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Original Article

Medullary nephritis in the diagnosis of acute cellular rejection

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ABSTRACT

Background: The purpose of this study was to understand the role of lymphomononuclear inflammation (nephritis) in the renal allograft medulla of transplant recipients with acute dysfunction, by comparing the immunophenotype of inflammatory cells present in the medulla and cortex of kidney graft biopsies.
Method: This is a retrospective study of 113 renal allograft needle biopsies, presenting with medullary nephritis, divided into two groups according to the main location of nephritis: in cortical and medullary regions (corticomedullary nephritis) or exclusively in the medullary region (medullary nephritis). We performed immunohistochemistry (IHC) of the cells composing the inflammatory foci, using anti-CD4, CD8, CD20, CD68, and CD138 antibodies, respectively for T-helper cells, cytotoxic T cells, B lymphocytes, macrophages and plasmocytes. The clinical follow-up of the patients was correlated with the morphological findings.
Results: The nephritis was corticomedullary in 66 of the 113 cases (58.4%) and exclusively medullary in the remaining 47 cases (41.6%). The immunophenotype of the inflammatory cells was similar in the cortical and medullary compartments and were mainly: cytotoxic T lymphocytes (CD8) and macrophages CD68. The immunosuppressive therapeutic response to acute cellular rejection (ACR), based on decreasing of serum creatinine values, was 81.8% in the patients of the corticomedullary nephritis group and 63.6% in those of the medullary nephritis group.
Conclusion: Medullary nephritis in renal allograft biopsies may indicate ACR, as could be noted by the immunophenotype, which presented the same cellular mediators of rejection seen in the allograft cortex, and by the positive immunosuppressive therapeutic response observed in most patients.
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Introduction

Biopsy has been an important diagnostic tool in acute rejection, which is a common complication in renal grafting, requiring immediate therapeutic management [1–4]. Acute rejection is defined as an acute deterioration in the allograft function, associated with specific pathological changes, presumed to be secondary to cell or humoral mediated immune mechanisms. Acute cellular rejection (ACR) is the more commonly observed form of rejection in the renal allograft and is characterized by lymphomononuclear (LMN) interstitial inflammation, with injury to tubules (tubulitis) and, more rarely, vessels (vasculitis). These changes are, most of the time, observed in the cortical region and meet the morphological criteria of the Banff classification, which postulates that an adequate and representative biopsy should contain at least seven glomeruli and one artery [5–7]. However, a biopsy not rare may represent only the medulla (in 5% of cases, according to a previous study) [8]. In this case, inflammation (nephritis) in the medullary region has proven to be a diagnostic challenge, especially if one cannot wait for a second sample. In Fig. 1 we illustrate a medullary biopsy with LMN nephritis.

The present study aimed to understand the role of nephritis in the medullary region of the renal allograft, in post-transplant patients with acute dysfunction. Through comparative immunohistochemistry (IHC) of the inflammatory cells in cortical and medullary regions and its correlation with the patients' immunosuppressive therapeutic response, we intend to demonstrate that medullary nephritis in the graft may indicate ACR.

Abbreviations: ACR, acute cellular rejection; IHQ, immunohistochemistry; LMN, lymphomononuclear; Ncm, corticomedullary nephritis; Nm, medullary nephritis.

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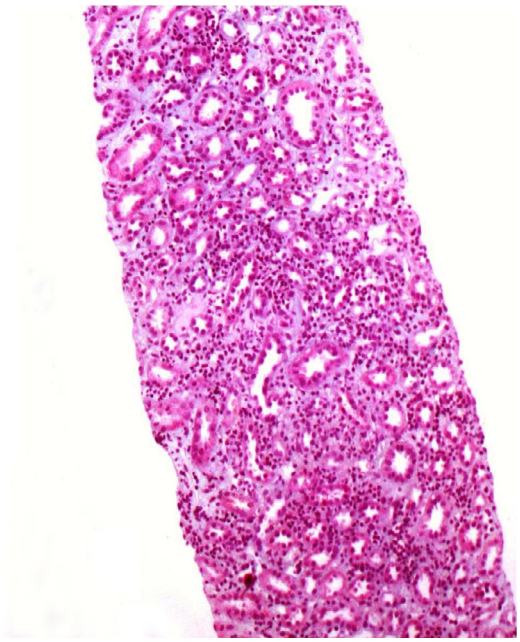

Fig. 1. Example of a biopsy with medullary nephritis. Here we show a biopsy where only the graft's medulla has been sampled and where there was dense tubulointerstitial lymphomononuclear inflammatory process (H&E, ×100).

Method

This paper reports a retrospective observational study on renal allograft needle biopsies presenting with medullary nephritis, which was performed by clinical indication in post-transplant patients with acute dysfunction. Among all consecutive needle biopsies received in our Department, between 2000 and 2010, from renal transplant recipients at the Hospital do Rim (Sao Paulo, Brazil), we selected those that presented with at least a mild degree of LMN inflammation and tubulitis in the medullary region (a minimum of i1 and t1 Banff scores) [5–7]. Biopsies without proper cortical representation (with less than seven glomeruli and one artery) were excluded from the study.

Relevant clinical and laboratory data were collected from the patients' charts, and renal function measurement was estimated from the serum creatinine values before and after biopsy. The standard immunosuppression regimen used a combination of three drugs: cyclosporine or tacrolimus, azathioprine or mycophenolate sodium, and a corticosteroid. In cases where immunosuppressive therapy for ACR was adopted, the patients received methylprednisolone at a dose of 0.5 or 1.0 g per day for 3 or 5 days (pulse therapy).

The therapeutic response was considered positive when a normalization of the serum creatinine value or its return to baseline value (before biopsy) was observed. We also measure the percentage of cases with positive therapeutic response to correlate with the predominant site of inflammatory changes observed and the diagnostic category given.

All histological analyses were performed independently by two experienced nephropathologists. Slides with 3 μm tissue sections were examined on haematoxylin and eosin (HE), Masson's trichrome (MA) and periodic acid-Schiff (PAS) stainings. The diagnoses were reviewed according to the criteria of the Banff 2009 classification [5–7] and concordance was obtained in all results. The biopsies were separated into two groups, according to the main location of nephritis: in both cortical and medullary regions (corticomedullary nephritis or Ncm) or exclusively in the medullary region (medullary nephritis only or Nm). In Fig. 2 we show an example of a case from the Nm group. To approach the Banff diagnostic categories, we applied the same criteria used to evaluate cortical rejection, measured separately in cortex and medulla, in both the groups Ncm (with corticomedullary nephritis) and Nm (with medullary nephritis only). The intensity of the inflamed area was scored 1–3, respectively for mild (10–25%), moderate (26–50%) or severe (more than 50%) tubulointerstitial inflammation The infiltrated lymphocytes per tubular cross section was also scored 1–3, respectively for mild (1–4), moderate (5–10) or severe (more than 10) tubulitis. The percentage of biopsies allocated to each Banff category was compared between the cortex and medulla.

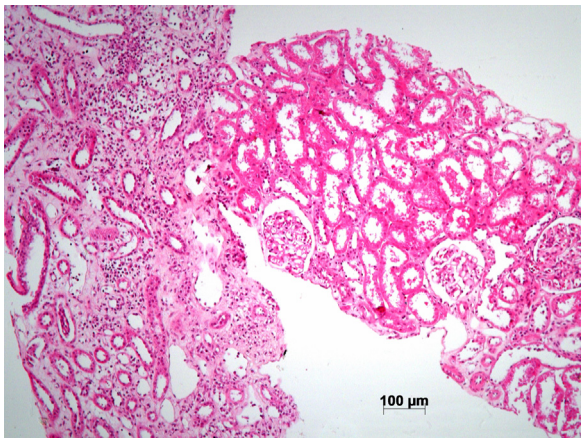

Fig. 2. Photomicrograph of a biopsy from the Nm group (with medullary nephritis exclusive). Note that only the medulla is involved by the process (left), sparing the cortex (right) (H&E, ×100).

To perform immunohistochemistry, 4 μm tissue sections were collected on polarized slides and submitted to the method using the Dako Autostainer system. The immunophenotype of inflammatory cells was evaluated for the CD4, CD8, CD20, CD68, and CD138 antigens, using the corresponding Ready-to-Use Flex MX antibodies (Dako products, California, USA) for *T-helper* lymphocyte, cytotoxic T lymphocyte, B lymphocyte, macrophage, and plasma cell. In addition, the C4d complement fraction was screened to detect any association with the less common type of rejection mediated by antibodies, i.e., acute humoral rejection. To exclude a possible

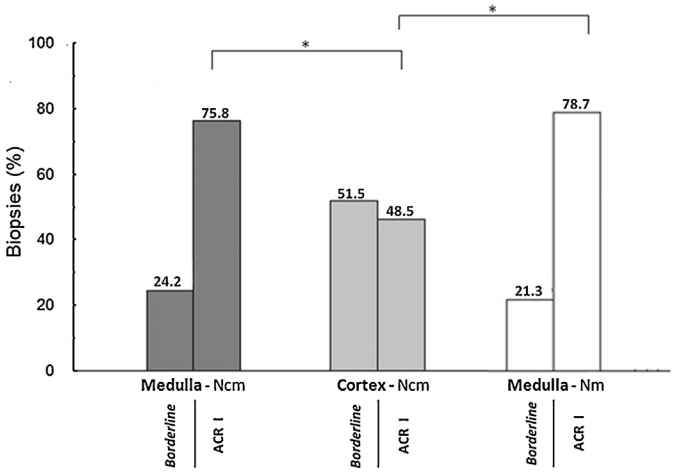

Fig. 3. Banff diagnostic categories applied to medullary nephritis. Acute Cellular Rejection type I (ACR I) prevailed over the *borderline* changes in the medulla of most cases: in 75.8% in the biopsies with corticomedullary nephritis (Ncm group; dark grey bars) and in 78.7% in those with solely medullary nephritis (Nm group; white bars). In the cortex (Ncm group; light grey bars), ACR I and borderline changes occurred in almost the same proportion of cases. The difference with the medulla was statistically significant ($^{*}p < 0.001$).

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