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ROLA BIOPSJI PROTOKOLARNEJ W DIAGNOSTYCE PRZESZCZEPU NERKOWEGO

STRESZCZENIE W JĘZYKI ANGIELSKIM

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

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ROLE OF PROTOCOL BIOPSY IN THE DIAGNOSIS OF RENAL TRANSPLANT

BACKGROUND

Improving long-term kidney graft survival remains one of the fundamental challenges in modern transplant medicine. The primary cause of late graft loss is the accumulation of irreversible chronic lesions, typically resulting from untreated or treatment-resistant rejection processes. A decline in kidney graft function, manifested by increased serum creatinine levels and decreased eGFR, usually reflects a late stage of underlying pathological changes. Importantly, such abnormalities can be detected much earlier through histopathological examination of renal biopsy specimens, providing an opportunity to initiate targeted therapy before irreversible organ damage occurs.

Protocol biopsies are designed to detect subclinical pathology at an early stage, when progression may still be preventable. Over the past 15 years, opinions regarding the diagnostic and prognostic value of protocol kidney biopsies have varied significantly. After the introduction of potent immunosuppressive drugs in the 1990s—leading to a decline in the incidence of T-cell–mediated acute rejection—many researchers questioned the rationale for performing protocol biopsies, arguing that they did not provide information that would impact therapeutic decision-making. However, recent studies have demonstrated that the true incidence of rejection, particularly antibody-mediated forms, is higher than previously thought and that such processes can progress silently, without clinical signs. These findings have renewed interest in protocol biopsies as a tool for detecting clinically inapparent pathologies at a stage when therapeutic intervention may alter the disease course.

Nevertheless, kidney biopsy is an invasive procedure and thus carries a risk of complications. In this context, it is essential to demonstrate the clinical utility of protocol biopsies through an analysis of histopathological findings in asymptomatic transplant recipients and to identify subgroups of patients who may benefit most from this strategy. Simultaneously, novel diagnostic options—such as the detection of kidney injury biomarkers in blood or urine (the so-called “liquid biopsy”)—are emerging. Protocol biopsies remain rarely used in kidney transplant monitoring both in Poland and globally. This likely reflects a lack of studies assessing their practical value in post-transplant management. The presented series of studies and derived conclusions represent another step toward the recognition and definition of the diagnostic role of protocol biopsy in transplant centers.

OBJECTIVE

The main objective of the study was to evaluate the diagnostic value of protocol biopsy and selected biomarkers of kidney damage (so-called liquid biopsy) in detecting subclinical changes in the transplanted kidney. The specific objectives of the study focused on the following issues: (i) evaluation of the efficacy of protocol biopsy in detecting subclinical lesions of the transplanted kidney - analysis of the frequency and histopathological characteristics of lesions in transplant recipients; (ii) evaluation of the diagnostic utility of protocol biopsy against selected biomarkers in identifying early graft damage - evaluation of the utility of "liquid biopsy" and classical laboratory indicators; (iii) identification of risk factors for adverse prognosis in transplanted kidney recipients - analysis of correlations between lipid profiles, inflammatory markers, and histopathology in protocol biopsy; (iv) price of safety and efficacy of protocol biopsy compared to standard methods of monitoring transplanted kidney function - analysis of complications and clinical efficacy of this method in daily transplant practice.

MATERIAL AND METHODS

The dissertation was based on four scientific publications, which together provided a structured foundation for analyzing the diagnostic and prognostic value of protocol biopsy and biomarkers of transplant kidney injury. The first study was conducted as a retrospective analysis of a consecutive series of 72 patients under the care of the Department of Transplant Medicine, Nephrology and Internal Medicine who underwent kidney transplantation between 2014 and 2018, followed by protocol biopsies of the transplanted kidney at the 3rd and 12th months after the procedure. Both clinical and laboratory data were analyzed, as well as the results of histopathologic examination of sections taken by thick-needle biopsy of the kidney. It should be emphasized that the author of the dissertation, doing his residency in nephrology at the Department of Transplant Medicine, Nephrology and Internal Medicine from 2016 to 2020, actively participated in the performance of transplanted kidney biopsy procedures in this subgroup of patients analyzed in the work who underwent kidney transplantation in 2016-2018, and also participated in the qualification and preparation of these patients and care in the period after kidney biopsy, as well as in the chronic care of these patients under the care of the Department. What was noteworthy about the results of the study was the relatively high frequency of visualized lesions, as 40% of the biopsy materials analyzed detected histopathological changes. Furthermore, the study established dyslipidemia as an independent risk factor for the development of clinically silent lesions in the transplanted kidney. The results of the study have proven the utility of using protocol biopsy as a diagnostic tool and represent

a further step toward developing a patient profile that will achieve the greatest benefit from the use of this invasive procedure.

The next two papers included in the publication series were an overview discussion of the current state of knowledge of protocol biopsy and other diagnostic tools, i.e. modern markers of kidney damage, or so-called liquid biopsy, taking into account the previous clinical experience at the author's home center.

The fourth paper was designed and conducted as a systematic review with meta-analysis. The purpose of this study was to determine the predictive value of the soluble receptor for urokinase plasminogen activator (suPAR) in patients with acute kidney injury (AKI). For this purpose, electronic writing databases (PubMed Central, EMBASE, Cochrane) were searched using predefined keywords. The final search of the above databases took place on January 10, 2023. The search revealed 335 publications, out of which 9 studies with a total of 6151 patients were included after full meta-analysis. The utility of suPAR in the prediction of acute kidney injury was demonstrated, which exemplifies the utility of modern, non-invasive markers of kidney injury in diagnosis and may exemplify the use of diagnostic methods other than biopsy, which could also be extrapolated to renal transplant recipients in the future.

RESULTS

The retrospective analysis included 72 kidney recipients who underwent a total of 144 protocol biopsies at the 3rd and 12th months after transplantation. Histopathological abnormalities were found in 40% of cases. The most common lesions were subclinical cellular rejection (19.4%), borderline lesions (8.3%), BK virus infection (5.6%), and thrombotic microangiopathy (2.8%). In many cases, these lesions were present with normal creatinine and eGFR values, confirming the value of protocol biopsy in detecting subclinical lesions not seen by routine laboratory diagnosis. Analysis of clinical data showed that patients with the presence of organic lesions in the graft had significantly lower levels of total cholesterol ($p = 0.003$), HDL ($p = 0.015$), LDL ($p < 0.001$), and triglycerides ($p = 0.044$) compared to patients without histopathological changes. Dyslipidemia was also found to be a risk factor for graft failure. In correlation analysis, ischemia ($r = 0.22$), BMI ($r = 0.21$), and hypercholesterolemia ($r = 0.20$) had the strongest positive correlation with the presence of lesions, while negative correlation was shown for HDL ($r = -0.33$), LDL ($r = -0.31$), and total cholesterol ($r = -0.30$) values.

The clinical results were complemented by an in-depth systematic analysis and meta-analysis on the role of selected biomarkers in the diagnosis of renal allograft injury. Special attention was paid to suPAR (soluble urokinase-type plasminogen activator receptor) protein, considered

an indicator of immune activation and risk of endothelial injury. The meta-analysis included 12 clinical trials involving 2,210 patients and showed a significant association between elevated suPAR levels and the incidence of acute kidney injury (AKI) - both in the general population and among transplant recipients. The pooled mean difference (MD) of suPAR levels between the group with and without recurrent AF was 2.22 (95% CI: 0.84-3.61; p = 0.002). The difference between groups was also significant in the subgroup of studies that assessed suPAR using the 3D technique (MD = 2.20; 95% CI: 0.42-3.98; p = 0.02). These results confirm that suPAR can be an effective non-invasive marker for early detection of renal graft injury, as well as its prognosis.

CONCLUSIONS

Protocol biopsy is an effective diagnostic tool for early detection of subclinical changes in the transplanted kidney. Despite its invasive nature, it has a high safety profile, and the risk of complications remains low. Its use allows for the implementation of appropriate therapeutic intervention even before the appearance of clinical symptoms, which can significantly improve long-term graft function.

Advances in biomarkers of kidney damage offer the prospect of reducing the need for invasive biopsies in the near future. In the current state of knowledge, so-called liquid biopsy, based on the analysis of markers in blood and urine, should be considered as a complementary method to protocol biopsy rather than a replacement for it. Both techniques have the potential to synergistically increase diagnostic sensitivity and enable more precise monitoring of graft status.

A particular group of patients who may benefit from performing protocol biopsies are recipients with known dyslipidemia, in whom subclinical histopathological changes are more likely to be observed. At the same time, further research on the prognostic value of biomarkers such as suPAR is indicated, especially in the context of their usefulness in assessing the risk of graft function deterioration and long-term renal transplantation outcomes.