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Meeting report

The 2022 Banff Meeting Lung Report

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ABSTRACT

The Lung Session of the 2022 16th Banff Foundation for Allograft Pathology Conference—held in Banff, Alberta—focused on non-rejection lung allograft pathology and novel technologies for the detection of allograft injury. A multidisciplinary panel reviewed the state-of-the-art of current histopathologic entities, serologic studies, and molecular practices, as well as novel applications of digital pathology with artificial intelligence, gene expression analysis, and quantitative image analysis of chest computerized tomography.

Abbreviations: ACR, acute allograft rejection; AI, artificial intelligence; AMR, antibody-mediated rejection; BAL, bronchoalveolar lavage; BALT, bronchus-associated lymphoid tissue; CLAD, chronic lung allograft dysfunction; dd-cfDNA, donor-derived cell-free DNA; DSA, donor-specific antibodies; Foxp3+, forkhead box protein 3+; ISHLT, International Society for Heart and Lung Transplantation; LASHA, lung allograft standardized histologic analysis; RAS, restrictive allograft syndrome; TBB, transbronchial biopsies; TCMR, T cell-mediated rejection; TLO, tertiary lymphoid organ; PAGO, pathology associated with graft outcome; REDCap, Research Electronic Data Capture; CNN, convolutional neural network; RNA, ribonucleic acid; PGD, primary graft dysfunction; FFPE, formalin fixed-paraffin embedded; B-HOT, Banff Human Organ Transplant; MB, mucosal biopsy; CXCR, CXC chemokine receptor; BOS, bronchiolitis obliterans syndrome; CT, computed tomography.

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Current states of need as well as prospective integration of the aforementioned tools and technologies for complete assessment of allograft injury and its impact on lung transplant outcomes were discussed. Key conclusions from the discussion were: (1) recognition of limitations in current standard of care assessment of lung allograft dysfunction; (2) agreement on the need for a consensus regarding the standardized approach to the collection and assessment of pathologic data, inclusive of all lesions associated with graft outcome (eg, non-rejection pathology); and (3) optimism regarding promising novel diagnostic modalities, especially minimally invasive, which should be integrated into large, prospective multicenter studies to further evaluate their utility in clinical practice for directing personalized therapies to improve graft outcomes.

1. Introduction

Lung transplantation offers patients with advanced, irreversible pulmonary dysfunction a viable therapeutic option that provides survival benefits and improved quality of life. Most patients ultimately develop chronic lung allograft dysfunction (CLAD), a term encompassing the two most common forms: bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS).[1]

Acute allograft rejection (ACR), a pivotal predictor of CLAD, has been the principal focus of pathologists in the assessment of transbronchial biopsies (TBB) after transplantation. The histopathologic criteria and grading of ACR are well recognized in consensus documents of the International Society for Heart and Lung Transplantation (ISHLT).[2] More recently, multidisciplinary efforts were established to elaborate the clinical, serologic, and pathologic components of antibody-mediated rejection (AMR).[3] However, there remain areas of need with respect to a consensus on non-rejection pathology associated with graft outcome as well as diagnostic modalities, preferably minimally invasive, allowing for a global assessment of allograft health or injury.

The 16th Banff Foundation for Allograft Pathology was held in conjunction with the Canadian Society of Transplantation on September 19–23, 2022, in Banff, Alberta. The Lung Session presented a multidisciplinary discussion on four specific areas of need related to allograft injury: (1) nonrejection pathology with emphasis on graft outcome; (2) new digital diagnostic techniques; (3) minimally invasive diagnostic technique; and (4) biopsy-based molecular diagnostics.

2. Classification updates

2.1. Non-rejection pathology associated with graft outcomes

Long-term allograft and patient survival remain challenges after lung transplantation. It is well established, across all transplanted solid organs, that the prevention of ACR remains a central pillar to preserve allograft function. ACR carries standardized nomenclature by the ISHLT, inclusive of adequacy assessment and severity grading with common reporting terminology.[2] In addition to ACR, other histologic lesions, such as patterns of acute and organizing lung injury, are associated with allograft loss, yet standardized terminology, nomenclature, and reporting schemes are lacking. Some of these patterns of lung injury are used as part of the histologic assessment of AMR[3] and have been linked to RAS and the presence of donor-specific antibodies (DSA).[4]

Recently, a multicenter, prospective observational study examining the frequency of acute and organizing lung injury provided further support for the association of late injury events and an increased risk of CLAD and allograft loss. The risk factors for late acute and organizing lung injury events included higher degree of donor/recipient human leukocyte antigen mismatch, infection (bacterial or viral), detection of DSA, grade 3 primary graft dysfunction, and the presence of early acute/organizing lung injury events.[5]

Given the significance of acute and organizing lung injury events in the progression to CLAD and graft loss, there is a need for consensus on non-rejection pathology associated with graft outcomes (PAGO). This consensus should include common terminology for patterns of injury (akin to that utilized for reporting of rejection) and provide sufficient descriptive versatility and flexibility while still allowing reproducibility among practicing pathologists.

2.2. Lung allograft standardized histologic analysis template

To improve the standardized pathology reporting and terminology a multispecialty panel of lung transplant experts recently published the lung allograft standardized histologic analysis (LASHA) template.[6] It is designed to serve as a comprehensive construct for reporting pathology findings in lung allograft specimens. As such, LASHA represents a crucial step forward in standardization, with an emphasis toward research endeavors.

The LASHA template has been recently updated and formulated in an electronic design of Research Electronic Data Capture (https://www.redcap.link/lasha), a secure web application for building and managing online databases. An important next step will be the validation of the parameters of the scoring system used to grade different lesions. After validation in large-scale studies, an optimized LASHA template could be included in routine clinical practice to enhance graft assessment—capturing non-rejection PAGO—and medical decision-making.

2.3. *Significance of tertiary lymphoid organs in the lung allograft*

Tertiary lymphoid organs (TLOs), accumulations of immune cells in peripheral, non-lymphoid tissues, are increased in chronic inflammatory states.[7] In the setting of transplantation, TLOs have generally been associated with the local generation of a deleterious alloimmune response that results in rejection. Bronchus-associated lymphoid tissue (BALT), often found in lung allograft biopsies, is a TLO consisting of aggregated T cell and B cell lymphocytes found adjacent to airways or vessels.

Within BALT, both humoral and cellular immune responses against foreign antigens or autoantigens can be propagated.[7] For example, BALT is observed in explanted pulmonary allografts with CLAD.[8] Experimentally, the development of BALT has been documented in an intrapulmonary rat tracheal allograft model.[9] Some rat lung transplantation models have suggested that pre-existing BALT in donor lungs may contribute to the development of accelerated rejection, although contradictory results have also been reported.[10]

TLOs have also been identified in mouse lung allografts after minor-mismatched or F1-to-parent lung transplantation and were associated with greater rejection and CLAD-related fibrosis features.[11-13] In addition, depletion of B cells decreased TLOs and rejection pathology.[12] In a major-mismatched mouse lung transplantation setting, BALT enriched with regulatory forkhead box protein 3^+ (Foxp3^+) was induced in tolerant lung allografts.[14] Additional work demonstrated that these Foxp3^+ T cells prevent the local activation of B cells, indicating that immunoregulatory circuits established within BALT are critical to maintain tolerance in this model.[15] Moreover, Foxp3^+ T cells can exit BALT via lymphatics and systemically downregulate immune responses.[16] Thus, TLOs, including BALT, may not be always deleterious and could drive graft tolerance.

At the histologic level, BALT can be mistaken for perivascular cuffing that characterizes ACR. Importantly, unlike the perivascular cuffing during acute rejection (AR), BALT contains high endothelial venules and lymphatic vessels. Also, BALT-containing, tolerant lung allografts generally have no lymphocytic infiltration into airway epithelium or endothelialitis. While BALT should not be confused with AR, its importance to the immune state of the allograft, including graft outcome, is of interest.

3. New technologies: digital image analysis and the role of artificial intelligence

In the last decade, a variety of new technologies have been introduced to clinical medicine with the aim of better clinical assessment and understanding of disease states. Digital pathology, similar to radiology, has recently evolved from computer-based platforms for whole slide and radiographic image review to a vast landscape employing quantitative analysis and artificial intelligence (AI) algorithms.

3.1. *AI in lung transplant pathology*

The landscape of digital pathology, coupled with AI and computational tools, is rapidly evolving. Computer-assisted digital pathology has the advantage of performing quantitative analysis, triaging negative or normal specimens, and predictive biomarker detection in addition to assisting with diagnostic error reduction. Depending on the model used, input and annotations from experts serve as the basis for training and teaching an AI algorithm.[17] A high-quality, multicenter data set of annotations serving as “ground truth” is needed to achieve the desired accuracy of the outcome.

The field of lung transplant pathology is frequently cited for poor interrater reliability in the assessment of ACR. A recent study from a high-volume transplant center reported early work utilizing deep learning via a convolutional neural network for the distinction of ACR from normal lung tissue. Annotations of A-grade (A1/A2) rejection and normal lung tissue were used to create a digitalized slide training set and then evaluated using the convolutional neural network. The algorithm distinguished ACR from normal alveolated lung tissue with 95% validation accuracy.[18]

The implementation of digital pathology requires basic resources for whole slide imaging as well as image management. The larger hurdle to overcome is high-quality, multicenter data set studies with annotations from expert pathologists, which will allow for the advancement of the field through simple diagnostic error reduction or more complex deep learning with integration of multidimensional clinical data sets and digital spatial transcriptomics for prognostication and tailored therapy.[19]

3.2. *Computed tomography imaging for classification of CLAD*

Recent ISHLT consensus guidelines have increased the importance of computed tomography (CT) imaging in the assessment of CLAD phenotypes.[1] Even in patients in whom CLAD phenotype diagnosis is undefined or unclassified, the CT pattern is independently predictive of outcome.[20] This has led to a series of investigations where CT volumetry and software algorithms have been utilized to improve differential diagnosis or estimate prognosis. A decrease in CT-estimated lung volume has been shown to be associated with RAS.[21] In addition, quantitative image analysis showed that patients with bronchiolitis obliterans syndrome had air trapping and were less likely to demonstrate features of interstitial lung diseases or ground glass opacification compared to patients with RAS.[22] More sophisticated algorithms are now under evaluation and show that machine learning approaches for CT lung texture analysis, with quantification of parenchymal and small airway abnormalities, can identify CLAD phenotypes and predict disease progression.[23-25] Although these approaches are potentially relevant for clinical adoption, their implementation is limited by international differences in CT protocols, software licensing, and the need for multicenter validation.

4. Noninvasive/minimally invasive diagnostic tools

Recognizing CLAD risk factors early is imperative to enable therapeutic intervention for early injury to (1) delay or prevent the progression to CLAD and (2) improve outcomes after transplantation. This challenge reflects the need for reliable biomarkers, such as those mentioned below, that could potentially facilitate early detection of rejection, other graft injuries, or CLAD development. Furthermore, an enduring goal in the monitoring of transplant recipients has been the development of noninvasive and minimally invasive tests. Reliable, cost-effective, and reproducible techniques are under investigation and in different stages of clinical acceptance. In this section, some of the most recent technologies are summarized.

4.1. Bronchoalveolar lavage (BAL) markers of lung injury

BAL is currently performed in conjunction with bronchoscopic TBB after lung transplantation. The primary clinical role for BAL has been to identify infection as a cause of graft dysfunction, but it has not been directly utilized for the diagnosis of rejection or non-rejection pathology or risk stratification. Theoretical advantages of BAL, compared with TBB, include (1) a larger area of lung that can be sampled, (2) greater technical reproducibility, and (3) a lower risk of complications.[26]

In a single-center study, transcriptomic analysis of the BAL cell pellet identified 72 differentially expressed genes during ACR. A genomic classifier based on only 4 genes was able to diagnose ACR with good performance, and a positive genomic classifier was associated with a greater risk of CLAD, especially when the TBB was negative for AR.[27]

Several observational studies have examined BAL supernatant protein and cytokine characteristics during ACR and non-AR lung allograft injury patterns.[28-32] A multicenter cohort showed that BAL concentrations of CXCR3 ligands (CXCL9 and CXCL10) were increased during ACR, as well as during the non-ACR injury patterns, lymphocytic bronchiolitis, and acute lung injury.[33] Importantly, during allograft injury, only high BAL levels of CXCL9 or CXCL10 carried an increased risk of CLAD.[34]

These findings suggest that BAL can provide global allograft assessment with lower risk; however, large prospective multicenter studies are needed to validate these data and enable translation of these findings into clinical tests.

4.2. Bronchial and bronchiolar brushings as a promising diagnostic tool

Emerging data suggest airway brushing may be a valuable technique for early CLAD diagnosis, endotyping, and therapeutic targeting. Bronchiolar brushing has been utilized in lung transplantation for over a decade and can demonstrate distinctive lymphocyte and epithelial phenotypes associated with CLAD.[35-37]

Advances in RNA sequencing now allow transcriptional analysis of airway brushings with improved throughput. Rejection-associated gene expression changes seen in bronchial brushings are analogous to those seen with ISHLT A-grade pathology and renal T cell-mediated rejection (TCMR), but not B-grade pathology or AMR.[38] An airway rejection gene signature was significantly increased in bronchiolar brushings from patients with CLAD compared with control samples, and declines in lung function predicted retransplantation or death only in subjects for whom bronchiolar bushings detected rejection.[35] Similar results were seen in airway brushings in CLAD, which could be validated across two sites.[39] Multicenter studies are underway to refine CLAD-specific gene signatures and allow for precision approaches to CLAD management.

4.3. Molecular assessment of allograft injury through donor-derived cell-free DNA

Donor-derived cell-free DNA (dd-cfDNA) has received attention in recent observational studies in lung transplant recipients. The ratio of dd-cfDNA/total-cfDNA remains relatively low during times of graft health but increases with injury. Single and multicenter studies have assessed circulating dd-cfDNA as a biomarker for posttransplant allograft injury[40]; the ratio (dd-cfDNA/total-cfDNA) can be associated with severity of injury.[41,42] With today's technology, the benefit of dd-cfDNA is limited to minimally invasive monitoring, potentially reducing the need for surveillance biopsies. Recent work has shown that dd-cfDNA levels may elevate in asymptomatic patients with acute graft dysfunction months earlier than injury would have been detected via other surveillance tools.[43] At this time, increased levels of dd-cfDNA do not give insight as to the etiology of the injury (ACR, AMR, infection, or other), and future studies are needed to move dd-cfDNA from a biomarker of injury to a biomarker that gives insight on etiology for guidance of therapeutic options.

5. Biopsy-based molecular diagnostics

5.1. Advances in biopsy-based molecular diagnostics in lung transplantation

Significant advances have been made using microarrays to measure gene expression changes within lung transplant biopsies. Based on previous associations of molecular signatures in other organs, Halloran and colleagues identified four distinct molecular transcriptomic archetypes in TBB: (1) normal, (2) TCMR, (3) AMR-like, and (4) injury.[44] Focusing on large airway mucosal biopsies rather than TBB, they identified the same four molecular archetypes, suggesting that these less invasive samples may be a viable alternative for the molecular diagnosis of lung transplant rejection.[45] The molecular signature for TCMR, particularly in mucosal biopsies, was significantly associated with graft loss in this cohort.[46] Focusing on TBB from patients with CLAD, they found that time posttransplant was generally associated with inflammation gene expression; however, after correcting for time, CLAD-related molecular changes demonstrated an association with parenchymal injury response.[47] This paradigm provides an opportunity for enhanced molecular understanding and diagnosis of these challenging phenotypes. Future multicenter studies are the next step to validate these molecular archetypes against a multidimensional data set, including histology findings from concurrent lung transplant biopsies. It is not yet possible to transition clinical practice and therapeutic decision-making from tissue-guided to molecular archetypal-guided without understanding the alignment of the two.

Parallel work has been performed utilizing the NanoString nCounter platform with formalin-fixed paraffin-embedded lung transplant samples. In collaboration with NanoString, the Banff Molecular Diagnostics Working Group recently developed a commercially available 770-gene Banff Human Organ Transplant (B-HOT) panel based on previously published gene expression signatures from kidney, liver, heart, and lung transplant biopsies, supplemented by transcripts representing relevant cellular pathways and cell types. In contrast to the dedicated fresh tissue samples generally required with microarrays and other gene expression platforms, utilization of formalin-fixed paraffin-embedded samples allows for retrospective analysis of archival tissue with associated clinical data sets. This sets the stage for expediting validation of transplant molecular diagnostics and thus further promoting research and clinical decision-making efforts.[48] Multiple multicenter validation studies utilizing the B-HOT panel are currently underway.

6. Summary and future directions

TBB has long been considered the "gold standard" for clinical monitoring after transplantation. However, the limitations are well recognized. Over the last decade, the field of lung transplantation has evolved from a somewhat insular collection of traditional medical disciplines to a complex, vibrant interdisciplinary network that adopts new insights in histopathology, immunologic mechanisms, molecular technologies, radiologic, and other imaging modalities in the management of lung transplant recipients. The application of AI to traditional histomorphology will likely further refine our understanding of graft injury but requires multi-institutional data sets and collaboration to increase generalizability. Together with molecular technologies, the dynamic changes occurring within the allograft will become better understood. Increasingly sensitive imaging modalities will provide more detailed inspection of the pulmonary compartments as well as predictive and prognostic information. To implement these diagnostic advances, multicenter, prospective studies are needed with subsequent careful evaluation to ensure that each modality is demonstrably additive and not simply repetitive and/or confirmatory.

As the field evolves, the TBB, rather than becoming obsolete, will need to adapt to the array of novel approaches. Ongoing, detailed, and standardized collection of histopathologic findings will serve to define morphologic criteria and subtle changes in lung morphology as well as aid in the quest for standardization of terminology. An unmet need and area of short-term (2-year) focus for the Banff Lung Group, arising out of the 2022 meeting, is to assess and refine non-rejection pathology associated with graft outcome (PAGO). The need for a detailed assessment of non-rejection histopathology is critical before standard reporting terminology can be proposed and integrated with the advanced ancillary studies outlined above. The long-term goal remains early detection—and hopefully prevention—of injuries leading to CLAD. The 2024 Banff meeting will be held on September 9–13, 2024, in Paris, France.

Declaration of competing interest

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