SAFETY AND SAMPLE ADEQUACY OF RENAL TRANSPLANT SURVEILLANCE BIOPSIES

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INTRODUCTION

Despite major advances in kidney transplantation reducing early acute kidney transplant rejection rates to less than 15% and increasing 1-year graft survival to more than 90%, long-term graft survival rates have remained unchanged with a 4% loss per year (1, 2). Immune injury due to acute or chronic rejection and non-immune factors, such as nephrotoxicity from calcineurin inhibitors, ischemia-reperfusion injury, recurrent glomerular disease, and allograft BK/polyoma viral infection, are potential threats that could be detected with surveillance biopsies at an early stage. Specific interventions targeting the pathophysiological cause of this dysfunction could then be applied which is likely to ameliorate long-term graft survival (3). The presence of interstitial fibrosis and tubular atrophy (IF/TA) is considered as a surrogate marker for long-term graft survival (4). Conversely, the identification of normal histology on a surveillance biopsy may be informative about the safety of a reduction in overall immunosuppression (5).

In a recent meeting of leading experts the consensus was that surveillance biopsies, in experienced hands, are a valuable means for detecting subclinical disease that can benefit...
Complication rates were retrospectively scored using the patients’ charts, discharge and follow-up letters and blood counts before and after biopsy (if available). The following data were collected for all patients: time post-transplantation (3m or 12m), haemoglobin, haematocrit, thrombocyte count and PT before biopsy and haemoglobin and haematocrit after biopsy in case of complications. Symptomatic complications (haematuria, pain, need for urinary catheter placement, haemorrhage, transfusion, peritonitis, graft loss, prolonged hospitalization) were classified as major or minor. Major complications were defined as those requiring an intervention for resolution, a transfusion of blood products or an invasive procedure (angiography or surgery), and those that led to acute renal obstruction or failure, septicemia, graft loss or death (7-9). In all other cases complications were considered minor.

In addition, we examined the histology reports for assessment of the adequacy of tissue samples. Specimen adequacy of renal allograft biopsies is defined in the Banff classification. An “adequate” sample is a biopsy with 10 or more glomeruli and at least two arteries. The threshold for a minimal sample is 7 glomeruli and one artery (10). Similar to Schwarz et al., we used the minimal threshold sample criteria as a definition for adequacy (7, 10).

RESULTS

We performed 282 surveillance biopsies in 248 patients between January 2006 and December 2011. We observed 6% complications (n = 17). None of the complications were major. 5.6% (n = 16) of the complications were bleeding related, with macroscopic haematuria being the most common (n = 10; 3.5%), followed by pain (n = 6; 2.1%) (Figure 1).

All patients with macroscopic haematuria or pain received a control ultrasound as well as a blood count. Three of the patients with macroscopic haematuria had a blood clot in the bladder visualized by ultrasound. They were advised to increase fluid intake and clot resolved spontaneously. In the other 7 patients with haematuria, ultrasound was normal. Haematocrit remained stable in all but one patient with haematuria, who had a decrease from 42.9% to 37.6%, without further deterioration or transfusion need.

In all patients presenting with pain, this minor complication occurred in the first hours following the biopsy, except in one patient having late presentation of pain. He came to the emergency department 5 days after the biopsy, complaining of pain in the area of the transplanted kidney. The patient started after spending a day in an amusement park. Ultrasound showed a perinephric hematoma in five patients (1.8%), including the one that presented late. One patient had a subcutaneous hematoma. As in the patients with haematuria, in those with pain haematocrit also remained stable in all but one. She had a decrease from 32.6% to 24.6% and remained hospitalized for one more day. Subsequently haematocrit remained stable and ultrasound before discharge showed already a decrease in the size of the hematoma. None of the patients with haematuria or hematoma required transfusion.

Only one complication was not related to bleeding and probably even not to the biopsy: one patient could not void spontaneously in the hours after biopsy and needed twice an
artery. These results are similar to previously published results (7). Forty-eight % of biopsies contained at least 10 glomeruli and two arteries. In our study, specimen inadequacy was mostly due to the lack of glomeruli (< 7 glomeruli in 25% of biopsies) and not arteries (0 arteries in only 6% of biopsies).

DISCUSSION

The exact importance of surveillance biopsies in the renal allograft is still debated because of absence of large-scale multicentre and controlled trials assessing the clinical benefit for the individual patient (11, 12). If one would consider such trials, surveillance biopsy should at least be proven to be safe. Up until now, only two studies have assessed the complication risk of surveillance biopsies (7, 13). The largest, a multicentre study by Furness et al. showed a large variability in reported complications between the different centres, undoubtedly attributable to the multicentric character of the survey with apparent differences in practice among centres with regard to the definition of contraindications for biopsy, anticoagulation management, observation period for complications and biopsy needle size (13).

Consequently, the current study provides a monocentric risk assessment quantifying minor and major complications of surveillance biopsies during a 6-year period based on a single standardized practice for every patient. After the biopsy, all patients were observed in-hospital during a 24h period based on the findings of Whittier et al. in the native kidney biopsies, suggesting that 89% of all complications occur within the first 24 hours (9). As a consequence, the current study should give an accurate account of the incidence of complications, because shorter observation periods carry a substantial risk of missing a significant proportion of complications. We did not observe any major complication in 282 surveillance biopsies. This is comparable to the low incidence reported by Furness (0.42%) and Schwarz (1%) (Table 1) (7, 13).

Although the definition of most major complications is straightforward (e.g. graft loss, death...), the need for blood transfusion is also considered as a major complication, but here interpretation is blurred by the lack of a standardized cut-off defining the need for it. In the present database, in one patient a drop in haematocrit from 32.6% to 24.6% was observed, but no transfusion of blood products was given since she was clinically stable. However, others might have decided to administer packed cells, hence qualifying this complication as major instead of minor.

In our current series, the incidence of minor bleeding complications was also very low (5.6%), comparable to what is reported in literature (7, 13) (Table 1). The most frequent minor complication reported here is post-biopsy haematuria (3.5%). To minimize the bleeding risk after an elective renal allograft surveillance biopsy, we preferred not to biopsy when patients were on aspirin. Although the impact of this measure on major complications is probably negligible as reported by others (7, 14), the rate of minor complications such as gross haematuria and perirenal hematomas is slightly higher under aspirin (7). Consequently, if taken for primary prevention, we chose to discontinue aspirin 7 days in advance, allowing turnover of platelets exposed to aspirin and minimizing the time interval without anticoagulation (15). Since aspirin should

intermittent bladder catheterization. He did not have haematuria and the problem resolved without further intervention.

The biopsies contained a median number of 9 glomeruli (range 0-39), 70% of biopsies met the criteria of minimal sample adequacy (10), containing at least 7 glomeruli and one
never be stopped in patients requiring it for secondary prevention, patients still on aspirin were deferred from the surveillance biopsy program.

Post-biopsy pain was recorded in 2.1% and was in nearly all patients associated with the presence of a perinephric or subcutaneous hematoma. Furness et al report post-biopsy pain in 1% of patients, with considerable variation in between hospitals (13).

The routine monitoring of post-biopsy haemoglobin levels is not recommended after renal biopsy, as decreasing haemoglobin is non specific and of little value in detecting significant complications (16). In 750 biopsies of native kidneys, Whittier et al showed a significant decrease in haemoglobin in both patients with a bleeding complication and in patients without. Although the magnitude of haemoglobin decrease was larger in patients with a complication (2.1 +/- 1.6 g/dL versus 0.9 +/- 0.8 g/dL), a decrease of ≥ 1.0 g/dL and ≥ 2.0 g/dL was observed in 46% and 9.6% of uncomplicated cases respectively (9). A drop in haemoglobin by ≥ 1 g/dL after biopsy is common and has been reported to occur in almost 50% of cases (9, 17). The cause of the “non-haemorrhagic” change in haemoglobin may be the result of multiple factors, including the development of a small subclinical perinephric hematoma, haemodilution as a result of the infusion of saline after biopsy, or postural haemodilution resulting from the resorption of interstitial fluid in severely oedematous patients after prolonged bed rest after biopsy (9).

Overall, the complication rate in surveillance biopsies is very low and lower compared to kidney allograft biopsies performed on indication or to biopsies of native kidneys (18, 19). The allograft kidney, located in the iliac fossa, is closer to the body surface than the native kidney, making localization of the organ for biopsy more straightforward than for native kidney. In addition, as surveillance biopsy is an elective procedure, all factors such as arterial hypertension or coagulation disorders that could cause complications can be anticipated, making it a safe diagnostic procedure. In our study, the patients stayed overnight for further observation in analogy with the practice often used for native biopsies, given the risk of delayed bleeding (9). However, the complication rate in surveillance biopsies of the kidney allograft is much lower. Other centres have pointed out that an 8-hour observation period after both transplant or native kidney biopsy is safe (20-22). Moreover, the 0.42% severe complications in surveillance biopsies reported by Furness et al., were all occurring within 4 h after biopsy (13). Our results also showed that post-biopsy complications are detected early after biopsy on the same day, with the exception of one patient, who presented five days later. Consequently, it could be defended that it is also safe to perform surveillance biopsies in an ambulatory setting with an observation period of 4 to 8 hours.

Since a post-biopsy Doppler ultrasound was not routinely performed in our study, intrarenal arterio-venous fistula formation could not be reported. Although arterio-venous fistulas have been reported in up to 11% of renal transplant surveillance biopsies, the clinical relevance is limited as > 75% disappears spontaneously within 1-2 years (7, 13). In the study by Schwarz et al, a Doppler ultrasound after biopsy was a standard procedure. They detected 122 arterio-venous fistulae after transplant biopsy (7.6%) (7). These were usually very small and when followed-up by Doppler ultrasound several weeks later, 77% had resolved spontaneously. Only three arterio-venous fistulae were large enough to induce possible hemodynamic consequences. However, the serum creatinine remained unchanged in these three patients. Consequently, just like haemoglobin monitoring after surveillance biopsies, systematic renal Doppler ultrasound after biopsy has shown to be of no value and thus is not indicated (16). As in our protocol, post-biopsy ultrasound can be reserved for patients with clinical signs, such as pain, hypotension or overt haematuria. Thus, not routinely performing a post-biopsy ultrasound, we report lower rates of perirenal hematomas in comparison with literature, since only a minority of these is clinically significant to lead to an ultrasound (20, 22).

Next to complication rate, specimen adequacy is an important issue making pathologic evaluation on the tissue more reliable and the risk of the procedure worthwhile for the patient. This is especially true in the setting of surveillance biopsies, where the potential benefit to the patient should outweigh the risk. Specimen adequacy is related to needle
size and the number of specimen cores. We have been using 16-gauge needles in our unit since 2002. In a large trial, this needle size has been shown to significantly increase specimen adequacy comparing to 18-gauge needles, allowing to meet the Banff criteria in nearly 80% of the samples, with comparable safety (7, 23). On the other hand, a larger needle of 14-gauge has been shown to result in larger rates of post puncture pain (23). We obtained minimal sample adequacy in 70% of the biopsies, defined as the presence of 7 or more glomeruli and at least one artery (10). This result is in concordance with another study also using a 16-gauge needle (7). Since in other studies sample adequacy is often defined as having enough material to make a reliable diagnosis, regardless of the number of glomeruli, a comparison with those reports is difficult (18, 20, 22, 23). As previously shown, we also found that specimen inadequacy is most often related to the lack of glomeruli and not of arteries (7).

It is recommended that at least two tissue cores be obtained, preferably at some distance from each other, to optimize sampling of pathologic processes such as rejection and infection, which may be focal in the allograft (12). We obtained 2 tissue cores but via the same skin site, so that local anaesthetics needed to be applied only once. We always take two samples, one to preserve in formaldehyde and one to preserve in Eurocollins®, a solution used for the preservation of kidney allografts. Eurocollins® proved to be an adequate transport medium, producing little artefacts and leaving the sample adequate for immunofluorescence and electron microscopic evaluation.

CONCLUSION

Reviewing the complications in 282 inpatient allograft biopsies, we conclude that our procedure for taking surveillance biopsies is safe, since there were no major complications and minor complications were rare and with negligible consequences. This procedure using 16-gauge needles also is efficient, as the majority of samples were adequate for diagnostic purposes.

CONFLICT OF INTEREST: None.