XXXVII$_{th}$ IPPA Advanced Course 2015
Fontainebleau, France

RENAL CYSTIC DISORDERS at Perinatal Autopsy

Anastasia Konstantinidou

National University of Athens, Greece

Birmingham Women's Hospital, U.K.

RENAL CYSTS

Renal cysts: heterogeneous group of parenchymal lesions

Deviation from normal differentiation/maturation ⟹ cyst formation

Potter classification *(1972)* Types I - IV (microanatomy)

Potter EL. Normal and abnormal development of the kidney. Chicago: Year Book Medical, 1972

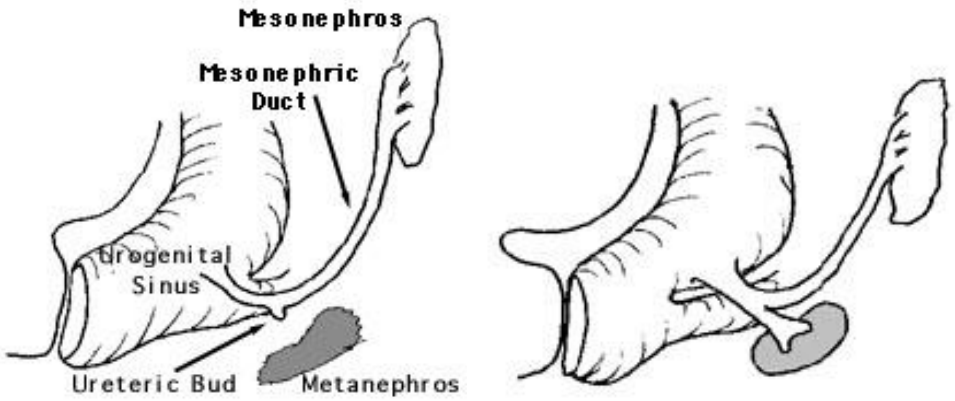
Renal cystic disorders

Clinical and genetic data

- Renal Dysplasia
- Polycystic Kidney Disease
  - ARPKD
  - ADPKD
- Glomerulocystic disease
- Medullary cysts
- Cystic disease and renal cysts in malformation syndromes and hereditary diseases

Renal dysplasia

Disorder of metanephric differentiation



Pathogenesis (2 theories)

1a. Failure of induction of nephrone formation:

Defective branching of the ureteric bud collecting ducts

or

1b. Failure of response : Abnormal differentiation of the metanephric blastema

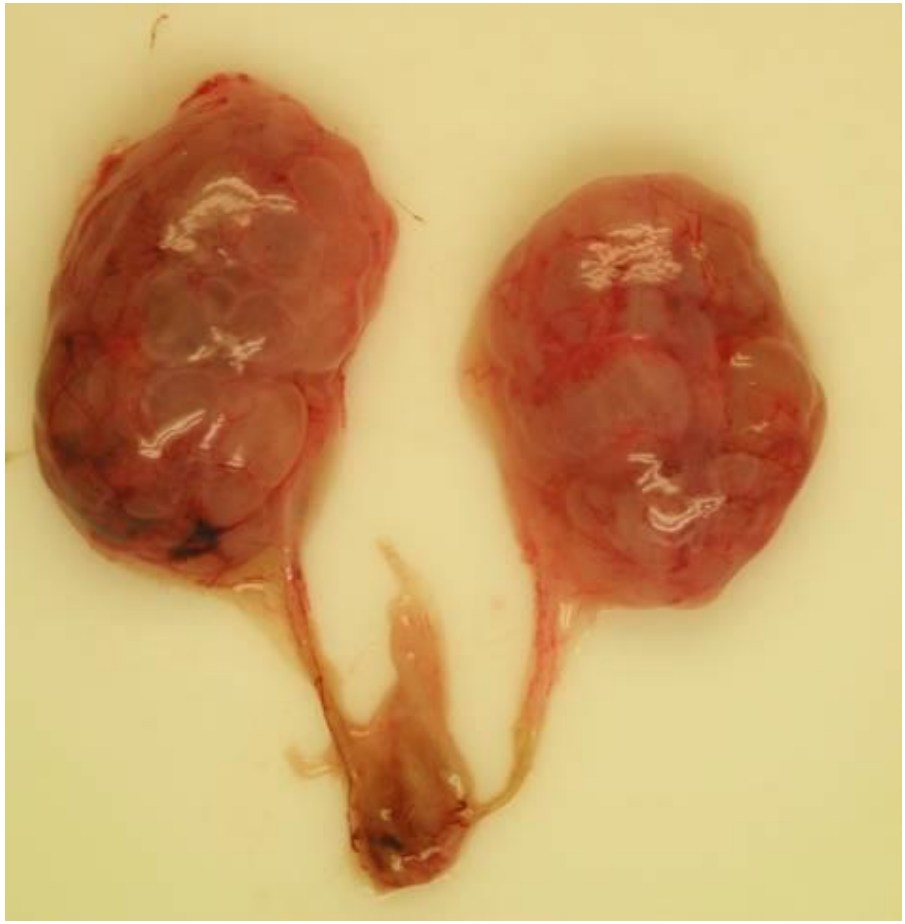
Histological structures that are not seen in normal nephronogenesis.

2. Intrauterine urinary tract obstruction

Reduced flow of fluid and urinary reflux results to incomplete formation of calices and fornices.

Cystic renal dysplasia

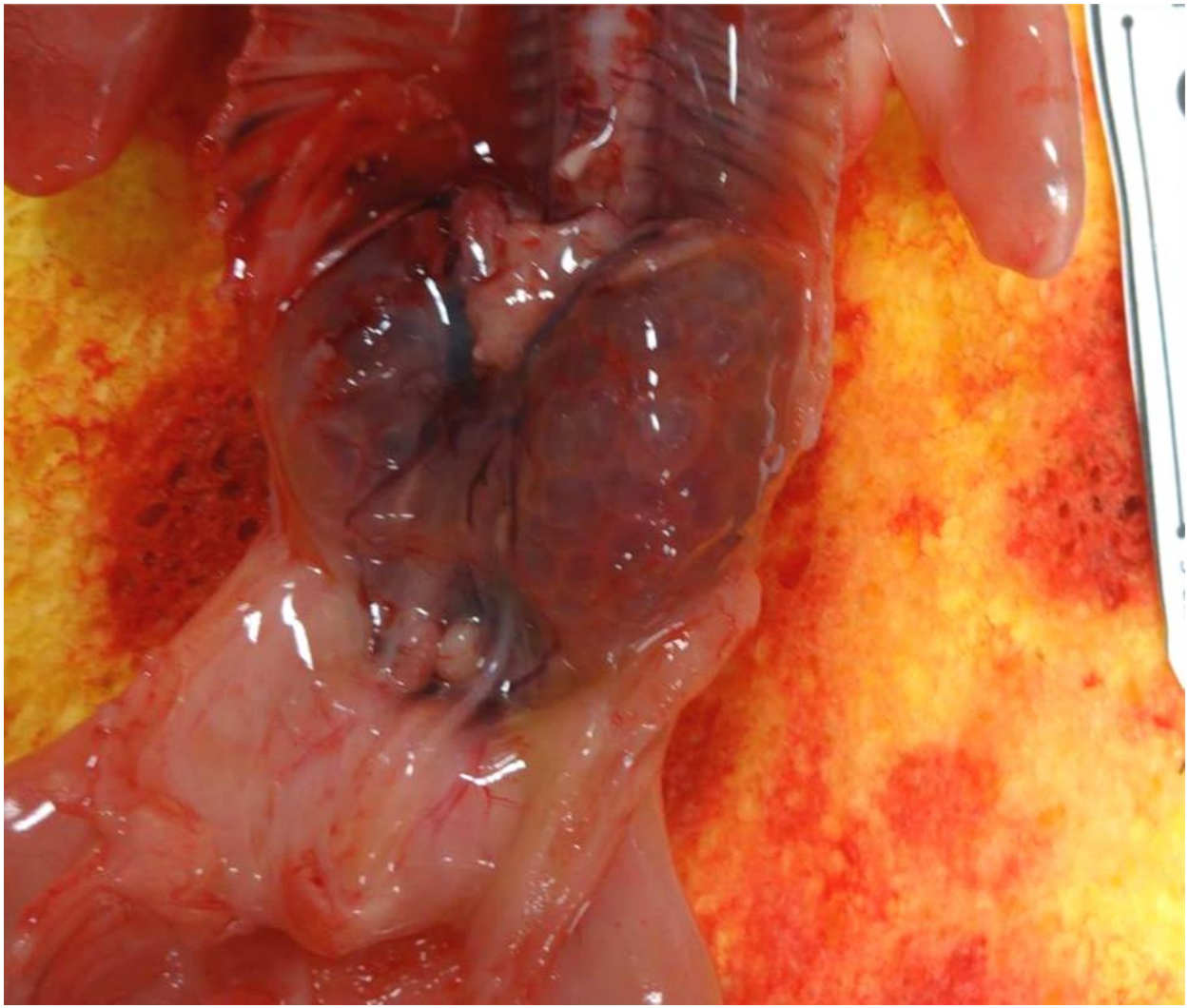
- Variably sized kidneys - reniform or distorted shape
- Usually macroscopically visible cysts, variably sized
- Bilateral, Unilateral, or Segmental
- 90% associated with ureter or other UT anomaly, obstructive or not

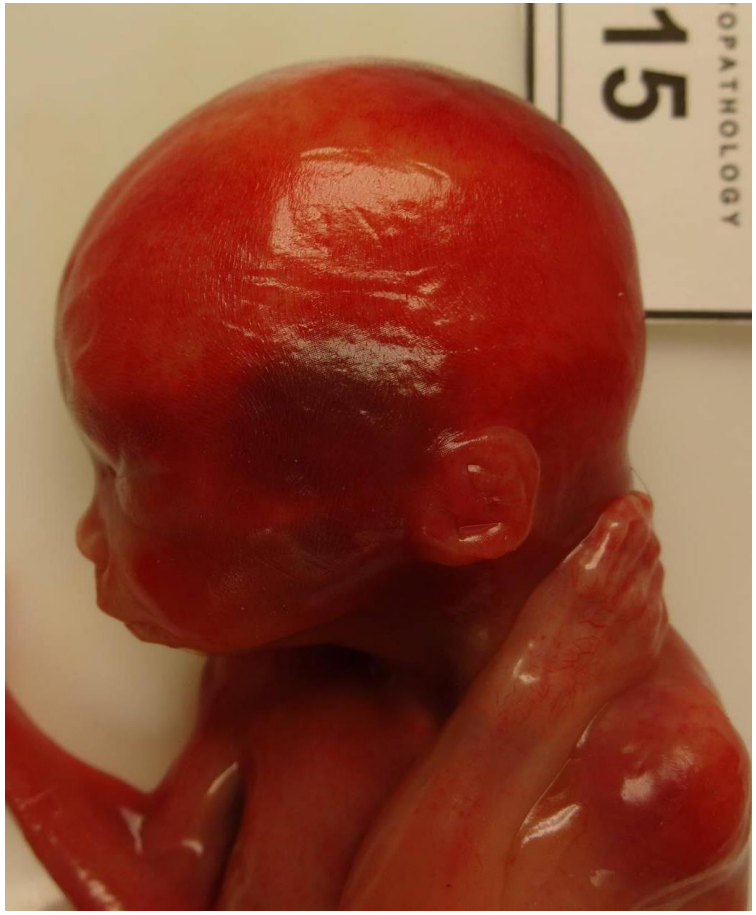


Unilateral dysplasia ⇨ contralateral compensatory renal hyperplasia

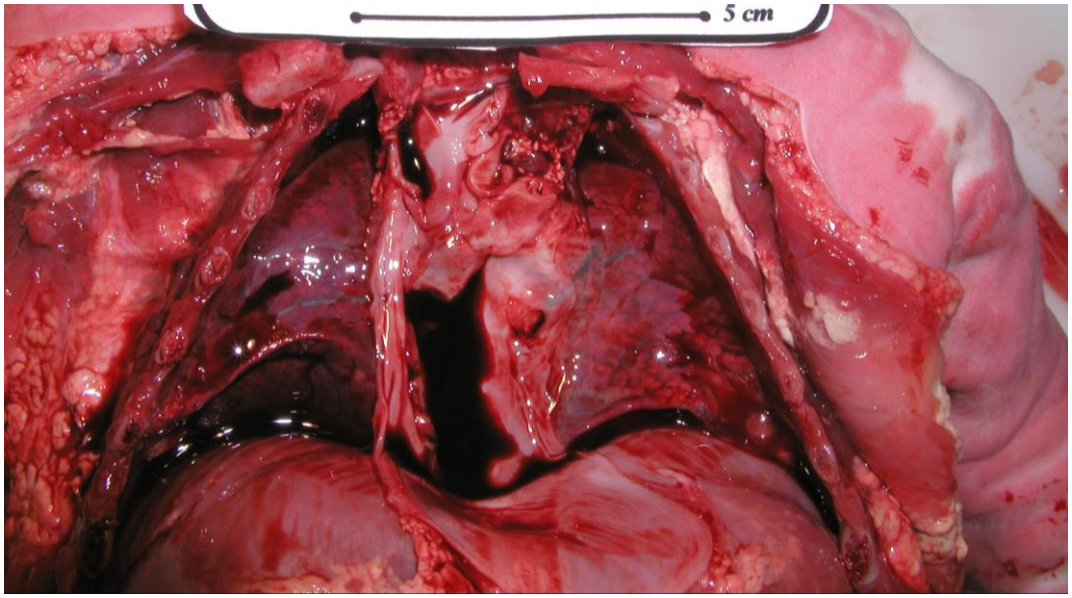
Cystic renal dysplasia

When bilateral, it is quite common for asymmetry to be present.





Oligohydramnios sequence



Pulmonary hypoplasia

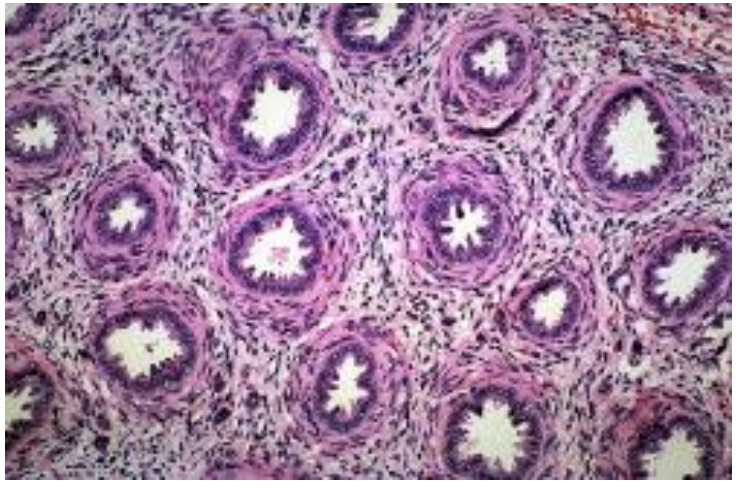
Renal Dysplasia – Histology

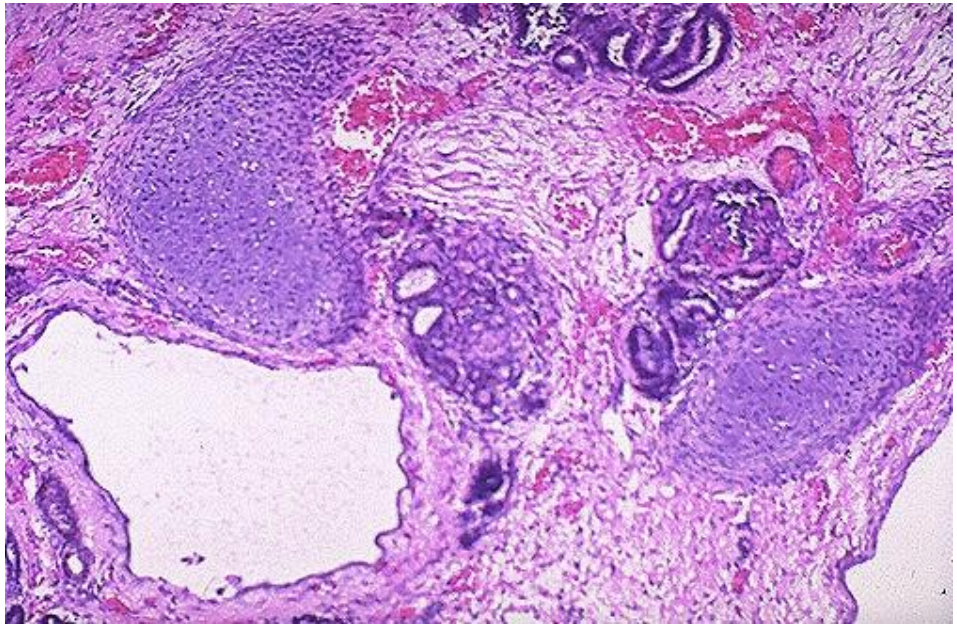
The structurally disorganized kidney contains normal metanephric elements.

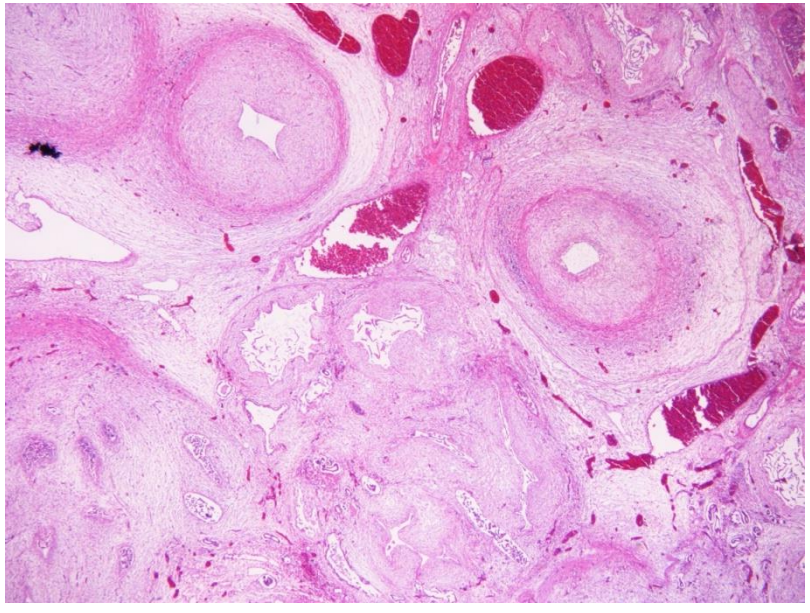
Three classical features:

- ✓ **Primitive ducts** surrounded by spindle cells (fibromuscular collars: collagen, smooth muscle)
- ✓ Islands of **metaplastic cartilage**
- ✓ **Loss** of normal structural **architectonics**

- ➢ Increased loose mesenchymal tissue
- ➢ Extratramedullary haemopoiesis

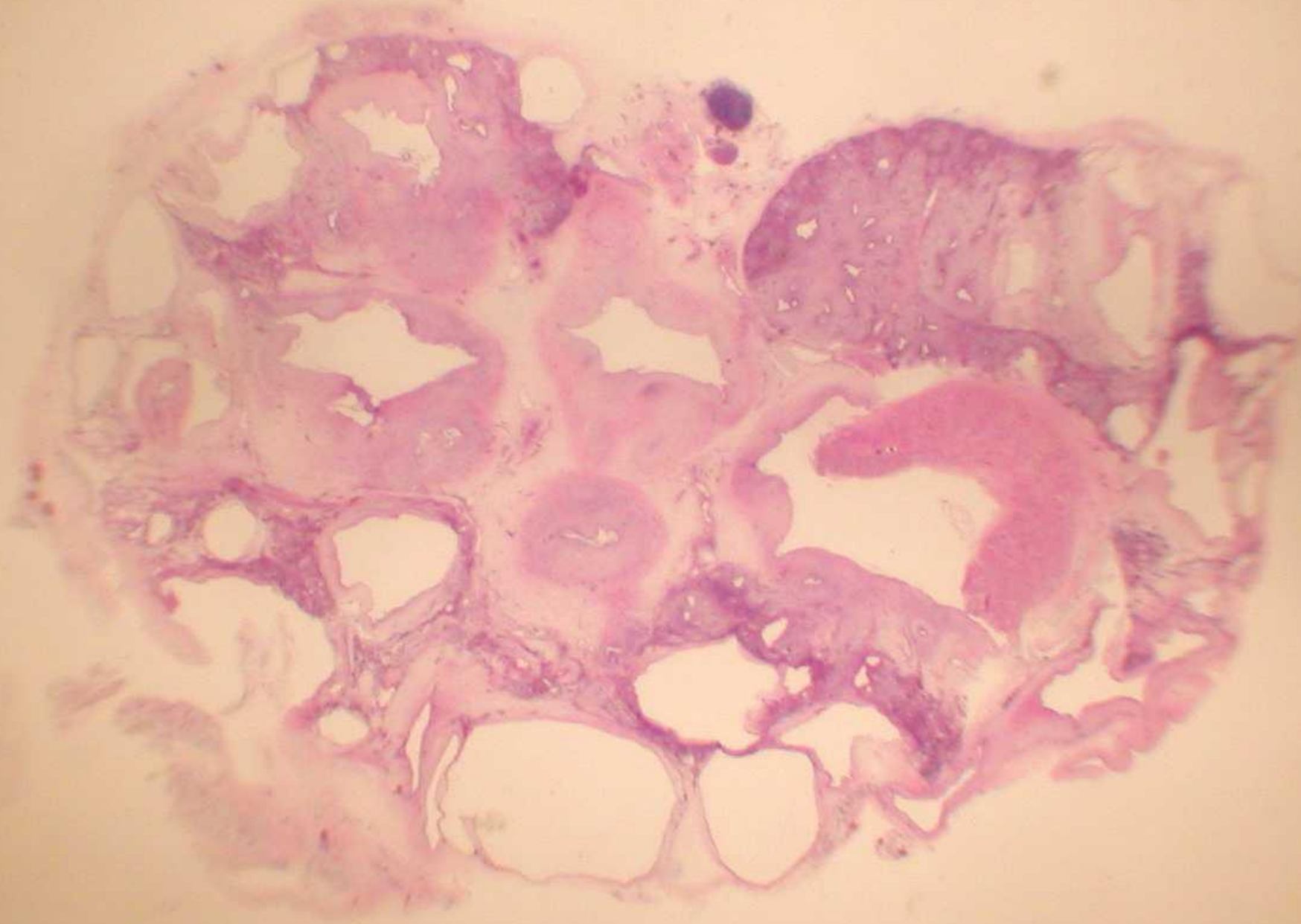






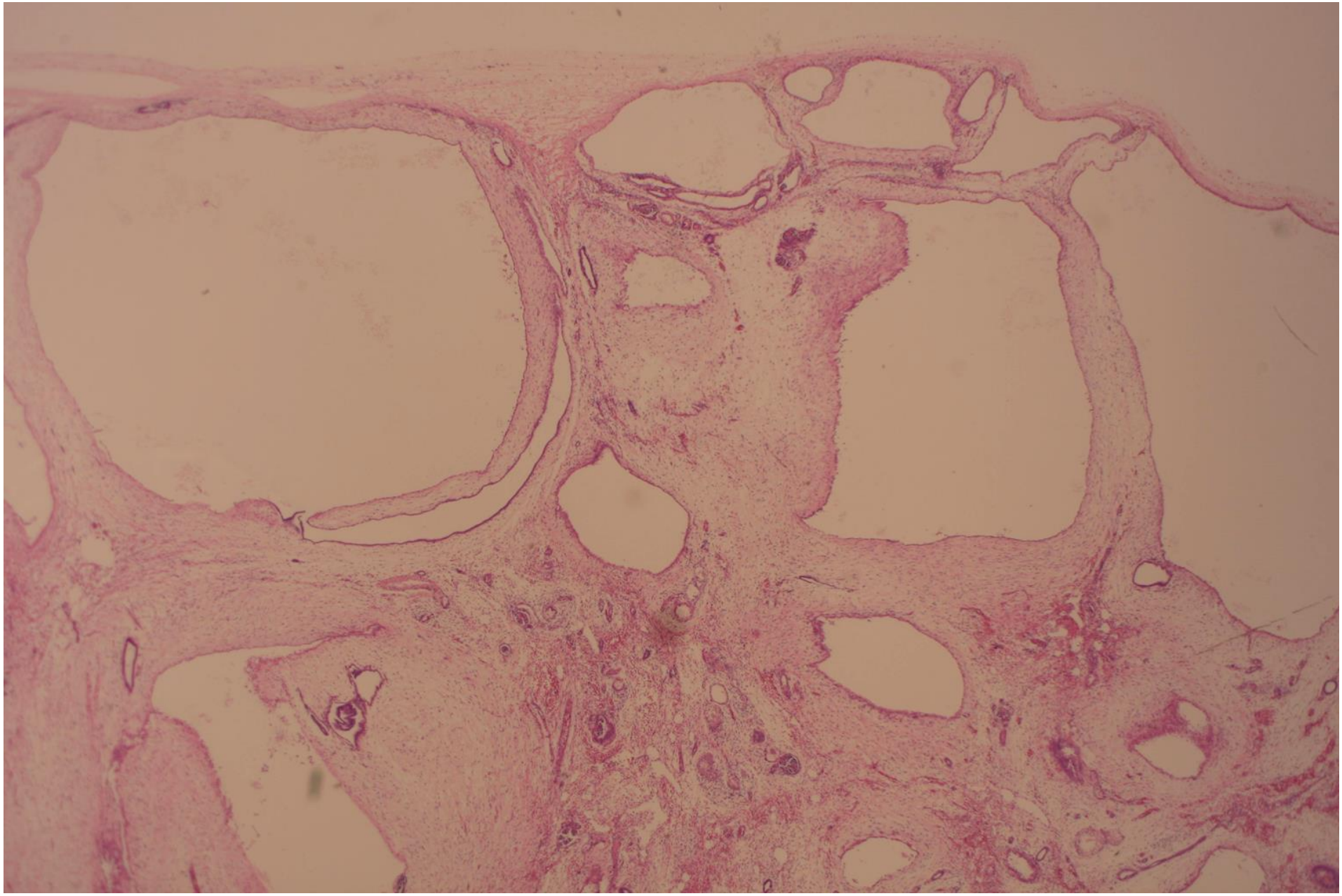
Cystic renal dysplasia

Potter type II



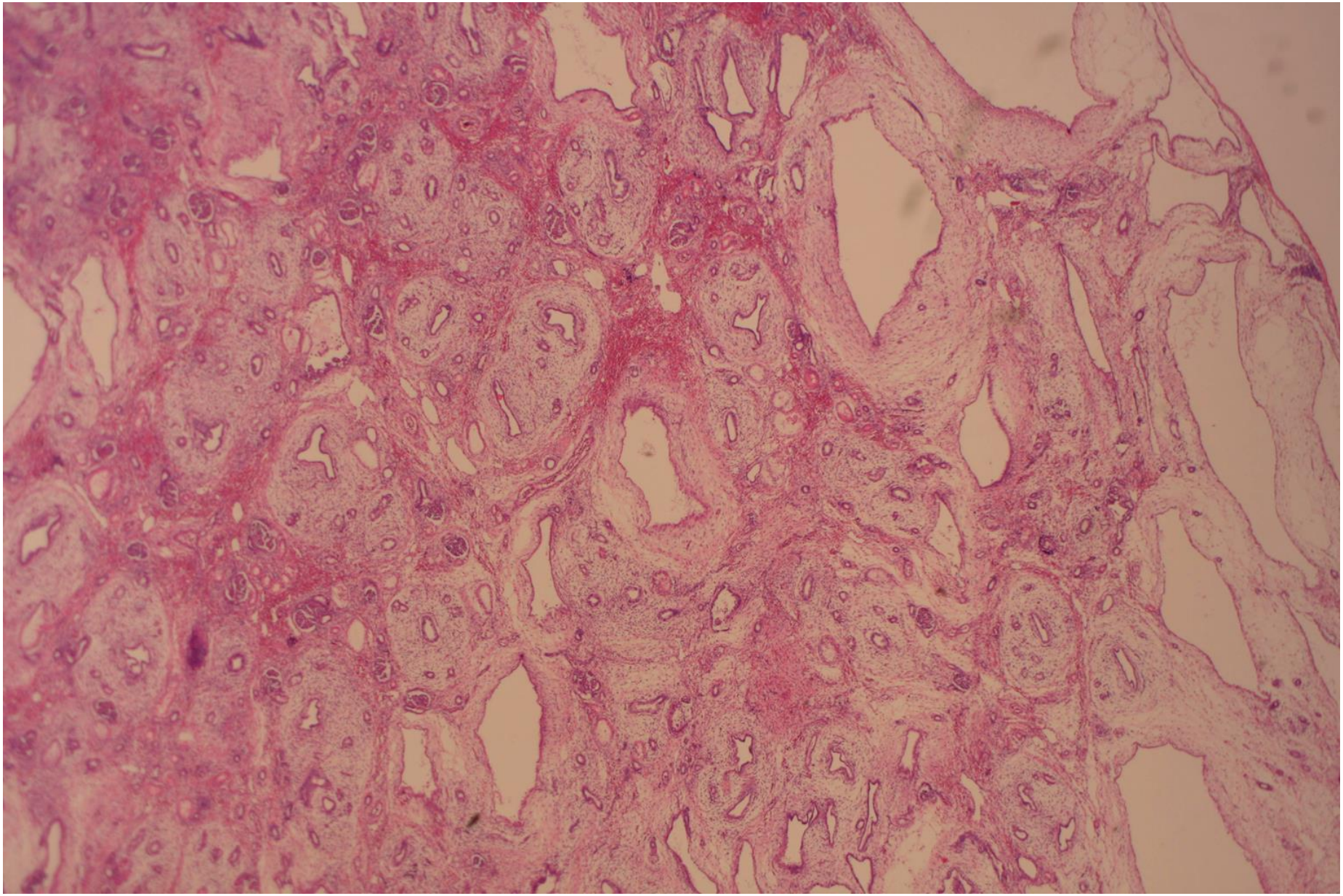
The cysts arise as ductal dilatations, most marked peripherally.

Cystic renal dysplasia



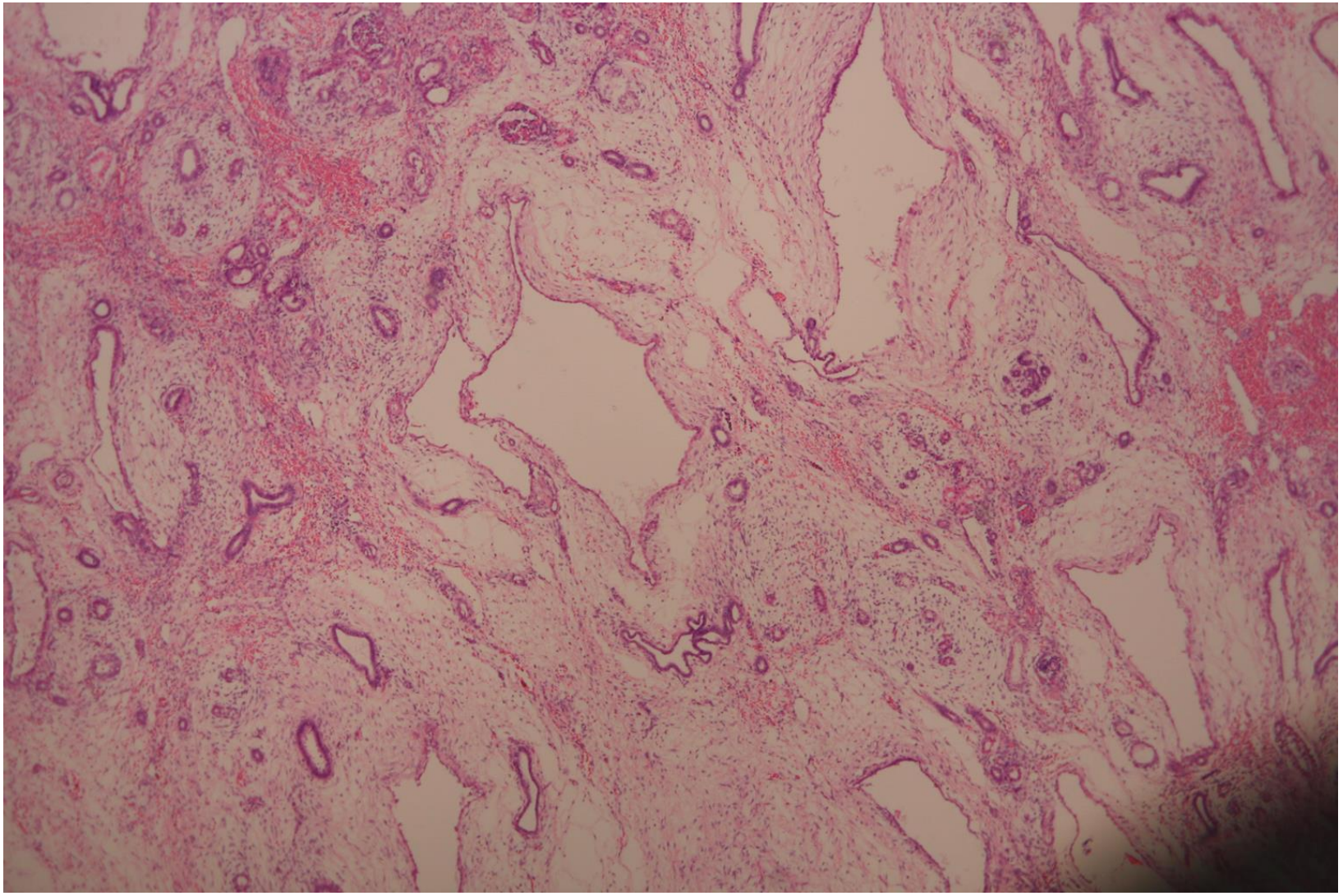
Peripheral irregular cysts

Cystic renal dysplasia

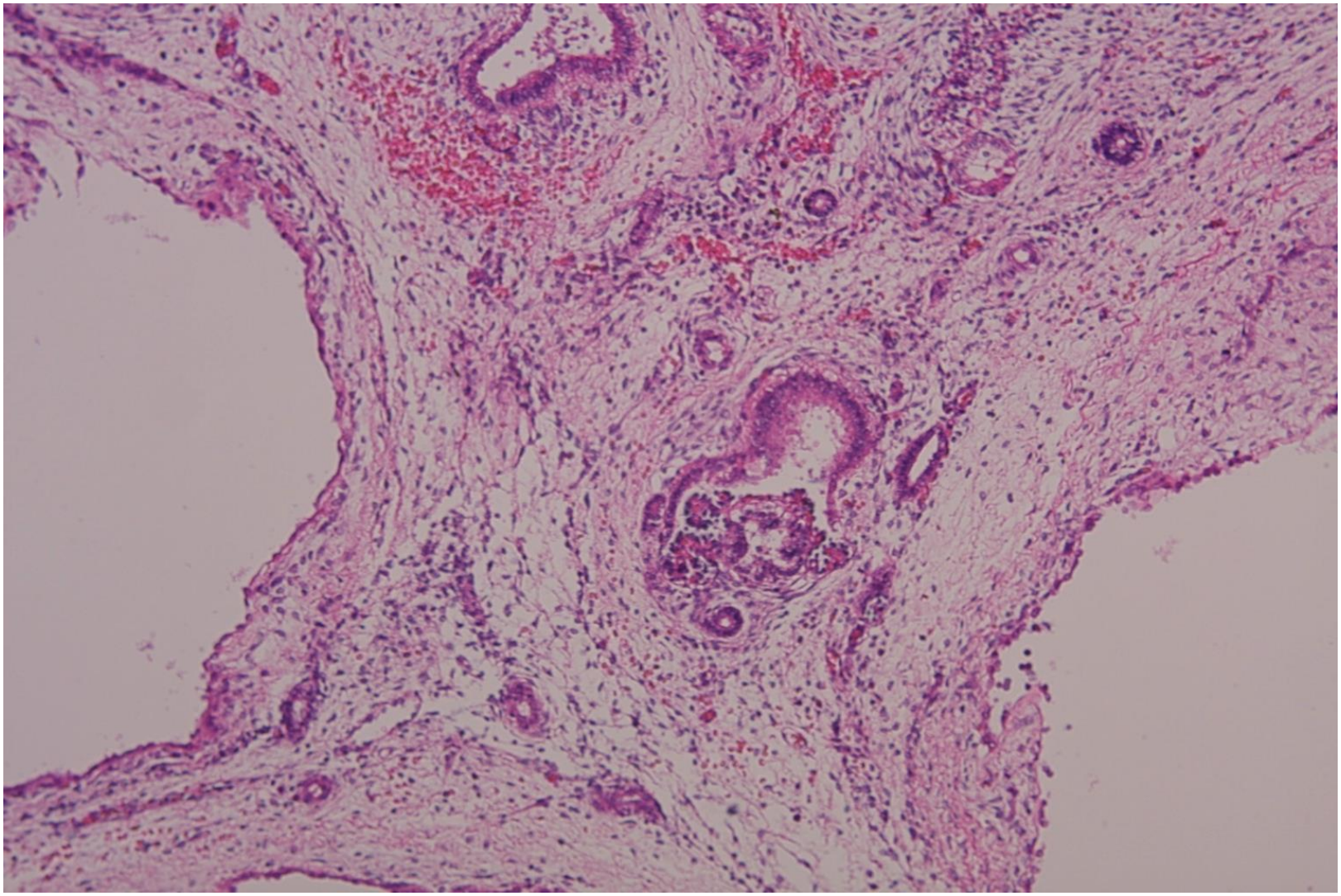


Central solid core containing a large number ofprimitive ducts with fibromuscular collars

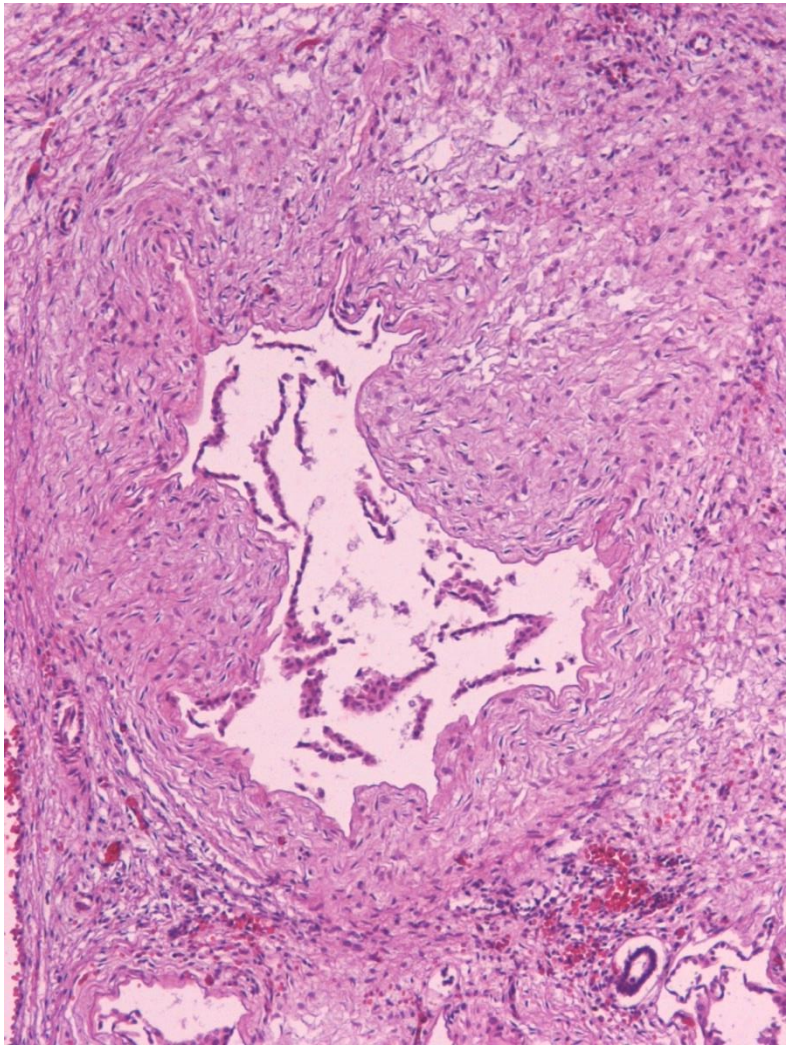
Cystic renal dysplasia



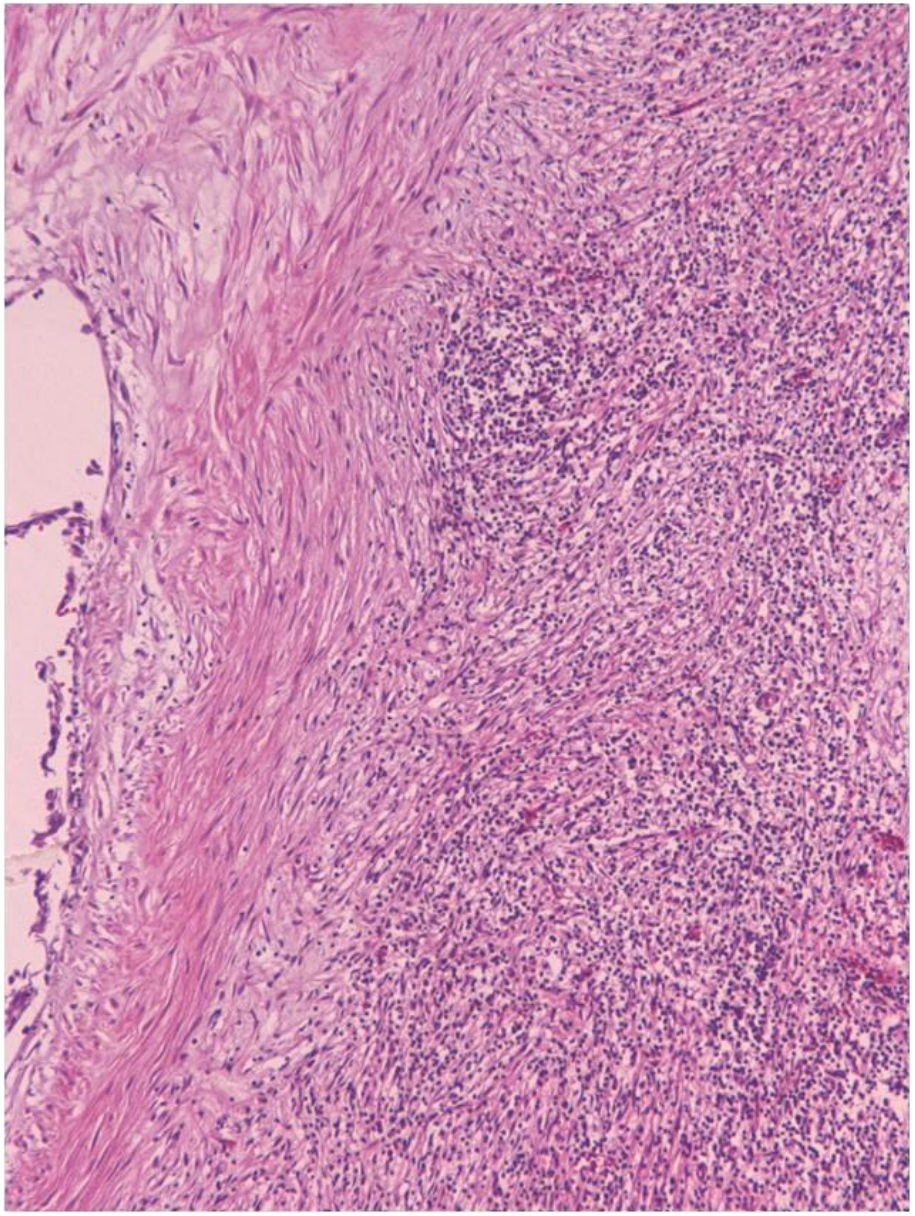
Increased loose mesenchymal tissue



Sparse nephronic structures in the cystic dysplastic kidney



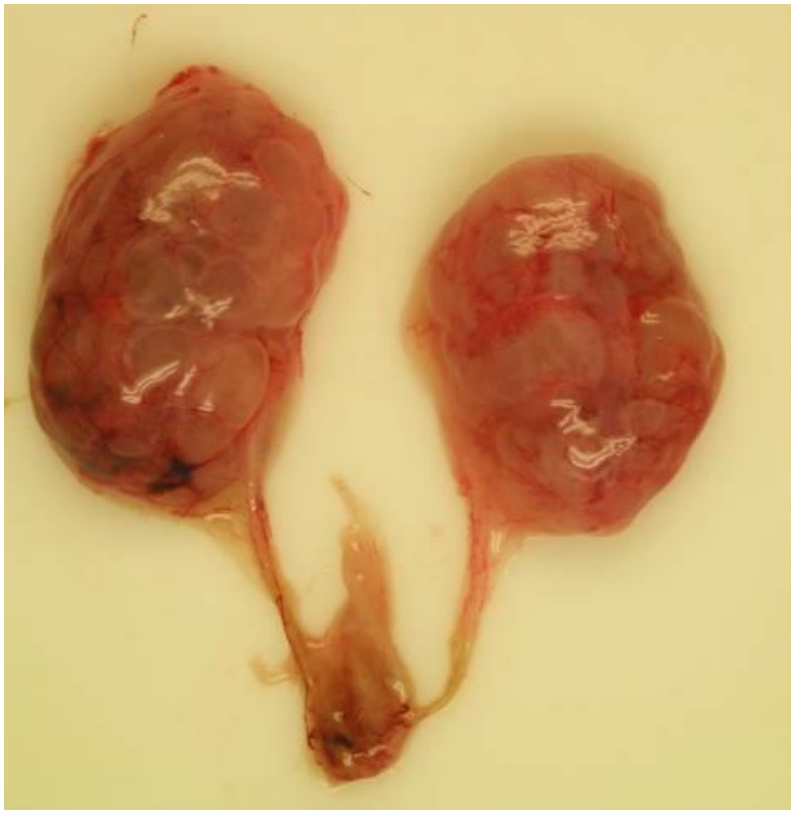
Duct epithelium: may be undifferentiated,
or cuboidal, cylindrical, ciliated



Extramedullary haemopoiesis

Renal dysplasia

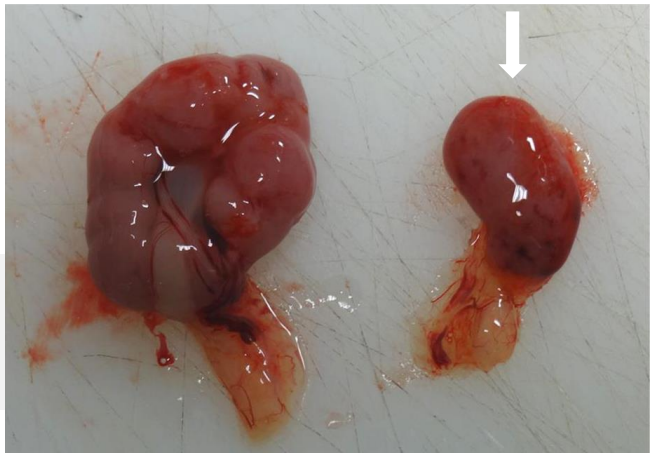
Multicystic dysplasia



Multicystic kidneys: end stage of cystic renal dysplasia

Enlarged, misshapen, irregularly cystic kidney

Aplastic dysplasia



Aplastic kidney: small, solid or minutely cystic

Cystic renal dysplasia

Obstructive dysplasia

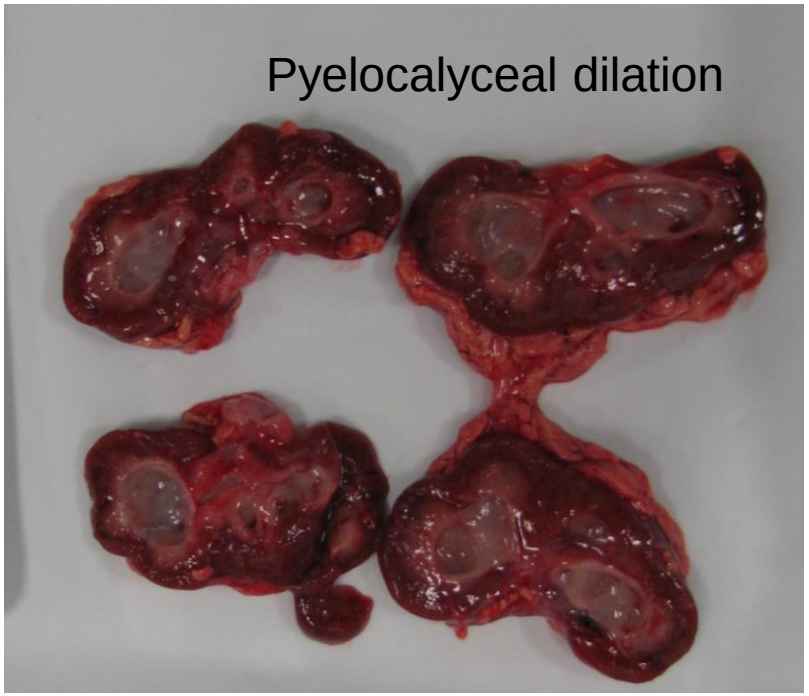
Prolonged distal urinary tract obstruction of the bladder outlet or urethra

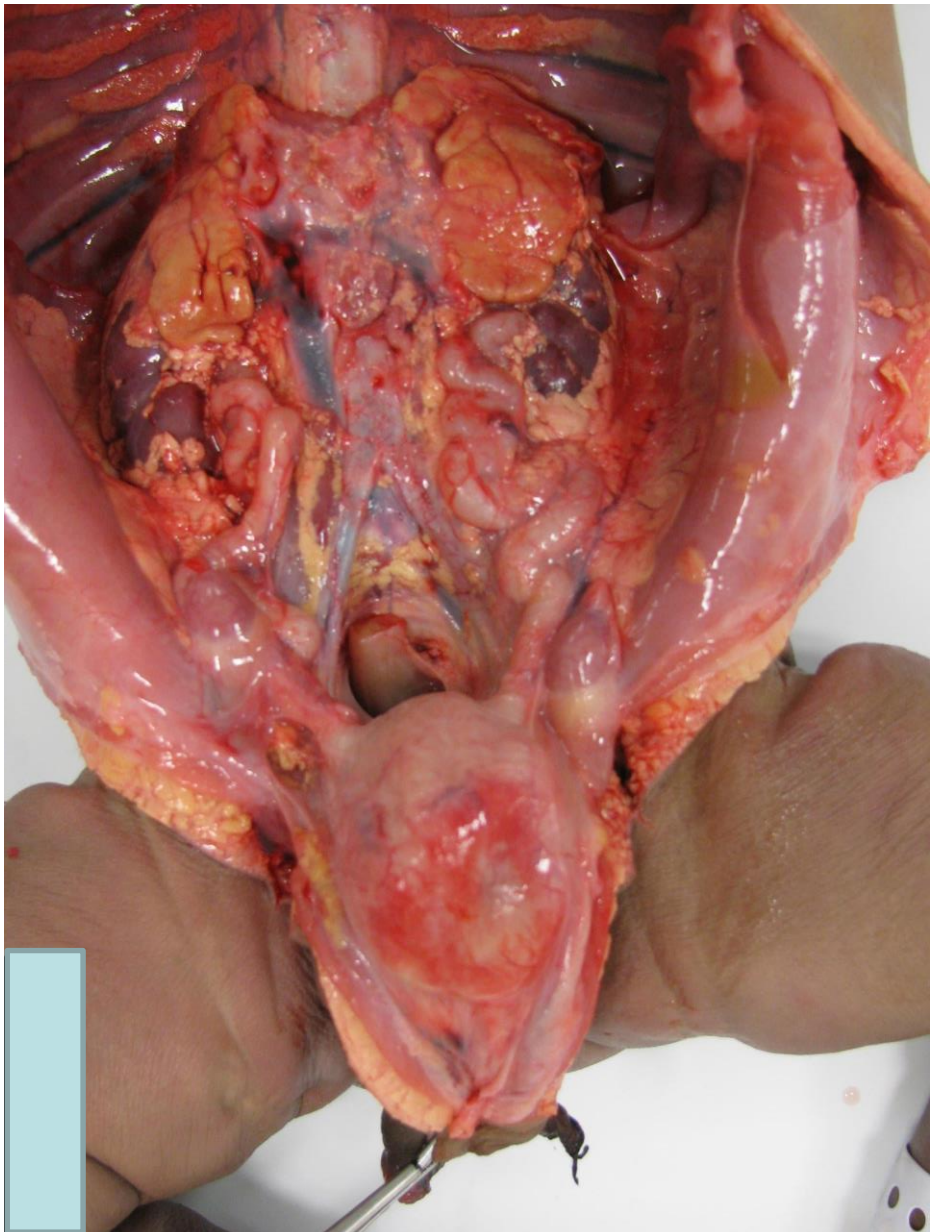
Lower obstruction

Hydronephrosis - Megaureters

Pyelocalyceal dilation

Cysts at the outer cortex

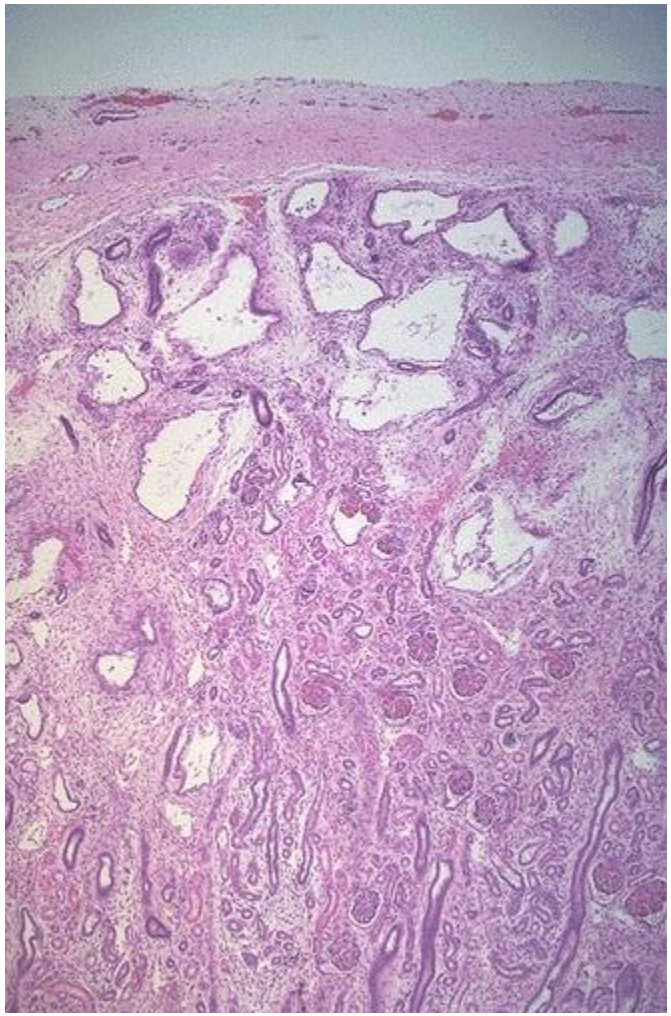




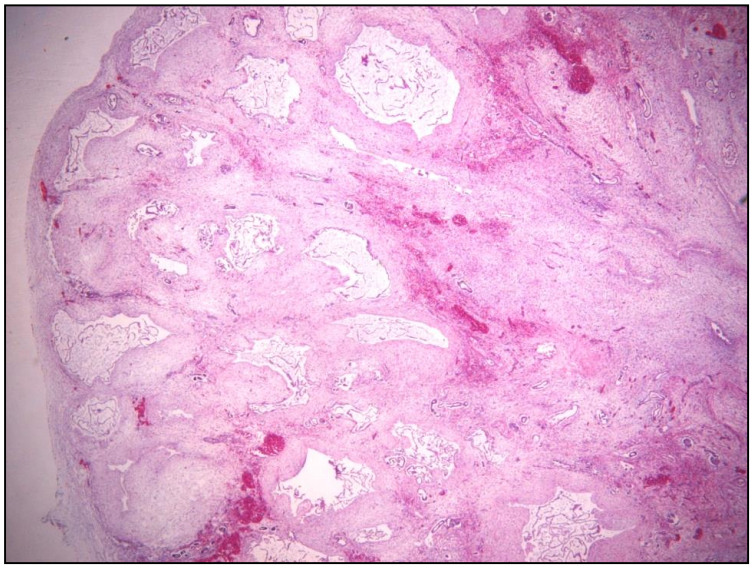
Cystic renal dysplasia

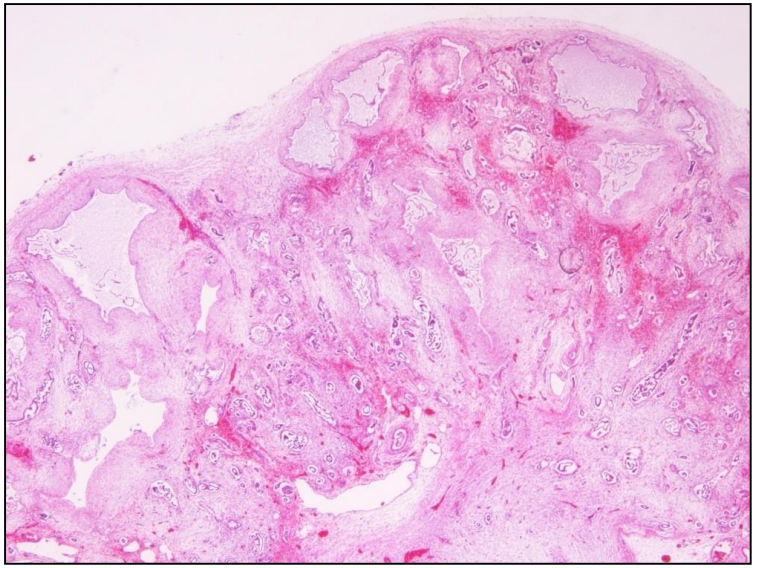
Obstructive dysplasia

Potter type IV



The cysts appear near the nephrogenic zone, because the developing glomeruli are most sensitive to the increased pressure.

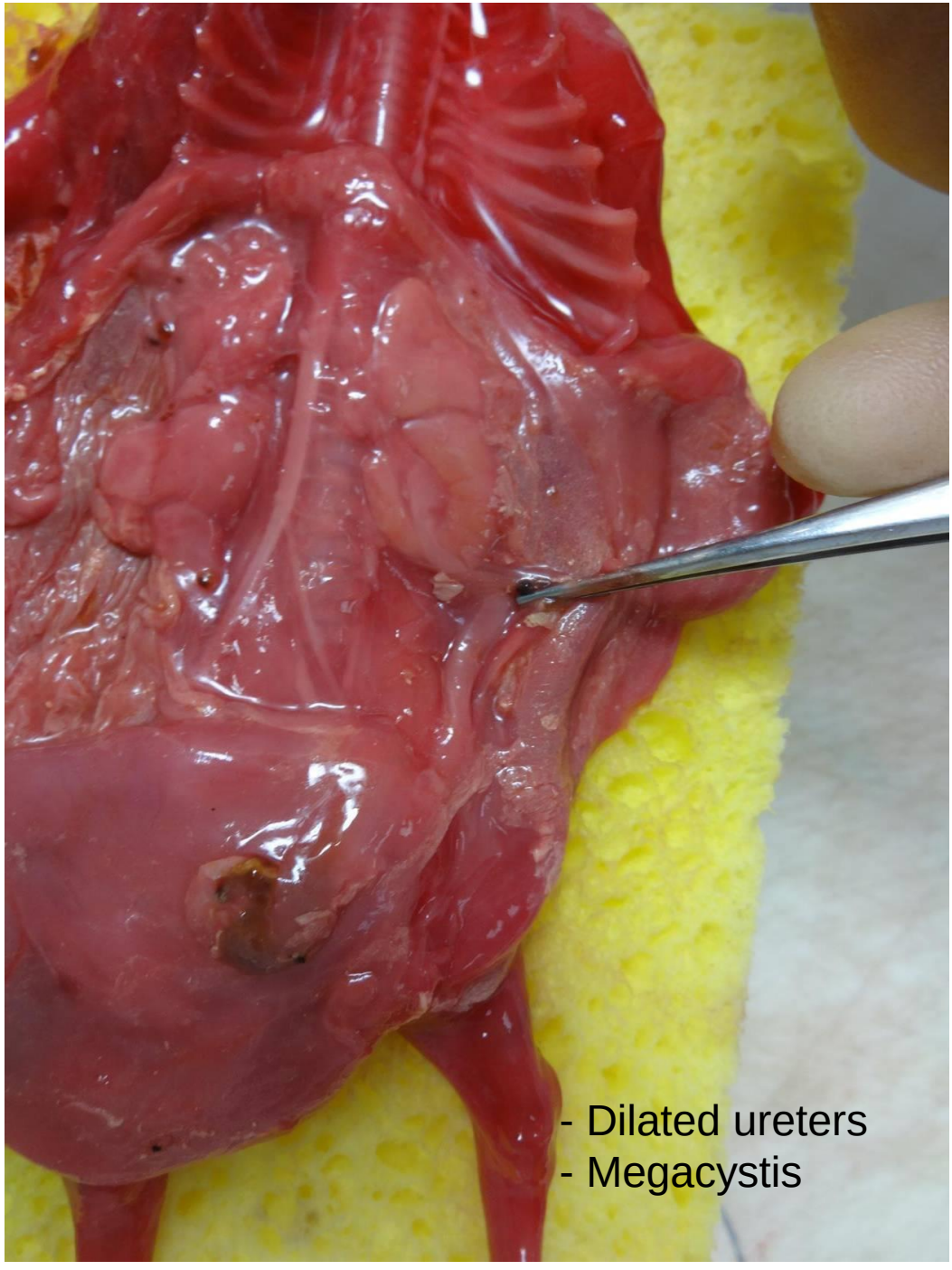




Dysplastic elements.
The medullary zone appears fibrotic.

LUTO: Lower Urinary Tract Obstruction

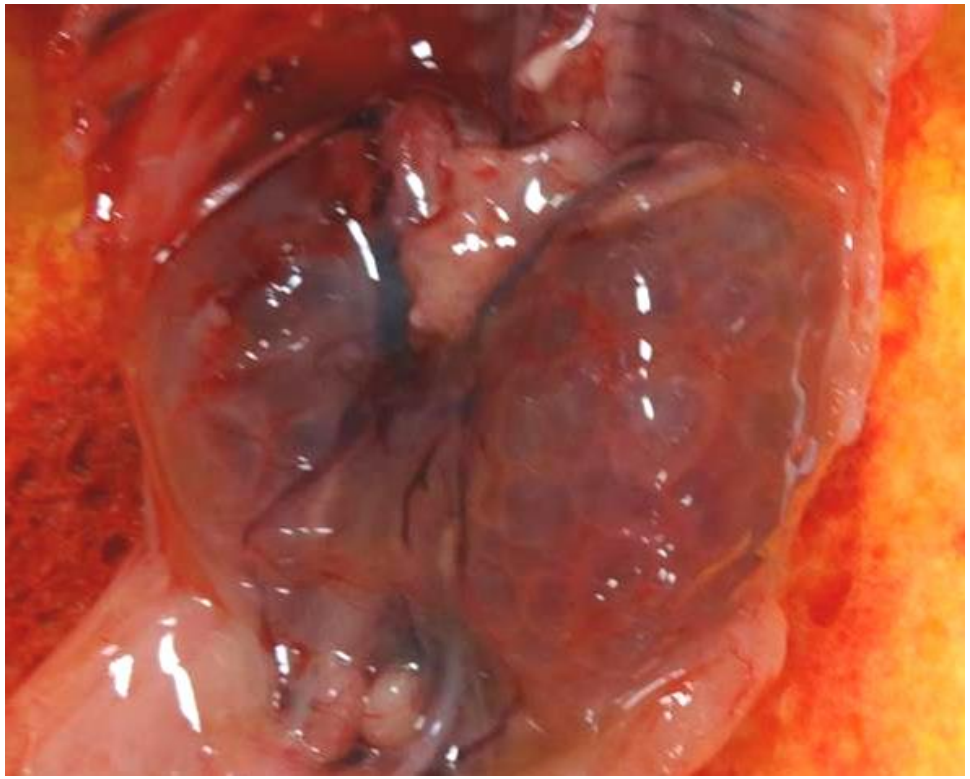
- urethral atresia
- posterior urethral valves
- bladder neck atresia
- vesico-ureteric junction obstruction
- duplex collecting system with obstructing ureterocoele

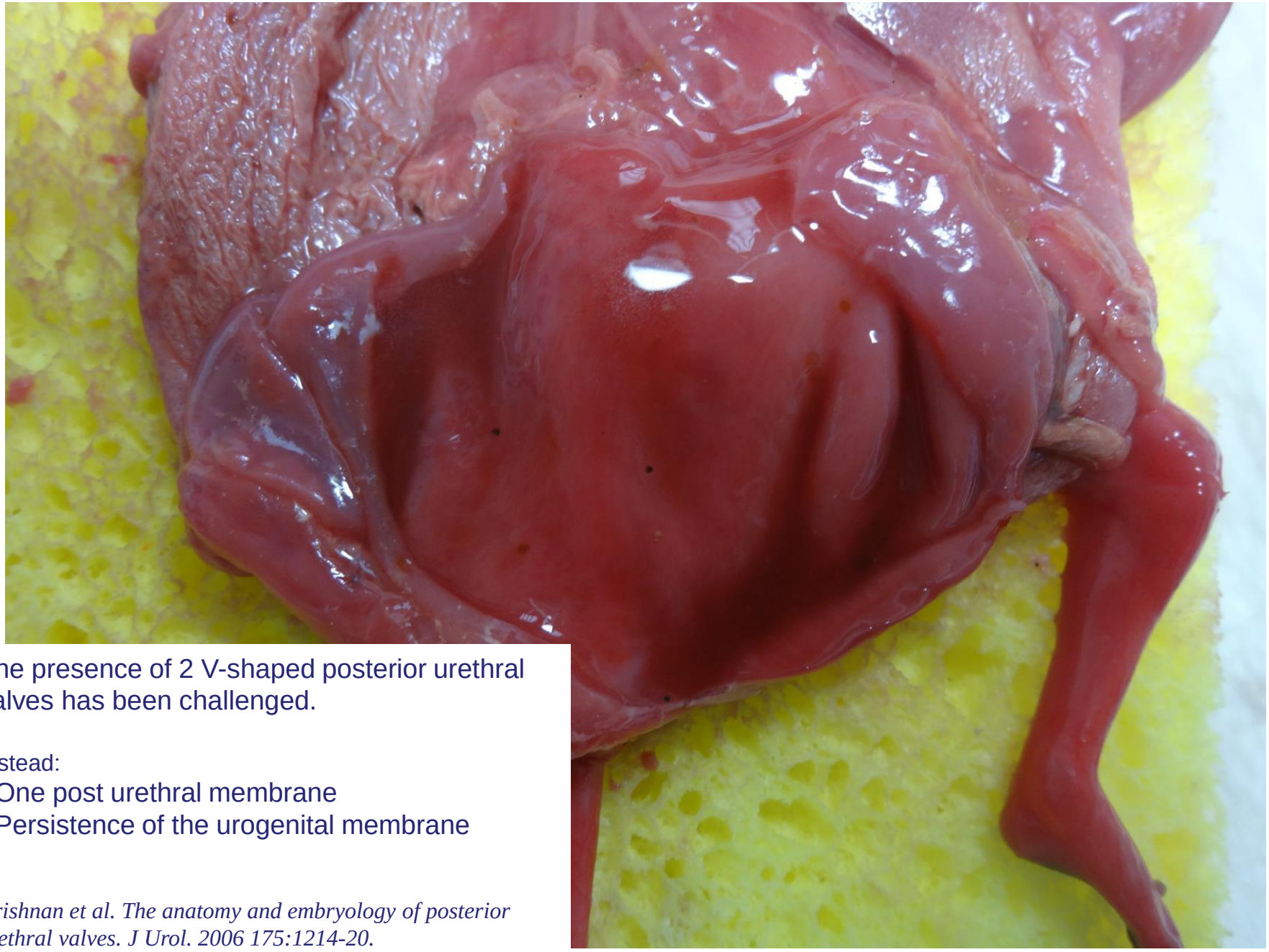


Cases with partial obstruction (eg. urethral valves) may lack renal dysplasia.

Urethral atresia is always associated with renal dysplasia.

Infravesicular obstruction may cause asymmetric renal dysplasia (L > R)
likely to be due to asymmetric VUR





The presence of 2 V-shaped posterior urethral valves has been challenged.

Instead:
- One post urethral membrane
- Persistence of the urogenital membrane

Krishnan et al. The anatomy and embryology of posterior urethral valves. J Urol. 2006 175:1214-20.

LUTO: Lower Urinary Tract Obstruction

“Prune Belly Syndrome”

Renal adysplasia - hypodysplasia
(HRA: Hereditary Renal Adysplasia)

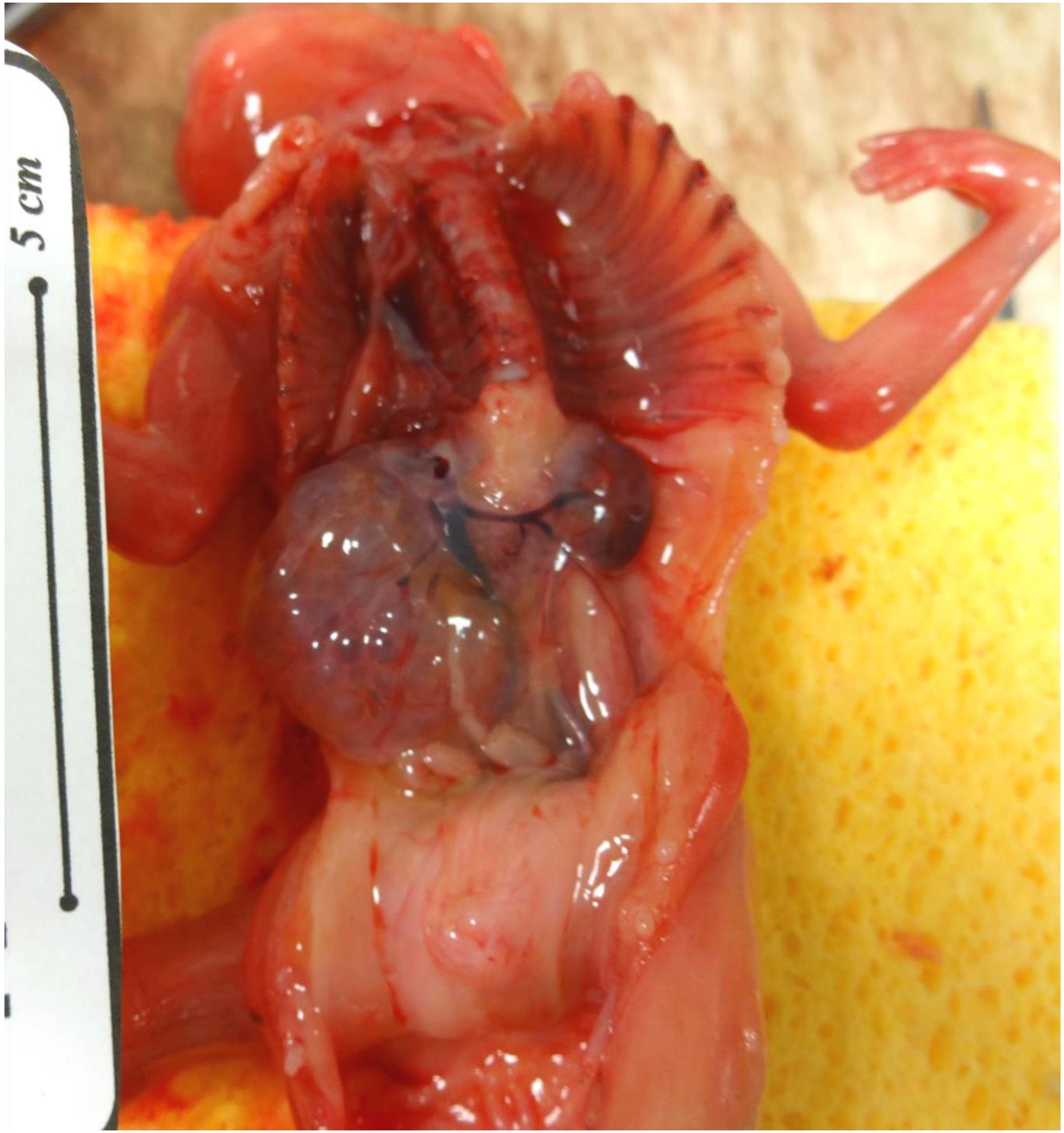
A-genesis
Adysplasia **+ Dysplasia**
A-plasia

includes:
renal aplasia, agenesis, hypoplasia, dysplasia,
or severe obstructive uropathy

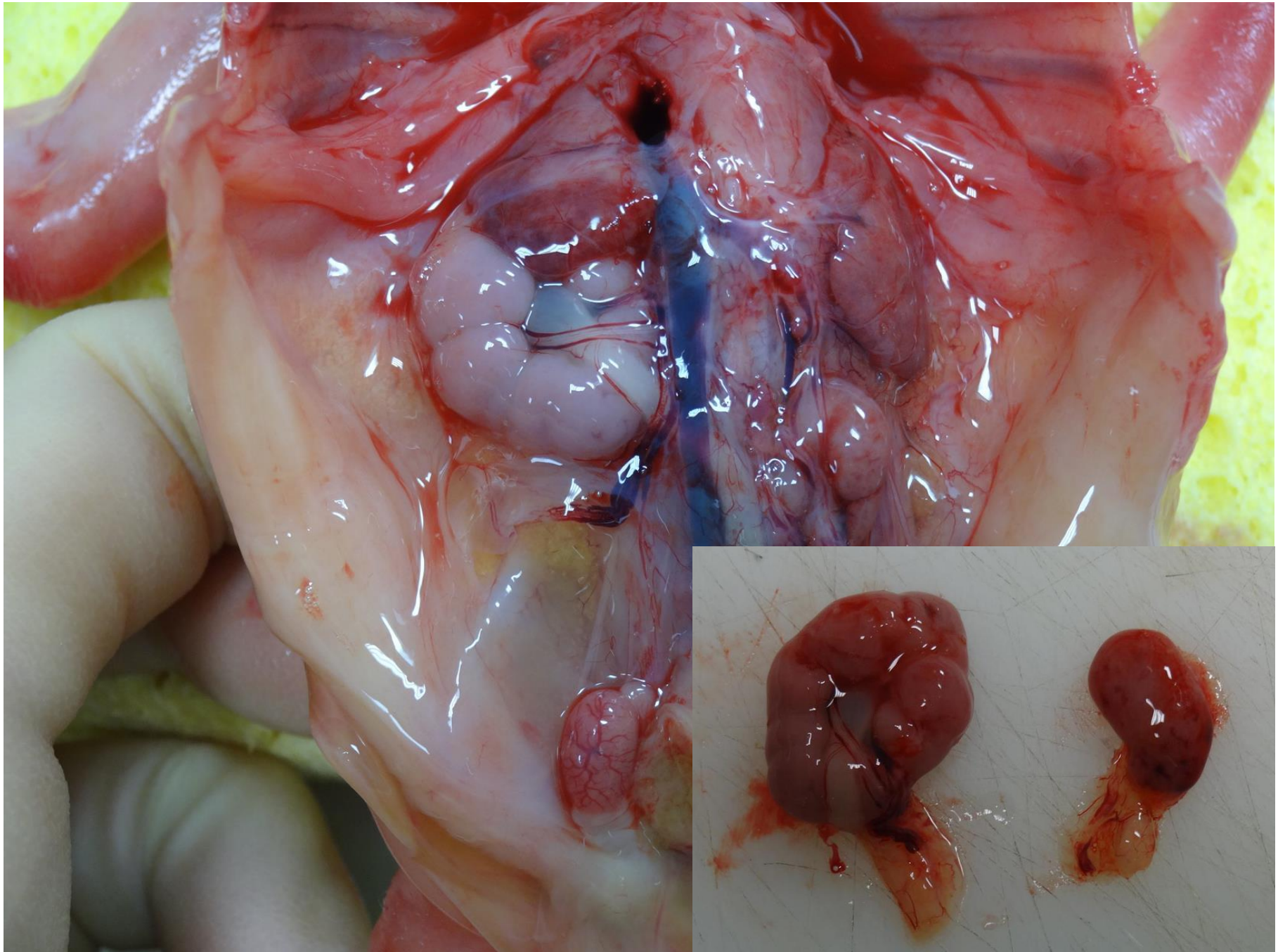
CAKUT (Congenital Anomalies of the Kidney and Urinary Tract)
These conditions may belong to a pathogenic continuum or phenotypic spectrum.

Renal adysplasia

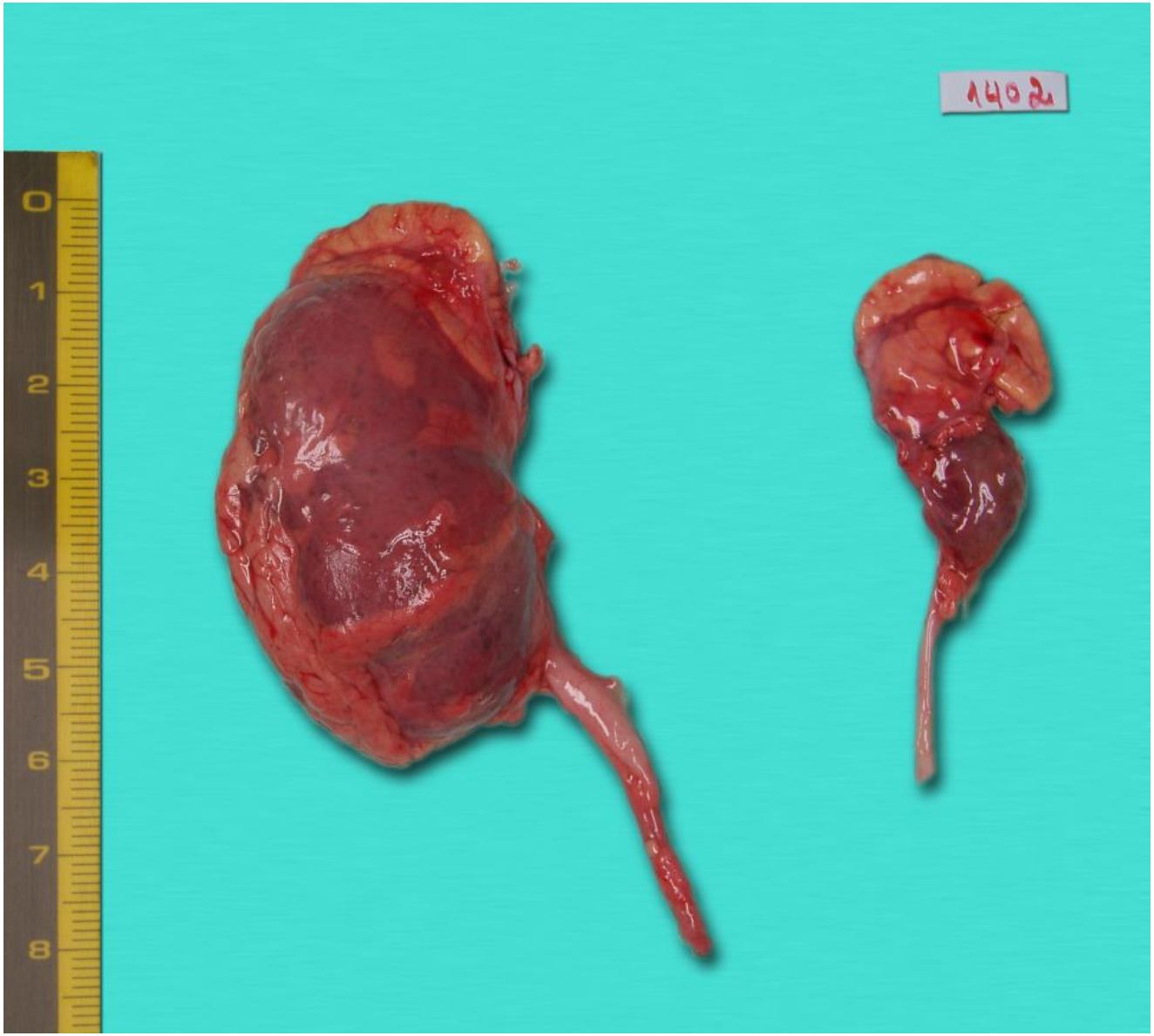
unilateral agenesis
contralateral dysplasia



Renal hypodysplasia (hypoplasia + dysplasia)



Renal adysplasia – hypodysplasia



Renal adysplasia - hypodysplasia
(HRA: Hereditary Renal Adysplasia)

AD, AR

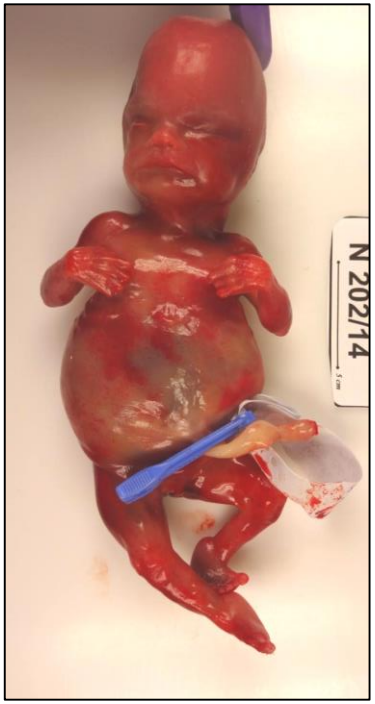
Location	Phenotype	Gene/Locus	Inheritance
10p13	Renal hypodysplasia/aplasia 1	ITGA8	AR
8q22	RHDA 2	FGF20	
10q11.21	Renal agenesis	RET	AR
10q24.31	Renal hypoplasia, isolated	PAX2	AR
1p33-p32	Renal hypodysplasia, nonsyndromic, 1	DSTYK	AD

9% of parents or sibs have asymptomatic renal anomalies.

Ultrasound study of the kidneys of parents, sibs, and other relatives is recommended in all families in which there is an individual with unilateral or bilateral renal agenesis, to exclude silent malformations.

Dominantly inherited renal adysplasia.
Am J Med Genet. 1987;26(4):863-72.

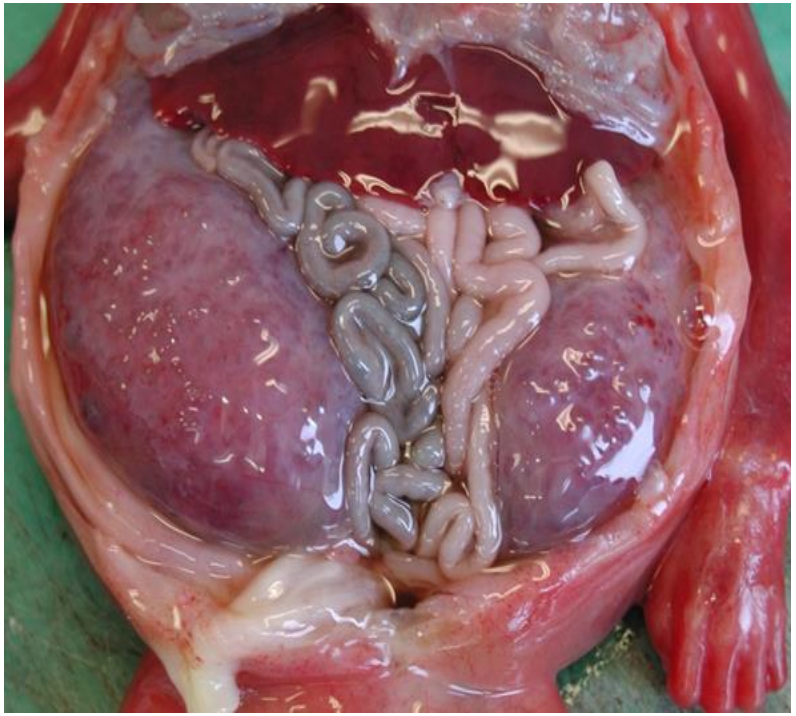
Integrin alpha 8 recessive mutations are responsible for bilateral renal agenesis in humans.
Am J Hum Genet. 2014; 94:288-94,.

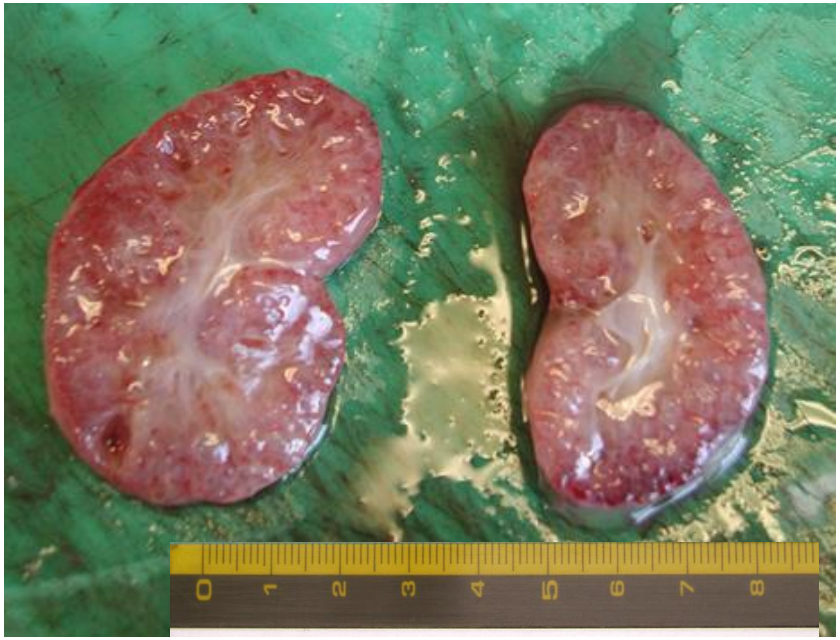


Diffuse non obstructive cystic renal dysplasia

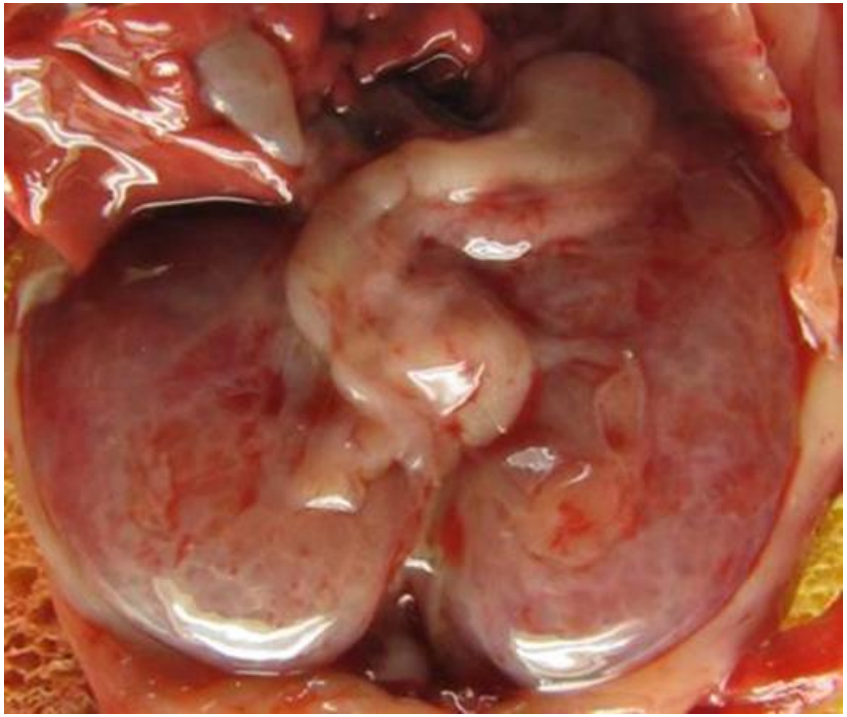
Bilateral diffuse cystic dysplasia of **Meckel type**

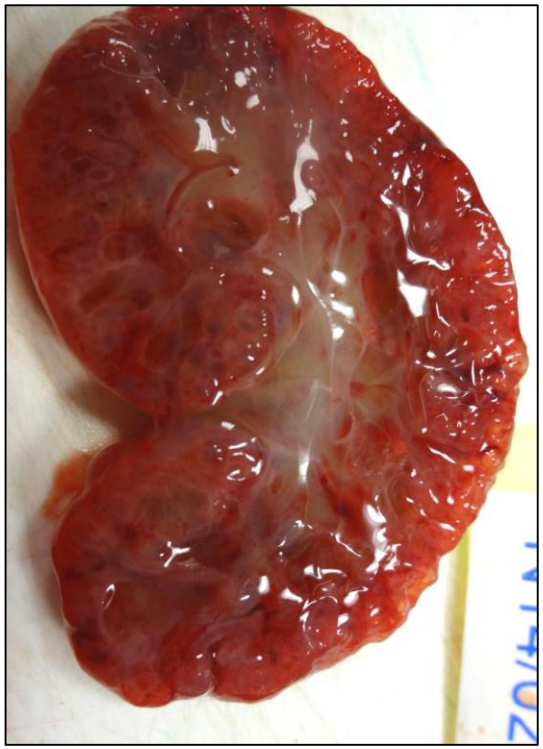
- Massive enlargement – Reniform shape
- Firm kidneys with visible small uniform cysts
- Medullary pyramids small and poorly demarcated
- Narrow pelvis
- Small patent ureters
- Hypoplastic bladder





Diffuse cystic renal dysplasia
Meckel type





Diffuse non obstructive cystic renal dysplasia
Meckel type

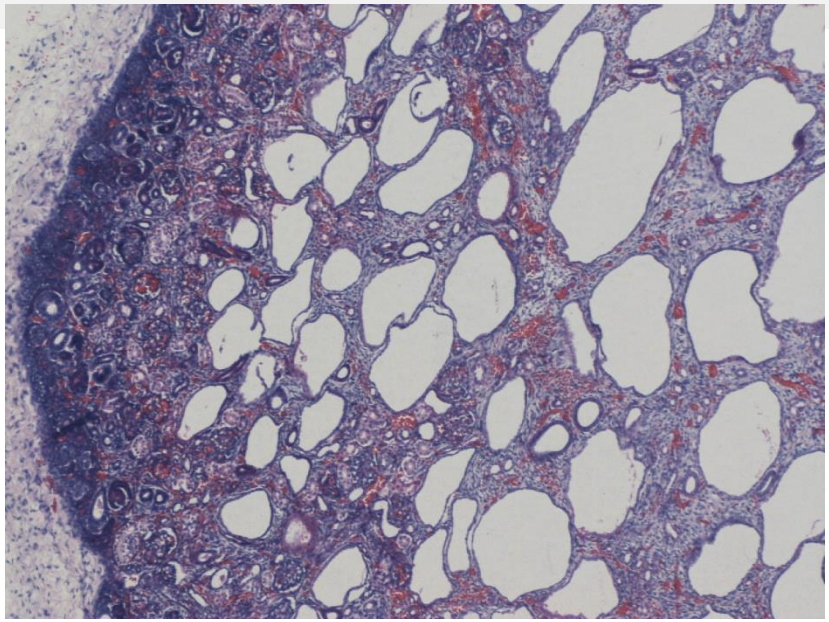
Histology

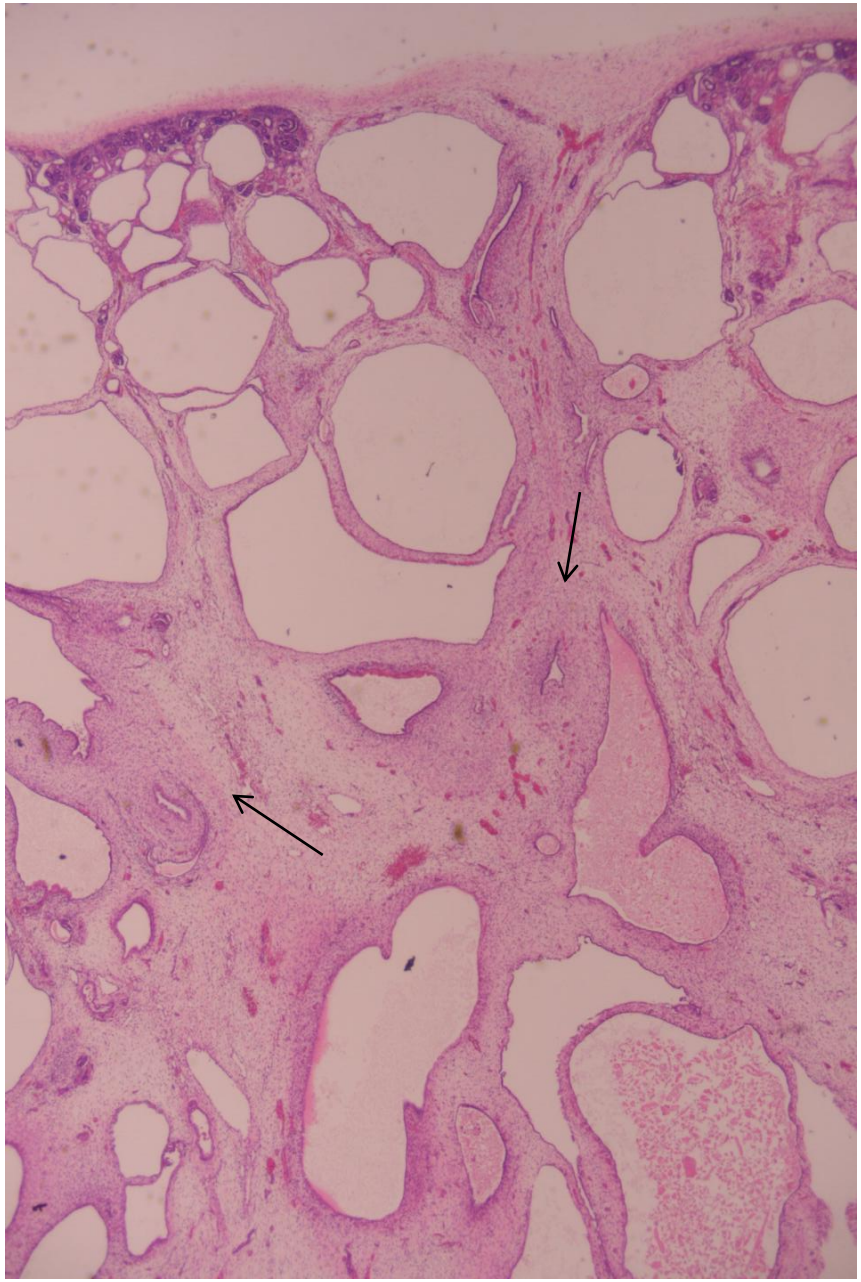
- Preservation of outer cortical rim
- Large number of cystic collecting ducts
- Restricted nephronic development
- Dysplastic elements:

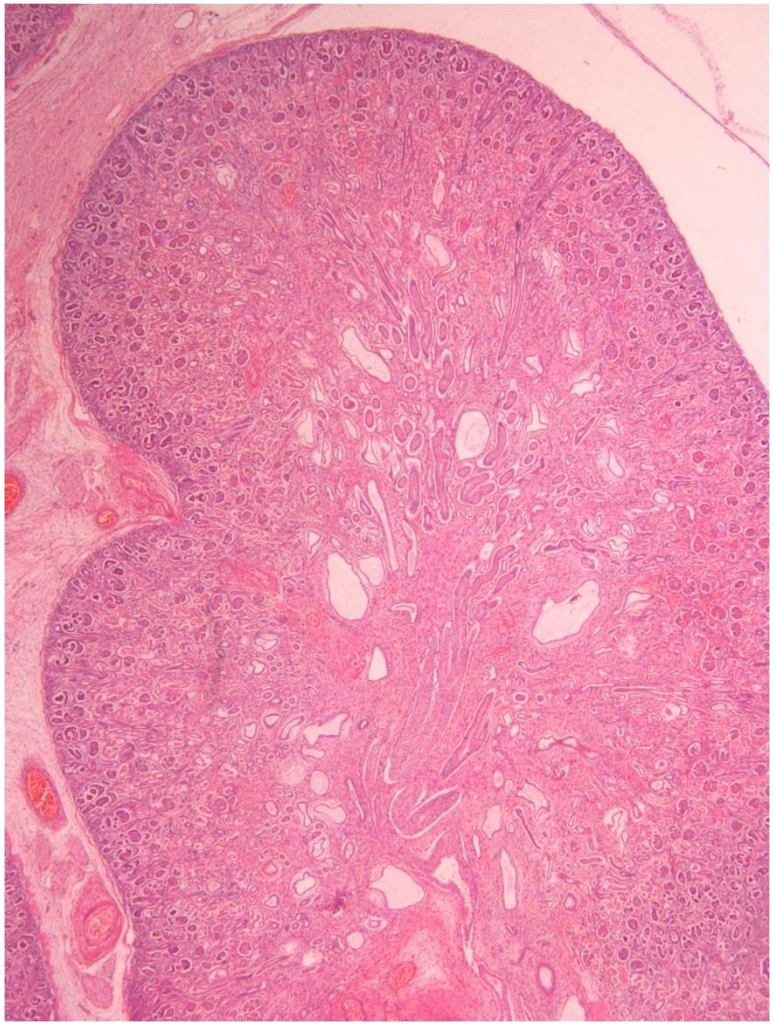
  Primitive ducts (arrows) usually few

  Undifferentiated epithelial lining

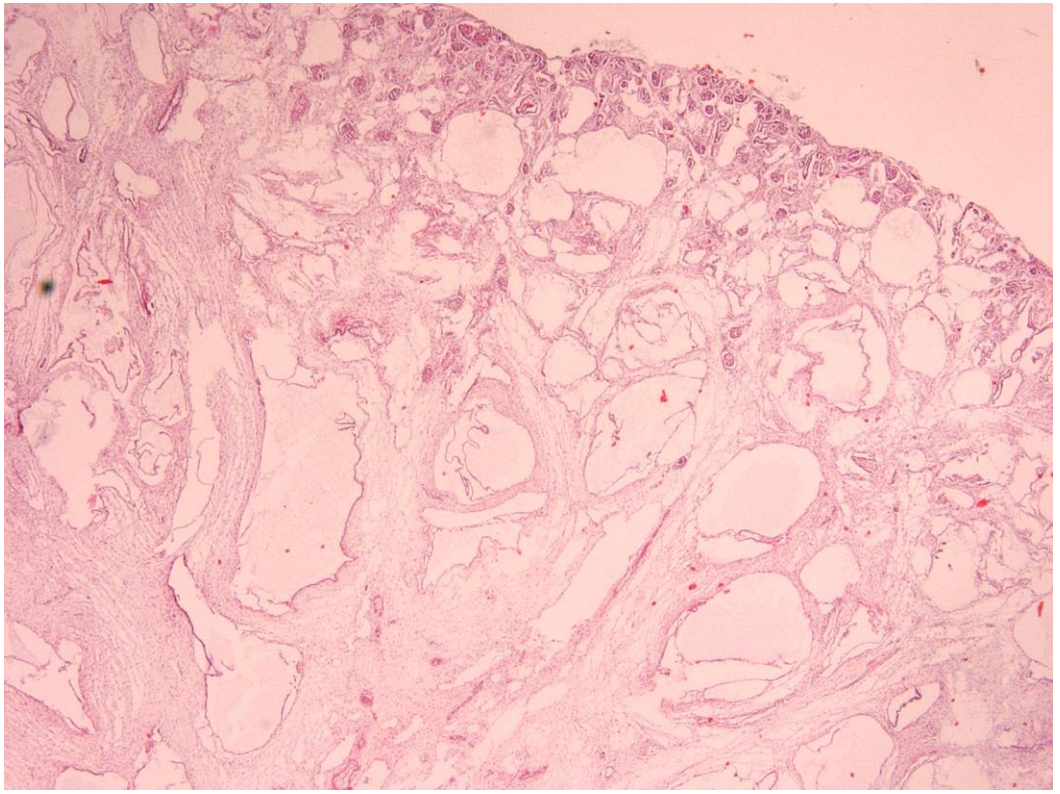
  Usually no metaplastic cartilage



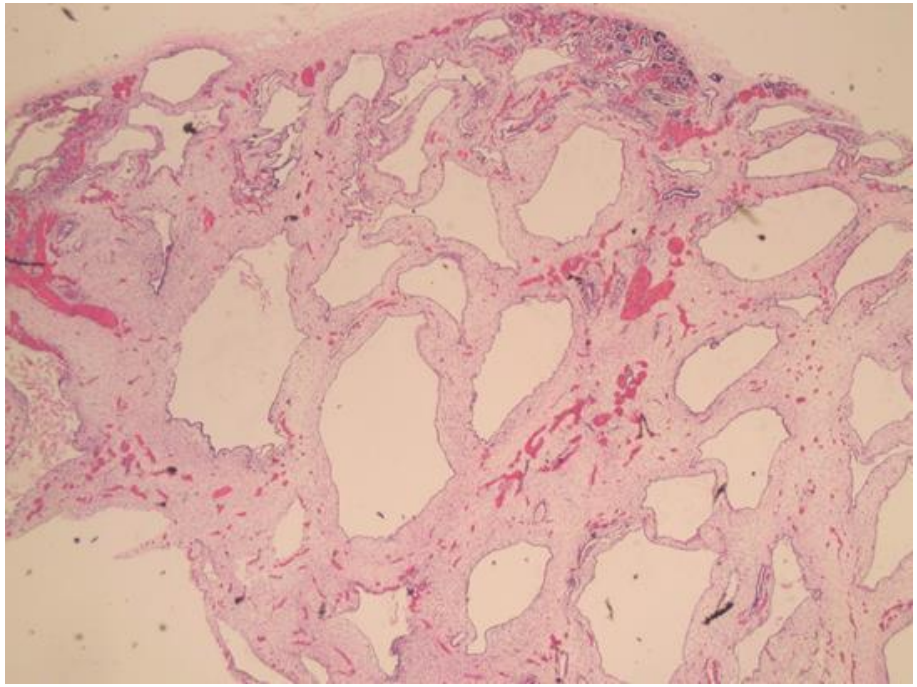


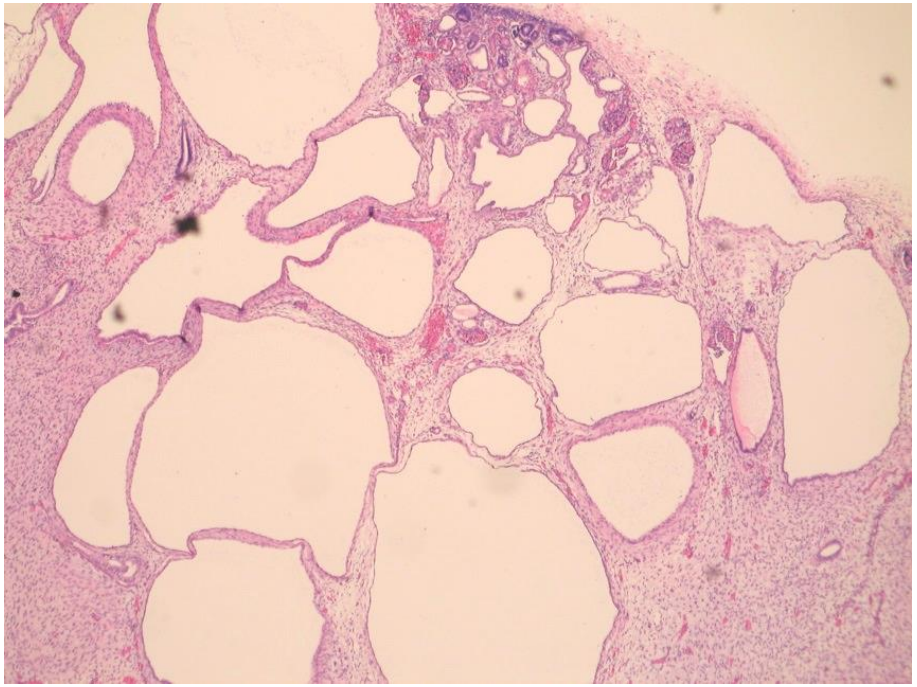


Early cystic changes in fetal Meckel syndrome

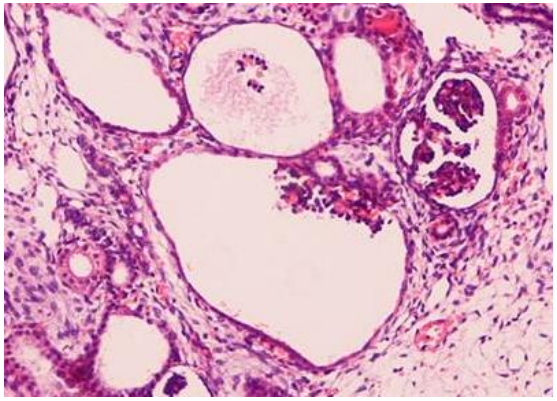


Outer nephrogenic zone in fetal Meckel syndrome

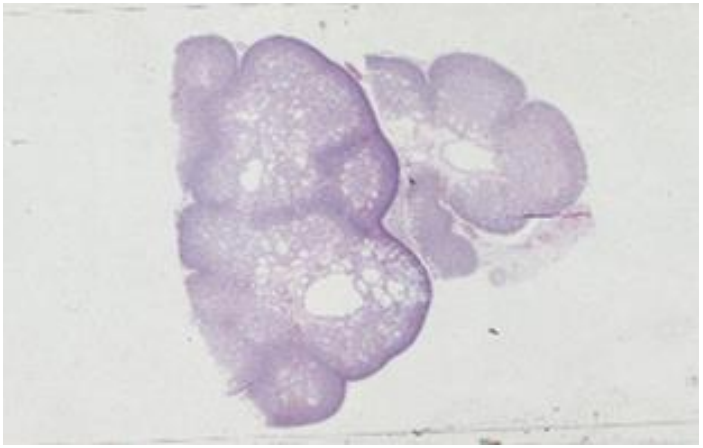


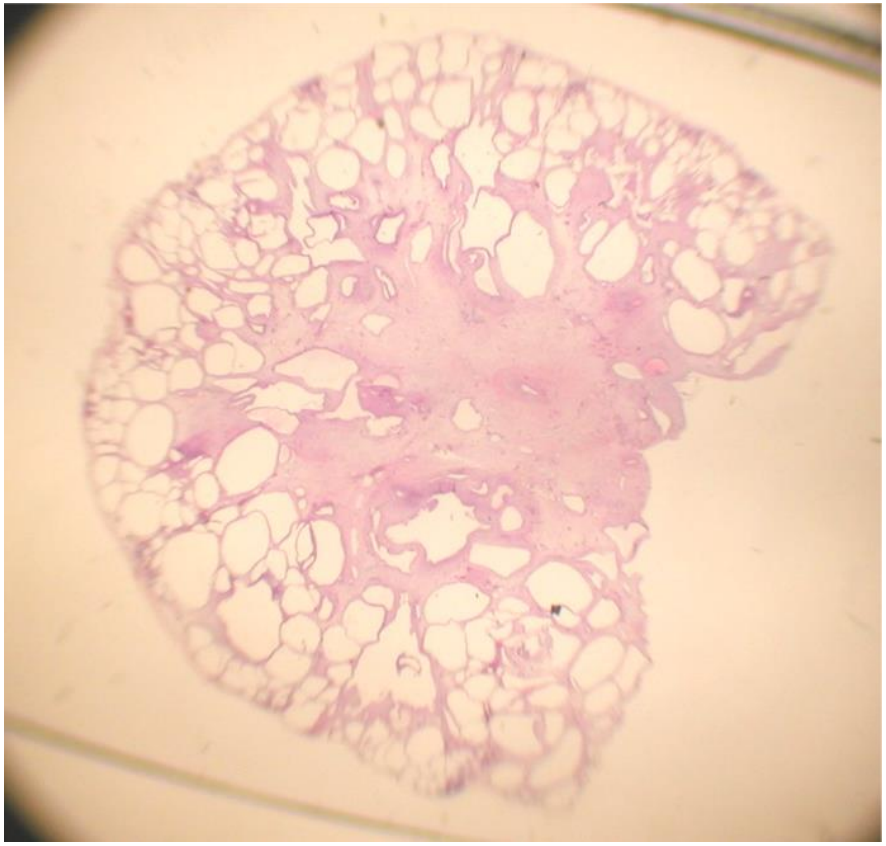


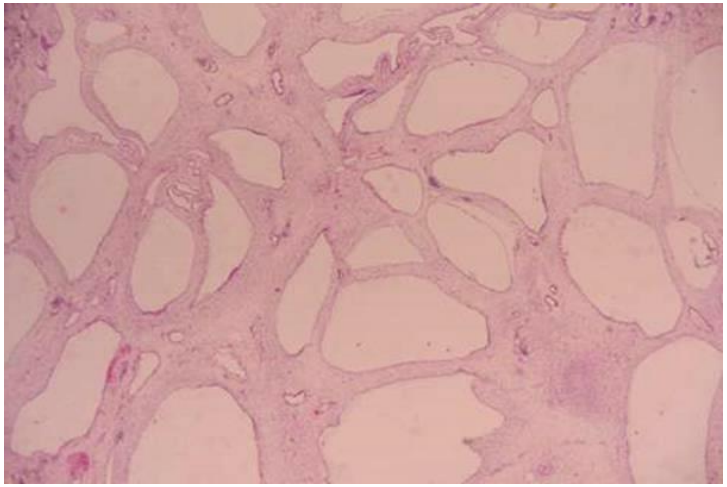
Meckel syndrome
Residual outer nephrogenic zone in late 3rd trimester
Ductal cysts



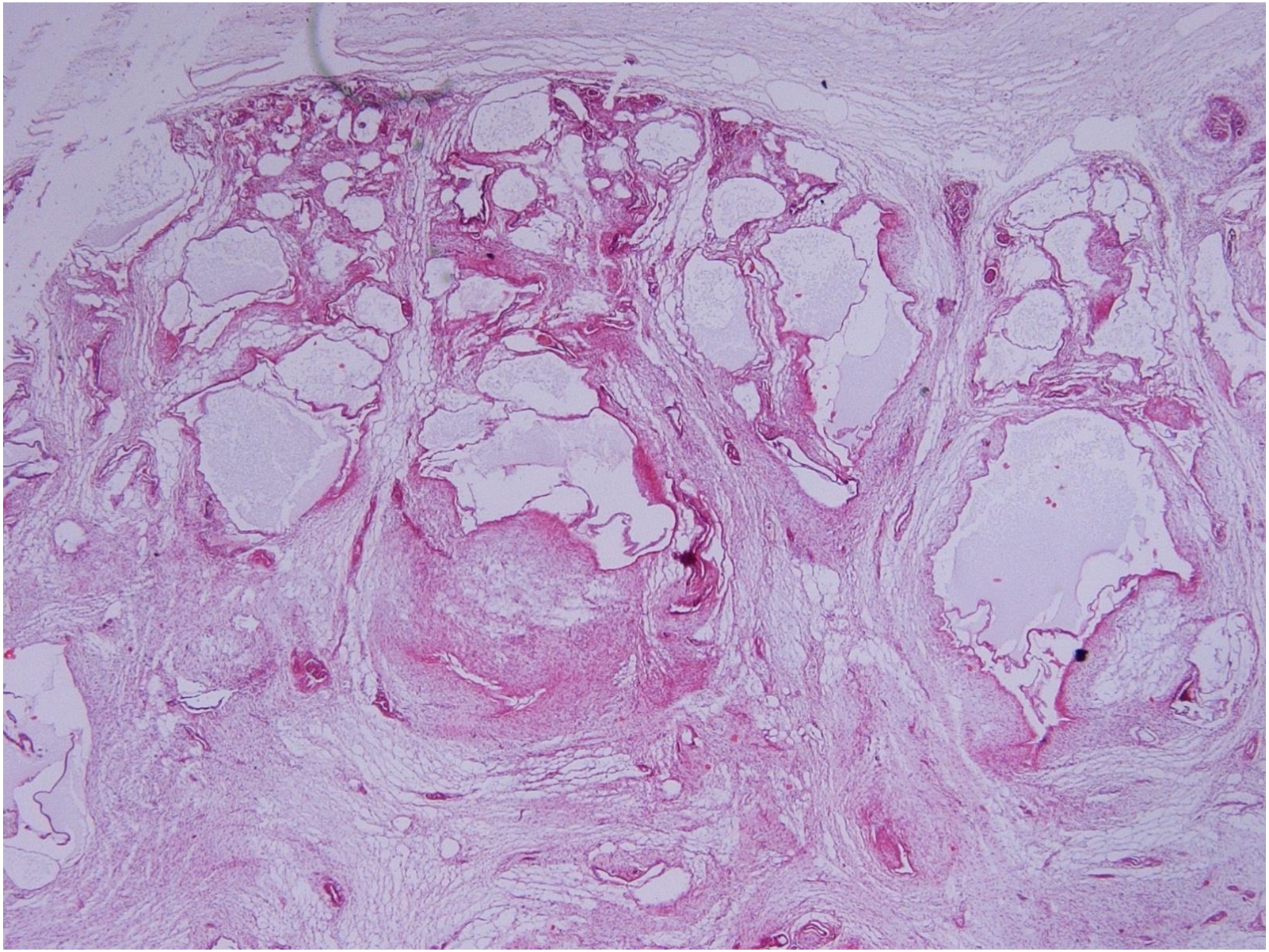
Sparse glomerular cysts may be present.







Diffuse, relatively regular cystic change in Meckel syndrome



Increased mesenchyma and dysplastic elements in Meckel syndrome

Renal Dysplasia

Clinical – Genetic association

- **Sporadic** renal dysplasia
  obstructive aetiology

- **Hereditary** renal adysplasia – hypodysplasia

- **Syndromic** Renal dysplasia
in congenital malformations syndromes and metabolic diseases (diffuse multicystic nonobstructive dysplasia Meckel-type is the commonest, encountered in ciliopathies.)

Potter classification

Type IIa (multicystic renal dysplasia)
Type IIb (aplastic renal dysplasia)
Type IV (obstructive renal dysplasia)

Meckel – Gruber syndrome (MKS)

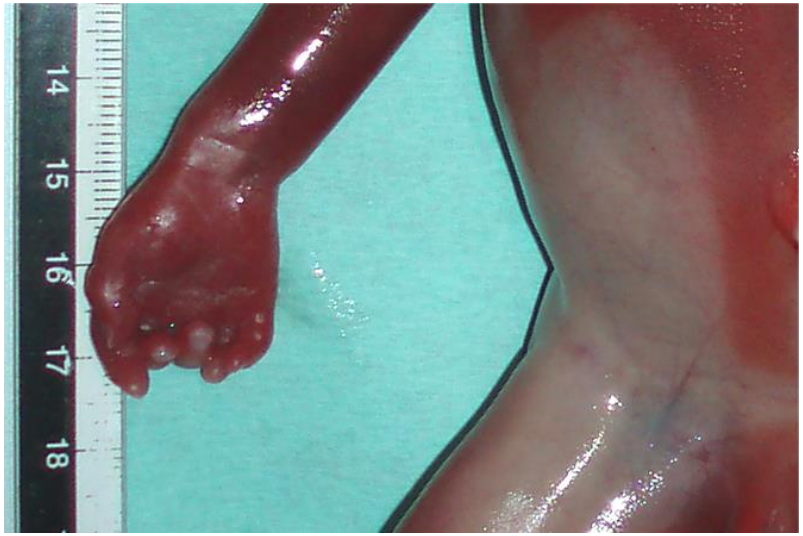
Meckel syndrome types according to OMIM

MKS1	17q22
MKS2	17q12.2
MKS3	8q22.1
MKS4	12q21.32
MKS5	16q12.2
MKS6	4p15.32
MKS7	3q22.1
MKS8	12q24.31

CILIOPATHIES

Meckel syndrome triad

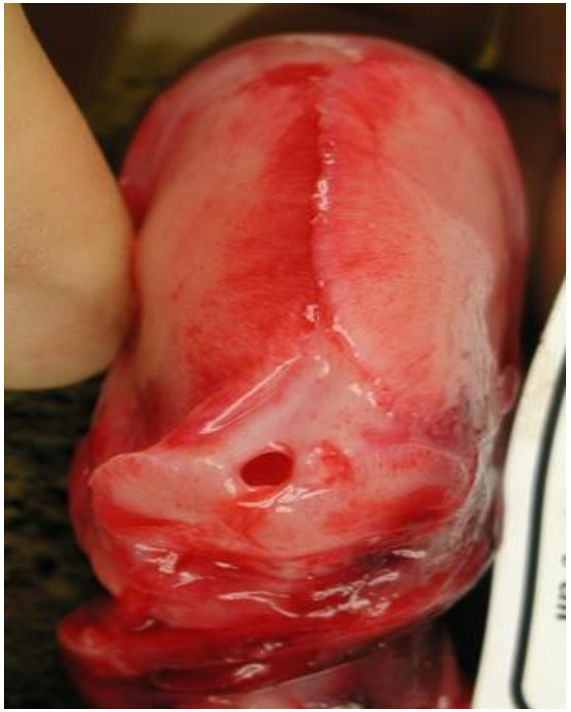
1. **Cystic renal disease** (constant)
2. CNS malformation
3. Hepatic abnormalities



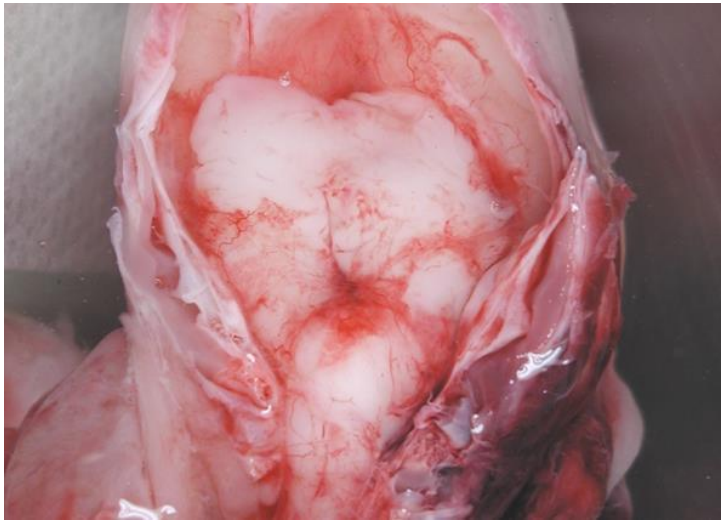
Other:
Polydactyly (postaxial)

Ambiguous genitalia

Cleft palate *et al.*

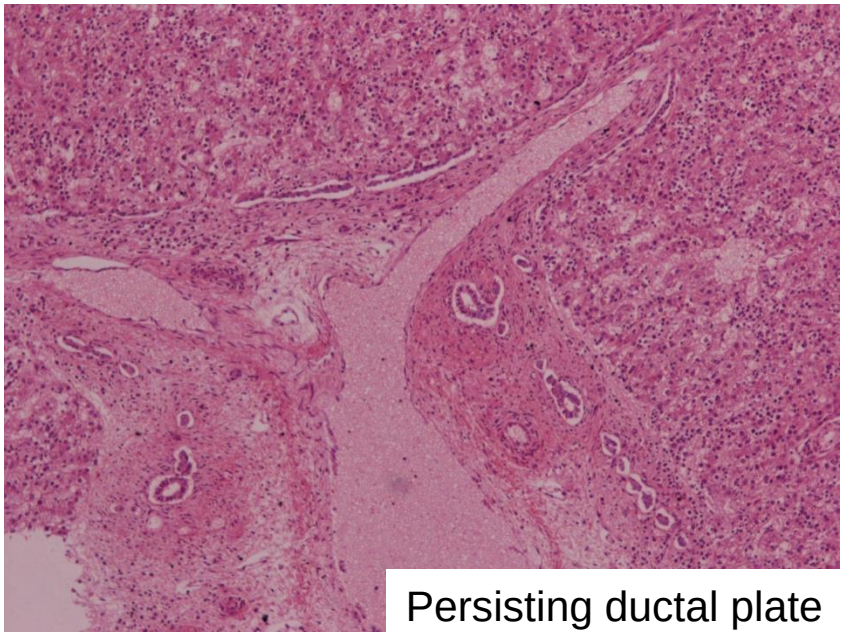


Occipital encephalocele



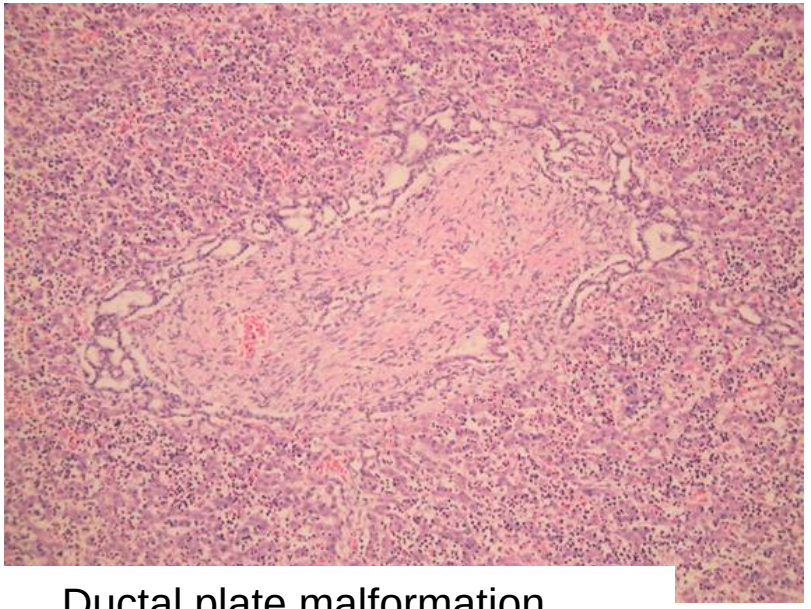
Dandy Walker malformation or variant

Hepatic abnormalities associated with diffuse multicystic renal dysplasia

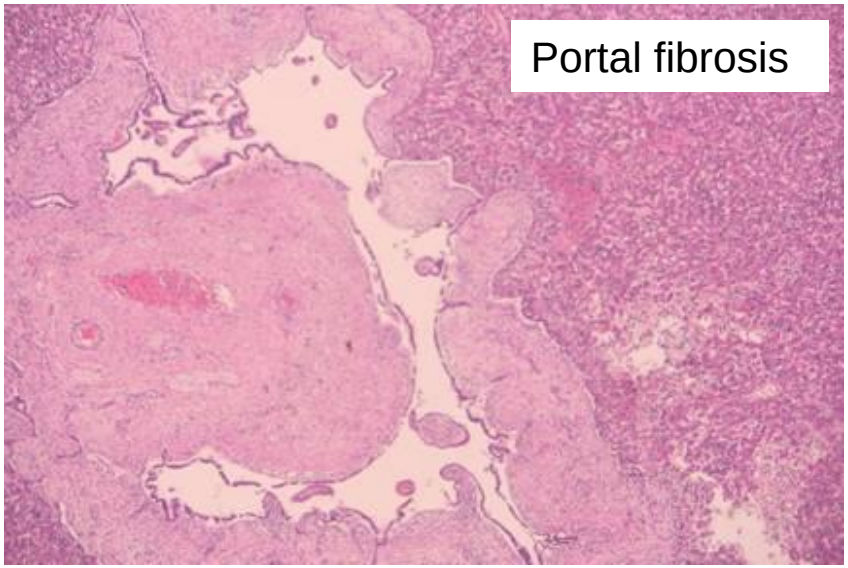


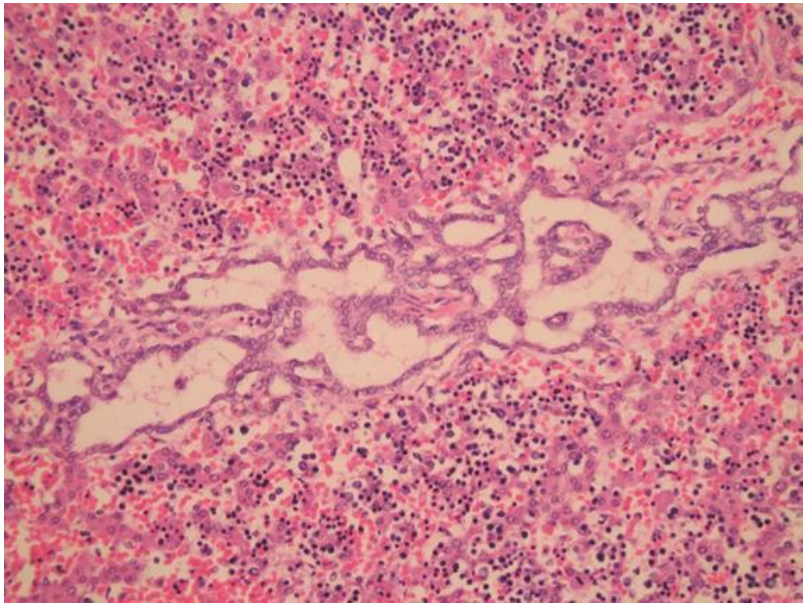
Persisting ductal plate

+

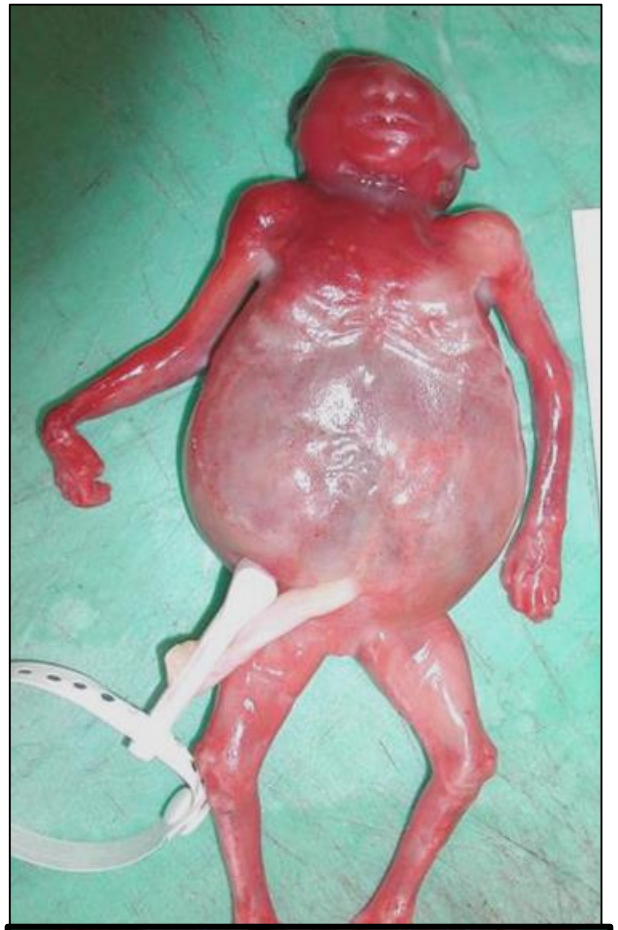


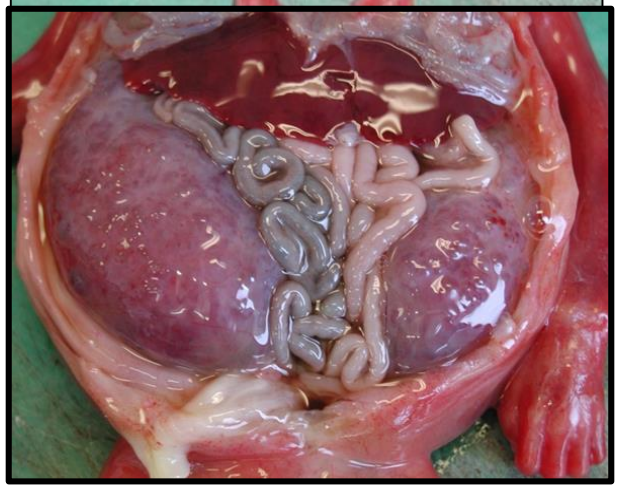
Ductal plate malformation



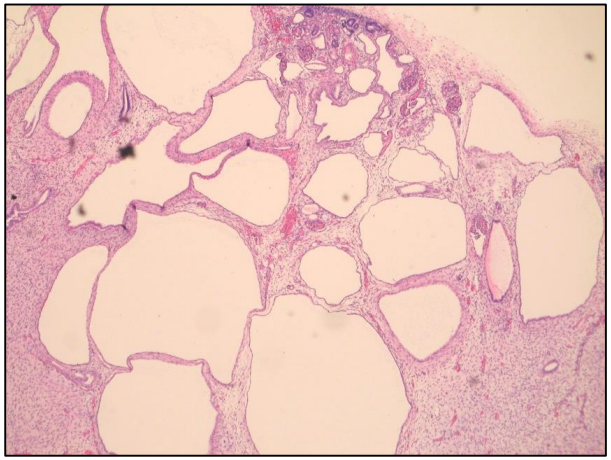


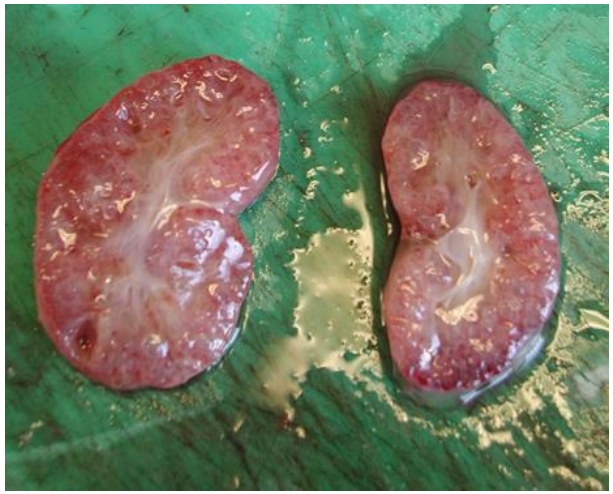
Meckel syndrome type 2 (MKS2) *TMEM216*

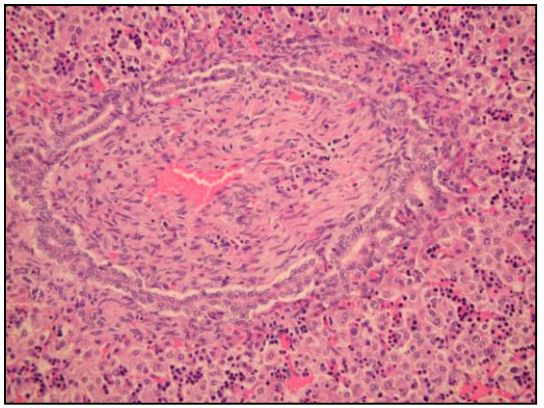




- **Anencephaly**
- Cardiac defect
- Diffuse cystic renal dysplasia
- Ductal plate malformation
- Adult type adrenal hypoplasia







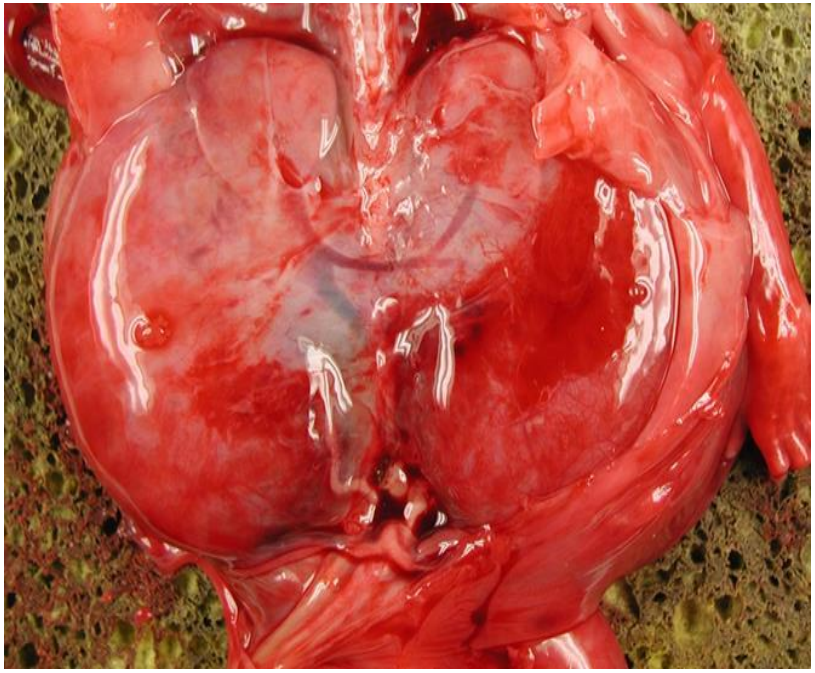
Renal-Hepatic-Pancreatic dysplasia 1 - MKS7

NPHP3 gene

Renal-Hepatic-Pancreatic dysplasia 2

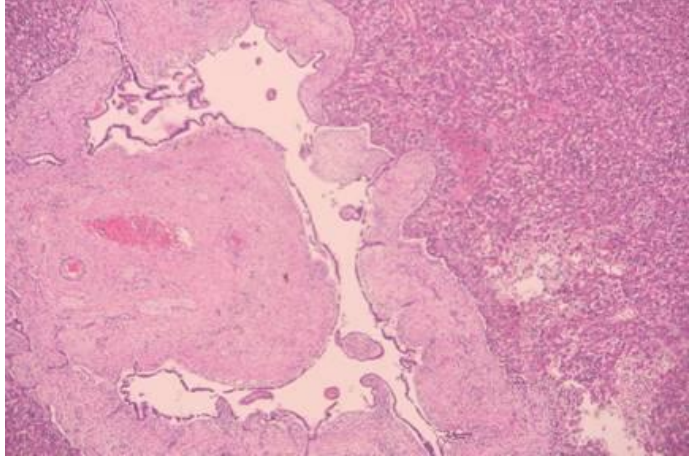
NEK8 gene

both are ciliary genes

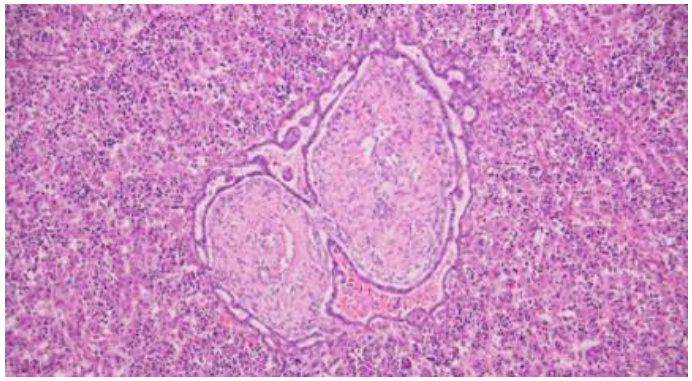


Massive enlargement of kidneys

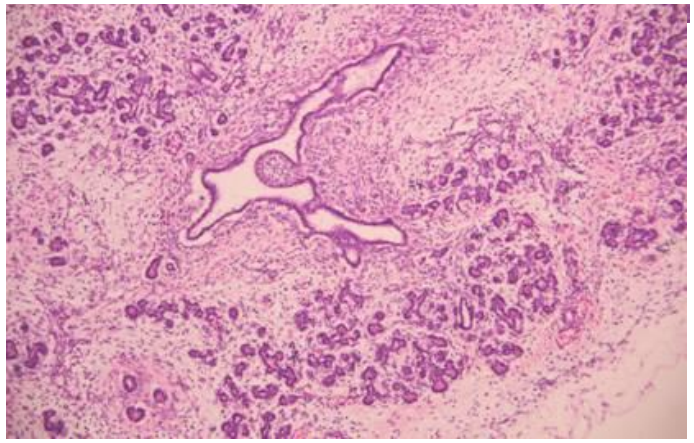
Histology: diffuse multicystic dysplasia Meckel-type



Liver: portal fibrosis



Liver: ductal plate malformation



Pancreas: ductal malformation

Joubert syndrome and related disorders (JSRD)

Renal disease: cystic renal dysplasia and nephronophthisis (tubulointerstitial nephritis and cysts at the cortico-medullary junction).

molecular genetics of JSRD includes eight mutations in the ciliary/ basal body genes: *INPPFE, AH11, NPHP1, CEP290, **TMEM67/MKS3**, RPGR1P1L, ARL13B, and CC2D2A*

Bardet–Biedl syndrome

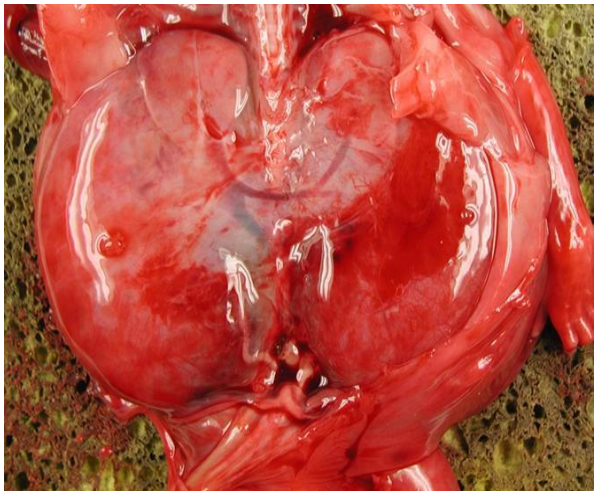
Renal disease: Renal dysplasia

Histologically,

the kidneys show extensive replacement of parenchyma by round cysts lined by flat to cuboidal epithelium [27].The glomeruli are preserved. Persistent fetal lobulations have been described suggesting a defect in renalmaturation.

At the present time, 18 genes have been associated with Bardet–Biedl syndrome: *BBS1, BBS2, ARL6 (BBS3), BBS4, BBS5, MKKS (BBS6), BBS7, TTC8 (BBS8), BBS9, BBS10, TRIM32 (BBS11), BBS12, MKS1 (BBS13), CEP290 (BBS14), WDPCP (BBS15), SDCCAG8 (BBS16), LTZFL1 (BBS17), and BBIP1 (BBS18).*

Renal-Hepatic-Pancreatic Dysplasia (RHPD) and Asplenia/Polysplenia
(Ivemark 2)



Renal disease: Diffuse cystic renal dysplasia
The kidneys in RHPD and polysplenia tend to be grossly more solid than kidneys with typical diffuse multicystic dysplasia Meckel-type.

NPHP3 gene (Meckel type7)
NEK8 gene

Short Rib Skeletal dysplasias

Renal disease: non specific cysts, cystic renal dysplasia Meckel-type, nephronophthisis

12 genes to date on OMIM

SRTD1 mapped to chromosome 15q13. SRTD2 (611263), caused by mutation in the IFT80 gene on chromosome 3q; SRTD3 (613091), caused by mutation in the DYNC2H1 gene (603297) on chromosome 11q; SRTD4 (613819), caused by mutation in the TTC21B gene (612014) on chromosome 2q24; SRTD5 (614376), caused by mutation in the WDR19 gene (608151) on chromosome 4p14; SRTD6 (263520), caused by mutation in the NEK1 gene (604588); SRTD7 (614091), caused by mutation in the WDR35 gene (613602); SRTD8 (615503), caused by mutation in the WDR60 gene (615462); SRTD9 (266920), caused by mutation in the IFT140 gene (614620); SRTD10 (615630), caused by mutation in the IFT172 gene (607386); SRTD11 (615633), caused by mutation in the WDR34 gene (613363); and SRTD13 (616300), caused by mutation in the CEP120 gene (613446).

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

Infantile ARPKD

6p21-6p12 *PKHD1*

(Polycystic kidney-Hepatic disease)

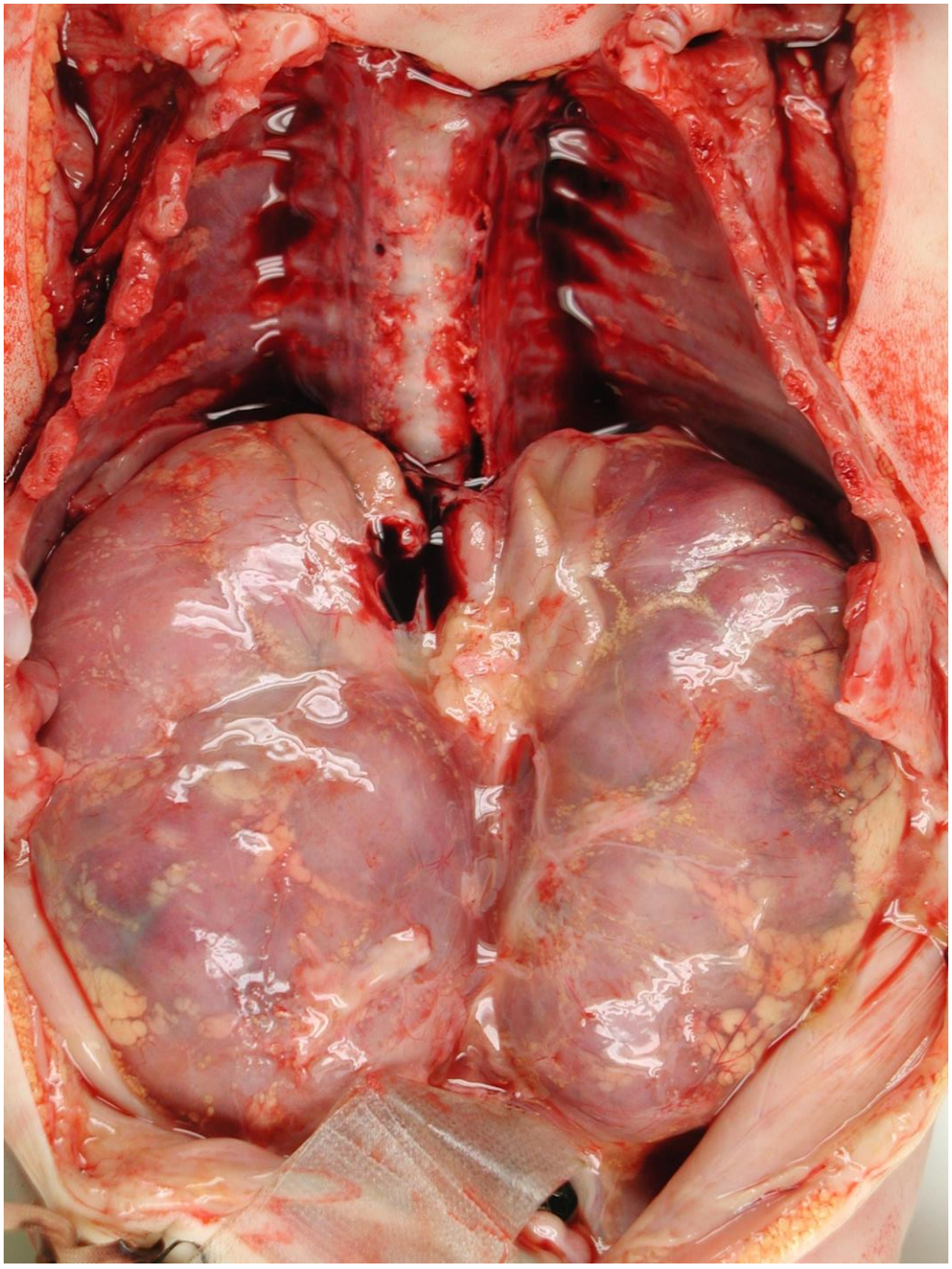
protein product: Fibrocystin

Classic form:

Stillbirth or early neonatal death due to pulmonary hypoplasia

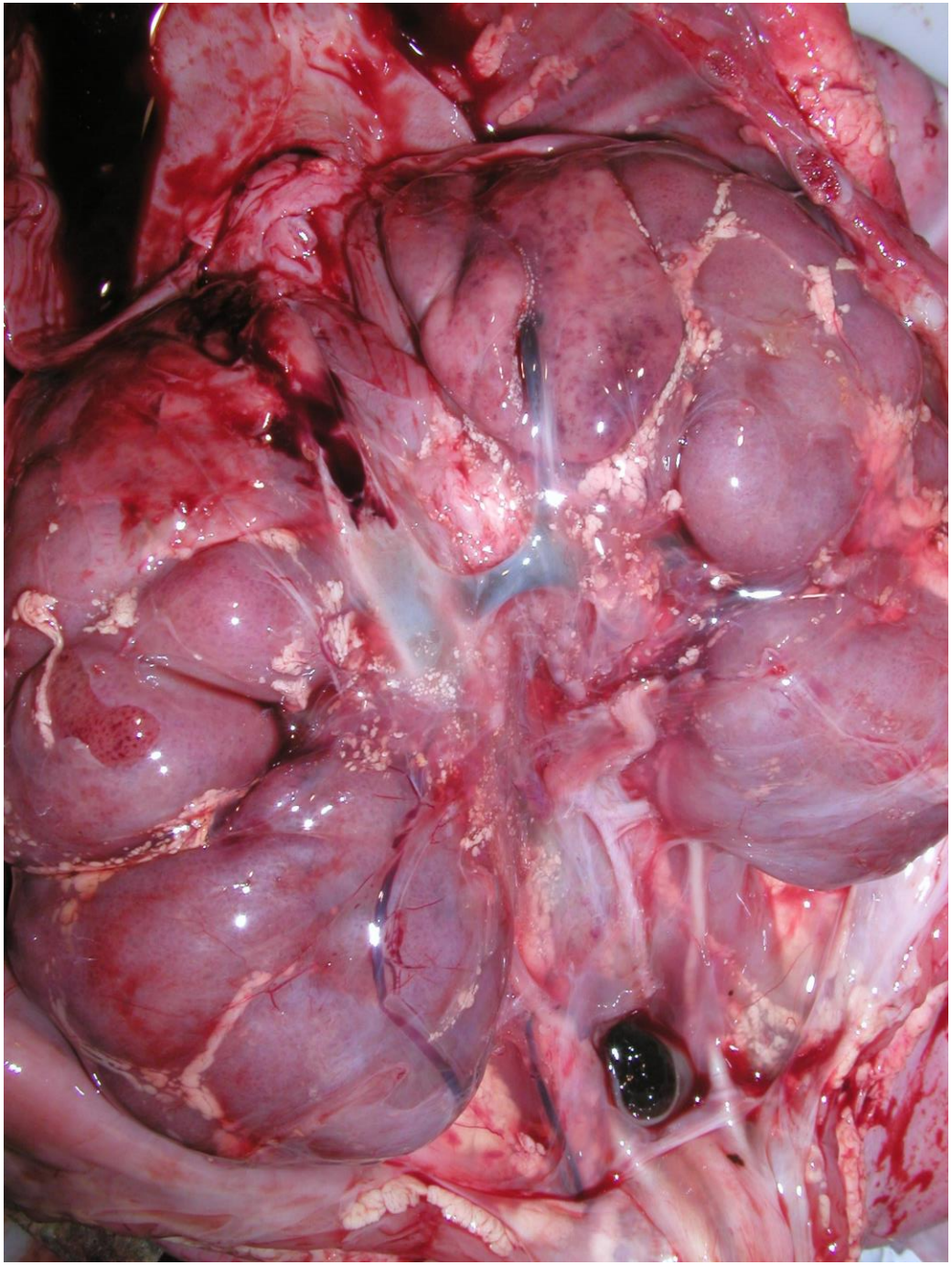
ARPKD associated with hepatic fibrosis:

clinically apparent in children even young adults

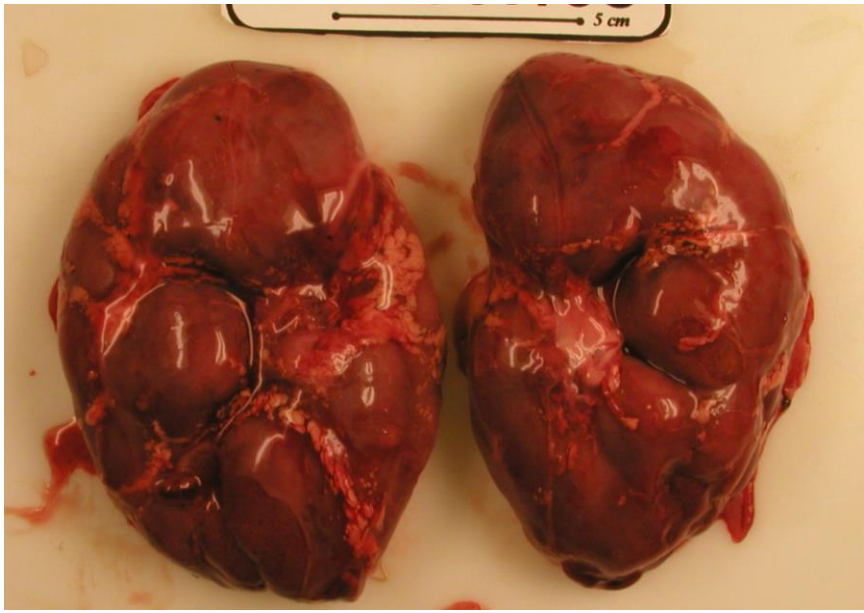


ARPKD

always bilateral involvement

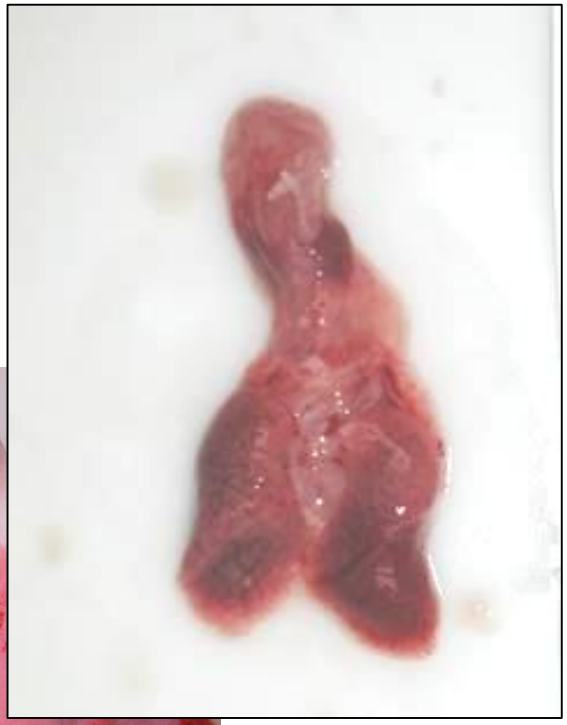


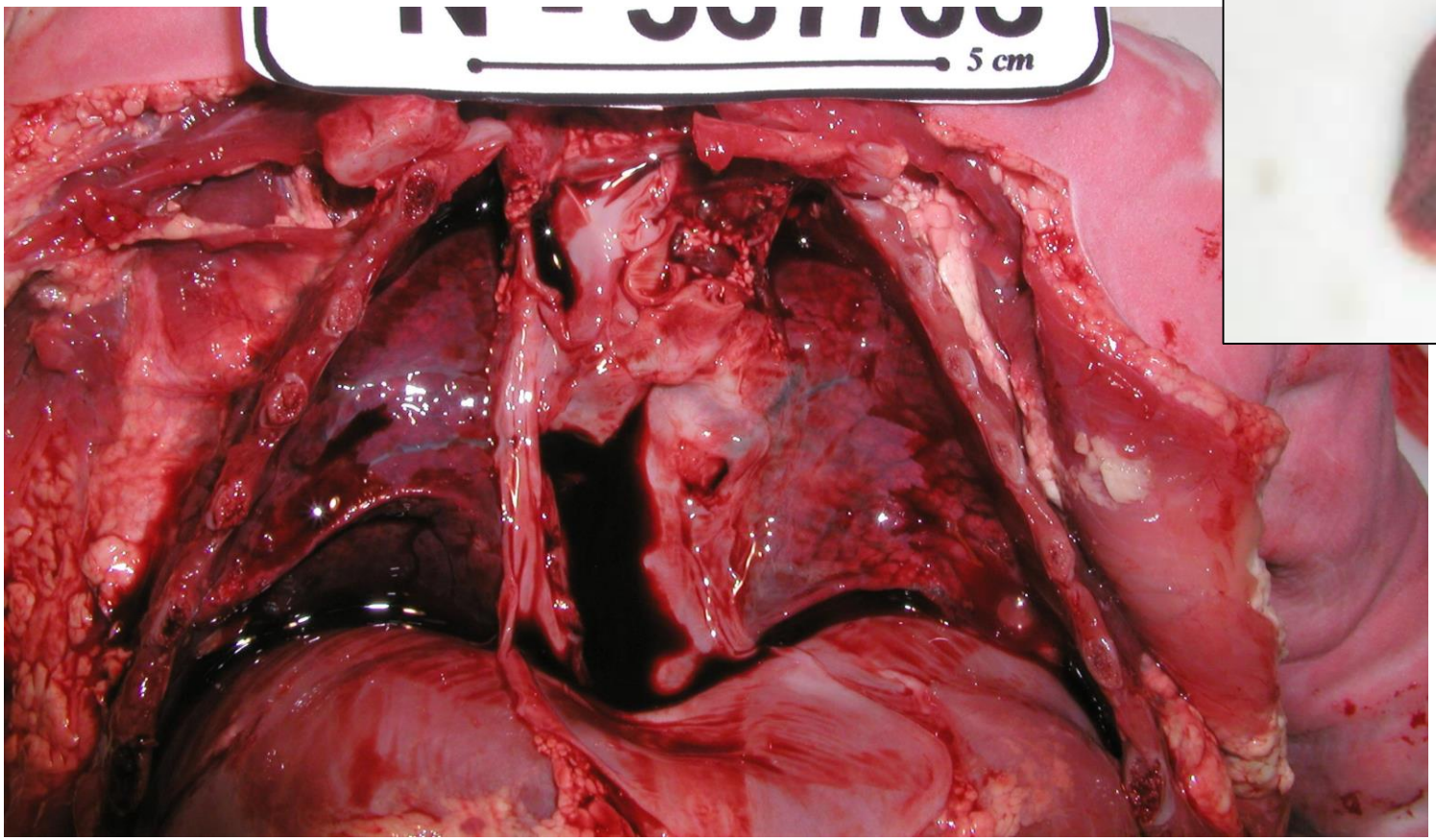
ARPKD



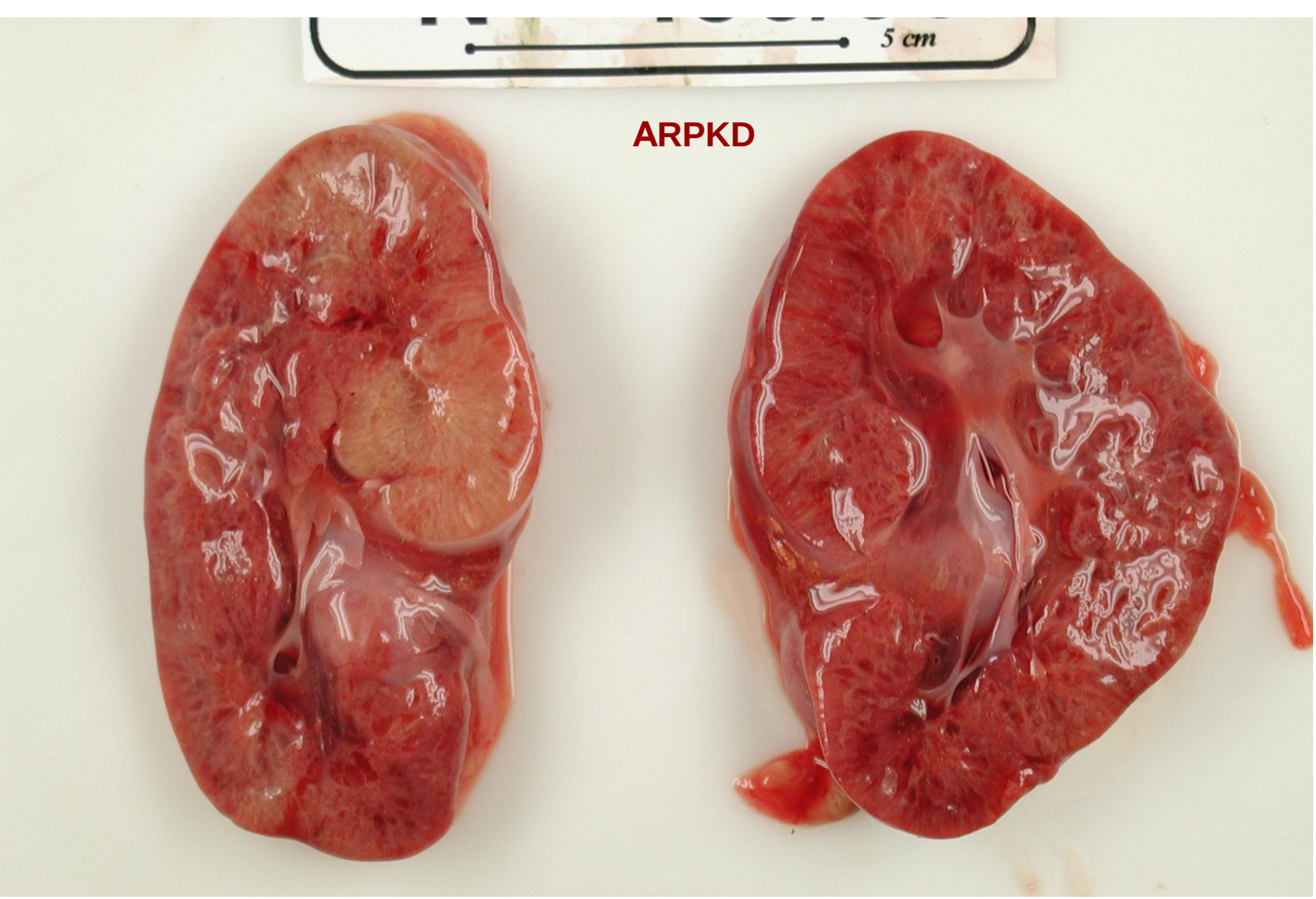
fetal lobulation prominent

ARPKD





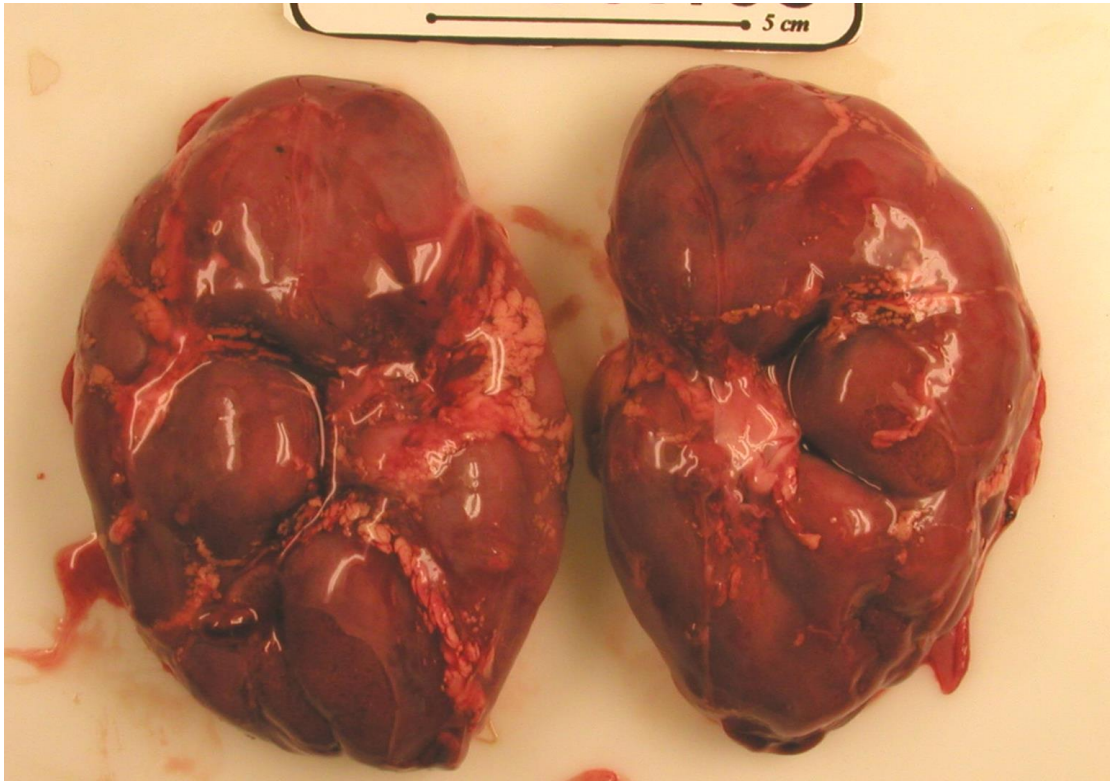
Pulmonary hypoplasia

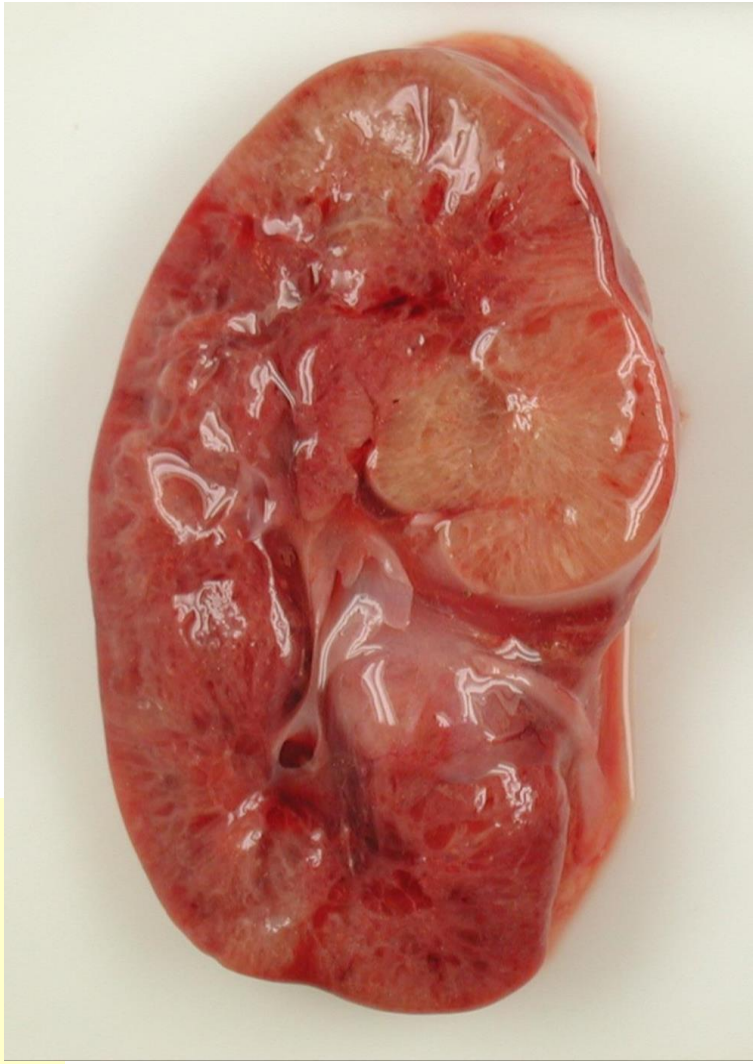


Cut surface: innumerable minute cysts

Sponge-like cut surface, fixed
Fusiform, radially oriented cysts in the cortex, round in deeper parts

ARPKD





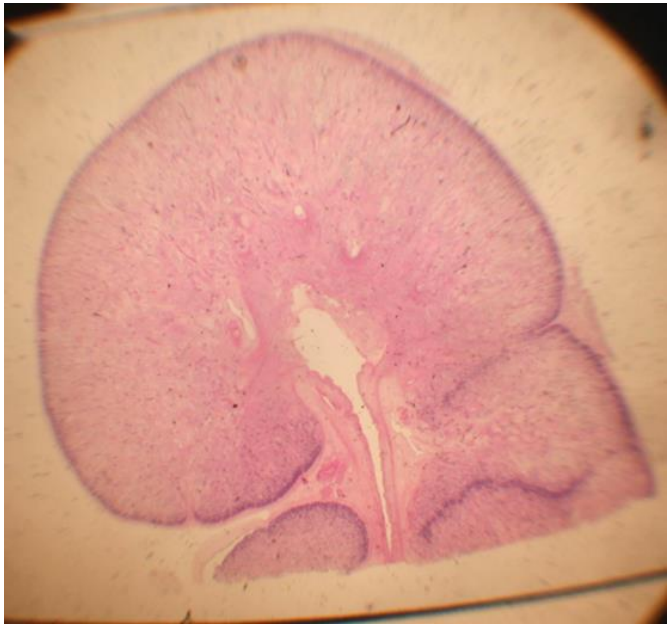
- bilateral massive enlargement – abdominal distention
- reniform shape preserved – accentuated fetal lobation
- minute innumerable radially oriented cysts (mm)
- cysts appear fusiform in the cortex – round in the medulla
- cortico-medullary border attenuated

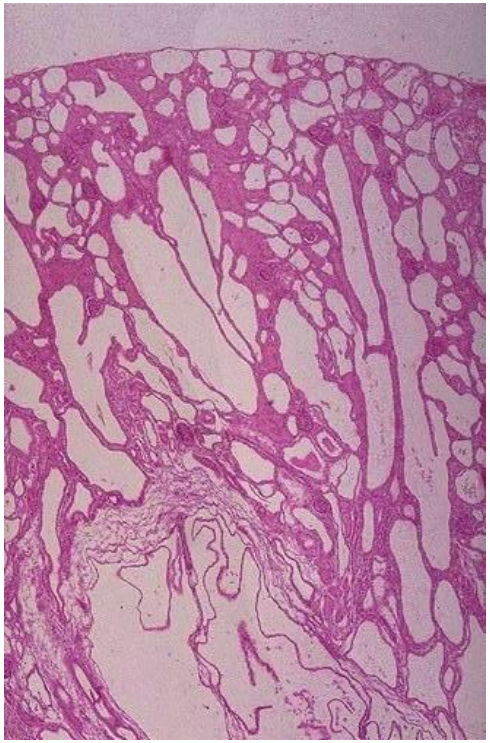
- **normal ureters**

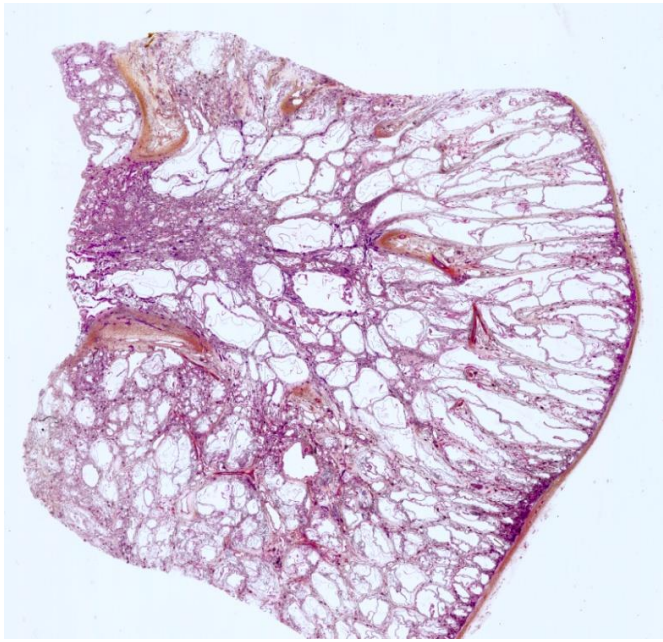
ARPKD

Histology

Potter type I (infantile)



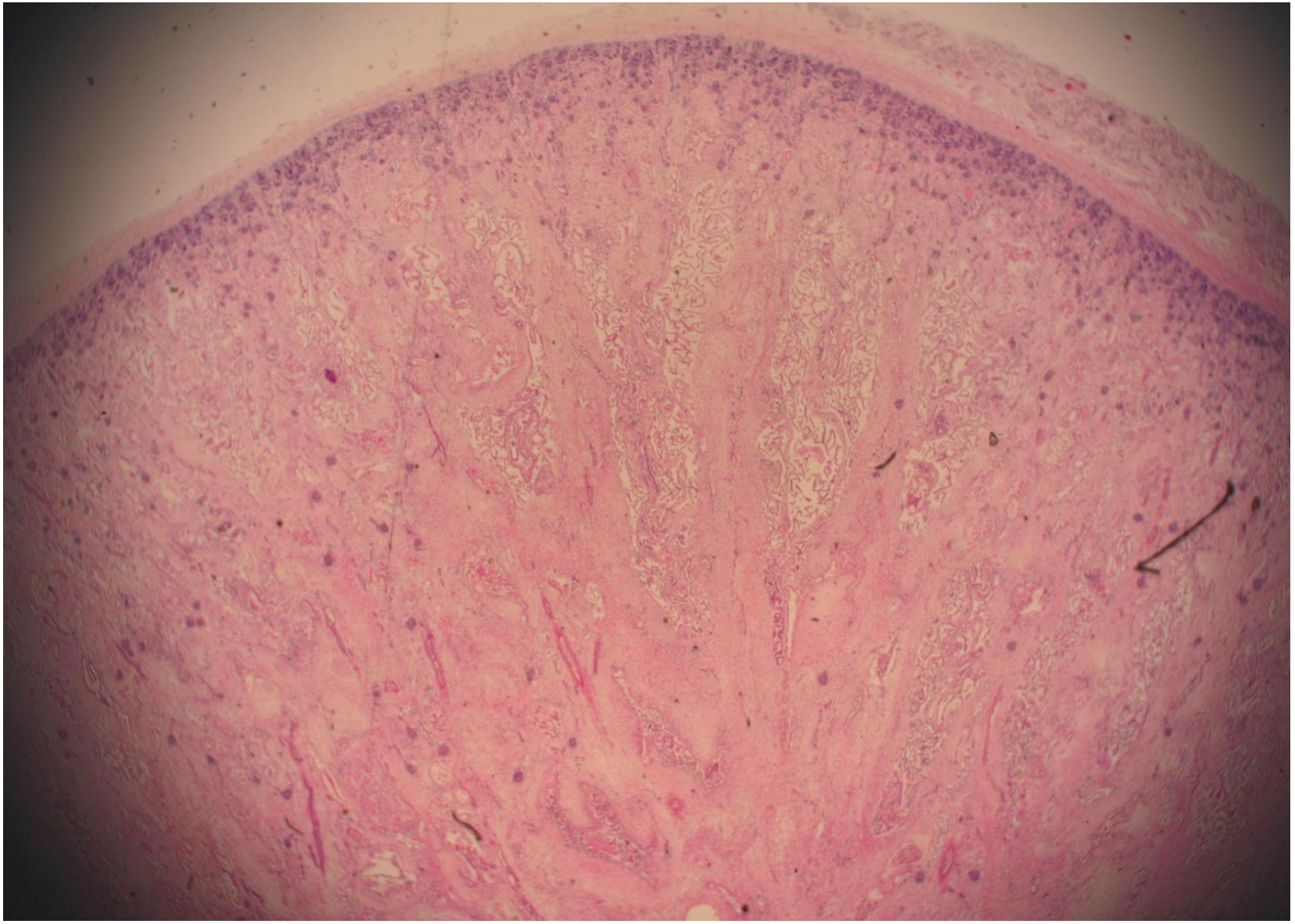




http://library.med.utah.edu/WebPath/RENAHTML/RENAL041.html

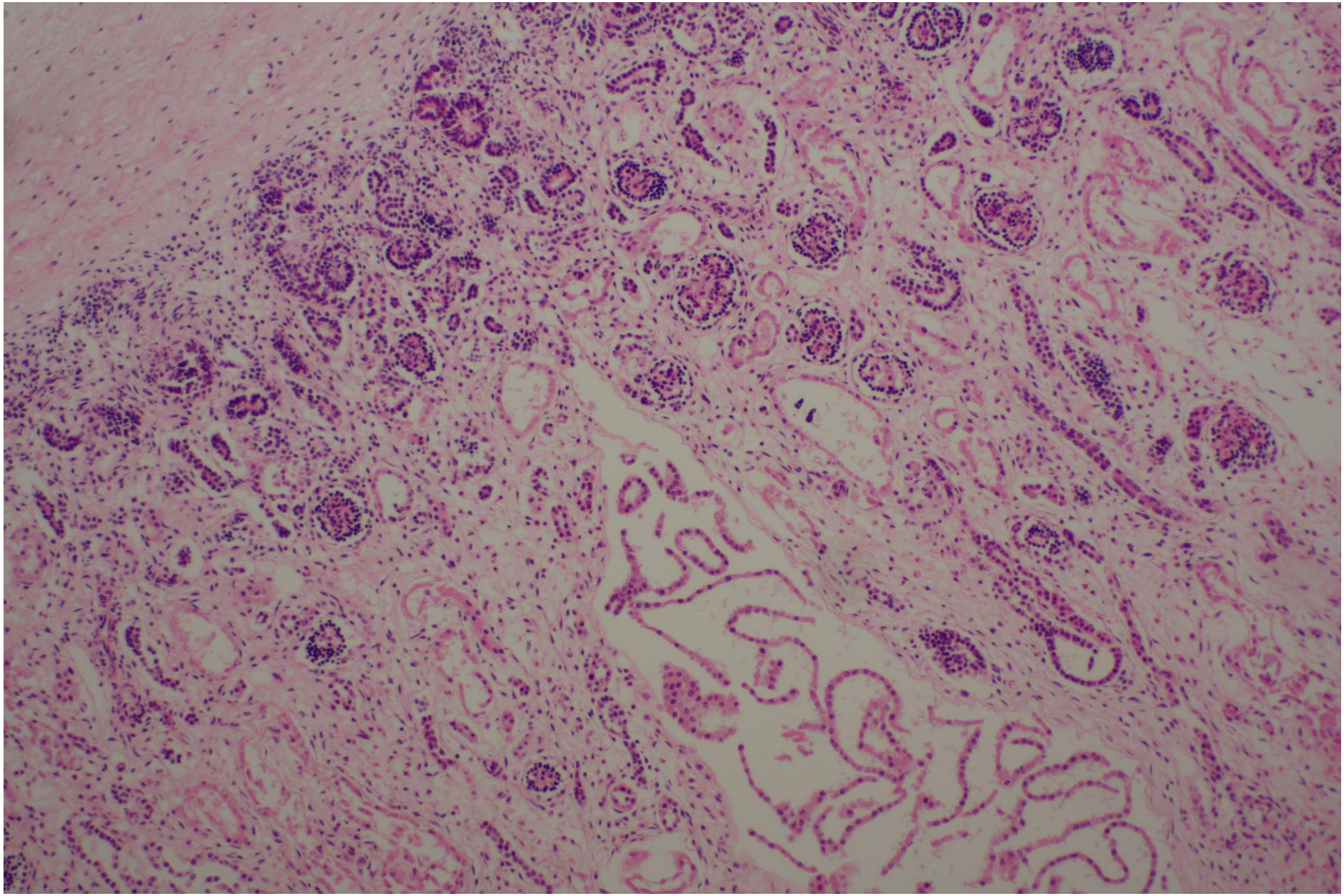
- Cystically dilated collecting ducts
- Glomerular cysts are rare (d.d. ADPKD)
- The cysts appear fusiform in the cortex (cuboid epithelium) and round towards the medulla (flattened epithelium)
- Normal nephrones separated by the cysts and interstitial oedema
- Increased connective tissue in the medulla

ARPKD

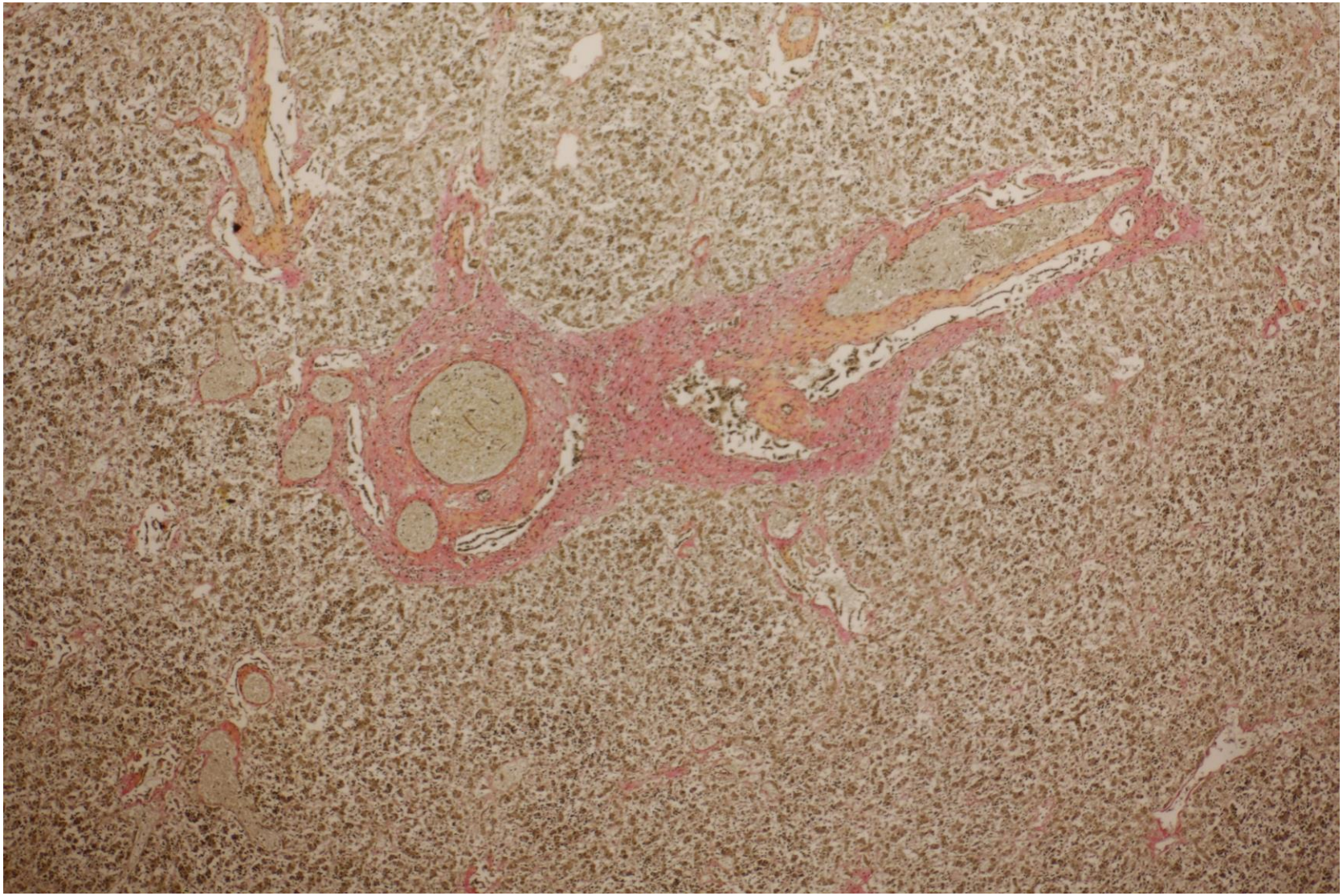


- Elongated, cigar-shaped cysts
- Nephrones and tubules are normal, although may appear decreased.

ARPKD



ARPKD

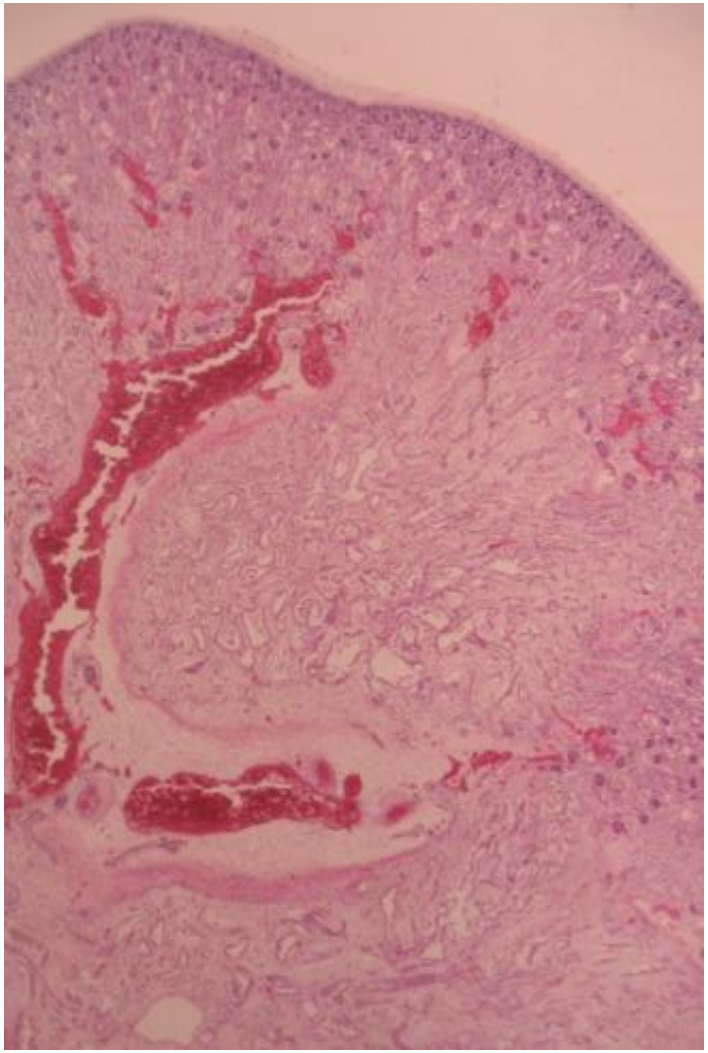


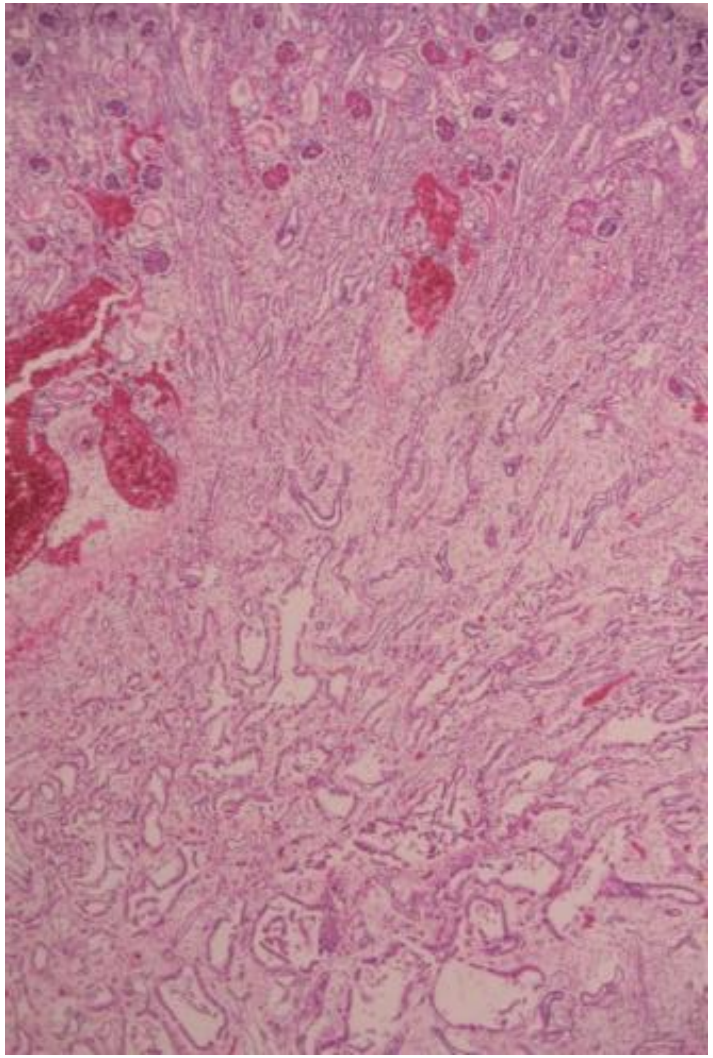
Ductal plate malformation

ARPKD

19/40w

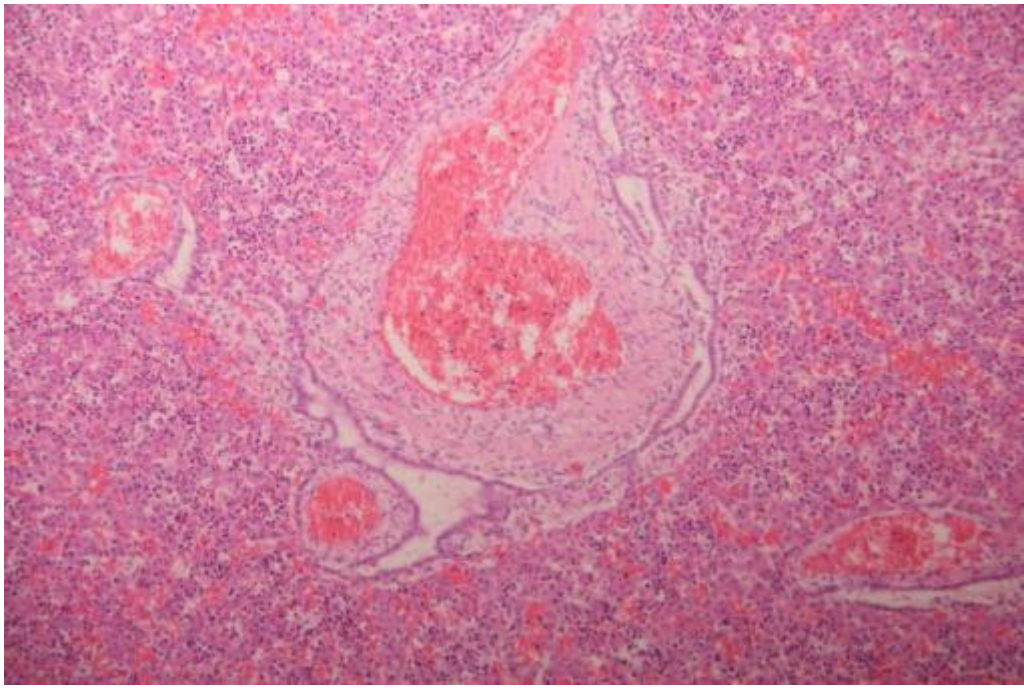
Early cystic changes in ARPKD



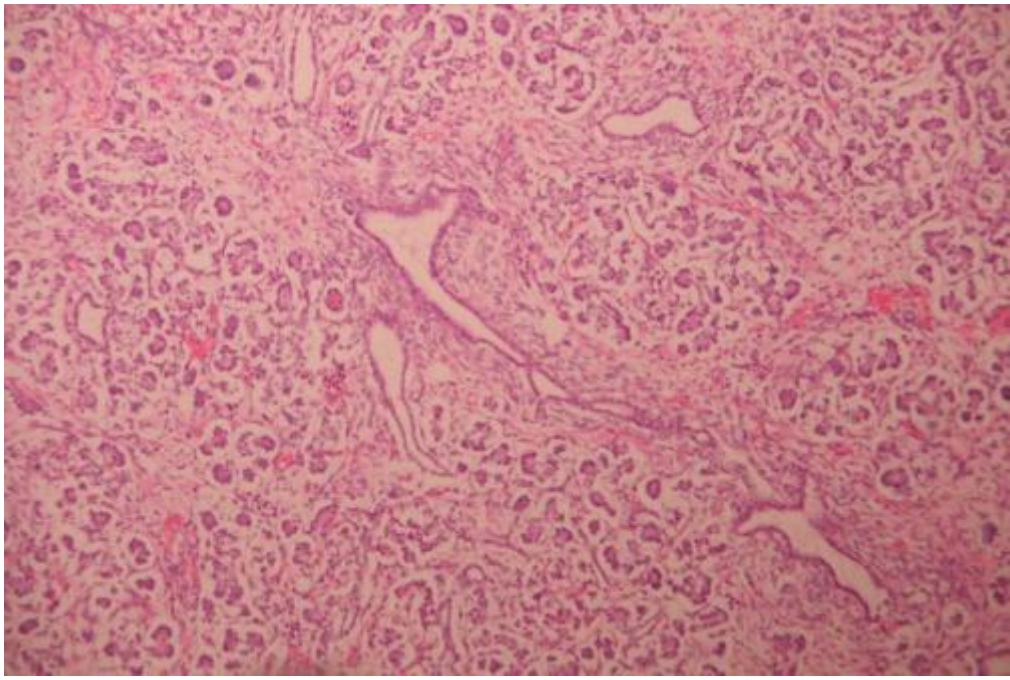


Early cyst formation in the medulla/pyramids and some mild cystic dilatation of renal tubules in the cortex.

- Ductal plate malformation of liver



- Cystic dilatation of pancreatic ducts



Potter type III

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Classic: common **Perinatal:** very rare

PKD1 – polycystin 1: wide phenotypic variability including clinical presentation *in utero.*

PKD2 – polycystin 2: slower rate of disease progression

PKD3

The marked phenotypic variability in ADPKD reflects the effects of different mutations of the same gene, mutations in different genes, or influences of other genetic or environmental factors on the expression of the mutated genes.

PKD1: 46 exons – large transcript and complex gene region

ADPKD

"Of 83 reported cases of ADPKD presenting in utero (excluding termination of pregnancy) or in the first few months of life, three were stillborn, 27 died <1 month of pulmonary or renal insufficiency or both, and six died <1 year of renal failure. Perinatal mortality in this group is therefore high, as a total of 43% died before 1 year.

Longitudinal follow up of 24 children in two studies showed that 67% of survivors developed hypertension, of whom three had end stage renal failure at a mean age of 3 years».

JMed Genet 1998;35:13-16

Fetal PM:

- (Generalised oedema)
- (Distended abdomen)
- Enlarged or normally sized kidneys
- Normal bladder and ureters
- On section: multiple cysts (1 – 10mm)
- Bilateral or unilateral involvement

Histology:

- Glomeruli predominantly affected
- Form of glomerulocystic disease
- Round glomerular and some tubular cysts

- Normal liver histology

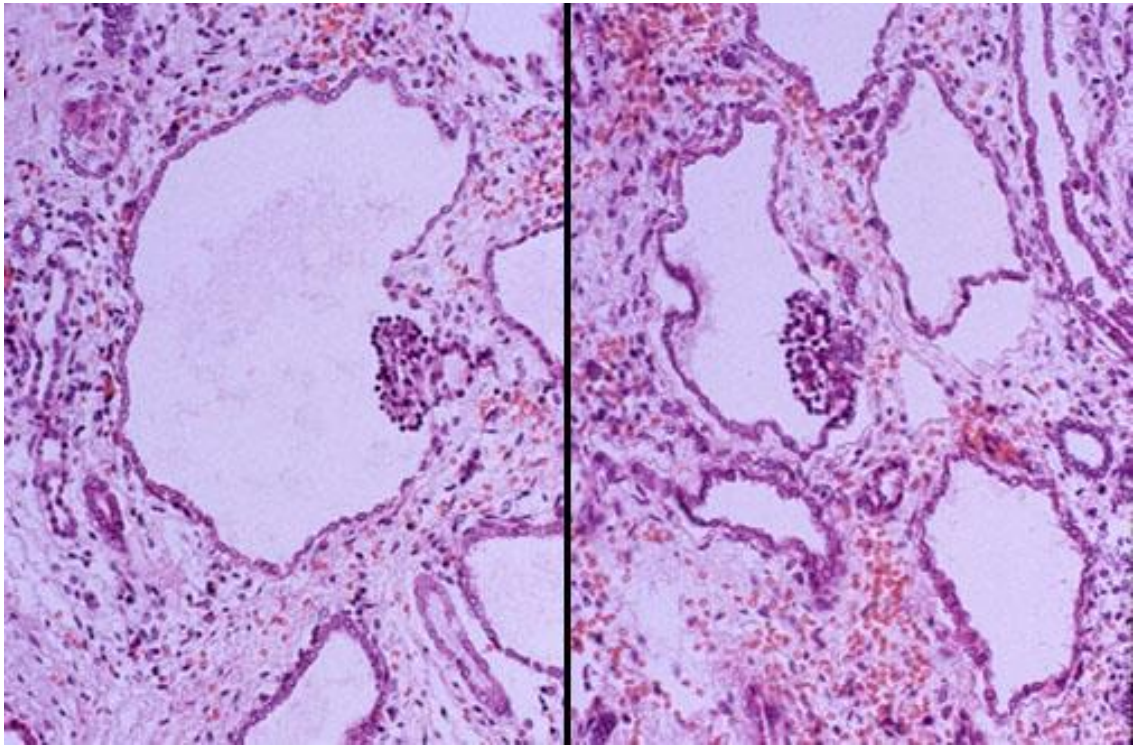
USS: earliest at 14 weeks showed bilaterally enlarged echogenic kidneys with several small cysts.
20-22w: oligohydramnios

Michaud J et al. Autosomal dominant polycystic kidney disease in the fetus. Am J Med Genet. 1994 Jul 1;51(3):240-6.

MacDermot, KD et al. JMed Genet 1998;35:13-16

Glomerular cysts

Dilatation of Bowman's capsule with glomerular shrinkage



Occur in:

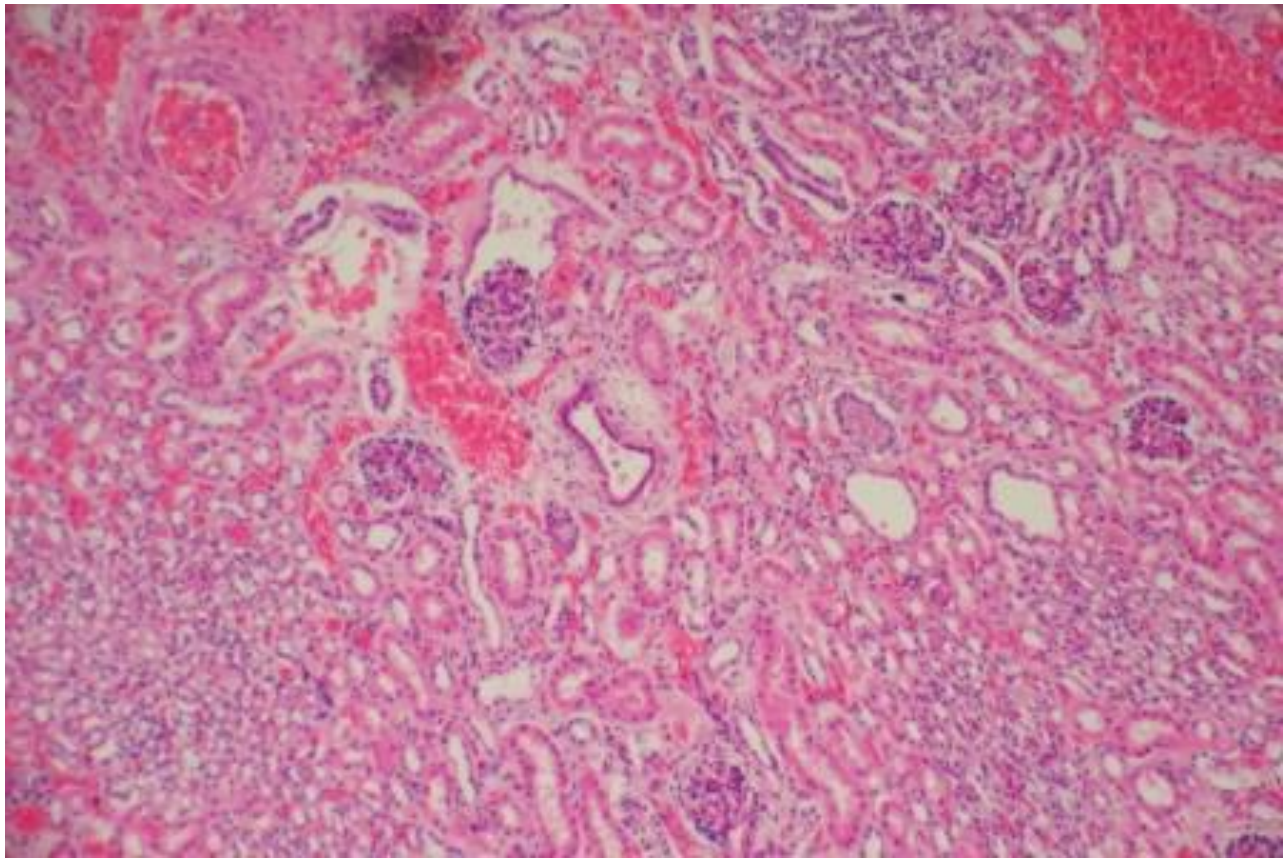
- Renal dysplasia
- ADPKD
- Hereditary syndromes
- Chromosomal (tris13)
- Sporadic cases

Prominent in:

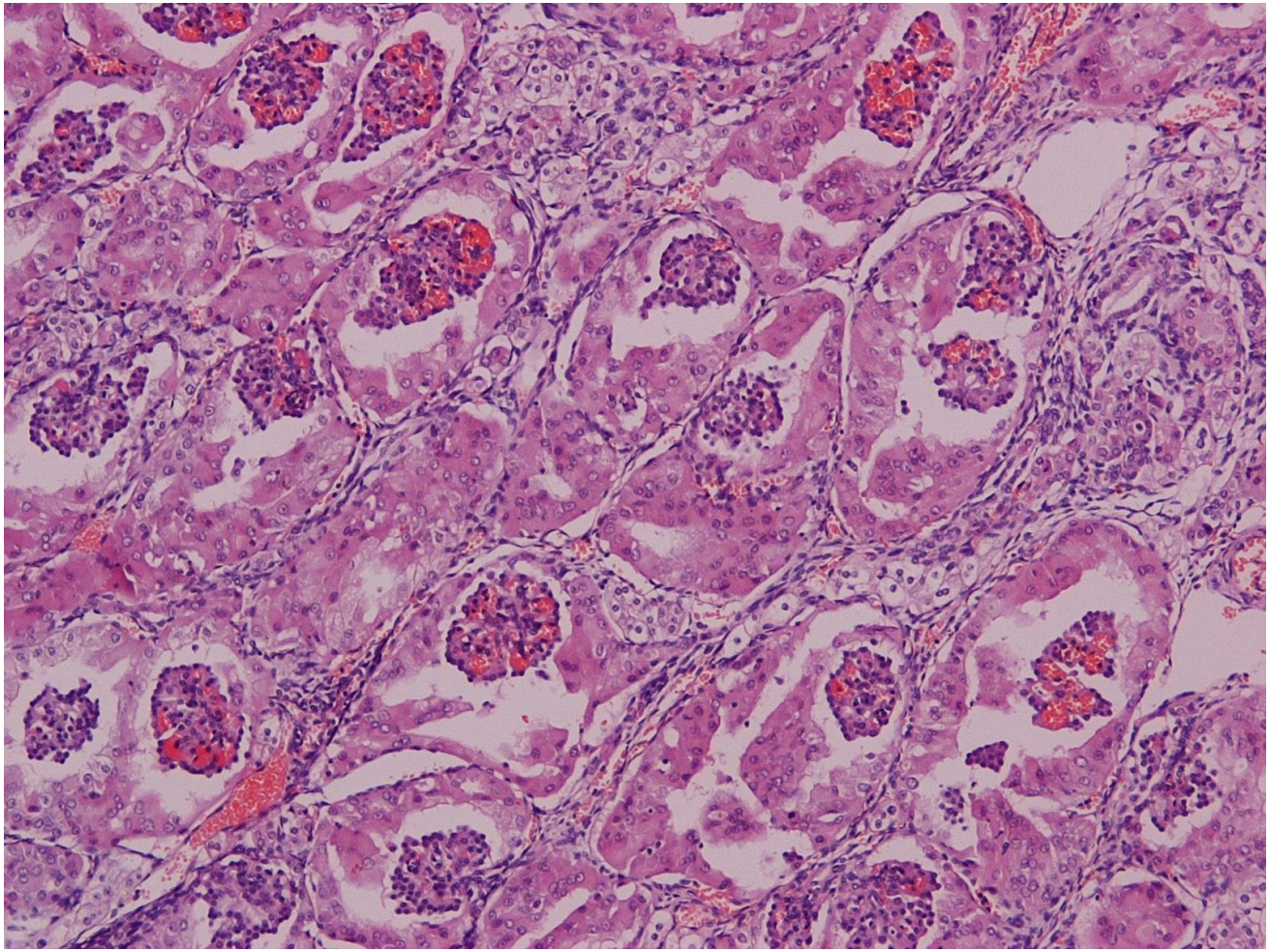
- Early-onset ADPKD
- Zellweger syndrome
- Glutaric Aciduria type II
- SRP II and Oro-facio-digital syndrome (OFD)
- Tuberous sclerosis
- von Hippel-Lindau disease

Glomerulocystic kidney

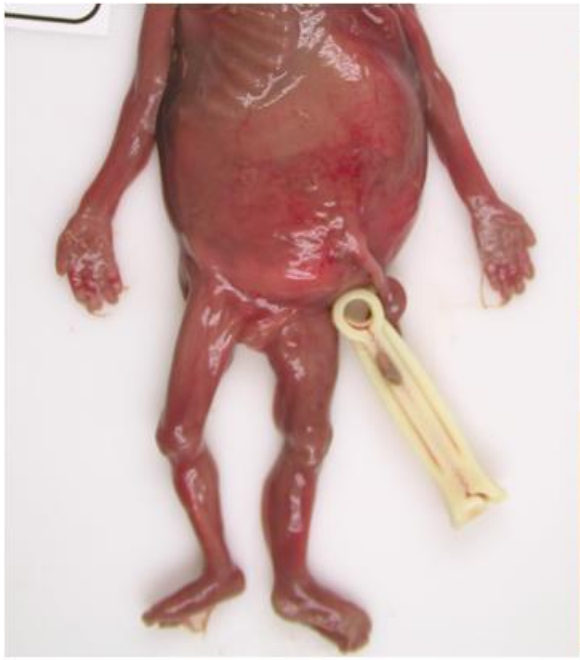
Gross: firm, small or large like in diffuse nonobstructive cystic dysplasia

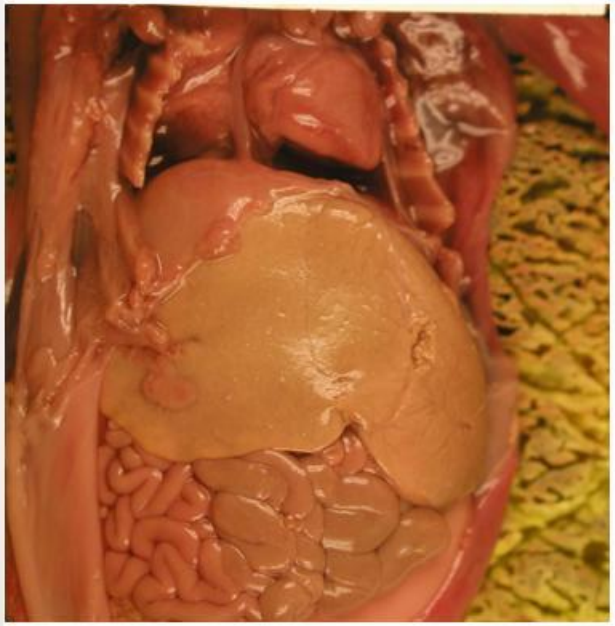


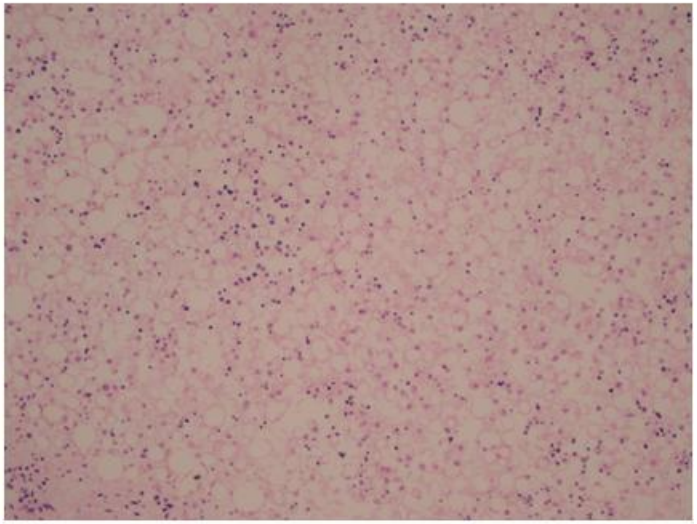
Glomerular, tubular and one primitive ductal cyst (with fibromuscular collar) are seen in this case of Zellweger syndrome.



Glomerular cysts lined by tall eosinophilic epithelium in Tuberous Sclerosis.

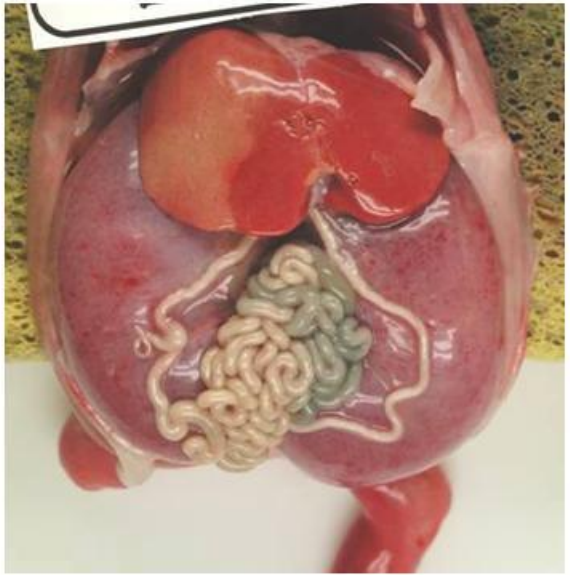


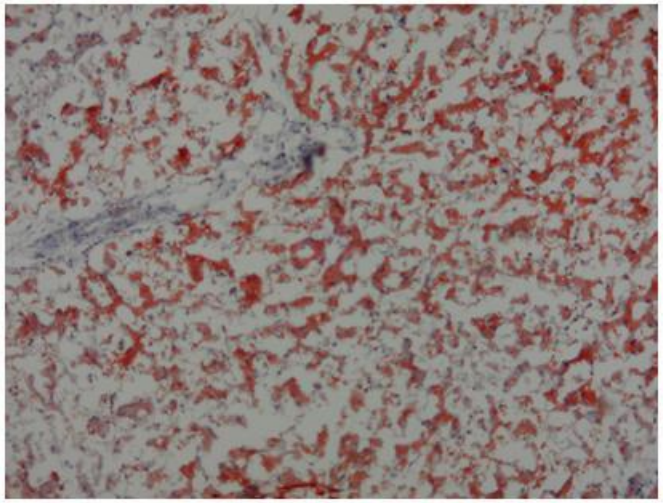




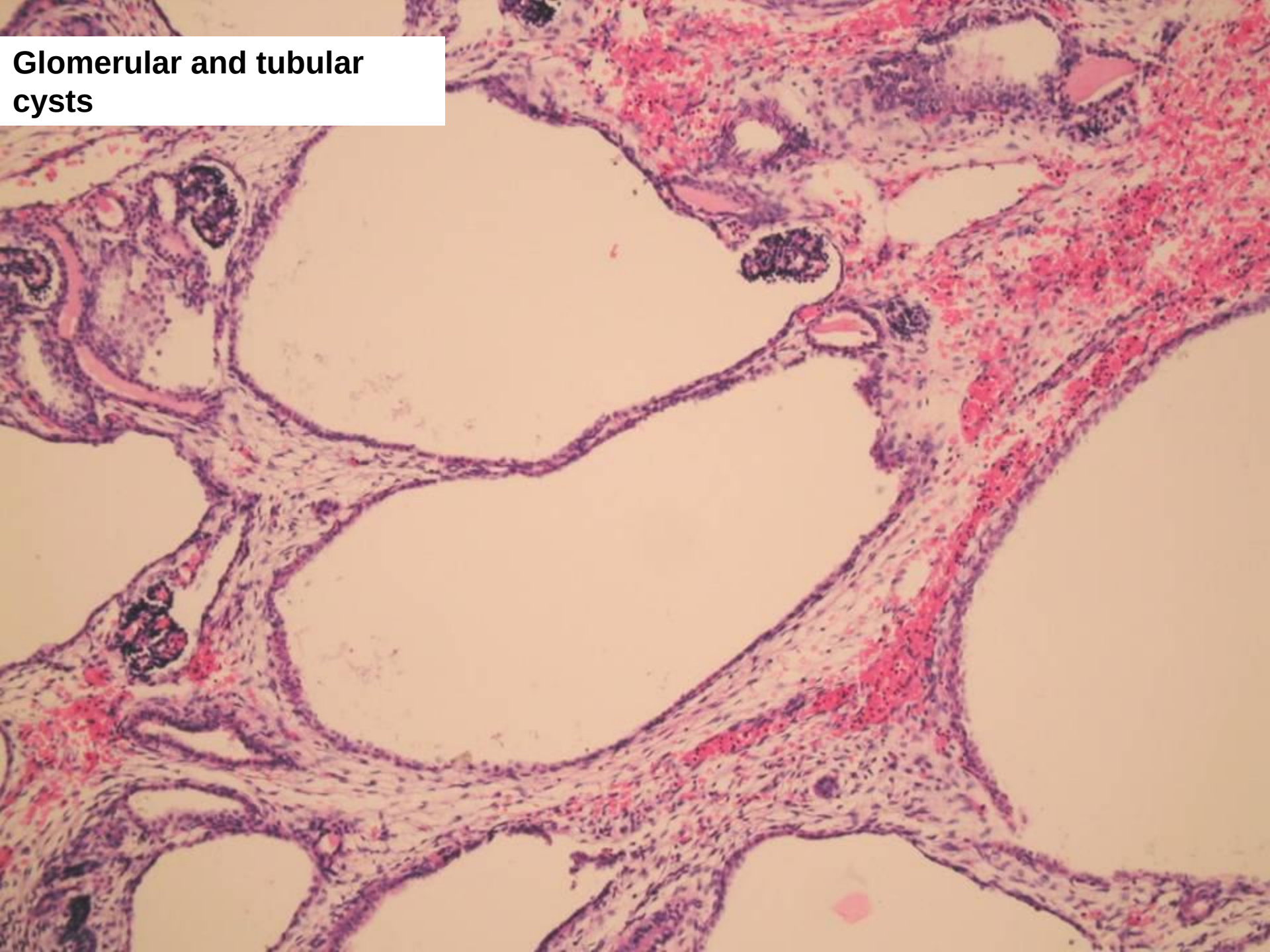
Massive renal enlargement

Fatty liver indicating metabolic disease

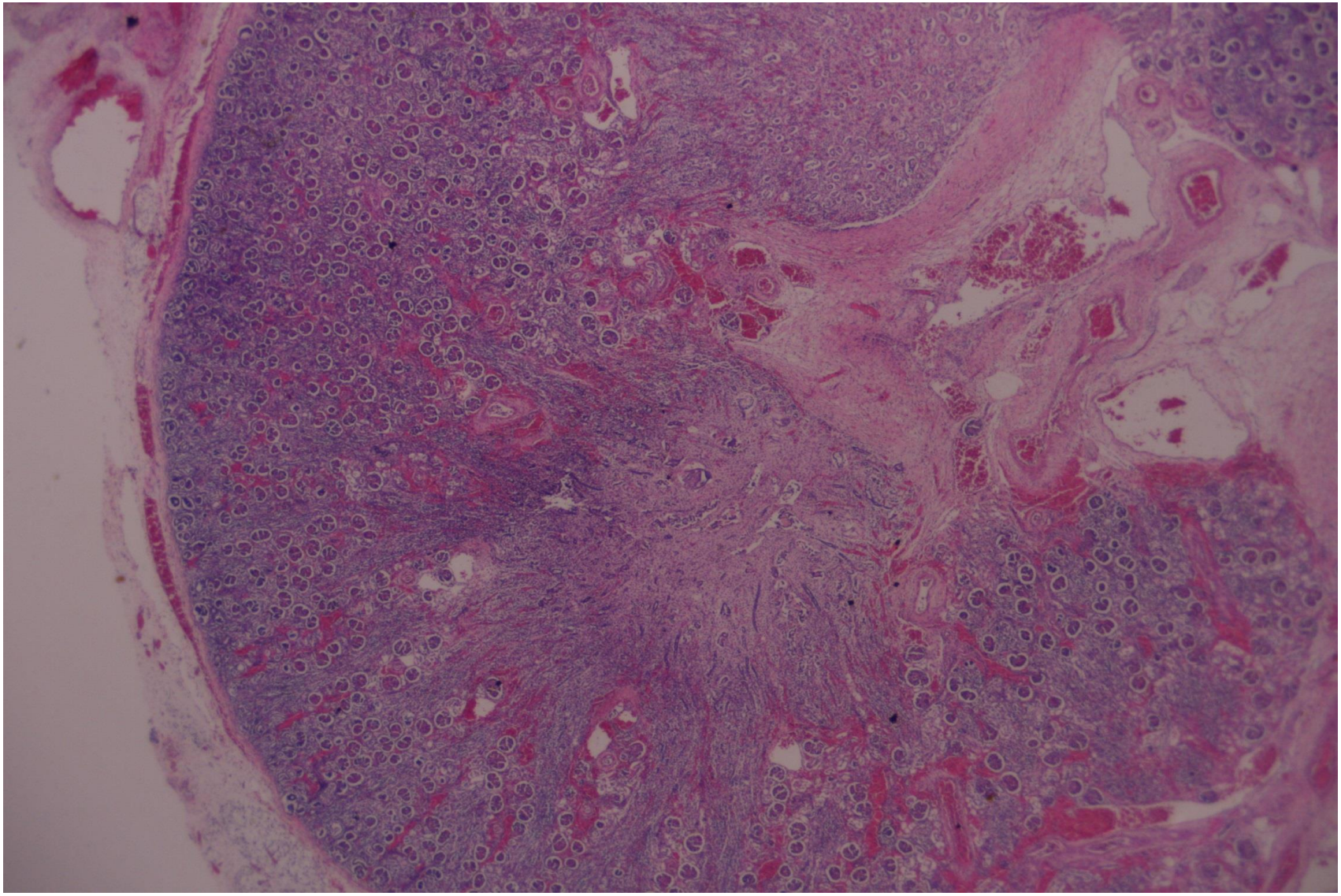




Glomerular and tubular cysts

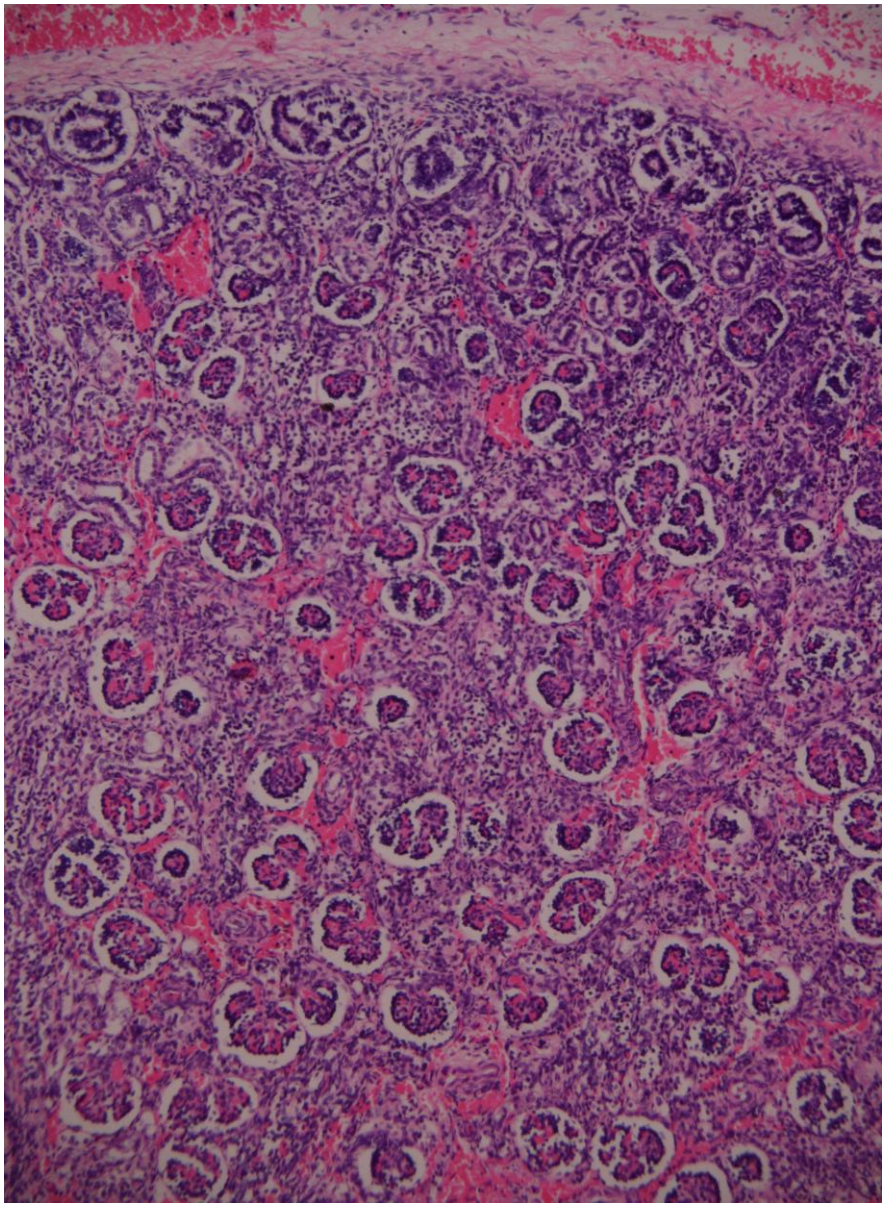


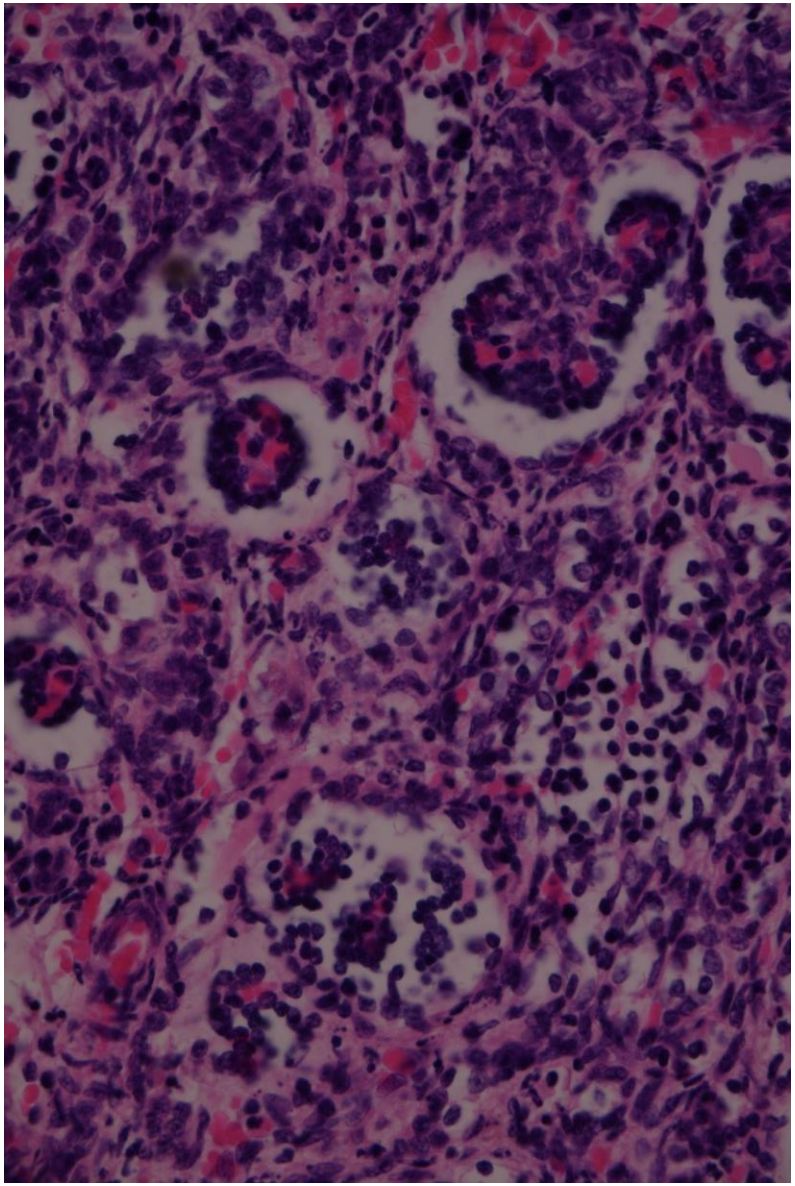
Renal Tubular Dysgenesis



microcystic change
tubular dilatation

Renal Tubular Dysgenesis





absence of proximal tubules

Simple cortical cysts or microcysts

Obstructive (Potter IV)

Simple cysts (cortical, medullary)

- Common in adults, extremely rare in neonates

Nonspecific cortical or corticomedullary microcysts

- Common in neonates, unknown etiology
- Glomerular or tubular
- Associated with chromosomal abnormalities (t18,13,21), hereditary syndromes and a large number of undetermined multiple malformation syndromes (“syndromic cysts”)
- Undetermined clinical significance

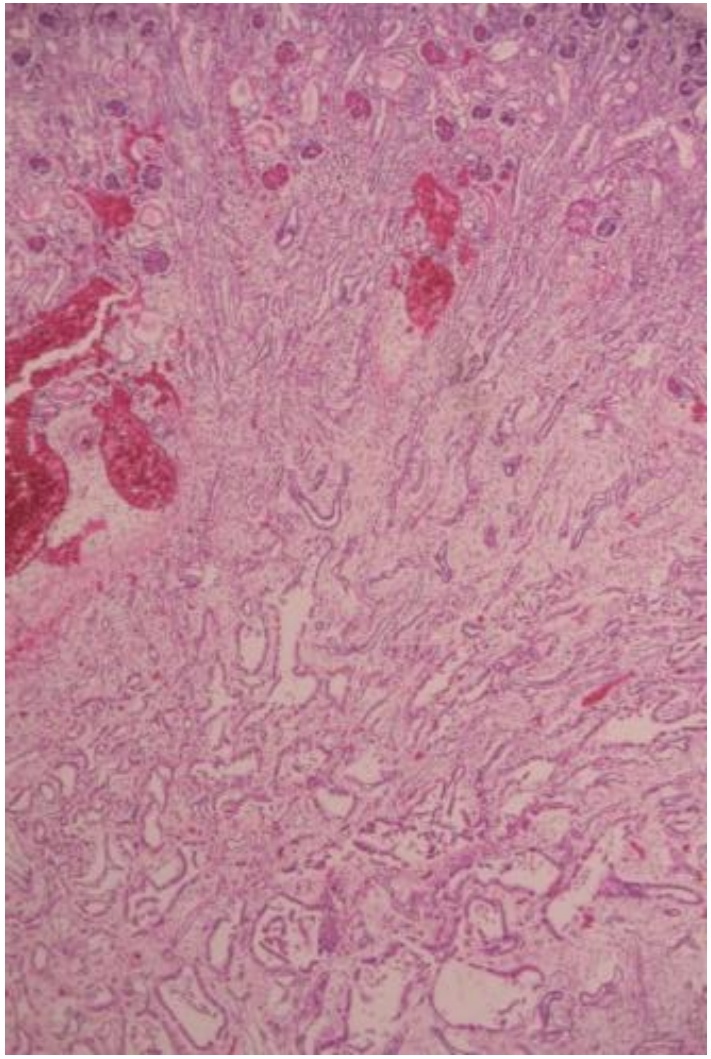
Medullary cysts

Late onset disease:
Medullary cystic kidney disease, Familial nephronophthisis and Medullary sponge kidney

In the fetal kidney:

Diffuse cystic dilatation of collecting ducts including those of the medulla are likely to represent ARPKD.

Scattered nonspecific medullary or corticomedullary microcysts may be seen in syndromes associated with medullary cystic changes (e.g. nephronophthisis and tubulointerstitial disease in some nonlethal skeletal dysplasias/ ciliopathies), but the renal changes in the fetal kidney are non contributory.



early ARPKD

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Thank you

Phil Cox

Beata Hargitai

Tamas Marton

Birmingham Women's NHS
NHS Foundation Trust