Renal Transplant Pathology Series-IV: Category 3-Borderline Changes

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Banff classification of renal allograft pathology has evolved considerably over the past 30 years and has truly become a multidisciplinary schema. With this evolution, it has also increased in complexity and level of difficulty. It is no longer possible for a sole histopathologist without input from other clinical colleagues and pathologists, such as immunologists, to accurately diagnose and classify renal transplant pathology, particularly rejection. 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 3. Borderline changes (BC)

In this tutorial, we will discuss the rationale behind the creation and the criteria for diagnosis of category 3 of Banff classification, i.e., borderline changes (BC), also known as borderline rejection (BLR). As discussed in previous issues of this section, renal allograft biopsies play a crucial role in the diagnosis and management of renal transplant recipients (RTRs). In this context, a precise and skillful interpretation of graft biopsies is of paramount importance in the optimal management of these patients. Banff classification of renal allograft pathology represents a standardized tool for reproducibly interpreting the pathological lesions and classifying the rejection processes. Banff classification of kidney transplant pathology was formulated in 1991 and was first published in full paper form in 1993. A major reshuffling of the classification took place in 1997 and from there onwards, Banff 97 classification and its regular updates achieved the status of a truly international benchmark for interpreting the renal allograft biopsies.

The Banff classification recognized a category of BC in reporting the renal graft pathological lesions since its beginning and the category still exists even after 30 years of refinements and evolutions in the classification. This category exists only in the tubulointerstitial type of rejection (i.e., in Type I rejection) and is used when there is

- Mild (i1) to moderate (i2) interstitial inflammation
- Tubulitis is of mild degree only (t1)
- No arteritis is present (v0).

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The clinical significance of this lesion is still controversial and is largely determined by the clinical phenotype of the case. The implications of this lesion may vary depending on the source of donor organ, time post-transplant and the indication and timing of renal graft biopsies. Most of the studies on this category have been carried out in deceased donor transplantation programs. Few studies are available on the clinical relevance of this finding in live-related renal transplant setting.

The criteria of BC diagnosis have changed over time but essentially consist of a combination of:

- Interstitial inflammation (i)
- Tubulitis (t) scores
- Below the threshold level required for the diagnosis of rejection, i.e., i2, t2.

The initial criteria for borderline infiltrates were established at the Banff 1991 Conference, describing a “very mild” category of acute rejection with no intimal arteritis and only mild to moderate focal mononuclear interstitial inflammatory cell infiltration (i1 or i2) with foci of mild tubulitis (t1; 1 to 4 mononuclear cells per tubular cross-section). In this initial classification, “no treatment” was recommended. This category was highly prevalent in both protocol and for-cause biopsies, being as high as 44% in 1-month protocol biopsies. In 2005, the Banff group expanded the “BC” category to include lesions with minimal interstitial inflammatory cell infiltration (i0) to i3 with t0 or t1 or t2, t3 with i0,i1. Clinical significance and optimal treatment of i0 borderline infiltrates is uncertain. Studies suggest that i0 borderline infiltrates may have a more favorable prognosis than borderline infiltrates with higher grades of interstitial inflammation (i1, i2 or i3). This created further confusion regarding the clinical significance and particularly the treatment of such cellular infiltrates.

The Banff diagnostic category 3, i.e., the BC, is the most controversial among all the diagnostic categories of renal allograft pathology. Its reported frequency varies widely and ranges from 46 to 74 % on for-cause graft biopsies performed at different time points after transplantation. This category is also the most problematic from the point of view of treatment of the patient. In fact, this category does not represent a true pathobiological phenomenon. Rather, it represents a heterogeneous group of lesions encompassing lesions with minimal, nonspecific, inconsequential inflammation to clinically significant T cell mediated rejection, capable of immune-mediated graft injury resulting in inferior functional, immunological and histological outcomes. In fact, it represents an arbitrary category of graft pathology that has been created primarily because of varying clinical criteria and timing of renal allograft biopsies. Ideally, a biopsy should be categorized as rejection or no rejection, but practically, it is always not so clear-cut.

We know that the biological process of rejection is a gradual and patchy process, which takes time to develop. If a biopsy is performed very early during the development of rejection, the pathological lesions will not have reached the threshold of diagnosis of rejection and will necessarily be classified as borderline category. Thus, there is a need to standardize not only the criteria for the diagnosis and classification of graft pathology but also for clinical indications and timing of biopsies, which are as variable as there are physicians and patients.

A series of representative images of biopsies with category 3 (BC) of Banff classification are illustrated in Figures 1 to 7.

Figure 1. Low-power photomicrograph showing two cores of renal allograft biopsy with minimal focal interstitial inflammatory cell infiltration amounting to i0 (<10% of the cross-sectional area of two cores). This degree of interstitial inflammation was initially not included in BC category. However, in 2005 revision of Banff classification, it was also included as a component of BC category. (H&E, ×40).

Figure 2. Low-power photomicrograph showing one of the two cores of renal allograft biopsy shown in Figure 1 with minimal focal interstitial inflammatory cell infiltration amounting to i0 (<10% of the cross-sectional area of two cores). (H&E, ×100).

Figure 3. Low-power photomicrograph showing single core of renal allograft biopsy with mild focal interstitial inflammatory cell infiltration amounting to i1 (10 to 25% of the cross-sectional area of the core). On its own, this degree of interstitial inflammation is not sufficient to diagnose rejection. (H&E, ×40).

Figure 4. Low-power photomicrograph showing single core of renal allograft biopsy with mild focal interstitial inflammatory cell infiltration amounting to i1 (10 to 25%% of the cross-sectional area of the core). (H&E, ×100).

Figure 5. Medium-power photomicrograph showing single core of renal allograft biopsy with moderate interstitial inflammatory cell infiltration amounting to i2 (25 to 50% of the cross-sectional area of the core). Even this degree of inflammation in the absence of t2 is insufficient to diagnose rejection. (H&E, $\times 200$).

Figure 6. High-power photomicrograph showing two tubules with 2-3 lymphocytes invading the basement membranes and surrounded by halo. Both of these score as t1. There is mild to moderate interstitial infiltrate and edema in the background. This combination of i and t scores qualifies for borderline category of Banff classification (PAS, $\times 400$).

Figure 7. High-power photomicrograph showing one tubule (in the lower mid field) with 3 lymphocytes invading the basement membrane and surrounded by clear hallow. This also scores as t1. There is mild interstitial infiltrate in the background. Both these findings represent borderline changes (PAS, $\times 400$).

Further reading:

1. Nankivell BJ, Agrawal N, Sharma A, Taverniti A, P'Ng CH, Shingde M, et al. The clinical and pathological significance of borderline T cell-mediated rejection. *Am J Transplant* 2019;19:1452-63.
2. Mubarak M, Shakeel S, Abbas K, Aziz T, Zafar MN, Naqvi SA, Rizvi SA. Borderline Changes on Dysfunctional Renal Allograft Biopsies: Clinical Relevance in a Living Related Renal Transplant Setting. *Exp Clin Transplant*. 2017 Feb;15(Suppl 1):24-27.
3. Figueiredo AC, Leal R, Mira F, Pardinhas C, Rodrigues L, Marques MG, Santos L, Romãozinho C, Sá H, Figueiredo A, Alves R. Borderline Changes in Renal Transplantation: Are We Aware of the Real Impact in Graft Survival? *Transplant Proc*. 2021 May 13:S0041-1345(21)00240-2.
4. Beimler J, Zeier M. Borderline rejection after renal transplantation--to treat or not to treat. *Clin Transplant*. 2009;23 Suppl 21:19-25.
5. Dale LA, Brennan C, Batal I, Morris H, Jain NG, Valeri A, et al. Treatment of borderline infiltrates with minimal inflammation in kidney transplant recipients has no effect on allograft or patient outcomes. *Clin Transplant*. 2020 Sep;34(9):e14019. doi: 10.1111/ctr.14019. Epub 2020 Jul 4.
6. Becker JU, Chang A, Nickleit V, Randhawa P, Roufosse C. Banff Borderline Changes Suspicious for Acute T Cell-Mediated Rejection: Where Do We Stand? *Am J Transplant* 2016;16:2654-60.