Plasma cell-rich acute rejection: A morphologic archetype of combined cellular and humoral rejection?

The rate of acute rejection (AR) in the setting of kidney transplantation has declined in recent years, mainly because of improved immunosuppressive regimens. When it occurs, it still remains a challenge for both the medium- and long-term graft survival.[1] Typically, AR is characterized by lymphocytic and macrophage infiltration in the interstitium followed by the attack of these cells, mainly the lymphocytes, on the tubular epithelial cells, which represent the main target of cell-mediated rejection.[2,3] Other inflammatory cells are also present, but usually in small numbers, often altogether constituting <10% of all the interstitial infiltrating cells. These include eosinophils, neutrophils, plasma cells, and mast cells. Among these, the plasma cell abundance in interstitial infiltrates has received much attention during recent past, and this has been recognized as a distinct morphological variant of AR.[4-9] The entity has not yet received due recognition by the Banff classification. Traditionally, Banff acknowledged that plasma cells in the interstitium may be a component of the rejection response, but may also signal past or concurrent infection.[2,3] It was recommended to indicate the presence of conspicuous numbers of cells other than lymphocytes including plasma cells by an asterisk mark on the "i" (interstitial inflammation) score.[2] Almost all the studies addressing the plasma cell-rich AR (PCAR) have found a delayed occurrence of this rejection and a uniformly poor prognosis.[4-9] Some more recent reports have identified the antibody-mediated component in the PCAR. This has added a new and interesting dimension to this entity. In fact, this should not be a surprising finding given the fact that many of the cellular rejections are accompanied by an antibody-mediated component.[10,11] With the increasing use and sophistication of the detection methods for the presence of antibody in the serum or antibody action on the graft tissue, the contribution of this component is likely to increase further.[12,13]

In this issue of the journal, Uppin *et al.* describe a series of seven patients with PCAR associated with antibody-mediated rejection (ABMR).[14] In addition to the conventional morphological study, they stained all the graft biopsies for C4d and screened for donor-specific antibodies (DSA) by the Luminex Technology. C4d was however done on paraffin-embedded tissues and not fresh frozen tissues. All biopsies were indication biopsies. They concluded that PCARs occur late and are associated with a poor prognosis as compared with classic ARs. The authors have probably included only those cases of PCAR in their series, which were accompanied by ABMR, but it must be kept in mind that PCAR is typically considered as a variant of cellular rejection, and not all cases of PCAR are associated with DSA. Nevertheless, this study provides evidence for the increasing role of antibodies in the PCAR setting. Of course, the majority of antibodies are directed against human leukocyte antigen (HLA) but increasingly nonHLA antibodies are also being implicated in graft dysfunction. The study also reports a poor graft outcome in spite of low chronicity scores and an aggressive treatment approach adopted in the study, which is somewhat surprising. We have instead found a good short to medium-term graft outcome with aggressive treatment of the antibody component of PCAR in spite of having higher chronicity scores.[15] The authors need to explore further the factors leading to the poor outcome of their cohort.

These recent observations highlight the need to investigate unusual cases of rejection (in terms of clinical presentation or morphology) for both the cellular and the antibody-mediated components, especially when there is plasma cell enrichment in the interstitial infiltrates. This is because both components require different modes of therapy and if appropriately treated, can have better outcomes. Ancillary techniques of immunofluorescence, immunohistochemistry, and antibody detection methods such as Luminex Technology are useful to realize this objective, but are not widely available, especially in developing countries. C4d staining and test have some limitations, and C4d negative ABMR has been recognized and incorporated in the latest update of Banff classification.[12] In such cases, the use of microcirculation inflammation scores can be helpful in diagnosing ABMR.

It has emerged from the above studies that one of the main factors predisposing to this type of rejection is the relative under-immunosuppression. This may be iatrogenic or due to noncompliance. In the study under discussion, the authors found noncompliance in around 43% of patients. In addition, two out of seven patients

were on antituberculous therapy (ATT). It is known that ATT drugs interact with calcineurin-inhibitors and may lead to inadequate immunosuppression. In fact, Lerut *et al*. described the distinct morphological phenotype of noncompliant patients' graft biopsies, in which plasma cells correlated with humoral mechanisms but not with noncompliance. This aspect needs further studies.

There are no standard guidelines for the management of PCAR. Different centers use different approaches including the use of B-cell and immunoglobulin targeted therapies. The late occurrence of this type of rejection, and higher chronicity scores account for the poor outcome of this variant of rejection. However, we have seen that the grafts can be salvaged by an aggressive treatment approach targeted against both cellular and humoral components.[15]

In conclusion, Uppin *et al*. deserve compliments for sharing their experience of an uncommon phenomenon affecting kidney grafts and providing a link between cellular and humoral components in PCAR. This experience should stimulate the authors for further studies for identifying the risk factors predisposing to this type of rejection and to elucidate the factors associated with poor outcome despite aggressive treatment.

M. Mubarak

Department of Histopathology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan

Address for correspondence:
Dr. M. Mubarak,
Department of Histopathology, Sindh Institute of Urology and Transplantation, Karachi - 74200, Pakistan.
E-mail: drmubaraksiut@yahoo.com

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