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Orıgınal Article

Histopathologic evaluation and complications of allograft biopsy in renal transplant recipients: In terms of radiologic imaging

Böbrek transplant alıcılarında allograft biyopsisinin histopatolojik değerlendirilmesi ve komplikasyonları: Radyolojik görüntüleme açısından

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ABSTRACT

Aim: Renal transplantation has become the treatment of choice for most patients with end-stage renal disease. Renal allograft biopsy is the most important technique in diagnosis of renal transplant dysfunction. In the light of radiological imaging, we investigated histopathologic evaluation and types and incidence of complications in renal transplant patients.

Material and Methods: In this retrospective study, histopathological biopsy results of patients with renal transplantation who underwent renal biopsy between January 2000 and December 2007 were evaluated in terms of the relationship between calcineurin inhibitor drug level and toxicity development. In addition, biopsy related complications were investigated.

Results: In a total of 386 patients were included in the study and 843 biopsies were performed on these patients. The amount of tissue was adequate in 812 biopsies (96%), inadequate in 6 biopsies (1%) and of limited adequacy in 27 biopsies (3%) for histopathologic evaluation. Acute rejection, tubular epithelial injury and chronic allograft nephropathy were the most frequent diagnoses. Complications of the biopsies were macroscopic hematuria in 4 biopsies (0.5%), perirenal hematoma in 6 biopsies (1%), and arteriovenous fistula in 1 biopsy (0.1%).

Conclusion: Renal biopsy in transplant patients to evaluate the renal allograft dysfunction is a safe method with very low incidence rate of complications.

Keywords: renal transplantation; allograft biopsy; bleeding; arteriovenous fistula

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Öz

Amaç: Böbrek nakli, son dönem böbrek yetmezliği olan hastaların çoğunda tercih edilen tedavi yöntemi haline gelmiştir. Renal allogreft biyopsisi böbrek nakli disfonksiyonunun tanısında en önemli tekniktir. Bu çalışmada, radyolojik görüntüleme ışığında renal transplant hastalarında histopatolojik değerlendirme ve komplikasyon tipleri ve sıklığının araştırılması amaçlandı.

Gereç ve Yöntemler: Bu retrospektif çalışmada, Ocak 2000 ve Aralık 2007 tarihleri arasında böbrek biyopsisi yapılan renal transplantasyonlu hastaların histopatolojik biyopsi sonuçları, kalsinörin inhibitörü ilaç düzeyi ile toksisite gelişimi arasındaki ilişki açısından değerlendirildi. Ayrıca biyopsi ile ilişkili komplikasyonlar araştırıldı.

Bulgular: Toplam 386 hasta çalışmaya dahil edildi ve bu hastalara 843 biyopsi yapıldı. Doku miktarı 812 biyopside (% 96) yeterli, 6 biyopside (% 1) yetersiz ve 27 biyopside (% 3) sınırlı ancak histopatolojik değerlendirme için yeterli bulunmuştur. Akut ret, tübüler epitel hasarı ve kronik allogreft nefropati en sık konulan tanılardı. Biyopsilerin komplikasyonları 4 biyopside makroskopik hematüri (%0.57), 6 biyopside perirenal hematom (% 1) ve 1 biyopside arteriyovenöz fistül (% 0.15) idi.

Sonuç: Böbrek allogreft disfonksiyonunu değerlendirmek için nakil yapılan hastalarda böbrek biyopsisi çok düşük komplikasyon oranına sahip güvenli bir yöntemdir.

Anahtar Kelimeler: böbrek nakli; allogreft biyopsisi; kanama; arteryo-venöz fistül

Introduction

Renal transplantation has become the treatment of choice for most patients with end-stage renal disease. However, the success of transplantation depends on the preservation of renal graft function. Since the early days of renal transplantation there has been a need for the means of examining allograft tissue in order to diagnose acute and chronic pathological processes in the allograft. Renal allograft biopsy is the most important technique in diagnosis of renal transplant dysfunction [1,2]. The transplant kidney, because of its extraperitoneal and relatively superficial location, is generally suitable for the percutanous needle biopsy approach. Biopsies are performed not only to establish a diagnosis in allografts with deteriorating function but also, using a protocol, to monitor the long-term effects of cyclosporine on the graft, and to detect a recurrence of the original disease in kidney transplant recipients [3].

Hematuria, perirenal hematoma, A-V fistula, pseudoaneurysm, arteriocalical fistula and graft loss can be seen as a complication of biopsy. Major complications reported after biopsies are perinephric or urinary bleeding. Transient microscopic bleeding is common and has no clinical significance [4].

In this study, we aimed to investigate the results of histopathologic evaluation and the types and incidence of complications in renal transplant patients after renal biopsies.

Material and Methods

Patients

Patients who underwent renal allograft biopsies in the Department of Interventional Radiology at Baskent University Hospital between January 2000 and December 2007 were included in the study. We retrospectively analyzed age, gender, donor source, number of transplantations, time passed since transplantation, number of biopsies, date of biopsy, histopathologic evaluation of biopsy, adequacy of specimens, protrombin time before biopsy, serum creatinine levels, complication rates of biopsies, type of calcineurin inhibitor drug, and serum calcineurin inhibitor drug levels. This study was approved by institutional ethical committee. Informed consent was obtained from all patients and the principles of the Helsinki Declaration were followed.

Biopsy procedure

The percutaneous needle biopsy was carried out under ultrasound guidance. The area skin over the transplant was sterilized and draped appropriately. Local anesthetic was injected. The kidney was intended to be punctured in one of the two poles, 18 G/15 cm Ace-Cut (TSK Laboratory, Japan) biopsy needle was advanced until it reached the renal capsule. However, the aim was to restrict the number of needle passes, and only rarely were more than 3 punctures performed. Patients were restricted to bed rest for 6 hours after the biopsy and vital signs were routinely monitored.

Biopsy preparation

Tissue was considered adequate for diagnosis when ten or more glomeruli and two or more arteries were obtained. The tissue was fixed in formalin. Sections cut at 3 to 4 microns were stained with hematoxylin and eosin (HE), Masson's trichome, periodic acid-Schiff (PAS) and methenamine silver. Histopathologic evaluations of biopsies were standardized according to the Banff 97 working classification.

In this retrospective study, we evaluated histopathologic results and complications of biopsy. We also analyzed the patients diagnosed with acute rejection, chronic allograft nephropathy and calcineurin inhibitor drug toxicitiy in biopsies, and we investigated the relationship of acute or chronic calcineurin inhibitor drug toxicity with serum drug levels in renal transplant patients.

Statistical analyses

Data are presented as percentages, mean ± SD, or medians. Statistical analysis was performed using one way ANOVA, Z test, Fisher's exact test, Pearson's correlation or Spearman's rank correlation coefficient. $p<0.05$ was considered as statistically significant.

Results

Totally 386 patients who underwent a total of 843 percutaneous renal allograft biopsies were included in the study. Among patients, 286 were male and 110 were female. The mean age was 37.8 years and ranging between 6 to 71 years.

Gender, donor source, recipient age, sample adequacy and PTZ values in patients with or without complications are summarized in Table 1. There was not any significant difference between patients with or without complications, regarding these parameters.

Table 1: Gender, donor source, recipient age, sample adequacy and PTZ values in patients with or without complications

	Number of biopsies	Number of complications	Complication rate (%)	p-value
gender				0.7414
female	222	12	5.4	
male	621	37	6.0	
Donor supply				0.6966
Cadaver				
	167	8	4.8	
live	676	28	4.1	
Donor age				0.0658
18 y<	12	2	16.7	
18 y≥	831	41	4.9	
Sample proficiency				
sufficient(1)	810	41	5.1	0.1802 (1 -2)
Enough at the border (2)	27	3	11.1	0.3954 (2 -3)
Not enough (3)	6	0	0.0	0.5686 (1 -3)
PTZ Value				0.516
15 sec <	610	35	5.7	
15 sec ≥	118	5	4.2	

Biopsies were performed on the 3rd -9344th days of the transplantation. One-nine biopsies were performed on each transplant kidneys. No increased risk of complications was found with an increasing number of biopsies (Table 2).

The amount of tissue was adequate in 812 biopsies, inadequate in 6 biopsies and of limited adequacy in 27 biopsies for histopathologic evaluation.

Histopathologic evaluations of the biopsies were standardized according to the Banff 97 working classification. Histopathologic evaluation of biopsies were normal in 12 patients, defined as nonspecific changes in 64 patients, borderline changes: suspicious for acute rejection in 90 patients, acute rejection in 274 patients, chronic allograft nephropathy (CAN) in 246 patients, chronic rejection in 7 patients, transplant glomerulopathy in 70 patients, de novo glomerulonephritis/recurrent disease in 48 patients, tubular epithelial injury in 208 patients, acute tubulointerstitial nephritis in 61 patients, chronic tubulointerstitial nephritis in 4 patients, acute tubular necrosis in 20 patients, hemorrhagic necrosis in 5 patients, calsineurin inhibitor drug toxicity in 82 patients, and amyloidosis, tuberculosis, viral, bacterial infection, lipiodozis in 19 patients.

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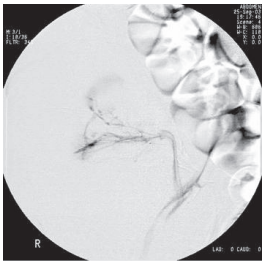
Table 2. Frequency of complications in relation to the number of biopsies performed per transplant

No. transplants	Biopsies	Complications n	(%)
166	1	4	2.4
105	2	2	1.9
55	3	11	20.0
31	4	10	32.3
12	5	1	8.3
17	6-9	6	35.3

Complications of the biopsies were macroscopic hematuria in 4 biopsies, perirenal hematoma in 6 biopsies, arteriovenous fistula in 1 biopsy. Arteriovenous fistula was treated with coil embolization. None of the patients with macroscopic hematuria required blood transfusion. None of the patients were expired due to the graft following biopsy.

Some cases are summarized below:

Case 1. An abdominal CT was performed on 26-year-old man following hemoglobin decrease after renal transplant biopsy. Retroperitoneal hematoma was revealed on CT. Renal and pelvic angiography was performed. Angiography demonstrated contrast agent leak from interlobar renal artery in kidney transplantation. Leak was treated with microcoil and histoacryl-lipiodol embolization (Figure 1A-B-C).



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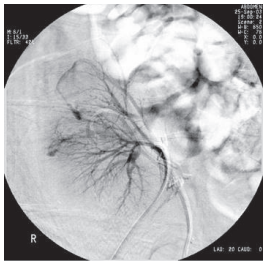

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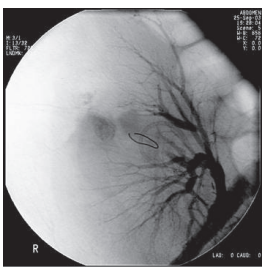
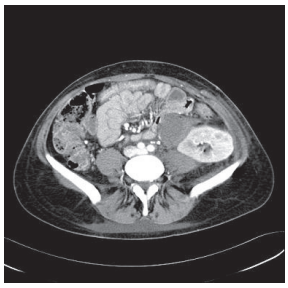


Figure 1 A-B-C: Angiography demonstrated contrast agent leak from interlobar renal artery in kidney transplantation. Leak was treated with microcoil and histoacryl-lipiodol embolization

Case 2. In a 25-year-old woman patient, hemoglobin decreased following renal transplant biopsy. Abdominal CT was performed. CT revealed perirenal hematoma in renal transplant (Figure A-B). After six month, A-V fistula was suspected in US. Renal angiography demonstrated A-V fistula in inferior pole of renal transplant. A-V fistula was treated with multiple coil embolization (Figure 2C-D-E).



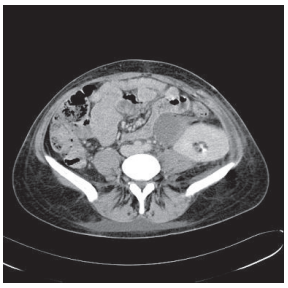
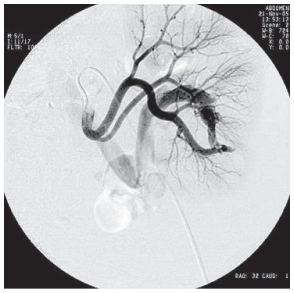


Figure 2 A-B: Abdominal CT revealed perirenal hematoma in renal transplant (Figure A-B).



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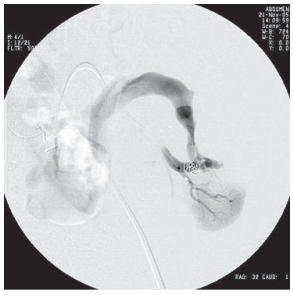

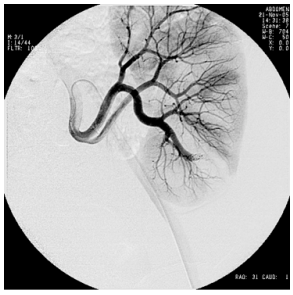

Figure 2 C-D-E: Renal angiography demonstrated A-V fistula in inferior pole of renal transplant. A-V fistula was treated with multiple coil embolization (Figure 2C-D-E).

Case 3. 53-year-old woman with renal transplant developed left quadrant pain and decrease in hemoglobin levels following renal transplant biopsy. Abdominal CT was performed. CT revealed perirenal subcapsular hematoma (Figure A), defect and lacking contrast media in inferior pole of transplant kidney (Figure B). During operation, the surgeons detected three lacerations in the transplanted kidney (Figure C). Then the surgeons performed packing with Surgicell and 2 unit ES and one unit fresh frozen plasma was given to the patient.

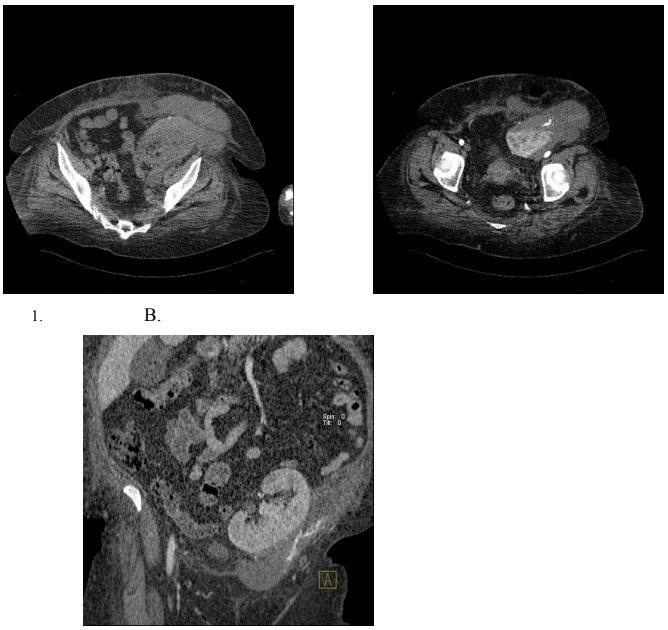

Figure 3 A-B-C: Abdominal CT revealed perirenal subcapsular hematoma (Figure A), defect and lacking contrast media in inferior pole of transplant kidney (Figure B). During operation, the surgeons detected three lacerations in the transplanted kidney (Figure C).

Case 4. 35-year-old woman patient's hemoglobin level decreased following transplant biopsy. Abdominal CT showed contrast-enhanced extravasation compatible with active hemorrhage and hematoma extending from the posteriomedial transplant kidney to the pelvis (Figure 20 A-B). The patient received 400 units / hour heparin infusion. 4 units of TDP and 2 units of ES were given. Then she was operated and hematoma was evacuated.

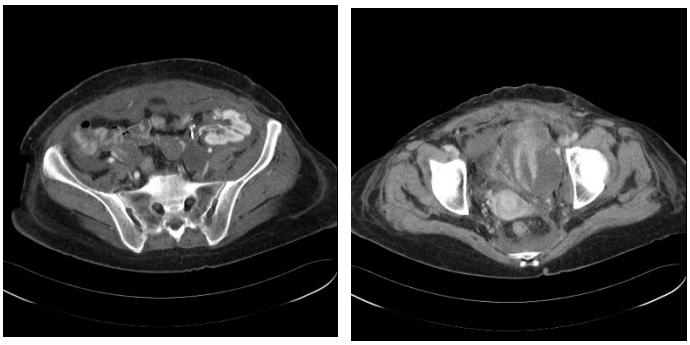

Figure 4 A-B: Abdominal CT showed contrast-enhanced extravasation compatible with active hemorrhage and hematoma extending from the posteriomedial transplant kidney to the pelvis (Figure 4 A-B).

Case 5: A 42-year-old male patient complained of right lower quadrant pain and decreased hemoglobin levels in the follow-up after transplant kidney biopsy. Abdominal CT examination showed a parenchymal defect in the posterior of the right kidney iliac fossa and a contrast agent extravasation compatible with active hematoma extending to the pelvis and retroperitoneal space (Figure 5). Thereafter, three units of TDP were administered. He was operated and hematoma was evacuated.

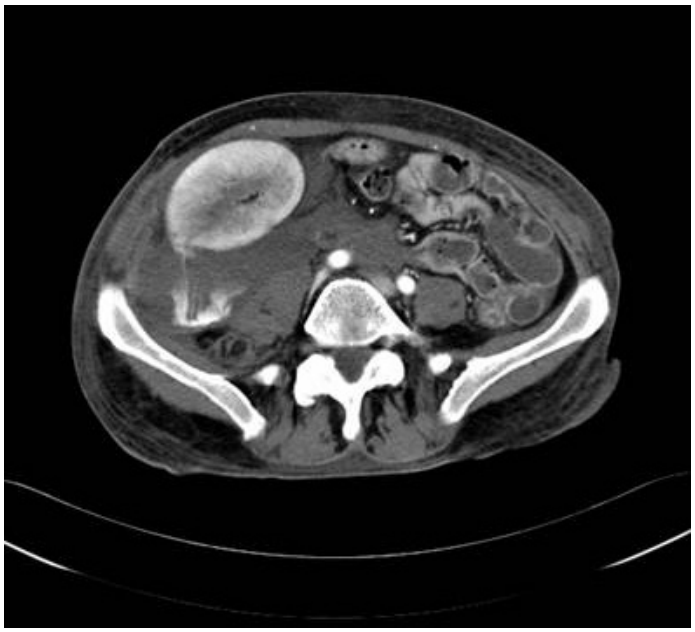

Figure 5: Abdominal CT examination showed a parenchymal defect in the posterior of the right kidney iliac fossa and a contrast agent extravasation compatible with active hematoma extending to the pelvis and retroperitoneal space

Case 6: A 56-year-old male patient underwent Doppler US examination after a transplanted kidney biopsy, and a hematoma in the left lateral iliac fossa was seen in the adjacent kidney, and a 14 F drainage catheter was placed in our interventional radiology unit. Then, a CT scan of the left iliac fossa revealed a hematoma adjacent to the transplanted kidney and a drainage catheter (Figure 6).

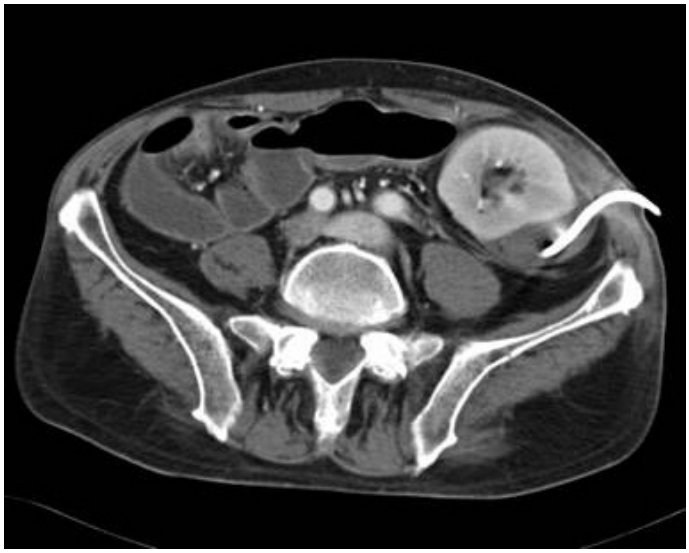

Figure 6: CT scan of the left iliac fossa revealed a hematoma adjacent to the transplanted kidney and a drainage catheter

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Calcineurin inhibitor drug toxicity was detected in 82 of the biopsies. Cyclosporine was used as the calcineurin inhibitor drug in 52 of these biopsies and tacrolimus was used in 30 of these biopsies. Cyclosporine levels detected during biopsy were 65-800 ng / ml (normal value 100-400 ng / ml) with a mean of 254.3 ng / ml, and tacrolimus level was 5-32 ng / ml (normal value 5-20 ng / ml). and a mean of 12.2 ng / ml. The effect of drug levels on the development of acute or chronic toxicity in calcineurin inhibitory drug users is shown in Table 3. There was not a significant relationship between low or high serum drug levels and toxicity development.

Table 3: Effect of drug level on the development of acute or chronic toxicity in calcineurin inhibitor drug users

	Number of patients using calcineurin inhibitor		
Calcineurin Inhibitor Drug Level	Cyclosporine (ST)	Tacrolimus (TT)	Total
Low (ST<400. TT<20)	49 %94.2	26 %86.7	75
High (ST>=400. TT>=20)	3 %5.8	4 %13.3	7
Total	52	30	82
Fisher exact test p-value =0.253			

Discussion

The most objective method for obtaining renal allograft pathologies is histopathological examinations performed by biopsy [1,2]. Therefore, allograft biopsy is currently the most reliable method for examining allograft dysfunction. Although it is an invasive method, the reason for its high rate of application is the lack of an alternative physical examination or laboratory examination. Although both clinical and other laboratory findings are very useful in reaching the diagnosis, they are insufficient to provide the information that the biopsy provides.

Non-invasive methods including; examination of peripheral T cells, lymphocyte activation markers, serum and urine cytokine levels and invasive methods including; fine needle aspiration and monoclonal antibody techniques could not replace biopsy even if diagnosis was used in renal allograft dysfunction [3,5]. Therefore, biopsy and histopathological examination have been accepted as the gold standard especially in allograft dysfunction. By evaluating the clinical findings together with biopsy, the status of the graft is best understood and some pathologies which are very difficult to differentiate with clinical findings are clarified. For example, allograft biopsy will provide the possibility to differentiate the pathologies such as cyclosporine toxicity and acute rejection and predict the graft survival, which may give the same findings as clinical investigations but treatment approaches are completely different [6].

Since the transplanted kidney is located under the abdominal muscles in the iliac fossa, it is suitable for percutaneous biopsy. US guided application increases the success of biopsy [7]. In our study, the histopathologically sufficient tissue access rate was satisfactory. Only 6 out of 843 biopsies showed insufficient material. Our success rate was calculated as 99.3%. In some series it is reported in proportions similar to ours [8]. US-guided biopsy was done to be effective in both to obtain the active tissue and decrease the risk of complications. In some studies, especially in rejection cases that can be treated, false negative results have been shown to decrease from 1% to 10.5% by performing two punctures and taking two samples [9]. The classification of histopathological examination was performed according to Banff classification, which has been studied in recent years and aimed to achieve a significant standardization by nephropatologists [10].

It was remarkable that the number of biopsies in our series was quite high. As the risk of complications decreased to negligible levels with imaging techniques, biopsy indications in transplanted patients have been expanded considerably. In addition, protocol biopsies have been proposed at certain times in order to determine the future graft survival or to detect subclinical acute rejection attacks. In some studies, it has been shown that especially protocol biopsies to be performed in the early period may affect subclinical rejection attacks that may adversely affect graft survival and are not reflected in laboratory findings [11]. In the study of Mao et al., it was emphasized that post-transplant biopsy performed at 1 month provides important clinical information in detecting pathologies and predicting graft survival as the risk factors for long-term graft survival [12]. This approach may be very invasive. However, it should be kept in mind that biopsy provide important information that may affect patient and graft survival in the presence of proper indication. In our study, biopsy was not performed in patients without any problem related to allograft functions.

Percutaneous kidney biopsies can be performed using 14 G, 16 G or 18 G, automatic or semi-automatic needles. In a study, it was reported that three different thickness needles can be used safely in renal allograft biopsy and there was no difference in terms of adequate tissue sample while pain complaints

were found more in those who underwent biopsy with a 14 G needle [13]. In another study, US guided biopsies with 18 G needles and 14 G needles without US guidance were compared in terms of complication and tissue sample adequacy and no significant difference was found [14]. In a study comparing the 18 G needle with 14 G, Boyvat et al, reported that tru-cut needle biopsy techniques have obtained enough tissue samples and found that there are fewer complications [15]. In our study, 18 G Ace-cut automatic needle was used and it was very successful in obtaining adequate tissue sample and low complication rate.

Hematuria, perirenal hematoma, A-V fistula, pseudoaneurysm, arteriocalical fistula and graft loss can be seen as a complication of biopsy [16]. The rate of asymptomatic microscopic hematuria to varying degrees after native kidney biopsies is 100% [17]. Therefore, it is not considered as a complication since it is a natural result of renal puncture. Transient macroscopic hematuria may occur and often regress by itself [7]. However, it may rarely require blood transfusion. The incidence of gross hematuria was 5-7% in transplant and native kidneys [3]. Blood transfusions were not required in 4 of our patients who developed macroscopic hematuria and hematuria regressed spontaneously.

There was no significant difference between the patients who developed complications, whether the age was less than 18 years or older, whether the donor source was cadaver or alive, the PTZ value was higher or lower than normal, and adequate or insufficient tissue samples were obtained. In a study conducted by Wilzeck et al., it was found that performing biopsy early or late after transplantation and normal or abnormal renal function did not differ in terms of complications [8]. In contrast, patients with acute vascular rejection had a higher risk of bleeding complications. This is thought to be mainly due to vascular fragility caused by inflammatory vascular changes in the transplant [8]. In our study, acute rejection in 2 patients, border-line changes in 1 patient, acute calcineurin inhibitory toxicity in 1 patient and tubule epithelial injury in 2 patients were detected. Another common complication after renal needle biopsies is the A-V fistula, and most traumatic fistulas spontaneously close in 1 to 18 months In one of our patients, A-V fistula was detected in the transplant kidney 6 months after biopsy and coil embolization treatment was applied. Graft loss is one of the major complications. The causes of graft loss due to excessive bleeding seen in the study of Wilzeck et al. were acute vascular rejection, and renal vein thrombosis, due to deep and excessive penetration of the kidney including not only the cortex but also the medulla [8].

In our study, and the only major complication was perirenal hematoma in 6 biopsies and A-V fistula in 1 biopsy. Large numbers of biopsy series in the literature have also reported low numbers of complications similar to our series. For example, in two large series of 1129 and 1390 biopsies, mortality was absent and graft loss was reported to be only 0.3% and 0.4% [8,18].

In our study, one of the most common histopathological diagnosis was CAN (chronic allograft nephropathy). Chronic allograft nephropathy is histopathology characterized by chronic changes in the arteries, interstitium, tubules and glomeruli. The development of CAN in the transplant kidney is associated with progressive loss of function and subsequent loss of graft.

Calcineurin inhibitors used in immunosuppressive therapy in renal allograft are CycA and tacrolimus. Calcineurin inhibitor drugs are nephrotoxic, and may cause acute or chronic toxicity. There are also studies suggesting that drug level is associated with toxicity and may cause CAN and graft loss in the future [20]. In our study, there was no relationship between acute and chronic toxicity and drug levels in tacrolimus and CycA groups. Histopathological findings of toxicity were observed even in patients with normal drug levels.

In the study of Liptak et al., the serum levels of these drugs do not correlate well with the extent of renal damage caused, and the clinical manifestation is nonspecific [21].

Conclusion

Biopsy performed to evaluate the renal allograft dysfunction in renal transplant patients is safe and the incidence of complications is significantly low. There is no correlation between developing acute or chronic calcineurin inhibitor drug toxicity with serum drug level.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest

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