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Coronavirus and Chronic Lung Allograft Dysfunction: Hiding in Plain Sight?

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Community-acquired respiratory viral (CARV) infections have long been thought to be associated with adverse outcomes in the pulmonary allograft, specifically as risk factors for acute and chronic rejection, the latter manifest as bronchiolitis obliterans syndrome, or more recently, as a restrictive phenotype, restrictive allograft syndrome, both of which fall under the umbrella term of chronic lung allograft dysfunction (CLAD).[1-5] Of late, the relationship with acute rejection has been questioned, and the weight of evidence now supports a dissociation between acute rejection and CARV as independent risk factors for CLAD.[6-9] A number of specific types of CARV are considered more likely to be associated with the development of CLAD. Paramyxoviruses, in particular parainfluenza, seem to cause significant acute loss of allograft function which often does not recover and may progress quite rapidly to high-grade bronchiolitis obliterans syndrome.[10] Therapeutic interventions are limited, with few studies showing benefit of treating parainfluenza.[11] However, some evidence suggests efficacy of both inhaled, intravenous, and oral ribavirin, as well as novel trial agents, for respiratory syncytial virus with a similar response for human metapneumovirus.[12-16]

Knowing that CARV are a key risk factor for poor outcomes after lung transplantation has galvanized interest in accurate diagnostics to precisely identify the causative viral agents especially for symptomatic lung transplant recipients with lower-respiratory tract infection, including pneumonia, which has been linked to a higher risk of developing CLAD.[17,18] Not all CARV exhibit lower-respiratory tract tropism, however, and it makes biological sense that high viral loads are associated locally with increased severity of airway epithelial damage, the defective repair of which may lead to airflow limitation.[19] Furthermore, the study published in this issue of Transplantation Direct by Magnusson et al[20] demonstrated persistence of viral detection for a minimum of 3 weeks in 19 patients who were viral positive. As the authors mentioned, it is difficult to ascertain whether this is the same strain of virus or a reinfection with a new strain; however, the extended time for viral clearance in this population may be associated with greater periods of airway damage due to both viral and immune-related mechanisms. Subanalyses of the subjects with viral persistence in regard to time to CLAD development and graft loss may provide important insights. Furthermore, incorporating analyses of viral load in both upper- and lower-respiratory tract samples of subjects with viral respiratory tract infection into this study may be useful in determining viral-related factors which predispose to CLAD development.

The current Magnusson et al article, therefore, adds to the body of literature describing CARV as a risk factor for CLAD. The term used by the authors in the title is "chronic rejection" but in the absence of a demonstrable immunopathological pathway, it is probably more accurate to just describe the outcome, namely, CLAD, which should not be construed as being synonymous with chronic rejection.[5] Conversely, chronic rejection is very likely a key contributor to CLAD.[21] Semantics aside, the authors show convincing evidence that early CARV, within the first postoperative year, are associated with CLAD. Strengths of the approach include the intensive follow-up during the first year and the use of a time-dependent multivariate Cox proportional hazards analysis which demonstrated independent risk factors of acute rejection and utilization of cyclosporine as the calcineurin inhibitor. Limitations include the relatively small number of enrolled subjects (n = 98), half of whom experienced graft loss during the study, and the potential for bias introduced by intensive sampling within the first postoperative year, rather than throughout the study, although this reflects real-world practice. Also, the effect size was modest (hazard ratio, 1.94; 1.03-3.66; $P = 0.041$).

Nasopharyngeal swabs were performed by a trained staff, which is a critically important factor in acquiring representative samples and examined along with bronchoalveolar lavage fluid using an in-house multiplex polymerase chain reaction for a broad range of CARV, as well as Chlamydophila and Mycoplasma. The most frequent viruses detected were human rhinovirus and Coronavirus species, all 4 species of which tested were found in bronchoalveolar lavage samples, attesting to lower-respiratory tract involvement. Coronaviruses, in otherwise healthy adults, may be associated with diverse health effects ranging from seemingly trivial upper-airway symptoms, such as mild rhinorrhoea, to fatal pneumonia as illustrated in the severe acute respiratory syndrome epidemic, a

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respiratory disease of zoonotic origin caused by the severe acute respiratory syndrome coronavirus. In lung transplant recipients, coronaviruses can be associated with acute febrile illnesses and are variably persistent for up to several months in some individuals even after the acute illness appears to have resolved, making the interpretation of a concurrent infection with another virus difficult to interpret.

The novel finding of this study was a clear time-dependent association between coronaviruses and the development of CLAD (hazard ratio, 2.30; 1.10-4.80; $P = 0.026$), a finding which has not been reported previously. Given the large number of studies reported in the area, it is tempting to ask how have we missed this association. Is it a matter of not seeing what is there, or not analyzing what we see? Alternatively, is it a regional idiosyncrasy? Examining prior studies in depth provides certain insights but not a complete answer. A broad range of diagnostic tools have been used with differing operational characteristics.[22] The multiplex polymerase chain reaction employed by the authors tests for a raft of viruses that previous tools have not examined. When coronaviruses have been detected, the frequency has been low, so perhaps the answer lies somewhere in between, namely, use of a sensitive tool reflecting a regional propensity.[2,3,9] Irrespective, it is an important addition to our knowledge which is worthy of further study.

Of interest, and perhaps reflecting the immunomodulatory effects of maintenance immune suppression, the authors found that the majority of CARV infections were asymptomatic. There is limited literature regarding the presence of asymptomatic viral carriage in transplant populations. However, screening studies, such as this one, which monitored viral presence in the absence of symptoms, serve to highlight that we have been unaware until now of the reasonably high rate of asymptomatic viral carriage. With the advent of next generation sequencing, a range of other respiratory viruses are being detected in the lower-respiratory tract of lung transplant patients in the absence of symptoms,[23,24] leading to many questions regarding the impact of this viral presence on clinical outcomes. It remains important to further examine this finding in future prospective studies of transient populations of the human respiratory virome, in which CARV appear to be not infrequent and possibly important constituents, especially in the immunosuppressed host. Whether CARV cause dysbiosis and whether they become resident species along with anelloviruses remains to be elucidated but the tools are at hand.[22,25]

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