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Chapter

Post-Biopsy Complications Associated with Percutaneous Kidney Biopsy

Paulo Ramos Botelho Antunes, Stanley Almeida Araújo, Silvana Maria Carvalho Miranda, Fabiano Franco Monteiro Prado, Luiz Felipe França Antunes, Elisa Carvalho de Siqueira, Fabrício Tinôco Alvim de Souza and Maria Carolina Barbosa Álvares

Abstract

Renal physiology and physiopathology have been the object of studies aimed at developing exams that can assist in the early diagnosis of the base disease. Chronic kidney disease consists of the progressive, irreversible loss of kidney function. Early detection and appropriate treatment can minimize the progression of the disease, lower the inherent costs, and improve the quality of life of affected individuals. Kidney biopsy is the key method in this evaluation, as it enables the histological and immunohistochemical analysis of specimens in a fast, safe, and economical manner. The main indications for kidney biopsy are nephrotic syndrome, acute kidney failure of unknown etiology, persistent hematuria and proteinuria, chronic kidney disease with conserved kidney dimensions, and transplanted kidneys (to evaluate stages of rejection, infection, and/or sclerosis). However, as an invasive method, kidney biopsy is not without complications. Post-biopsy complication rates range from 5 to 15%, with 6.6% considered minor (macrohematuria with no need for blood transfusion) and another 7.7% considered major (hemorrhage requiring blood transfusion or other approaches). In this chapter, we address the main aspects of kidney biopsy, the technical procedures for its execution, and the management of the main complications stemming from this procedure.

Keywords: kidney biopsy, percutaneous kidney biopsy, post-biopsy complications, complications, ultrasound-guided biopsy

1. Introduction

Renal lesions are subdivided based on duration as acute kidney injury (AKI) and chronic kidney disease (CKD). AKI has numerous hemodynamic, inflammatory, toxic, and obstructive causes, which, when diagnosed and treated early, can be reversed, thereby avoiding permanent damage [1, 2]. CKD, however, is the clinical detection of a progressive, irreversible loss of kidney function, for which the aim of therapy is to minimize the progression of the disease [2].

Percutaneous kidney biopsy has become part of clinical practice in nephrology, as it enables the diagnosis, prognostic assessment, and therapeutic guidance of kidney diseases [3, 4]. Since its advent in the 1950s, advances have been achieved in the technique to improve the diagnostic yield and minimize complications [5].

2. Percutaneous ultrasound-guided renal biopsy

2.1 Indications

The indication for a kidney biopsy is determined mainly by signs and symptoms [4]. The global rate of biopsy (number of procedures per million [ppm]) in native kidneys ranges from more than 250 ppm in Australia to less than 75 ppm in the United States. This divergence in kidney biopsy rates is influenced by the prevalence of kidney disease as well as different opinions regarding the value of the procedure in terms of diagnosis, prognosis, and therapy [6].

The main objectives that lead to the indication for kidney biopsy are the need for a precise diagnosis and treatment, the need to determine the degree of activity and chronicity of the lesion in order to establish the prognosis and possible response to treatment, and the evaluation of genetic diseases [6]. The diagnostic contribution of a kidney biopsy is undeniable in cases of nephrotic syndrome, systemic disease kidney failure, unexplained AKI, and transplanted kidney dysfunction [7].

For cases of idiopathic nephrotic syndrome in adults and children older than 6 years of age, the indication for a kidney biopsy is extremely important, as the findings often influence therapeutic decision-making [8]. In a prospective study involving 276 biopsies of native kidneys, the diagnosis resulting from the biopsy influenced the management of 86% of cases of nephrotic syndrome [9]. However, there is a variety of clinical situations of nephrotic syndrome for which a kidney biopsy is not generally performed at the time of diagnosis, such as in cases of children between 1 and 6 years of age due to the high prevalence of minimal change disease [10, 11]. In such situations, corticotherapy is indicated and biopsy is only performed in cases of therapeutic failure or the appearance of another sign or symptom not associated with minimal change disease [11]. Biopsy is also not performed initially in cases of secondary nephrotic disease clearly associated with the introduction of a medication known to cause this condition, such as non-steroidal anti-inflammatory drugs, gold salts, pamidronate, penicillamine, and lithium. This group includes patients with longstanding diabetes with gradual proteinuria progression, those with morbid obesity and slowly increasing proteinuria accompanied or not by diabetes and worsening kidney function, those with systemic diseases such as primary or secondary amyloidosis in which the diagnosis can be made through less invasive methods, such as adipose tissue biopsy, and patients known to have malignant diseases involving nephrotic syndrome [6]. Patients with nephrotic syndrome generally exhibit hematuria, proteinuria, hypertension, and renal dysfunction, and the condition is also often associated with systemic diseases. Therefore, kidney biopsy contributes to the diagnosis, therapeutic decision-making, and classification of the disease (e.g., systemic lupus erythematosus). In suspected cases of post-streptococcal glomerulonephritis, biopsy is only recommended when a gradual worsening in serum levels of creatinine, prolonged hypocomplementemia, and recurring hematuria are observed [6, 7].

Cases of systemic diseases with kidney failure include non-nephrotic proteinuria, isolated glomerular hematuria, and unexplained CKD. Protein is a marker and factor related to the progression of kidney disease. Studies have demonstrated a relation between the degree of proteinuria and the progression of CKD in cases

of non-nephrotic proteinuria [7]. Thus, many nephrologists routinely perform a kidney biopsy in patients with higher non-nephrotic proteinuria (1–2 g/day) in the absence of another clinical condition that might explain the findings (e.g., diabetes mellitus or hypertension). However, in situations of low-grade proteinuria (500–1000 mg/day) in the absence of glomerular hematuria, altered kidney function, and clinical/serological evidence of a systemic disease, a biopsy is generally not performed [6]. Biopsy in cases of isolated glomerular hematuria remains controversial, as the procedure exerts little influence on therapeutic decision-making. When performed, the conditions most often encountered are Alport syndrome, thin basement membrane nephropathy, and immunoglobulin A nephropathy. In a prospective analysis, biopsy influenced the therapeutic decision-making in only one of the 36 procedures performed [9]. For patients with unexplained CKD, a kidney biopsy can provide important information, despite the greater risk of complication. In cases of exacerbated CKD, a biopsy may reveal lesions that can be treated and reversed. Moreover, a biopsy can contribute important knowledge to clinical management in cases of the need for a kidney transplant [7].

For patients with unexplained AKI, biopsy is indicated in cases of an uncertain etiology and can influence clinical management in 71% of cases [9]. Biopsy is also particularly useful for early or late-onset dysfunction of a renal graft. In cases of acute graft dysfunction, the procedure enables confirming the diagnosis of rejection and specifying the pathological mechanism (acute cellular rejection or antibody mediated rejection). Late biopsies also furnish essential information to assist in differentiating the causes of chronic nephropathy of the graft, such as chronic rejection, transplant glomerulopathy, nephrotoxicity, viral disease, lymphoproliferative diseases, and relapse of the base disease. The simplicity of the technical procedure and richness of the diagnostic and prognostic information make biopsy indispensable to the follow-up of renal grafts [7].

Contraindications for kidney biopsy may be absolute or relative. For percutaneous kidney biopsies, absolute contraindications include uncontrolled severe hypertension, the inability of the patient to cooperate with the biopsy, having only one kidney, and uncontrollable hemorrhagic diathesis, whereas relative contraindications include severe azotemia, anatomic kidney abnormalities, anticoagulation, pregnancy, and urinary tract infection [3].

2.2 Techniques and materials

Kidney biopsies can be guided by different imaging methods, the most common of which are ultrasound (US) and computed tomography (CT) due to their good performance and broad availability. In contrast, magnetic resonance is employed little due to the greater cost and need for specific material. The choice between US and CT should be individualized and based on the physician's experience, kidney volume, location of the biopsy site, patient's clinical condition, and the availability of the equipment. US is generally the imaging method of choice for guiding a kidney biopsy, since it enables obtaining samples from virtually any site and visualizing the needle in real time. It also does not expose the patient to radiation, can be performed in any environment, including at the bedside, and enables the continual monitoring of any pre-operative complications. It is also the method of choice for post-procedure follow-up, enabling the early detection of complications [4].

To be successful, US-guided kidney biopsy requires specific conditions. The patient must be placed in ventral decubitus on the examining table and the procedure must be performed in a sterile environment. The transducer should be covered with a sterile film. There are specific transducer covers on the market, but a sterile glove can be used in cases of emergency. Antisepsis should be performed on the

entire side of the back corresponding to the kidney to be biopsied. The selection of the puncture site is determined by US considering the best path (least distance between the skin and renal capsule and the absence of vascular structures and/or interposed intestinal loops). This region in the center of the US image ensures the safest path for the biopsy and provides better control and resolution of the image.

Once the region to be punctured has been defined, the skin at the puncture site is anesthetized and the area of anesthesia is then extended to the deep layers, preferably reaching the perirenal layers, including adjacencies external to Gerota's fascia and the renal capsule. An alternative is the use of a long 18G peripheral intravenous catheter with the administration of 20 ml of anesthetic solution (10 ml of 2% xylocaine with no vasoconstrictor +10 ml of 0.9% saline solution or bi-distilled water). The entire anesthetic procedure as well as the subsequent steps should be guided by US. Some authors prefer performing a biopsy with their hands free. The two techniques (with or without US) have the same rates of minor and major complications and obtain adequate material for analysis, but the hands-free method requires greater experience and has a somewhat slower learning curve [1, 12]. Next, the biopsy needle is aligned with the transducer (when US is used) and introduced at a 45° angle to the skin. To ensure the safety of the procedure and control of complications, both the needle and its path should be kept within the US viewing field. The path to follow with the needle in the renal parenchyma should only involve the renal cortex (glomerular region), without transfixing the renal medulla, which contributes little to the study and has large-caliber vessels that could be associated with vascular complications; this also avoids the occurrence of injury to the renal calyces and pelvis [4, 13]. The number of fragments to collect depends on the number and types of exams requested as well as the presence of the pathologist during the exam, who may express opinions regarding the quality of the specimen collected. In procedures without the presence of a pathologist, two fragments are normally collected for each exam solicited.

Different needle calibers, lengths, and tip shapes are available on the market for the collection of material for microscopic analysis. Thin-needle punctures are performed with calibers ranging from 20 to 25, whereas thick-needle biopsies are performed with 14- to 19-gauge needles. Authors state that thin needles provide smaller fragments for analysis, but the fragments have similar quality and anatomopathological interpretation to those obtained with thick needles. Nonetheless, larger fragments enable a more complete study of renal pathologies. Moreover, although a smaller caliber is related to a lower rate of complications stemming from the procedure, it does not assist in the renal evaluation [14]. Along with a core biopsy needle (thick needle), coaxial needles can be used, which have a larger diameter with sufficient inner diameter to enable the navigation of the core biopsy needle in its interior. The use of coaxial needle kits avoids multiple punctures of the capsule, as this mechanism enables acquiring several tissue samples with a single perforation, which reduces the procedure time. However, portions of the organ cannot be sampled with this method and the use of such needles increases the cost of the procedure. The use of coaxial needles enables the operator to easily embolize the needle path with an absorbable gelatin sponge when removing the outer needle at the end of the procedure. This embolization promoted by the coaxial method is believed to reduce the risks of post-biopsy bleeding, but this characteristic is reported to not be an advantage of the method. Thus, both the coaxial and non-coaxial techniques do not appear to influence the bleeding complication rate [15]. The use of spring-loaded tools is currently recommended. These needles are classified based on the form of discharge into the tissue: automatic or semi-automatic (disposable). Such tools are reported to be more effective and safer than classic percutaneous renal biopsies that use the Tru-Cut or Vim-Silverman needle. Automatic tools are more

economical, since only part of the kit is disposable. However, the disadvantage is the lower control over the progression of the needle during discharge and capture of the fragment as well as the longer procedure time due to the increase in the number of preparation steps of the needle/spring-loaded tool with the risk of contamination. Semi-automatic tools are more costly due to the fact that the entire system is disposable. The advantages are the security in maintaining all material sterile throughout all steps of the procedure, greater control over the advancing of the needle for the extraction of the fragment, the possibility of checking the intralesional position prior to discharge, and the reduction in procedure time, since no preparation of the needle and spring-loaded tool is needed.

Prior to presenting the biopsy technique to the patient or legal guardian, it is advisable to consult with the physician in charge of the procedure. This moment orientates the patient and family regarding the risks, benefits, and preparation for the procedure. It is also possible to identify possible techniques linked to the peculiarities of each patient, such as having a physical disability that precludes the standard position, deforming kyphoscoliosis, scars, skin diseases, and anxiety disorders. To ensure a successful examination, it is of extreme importance to evaluate recent laboratory exams (within the previous 30 days) and determine the patient's health condition. Patients should meet basic criteria before being submitted to the procedure (**Table 1**). If a patient does not meet the minimum requirements, the procedure should be rescheduled until after the base disorder has been corrected. For patients with an urgent need for the procedure, immediate corrective measures should be assessed. For instance, plasma and platelet transfusion may be options in cases of a high international normalized ratio (INR) and low platelet count, respectively. An imaging study should be performed prior to the kidney biopsy to gain knowledge on renal anatomy and determine the presence of ectopias, congenital dysplasia, or polycystic kidneys.

2.3 Quality of material/pathologist present

A kidney biopsy is an important diagnostic tool and considered the "gold standard" for the best definition of the majority of nephropathies. It is capable of changing the clinical diagnosis approximately 50% of the time and changing the therapy to be administered approximately 40% of the time [16]. For this to happen, however, an adequate sample must be obtained.

A 19-gauge needle generally furnishes very small, narrow specimens that are often inadequate for the assessment of vessels. Thus, smaller needles, such as 18 or

Criteria that impede a kidney biopsy
Clotting disorders characterized by prothrombin activity <60%
INR > 1.3
Platelet count <60,000/mm^3
Use of anticoagulant
Systolic BP > 140 mm Hg
Urinary infection
Acute persistent cough
Skin lesions at puncture site
Altered mental state

Table 1.
Conditions that impede a kidney biopsy.

16 gauge, are advisable [17, 18]. Depending on the needle used, the difference in the obtainment of glomeruli can be as high as 300% [19]. The quantity of glomeruli needed for a secure diagnosis depends mainly on the diagnostic hypothesis and the clinical condition of the patient. For virtual exclusion (with greater than 95% certainty) of the diagnosis of focal segmental glomerulosclerosis, it is essential to have at least 25 glomeruli representing the juxtamedullary portion, as the focal disease affects some glomeruli while sparing others of morphological abnormalities seen with light microscopy and a good sample is important to the best definition of the disease [20]. In contrast, the diagnosis can be confirmed with a single glomerulus for other diseases, such as membranous glomerulopathy, in which diffuse morphological changes are similar in all glomeruli. For still other diseases, such as myeloma nephropathy, the diagnosis is essentially confirmed with representation of the medullary portion. In the analysis of transplanted kidney tissue, the aim is to achieve at least two core fragments exhibiting at least 7–10 glomeruli, two arteries, and the medullary portion (minimum assessment criteria defined by the Banff Meeting) [21].

In the evaluation of most glomerulopathies by light microscopy or immunofluorescence microscopy, 8–10 glomeruli are needed [22]. During the US-guided removal of the fragment, the evaluation of a pathologist is very important, as he/she is capable of determining the adequacy of the sample. The examination of the fresh material determines its sufficiency (quantity of glomeruli) for testing the main clinical hypotheses and provides information on medullary representation as well as the representation of larger vessels (**Figure 1**).

After determining the ideal amount of material and its representation of the renal parenchyma, the pathologist stores the samples in specific solutions for different analyses. The solutions should not come into contact with each other, as this would render the subsequent analyses unviable. The largest portion of the fragments should be allocated to light microscopy analysis. The most widely used fixatives are

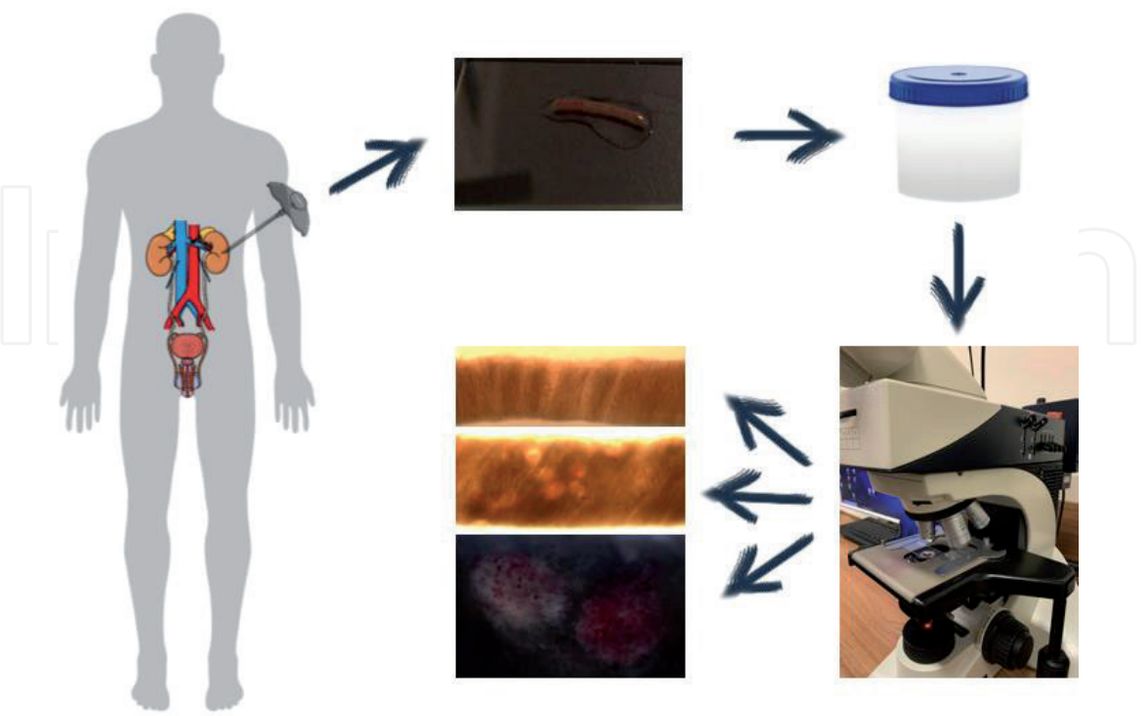

Figure 1.
Ultrasound-guided kidney biopsy. Fragment stored in 0.9% NaCl and analyzed under a light microscope. Renal medulla with medullary rays and characteristic striation. Multiple small round structures (glomeruli) distributed in renal cortex—some paler, others congested with numerous red blood cells (details of two glomerular structures).

10% neutral buffered formalin, paraformaldehyde, and Bouin's solution. In these media, the sample remains viable for analysis for several days. However, earlier histological processing results in analyses of better quality. For the analysis of antigens, such as IgG, IgM, IgA, complement components C3 and Cq1, fibrinogen as well as κ and λ chains, immunofluorescence microscopy should be used. Therefore, the sample should be stored in 0.9% saline solution—if the collection site is near the analysis site—and kept chilled (but not frozen) to obtain the best possible results. If rapid analysis (within several hours) is not possible, the sample should be placed in a transport solution, such as Michel's or Zeus solution. Although this solution preserves the sample for several days, better results are achieved the earlier the sample is taken for analysis, with poor or even impossible results if the sample is analyzed 5–7 days after being collected [23]. For transmission electron microscopy, a small portion is needed of the cortical parenchyma, with two glomeruli. This analysis is essential to the evaluation of podocytopathies, thin basement membrane disease, and metabolic disease. The fragments should be fixed within minutes after collection in a specific solution (glutaraldehyde or Karnovsky's solution). In the presence of a pathologist, a small portion may be acquired (1 and 2 mm) and fragmented until obtaining the quantity of glomeruli needed. This material should be placed in a buffered solution after fixation (1–2 days after collection), as the aim of the analysis is to examine the ultrastructure, such as the cytoplasmic membrane, reticulum, and immune deposits, which are lost if not fixed soon enough.

When a biopsy is performed without the presence of a nephropathologist, it is advisable to remove at least one fragment (if possible, two) from the renal parenchyma for each solution. Immunohistochemical analysis for the study of C4d, polyomavirus, adenovirus, cytomegalovirus, PLA2R, IgG4, etc. should be performed with material embedded in paraffin, which is preserved for light microscopy.

2.4 Complications and management

A kidney biopsy is considered a minimally invasive method but is not without complications. Depending on the severity, such events are classified as minor and major, which require different forms of treatment (**Table 2**). Minor complications include hematuria, small perirenal hematomas, arteriovenous fistulas, and pain, all of which normally resolve spontaneously [24]. Major complications include massive bleeding with hemodynamic instability, voluminous perirenal hematomas with refractory disabling pain, and important hematuria with obstruction of the urinary tract by clots. In such cases, management is normally necessary.

Among all forms of complication, bleeding is the most frequent and occurs mainly within the first 12–24 hours after the procedure in nearly all patients [4, 25].

Complications	**Management**
Major complications	
Disabling intense pain	Optimization of analgesia (use of opioids)
Hemodynamic instability with blood transfusion	Endovascular treatment (embolization)
Clot obstructing urinary tract	Irrigation with three-way probe
Minor complications	
Arteriovenous fistula	Conservative
Hematuria	Hydration

Table 2.
Post-biopsy complication and proper management for each.

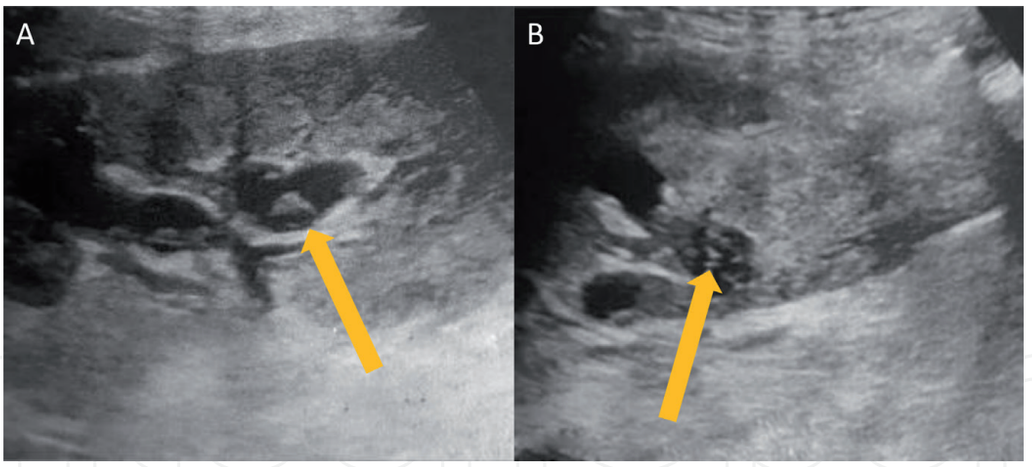

Figure 2.
Exploratory ultrasound performed on patient with gross hematuria, 24 hours after percutaneous native kidney biopsy. (A and B) Multiple pelvic blood clots (arrow) after renal biopsy.

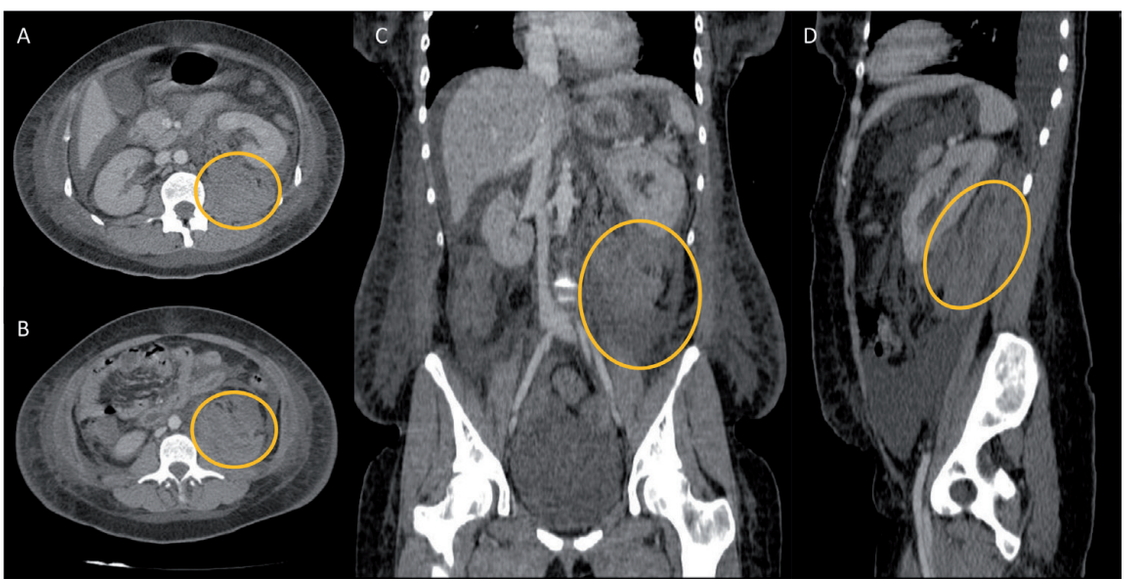

Figure 3.
Perirenal hematoma, an hour after percutaneous native kidney biopsy. Computed tomography (CT) scan slices of the abdomen revealed voluminous perirenal hematoma (yellow circle), on the left side. (A and B) Axial scan slices. (C) Coronal scan slice. (D) Coronal scan slice.

Microscopic hematuria, mild low back pain, and a slight drop in the hemoglobin concentration are frequent findings and should not be considered complications [25]. However, the persistence of these symptoms for more than a week may require a detailed investigation with imaging exams. Post-biopsy chronic hypertension, the puncture of other organs, and perirenal soft part infections have been described but are very rare.

The literature reports variable complication rates, generally ranging from 5 to 16%, with macroscopic hematuria in 3–9% of cases and the need for transfusions in 0.1–3.0% of cases [14, 26–29]. In such cases, an exploratory ultrasound examination should be performed (**Figure 2**). Burstein et al. found post-biopsy complications in 14.3% of patients, with 6.6% considered minor and another 7.7% considered major (hemorrhages requiring blood transfusion or another approach) [28]. González-Michaca et al. found major complications in 2.4% of patients and minor complications in 8.65%, the most frequent of which was perirenal hematoma [30, 31]. Native kidneys tend to have a lower complication rate than transplanted kidneys (13.9 and 24.4%, respectively) [32].

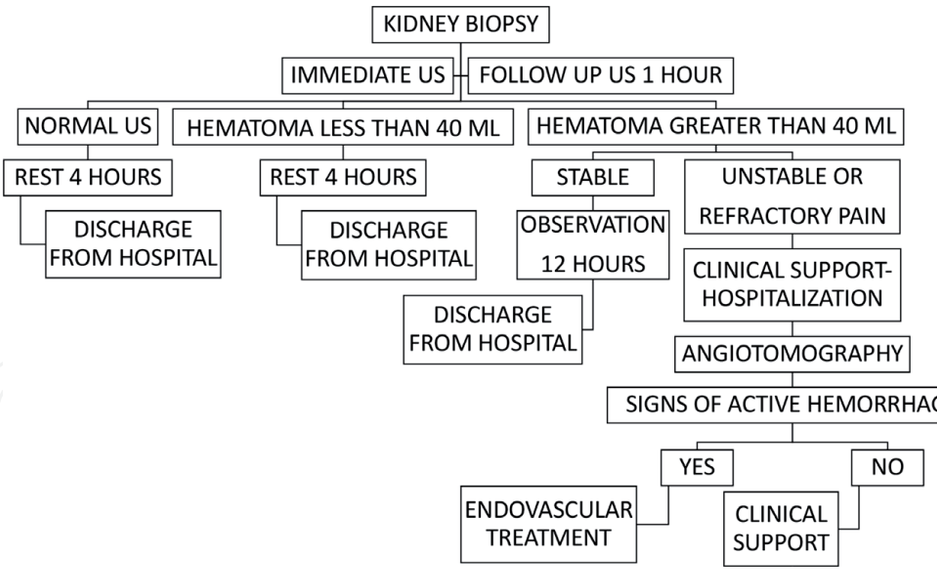

Figure 4.
Post-biopsy procedures and management.

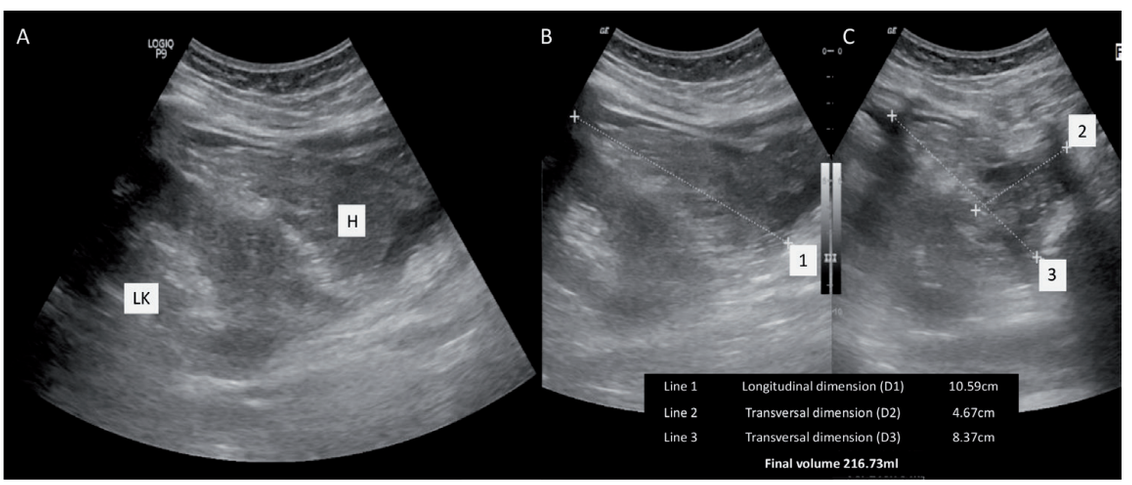

Figure 5.
Perirenal hematoma, observed an hour after percutaneous native kidney biopsy. (A) Longitudinal ultrasonography exhibiting hematoma area near the posteroinferior border of the left kidney. (B and C) Longitudinal (line 1) and transversal dimension on ultrasound (line 2 and 3) estimated the final volume of 216.73 ml of hematoma area. LK, left kidney; H, hematoma.

After a kidney biopsy, patients should remain in observation for at least 4 hours. They are placed at absolute rest in dorsal decubitus and are monitored in this period with the constant evaluation of vital signs. It is also advisable to perform renal ultrasound 1 hour after the procedure in all patients submitted to percutaneous kidney biopsy. The aim of this measure is to evaluate the biopsied area and anticipate possible post-procedure complications, thereby enabling immediate, effective therapeutic support (**Figure 3** and **Figure 4**).

The volume of the perirenal hematoma formed and the complication rates associated with this procedure have a direct relation of proportionality. Hematomas formed in the first hour after the procedure with volumes greater than 40 ml are related to a greater risk of developing major complications [14] (**Figure 5**). For cases of minor complications, the patient should receive clear orientation regarding the expected benign evolution of the case and receive medication for the symptoms based on individual need. These patients should be required to return after 7 days for a follow-up ultrasound and definitive discharge of the case if no imaging abnormalities are found and there are no new complaints. In cases of hemodynamic

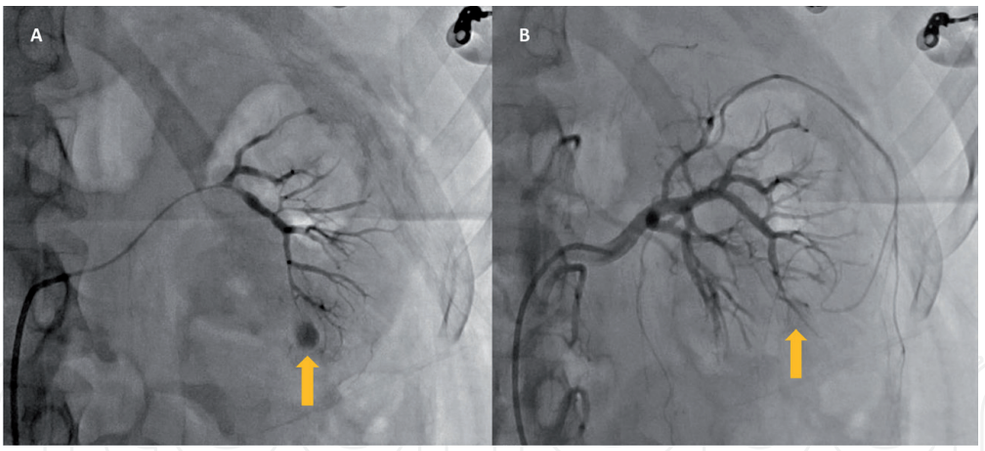

Figure 6.
Renal arteriography, 2 hours after percutaneous native kidney biopsy. (A) Pre-embolization arteriography revealed pseudoaneurysm in a lower renal pole (yellow arrow). (B) Post-embolization superselective arteriography revealed absence of pseudoaneurysm with preservation of the local vasculature (yellow arrow).

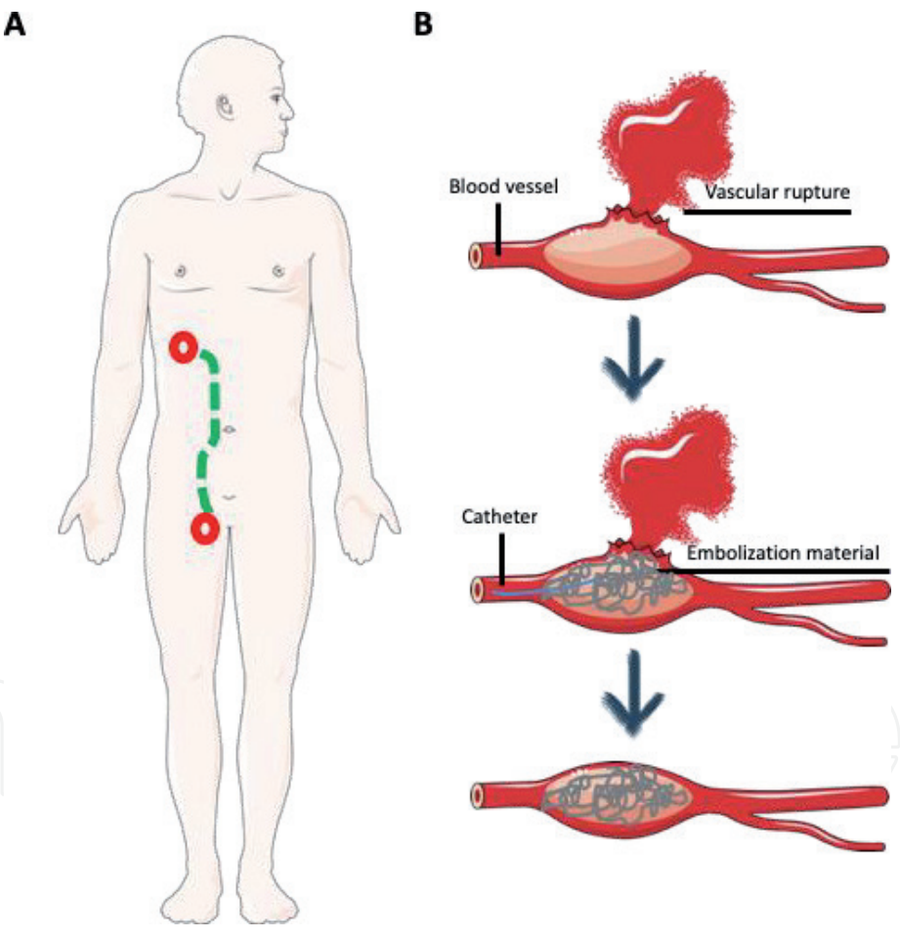

Figure 7.
Endovascular embolization. (A) A catheter is inserted into femoral artery, by the groin area to access vessels of the kidney and into vascular rupture site. (B) Rupture in arterial blood vessel, which will receive a catheter and embolization material to achieve occlusion.

instability, the patient should receive adequate clinical measures at an intensive care unit, followed by an angiographic study. Digital angiography remains the gold standard for the anatomic study of the renal arteries, but computed tomography angiography (angiotomography) has gained popularity, offering comparable accuracy and the advantage of evaluating not only the lumen, but its walls and other visceral changes [32].

After renal vascular mapping and if signs of active bleeding are identified (active escape of contrast medium, pseudoaneurysms, or arteriovenous fistulas), endovascular treatment is indicated, which is a minimally invasive procedure that should be performed by an interventionist radiologist or professional who is duly trained and certified in endovascular techniques (**Figure 6**). The procedure can be performed through femoral or radial artery access, always initiated with an anatomic study of the renal arteries and respective variations. When a probable focal hemorrhage is identified, superselective arteriography is performed in a coaxial system with a microcatheter and microguide, followed by superselective embolization techniques performed on the compromised vessel. For interventional treatment, the selection of appropriate embolic agents for superselective embolization is the key to achieving desirable outcomes (**Figure 7**). Embolic agents include PVA particles, coils, and gelatin sponge strips, which can be used either alone or in combination [33]. The de-vascularized area will suffer infarction, which could cause a momentary change in renal function. Thus, more selective catheterism leads to a lower risk of this complication. Pseudoaneurysms are pulsating masses at puncture sites due to the rupture of the arterial wall and extravasation of blood, generally associated with local pain and hematoma. Hemodynamic instability and a drop in hemoglobin concentration may be related to the rupture of pseudoaneurysms. The treatment for pseudoaneurysms and arteriovenous fistulas is recommended for persistent bleeding for more than 72 hours or in cases of the accentuated loss of kidney function after the procedure. It should be stressed that most pseudoaneurysms less than 2.0 cm and arteriovenous fistulas progress with thrombosis and spontaneous resolution within 4 weeks, making conservative treatment the conduct of choice in cases without hemodynamic instability. Patients should remain in intensive care for at least 24 hours after the procedure and a follow-up imaging method should be performed prior to the decision regarding the discharge of these patients.

3. Conclusion

Imaging-guided renal biopsy is a useful tool for the evaluation and management of renal diseases. This chapter summarizes that percutaneous ultrasound-guided renal biopsy is a safe technique which allows the evaluation of renal disease but is associated with post-biopsy complications. We discuss indications and approach to imaging-guided percutaneous renal biopsies as well as complications and management associated with this.

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Conflict of interest

The authors declare no conflict of interest.

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