Histological assessment of pre-implantation allograft biopsies: does it matters?

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We often face the dilemma of accepting or rejecting extended criteria or "high risk" kidneys and having to make a quick decision, usually in the middle of the night and without much time to think.

Histological assessment by biopsy prior to implantation, also called zero-hour biopsy, may be useful to report on the status of the organ. However, the question that requires urgent answering is: can these biopsies predict the short and long term outcomes of these grafts and provide prognostic information, in addition to the chronic lesions associated with the donor kidney?

The first recommendation for pre-implant biopsy was made in 1995, by Gaber *et al.*, and since then several studies have sought to establish the predictive value of these biopsies, yielding controversial results.[1] For instance, in Europe they rarely do pre-implantation biopsies, and extended criteria donor kidneys (ECD) are successfully transplanted, according to the program called Senior Kidney Transplant Program, while in the U.S. the discarding rate of these kidneys is about 40%.[2-4]

In this JBN issue, Pegas *et al.* tried to answer this question by retrospectively analyzing 110 pre-implantation biopsies (harvested in wedge shapes) from living donors (LD, n = 27), "standard" (SCD, n = 47) and expanded criteria (ECD, n = 36) kidneys. The vast majority of recipients was treated with calcineurin inhibitors (74%), mycophenolic acid (90%) and 30% received induction therapy with monoclonal anti-interleukin 2 receptor antibodies. The MDRD formula was used to calculate the glomerular filtration rate (GFR), which was correlated with the findings from the donor biopsy and classified according to the Remuzzi criteria.[5]

The outcomes were analyzed after one year of transplantation and, as expected, the authors found that LD recipients had better GFR rates than recipients from deceased donors. Also, GFR rates from SCD recipients were better than their ECD counterparts, regardless of histological findings. Still, kidneys with mild histological changes had GFR rates better than those with moderate/intense lesions. The one-year survival of 110 recipients studied was not different when stratified according to histological scores (mild, moderate, severe), although the survival of the population whose kidneys showed marked lesions was numerically lower.

Using multivariate analysis applied to the entire study population, the authors showed that the lesions from glomerulosclerosis and atherosclerosis were significantly associated with lower rates of GFR after 1 year. However, the same analysis carried out for the population of deceased donors only showed association between GFR and glomerulosclerosis.

Unfortunately, Pegas *et al.* did not report, even if only for discussion purposes, the GFR results from ECD and SCD correlated with the histological scores used to evaluate the different kidney compartments. Moreover, and as acknowledged by the authors themselves, their study had limitations that prevented definitive conclusions: a small sample, a group of heterogeneous biopsies from

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LD, SCD and ECD, small number of recipients receiving induction therapy - which could explain the 35% rejection rate and the high DGF rate.

Interestingly, three of the five kidneys that met the histologic criteria for disposal and were transplanted had good outcomes after 1 year and also, as mentioned by the authors, against logic itself, kidneys with a marked degree of histological lesions showed GFR that was not different from those with lesions classified as mild/moderate. These contradictory findings illustrate the uncertainty surrounding the decision process to discard a kidney based solely on the histological findings of the biopsy.

Unambiguous guidance on the appropriate method to obtain and report the results of preimplantation biopsies are still unclear and, therefore, the value of information from them remains controversial. For example: what is the right time to make a biopsy (before or after organ reperfusion)? Should histological lesions be classified by the current Banff or other criteria? How should one evaluate the impact of the score used to evaluate the biopsies from ECD kidneys in patient outcomes? Do the benefits of information obtained from these biopsies outweigh the risks of possible complications (bleeding of heparinized recipients)?

The growth of molecular techniques used to define the molecules that could be associated with the risk of graft dysfunction, early and later on, enabling the identification of molecular transcripts expressed in pre-implantation biopsies, will certainly be very useful for predicting outcomes from different types of kidneys.[6] We recently reported that ECD kidneys have an inflammatory molecular profile and suggested that in addition to histopathological findings, these results could explain the worse outcomes observed among the recipients of these kidneys.[7]

The use of these new molecular techniques to evaluate pre-implantation biopsies certainly provide more information and support for the transplant physician to better make this difficult decision of accepting or discarding a kidney.

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