ACR and described what was essentially a “rule of threes” for technical considerations in processing and evaluating these specimens: (1) a minimum of THREE myocardium-containing fragments, (2) a minimum of THREE levels examined, and (3) the use of the THREE-tiered grading scheme set forth by the International Society for Heart and Lung Transplantation (ISHLT) in 2004 [1].

Dr. Angelini reviewed outcomes data and briefly discussed the role that the detection, and subsequent treatment, of rejection had played in improving outcomes. She noted that approximately 40% of transplant endomyocardial biopsies contain at least mild ACR. Specifically, she reviewed data showing a correlation between ACR (both severity and frequency) and the development of allograft vasculopathy [2].

Despite our understanding of the significance of ACR, there is work to be done. Interobserver variability in assigning grades to ACR in cardiac biopsies remains suboptimal. While some improvement was demonstrated during the transition from the 1990 to the 2004 scheme, the overall reproducibility between centers and pathologists has remained somewhat weak [3,4]. So, in effect, our work as pathologists in the monitoring of these allograft specimens continues to evolve. It is important work for our patients, but we must continue to refine our strategies. More specifically, we must work to improve reproducibility of our grading systems and gain a better understanding of the impact of mixed ACR/antibody-mediated rejection (AMR) in patients.

### Antibody-mediated rejection

Dr. Dylan Miller, from the University of Utah and Intermountain Central Lab in Salt Lake City, Utah, gave a brilliant dissertation on the historical aspects and mechanisms of AMR in cardiac allografts. He noted the evolution in grading schemes, again set forth by the ISHLT and last revised in 2013, and discussed their similarities to the TNM staging system so well established in oncologic pathology [5].

The topic of AMR is undoubtedly complex. Current diagnostic strategies involve a multidisciplinary approach that includes biopsy studies (morphology and complement staining), evaluation for serum donor-specific antibodies, and clinical parameters (e.g., graft dysfunction). Dr. Miller analogized this to a pyramid model of complexity that was quite apt and memorable.

From a practical standpoint, the morphologic similarities between AMR and those of high-grade ACR are striking, highlighting the importance of immunohistochemical workup in the former.

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The use of serum donor-specific antibodies and underlying immunobiology of antigen–antibody complexes was also discussed. He concluded his session by briefly reviewing treatment strategies that may be deployed to combat AMR in transplant recipients.

## Surgical issues in cardiac allograft rejection

Dr. Ahmet Kilic from the Johns Hopkins Hospital in Baltimore, Maryland, provided for a clinical/surgical perspective on issues surrounding cardiac allograft rejection [6]. He nicely summarized recent survival data provided by the United Network for Organ Sharing. The impact of substance abuse and the drug crisis on the donor pool was also discussed.

The increased utilization of left ventricular assist devices as bridges to transplantation was noted, as well as some of the important hemodynamic and immunologic changes that result from such mechanical support. Clearly, much work is to be done in this area, and pathologists remain central to such. Treatment approaches for both ACR and AMR were central to the discussion. Dr. Kilic's companion article to his session is contained in this issue of *Cardiovascular Pathology* and provides an excellent and detailed description of the surgical issues summarized above.

## Emerging methods of monitoring for cardiac allograft rejection

Dr. Bruce McManus, from the University of British Columbia and St. Paul's Hospital in Vancouver, Canada, began his session by reviewing the ecosystem of molecular tests in clinical care. He used a number of examples, such as cholesterol screening, *BRCA1* testing, etc., as successful assays that have improved overall outcomes (from Omics data to accurate and actionable biomarker tests). He asked the provocative question as to whether these newer methodologies could replace traditional biopsy screening of the transplant population given the overall expense, emotional burdens, health risks, and aforementioned issues of reproducibility associated with endomyocardial biopsy specimens.

Transplant biomarker development data were reviewed, including Affymetrix, NonoString, and HEARTBiT. The goals of these tests are largely to allow for less invasive means of monitoring for rejection. While the data for these assays are still mixed, some promise has been shown. Undoubtedly, the technology is something to be watched over the coming years. Whether or not it will be used as a complementary assay to traditional biopsy or replace it altogether remains to be seen.

## The history of endomyocardial biopsy in cardiac transplantation

Dr. Gayle L. Winters, from the Brigham and Women's Hospital in Boston, Massachusetts, took the podium to offer a somewhat contrasting view to Dr. McManus'. Her talk, for which the title accurately reflected her premise, focused on the fact that, despite limitations, the biopsy was still the gold standard. Her dissertation was a phenomenal historical perspective, and first-hand account, of the evolution of the biopsy and grading systems that have been used in cardiac transplant patients.

She reviewed the rational for the technical considerations that Dr. Angelini had reminded us of, providing data-driven insights into why those criteria were established. She gave a significant nod to the pioneering work of Dr. Margaret E. Billingham and the role she played in allograft surveillance and the development of the biopsy technique.

## The Society for Cardiovascular Pathology's 2019 Distinguished Achievement Awardee: Dr. Gayle L. Winters

In addition to giving the keynote lecture at our companion society session, Dr. Gayle Winters was honored as the Society's Distinguished Achievement awardee in recognition of her global stature in cardiovascular pathology [7]. This is particularly true in light of her profound contributions to the field of transplant pathology. She received her Bachelor of Science in biology from Purdue University and her Doctor of Medicine from Loyola Stritch School of Medicine. She stayed on at Loyola to do a year of general surgery residency and then a residency in anatomic and clinical pathology, followed by a fellowship in surgical pathology.

She earned a faculty position at Loyola and quickly rose to the rank of Associate Professor of Pathology before being recruited to the Brigham and Women's Hospital in 1992. It was there that she served, until this year, as a Senior Pathologist and Associate Professor of Pathology at Harvard Medical School.

Dr. Winters has an international reputation as a heart transplant pathologist and has served on the editorial boards of *Circulation*, *Cardiovascular Pathology*, *The Journal of Heart and Lung Transplantation*, and *Advances in Anatomic Pathology*. Within the Society for Cardiovascular Pathology, she has held myriad leadership positions, including Secretary, Acting Treasurer, Vice-President, and President. She also served as the editor for *Cor Notes*, the Society's newsletter.

Among her many contributions to the field of cardiovascular pathology, she was a member of the working group and coauthor on the original 1990 grading system for cardiac transplant biopsies, as well as the revision in 2004 and the grading system for antibody-mediated rejection established in 2011 [1,5,8]. These grading schemes, as noted throughout this editorial, form the foundation for much of the academic and clinical work in cardiac transplantation over the years. She also made important contributions in the areas of determining the clinical significance of Quilty lesion and allograft vasculopathy.

In addition to her research and clinical interests, Dr. Winters is a renowned educator. She served as the director of the autopsy service at the Brigham and Women's Hospital and the director of the residency program for 14 years. She has taught countless medical students, residents, and fellows over her tenure, several of whom are active members in the Society for Cardiovascular Pathology.

In short, Dr. Winters embodies the professionalism, academic curiosity, and grit that have built our Society over the years and is most deserving of the high honor of the SCVP's Distinguished Achievement Award. We had a wonderful time celebrating with Dr. Winters and wish her the best in her retirement.

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