Polycystic Kidney Disease

Clinical case

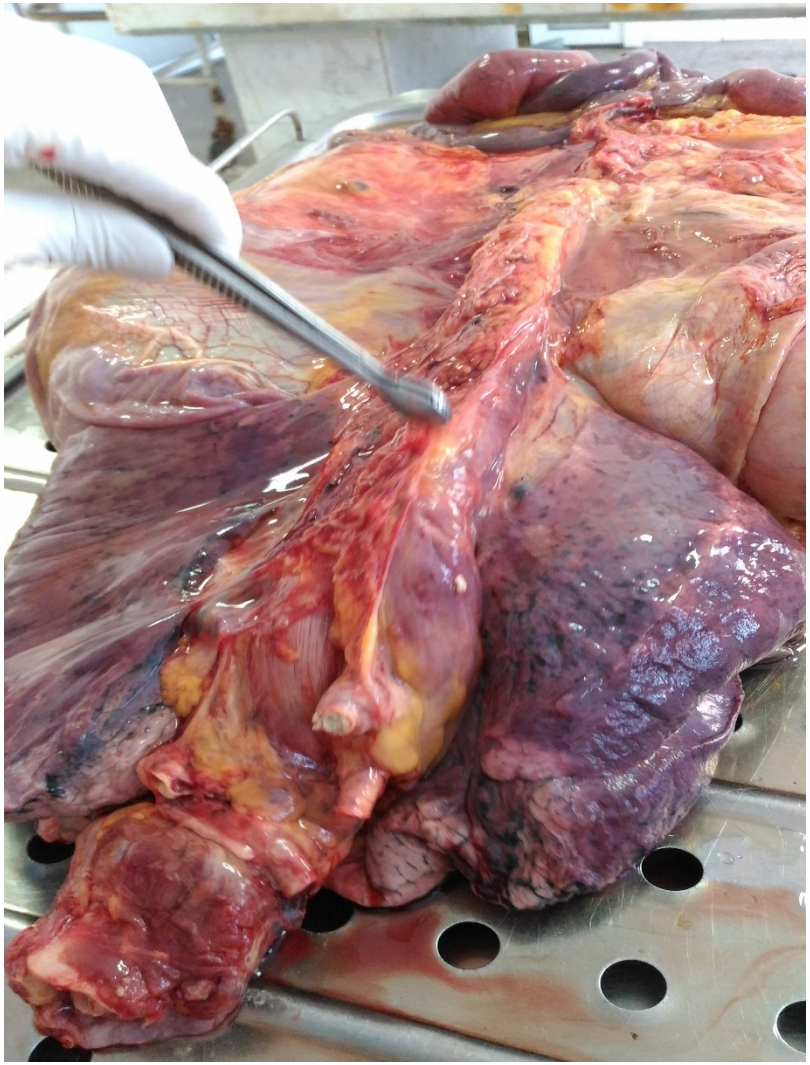
Patient B, 65 years old, diagnosis Polycystic Kidney Disease

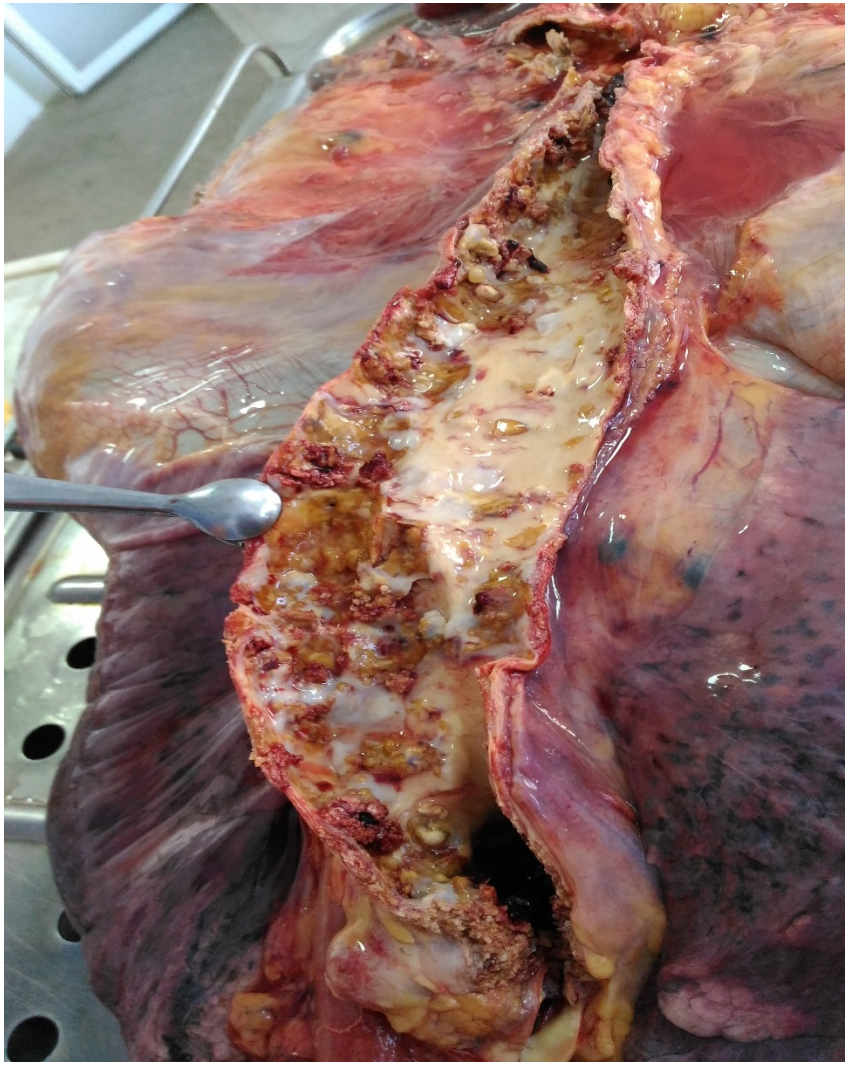
Admitted to the Republican Clinical Hospital “T. Mosneaga” for diagnosis and treatment.

During hospitalization, severe complications occurred that lead to the death of the patient.

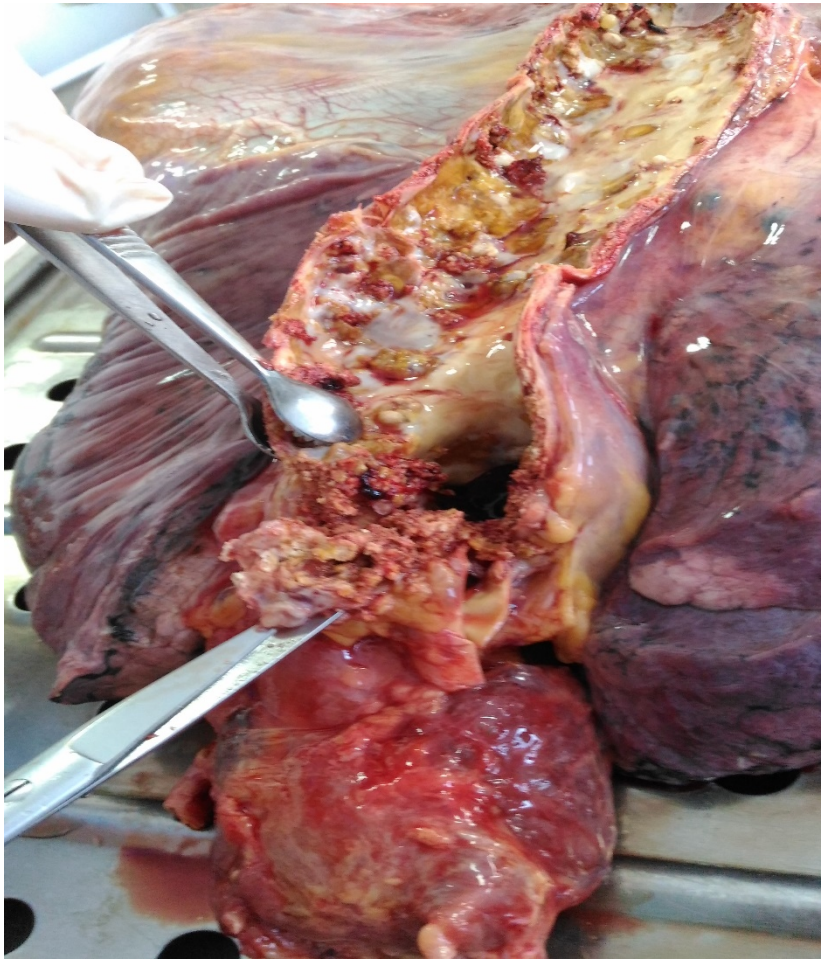
1 – aorta

2 – aortic dissection: severe atherosclerotic changes – throughout the aorta atherosclerotic plaques with atheromatosis



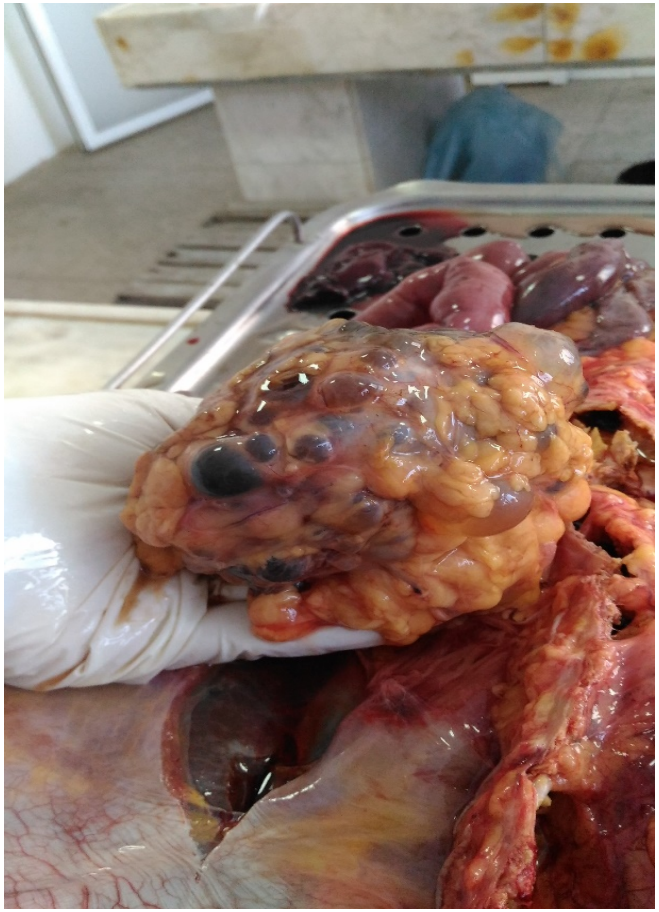


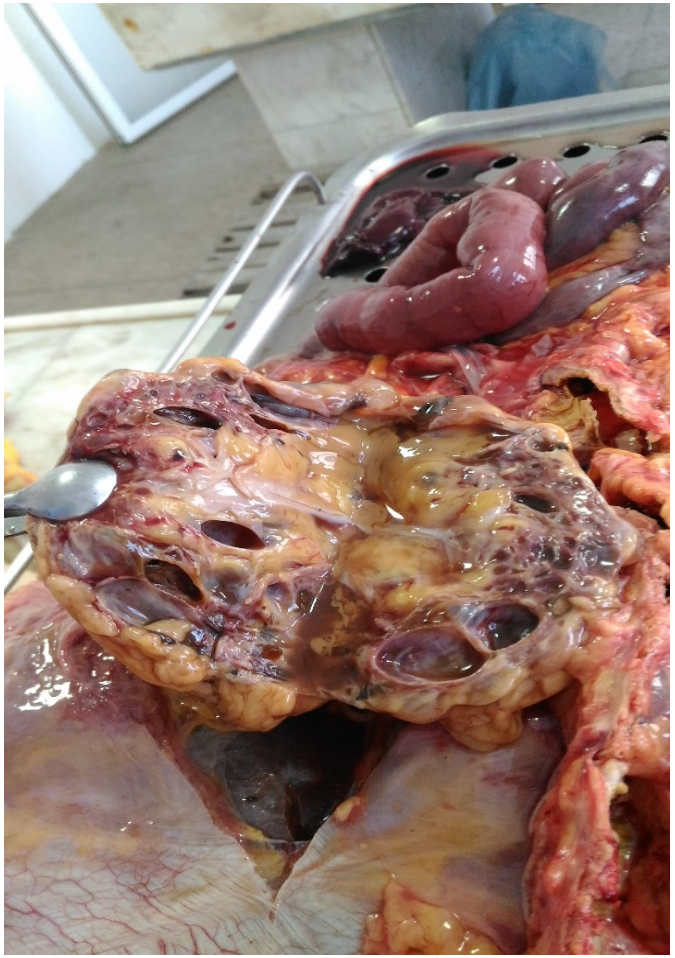
1 – aortic arch with severe ulcerations
2 – aorta with onset of dissection



1 – polycystic kidney

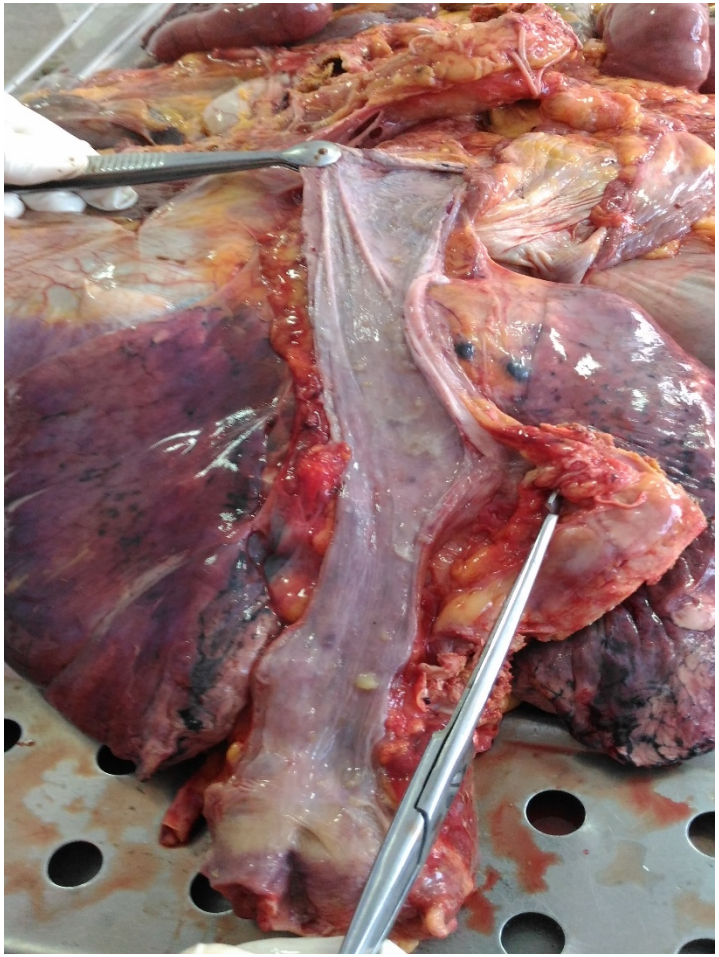
2 – section of polycystic kidney: multiple cavities of different size, the wall of the cysts is thin, semitransparent, inner surface smooth, the content yellowish and hemorrhagic, renal cortex thinned to 0.2 cm, renal pyramids are not observed. The pelvis is rich in fat tissue.

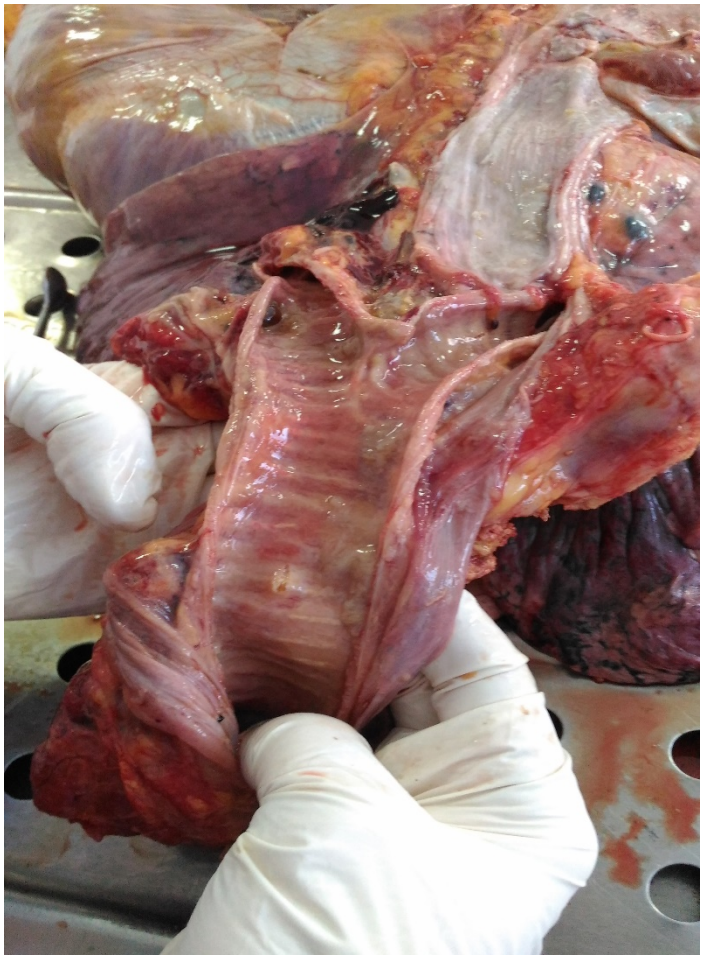




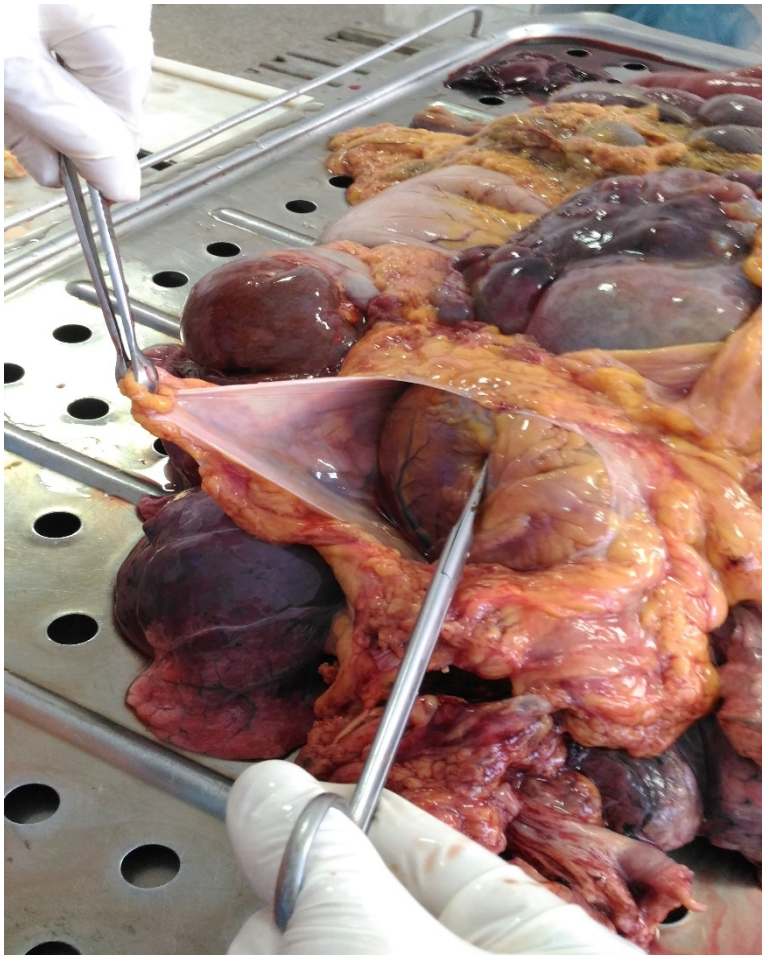
1 – dissected esophagus – grayish mucosa, flattened folds

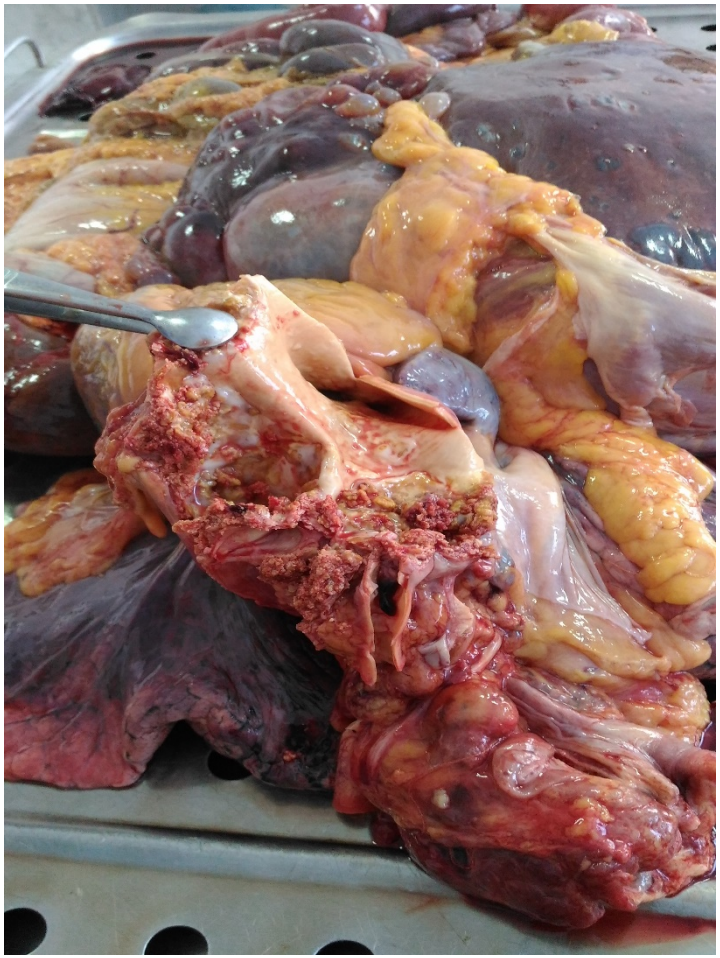
2 – dissected trachea and bronchi, reddish-speckled with small quantities of mucus



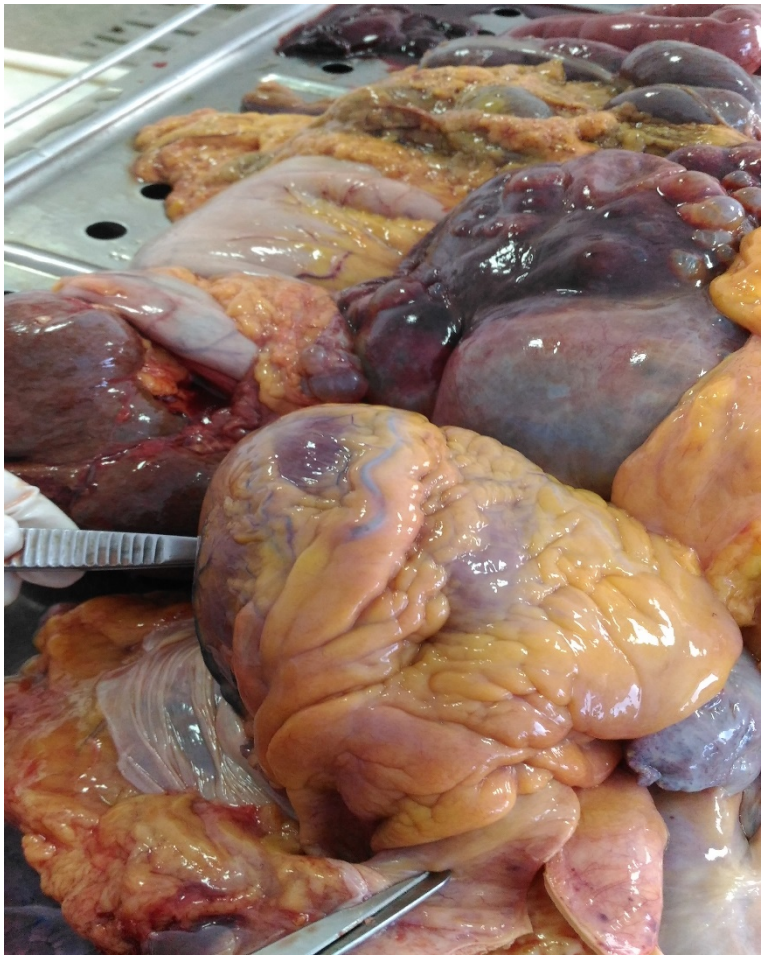


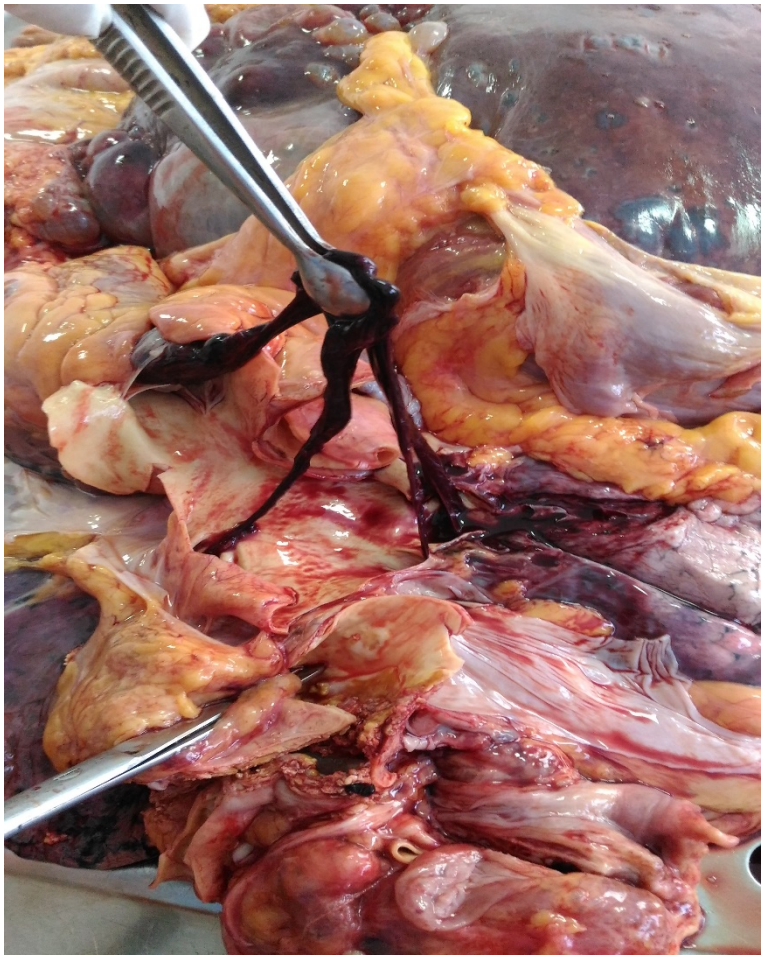
1 – the heart with the dissection of pericardium
2 – aortic arch





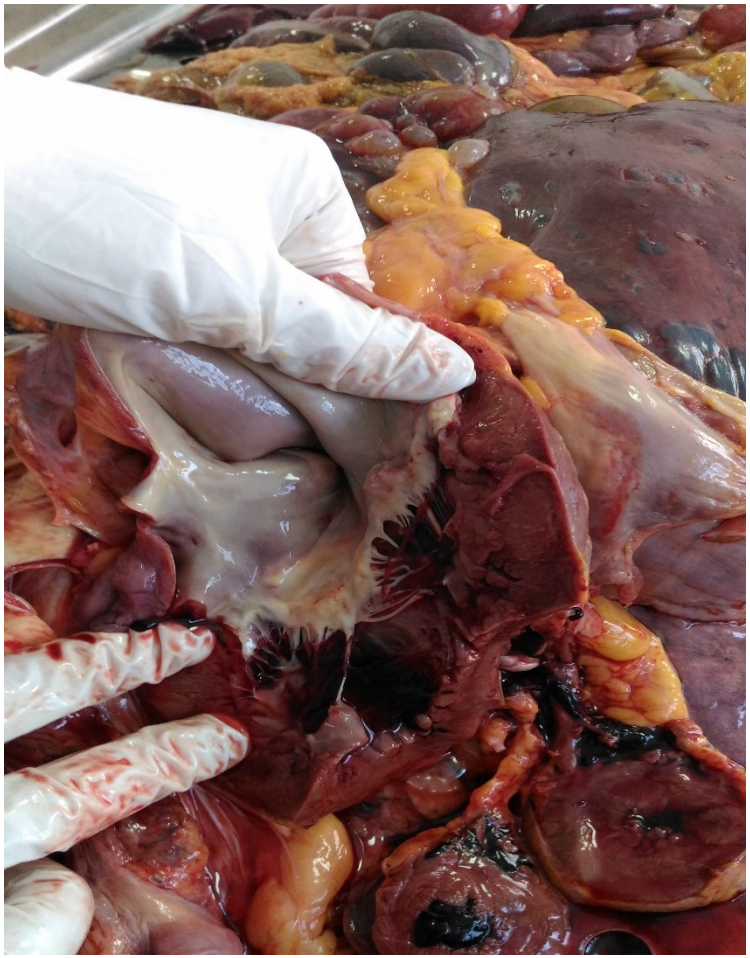
1 – the heart with lipid deposits in moderate quantities
2 – postmortum blood clot in the pulmonary artery

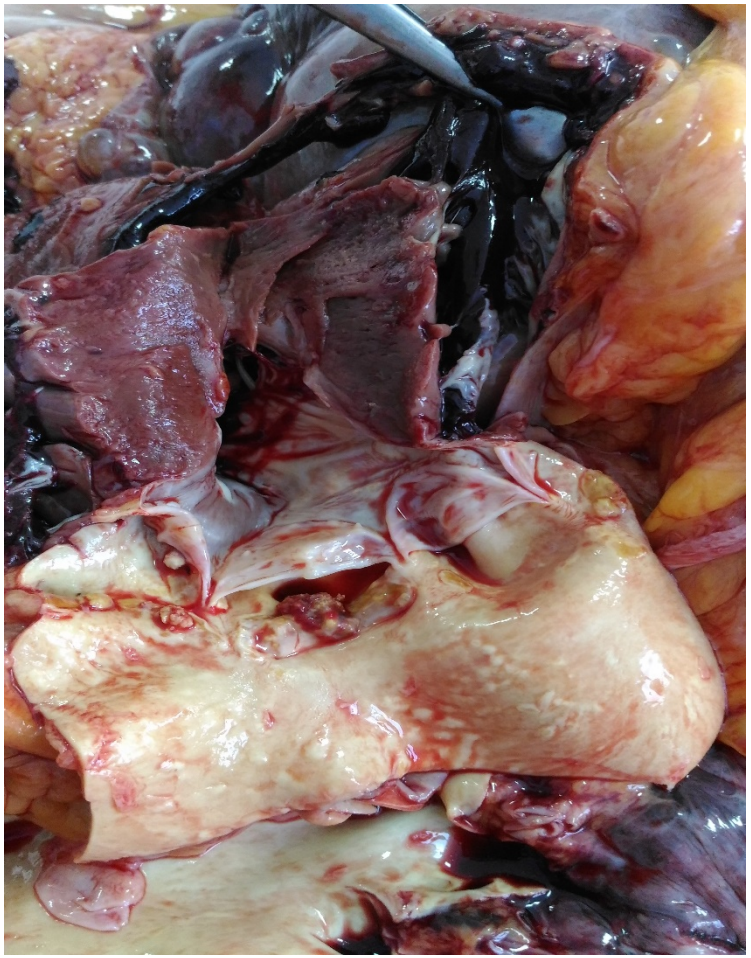




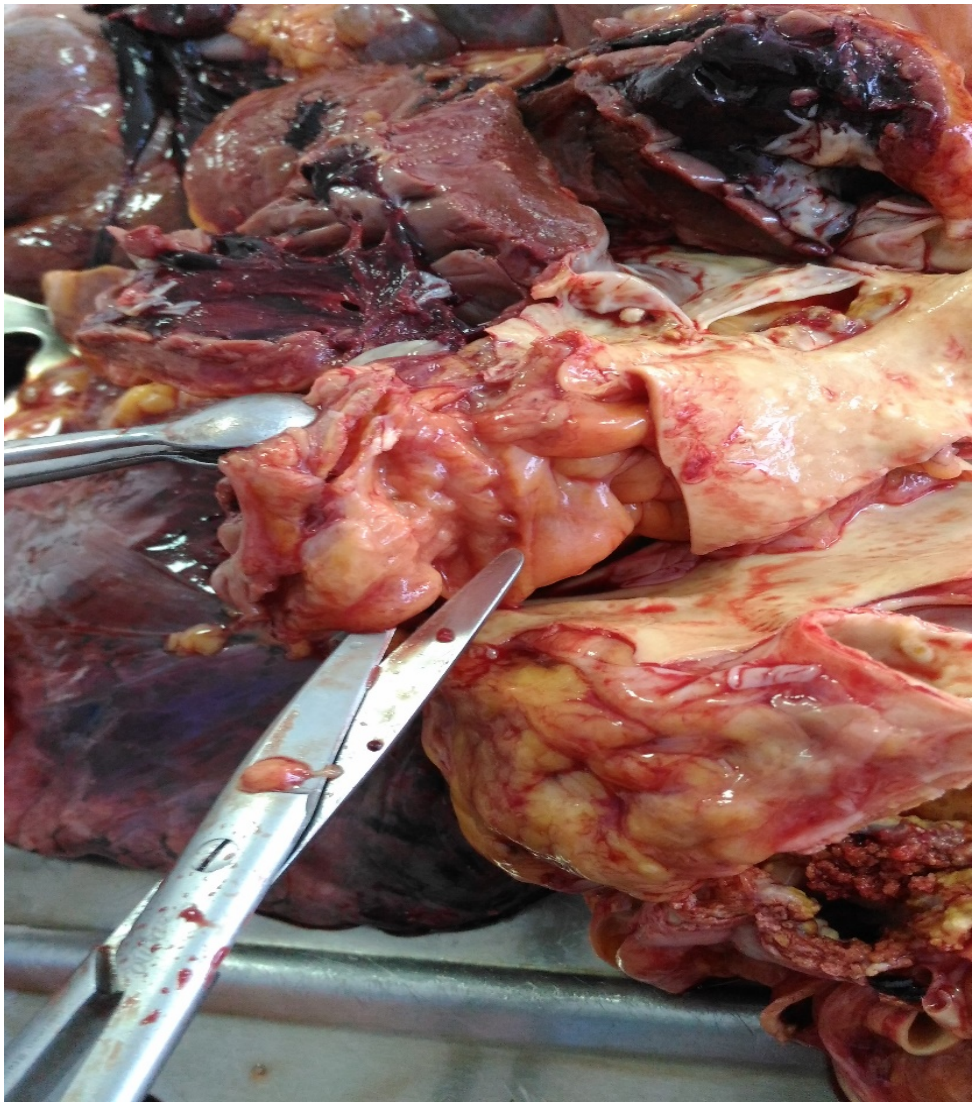
1 – the opened heart: mitral valve leaflets, with minimal changes

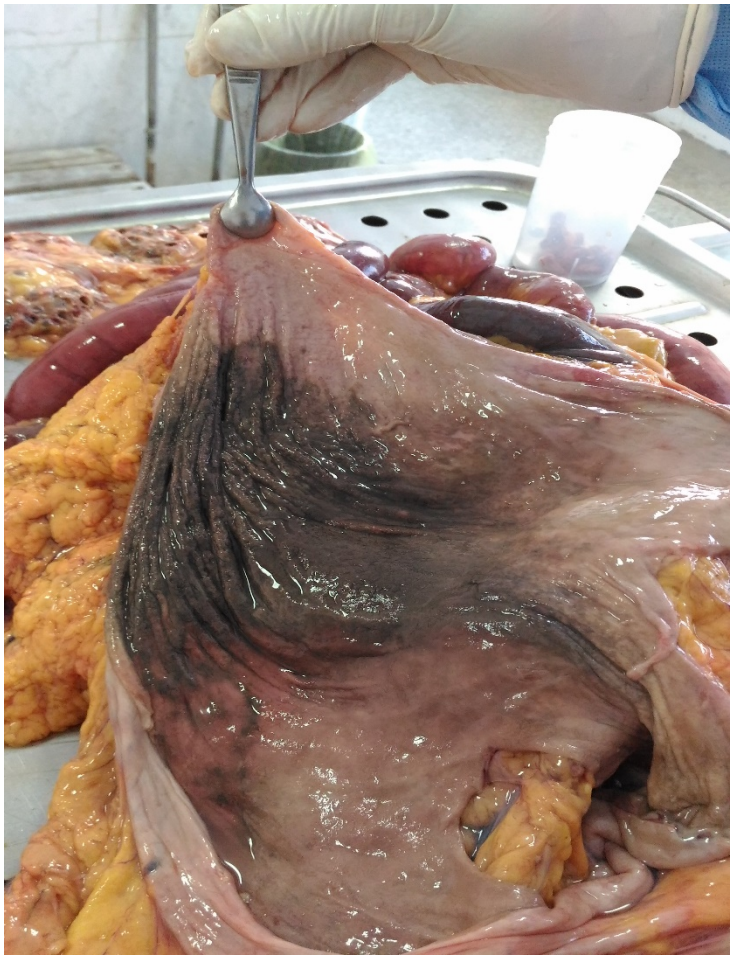
2 – aortal valve with sclerosis and atheromatosis and atherocalcinosis.



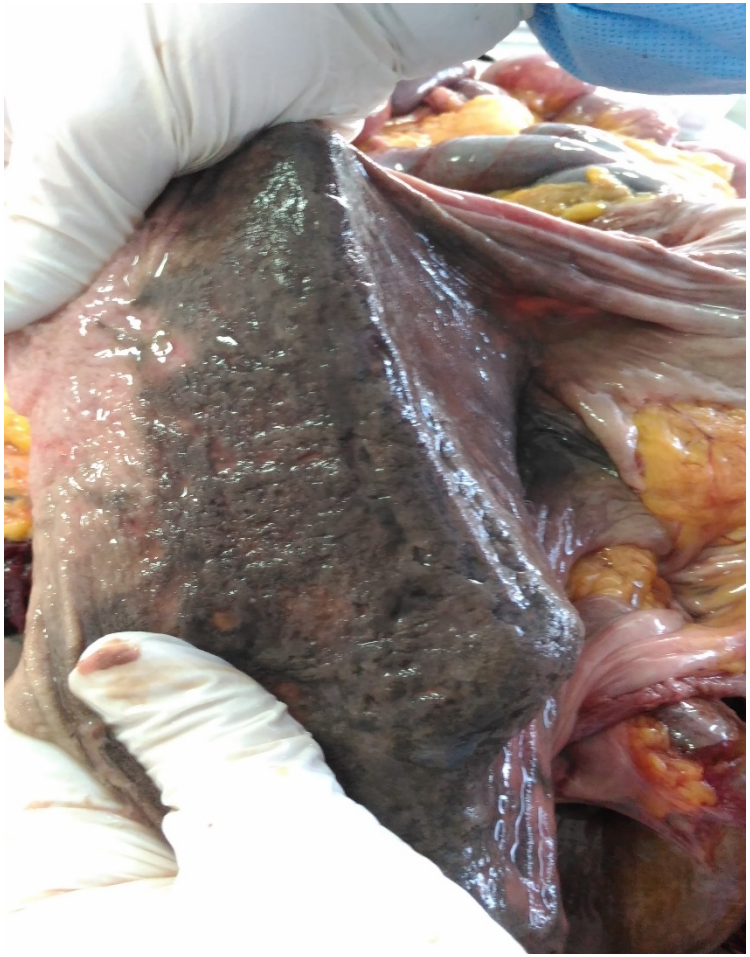


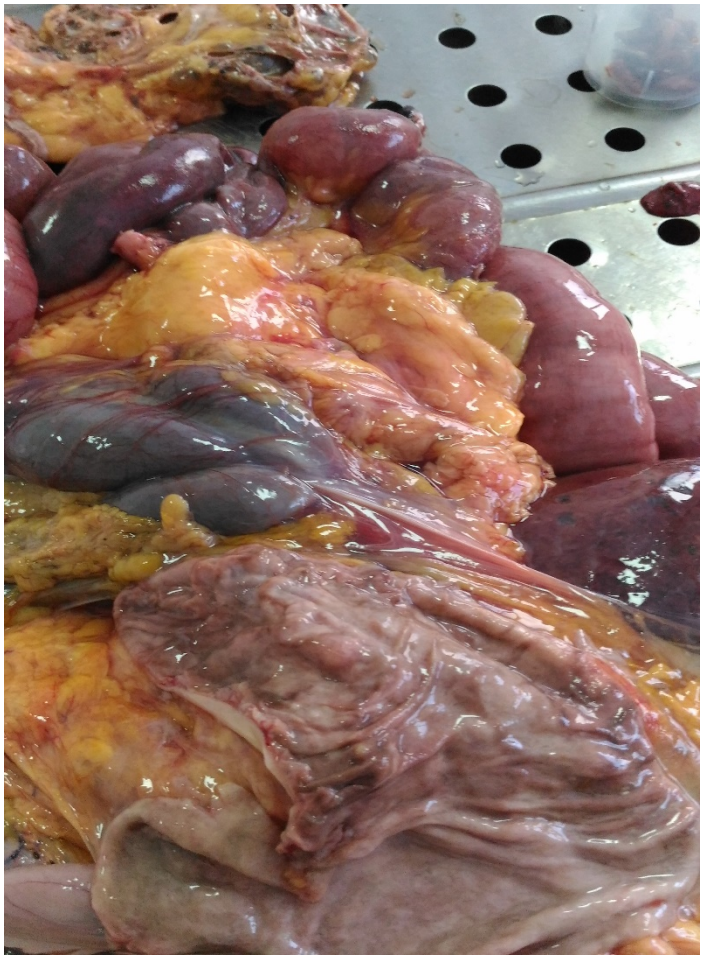
1 – opened heart: brown myocardium with small grey grooves (signs of diffuse atherosclerotic microfocal cardiosclerosis)
2 – opened stomach with violet-black center, postmortem venous stasis, the folds are not seen



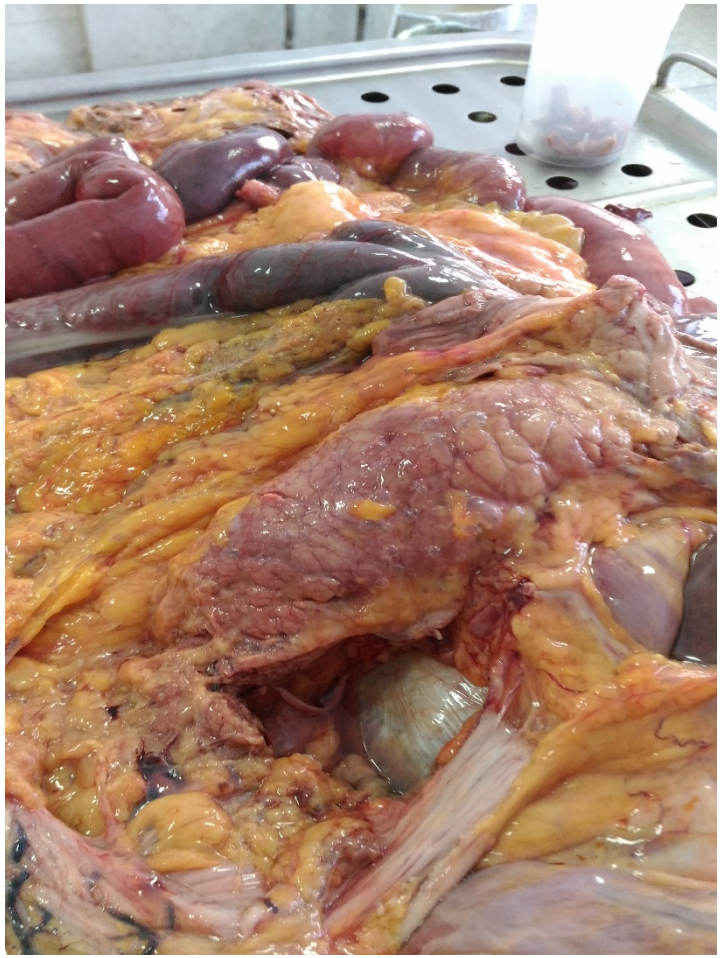


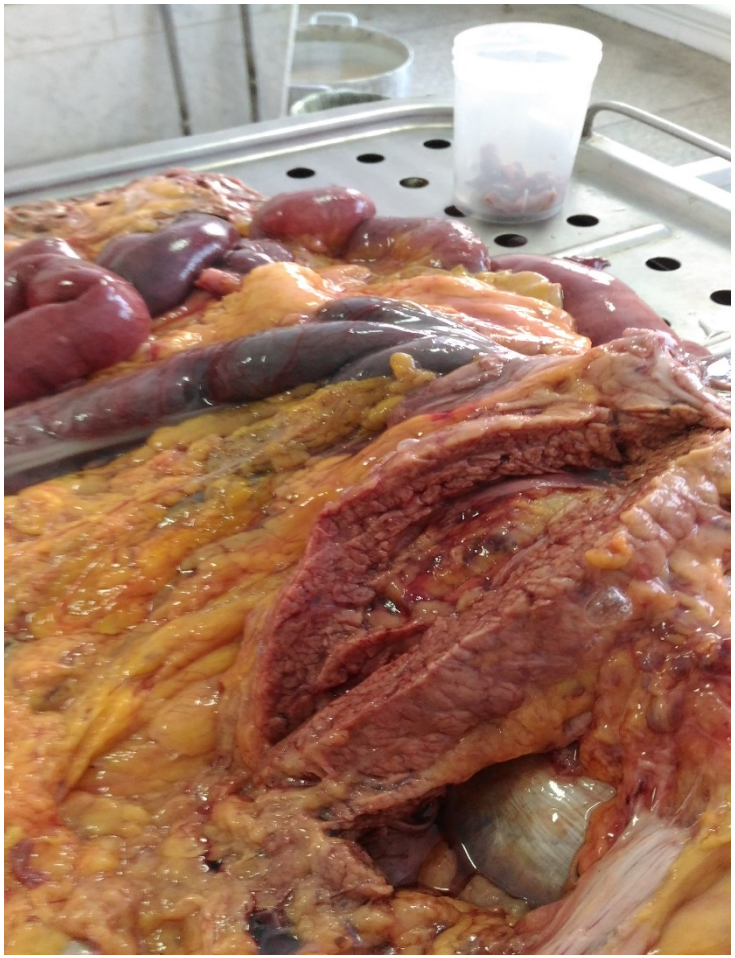
1 – opened small intestine with bleeding in the sectoral wall (macroscopic signs of chronic uremia)
2 – moderately aired small intestine



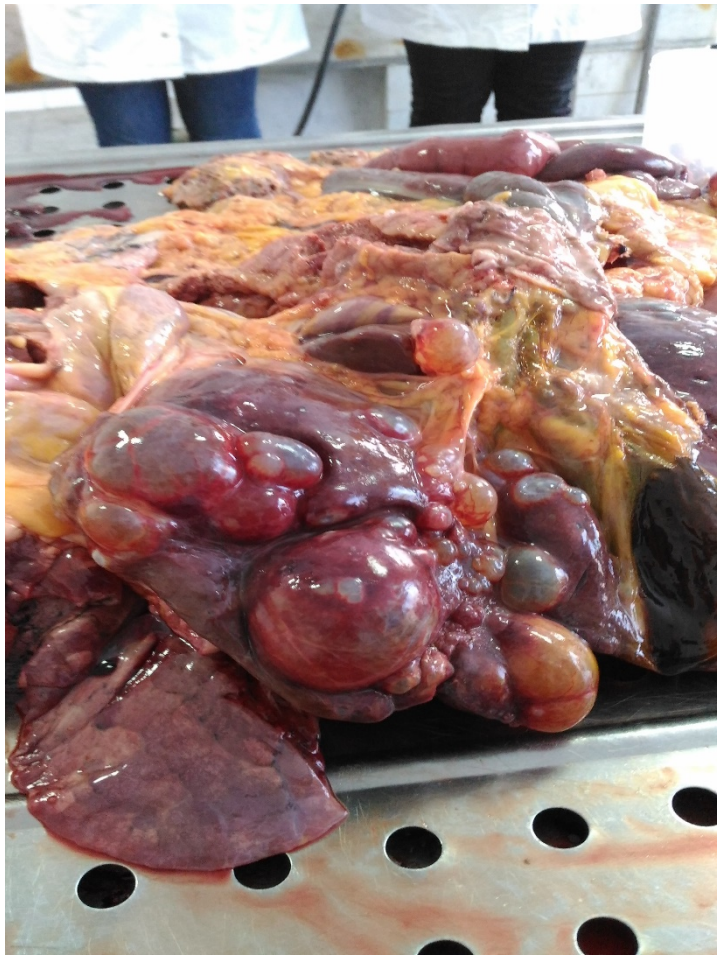


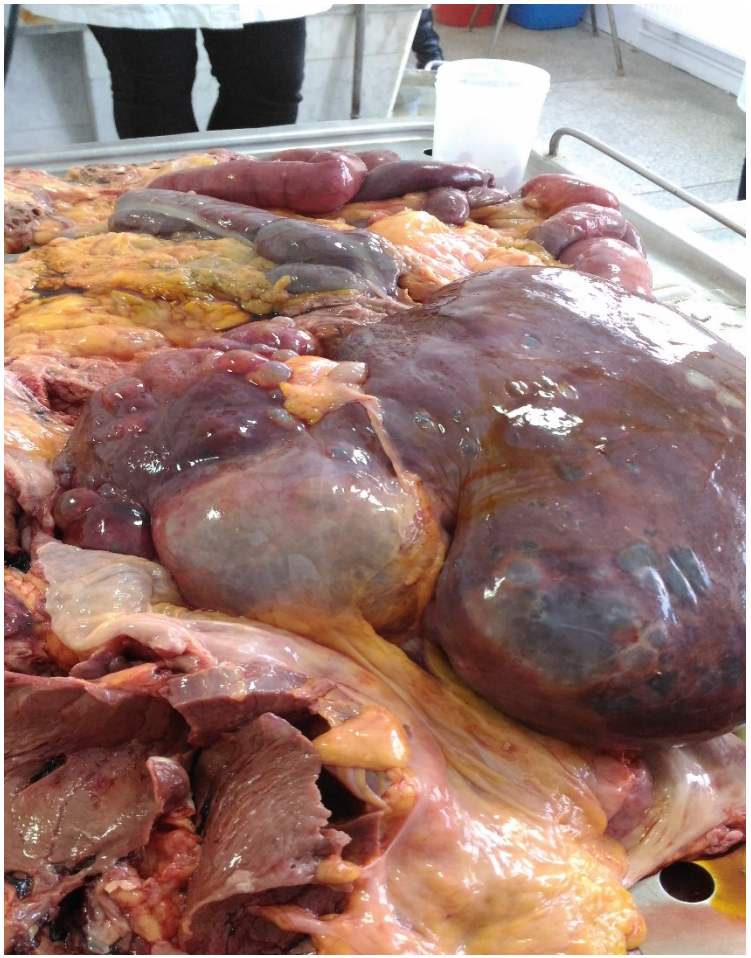
1 – pancreas
2 – pancreas cross section, without macroscopic changes



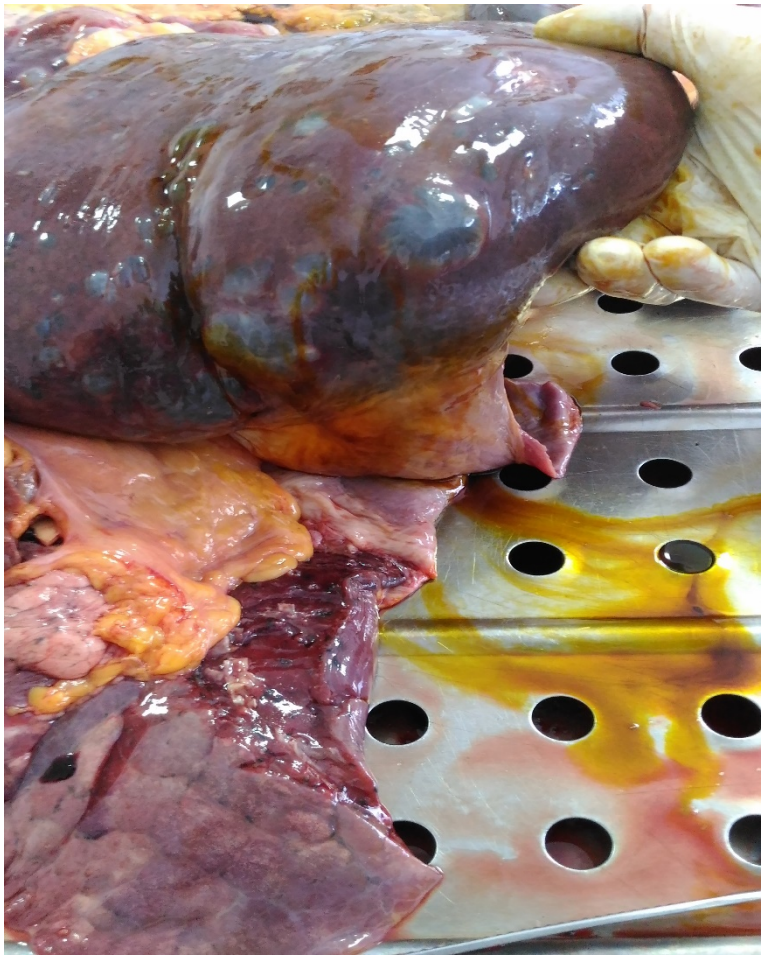


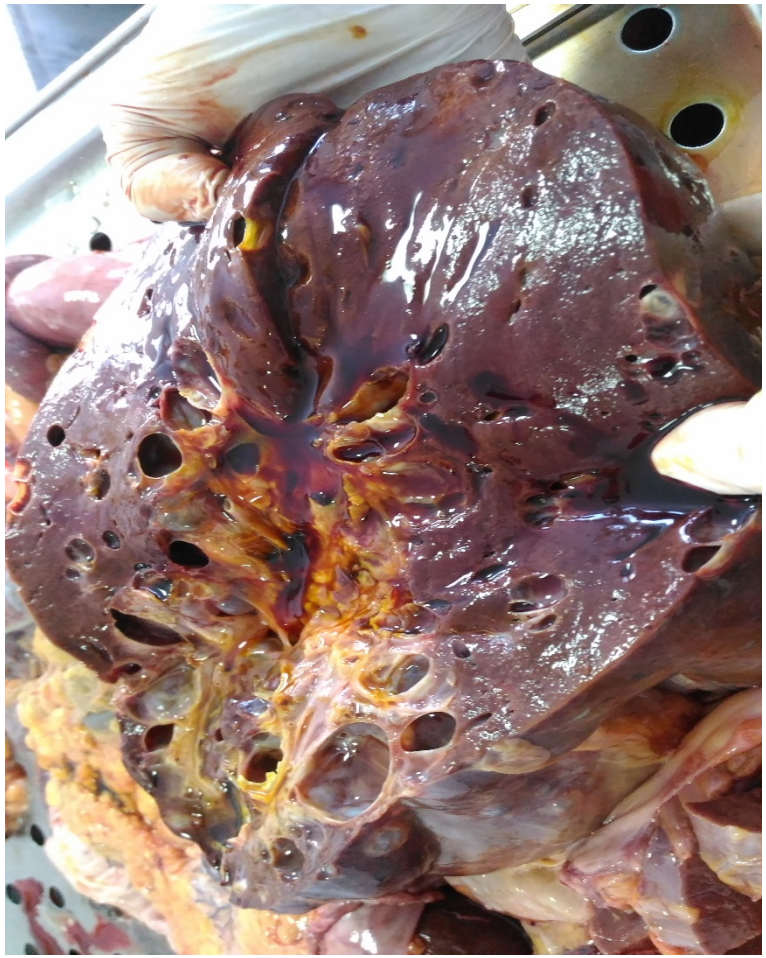
1 – polycystic liver from the side of the gallblader, the wall of the cyst is this, semitransparent, with hemorrhagic content
2 – polycystic liver, diaphragmic side





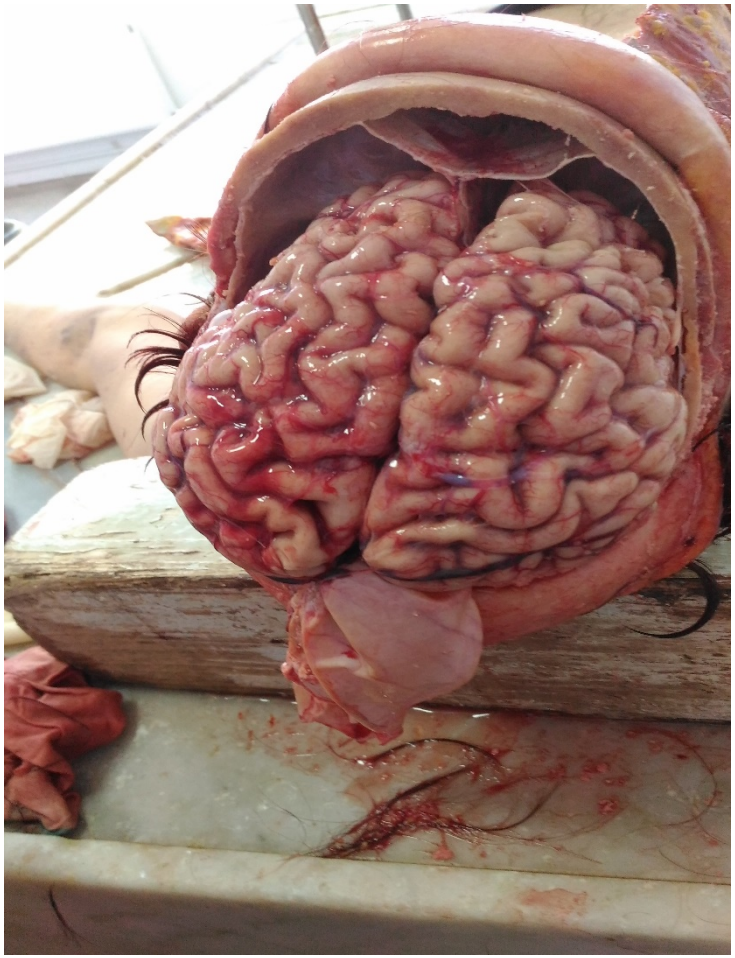
1 – polycystic liver
2 – polycystic liver in cross-section

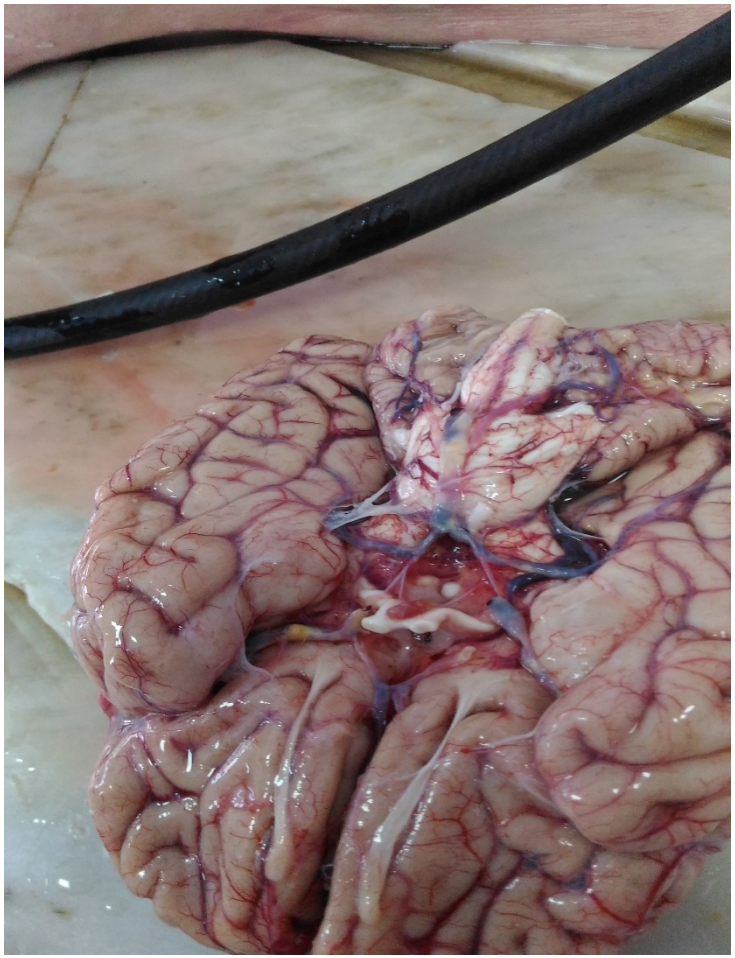




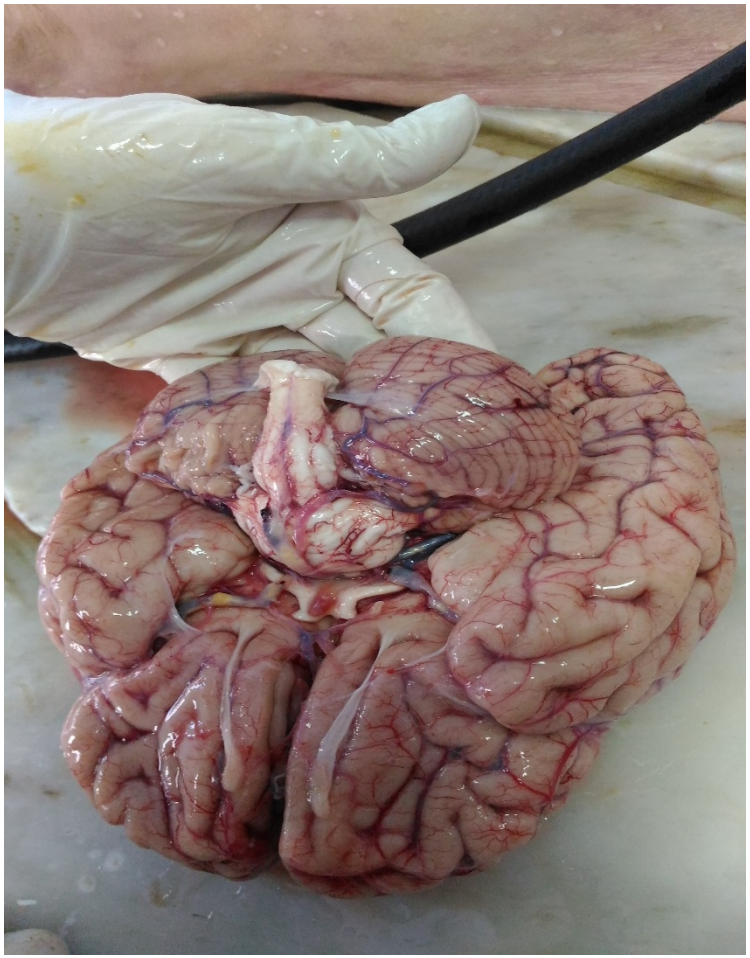
1 – brain: symmetrical cerebral hemispheres, well-marked circumvolutions

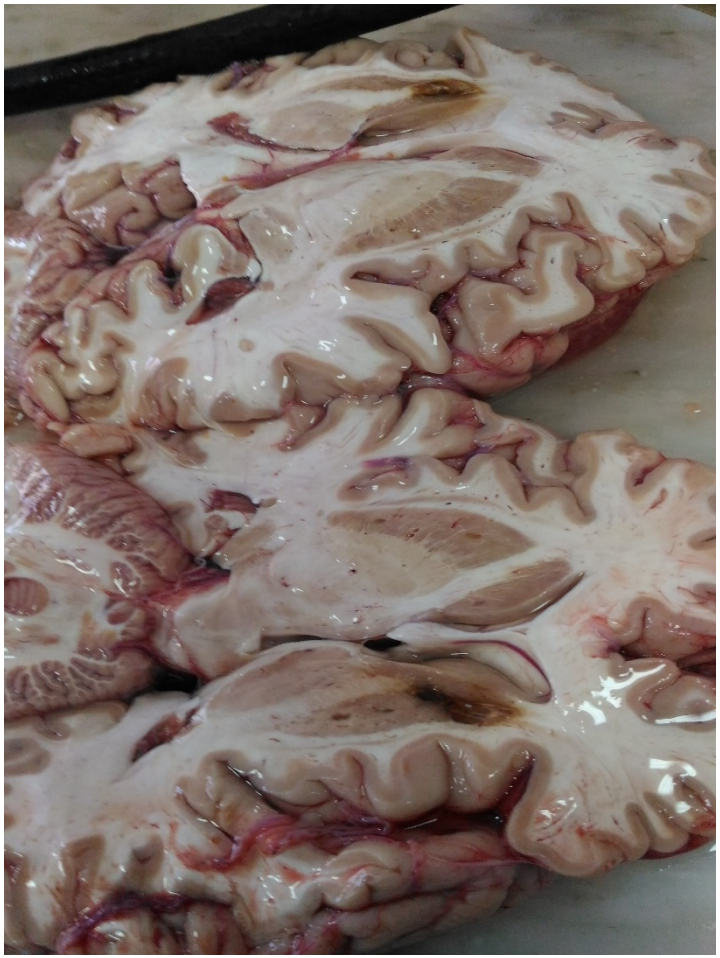
2 – brain: with atherosclerosis of the cerebral vessels



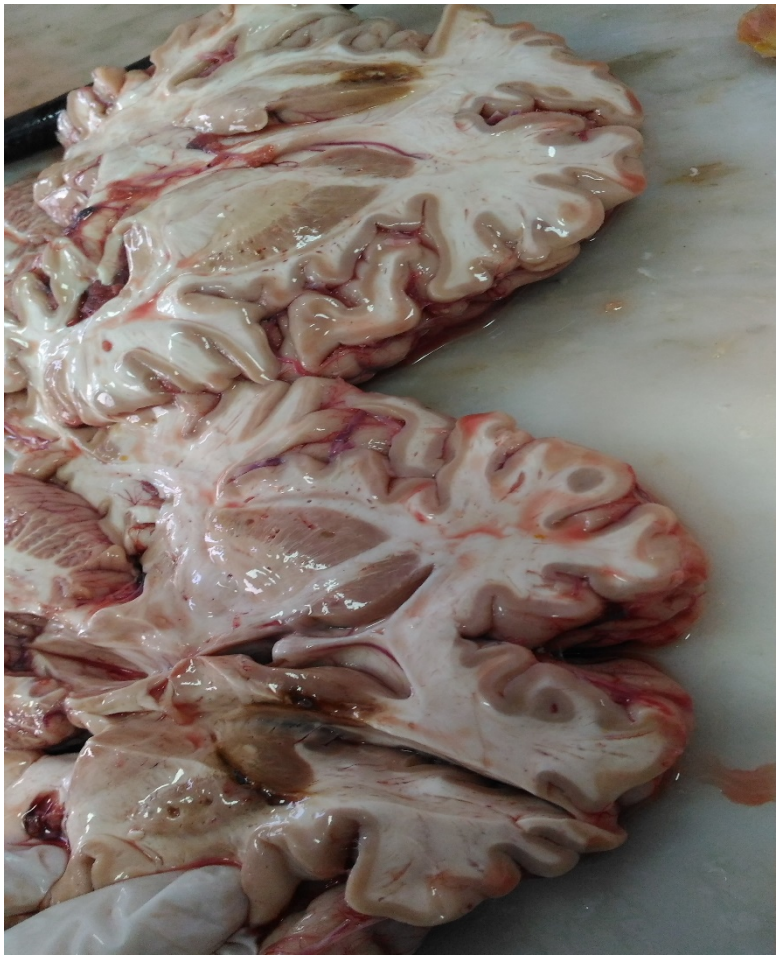


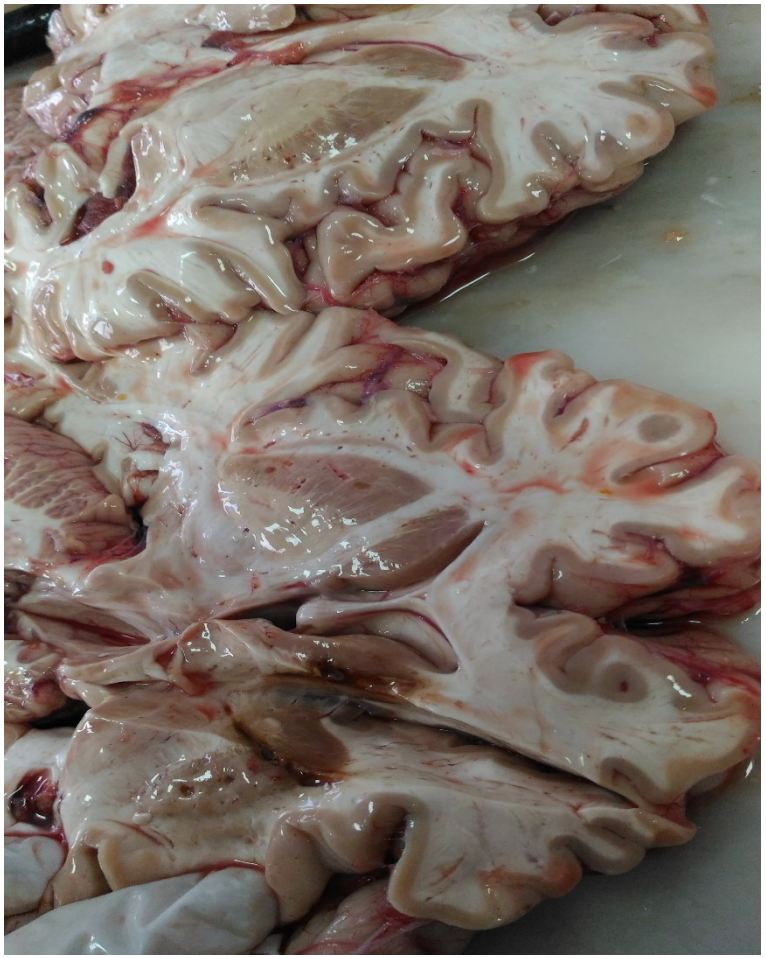
1 – brain: cerebellum, moderate groove due to foramen magnum herniation
2 – brain: bleeding spot in the past





1 – brain: cross-section – bright, unchanged layers
2 – brain: lateral ventricles in the form of a crack





Clinical caze

What do you think - what is the cause of death????

Clinical caze

At autopsy was determined the cause of death:

Multiple Organ Dysfunction Syndrome, with severe hepatorenal failure.

Polycystic Kidney Disease

Presentation outline

1. *Definition*
2. *Epidemiology*
3. *Etiology*
4. *Pathogenesis*
5. *Classification*
6. *Clinical manifestations*
7. *Laboratory diagnosis and imaging*
8. *Treatment*
9. *Prognosis*

Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disease.

It is a multisystem disorder characterized by multiple, bilateral renal cysts and associated with cysts in other organs, such as liver, pancreas and arachnoid membranes.

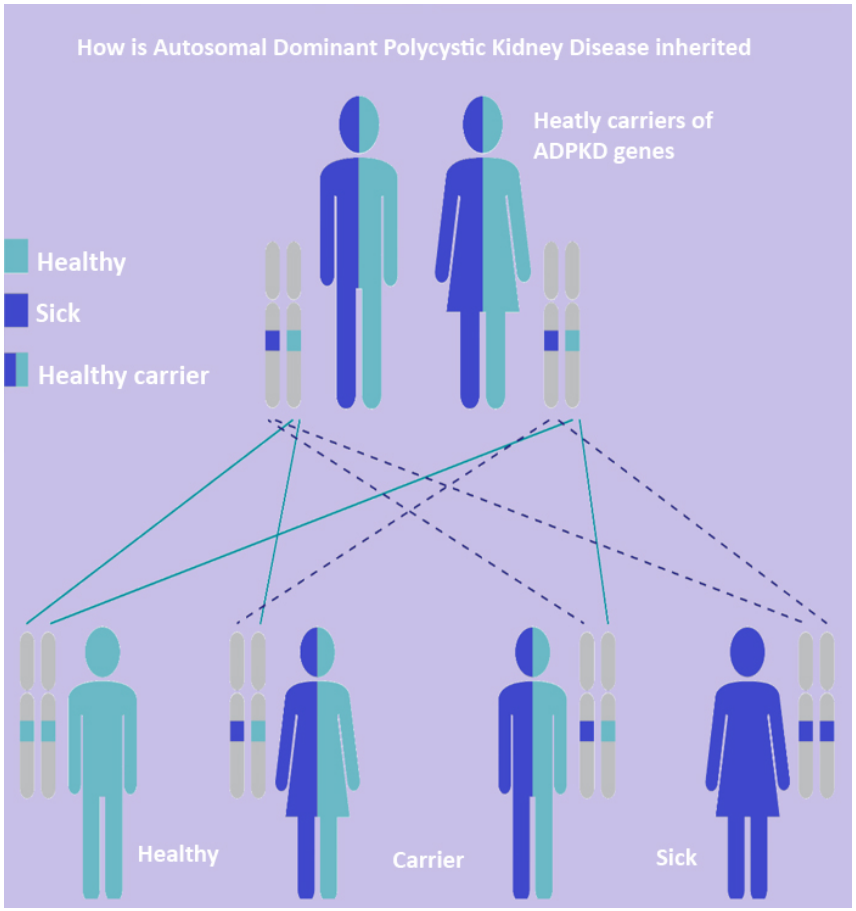
Epidemiology

ADPKD occurs in worldwide and all races.

The estimated prevalence of ADPKD at birth is estimated between 1:400 to 1:1000.

Globally, ADPKD is responsible for up to 10% patients with end-stage renal disease (ESRD) that require renal replacement therapy (RRT).

Etiology, Pathogenesis, Genetics

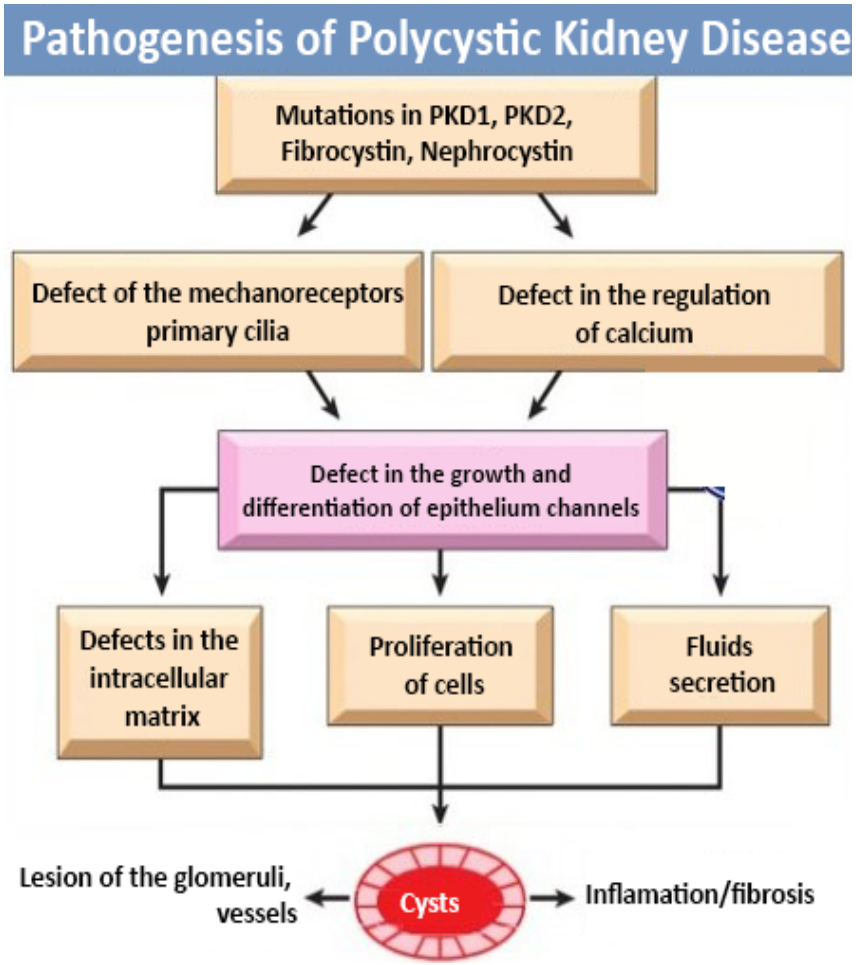


Most cases of ADPKD are caused by mutations of two genes: PKD1 or PKD2 which encodes the polycystin-1 (PC1) and polycystin-2 (PC2) proteins.

PKD1 gene is located on chromosome 16p13.3 and PKD2 gene is located on chromosome 4q21.

Both genes are expressed by most epithelial cells in the body.

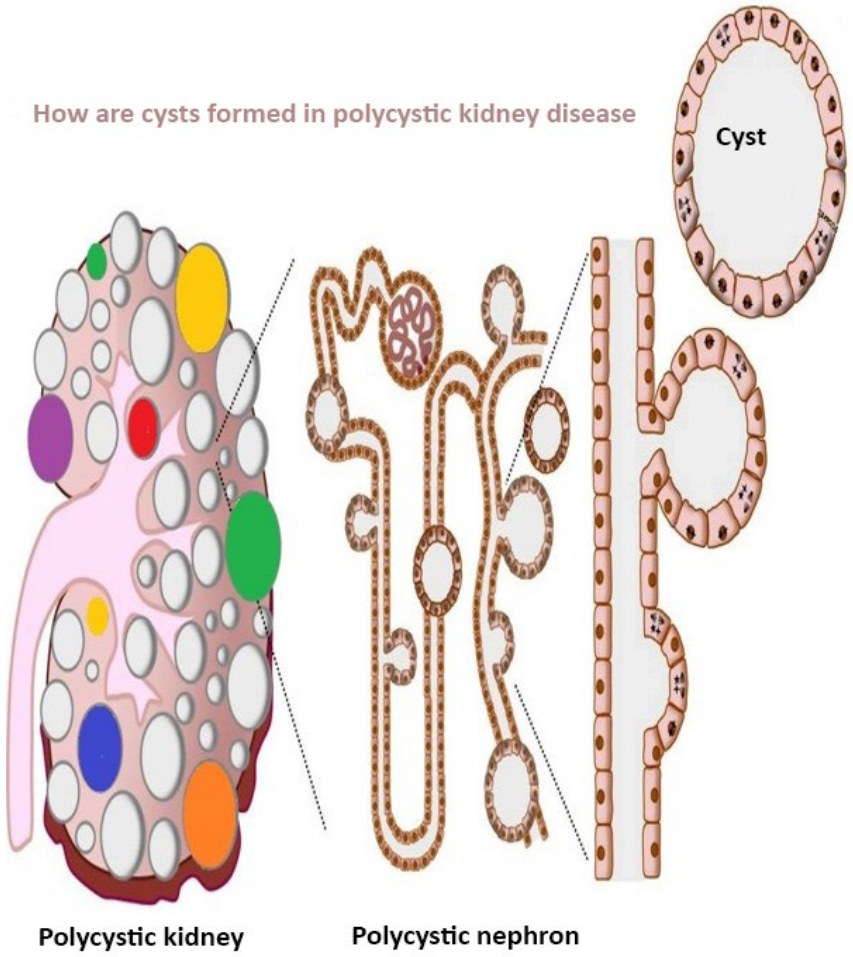
Etiology, Pathogenesis, Genetics



The proteins PC1 and PC2 interact together with other multiple proteins at different extracellular and intracellular sites.

The complex PC1-PC2 has the role of a mechanosensory by sensing the luminal flow and regulation of cell proliferation, adhesion, differentiation and maturation.

Etiology, Pathogenesis, Genetics



The mechanism behind the cysts formation in ADPKD is not fully understood, however there are a few theories: weakened tubular basement membrane and intratubular obstruction from hyperplastic cells.

Etiology, Pathogenesis, Genetics

The cysts in ADPKD begin to form as outpouchings from preexisting renal tubules.

Most of the cysts in adults are derived from distal nephron and collecting duct.

As the cysts grow larger than a few millimeters in diameter, they detach from the tubule of origin.

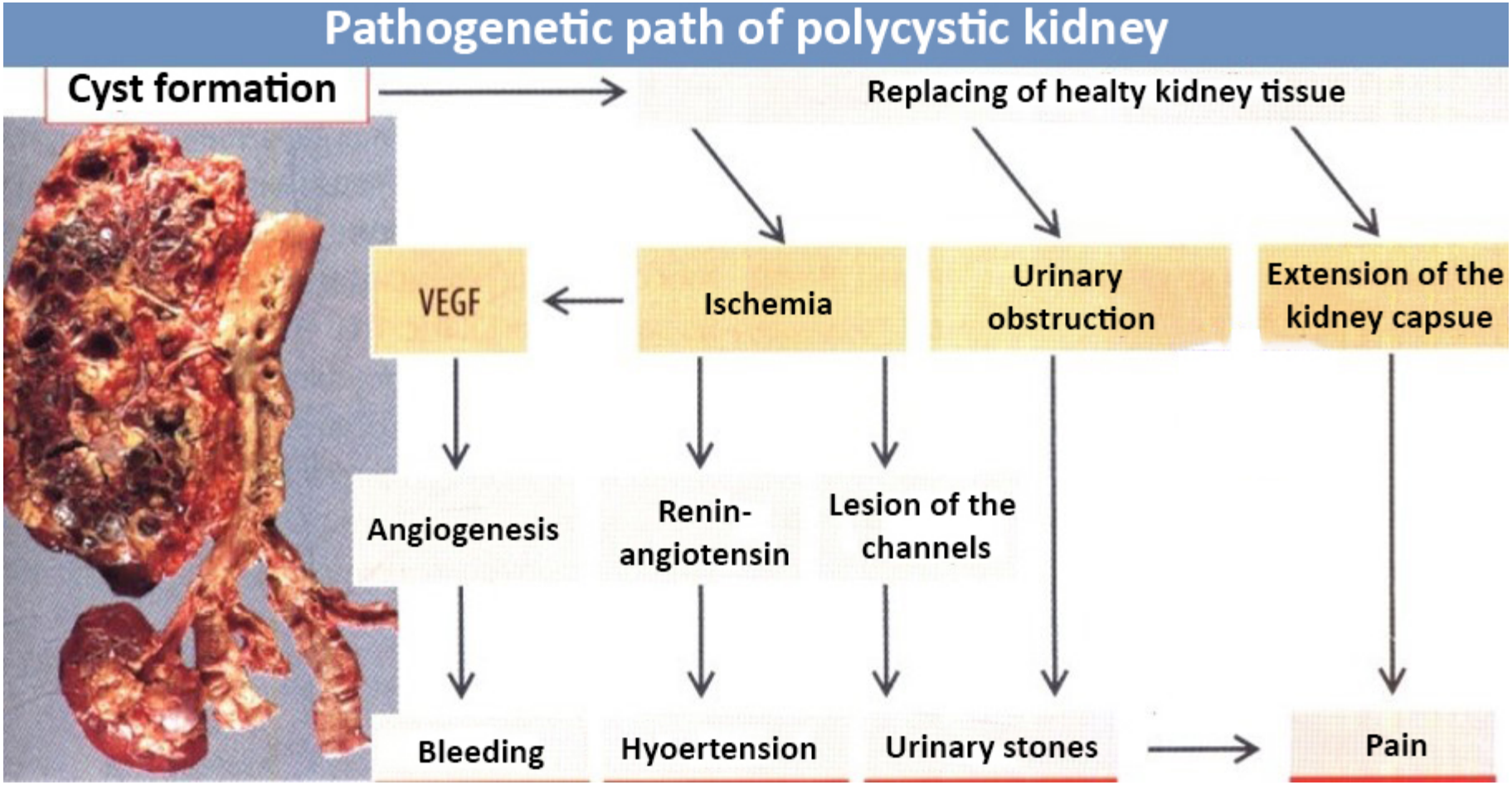
At the end stage of the diseases, kidney size can grow more than 20 times normal.

There are some estimates that cysts are formed only in less than 1% of nephrons, however due to local tissue ischemia and pro-fibrotic cytokine release, the rest of the nephrons are undergoing through a process of scarring.

Up to 90% of adults with ADPKD also develop cysts in the liver that contain a liquid similar to bile.

Clinical manifestations

As mentioned above, ADPKD is a disease that can affect multiple body systems.



A decrease in the formation and secretion of citrate and ammonia in damaged proximal tubules causes urolithiasis. The absence of citrate in the urine predisposes to the precipitation of Ca2 + salts; a decrease in the production of ammonia requires an increase in the acidity of the urine to eliminate the daily acid load, i.e., it favors the deposition of uric acid, which dissolves much worse in an acidic environment than in an alkaline one.

Renal manifestations

Flank and Abdominal pain

Pain in ADPKD is frequent and can be caused by cyst hemorrhage, infection, renal calculi and even tumors.

Abdominal pain can be generated by liver cysts.

In advanced stages of ADPKD, when the kidneys size increases tremendously, patients can suffer from chronic kidney pain, which is dull and persistent and caused by the stretching of the renal capsule.

Renal manifestations

Hematuria

Macroscopic hematuria can occur in up 40% of patients over the course of the disease.

Visible hematuria has been associated with a faster progression of CKD.

A patient with gross hematuria can have recurrent episodes.

It is believed that a rupture of a cyst into the collecting system causes macrohematuria.

Hematuria due to a ruptured cysts will usually resolve within 2 to 7 days and only requires conservative treatment (bedrest, hydration, and analgesics that exclude NSAIDs).

Frequent episodes of macrohematuria has been correlated to larger kidneys size, hypertension and lower GFR (Glomerular Filtration Rate).

Nephrolithiasis can also be a cause of hematuria, particularly microscopic.

If hematuria persists more than a week in a patient over 50 years, a neoplasm should be excluded.

Renal manifestations

Nephrolithiasis

It can occur in about 20% of patients with ADKPD.

Most stones are composed of uric acid, calcium oxalate or both, which is in contrast with the idiopathic stone formers, in whom stones are mainly composed of calcium oxalate.

The exact mechanism by which renal stones are formed is not known, but it is considered that the urinary stasis due to distorted renal anatomy, decreased ammonia excretion, low urinary pH and citrate concentration, hyperuricosuria and hypercalciuria have a role in stone formation.

Nephrolithiasis should be suspected if the patients presents with acute flank pain.

The preferred method to detect stones is CT urography, however, if that is not available, intravenous urography should be performed.

Ultrasound is not the method of choice to detect renal stones, because large cysts can obscure the view of collecting system, but it should be performed in all patient due to its advantages (non-invasive, relatively inexpensive and quick procedure).

Renal manifestations

Urinary Tract Infection and Cyst Infection

Urinary tract infections (UTI) are common in patients with ADPKD, however, it should be mentioned that sterile pyuria is often found in these patients, therefore the diagnosis of UTI should not be made solely after a urinalysis.

Like in the general population, UTI are more frequent in females.

The most common bacteria that cause UTI are *Escherichia coli*, *Klebsiella* and *Proteus* species.

UTI can present as a cystitis, acute pyelonephritis, cyst infection or renal abscess.

The usual route of infection ascending from the bladder; therefore, it is imperative to treat lower UTI as soon they are diagnosed.

CT and MRI are sensitive to detect complicated cysts but are not specific for infection.

When a patient with ADPKD presents with flank pain and fever, but with a negative urine culture, cyst aspiration should be performed under US or CT guidance to culture the organism.

Renal manifestations

Hypertension

It is one of the most common clinical finding in patients with ADPKD.

It is present in approximately 50% of 20-34 year-old patients with ADPKD and normal function, but it will reach nearly 100% in patients with ESRD.

Hypertension is a major contributor in the progression of renal and cardiovascular disease and mortality.

Quite often, the diagnosis of hypertension is made late.

Ambulatory blood pressure monitoring may reveal blood pressure elevations.

The diagnosis and treatment of hypertension is imperative in patients with ADPKD, because uncontrolled blood pressure increases the morbidity and mortality of these patients.

Renal manifestations

Renal Cancer

The literature is conflicting regarding the frequency of renal cell carcinoma (RCC) in patients with ADPKD compared with general population.

Some studies have shown that RCC is more frequent.

RCC can present with fever, are often bilateral, multicentric and sarcomatoid in type. It is difficult to diagnose RCC in ADPKD.

The clinician should suspect RCC if the patient complains of systemic signs and symptoms (fever, weight loss, fatigue) that are out of proportion to the severity of renal disease.

A CT or MRI can be helpful to distinguish RCC from a complex cyst. Percutaneous aspiration and cytological examinations should be performed on suspicious cysts.

Renal manifestations

Concentrating defects

The kidneys of patients with ADPDK lose their ability to concentrate the urine, even in early stages.

These patients can complain of increased thirst, polyuria, nocturia and urinary frequency.

The cause of concentrating defects is still unknown, but it is believed it is due to the disruption of the tubular architecture, cell function defect or early tubulointerstitial disease.

Renal manifestations

Proteinuria

Low-grade proteinuria may be present in patients with ADPKD (usually <1 g/24h).

Renal manifestations

End-Stage Renal Disease

Usually, patients will have a normal renal function until the fourth to sixth decade of life, even if the cysts are growing relentlessly.

This can be explained by the compensatory adaption of the normal nephrons.

However, ESRD is not inevitable, up to 77% of patients at age 50 are alive with preserved renal function, and 52% at age 73.

Extrarenal manifestations

Polycystic Liver Disease

It is the most common extrarenal manifestations.

It is associated with PKD1 and PKD2 genotypes.

In children, hepatic cysts are rare, but their frequency increases with age.

In one large study, hepatic cysts were detected in 58%, 85% and 94% in participants age 15 to 24, 25 to 34 and 35 to 44 years.

Hepatic cysts are usually asymptomatic, however due to an increased life span of patients with ADPKD after the implementation of RRTs, symptoms are more frequent.

It can present with dyspnea, orthopnea, early satiety, gastroesophageal reflux, uterine prolapse.

These symptoms are the results of mass effect of the cysts.

Other complications are cause by extrinsic compression of the intrahepatic inferior vena cava and hepatic veins.

Extrarenal manifestations

Cerebral aneurysms

The prevalence of cerebral aneurysms in ADKPD is approximately 5% in young adults and increases up to 20% in patients over 60 years old.

A ruptured cerebral aneurysm is the most serious complication of PKD.

Most cerebral aneurysms are asymptomatic; however, screening is not indicated for all patients with ADPKD.

Indications to screening are:

- high-risk patients, those previous rupture
- a positive family history of an intracerebral bled or intracranial symptoms
- a high-risk occupation (e.g. airline pilot)
- prior to a surgery with expected hemodynamic instability.

The preferred method for screening is magnetic resonance angiography, because is noninvasive and does not require intravenous contrast administration.

However, a CT angiography can be also performed if there are no contraindications to intravenous contrast administration.

Extrarenal manifestations

Cardiac disease

The most common cardiac abnormality in patients with ADPKD is mitral valve prolapse and aortic regurgitation.

It is believed that these are caused by generalized abnormalities in collage and extracellular matrix.

These are usually asymptomatic and usually demonstrated by echocardiography.

These lesions can progress over time, but rarely require valve replacement.

Extrarenal manifestations

Other extrarenal manifestations

Cysts have been described in other organs as well, such as pancreas, seminal vesicles and arachnoid membrane.

Pancreas cysts are present in 5% of patients, while arachnoid cysts in 8%.

Although sperm abnormality is common in ADPKD patients, it rarely causes male infertility.

There have been noted increased frequency of spinal meningeal diverticula, colonic and duodenal diverticula.

Diagnosis and screening

Genetic testing is usually performed only for research purposes or in special clinical situations, due to the high cost and suboptimal sensitivity caused by a high number mutation variants.

Most of the time, clinical diagnosis is relatively easy.

The diagnosis of ADPKD relies principally upon imaging of the kidney.

Typical findings include large kidneys and extensive cysts scattered throughout both kidneys.

Because of cost and safety, ultrasonography is most commonly used as the imaging modality.

There have been devised ultrasound diagnostic criteria (Table 1 and Table 2).

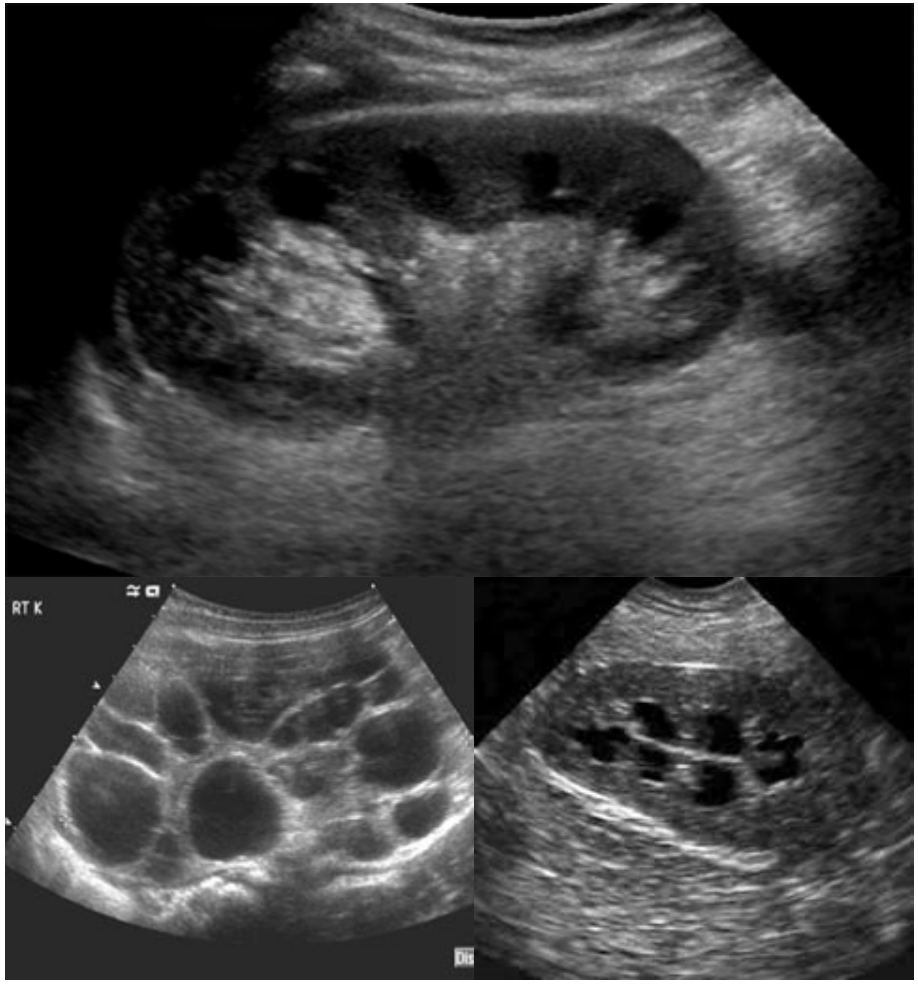
Ultrasound-based Ravine's criteria for PKD 1 ADPKD diagnosis

Age	Number of cysts	
	Positive family history	Negative family history
<30	At least 2 in one or both kidneys	At least 5
30-59	At least 2 in each kidney	At least 5
>60	At least 3 in each kidney	At least 8

Ultrasound-based Demetriou criteria for type 2 ADPKD diagnosis in patients with a positive family history

Age	Number of cysts
15-19	One in each kidney or 2 unilaterally
20-29	>3 in total, at least 1 in each kidney
30-59	At least 2 in each kidney
>60	At least 4 in each kidney

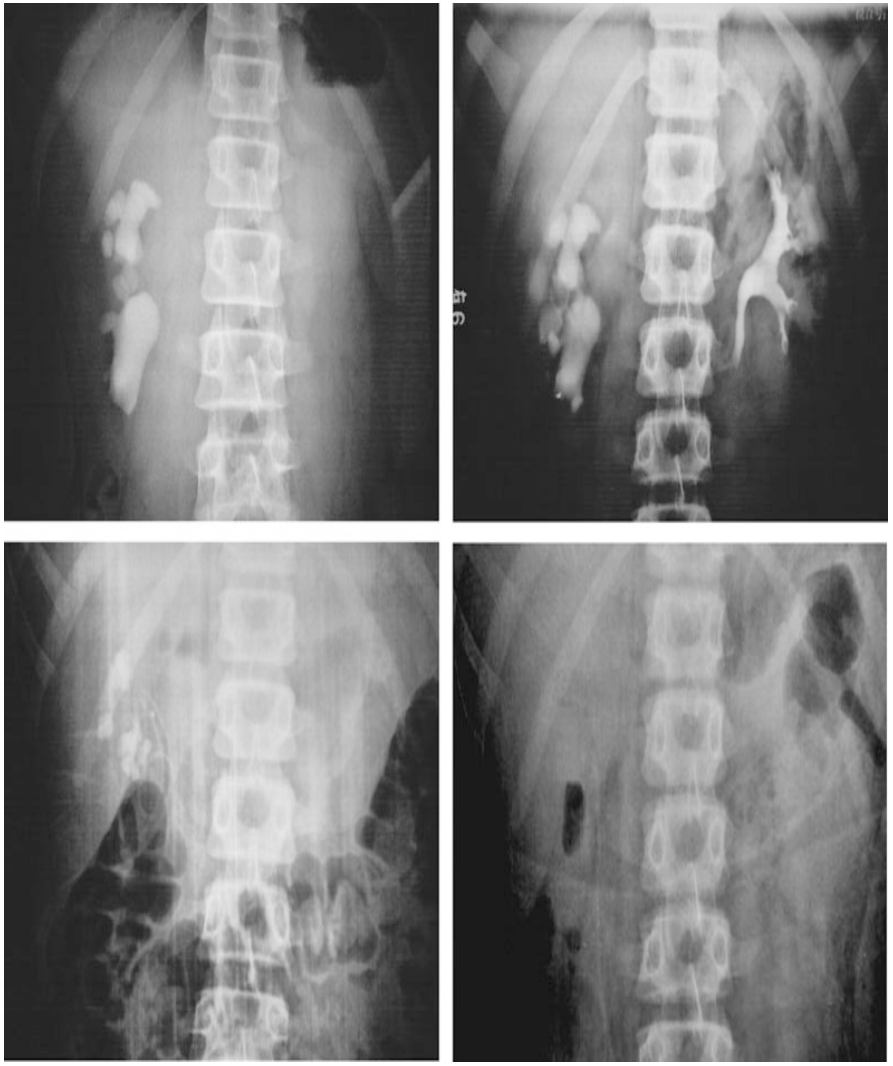
Renal Ultrasound



Ultrasound allows you to identify the cystic nature of the volumetric formation, to assess the clarity of the contours, to determine the size and location, to clarify the relationship with the adjacent organs.

In 90% of cases, this method makes it possible to determine further tactics in relation to the patient.

Intravenous urography

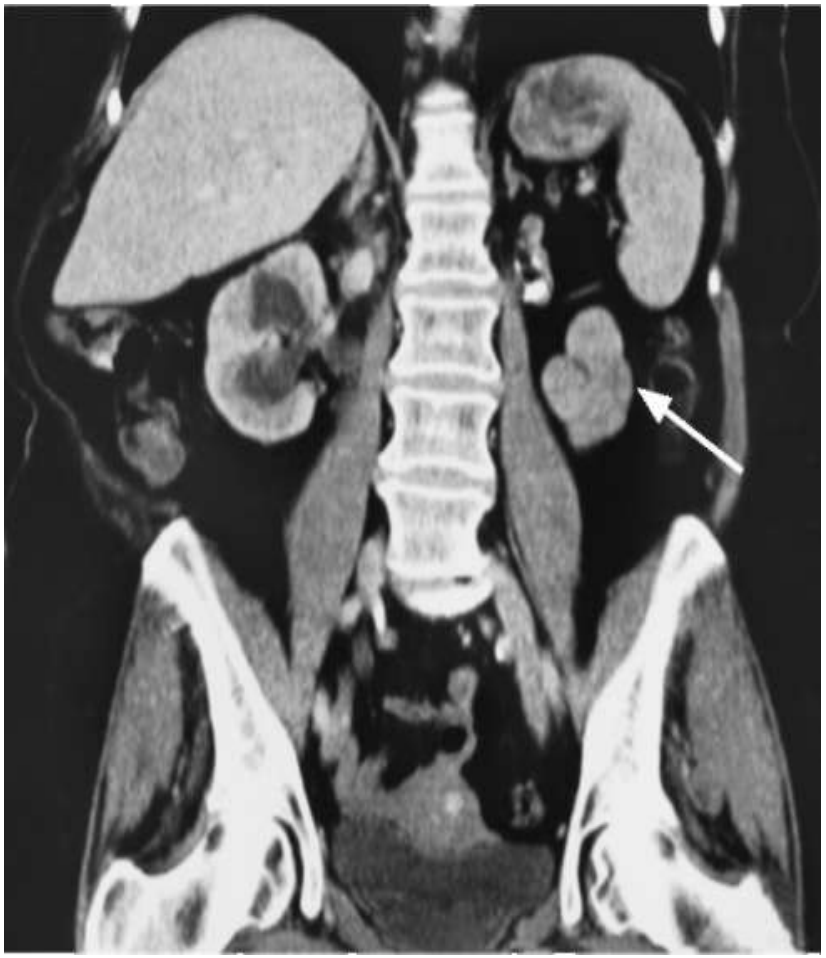


Urografia cu filme precoce evidențiază semnele clasice:

- Nefromegalie bilaterală cu contur boselat
- Bazinet alungit, subțire, niciodată ectaziat
- Arborele pielocaliceal, în ansamblu, are diametrul longitudinal crescut, concordant cu cel al rinichiului

Modificări caliceale: dezorientări, devieri, arcuiri, tracționări, amprente chistice, dilatări și amputații cu contur net.

Computer Tomography



The most accurate method for diagnosing kidney cysts.
It is the method of choice for solving the question of a possible oncological process, assessing the state of blood supply to education, determining the size, contours, the spread of education inside and outside the kidney.
CT allows you to get a highly informative direct image of the structure of the kidneys and existing neoplasms.

Differential diagnosis

Multiple benign simple cysts.

- Simple renal cysts uncommon in patients younger than 30 years old.
- It is uncommon for patients aged 30 to 59 years to have at least two cysts in each kidney.

Differential diagnosis

Localized renal cystic disease.

- No family history.
- Imaging studies revealed multiple cysts of various sizes separated by normal or atrophic parenchyma involving one kidney.
- In contrast to PKD, localized cystic disease is neither bilateral nor progressive.

Differential diagnosis

Acquired renal cystic disease.

- Chronic renal failure (particularly patients on maintenance hemodialysis or peritoneal dialysis) is frequently associated with the development of multiple and bilateral small cysts; these cysts are usually <0.5 cm in diameter but can be as large as 2 to 3 cm.
- Acquired cystic disease is usually easily distinguished from ADPKD since there is no family history of ADPKD and the kidneys are small to normal in size, with a smooth contour, as opposed to usually extreme renal enlargement, with a cystic contour

Differential diagnosis

Medullary sponge kidney.

- Characterized by tubular dilatation of the collecting ducts confined to the medullary pyramids.
- The urographic appearance of the kidneys in this disorder can mimic those in ADPKD, but the renal cortex is spared on CT or MRI.

Differential diagnosis

Other genetic disorders:

- Autosomal recessive polycystic kidney disease
- Autosomal dominant tuberous sclerosis complex
- Autosomal dominant von Hippel-Lindau disease
- Autosomal dominant tubulointerstitial kidney disease
- Autosomal dominant hepatocyte nuclear factor-1beta (HNF-1B) nephropathy
- Autosomal dominant polycystic liver disease
- X-linked dominant orofaciodigital syndrome type I

Complications

1. Infection of cysts with the onset of pain and fever.
2. Cyst rupture - is accompanied by sharp pain and subsequent appearance of blood in the urine.
3. Disruption of urine flow.
4. The formation of calculi and the development of renal colic are considered a frequent complication of polycystic.
5. With a long evolution of the disease, it leads to loss of function, along with the development of renal failure and the need for hemodialysis - an artificial kidney.

Treatment

Firstly, it should be identified individuals who are at high risk for progression of CKD because this is important for prognostic reasons and can help to identify patients who may benefit from specific therapies.

Mayo Clinic has devised a classification tool that categorized patients into five prognostic classic (classes 1A, 1B, 1C, 1D, and 1E).

To use the Mayo classification, the doctor requires demographic data, such as patient's age, height and total kidney volume that is obtained from a CT or MRI.

Treatment

Dietary sodium restriction

The goal of sodium is 2 grams per day or less.

Higher sodium excretion was associated with an increased risk of kidney growth and eGFR decline.

Treatment

Increased fluid intake

If the GFR > 30 mL/min/1.73 m^2, ADPKD patients should drink >3 L of fluid per day.

Increasing fluid intake to suppress plasma vasopressin levels has been postulated as a possible therapeutic mechanism to inhibit cyst growth in ADPKD.

Treatment

Hypertension

Control of high blood pressure is imperative, because it accelerated the decline of renal function.

If there are no contraindication, then angiotensin-converting enzyme (e.g. enalapril, ramipril, lisinopril) or angiotensin receptor blocker (e.g. telmisartan, valsartan) are preferred.

The blood pressure goal is <130/80 mmHg.

Treatment

Novel therapies

So far, only ***tolvaptan***, a vasopressin antagonists entered clinical practice in some countries.

Tolvaptan is recommended in adult patients with ADPKD who have an estimated glomerular filtration rate (eGFR) ≥25 mL/min1.73 m2 and who are at risk of rapid progression.

Somatostatin analogues have been proposed, but they lack demonstrable benefits.

A phase II study has examined the safety and efficacy of ***bosutinib***, an oral tyrosine kinase inhibitor.

Treatment

Transplantation

It is the treatment of choice in patients with ESRD.

The rate of complications is similar to the general population. In the past, patients were undergoing pretransplantation nephrectomy, however, today, nephrectomy is avoided whenever possible.

Unilateral or bilateral nephrectomy may be considered if:

- There are recurrent infections.
- Suspected malignancy.
- Uncontrollable renal hemorrhage among patients who have a contraindication to or failure of intra-arterial embolization.
- Development of ventral hernia due to massive kidney sizes.

Treatment

Hemodialysis

Survival of patients with ADPKD undergoing hemodialysis may be better (by 10 to 15 percent at five years) than that of patients with other causes of ESRD, including nondiabetic patients.

This difference in survival is primarily due to a lower incidence of coronary artery disease in these generally healthier patients with ADPKD.

Thank you for your attention

ADPKD - Autosomal Dominant Polycystic Kidney Disease

CKD – Chronic Kidney Disease

CT – Computer Tomography

ESRD – End-Stage Renal Disease

GFR – Glomerular Filtration Rate

MRI – Magnetic Resonance Imaging

NSAIDs – Nonsteroidal Anti-inflammatory Drugs

PC1 – Polycystin-1

PC2 – Polycystin-2

RCC – Renal Cell Carcinoma

RRT – Renal Replacement Therapy

US – Ultrasound

UTI – Urinary Tract Infection