The Incidence of Major Hemorrhagic Complications After Renal Biopsies in Patients with Monoclonal Gammopathies

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Background and objectives: Monoclonal gammopathies frequently cause renal disease, but they may be an incidental finding. Assessment of renal pathology in the context of renal dysfunction and a monoclonal gammopathy therefore serves as a useful diagnostic tool and, in addition, provides prognostic information. There is, however, a theoretical risk of increased hemorrhagic complications from renal biopsies in this setting. The purpose of this study was to determine the incidence of significant hemorrhagic complications after renal biopsies in patients with monoclonal gammopathies.

Design, setting, participants, & measurements: The case notes of 1993 unselected patients from four teaching hospitals within the United Kingdom who underwent native or transplant renal biopsies between 1993 and 2008 were reviewed. Subjects were categorized as having a monoclonal gammopathy or not, and the incidence of major hemorrhagic complications between groups was compared.

Results: In total, 74 (3.7%) patients (native and transplant biopsies) had a major hemorrhagic complication. One hundred forty-eight subjects with a monoclonal gammopathy were identified. The complication rate in this group was 4.1% compared with 3.9% in the control population (native biopsies only; $P = 0.88$).

Conclusions: In the population studied, the rate of major hemorrhagic complications after percutaneous renal biopsy was not significantly greater in patients with a monoclonal gammopathy.

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Paraproteins are frequently detected in patients with renal disease, both as an incidental finding and as the underlying cause of the renal injury. The renal disorders associated with paraproteins are well described (1,2). In the context of severe acute kidney injury, cast nephropathy (myeloma kidney) is the most frequent finding (2,3). In contrast, patients presenting with heavy proteinuria and milder renal impairment are more likely to have amyloidosis (2,4) or light chain deposition disease (2,5). The conclusion that the presence of a paraprotein in the context of renal injury equates to a causal association cannot be drawn because of the high frequency of incidental paraproteins in this setting (6). For this reason, assessment of renal pathology is essential. In addition to confirming the underlying disorder and therefore allowing the initiation of disease specific treatment, pathologic features are also prognostic of clinical outcomes (2,5,7).

Despite these advantages, many clinicians are reluctant to perform percutaneous renal biopsies in patients with paraproteins because of the theoretical risk of a higher rate of hemorrhagic complications (8,9). Indeed, there are a number of mechanisms by which paraproteins might confer this increased risk (10,11). Therefore, renal histology has not been used as an inclusion criterion for some studies that have investigated the optimal treatment strategies for paraprotein-related renal disease (9). In turn, this makes interpretation of the results of these studies difficult (12–14). However, clear evidence that performing percutaneous renal biopsies in these patients is associated with an actual higher incidence of clinically significant hemorrhagic complications is not well reported. In fact, recent work has implied that the procedure is relatively safe in patients with amyloidosis, traditionally the subgroup considered to be most at risk (15). The purpose of this study was to determine the incidence of major hemorrhagic complications after percutaneous renal biopsies in a large population of patients with monoclonal gammopathies.

Table 1. Population demographics

	No monoclonal Disease (*n* = 1855)	Monoclonal Gammopathy[a] (*n* = 138)
Mean age (years)	50	67[b]
Gender (percentage male)	59	50
Biopsy (native/ transplant)	1056/799	137/1
Complication rate	3.7%	4.3%[c]

[a]Histologic evidence of a renal injury secondary to a monoclonal gammopathy.

[b]The population with monoclonal gammopathies were significantly older ($P < 0.001$).

[c]The complication rates were not significantly different ($P = 0.81$).

Materials and Methods

The electronic databases from four large teaching hospitals within the United Kingdom, University Hospital Birmingham, Birmingham; The Royal Free Hospital, London; The Royal London Hospital, London; and King's College Hospital, London, were searched to identify an unselected population of patients with both renal impairment and a monoclonal gammopathy in whom a renal biopsy was undertaken. Renal impairment was defined as being present if at least one of the following criteria were met: an estimated GFR of <60 ml/min (using the Modification of Diet in Renal Disease equation) (16) or proteinuria of >0.5 g/24 h as estimated by either a spot urine protein-to-creatinine ratio or a 24-hour urine collection. A comparative control population was also identified from the same units.

Retrospective analysis of the patients' records was undertaken to determine the incidence of significant hemorrhagic complications after renal biopsy. These were defined as a confirmed hematoma (hemorrhage) on radiologic imaging (ultrasound or computer tomography) or documented macroscopic hematuria. Radiologic imaging was only performed in those cases where the clinical picture was suspicious for bleeding postprocedure, *i.e.,* patients who became hemodynamically unstable, had significant pain, or had persistent significant hematuria. Hemoglobin was not routinely measured postprocedure. Rates of radiologic and surgical interventions were also collected.

The percutaneous renal biopsies were undertaken using real-time ultrasound imaging using spring-loaded automated devices. Local protocols were adhered to regarding prebiopsy screening of hematologic parameters, BP, and kidney size. Briefly, correction of hematologic parameters was required prebiopsy if platelets were $<100 \times 10^9$/L and/or the international normalized ratio was >1.4. Biopsies were not performed if prebiopsy ultrasound scanning showed evidence of obstruction or kidney sizes of <8 cm bilaterally. A biopsy was not performed if prebiopsy BP exceeded 160 mmHg systolic or 90 mmHg diastolic.

Patients with renal disease secondary to monoclonal gammopathies were defined as a histologic diagnosis of myeloma kidney (cast nephropathy), amyloid, and monoclonal free light chain deposition (light chain deposition disease or crystal deposits within the tubules). Patient variables and rates of hemorrhagic complications were compared between study groups using a *t* test and the χ^2, as appropriate (SPSS 14.0; SPSS, Chicago, IL). Values of $P < 0.05$ were considered statistically significant.

Results

The outcomes for 1993 patients who underwent renal biopsies between January 1993 and December 2008 were reviewed. A total of 1193 native and 800 transplant biopsies were performed (Table 1). In total, 74 patients had a significant hemorrhagic complication (3.7%). Of these, 64 had macroscopic hematuria (3.2%), 15 had a confirmed radiologic hematoma (0.7%), and 5 required radiologic intervention (0.3%). No patients required surgical intervention or died as a result of the renal biopsy. Seven patients required a blood transfusion, and of the 64 patients where data were available, 39 had an indwelling urinary catheter placed.

The risk of a hemorrhagic complication was not associated with the patients' age (48 ± 15 *versus* 55 ± 17 [SD] years in the patients with and without complications, respectively; $P = 0.13$) or degree of renal dysfunction (serum creatinine 3.15 ± 2.38 *versus* 3.24 ± 2.59 mg/dl, respectively; $P = 0.81$). Nor was there a significant difference in the rate of complications between patients undergoing native and transplant renal biopsies (4.0 and 3.3%, respectively; $P = 0.4$).

One hundred thirty-eight patients were identified to have a histologic lesion associated with a monoclonal gammopathy (Table 2). In addition, a further 10 patients were known to have multiple myeloma but did not have histologic evidence of a monoclonal process. One biopsy was of a renal transplant in this population; the remainder were native. In total, 4.1% of the 147 patients with a monoclonal gammopathy undergoing a native renal biopsy had a significant hemorrhagic complication. This was not significantly greater than those patients without a monoclonal gammopathy undergoing native biopsies (3.9%, $P = 0.88$). The rate of complications in patients undergoing native renal biopsies with biopsy-proven monoclonal renal dis-

Table 2. Renal findings in patients with monoclonal gammopathies and associated hemorrhagic complications

	Percentage (*n*)	Bleeding Complications (*n*)
Amyloid	23.7 (35)	0
Cast nephropathy	62.2 (92)	6[a]
Mixed amyloid and cast	3.4 (5)	0
LCDD	0.7 (1)	0
Intraglomerular crystal deposition	0.7 (1)	0
ATN	2.7 (4)	0
Other renal findings[b]	6.8 (10)	0

ATN, acute tubular necrosis; LCDD, light chain deposition disease.

[a]Two of the six bleeding complications in patients with cast nephropathy were hematomas. One of these required radiologic intervention. The remaining four complications were significant hematuria and did not require radiologic intervention.

[b]Other renal findings included diabetic nephropathy; hypertensive damage; end-stage kidney; membranous nephropathy; and focal segmental glomerular sclerosis.

ease was 4.4%, which was not significantly higher than those without monoclonal gammopathies (3.9%, $P = 0.67$). Thirty-five patients had a renal diagnosis of amyloid. None of these had a significant hemorrhagic episode. In comparison, 6.5% of the 92 patients with cast nephropathy did have a significant bleeding episode ($P = 0.12$; Table 2).

Discussion

The overall rate of clinically significant hemorrhagic complications in this study was 3.7%. This is comparable to previous work, where major hemorrhagic complication rates after native renal biopsies were reported as ranging from 1 to 8% (15,17–21). This study included 148 patients with a known monoclonal gammopathy. Major hemorrhagic complications occurred in 4.0% of these cases. This was not significantly greater than the incidence in patients without monoclonal gammopathies undergoing native renal biopsies (3.9%).

Numerous studies have investigated the potential risk factors for complications after percutaneous renal biopsy (17–20). Although monoclonal gammopathy–associated disease has been suggested to confer an increased risk of hemorrhagic complications (8,9), the current evidence supporting this theory is sparse. Moreover, a recent study to investigate the use of plasma exchange in treating cast nephropathy reported no complications after renal biopsies in 28 patients with myeloma (12). To date, there has not been a study specifically designed to examine the hemorrhagic complication rate of biopsies performed in patients with monoclonal gammopathies. A few studies have analyzed the bleeding risk associated specifically with amyloidosis. Eiro *et al.* (20) found a higher rate of bleeding (defined as drop in hemoglobin by >1 g/dl) in patients with amyloidosis compared with other histologic findings, although this considered just four patients with the diagnosis. Conversely, Soares *et al.* (15) found 4% of 101 patients with amyloidosis developed a major hemorrhagic complication; this was not significantly greater than the control group. This study included 35 patients with amyloidosis. None of these had a significant hemorrhagic complication.

The six major hemorrhagic complications seen in patients with monoclonal gammopathies in this study all occurred in patients with cast nephropathy. This presumably reflects the clinical context, acute kidney injury, in which a diagnosis of cast nephropathy will be made. Potentially, however, this could also relate to the higher serum concentrations of monoclonal free light chains likely to have been present in these patients (22). Coating of platelets with free light chains is one recognized mechanism by which patients with monoclonal gammopathies have an increased bleeding risk (10). Other more common mechanisms, in this context, include thrombocytopenia caused by bone marrow infiltration and clotting defects caused by sepsis and uremia. Less common hematologic irregularities arising in association with paraproteins include heparin-like circulating anticoagulants, factor X deficiency, endothelial interference, in cases of amyloidosis, and acquired von Willebrand syndrome (10,11). A number of these conditions will result in abnormal coagulation profiles, although some will be more difficult to detect. The protocols used by the institutes in

this study included routine prebiopsy screening for impairment of clotting. Procedures were not performed if these parameters were outside the accepted reference ranges. The results suggest that, when this approach is followed, renal biopsies can be undertaken safely in these patients. This observation is particularly important in the context of considering new invasive treatment options (23,24).

In our 148 patients with a renal injury and a known paraproteinemia, by far the most common histologic diagnosis was cast nephropathy, which was found in 62% of cases. This was followed by amyloidosis at 23%. Additionally, a further 3.4% of biopsies showed cast nephropathy mixed with amyloidosis. These results are consistent with previous studies describing the range of potential histologic findings in patients presenting with renal impairment and an associated monoclonal gammopathy (1,2,12).

The principal limitation of this study relates to its retrospective nature. With this limitation, it was not possible to identify cases where there were minor hemorrhagic complications. Previous work has indicated that a high proportion of patients will acquire a small hematoma after a renal biopsy, whatever the underlying diagnosis (20,25). However, these are unlikely to be of clinical significance, and it can be argued that their detection is unnecessary. Second, although this is the largest series to date to report the incidence of major hemorrhagic complications after renal biopsies in patients with monoclonal gammopathies, because of the relative rarity of these conditions, the number of patients studied is still relatively small.

Conclusions

This study showed that the risk of a major hemorrhagic complication in patients with a monoclonal gammopathy after a percutaneous renal biopsy is not increased. We suggest that the assessment of renal histology in patients with monoclonal gammopathies remains a valuable diagnostic tool to guide management and help predict clinical outcomes for these.

Acknowledgments

Disclosures

None.

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