Renal Transplant Pathology Series-V: Banff Category 4 – Acute rejection (Acute/active T-cell-mediated rejection [TCMR]) Part II (Plasma cell-rich acute rejection)

Muhammed Mubarak, Shaheera Shakeel, Rahma Rashid

Correspondence to
Dr. Muhammed Mubarak

**Professor of Pathology and HOD
JK Department of Histopathology,
Sindh Institute of Urology and Transplantation (SIUT),
Karachi, Pakistan.**

DOI: 10.53778/pjkd54189

Email address: drmubaraksiut@yahoo.com

PJKD 2020;5(4):115-119

Banff classification of renal allograft pathology has evolved considerably over the past 30 years and has undergone significant changes in many of the original diagnostic categories. With this evolution, it has increased in complexity and level of difficulty in routine clinical application. To make it user friendly, this series of tutorials has been planned. In this pictorial, we aim to provide an illustrated presentation of the Banff classification categories and practical tips and tricks to identify and report the lesions. This will be useful for better understanding of renal transplant pathology for trainees and residents of nephrology and histopathology as well as for practicing pathologists and nephrologists.

Banff category 4. Acute rejection (Acute/active T-cell-mediated rejection [TCMR])- Part II (Plasma cell-rich acute rejection)

The main lesion of acute/active T-cell-mediated rejection (TCMR) was discussed in the previous issue of PJKD. In this issue, a special type or variant of active rejection, *i.e.*, plasma cell-rich acute/active rejection (PCAR) is discussed. Although, it is not included as a formal category in the synoptic table of the Banff classification, it is discussed in text in Banff classifications under the TCMR category. Herein, we discuss this entity along with a few representative images and explanation of the lesions.

Plasma cell-rich acute rejection (PCAR):

Plasma cell-rich acute rejection (PCAR) is a rare subtype of rejection with delayed presentation, usually developing 6 months after transplantation. There are no standardized or uniform criteria for the diagnosis of PCAR, which is reflected by varying rates of its incidence in different biopsy series varying from 4% to 14%. This entity has not yet been properly classified in Banff classification, which was last updated in 2019. Some authors have suggested 10% plasma cells in the graft interstitial infiltrate as the minimum threshold for diagnosing this variant of rejection. Other authors have used the cut off value of 20% of plasma cells to classify it. Still others have used the criteria of at least 300 plasma cells per 10 high power fields (40x) to diagnose PCAR. This morphologic pattern of acute rejection has typically been classified as part of TCMR but it may represent mixed type of antibody-mediated rejection (AMR) and TCMR.

The etiology and precise pathogenesis of plasma cell infiltration in graft parenchyma is not well understood. Previous studies have found plasma cells in graft interstitium associated with drug hypersensitivity, infections or post-transplant lymphoproliferative disorder (PTLD) nephropathy. Moreover, reflux nephropathy, Epstein-Barr virus infection and polyoma virus nephropathy (PVN) cases also feature plasma cell infiltration in graft parenchyma. After the above causes are excluded by carefully relevant investigations, the presence of plasma cells in the interstitial infiltrate should raise the suspicion of PCAR. Banff classification has acknowledged the proposal of presence of plasma cells as a component of cellular rejection process. It was recommended to use asterisk (*) with i (interstitial inflammation) if significant number of plasma cells are found in the infiltrate. In

fact, the term plasma cell-rich was coined by Lorraine Racusen, whose group first defined this entity. With the advancements in circulating antibody detection methods, a few researchers including ourselves have found antibodies in the serum of a significant number of patients with PCAR, indicating a concurrent component of AMR. At the same time, it has been reported that not all cases of PCAR are associated with donor specific antibodies (DSA); as a result, this entity is considered as an aggressive variant of TCMR. One additional risk factor for plasma cell infiltration in the graft parenchyma, which has been highlighted by some recent studies, represents under-immunosuppression, which may be iatrogenic or due to non-compliance to therapy. According to one study from Germany, plasma-cell enrichment is not a prognostic marker on its own, but it is an indicator of a more adverse outcome because it is often accompanied by the appearance or subsequent development of vascular rejection or transplant glomerulopathy (TG). The detection of PR-rich rejection processes should therefore encourage the clinician to intensify the immunosuppressive treatment. Plasma cells are usually found in clusters but may be found in dispersed form. It should be noted that plasma cells do not invade the tubules; hence, they are not associated with plasma cell tubulitis. However, concomitant lymphocytic tubulitis is often found and determines the type of rejection.

There are no standardized treatment protocols for PCAR, mainly due to scarcity of cases reported in the literature and ambivalence in diagnostic criteria. B cell and immunoglobulin targeted therapies have been used by different centers. Several authors have suggested that despite of aggressive immunotherapy, PCAR has uniformly poor prognosis in terms of graft loss. Some authors have found PCAR to be resistant to aggressive management including steroid pulse therapy, intravenous immunoglobulins, anti-thymocyte globulins (ATG) and in some cases, plasmapheresis also. These observations validate the overall poor response of PCAR to augmented immunosuppression. More recent reports, however, have shown good response to combined multimodal therapy directed against both T cells and antibodies. We have recently reported that graft loss can be prevented by using aggressive and targeted therapy against both cellular and humoral components. In one of the studies done at our institute, the authors used proteasome inhibitors, in addition to aggressive multimodal therapy, in the treatment of PCAR which has traditionally been used in the desensitization protocols. It was concluded that PCAR can be resolved with improved graft survival of 90% at 2 years with the advent of Bortezomib-based treatments.

Figure 1: Low-power photomicrograph showing two cores of renal allograft biopsy with almost diffuse interstitial inflammatory cell infiltration amounting to i3 (>50% of the cross-sectional area of two cores). The nature of the cellular infiltrate or tubulitis (t) cannot be appreciated at this magnification (H&E, ×40).

Figure 2: High-power photomicrograph showing a representative area of renal allograft biopsy with almost diffuse interstitial inflammatory cell infiltration amounting to i3 (>50% of the cross-sectional area of two cores). At this magnification, many eosinophils (bright red cytoplasm and bilobed nuclei) and plasma cells (large oval cells with eccentric nuclei and abundant amphophilic cytoplasm) can be appreciated. There is also accompanying prominent interstitial edema (H&E, $\times 400$).

Figure 3: High-power photomicrograph showing a representative area of renal allograft biopsy with almost diffuse interstitial inflammatory cell infiltration amounting to i3 (>50% of the cross-sectional area of two cores). At this magnification, many eosinophils (bright red cytoplasm and bilobed nuclei) and plasma cells (large oval cells with eccentric nuclei and abundant amphophilic cytoplasm) can be appreciated. Note that plasma cells are often found in clusters (circle) (H&E, $\times 400$).

Figure 4: Another high-power photomicrograph showing two clusters of plasma cells (large oval cells with eccentric nuclei and abundant amphophilic cytoplasm) (circles) Rest of the cells comprise of lymphocytes and histiocytes (H&E, $\times 400$).

Figure 5: A high-power photomicrograph showing three tubules with varying degrees of lymphocytic tubulitis. These tubules are only mildly atrophic, hence can be used for scoring “t” lesion. Note the presence of plasma cells in the background interstitial inflammatory cell infiltrate. Plasma cells are incapable of invading the tubules; hence, no plasmacytic tubulitis is reported (PAS, $\times 400$).

Figure 6: A high-power photomicrograph showing significant amount of interstitial fibrosis (stained green) in a case of plasma cell rich rejection. This amount of interstitial fibrosis may be accompanied by suboptimal response to therapy (Trichrome, $\times 400$).

Further reading:

1. Charney DA, Nadasdy T, Wing-Hong-A, Racusen LC. Plasma cell-rich acute renal allograft rejection. *Transplantation* 1999; 27: 791-7.
2. Mubarak M. Plasma cell-rich acute rejection: A morphologic archetype of combined cellular and humoral rejection?. *Indian J Nephrol*. 2016;26(3):157-158.
3. Mubarak M, Abbas K, Zafar MN, Aziz T. Immunohistopathologic characterization of plasma cell-rich acute rejection in living-related renal transplant recipients. *Exp Clin Transplant*. 2017;15(5):516-520.
4. Rogers NM, Lawton PD, Jose MD. Plasma cell infiltrates and renal allograft outcomes in indigenous and non-indigenous people of the Northern Territory of Australia. *Nephrology* 2011; 16:777-83.
5. Gupta R, Sharma A, Mahanta PJ, Agarwal S K, Dinda A K. Plasma cell-rich acute rejection of the renal allograft: A distinctive morphologic form of acute rejection? *Indian J Nephrol* 2012; 22:184-8.
6. Desvaux D, Le Gouvello S, Pastural M et al. Acute renal allograft rejections with major interstitial oedema and plasma cell-rich infiltrates: high gamma-interferon expression and poor clinical outcome. *Nephrol Dial Transplant* 2004; 19(4):933-9.
7. Gärtner V, Eigentler TK, Viebahn R. Plasma cell-rich rejection processes in renal transplantation: morphology and prognostic relevance. *Transplantation* 2006; 81(7):986-91.
8. Meehan SM, Domer P, Josephson M et al. The clinical and pathologic implications of plasmacytic infiltrates in percutaneous renal allograft biopsies. *Hum Pathol*. 2001; 32(2):205-15.
9. Martin L, Charon-Barra C, Bocrie O et al. Detection of plasma cells, C4d deposits and donor-specific antibodies on sequential graft biopsies of renal transplant recipients with chronic dysfunction. *Transpl Immunol* 2010; 22(3-4):110-4.
10. Raghavan R, Jeroudi A, Achkar K, Gaber AO, Patel SJ, Abdellatif A. Bortezomib in kidney transplantation. *J Transplant*; 2010;2010:698594
11. Abbas K, Mubarak M, Zafar MN, Musharraf W, Imam M, Aziz T, Rizvi AH. Management of Plasma Cell-Rich Acute Rejection in Living-Related Kidney Transplant: Role of Proteasome Inhibitor. *Exp Clin Transplant*. 2019;17(1):42-46.