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The role of protocolar biopsy in the diagnosis of kidney allograft dysfunction

Abstract

Core-needle biopsy in patients with impaired renal transplant function and histopathological evaluation of the obtained tissue samples is a recognized diagnostic method of numerous graft pathologies. Until now the use of this invasive procedure in patients with no revealed signs of transplant pathology and with a stable function of the transplanted kidney at planned intervals after transplantation (the so-called protocol biopsies) has seemed inconclusive.

It is known that changes in the biopsy of the transplanted kidney are an earlier marker of transplant pathology in relation to laboratory abnormalities and the appearance of clinical symptoms, and the accumulation of subclinically progressing chronic changes is currently considered to be the main cause of renal graft loss. The histopathological evaluation also allows for the assessment of prognosis and the introduction of possible changes in the ongoing treatment. Opponents of protocol biopsy emphasize that it is an invasive procedure and exposes the patient to complications. Due to controversial reports on the usefulness of this method, protocol biopsies are not a routine tool for monitoring transplantation in transplant centers both in Poland and in the world. There is no established regimen for performing them.

This review article summarizes the current state of knowledge concerning the use of protocol biopsies in the diagnosis of transplanted kidney.

Key words: protocolar biopsy, kidney transplantation, sublinical antibody mediated rejection, subclinical T cell mediated rejection

INTRODUCTION

Extending long-term survival of the kidney graft constitutes one of the main challenges in organ transplantation. The main cause of graft loss in the long-term follow-up period is the accumulation of irreversible chronic lesions resulting from untreated or unresponsive to treatment rejection-related processes [1]. Deterioration of the graft kidney function, manifested by increased creatinine levels and decreased eGFR, is usually a late symptom of the developing pathology.

Such lesions may be detected by histopathological examination of a kidney graft specimen at a much earlier stage, which offers a chance to initiate treatment before irreversible chronic graft damage takes place. Protocol biopsy is dedicated to detecting graft pathologies at an early stage, when injury progression may still be halted**.** In the last 15 years, opinions on the diagnostic and prognostic utility of the graft kidney biopsy have varied. Following the introduction of potent immunosuppressants in the 1990s and the resulting drop in the incidence rates of acute T cell-mediated rejections (TCMR), many researchers came to believe that protocolar biopsies were unwarranted as they failed to provide information that would lead to therapeutic management modification. However, recent years have shown that graft kidney dysfunction is caused primarily by an antibody-mediated rejection (ABMR) process and is associated with the *de novo* production of donor-specific antibodies (DSA) at any time after transplantation [2]. The rejection may be clinically silent. The findings have shed light on potential utility of protocol biopsy as a tool for detecting clinically silent pathologies at a stage where progression can still be halted. A wealth of information was provided in the 2015 publication, in which Loupy et al. presented the results of 1001 protocol biopsies, performed 12 months after kidney trans-

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plantation (KTx), which revealed subclinical T cell-mediated rejection in 13% and subclinical ABMR in 14% of cases. In the further 8-year follow-up period, patients with subclinical ABMR had significantly worse graft survival (56%) compared with patients with subclinical TCMR (88%) and patients without rejection (90%) ($p < 0.001$). In a multivariate analysis, subclinical ABMR one year after KTx was associated with a 3.5-fold increase in graft loss, decrease in eGFR and proteinuria. As for patients with subclinical TCMR one year after KTx, only those who had developed DSAs and graft glomerulopathy had a higher risk of graft loss, compared with patients without rejection. According to the Authors, subclinical ABMR and TCRM affect graft survival in a different way. Subclinical ABMR was a risk factor for graft function deterioration and loss regardless of baseline DSAs status, eGFR and proteinuria. Subclinical T cell-mediated rejection did not lead to graft function deterioration but increased de novo production of DSAs [3].

The publications available focused also on identifying specific groups of patients who might require intensive histopathological surveillance and would benefit from protocol biopsy as a sensitive diagnostic tool [4]. Despite its likely benefits, protocol biopsy is rarely used to monitor the graft kidney function, either in Poland or worldwide. According to UNOS (United Network for Organ Sharing) survey from 88 transplant centers in US forty percent (n = 36) centers reported performing protocol biopsies (20% in all cases and 20% in select cases). The most common time points for performing protocol biopsies were 3- and 12-months (72% each), 6-months (44%), 1-month (31%), and 24-months (25%). Two centers reported performing them at 60 months post transplantation. For diagnosing TCMR, 100% used indication biopsy, 28% used protocol biopsy, 2% used serum biomarkers, and none used urine cytokines. For ABMR, 99% used indication biopsy, 34% used protocol biopsy, 72% used DSA, 21% used C1q positive DSA, and none used gene profiling [5].

TECHNIQUE AND SAFETY OF THE PROCEDURE

The procedure is carried out by nephrologists or surgeons, and occasionally by other specialists. Given the non-anatomical location of the transplanted kidney, most centres perform an ultrasound scan immediately before the procedure to accurately assess the graft topography and rule out possible contraindications to the procedure. In patients receiving an anticoagulant or antiplatelet therapy, protocol biopsy may usually be planned in advance or such therapy may be discontinued and, if the patient's condition so requires, low molecular weight heparin may be administered temporarily, which may then be discontinued immediately before the procedure [6].

The most common complications of graft kidney biopsy include perirenal haematomas, while intrarenal arteriovenous fistulas are a little less common. The estimated incidence rates of graft kidney biopsy complications requiring therapeutic management, e.g. blood transfusion or surgical intervention, range from 0% to 4% according to different authors, however, protocolar biopsy is associated with an up to 10-fold lower risk of complications compared with biopsy performed "when indicated" [7]. This is related to the planned preparation for the procedure, as well as the patient's good condition at baseline (usually). Taking into account the data available, the prevailing opinion is that protocolar biopsy of the graft kidney is a safe procedure, associataed with only a low risk of complications, and may be offered to kidney transplant recipients as a routine diagnostic procedure [8].

PRACTICAL UTILITY OF PROTOCOLAR BIOPSIES

Protocolar biopsies are performed at fixed intervals, and the exact schedule depends on the centre's experience and clinical situation. Typically, the first protocolar biopsy is performed on the operating table, during the transplantation procedure, immediately after organ reperfusion. Some authors even propose biopsy "0" (the so-called implantation biopsy), immediately after transplantation, and the so-called biopsy "1 hour," performed one hour after reperfusion, which is supposed to allow for a more accurate assessment of the graft kidney baseline status and the prognosis, taking into account possible early immune reactions and reperfusion-related damage. Such biopsy, in addition to baseline graft assessment, may offer some prognostic information — it has been demonstrated that detection of interstitial fibrosis with tubular atrophy (IF/TA) in specimens collected in the first hours after organ implantation constitutes a negative

prognostic factor and is associated with lower eGFR of the graft [9]. Similarly, the presence of IF/TA, particularly in combination with features of chronic inflammation identified by subsequent biopsies, also constitues an unfavourable prognostic factor for graft survival. Clearly, the time points may be affected by the patient's individual clinical situation, including the baseline donor-recipient immunological risk status, immunosuppressive and induction therapy, further plans, e.g. minimisation of immunosuppression (IS), and chronically elevated serum levels of calcineurin inhibitors [10]. In general, it is thought that earlier protocolar biopsies are associated with a greater chance of detecting subclinical alloimmune responses (which usually develop within the first three months of transplantation; such biopsy may provide important data that may affect decisions on further IS treatment and possibly minimization of IS), while 1-year biopsies offer a greater chance of detecting graft pathologies such as BK virus infection, recurrence of the underlying disease (glomerulonephritis), lesions resulting from nephrotoxicity of calcineurin inhibitors or signs of chronic inflammation, which has a prognostic value. Subsequently 3-, 5-, 7-, and even 10-year biopsies can be performed to evaluate chronic ABMR, the main cause of graft loss. Annual DSA monitoring is strongly recommended for all kidney transplant recipients. TCMR usually disappeares by the 3-year biopsy. Based on detecting pathological changes from protocol biopsy there is possibility of changing diagnosis, changing treatment, reducing immunosuppression dose [11, 12].

Protocol biopsies may be a useful tool to detect viral infections such as BKVN because early diagnosis is necessary to resolve infection and prevent chronic damage. Buehrig et al. demonstrated that all patients with BKVN diagnosed by protocol biopsies and managed by immunosuppression reduction had a satisfactory outcome by 6 months after diagnosis; in contrast, 70% of those with a late diagnosis by indication biopsies had deterioration of kidney function or graft loss. Since many reports support the utility BK virus DNA PCR as a screening strategy for BKVN, protocol biopsies only for BKVN may be unnecessary [13].

Recurrence of native kidney disease following kidney transplantation affects between 10% and 20% of patients, and accounts for up to 8% of graft failures at 10 years post transplant. Subclinical recurrence of both primary and secondary glomerular diseases is well recognized. Asymptomatic histological recurrence in renal allografts may be missed if protocol biopsies are not available. However the histological diagnosis may be missing because many transplant biopsies are not routinely processed using immunofluorescence and electron microscopy. Another limitations of utility of protocol biopsy for diagnosis of recurrent glomerulonephritis include unknown cause of native kidney disease, donor transmitted glomerulonephritis, lack of histologic features of FSGS in early stage of recurrence. Recurrence of glomerulonephritis in majority of patients is diagnosed in biopsy for cause due to proteinuria [14].

It should be emphasised that both T cell-mediated rejection and antibody-mediated rejection may have subclinical presentation. Early initiation of treatment of these pathologies allows to prevent progression of the lesions as well as the development of IF/TA or chronic graft glomerulopathy, thereby extending graft survival. One cannot omit the psychological aspect of the surveillance biopsies in graft recipients – when presented with the current state of knowledge of graft kidney protocolar biopsy and the benefits associated with the procedure, as well as the risks associated with this invasive procedure, few patients refuse to consent to biopsy and inclusion in the protocolar biopsy programme. This is all the more noteworthy as protocolar biopsy is associated with hospitalisation at the primary centre, which on the one hand constitutes an inconvenience, especially that protocolar biopsy is not performed because of any indications, but on the other — means an opportunity of medical surveillance in the inpatient settings.

It is important to dispel doubts about the eligibility of specific patient groups to protocolar biopsy. There have been reports on groups of patients in whom protocolar biopsies do not provide significant benefits with respect to the risk associated with the procedure. Biopsies performed within the first two weeks of transplantation appear to be of no benefit to low-risk patients in whom immunosuppression protocols with induction are used and who subsequently receive calcineurin inhibitors, even if delayed graft function (DGF) is the indirect indication for such a procedure [15]. This is supported by the predomiant opinion that this invasive procedure is not necessary in the case of patients with low immunological risk. Many of the publications available em-

phasise the need for individualised assessment of eligibility to biopsy, taking into account not only the immunological factors concerning the donor-recipient relationship but also the clinical profile of the recipient. Factors that should be taken into account in the eligibility assessment include the patient's age, cardiovascular diseases (heart failure before/after transplantation, atherosclerosis), type 2 diabetes mellitus, post-transplant urinary tract infections, serious infections, rejection episodes and cancer [16]. In each case, the decision to propose protocolar biopsy to a patient should be made on a case-by-case basis, taking into account a wide range of factors as well as the centre's experience in this area.

RECENT LITERATURE REVIEW

Researchers from Taiwan analysed the results of protocolar biopsies in 68 kidney recipients and compared them with the results of biopsies in 122 stable recipients two years after transplantation. The rejection process was identified by 13 protocolar biopsies, and in 11 cases borderline lesions were detected. Patients were administered glucocorticoid pulses. Over the 5-year follow-up period, graft survival was better in the protocolar biopsy group ($p = 0.0143$). In four and 17 recipients in the protocolar biopsy group and non-protocolar biopsy group, respectively, a biopsy performed because of indications confirmed the rejection process. In the recipients with the rejection process detected, the graft function was better in the protocolar biopsy group compared with the non-biopsy group. However, no difference in graft survival were observed in the 12-year follow-up period. In addition, in nine protocolar biopsies different types of glomerulopathy were identified, the most common (in four cases) being IgA glomerulopathy. No patient lost the graft because of GN. The Authors conclude that protocolar biopsy allows to detect subclinical rejection, and early intervention increase 5-year graft survival rates [17].

In a retrospective study, French researchers from Grenoble assessed the role of protocolar biopsy performed in 333 kidney transplant recipients in 2007–2013; 282 subjects had not undergone kidney biopsy, they constituted the control group. In patients who had undergone a kidney biopsy, 5-year graft survival rates were better regardless of the patient survival rates ($p < 0.001$), compared with patients who had not undergone protocolar biopsy. As for graft kidney specimens, 212 (64%) were normal, 87 (26%) showed IF/TA of varying grade and 24 (7%) showed features of subclinical rejection, including borderline lesions in 20; the patients were effectively treated with GS pulses. Nine biopsies revealed: recurrence or de novo GN in five patients, BKV nephropathy in two patients, acute CNI nephrotoxicity in one patient and features of pyelonephritis in one patient. Among patients who had undergone biopsy, 87 (26%) had IF/TA score of > 0, and recipients with IF/TA score of 3 had the worst graft survival rates. One hundred and forty-four patients (44%) presented cv lesions (*fibrosis endarteritis*); cv2 and cv3 lesions were associated with the worst 5-year graft survival rates. According to the Authors, protocolar biopsy performed at three months improves graft survival rates, primarily thanks to early treatment of immune-mediated lesions [18].

Korean authors assessed safety and feasibility of protocolar biopsy two weeks and twelve months after KTx. In 2012–2019, 842 protocolar biopsies were performed two weeks after KTx and 399 biopsies – one year after KTx. Biopsies were technically successful and safe; the complication rates were 0.3% in the case of biopsies performed two weeks and 0.2% in the case of biopsies performed twelve months after KTx. The incidence rates of subclinical rejection were 15.4% (130/842) and 33.6% (134/399) for biopsied performed two weeks and twelve months after KTx, respectively ($p < 0.001$). The authors do not provide long-term results but emphasise that protocolar biopsy is safe and can detect the subclinical rejection process (19).

The authors from Malaysia evaluated protocolar biopsies performed in 147 recipients (334 biopsies were performed between one month and 22 years after KTx, each recipient had undergone 1–7 biopsies) between 2012 and 2017. No rejection was detected in 161 (48.2%) cases, borderline lesions were found in 145 (43.4%) cases, and subclinical rejection — in 28 (8.4%) cases. Immune-mediated lesions were more common in the first five years after KTx. Borderline lesions were identified in 59 (36.4%), 64 (54.2%) and 22 (40.7%) biopsies at < 1 year, 1–5 years and > 5 years, respectively ($p = 0.011$). Subclinical rejection was found in six (3.7%) biopsies at < 1 year, 18 (15.3%) biopsies in the period of 1–5 years and four (7.4%) biopsies at > 5 years after KTx ($p = 0.003$). IF/TA, *de novo* or recur-

rent glomerulopathy and other unexpected lesions were found in 40 (12%), 10 (3%) and 12 (3.6%) biopsies, respectively. Recipients of kidney transplants from living donors had significantly lower rates of subclinical rejection ($p = 0.007$). The authors emphasised that in spite of stable graft function, morphological examination relatively frequently revealed subclinical rejection [20].

Another publication from Spain concerns the analysis of protocolar biopsies performed 4–6 months and 12 months after KTx, in 2015–2021; 134 biopsies were performed in 100 patients — 71 biopsies 4–6 months and 63 biopsies 12 months after KTx. The biopsies revealed 19 (14%) cases of subclinical rejection and 10 (7.4%) cases of borderline lesions. In addition, nephrocalcinosis was reported in 4.4% patients, IgA nephropathy in 2.2% patients and BK virus nephropathy in 1.5% patients. Protocolar biopsy findings lead to a therapeutic intervention in 45 patients (in 33% of all biopsies), most commonly the administration of methylprednisolone pulses (12.6%) and conversion to mTOR inhibitors (8.9%). In the Authors' opinion, protocolar biopsy is a useful tool for graft function monitoring as well as early detection and treatment of subclinical lesions [21].

Mareena S. Zachariah et al. presented 5-year results of 261 protocolar biopsies in 159 kidney recipients (2004–2012), performed 3–9 months (early) and subsequently 12–24 months (late) after KTx. The morphological image was classified as: IF/TA (interstitial fibrosis/tubular atrophy), subclinical acute rejection with IF/TA and border lesions with IF/TA. The effect of these lesions on glomerular filtration rate (eGFR) was assessed with respect to eGFR 12 months after KTx. In early biopsies, normal kidney was found in 105 (66%) recipients while in the remaining 54 (34%) subjects the following pathologies were identified: subclinical acute rejection plus IF/TA in seven recipients (4.4%), borderline lesions plus IF/TA in 17 (10.69%) recipients and IF/TA in 30 (18.87%) recipients. Late biopsies were performed in 102 recipients — in 59 (58%) no pathology was identified while in 43 (42%), the findings were as follows: subclinical acute rejection plus IF/TA in four (4%) recipients, borderline lesions plus IF/TA in 8 (9%) recipients and IF/TA in 30 (29%) recipients. Glomerular filtration rate at 12 months was related to eGFR at three months, the donor's age, delayed graft function and early protocolar biopsy findings. Changes in eGFR over time were associated with IF/TA in early biopsies and subclinical rejection and borderline lesions in late biopsies. In the long-term follow-up, the final eGFR values were related to IF/TA in early biopsies and subclinical rejection in late biopsies. Early protocolar biopsies allowed to predict eGFR at 12 months, while late biopsies — graft function over time. The presence of borderline lesions in the protocolar biopsy was predictive of long-term graft function [22].

Observational study from Author's transplant centre included 61 patients who underwent protocol biopsy 12 months after the transplantation. The biopsy results revealed abnormal histologic material in 37 patients (60%), mild inflammatory lesions in 21 patients, interstitial fibrosis and tubular atrophy (IFTA) grade II to III in 12 and BK virus nephropathy in 4. Immunosuppressive treatment was modified in the group with mild inflammatory changes and in the BKV group after the biopsy result. In the group with mild inflammatory lesions, renal function was stable during 5-years follow-up. In the BKV nephropathy group, there was a significant reduction in serum creatine levels. Protocol biopsies are useful for detecting early pathologies and preventing allograft failure. Patients with detectable pathology that can be treated or in whom therapy modification is possible will benefit from protocol biopsies [23].

Naumnik et al. from another polish transplant center reported results of a prospective observational study involving seventeen kidney recipients transplanted who underwent "zero", 3-month and 12-month allograft biopsies as well as DSA assessment. Histologic analysis of the biopsies showed subclinical acute cellular rejection in 17.6% of patients at 3-months post transplantation, and additional case of borderline rejection at the 12-month point. Moreover, two cases (11.8%) of polyomavirus BK nephropathy were diagnosed (one at 3 and one at 12 month point). None of the patients developed de novo DSA. Protocol biopsies allowed Authors' to detect significant proportion of patients with subclinical, but histologically relevant acute cellular rejection and BK nephropathy. Early therapeutic intervention had beneficial effects in a 4-year follow up [24].

The Authors from Korea evaluated the 504 patients who underwent protocolar biopsies and 350 who did not undergo protocolar biopsy.

Biopsies were performed 2 weeks and one year after transplantation, 207 recipients underwent single biopsy and 297 recipients the double biopsy. The double protocol biopsy group had advantages in 5-year graft survival, CKD progression, and new-onset CKD. Authors conclude, that protocol biopsy can play a protective role in the maintenance of kidney grafts in kidney transplant recipients [25].

Mehta et al. evaluated the long-term impact of early subclinical inflammation through surveillance biopsy in a prospective observational cohort of 586 patients who underwent protocol biopsy in their first year post-transplant. Patients were classified based on their biopsy findings: 282 with no significant inflammation and 304 with subclinical inflammation and tubulitis (182 with subclinical borderline changes and 122 with subclinical T Cell mediated rejection). Adjusted odds of having a subsequent clinical biopsy proven acute rejection and death-censored graft loss were significantly higher in the subclinical inflammation group compared to no subclinical inflammation during 5-year follow-up. Overall, Authors highlighted the need for identifying patients with subclinical inflammation through surveillance biopsy and develop strategies to prevent further alloimmune injuries [26].

De novo donor-specific antibodies (dnDSAs) are associated with the development of ABMR and graft loss. A multicentre (nine centres) French study retrospectively assessed whether or not regular monitoring for *de novo* DSAs combined with biopsy should become a routine practice. In patients with *de novo* DSAs (MFI > 1000) and stable kidney function biopsies were performed. Biopsies were performed in 123 patients, on average 65.3 (median) months after KTx. Renal function had remained stable for the three preceding months. Subclinical ABMR was found in 51 (41.4%) patients, including 32 (26%) cases of active ABMR and 19 (15.5%) cases of chronic active subclinical ABMR. No ABMR was identified in 72 biopsies (58.5%). The predictors for active subclinical ABMR were as follows: dominant DSAs MFI > 4,000; MFI of the sum of DSAs > 6300, recipient's age < 45 years, and no use of GS at the time of biopsy. Proteinuria of > 200 mg/g was a predictor of chronic active subclinical ABMR. Patients with active ABMR had greater declines in GFR within five years of biopsy and worse graft survival. Biopsy in patients with *de novo* DSAs allowed to detect ABMR in 40% of cases, but the Authors did not see any improvement after treatment [27].

Early diagnosis and treatment of subclinical ABMR based on the donor-specific antibody (DSA) testing may result in better outcomes. Filippone and Faber reviewed the literature on subclinical antibody-mediated rejection (ABMR) associated with donor specific antibodies. Subclinical ABMR occurs in up to 40% of patients transplanted with preexisting DSA routinely having biopsies within the first year following transplantation and subclinical ABMR occurs in up to 40% of patients with dnDSA if biopsied by protocol at the time of initial dnDSA detection. Subclinical AMR portends adverse outcomes (worse kidney function and graft loss) whether associated with preexisting DSA or dnDSA. They recommend to perform protocol biopsies within the first year following transplantation in all patients transplanted with preexisting DSA and in all patients with dnDSA at initial detection [28].

Recently published by ESOT Working Group on Subclinical DSA Monitoring "The Clinical Utility of Post-Transplant Monitoring of Donor-Specific Antibodies in Stable Renal Transplant Recipients: A Consensus Report With Guideline Statements for Clinical Practice" recommends a routine antibody monitoring at three to six months post-transplant and annually thereafter. Monitoring for dnDSA during functional graft life is a continuous process and should not change upon detection of dnDSA [29].

All the publications presented concern retrospective observational studies, often single-centre studies, involving various study populations and biopsies performed at different post-transplantation time points; also objectives were different; however, they show that protocolar biopsies can detect subclinical rejection or borderline lesions, which may have a beneficial effect on the preservation of good graft function. Early diagnosis of subclinical antibody-mediated rejection has an additional prognostic value, although no effective therapies for this pathology are available today. Large prospective studies are necessary to fully assess the utility of protocolar biopsy.

SUMMARY

Protocol biopsy of the graft kidney is a safe diagnostic tool serving to detect pathologies at an early stage. No doubt, the introduc-

tion of protocol biopsy into clinical practice has also allowed to broaden our the knowledge of the pathophysiology of the graft kidney lesions. However, at present, the role of protocol biopsy as a routine diagnostic tool is still under discussion, therefore it is not performed in all centres. Based on the experience gained so far, it seems possible to limit this examination to the groups of patients who would derive the greatest clinical benefit. Such groups would include primarily patients with an increased risk of rejection, higher sensitisation degree and after incompatible transplantation (immunologic or blood type incompatibilities), as well as patients in whom IS minimisation protocols are used, with lower doses of calcineurin inhibitors or steroids. However, this requires further analyses. Certainly, the decision to provide surveillance via protocol biopsy should always be made on a case-by-case basis, taking into account not only immunological but also clinical factors, as well as the centre's experience. With time and with the development of the immunosuppressants segment and noninvasive diagnostic techniques, the role of graft kidney biopsy, including protocol biopsy, will decrease. There have already been reports of non-invasive tests with similar sensitivity and specificity in diagnosing graft rejection. However, their introduction into routine clinical practice will require time and further testing. Noninvasive biomarkers include urine chemokines, TTV replication, gene profiling, proteomics and dd cf DNA. The latter seems to be the most promising biomarker and currently commercially available in some countries [30, 31].

AUTHOR CONTRIBUTIONS

Łukasz Jankowski — research concept and design, collection and/or assembly of data, data analysis and interpretation, writing the article, critical revision of the article, final approval of the article;
Julia Stępień — writing the article, final approval of the article;
Marcin Jurczak — writing the article, final approval of the article;
Zuzanna Sala — writing the article, final approval of the article;
Magdalena Durlik — critical revision of the article, final approval of the article.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

References

1. Ndemera H, Bhengu B. Factors Contributing to Kidney Allograft Loss and Associated Consequences among Post Kidney Transplantation Patients. Health Science Journal. 2017; 11(3), doi: 10.21767/1791-809x.1000504.
2. Sellarés J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. Am J Transplant. 2012; 12(2): 388–399, doi: 10.1111/j.1600-6143.2011.03840.x, indexed in Pubmed: 22081892.
3. Loupy A, Vernerey D, Tinel C, et al. Subclinical Rejection Phenotypes at 1 Year Post-Transplant and Outcome of Kidney Allografts. J Am Soc Nephrol. 2015; 26(7): 1721–1731, doi: 10.1681/ASN.2014040399, indexed in Pubmed: 25556173.
4. Pani A, regorini M, Rampino T, et al. L'utilita' delle biopsie protocollari nel trapianto di rene: pro e contro [The usefulness of protocol biopsies after kidney transplant: pros and cons]. G Ital Nefrol. 2010; 27: 339–352.
5. Sood P, Cherikh WS, Toll AE, et al. Kidney allograft rejection: Diagnosis and treatment practices in USA-A UNOS survey. Clin Transplant. 2021; 35(4): e14225, doi: 10.1111/ctr.14225, indexed in Pubmed: 33455009.
6. Chapman JR. Do protocol transplant biopsies improve kidney transplant outcomes? Curr Opin Nephrol Hypertens. 2012; 21(6): 580–586, doi: 10.1097/MNH.0b013e32835903f4, indexed in Pubmed: 23042026.
7. Morgan TA, Chandran S, et al. Complications of Ultrasound-Guided Renal Transplant Biopsies. Am J Transplant. 2016: 1298–1305, doi: 10.1111/ajt.13622, indexed in Pubmed: 26601796.
8. Furness PN, Philpott CM, Chorbadjian MT, et al. Protocol biopsy of the stable renal transplant: a multicenter study of methods and complication rates. Transplantation. 2003; 76(6): 969–973, doi: 10.1097/01.TP.0000082542.99416.11, indexed in Pubmed: 14508363.
9. Fahmy LM, Massie AB, Muzaale AD, et al. Long-term Renal Function in Living Kidney Donors Who Had Histological Abnormalities at Donation. Transplantation. 2016; 100(6): 1294–1298, doi: 10.1097/TP.0000000000001236, indexed in Pubmed: 27152920.
10. Huang Y, Farkash E. Protocol Biopsies: Utility and Limitations. Adv Chronic Kidney Dis. 2016; 23(5): 326–331, doi: 10.1053/j.ackd.2016.09.002, indexed in Pubmed: 27742388.
11. Sakai K, Oguchi H, Muramatsu M, et al. Protocol graft biopsy in kidney transplantation. Nephrology (Carlton). 2018; 23 Suppl 2: 38–44, doi: 10.1111/nep.13282, indexed in Pubmed: 29968403.
12. Tanabe T. The value of long-term protocol biopsies after kidney transplantation. Nephrology (Carlton). 2014; 19 Suppl 3: 2–5, doi: 10.1111/nep.12253, indexed in Pubmed: 24842813.
13. Buehrig CK, Lager DJ, Stegall MD, et al. Influence of surveillance renal allograft biopsy on diagnosis and prognosis of polyomavirus-associated nephropathy. Kidney Int. 2003; 64(2): 665–673, doi: 10.1046/j.1523-1755.2003.00103.x, indexed in Pubmed: 12846764.

14. Morozumi K, Takeda A, Otsuka Y, et al. Recurrent glomerular disease after kidney transplantation: an update of selected areas and the impact of protocol biopsy. Nephrology (Carlton). 2014; 19 Suppl 3: 6–10, doi: 10.1111/nep.12255, indexed in Pubmed: 24842814.
15. Abeling T, Scheffner I, Karch A, et al. Risk factors for death in kidney transplant patients: analysis from a large protocol biopsy registry. Nephrol Dial Transplant. 2019; 34(7): 1171–1181, doi: 10.1093/ndt/gfy131, indexed in Pubmed: 29860340.
16. Favi E, James A, Puliatti C, et al. Utility and safety of early allograft biopsy in adult deceased donor kidney transplant recipients. Clin Exp Nephrol. 2020; 24(4): 356–368, doi: 10.1007/s10157-019-01821-7, indexed in Pubmed: 31768863.
17. Chen CC, Lin WC, Lee CY, et al. Two-year protocol biopsy after kidney transplantation in clinically stable recipients - a retrospective study. Transpl Int. 2021; 34(1): 185–193, doi: 10.1111/tri.13785, indexed in Pubmed: 33152140.
18. Terrec F, Noble J, Naciri-Bennani H, et al. Protocol Biopsies on de novo Renal-Transplants at 3 Months after Surgery: Impact on 5-Year Transplant Survival. J Clin Med. 2021; 10(16), doi: 10.3390/jcm10163635, indexed in Pubmed: 34441931.
19. Lim M, Park BK, Lee KW, et al. Two-Week Protocol Biopsy in Renal Allograft: Feasibility, Safety, and Outcomes. J Clin Med. 2022; 11(3), doi: 10.3390/jcm11030785, indexed in Pubmed: 35160237.
20. Fu MS, Lim SJ, Jalalonmuhali M, et al. Clinical Significance of Renal Allograft Protocol Biopsies: A Single Tertiary Center Experience in Malaysia. J Transplant. 2019; 2019: 9153875, doi: 10.1155/2019/9153875, indexed in Pubmed: 31186948.
21. Santana Quintana CA, Gallego Samper R, Santana Estupiñán R, et al. Experience and Utility of the Protocol Kidney Biopsy in the First Year of Kidney Transplantation. Transplant Proc. 2022; 54(9): 2443–2445, doi: 10.1016/j.transproceed.2022.10.008, indexed in Pubmed: 36328815.
22. Zachariah MS, Dwivedi AK, Yip CS, et al. Utility of Serial Protocol Biopsies Performed After 1 Year in Predicting Long-Term Kidney Allograft Function According to Histologic Phenotype. Exp Clin Transplant. 2018; 16(4): 391–400, doi: 10.6002/ect.2016.0323, indexed in Pubmed: 29206090.
23. Cieślik A, Burban A, Gniewkiewicz M, et al. The Importance of 1-Year Protocol Biopsy in the Long-Term Prognosis of Kidney Transplants-5-Years Follow-Up. Transplant Proc. 2023; 55(9): 2053–2057, doi: 10.1016/j.transproceed.2023.08.022, indexed in Pubmed: 37778932.
24. Naumnik B, Kowalewska J, Hryszko T, et al. Single center experience of subclinical rejections and BK nephropathies by kidney allografts' surveillance biopsies. Adv Med Sci. 2017; 62(1): 110–115, doi: 10.1016/j.advms.2016.07.005, indexed in Pubmed: 28242482.
25. Lee O, Kim MJ, Lee JE, et al. The Protective Role of Protocol Biopsy for Allograft Kidney Maintenance in Kidney Transplantation. Transplant Proc. 2023; 55(4): 756–768, doi: 10.1016/j.transproceed.2023.01.029, indexed in Pubmed: 36990887.
26. Mehta RB, Melgarejo I, Viswanathan V, et al. Long-term immunological outcomes of early subclinical inflammation on surveillance kidney allograft biopsies. Kidney Int. 2022; 102(6): 1371–1381, doi: 10.1016/j.kint.2022.07.030, indexed in Pubmed: 36049641.
27. Bertrand D, Gatault P, Jauréguy M, et al. Protocol Biopsies in Patients With Subclinical De Novo Donor-specific Antibodies After Kidney Transplantation: A Multicentric Study. Transplantation. 2020; 104(8): 1726–1737, doi: 10.1097/TP.0000000000003055, indexed in Pubmed: 32732853.
28. Filippone EJ, Farber JL. The Problem of Subclinical Antibody-mediated Rejection in Kidney Transplantation. Transplantation. 2021; 105(6): 1176–1187, doi: 10.1097/TP.0000000000003543, indexed in Pubmed: 33196628.
29. van den Broek DAJ, Meziyerh S, Budde K, et al. ESOT Working Group Subclinical DSA Monitoring. The Clinical Utility of Post-Transplant Monitoring of Donor-Specific Antibodies in Stable Renal Transplant Recipients: A Consensus Report With Guideline Statements for Clinical Practice. Transpl Int. 2023; 36: 11321, doi: 10.3389/ti.2023.11321, indexed in Pubmed: 37560072.
30. Nolan N, Valdivieso K, Mani R, et al. Clinical and Analytical Validation of a Novel Urine-Based Test for the Detection of Allograft Rejection in Renal Transplant Patients. J Clin Med. 2020; 9(8), doi: 10.3390/jcm9082325, indexed in Pubmed: 32707779.
31. Martuszewski A, Paluszkiewicz P, Król M, et al. Donor-Derived Cell-Free DNA in Kidney Transplantation as a Potential Rejection Biomarker: A Systematic Literature Review. J Clin Med. 2021; 10(2), doi: 10.3390/jcm10020193, indexed in Pubmed: 33430458.