RENAL MEDICINE

KIDNEY DISORDERS

Kenneth Alonso, MD, FACP

Embryology

- Mesonephric duct is derived from mesoderm.
- It forms as a longitudinal solid cord of tissue dorsolateral to the mesonephric tubules in the thoracic region.
- The cords grow caudally and fuse with the ventrolateral wall of the cloaca, forming the urogenital sinus.
- Subsequently canalizes.
- At 10th week it drains urine from the mesonephros.

Anatomy

- The kidneys lie below the diaphragm and are anterior to the psoas major, quadratus lumborum, and transversus abdominis muscles.
- The subcostal, ilio-inguinal, and ilio-hypogastric nerves lie posterior to the kidneys.
- Anterior to the right kidney are the liver, right colic flexure, and the 2nd portion of the duodemun.
- Anterior to the left kidney are the stomach, spleen, and splenic flexure.
- Suprarenals lie above and anterior to the kidneys.
- Innervated from T10-L1.

Renal agenesis

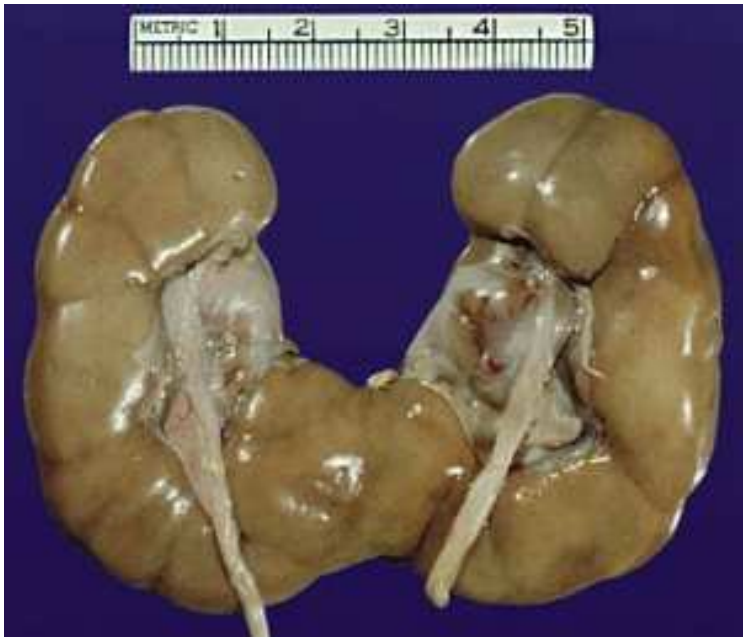
- Often bilateral
- Potter sequence
- Flattened nose
- Epicanthal folds
- Low set ears
- Defects in extremity development
- Associated with pulmonary hypoplasia
- Oligohydramnios common finding
- Diagnosis made by ultrasound examination
- ITGA8 mutation at 10p13

Renal agenesis

- May be unilateral as well
- Compensatory hypertrophy of other kidney
- Hyperfiltration at the glomerulus

- Horseshoe kidney
- Fusion of both kidneys
- Most common congenital renal abnormality
- 90% midline
- Often trapped behind inferior mesenteric artery
- Susceptible to trauma
- Predisposed to obstruction
- Frequent in those with Edwards' syndrome or trisomy 18 (67%) and Turner's syndrome (14%)

Horseshoe kidney



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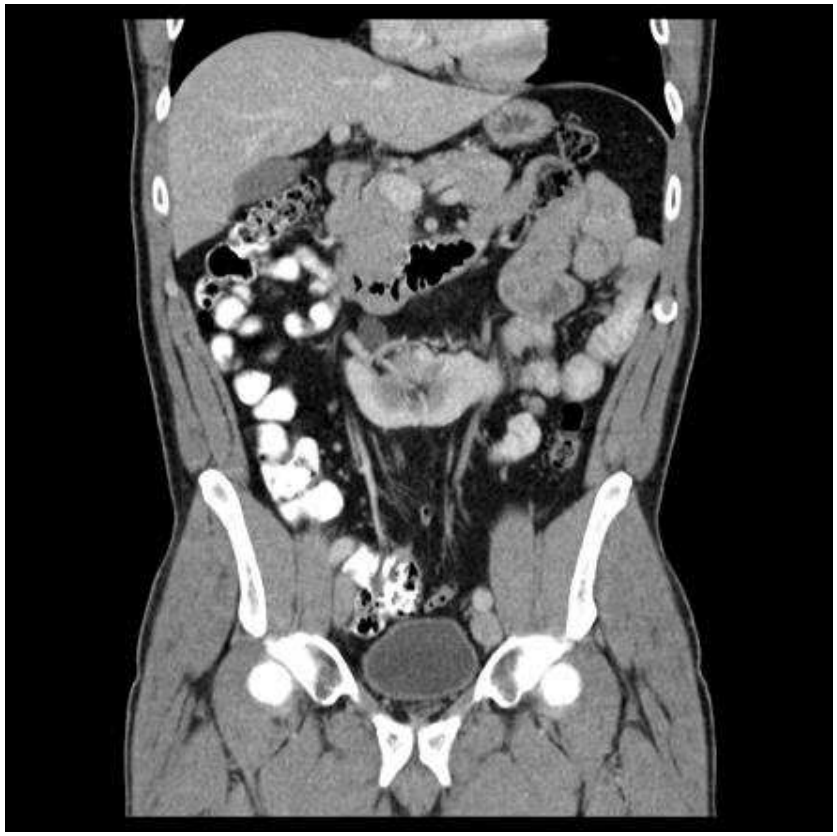

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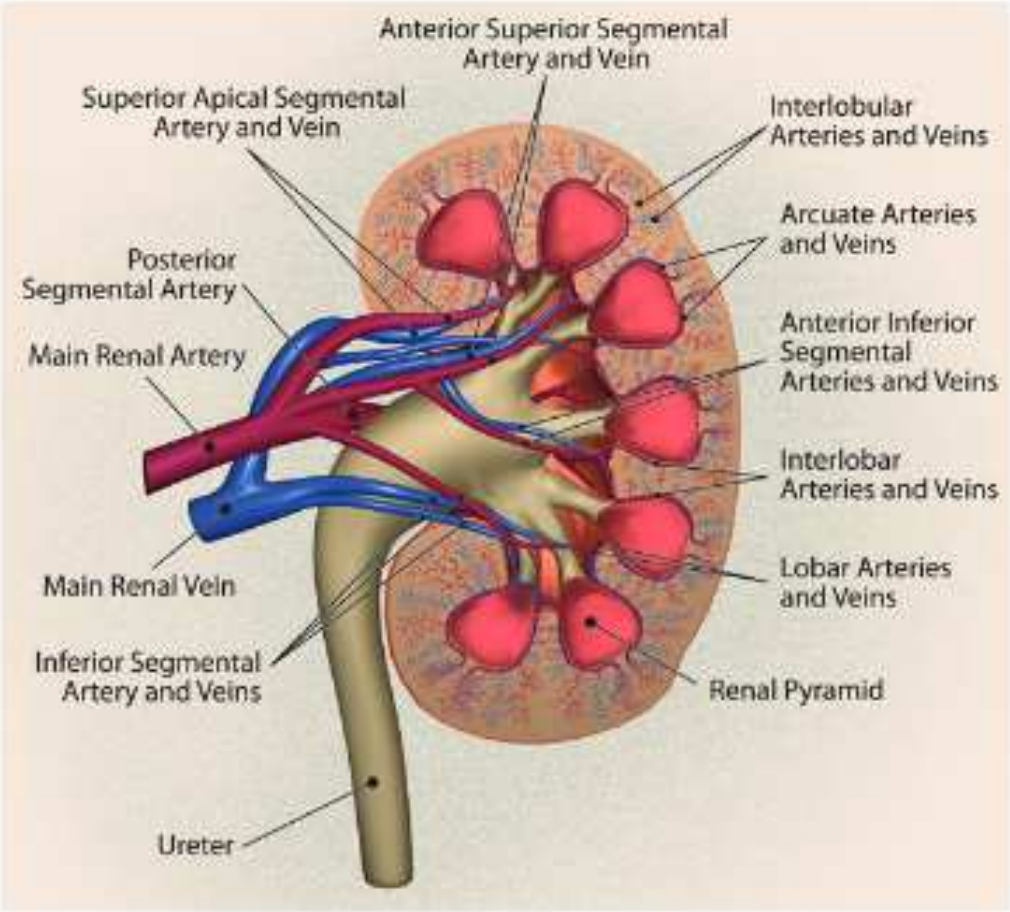
Renal vessels

- The kidney is richly supplied by blood vessels.
- The cortex receives 90% of the total renal blood supply.
- The kidney converts more than 1700 liters of blood daily into 1 liter of urine.



https://pubs.rsna.org/doi/pdf/10.1148/rg.2017160060
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RENAL CIRCULATION

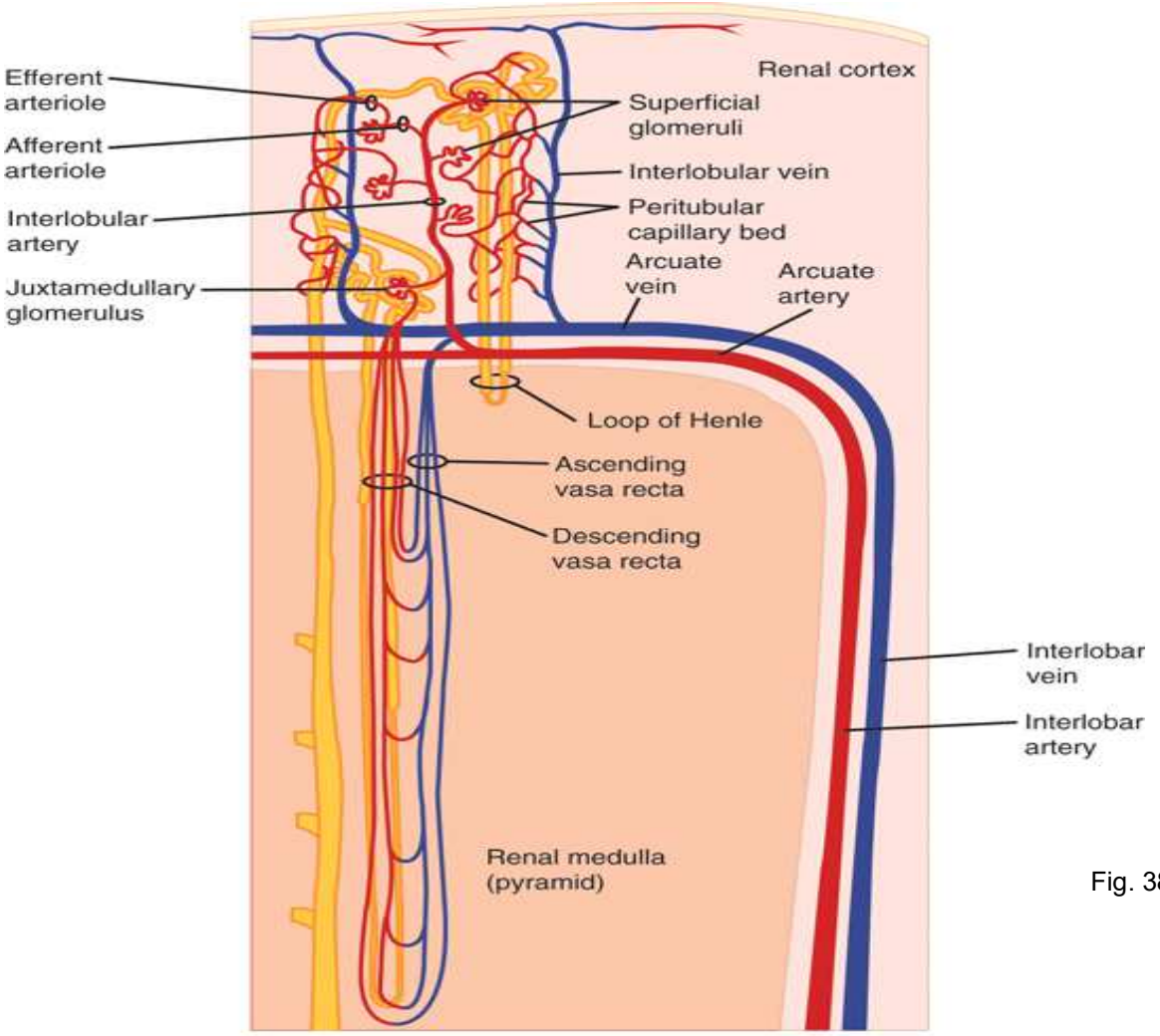


Fig. 38-3 Accessed 02/01/2010

Renal artery

- The main renal artery divides into anterior and posterior sections at the hilum.
- From these emerge interlobar arteries
- Give rise to the arcuate arteries which arch between cortex and medulla
- Define the cortico-medullary junction
- Giving rise to the interlobular arteries.

Interlobular arteries

- Afferent arterioles arise from interlobular arteries
- Enter the glomerular tuft, where they progressively subdivide into 20 to 40 capillary loops arranged in several units or lobules architecturally centered by a supporting mesangial stalk.
- Capillary loops merge to exit from the glomerulus as efferent arterioles.

Vasa recta

- In general, efferent arterioles from superficial nephrons form a rich vascular network
- Encircles cortical tubules (peritubular vascular network) and deeper juxtamedullary glomeruli
- Give rise to the vasa recta
- Which descend as straight vessels to supply the outer and inner medulla.
- These descending arterial vasa recta then make several loops in the inner medulla and ascend as the venous vasa recta.

Efferent arteries

- Largely end-arteries.
- Occlusion of any branch usually results in infarction of the specific area it supplies.
- All tubular capillary beds are derived from the efferent arterioles.
- Mesothelial cells about the capillaries are continuous with smooth muscle cells of the hilus arterioles.

Renal medulla

- The medulla does not have its own arterial blood supply but is dependent on the blood emanating from the glomerular efferent arterioles.
- The blood in the capillary loops in the medulla is not well oxygenated.
- The medulla is vulnerable to ischemia.
- Injury manifest as asymptomatic hematuria
- Loss of concentrating ability
- May lead to renal papillary necrosis

Glomerulus

- The glomerulus consists of an anastomosing network of capillaries lined by fenestrated endothelium invested by two layers of epithelium.
- The endothelial cell body is oriented to the mesangium.
- The fenestrated endothelial cytoplasm lines the inner aspect of the glomerular basement membrane
- Presumably allows the plasma flowing through the capillaries to reach the glomerular basement membrane

Glomerulus

- Podocytes (visceral epithelial cells) send out a multitude of extensions called foot processes that interdigitate with those of adjacent podocytes and cover the outer aspect of the glomerular capillary.
- The foot processes are connected by a unique cell-cell junction called the slit diaphragm that maintains defined spacing between the processes and at the same time permits the efficient flow of water and small solutes across the filtration barrier.
- Podocytes are separated from the endothelial cells by the glomerular basement membrane.

Glomerulus

- Adjacent foot processes (pedicels) are separated by 20- to 30-nm-wide filtration slits, which are bridged by a thin diaphragm of transmembrane proteins above the glomerular basement membrane.
- The podocyte turns 180^{o} into the glomerular basement membrane and are linked with integrins to the glomerular basement membrane.
- Diaphragm-cytoskeleton-podocyte
- Podocytes do not proliferate after injury.

Glomerulus

- The glomerular capillary wall is the filtering membrane.
- The parietal epithelium, situated on Bowman's capsule, lines the urinary space, the cavity in which plasma filtrate first collects.

Glomerular basement membrane

- Lies between, and is initially synthesized by, the glomerular endothelial cells that line the glomerular capillaries and the podocytes
- The glomerular basement membrane consists of:
- Laminin
- Type IV collagen
- Nidogen
- Heparan sulfate proteoglycan (agrin)
- The glomerular basement membrane acts as a scaffold for capillaries and reflects over the mesangium.

Glomerular basement membrane

- Type IV collagen is a monomer that contains a triple helix molecule (of α-chains) at the center and contains a globular non-collagenous domain at its carboxyl terminus.
- The non-collaegnous domain is important for the helical structure and for assembly of collagen monomers into the basement membrane.
- The antigens in the non-collagenous domain are the targets of antibodies in anti-glomerular basement membrane nephritis.
- Genetic defects in the α-chains underlie some forms of hereditary nephritis.

Glomerular basement membrane

- Nephrin is the principal transmembrane protein connecting podocytes.
- Its extracellular portion contains immunoglobulin like domains.
- Nephrin molecules extened towards each other from the podocytes and dimerize, forming a zipper-like structure that is the slit diaphragm.
- Within the podocyte they connect with C2D-associated protein and the actin cytoskeleton.
- Podocin also connects with the C2DAP.

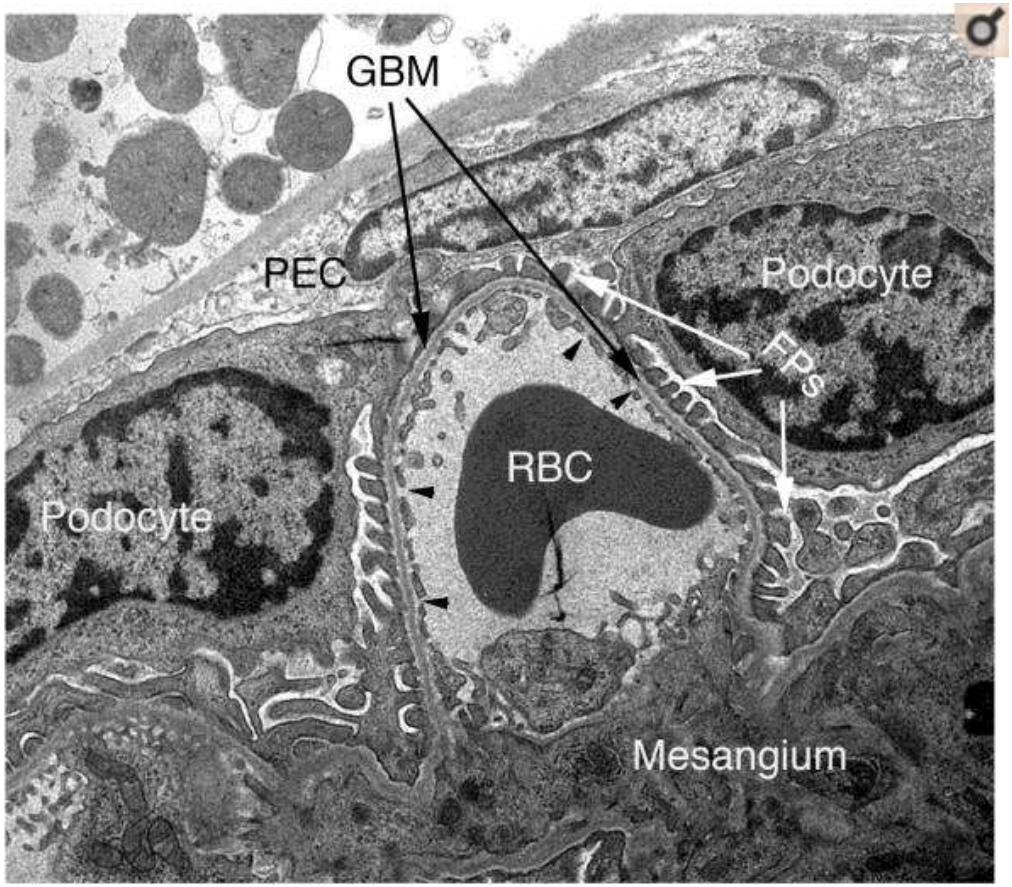
Glomerular basement membrane

- The acidic porous nature of the glomerular basement membrane results from attached proteoglycans and glycoproteins
- Determines its permeability characteristics.
- Potential differences of −0.02 to −0.05 mV can induce electrophoretic effects that significantly influence the glomerular sieving coefficient of albumin
- Proteins >70 kD are not filtered.
- Anionic proteins are not filtered.

Glomerular basement membrane

- There is a thick electron-dense central layer, the lamina densa, and thinner electron-lucent peripheral layers, the lamina rara interna and lamina rara externa.

Glomerular basement membrane



Miner, JH, "The Glomerular Basement Membrane," Exp. Cell Res 2012; 318(9): 973-978. Fig. 1 Accessed 02/20/2020

A red blood cell (RBC) is present in the capillary lumen, which is lined by an endothelial cell with fenestrations (black arrowheads). The glomerular basement membrane (GBM) is a ribbon-like extracellular matrix that lies between the endothelium and the podocyte foot processes (FPs). The mesangium contains mesangial cells and their associated matrix. A parietal epithelial cell (PEC) is visible lining Bowman's capsule.

Mesangium

- The entire glomerular tuft is supported by mesangial cells lying between the capillaries.
- Basement membrane-like mesangial matrix forms a meshwork through which the mesangial cells are centered.
- Mesangial cells are of mesenchymal origin
- Similar to vascular smooth muscle cells and pericytes
- They are contractile, phagocytic, and capable of proliferation, of laying down both matrix and collagen, and of secreting a number of biologically active mediators.

Histologic patterns of glomerulonephritis

- Minimal or no detectable abnormalities
- Membranous glomerulonephritis
- Focal proliferative glomerulonephritis
- Diffuse proliferative glomerulonephritis
- Membranous glomerulonephritis
- May see Type III hypersensitivity reaction with circulating antigen-antibody complexes (systemic lupus erythematosus)
- Through cell mediated immunity;
- Or activation of alternative complement path.

Thin basement membrane

- Asymptomatic hematuria.
- May see proteinuria as well.
- Very common.
- No progression.
- Autosomal dominant
- Thin glomerular basement membrane on electron microscopy.
- Mutations in coding for α_3 or α_4 chains of type IV collagen.

Thin basement membrane

- Alport's syndrome
- X-linked disease
- Systemic disorder involving lens and audition.
- Hematuria is manifest due to mutations in coding α_3, α_4, or α_5 chains of type IV collagen.
- As coding for α_5 is also associated with coding for assembly of the collagen network, basement mebranes show marked attenuation and pronounced splitting and lamination of the lamina densa (as if it were a weave).
- Progresses to chronic renal failure over 20 years.

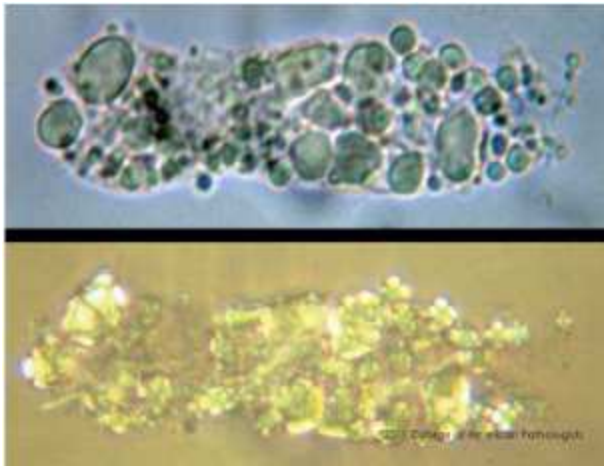
Minimal change glomerulonephritis

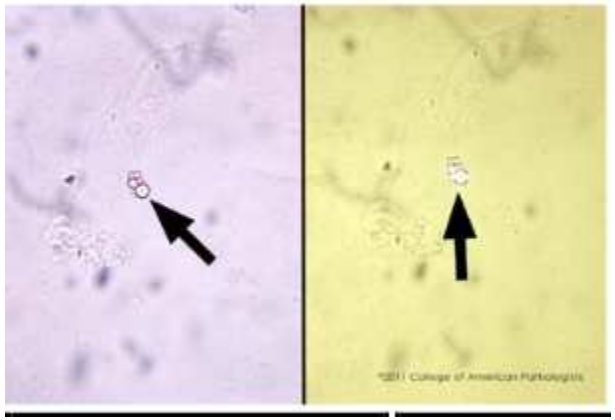
- Nephrotic syndrome if >3.5gm proteinuria over 24 hours.
- Often with lipidemia and lipiduria.
- LDL released from liver to maintain
- IgG lost
- Oval fat bodies in urine
- Cause of nephrotic syndrome in 80% of children aged 4-8 years; in 20% of adults.
- Normal appearing glomerulus by light microscopy but effacement of the foot processes of the visceral epithelial cells on electron microscopy.

Minimal change glomerulonephritis

- May be caused by NSAIDs
- Or seen in lymphoproliferative disorders.
- Probable immunologic origin.
- Cytokine mediated damage.
- Diminished membrane charge
- Responds to corticosteroids
- May not need to biopsy child unless failure to respond to steroids
- Always biopsy adult
- Cyclophosphamide in steroid failure in adult.

Urinary sediment





Left: Fatty cast (lower photo is with polarized light).
Right: Fat globule (right frame is with polarized light).
Note “Maltese cross” appearance of oval fat body.
http://webapps.cap.org/apps/docs/committees/hematology/microscopy_discussion_2011_cma.pdf
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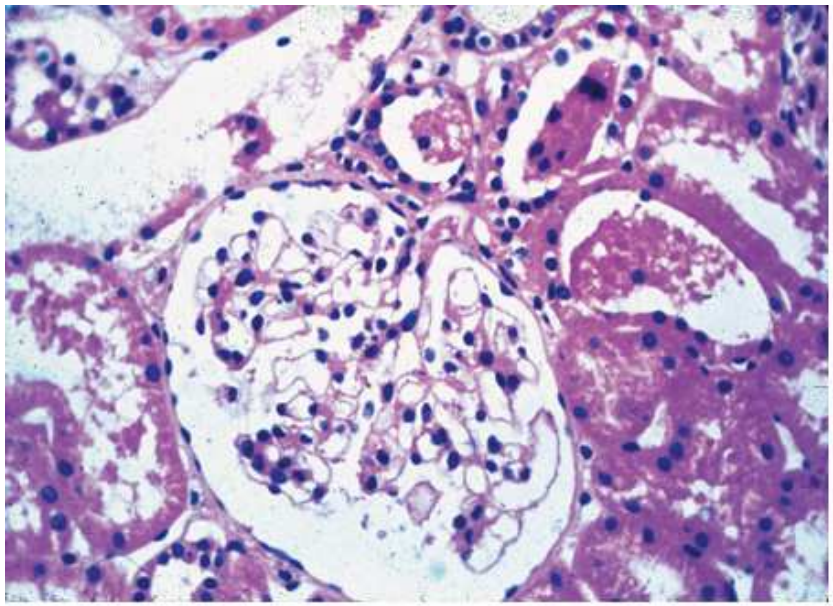
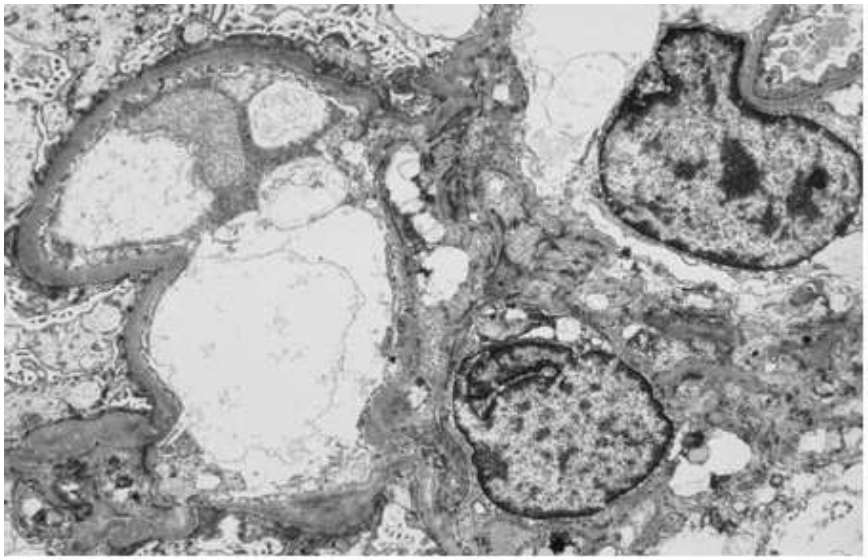
Minimal change disease





(ABF/Vanderbilt Collection.)
Fig. e9-1 Accessed 02/01/2010

Light microscopy is unremarkable (left), while electron microscopy (right) reveals podocyte injury evidenced by complete foot process effacement.

Focal segmental glomerulosclerosis

- One third of cases of nephrotic syndrome in adults
- 50%, if of Sub-Saharan ancestry
- 15-20% familial.
- Secondary causes:
- Sickle cell disease
- Active HIV infection
- Long term steroid or cyclosporine use.

Focal segmental glomerulosclerosis

- Molecular alterations:
- NPHS1 (19q12), nephrin abnormality
- NPHS2 (1q25-31), podocin abnormality
- Podocyte actin binding protein (α-actinin 4) abnormality
- TRPC6 abnormality (increase Ca^{2+} flux)

Focal segmental glomerulosclerosis

- Less than 50% of glomerulus involved.
- Microsocopic:
- Collapse of capillary loops is pathognomonic.
- There is an increase in matrix, and segmental capillary protein deposition is noted in affected glomeruli.
- Foam cells are often present.
- There is compensating hypertrophy of unaffected glomeruli.
- Generally involves juxtamedullary glomeruli.

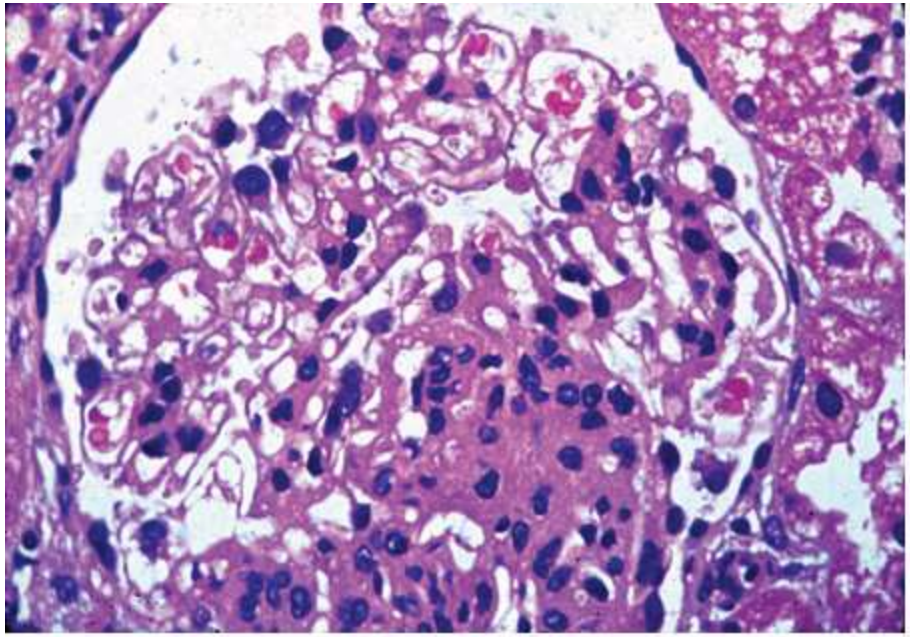
Focal segmental glomerulosclerosis

- IgM and C3 deposited in sclerotic segments.
- In HIV nephropathy
- May see collapse of glomerular tuft with narrowing of capillary lumina, proliferation and swelling of visceral epithelial cells, and accumulation of intracellular protein droplets by visceral epithelial cells.

Focal segmental glomerulosclerosis

- Poor prognosis as it proceeds to end stage renal disease at a relatively constant rate independent of underlying disease activity.
- 20% proceed at rapid rate (renal failure by 2 years)
- ACE inhibitors employed.
- Up to 50% recurrence in those renal allografts for treatment of this disease.

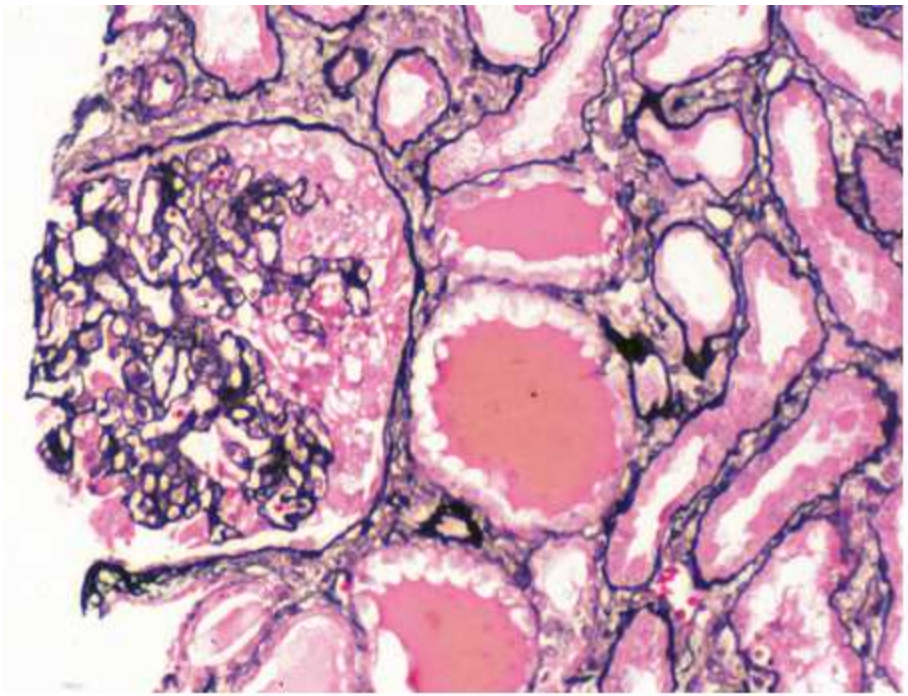
Focal segmental glomerulosclerosis



There is a well-defined segmental increase in matrix and obliteration of capillary loops

(EGN/UPenn Collection.)
Fig. e9-2 Accessed 02/01/2010

Collapsing glomerlopathy



There is segmental collapse of the glomerular capillary loops and overlying podocyte hyperplasia. This lesion may be idiopathic or associated with HIV infection and has a particularly poor prognosis.

(ABF/Vanderbilt Collection.)

Fig. e9-3 Accessed 02/01/2010

Membranous glomerulopathy

- 30-40% of adult cases.
- Males predominate.
- Peak incidence between 30-50 years of age.
- Minimal clinical manifestations
- Mild hematuria or transient proteinuria.
- 15% of cases have identifiable cause.
- Antibody to phospholipase A receptor (PLA2R) in podocyte

Membranous glomerulopathy

- Penicillamine, gold, captopril, and NSAIDs are medications associated with membranous change.
- Carcinomas of the colon, lung, and melanoma are associated with membranous change.
- Hepatitis B, hepatitis C, syphilis, malaria, schistosomiasis are also associated with membranous change.
- Autoimmune diseases are also associated with membranous change (15% of SLE patients; thyroiditis).
- Reversible if NSAID induced.

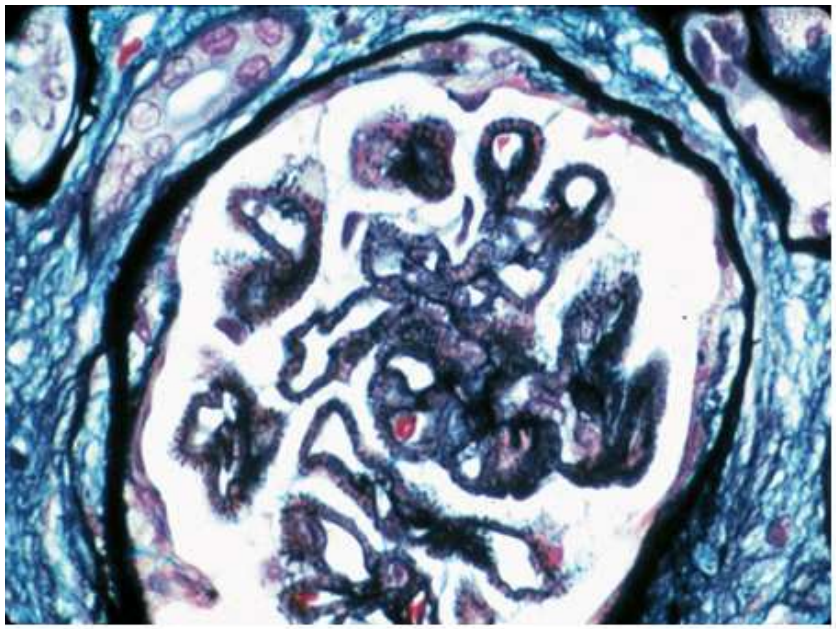
Membranous glomerulopathy

- Microscopic:
- Mesangial cell proliferation and lack of involvement of glomerular capillary walls.
- There is a slight to moderate increase in the intercapillary mesangial matrix as well as in the number of mesangial cells.
- Basement membrane may split ("railroad track").
- No inflammation.

Membranous glomerulopathy

- Diffuse granular mesangial deposits of IgG and C3 are always present.
- Antigen not identified; may be LDL receptor.
- Membrane attack complex damages capillary wall.
- Subepithelial deposits noted on electron microscopy.

Membranous glomerulopathy



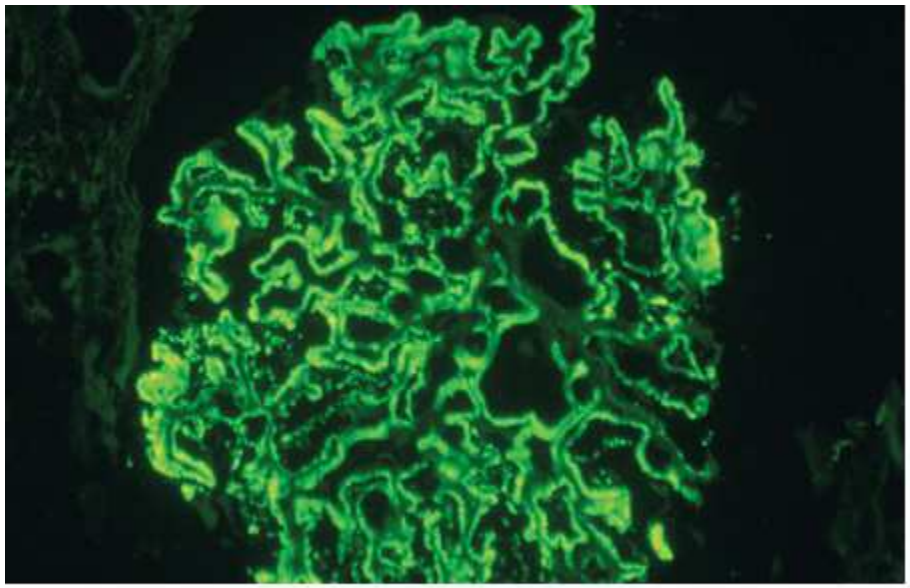


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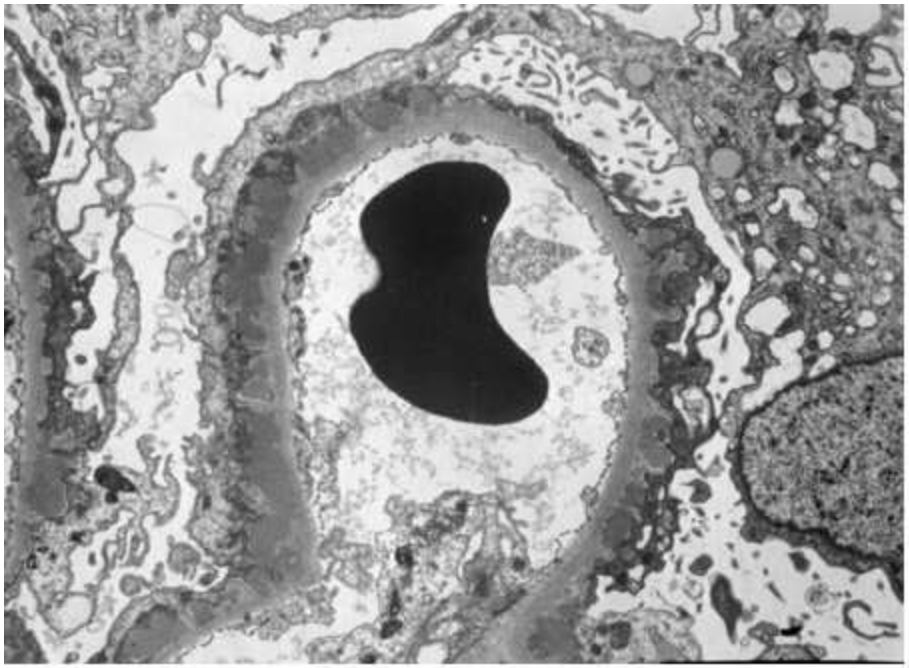
Fig. e9-54 Accessed 03/17/2010

Membranous glomerulopathy is due to subepithelial deposits, with resulting basement membrane reaction, resulting in the appearance of spike-like projections on silver stain (left). The deposits are directly visualized by fluorescent anti-IgG, revealing diffuse granular capillary loop staining (right).

Membranous glomerulopathy



The subepithelial location of the deposits and early surrounding basement membrane reaction with overlying foot process effacement is evident.

(ABF/Vanderbilt Collection.) Fig. e9-5
Accessed 03/01/2010

Membranoproliferative glomerulonephritis I

- MPGN I is an immune complex glomerulonephritis.
- Two-thirds of MPGN cases.
- 5-10% of all cases of nephrotic syndrome
- More common in children and young adults.
- Deficiency of C3 (hypercatabolism)
- High rates of end stage renal disease in Navajo

Membranoproliferative glomerulonephritis I

- Granular deposits of IgG and C3 are found in mesangial cells and capillary walls.
- Distinguish from membranous glomerulopathy
- "Wire-loop" lesions correspond to subendothelial deposits of immune complexes.
- Membrane attack complex damages capillary wall.

Membranoproliferative glomerulonephritis I

- Occasionally find with fibrillar deposits in the mesangium and glomerular capillary walls.
- Polyclonal IgG_4, C3, and light chains seen with immunofluorescence microscopy.
- Subepithelial deposits on electron-microscopy.

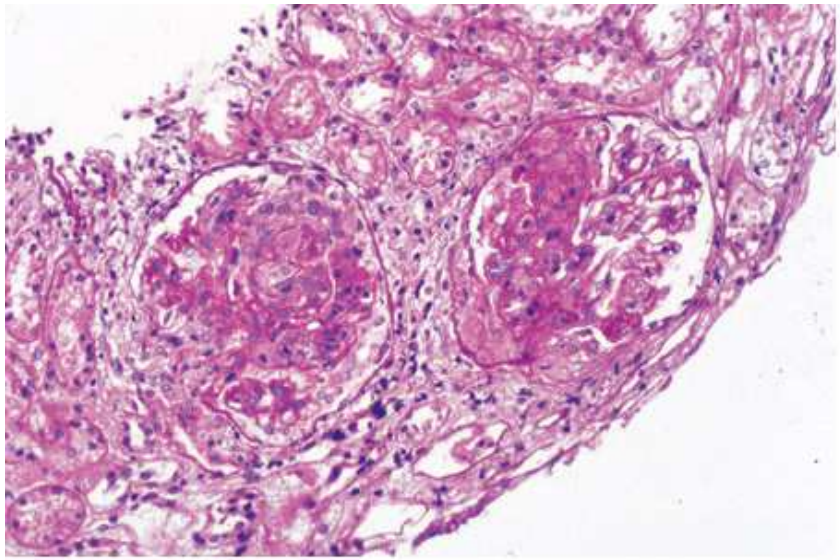
Membranoproliferative glomerulonephritis I

- Secondary disease associated with:
- Chronic infection
- Hepatitis B, Hepatitis C, HIV, Schistosomiasis
- SLE or cryoglobulinemia
- α_1-antitrypsin deficiency
- Malignancy.
- Complement activation

International Society of Nephrology and Renal Pathology Society Classification of Lupus Nephritis

- Class I Minimal mesangial disease
- No change by light microscopy
- Class II Mesangial proliferative disease
- May see nephrotic syndrome
- Class III Focal disease
- Fewer than 50% of glomeruli involved
- Class IV Diffuse disease
- Class V Membranous disease
- Subepithelial and mesangial deposits
- Nephritic syndrome
- Class VI Advanced sclerosis

Membranoproliferative glomerulonephritis I



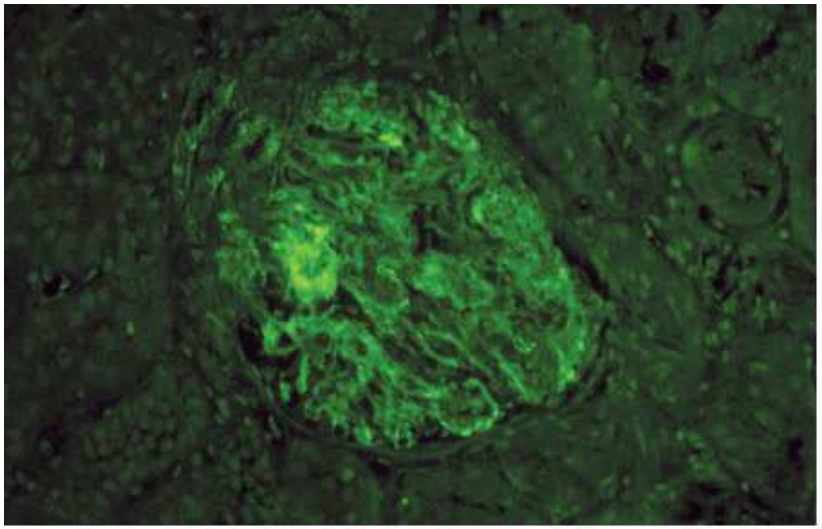


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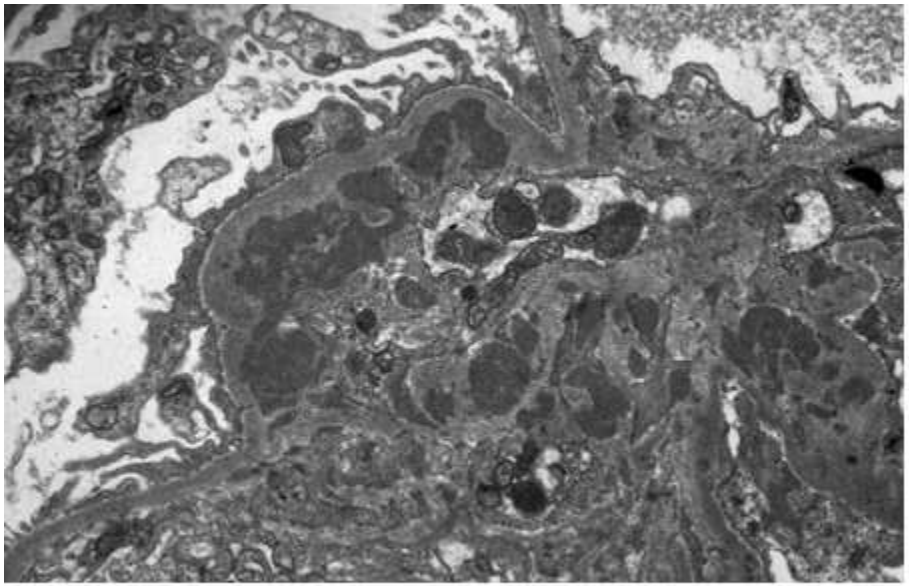
Fig. e9-10 Accessed 03/17/2010

Proliferative lupus nephritis manifests as endocapillary proliferation, which may result in segmental necrosis due to deposits, particularly in the subendothelial area (left)). Chunky irregular mesangial and capillary loop deposits are evident on immunofluorescence, with some of the peripheral loop deposits having a smooth, molded outer contour due to their subendothelial location. (right)

Membranoproliferative glomerulonephritis I



Lupus nephritis.
Subendothelial, mesangial, and rare subepithelial dense immune complex deposits are evident, along with extensive foot process effacement.

(ABF/Vanderbilt Collection.) Fig. e9-10
Accessed 03/17/2010

Membranopoliferative glomerulonephritis II

- MPGN II is autoimmune.
- Alternative complement pathway activated.
- May present as nephritis (blood in urine).
- Glomerular basement membrane may split ("railroad track").
- Circulating antibody to C3.

Membranopoliferative glomerulonephritis II

- IgG not found on immunofluorescent tissue staining.
- Dense deposits are found in the glomerular basement membrane on electron microscopy.
- One-third of MPGN cases.
- Transplant often only successful treatment for MPGN.
- However, success rates are lower than for other diseases

Membranoproliferative glomerulonephritis II

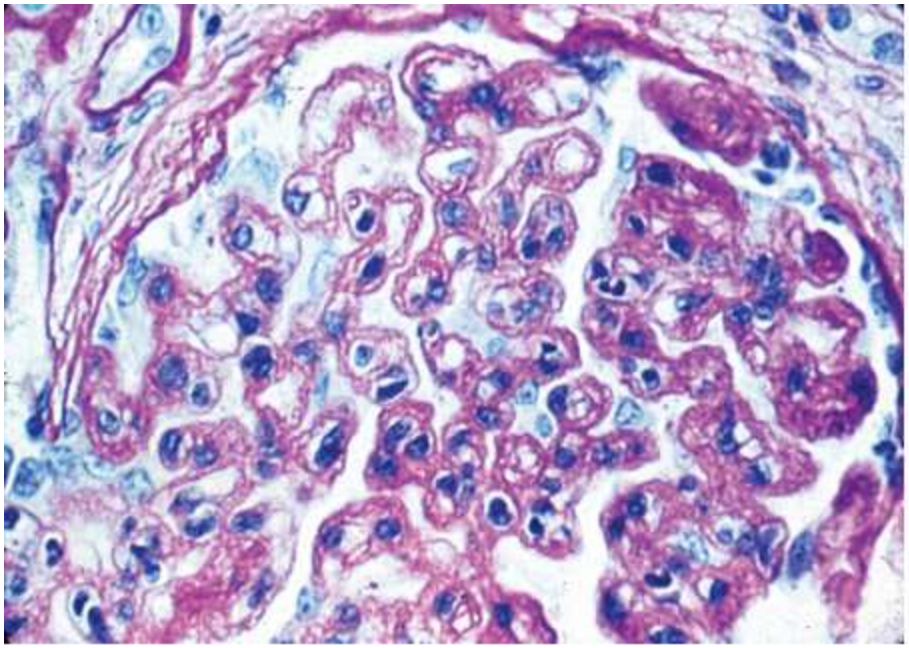
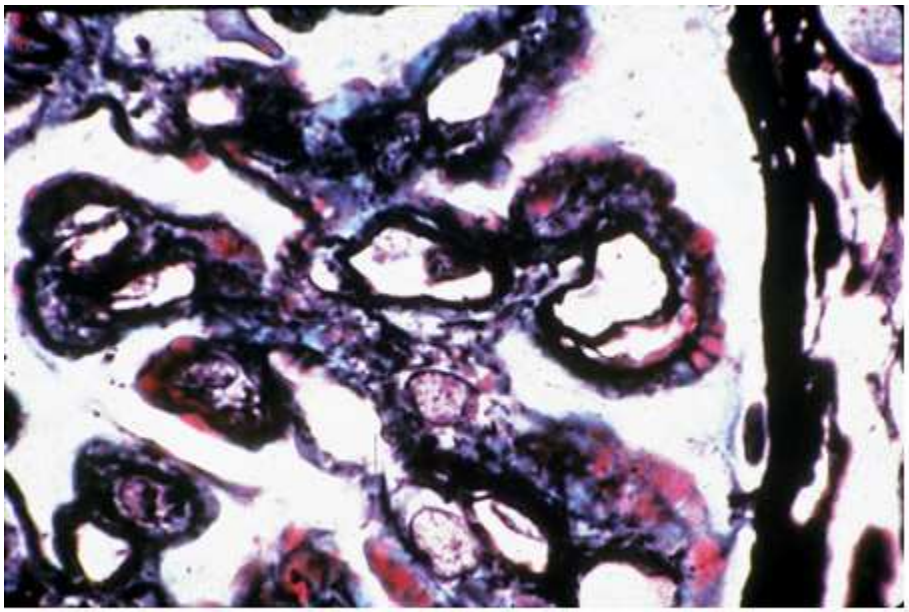


Fig. e9-7 Accessed 03/17/2010

There is mesangial expansion and endocapillary proliferation resulting in the “railroad-track" sign of cellular interposition along the glomerular basement membrane.

(EGN/UPenn Collection.)

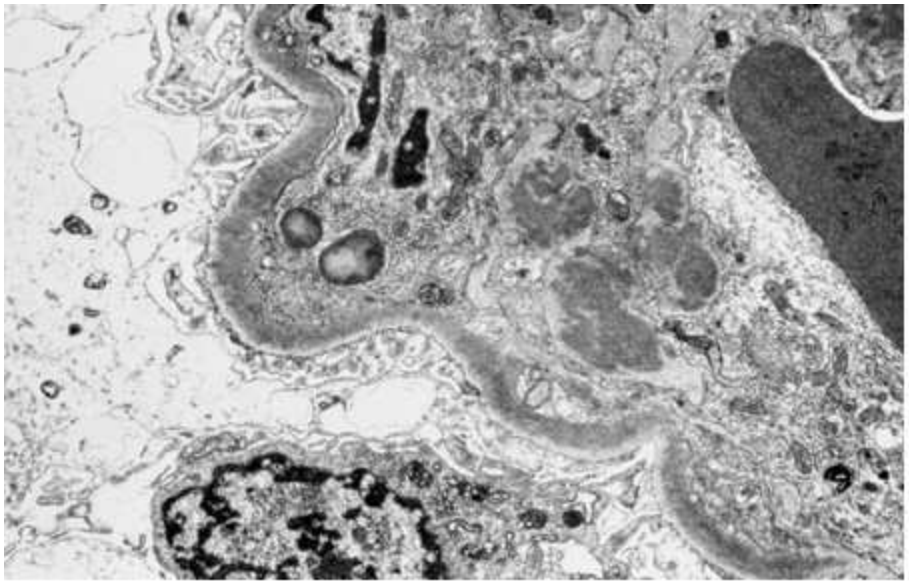
Membranoproliferative glomerulonephritis



(EGN/UPenn Collection.)
Fig. e9-8 Accessed 03/17/2010

This specimen shows pink subepithelial deposits with spike reaction and the “railroad-track" sign of reduplication of glomerular basement membrane, resulting from subendothelial deposits, as may be seen in mixed membranous and proliferative lupus nephritis (ISN/RPS class V and IV) or membranoproliferative glomerulonephritis type III.

MPGN II



Electron microscopy, demonstrates a dense transformation of the glomerular basement membrane with round, globular deposits within the mesangium.

(ABF/Vanderbilt Collection.)

Fig. e9-9 Accessed 03/17/2010

Thrombotic microangiopathies

- Classical hemolytic uremic syndrome
- Acute bleeding
- Oliguria
- Hematuria
- Thrombocytopenia with microangiopathic hemolytic anemia.
- May have neurologic symptoms.

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Thrombotic microangiopathies

- Increased expression of leukocyte adhesion molecules on epithelial cells
- Direct binding and activation of platelets.
- Endothelin and TNF-α production as well as diminished NO production
- Induce vasoconstriction.

Thrombotic microangiopathies

- Atypical hemolytic uremic syndrome
- Acute bleeding
- Thrombocytopenia with microangiopathic hemolytic anemia.
- May have neurologic symptoms.
- Uncontrolled complement activation in those with defects in complement factor H (fails to break down C3 convertase).
- A small percentage of patients lack membrane cofactor protein CD46, or complement factor I.

Thrombotic microangiopathies

- Precipitated by:
- Mitomycin, cisplatin, gemcitabine, and cyclosporine.
- May also be seen as a complication of the post partum period
- May be part of the antiphospholipid syndrome.

Thrombotic microangiopathies

- Thrombotic thrombocytopenic purpura (TTP)
- Non-immune related decreased platelet survival as a result of platelet activation and aggregation.
- Petechiae.
- Neurologic involvement prominent.
- Deficient vWF metalloproteinase, (ADAMTS13) permitting accumulation of vWF multimers and platetelet aggregation.

Thrombotic microangiopathies

- Often skin biopsy needed to differentiate.
- Thrombotic thrombocytopenic purpura responds to plasma exchange.
- Typical hemolytic uremic syndrome ameliorates with treatment of underlying disorder, although progression to chronic renal disease common.
- Atypical hemolytic uremic syndrome has a worse prognosis.

Focal proliferative glomerulonephritis

- IgA nephropathy
- Most common nephropathy world-wide.
- ages 10 - 29 years
- usually males
- May present with gross or microscopic hematuria after respiratory infection but no evidence of systemic disease
- More common in southern Europe, Asia and Native Americans
- Less common in individuals of Sub-Saharan lineage
- Up to 15% have systemic disorder.
- Related to Hoenich–Schoenlein purpura.

Focal proliferative glomerulonephritis

- Excess amounts of poorly galactosylated serum immunoglobulin IgA1 trigger the generation of glycan specific IgG and IgA autoantibodies,
- Alternate complement pathway activated.
- Focal epithelial cell proliferation.
- No inflammation.
- Polyclonal IgA1 deposition in mesangium.
- IgG, IgM, and/or C3 may be deposited as well.
- Dense deposits in mesangial cells and in paramesangium on electron microscopy.

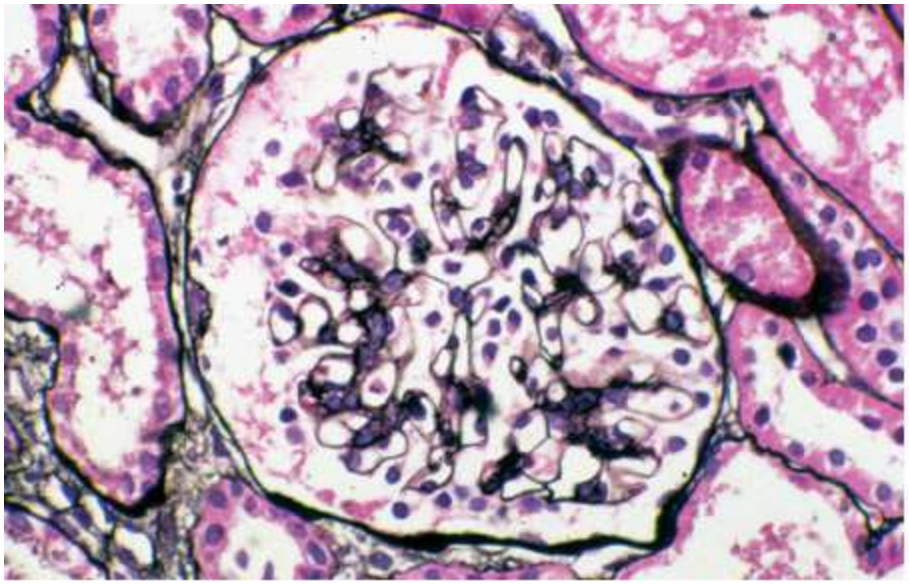
Focal proliferative glomerulonephritis

- Slowly progressive
- 25 - 50% have renal failure at 20 years
- 20% recur after transplantation
- Secondary disease:
- May also see in microangiopathic hemolytic anemia and thrombocytopenia (hemolytic uremic syndrome).
- May be seen in celiac disease or in liver disease where there is defective clearance of IgA complexes.

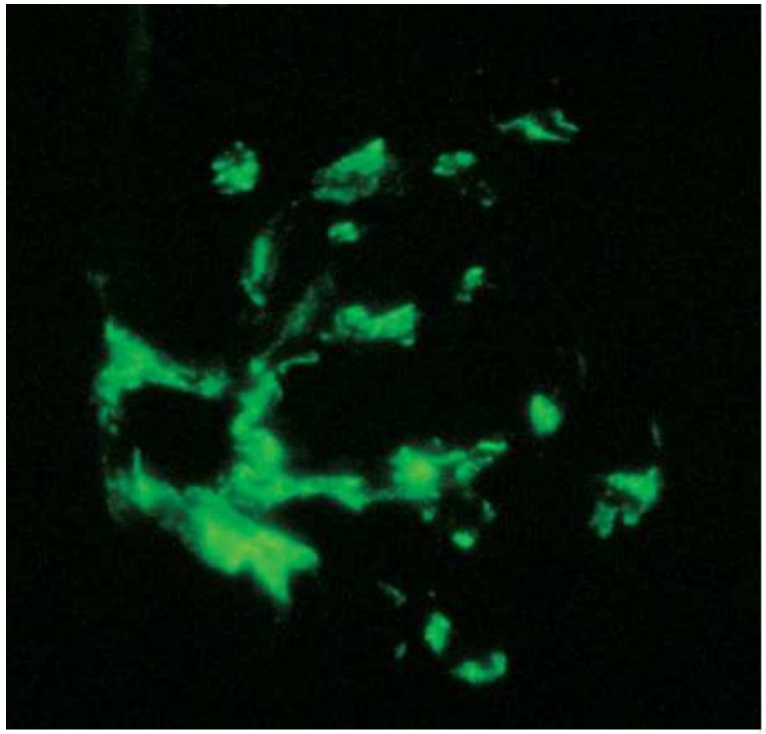
Henoch-Schöenlein purpura

- Children.
- Purpuric rash on the extensor surfaces and buttocks.
- May see lower extremity arthralgia.
- Colicky abdominal pain. May be associated with intussusception.
- Elevated serum IgG and IgA.
- Associated with focal progressive glomerulonephritis. Biopsy shows vasculitis with IgA and complement deposition.
- Responds to corticosteroids.
- May clear rapidly with plasmapheresis.

IgA nephropathy



(ABF/Vanderbilt Collection.) Fig. E9-6 Accessed 03/01/2010



There is variable mesangial expansion due to mesangial deposits, with some cases also showing endocapillary proliferation or segmental sclerosis (left). By immunofluorescence, deposits are evident (right).

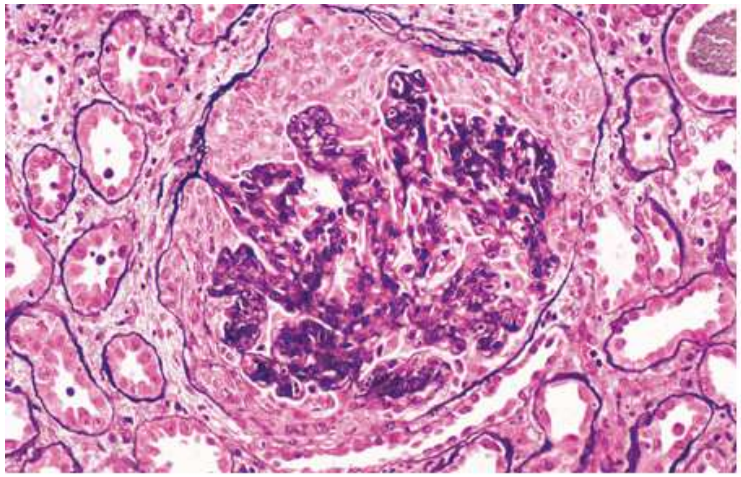
Proliferative glomerulonephritis

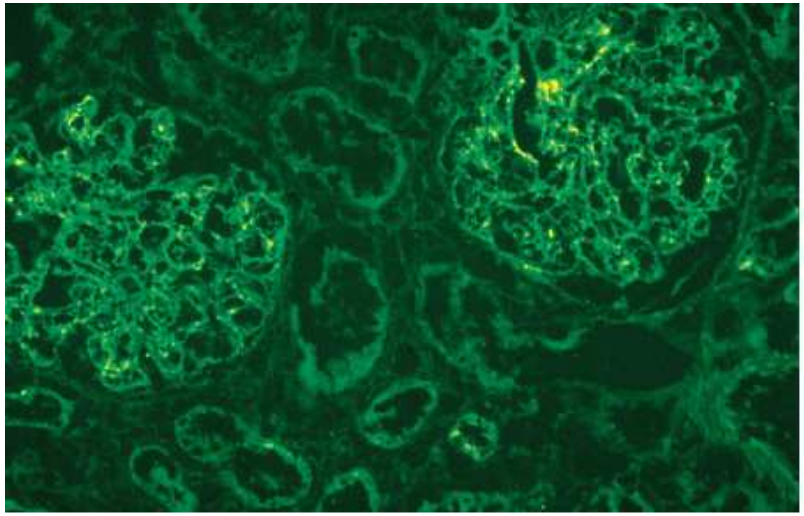
- Presents as acute nephritis (blood in urine) 1-2 weeks after Streptococcal infection.
- Circulating antibody reactive to antigen incorporated into membrane.
- Streptococcal M protein types 12, 4, 1 reacts with nephritis associated plasmin receptor,
- Streptococcal pyogenic exotoxin B reacts with its zymogen precursor, a plasmin receptor.

Proliferative glomerulonephritis

- Diffuse glomerular epithelial proliferation in glomerulus with leukocyte infiltration present
- Granular IgG and C3 immunofluorescent staining in glomerular basement membrane.
- Subepithelial deposits on electron microscopy.
- Resolves spontaneously in 95% of children, 60% of adults.

Post-streptococcal glomerulonephritis

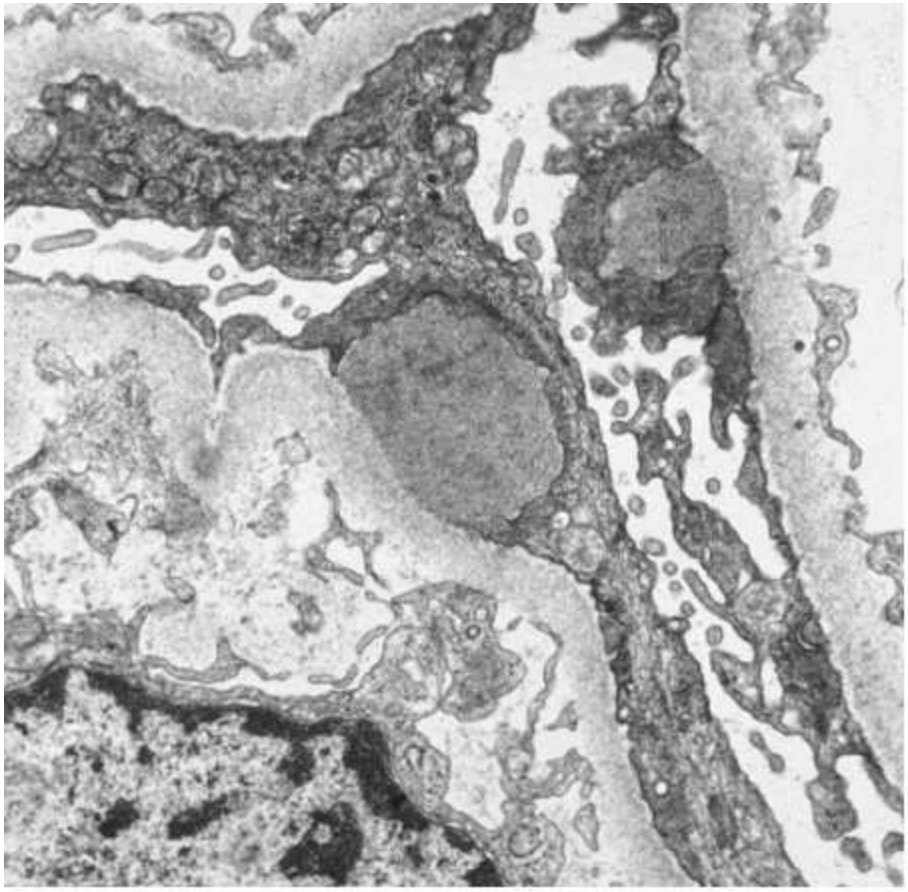




Diffuse glomerular epithelial proliferation in glomerulus (left); granular IgG and C3 immunofluorescent staining in glomerular basement membrane (right)

Fig. e9-4 Accessed 03/01/2010

Post-streptococcal glomerulonephritis



Subepithelial hump-shaped deposits are seen by electron microscopy.

(ABF/Vanderbilt Collection.)

Fig. e9-4 Accessed 03/17/2010

Rapidly progressive proliferative (crescentic) glomerulonephritis I

- Goodpasture's syndrome
- Autoimmune disease principally affecting men
- Usually ages 15 - 29 years
- Simultaneous massive hemorrhagic interstitial pneumonitis and rapidly progressive (crescentic) glomerulonephritis
- Hemoptysis and hematuria
- May be preceded by chemical or drug exposure, viral infection or malignancy

Rapidly progressive proliferative (crescentic) glomerulonephritis I

- Diffuse glomerular epithelial proliferation in glomerulus with leukocyte infiltration present.
- There is collapse of the glomerular tuft with crescentic proliferation of epithelial cells internal to Bowman's capsule.
- Goodpasture antigen is a peptide within the non-collagenous portion of the α_3 chain of type IV collagen.
- HLA-DRB1 commonly found in patients.

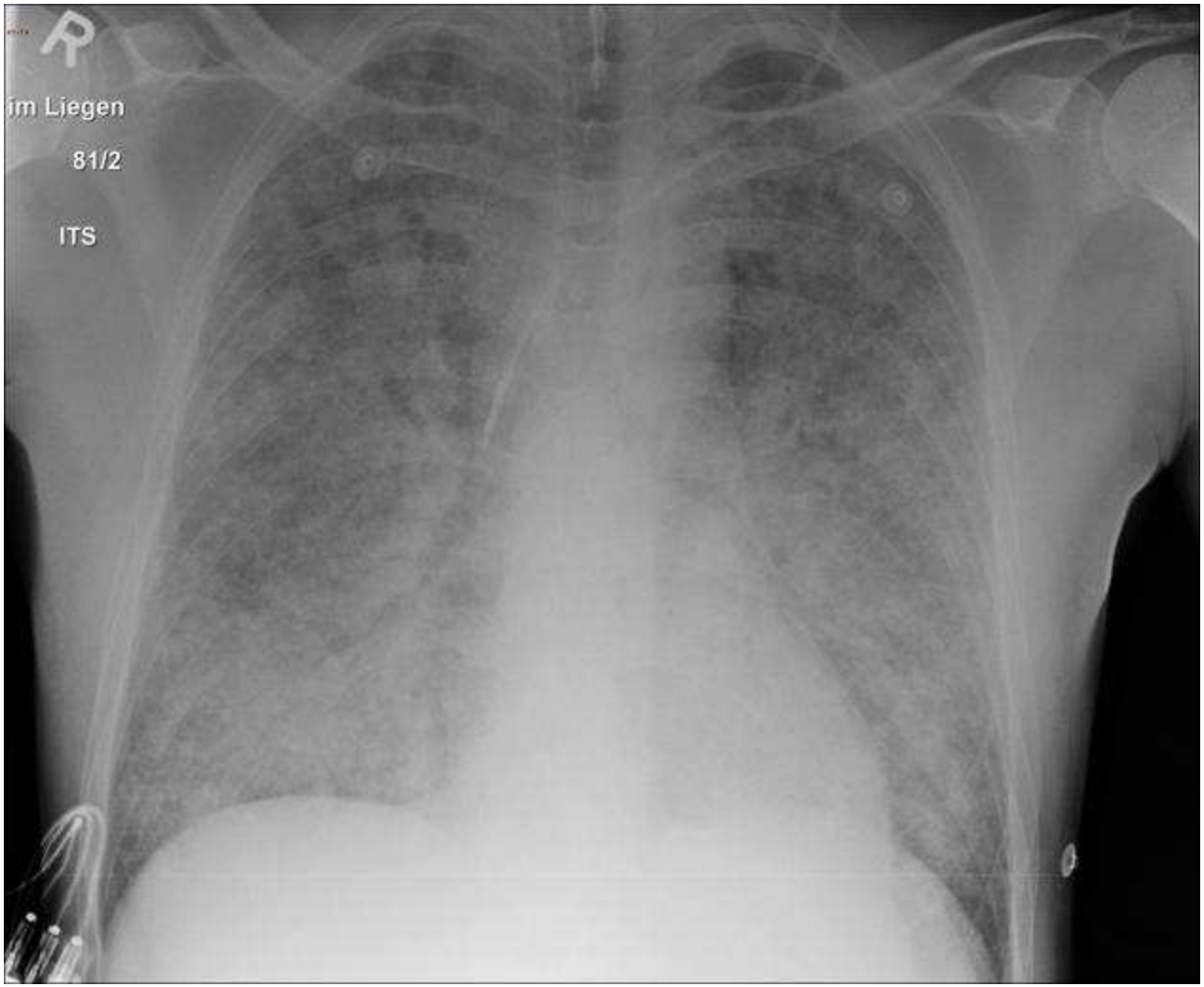
Rapidly progressive proliferative (crescentic) glomerulonephritis I

- Linear deposition of anti-GBM and C3 on glomerular basement membrane with immunofluorescent staining is noted in Goodpasture's syndrome.
- Type II hypersensitivity reaction
- Fibrin is present in crescents.
- The glomerular basement membrane is disrupted.
- No deposits on electron microscopy.
- Corticosteroids and cyclophosphamide with or without plasmapheresis as therapy.

Histology

- Lungs:
- Heavy, focal necrosis of alveolar wall
- Fibrous thickening of septa with mild hyperplasia of alveolar lining cells
- Organization of blood in alveolar space
- Hemosiderin laden macrophages
- Linear deposits of immunoglobulin along basement membrane
- Kidney:
- Focal proliferative to crescentic glomerulonephritis
- Linear deposits of immunoglobulin and complement along basement membrane

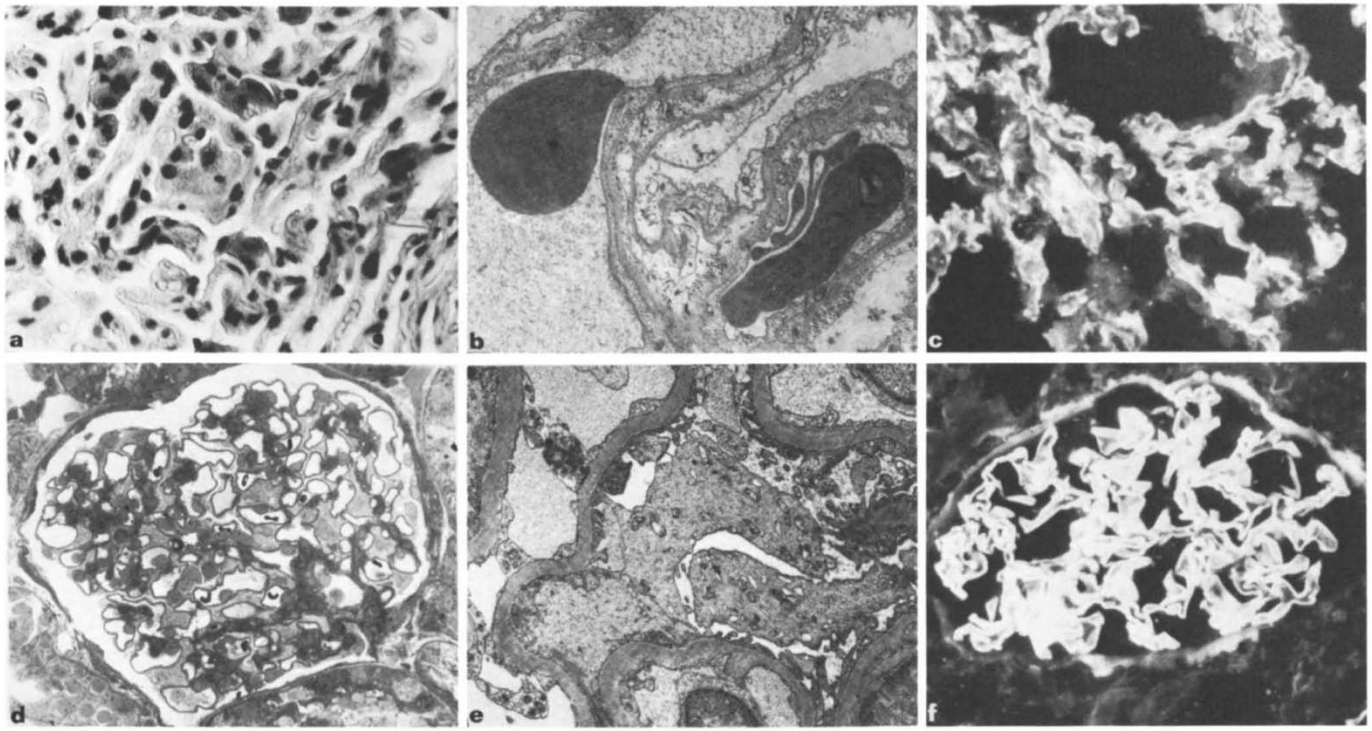
Goodpasture's syndrome



May be difficult to distinguish from pulmonary edema.

In the majority of cases, there are bilateral, coalescent airspace opacities on chest x-ray, which in several days resolve to give reticular opacities in the same distribution

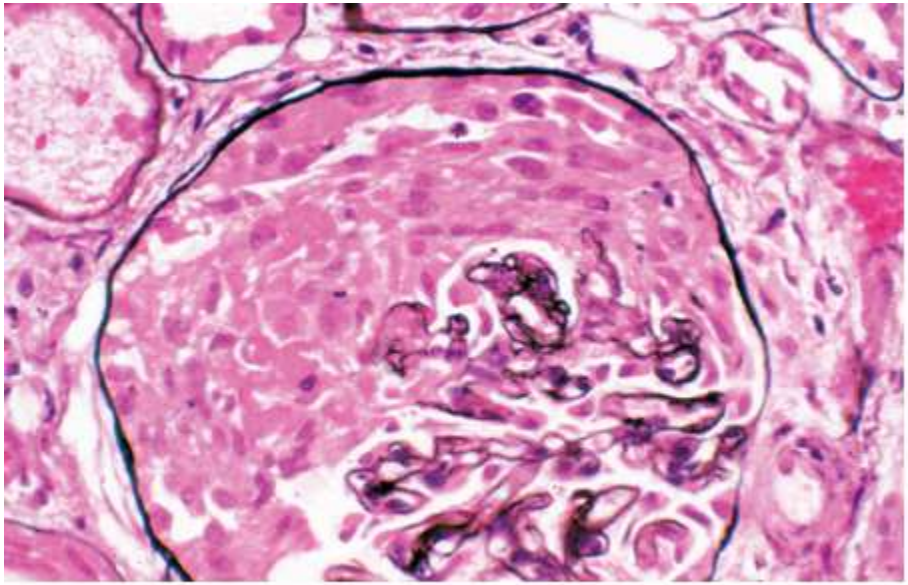
https://radiopaedia.org/articles/goodpasture-syndrome
Accessed 02/20/2020



DOI: 10.7326/0003-4819-89-5-635
Accessed 02/20/2020

Upper panels: transbronchial lung biopsy, a. Light microscopy, H&E x 300 b. Electron microscopy showing no electron-dense deposits, x 18 000 c. Immunofluorescent staining showing strongly positive linear deposits of IgG, x 200 . Lower panels: kidney biopsy, d. Normal light microscopy, x 300 . e. Electron microscopy showing normal glomerular basement membranes and no electron-dense deposits, x 9000 . f. Strongly positive linear deposits of IgG by immunofluorescent staining; x 200 .

Goodpasture's



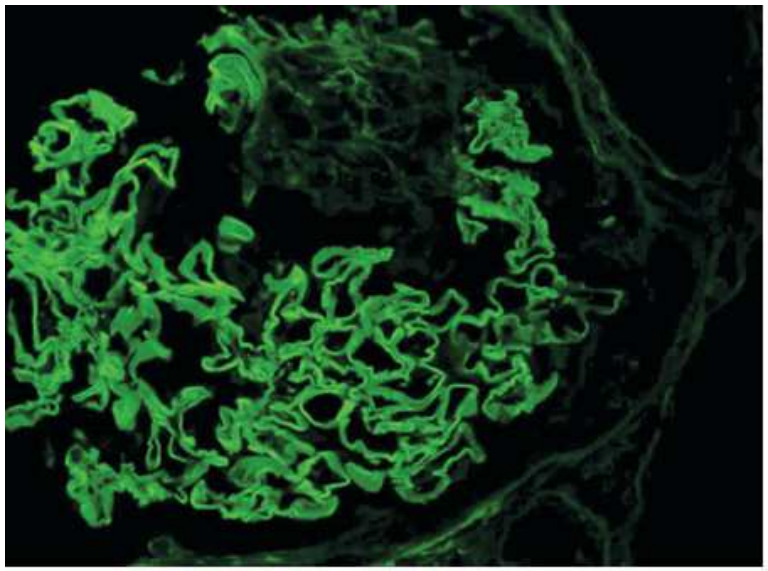


Fig. e9-12 Accessed 03/17/2010

There is segmental necrosis with a break of the glomerular basement membrane and a cellular crescent (left). Immunofluorescence for anti-GBM hows linear staining of the glomerular basement membrane with a small crescent at 1 o'clock. (ABF/Vanderbilt Collection.)

Rapidly progressive proliferative (crescentic) glomerulonephritis II

- Wegener's granulomatosis presents as acute nephritis (blood in urine).
- Diffuse glomerular epithelial proliferation in the glomerulus with leukocyte infiltration present.
- Crescent formation results from proliferation of parietal epithelium.
- The basement membrane may be disrupted.
- Fibrinoid necrosis.

Rapidly progressive proliferative (crescentic) glomerulonephritis

- C-ANCA and p-ANCA present.
- Vasculitis (pauci-immune type).
- No immune complexes noted on immunofluorescent staining.
- Corticosteroids and cyclophosphamide with or without plasmapheresis as therapy.
- Differentiate from p-ANCA diseases: microscopic polyangitis and Churg-Strauss disease (granulomata and eosinophilia)

Wegener's granulomatosis

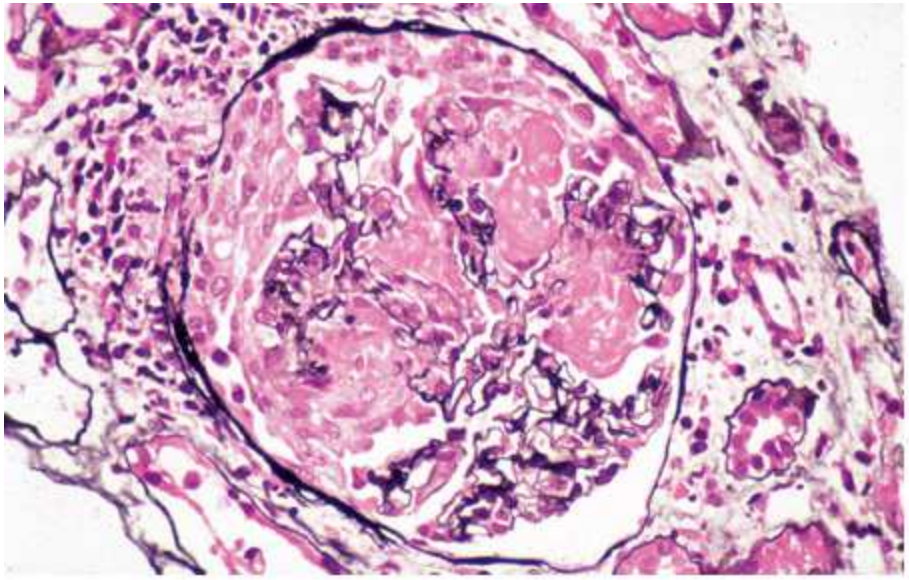


Fig. e9-11 Accessed 03/17/2010

This pauci-immune necrotizing crescentic glomerulonephritis shows numerous breaks in the glomerular basement membrane with associated segmental fibrinoid necrosis, and a crescent formed by proliferation of the parietal epithelium. Note that the uninvolved segment of the glomerulus (at 5 o'clock) shows no evidence of proliferation or immune complexes.

(ABF/Vanderbilt Collection.)

Rapidly progressive proliferative (crescentic) glomerulonephritis III

- Essential mixed cryoglobulinemia presents with:
- Cutaneous vasculitis
- Synovitis
- Proliferative glomerulonephritis.
- Diffuse glomerular epithelial proliferation in the glomerulus with leukocyte infiltration present.
- Cryoglobulins of IgG and IgM immune complexes noted on immunofluorescent staining.

Rapidly progressive proliferative (crescentic) glomerulonephritis III

- Membranoproliferative glomerulonephritis form is associated with Hepatitis C infection.
- Corticosteroids and cyclophosphamide with or without plasmapheresis as therapy.

Collagen type III glomerulopathy

- Proteinuria
- Microscopic hematuria
- 70% have chronic anemia
- Hypertension
- May be associated with hemolytic uremic syndrome
- Diffuse increase in mesangial matrix and widening of glomerular capillary walls
- Stain for Collagen type III in mesangium and in capillary walls (normally absent)

Chronic changes in glomerulonephritis

- Immune complex disease of any sort can lead to rapidly progressive proliferative (crescentic) glomerulopnephritis.
- Resembles RPGN II.
- However, does not respond to plasmapheresis.
- Chronic glomerulonephritis is characterized by multiple sclerotic glomeruli.
- Hypertension.
- May lead to renal failure.

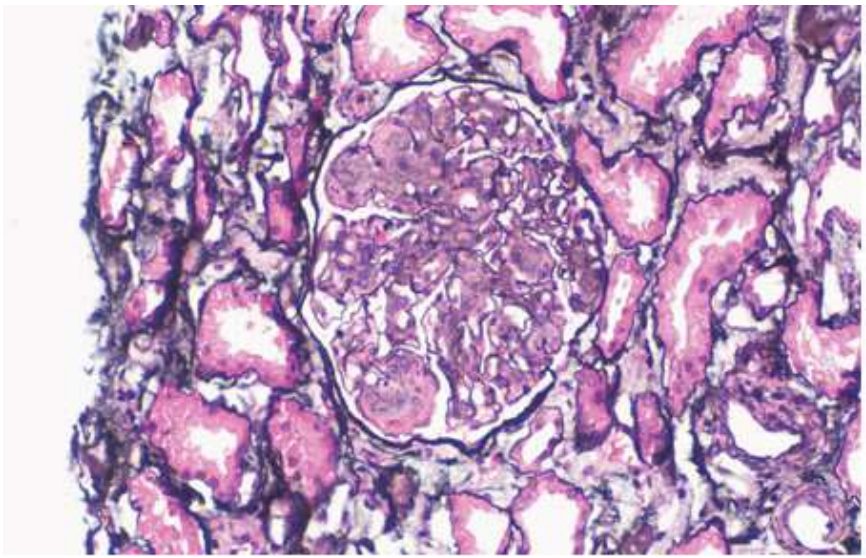
Complications of myeloma

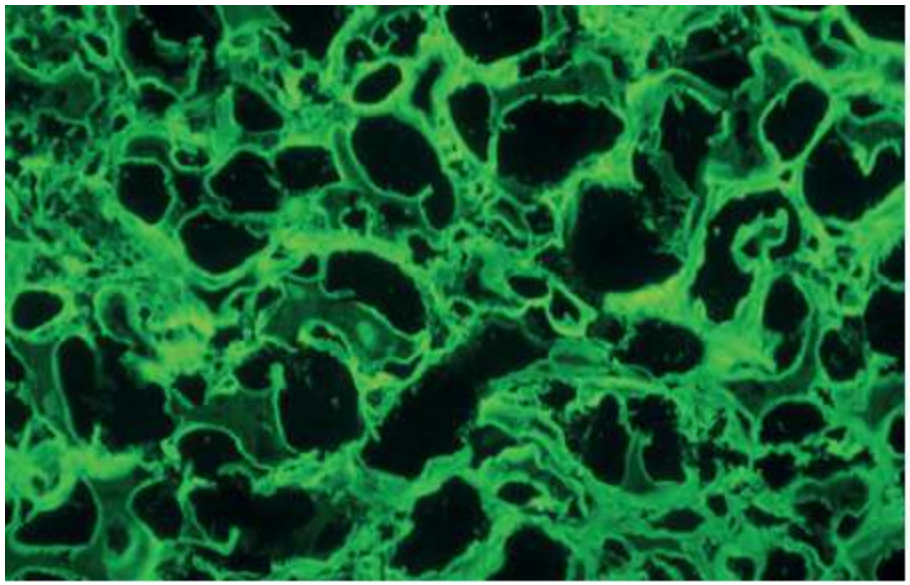
- Immunoglobulin (Bence-Jones protein) deposition leads to nodular mesangial expansion with granular deposits of immunoglobulin.
- Macrophages and giant cells may be seen.
- Does not involve vessels.
- Immunoglobulin demonstrated on gomerular tufts and renal tubules with immunofluorescent staining.
- No deposits on electron microscopy.

Complications of myeloma

- Combine with Tamm-Horsfall protein to produce tubular casts.
- Complications of dehydration, hypercalcemia, hyperuricemia.

Light chain deposition disease





Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com
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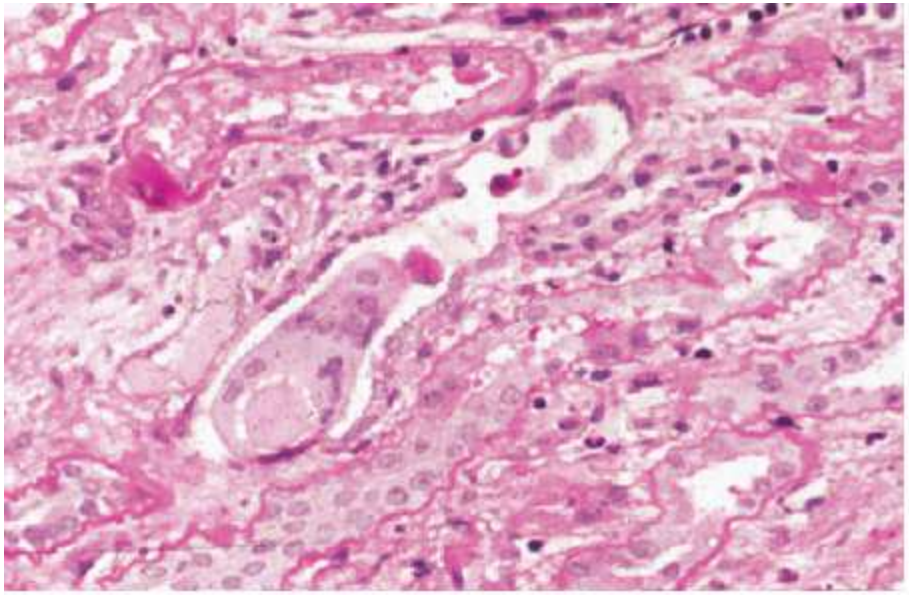
Fig. e9-14 Accessed 03/17/2010

There is mesangial expansion, often nodular by light microscopy (left). Immunofluorescence shows monoclonal staining of tubules and glomerular tufts (right). More commonly kappa light chain is involved.
(ABF/Vanderbilt Collection.)

Light chain cast nephropathy



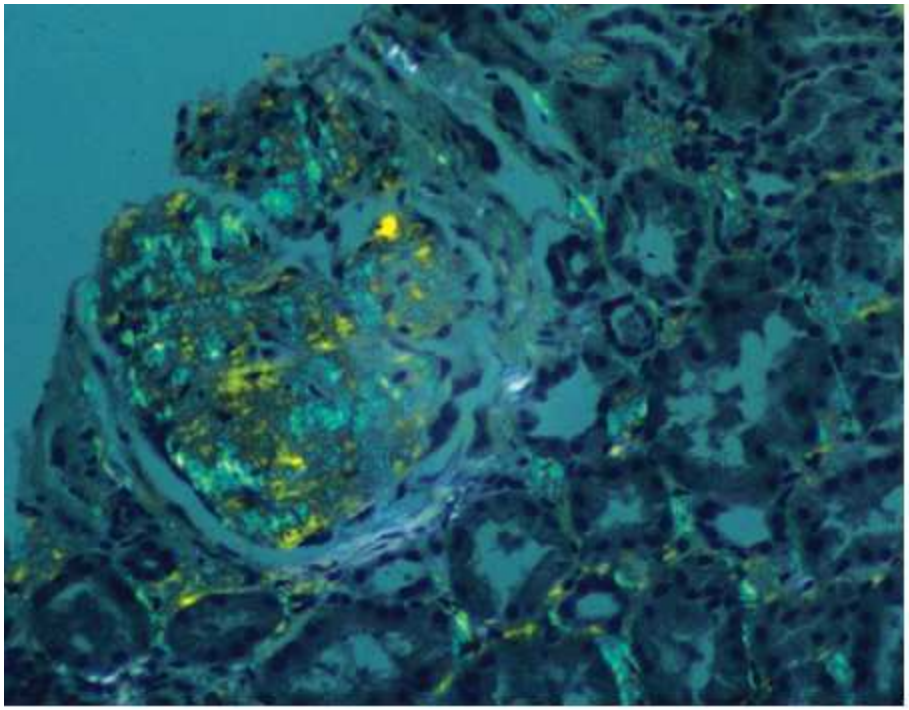
Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com

Monoclonal light chains precipitate in tubules and result in a syncytial giant cell reaction surrounding the cast, and a surrounding chronic interstitial nephritis with tubulointerstitial fibrosis.

(ABF/Vanderbilt Collection.)

Fig. e9-15 Accessed 03/17/2010

Amyloidosis



Amyloidosis shows amorphous, acellular expansion of the mesangium, with material often also infiltrating glomerular basement membranes, vessels, and in the interstitium, with apple-green birefringence by polarized Congo red stain. The deposits are composed of randomly organized 9- to 11-nm fibrils by electron microscopy. Principally AL or AA type amyloid (Igλ).

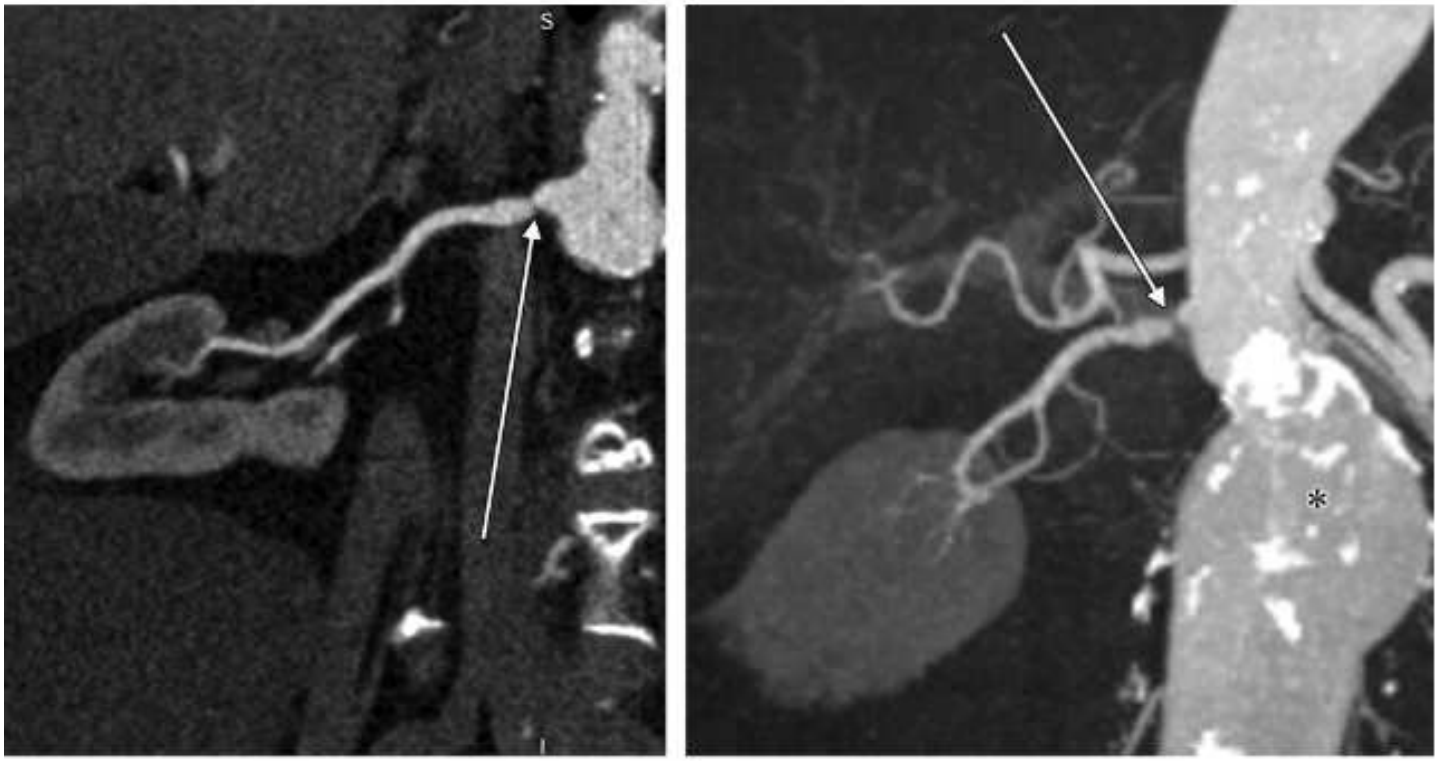
(ABF/Vanderbilt Collection.)

Fig. e9-13 Accessed 03/17/2010

Hypertension

- 70% of the causes of renovascular hypertension are due to arteriosclerosis of the renal artery.
- Estimated GFR (MDRD formula) more accurate than 24h creatinine clearance in chronic renal disease if eGFR <60ml/min.
- Cystatin C more accurate prognostic marker
- ACE inhibitor plus hydrochlorthiazide plus angiotensin receptor blocker in stepwise fashion.
- Control glucose, lipids.
- Sucroferrose oxyhydroxide to reduce phosphate levels (ferritin stable after 24 weeks of use).
- No dihydropiyridines, COX-2 inhibitors.

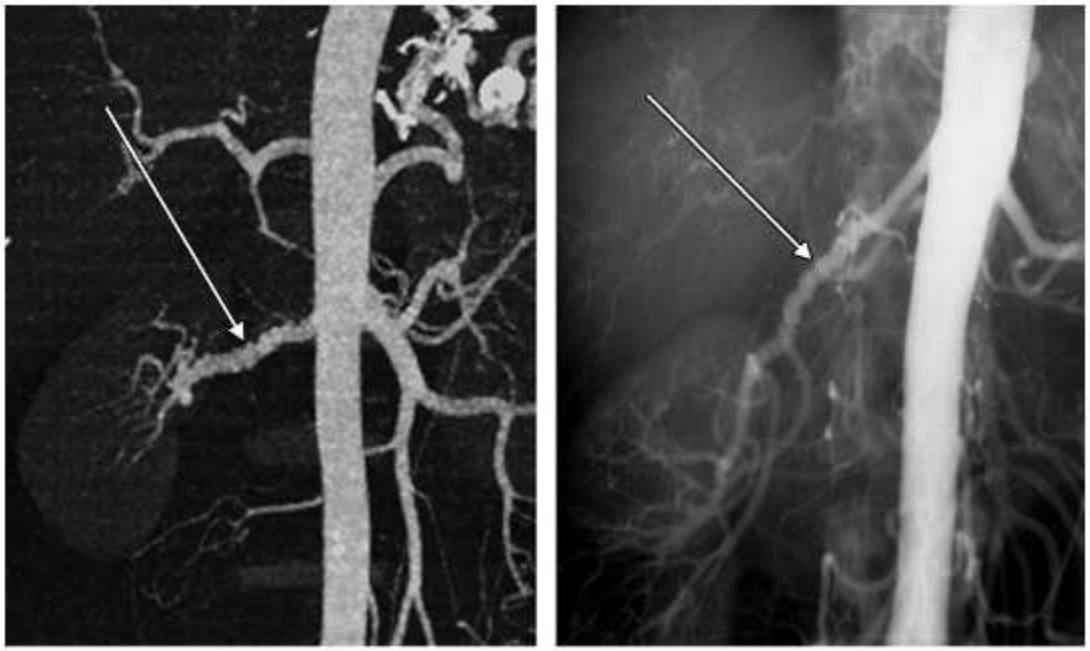
Renal artery stenosis



https://pubs.rsna.org/doi/pdf/10.1148/rg.2017160060
Figure 4
Accesssed 02/20/20

Atherosclerotic renal arterystenosis. (a) coronal maximum intensity projection (b) images from a CT angiogram show a focal severe short segment of narrowing (arrow) of the proximal renal artery. Additional atherosclerotic changes and a fusiform aneurysm are present in the infrarenal abdominal aorta (*in b).

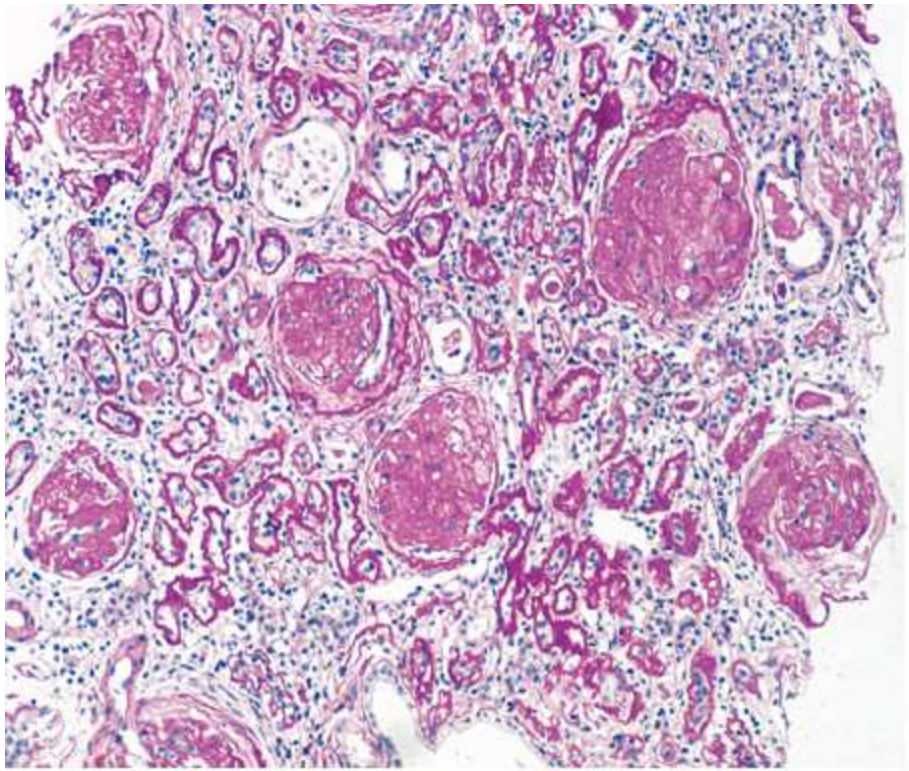
Fibromuscular disease



https://pubs.rsna.org/doi/pdf/10.1148/rg.2017160060
Figure 5.
Accessed 02/20/2020

(a) CT angiogram shows a “string of pearls” appearance (arrow) of the right main renal artery. This appearance is consistent with fibromedial dysplasia, the most common subtype. (b) Digital subtraction angiogram confirms the presence of multiple alternating areas of narrowing and dilatation (arrow) of the right renal artery.

Arteriolar nephrosclerosis

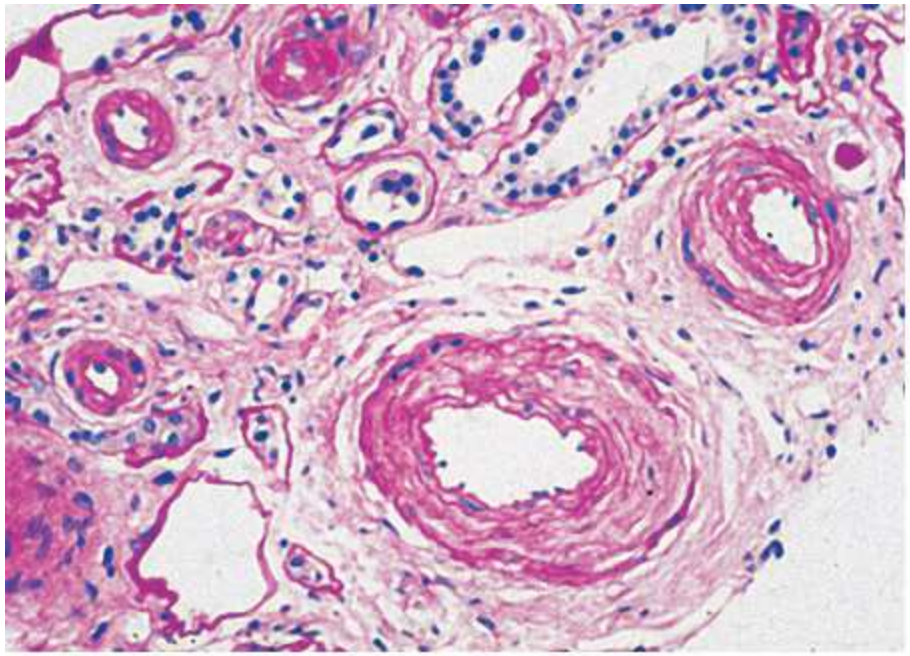


Hypertension-associated injury often manifests extensive global sclerosis of glomeruli, with accompanying and proportional tubulointerstitial fibrosis and pericapsular fibrosis, and there may be segmental sclerosis. Kidney may be scarred and show superficial petechiae (“flea bitten” appearance).

(ABF/Vanderbilt Collection.)

Fig. e9-19 Accessed 03/17/2010

Malignant hypertension



The vessels show disproportionately severe changes of intimal fibrosis, medial hypertrophy ("onion skinning"), and arteriolar hyaline deposits (fibrinoid necrosis) .

(ABF/Vanderbilt Collection.)

Fig. e9-20 Accessed 03/17/2010

Diabetic nephropathy

- Asymptomatic until renal failure presents
- Most common cause of end stage renal disease
- Microalbuminuria if spot urine ratio of albumin to creatinine is 30-299 (mcg/mg).
- Microalbuminuria presents 10-15 years after onset of diabetes mellitus;
- Progresses in 80% over the ensuing 10-15 years
- End stage renal disease develops in 50% of type I diabetes mellitus patients with overt nephropathy within 10 years (75%, 20 years);
- For type II, 20% within 20 years

Diabetic nephropathy

- Non-enzymatic glycosylation of proteins
- Affects glomerular basement membrane
- Protein into mesangium
- Nodular change
- Affects both afferent and efferent arterioles
- Hypertension

Diabetic nephropathy

- Screen for microalbuminuria at the time of diagnosis for patients with type 2 diabetes mellitus.
- Screen for microalbuminuria at year 5 for patients with type 1 diabetes mellitus.
- First void specimen preferred.
- Else, check at same time on repeat specimens (diurnal variation present).
- Check renal function annually.
- Screen for retinopathy as well.
- Control hypertension and diabetes with an ACE inhibitor or Angiotensin Receptor Blocker and an SGLT2 inhibitor.

Diabetic nephropathy

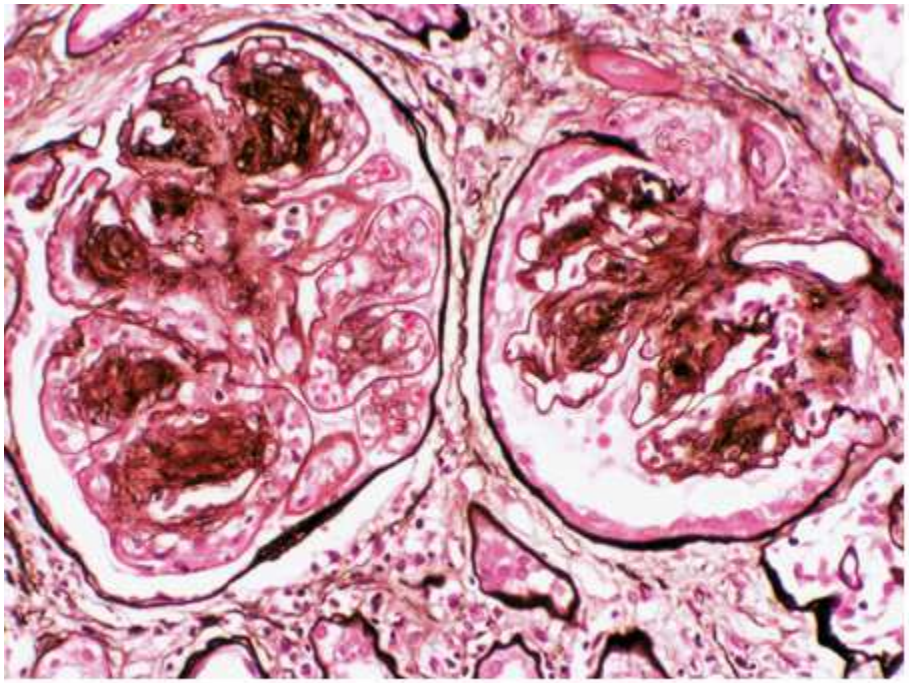


Fig. e9-18 Accessed 03/17/2010

There is nodular mesangial expansion, so-called Kimmelstiel-Wilson nodules, with increased mesangial matrix and cellularity, microaneurysm formation in the glomerulus on the left, and prominent glomerular basement membranes without evidence of immune deposits and arteriolar hyalinosis of both afferent and efferent arterioles.

(ABF/Vanderbilt Collection.)

Chronic kidney disease

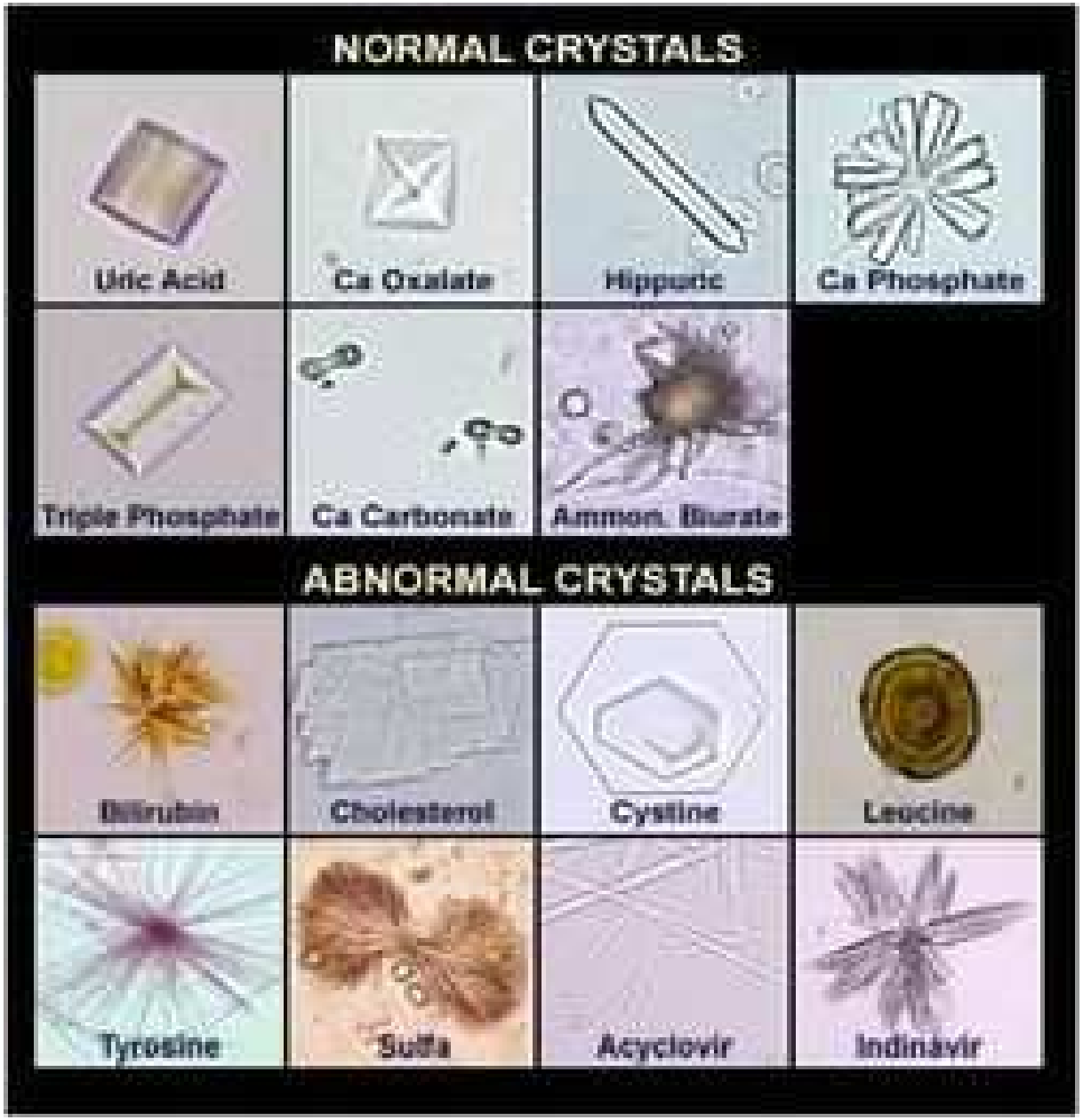
- **Laboratory diagnosis**
- GFR <60ml/min/1.73m^2 BSA
- albumin (mg)/creatinine (g) <30 (urine)
- eGFR groupings
- >90, 60-89, 45-59, 30-44,<30 ml/min
- eGFR based on cystatin -creatinine calculation corrected for sex, age, race, BMI most accurate
- BMI lower than 25 or higher than 31 also associated with diminished GFR

Nephrolithiasis

- Present with excruciating back and flank pain which may radiate to abdomen or groin.
- Abdominal tenderness is unusual.
- Hematuria is usually present.
- Its absence does not exclude the diagnosis.
- Calcium oxalate stones (75%)
- Uric acid stones (up to 10%)
- Struvite or magnesium ammonium phosphate stones (15%, often secondary to infection)
- Calcium phosphate stones
- Cystine stones (1-2%)

Nephrolithiasis

- Supersaturation secondary to increased salt excretion with inadequate diluting fluid volume leads to stone formation
- Non-contrast helical CT renal scan is test of choice. Positive likelihood ratio (LR+, 48); LR-, 0.05.
- Nifedipine increases likelihood of stone passage.
- Lithotripsy or uteroscopy to remove persistent ureteral stones.



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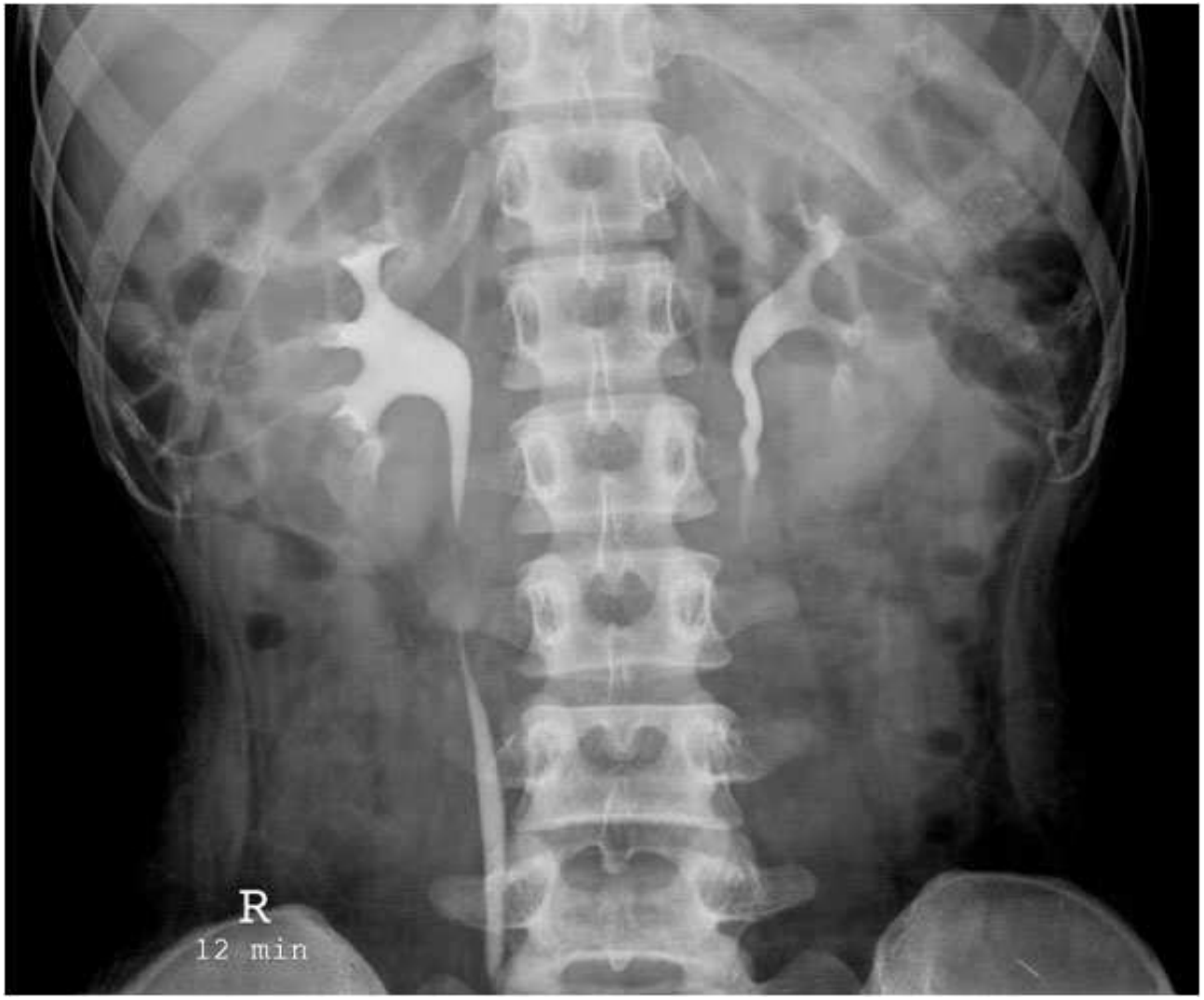
Accessed 02/20/2020

Ureteral obstruction



http://cfs2.tistory.com/upload_control/download.blog?fhandle=YmxvZzMyNTkxQGZzMi50aXN0b3J5LmNvbTovYXR0YWNoLzQvNDI4LmpwZw
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Accessed 02/20/2020

Congenital anomalies

- 10% newborns have potentially serious urinary abnormalities.
- Renal dysplasia (characterized by immature mesenchyme and tubular ducts) and hypoplasia account for 20% of renal failure in children.
- Usually unilateral
- Adult polycystic disease accounts for 10% of renal failure in adults.
- WT1 gene abnormalities account for structural abnormalities.

Congenital anomalies

- Enzymatic defects in transport (cystinuria) as well as metabolic defects (renal tubular acidosis) may also be seen.
- Horseshoe kidney is common.
- In pelvis, generally.

Adult onset polycystic disease

- Often present with hematuria or flank pain.
- May be hypertensive, have a history of renal stones or urinary tract infections.
- Multiple renal cysts, hepatic cysts if both alleles of the affected gene involved.
- 97% with von Meyenburg complexes in liver
- 10-30% have cerebral (“Berry”) aneurysm
- 20% have mitral valve prolapse
- Renal failure onset 40-50 years of age.

Adult onset polycystic disease

- Autosomal dominant.
- 85% involve PKD1 gene (16q13.3);
- PKD2 gene at 4q21 and associated with milder disease.
- Genes code for integral (cilium based) membrane proteins that act to regulate Ca^{2+} flow in renal tubular cells.
- Intraluminal fluid volume expands.

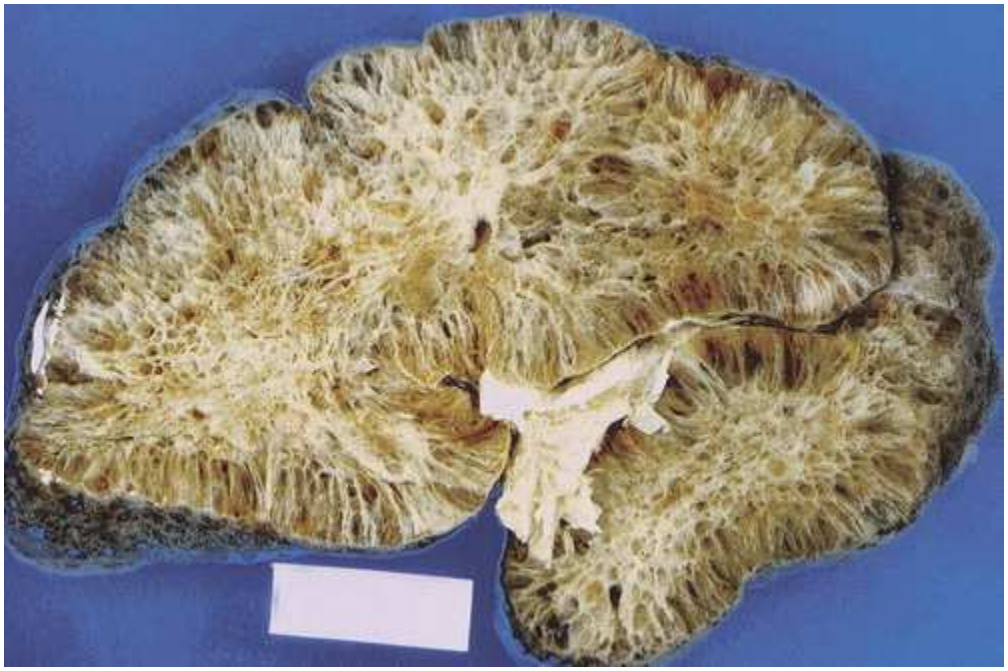
Adult onset polycystic disease

https://webpath.med.utah.edu/RENAHTML/RENAL049.html
Accessed 02/20/2020

Childhood onset polycystic disease

- Enlarged, cystic kidneys at birth
- May see congenital hepatic fibrosis
- If not transplanted, die in childhood from renal failure
- Autosomal recessive.
- PKHD1 gene (6p21-23)
- Codes for immunoglobulin like (cilium based) integral membrane protein with a large extracellular region that has a role in collecting duct and biliary differentiation.

Childhood onset polycystic disease



Photograph of a bivalved kidney reveals multiple ectatic collecting ducts, radially oriented from the center of the kidney to the surface. The corticomedullary junction is obliterated by the numerous abnormal ducts.

https://pubs.rsna.org/doi/figure/10.1148/radiographics.20.3.g00ma20837#F9B
Figure 4
Accessed 02/20/2020

Medullary cystic disease

- Familial juvenile nephronophthis
- Chronic renal failure onset in childhood.
- Salt-wasting, polyuria, growth retardation, anemia may be noted.
- Shrunken kidneys
- Cortico-medullary cysts
- Autosomal recessive.
- NPH1, NPH2, NPH3 mutations affect ciliary based proteins.

Medullary sponge kidney

- Usually presents in childhood
- May present with:
- Hematuria
- Urinary tract infection
- Urinary stones
- Medullary cysts on imaging studies.
- Does not progress to end stage renal disease

Medullary cystic disease

- Acquired renal cystic disease
- May see simple cysts in normal kidneys or cystic degeneration of kidneys in end-stage disease.
- Hematuria as presenting sign.
- Erythrocytosis may be present at end-stage.
- Retention cyst
- Derived from tubular obstruction

Tubulointerstitial disease

- Acute tubulointerstitial nephritis
- Rapid clinical onset
- Histologically:
- Interstitial edema, often accompanied by leukocytic infiltration of the interstitium and tubules, and focal tubular necrosis.
- There is no glomerular injury.
- 15% of cases with acute renal failure.

Tubulointerstitial disease

- Chronic interstitial nephritis
- Infiltration with predominantly mononuclear leukocytes
- Prominent interstitial fibrosis
- Widespread tubular atrophy.

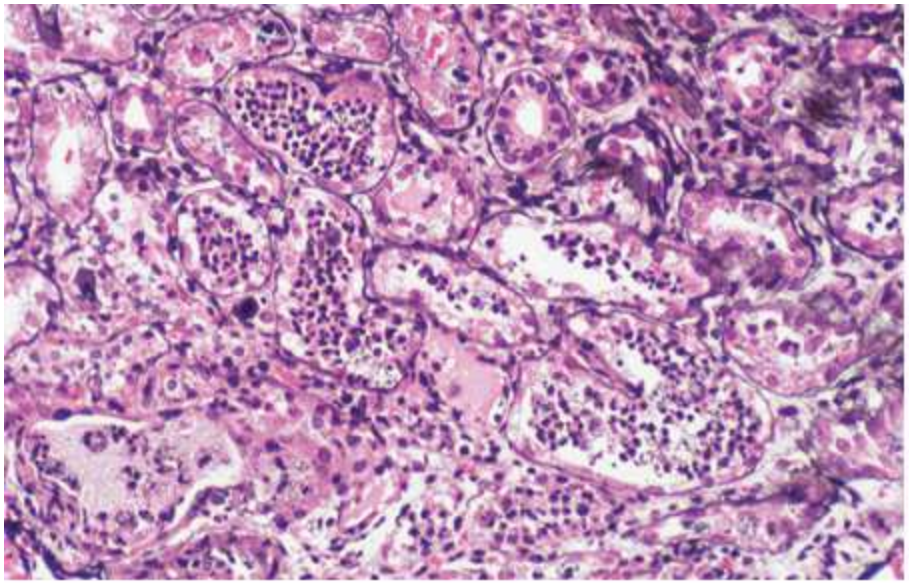
Tubulointerstitial disease

- Pyelonephritis
- 30% of children with pyelonephritis associated with vesico-ureteral reflux.
- Intrarenal reflux common at upper and lower poles of kidney.
- Females have short urethra
- Common causes:
- Escherichia coli
- Proteus
- Klebsiella
- Enterobacter
- Streptococcus fecalis

Tubulointerstitial disease

- Immunocompromised:
- Usually ascending infection.
- Polyoma virus
- CMV
- Adenovirus

Acute pyelonephritis



There are characteristic intratubular plugs and casts of neutrophils with inflammation extending into the surrounding interstitium, and accompanying tubular injury.

(ABF/Vanderbilt Collection.)

Fig. e19-235 Accessed 03/17/2010

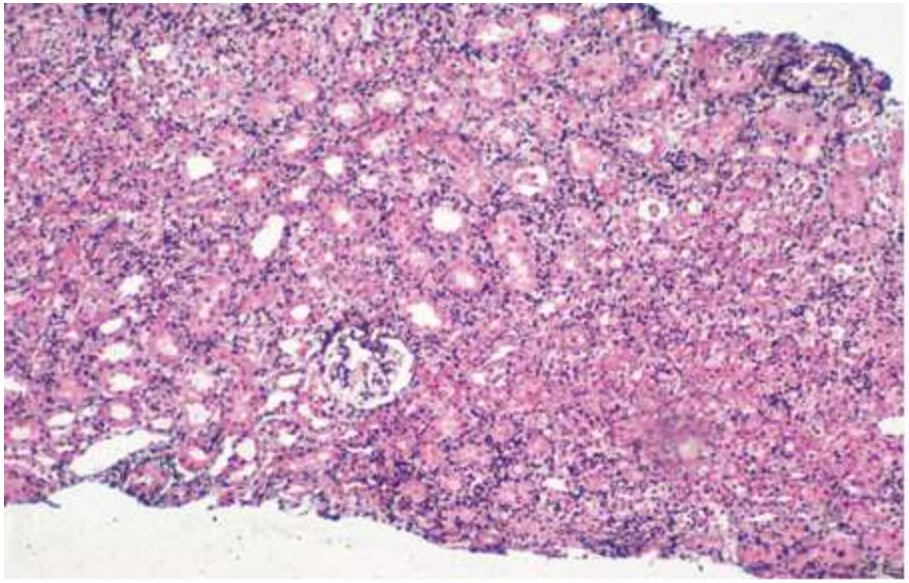
Tubulointerstitial disease

- Interstitial disease
- There may be necrosis of papillae. Scarring may result.
- Causes:
- Phenacetin containing analgesics (reactive oxygen species)
- Heavy metals
- Drug reactions (eosinophilic infiltrates)
- Crystal disease (urates, oxalates)

Tubulointerstitial disease

- NSAID nephropathy is of hemodynamic origin (COX 2 prominent in kidneys).
- Eosinophils in the urine has a positive likelihood ratio (LR+) of 3.9; LR-, 0.4.
- Biopsy diagnostic.

Acute interstitial nephritis



There is extensive interstitial lymphoplasmocytic infiltrate with mild edema and associated tubular injury which is frequently associated with interstitial when caused by a drug hypersensitivity reaction.

(ABF/Vanderbilt Collection.)

Fig. e19-25 Accessed 03/17/2010

Acute kidney injury

- increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 mcmol/L) within 48 hours
- increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within prior 7 days
- urine volume < 0.5 mL/kg/hour for 6 hours
- Presume normal baseline if older GFR not noted

Acute tubular necrosis

- Clinicopathologic condition characterized by destruction of tubular epithelial cells and acute loss of renal function.
- Most common cause of acute renal failure.
- Ischemia due to decreased or interrupted renal blood flow is principal cause.
- Obstruction noted in 17% of outpatient cases with acute renal failure (hospitalized patients, 2%).
- Nephrotoxic causes as well

Acute tubular necrosis ischemic

- Focal epithelial necrosis at multiple points along the nephron on biopsy.
- Straight portion of the proximal tubule and ascending thick limb in the renal medulla particularly vulnerable to injury.
- Hyaline casts and pigmented granular casts noted particularly in distal tubules and collecting ducts on biopsy.
- Casts contain Tamm-Horsfall protein as well as plasma proteins.

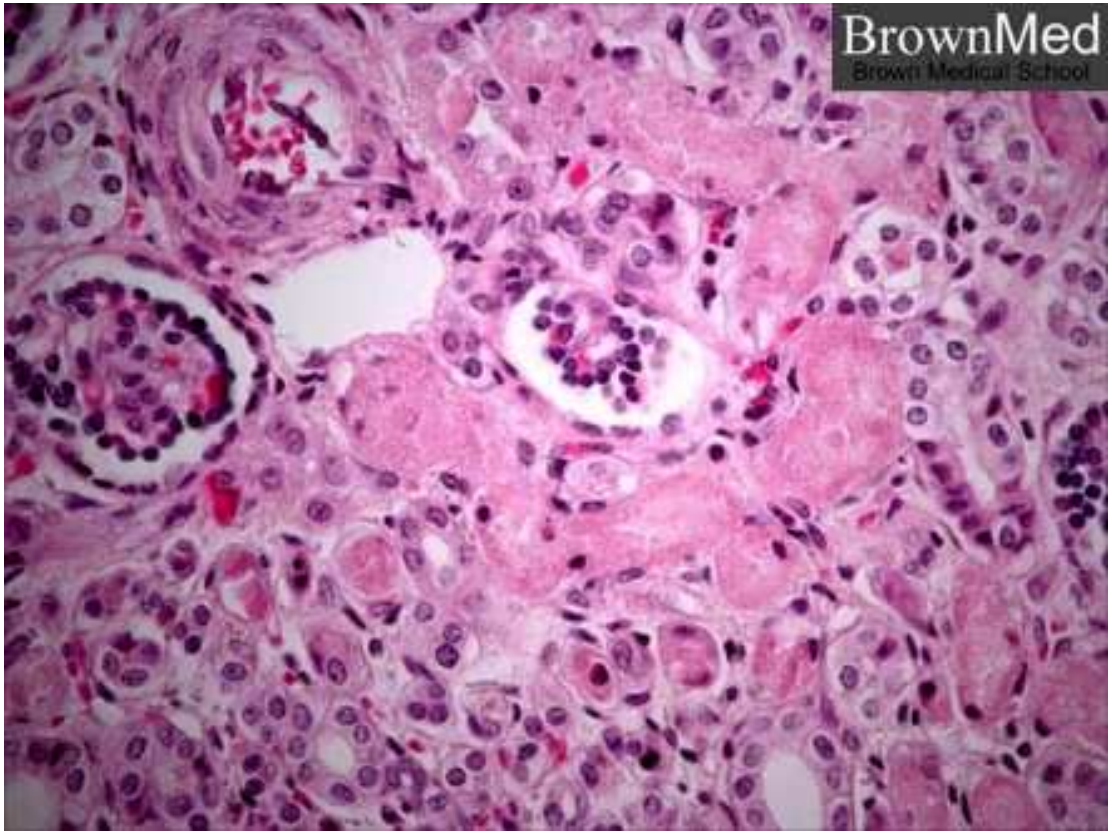
Acute tubular necrosis ischemic

- Ischemia leads to depletion of ATP.
- Increased intracellular Ca^{2+} leads to activation of proteases (principally calpain), phospholipases, and capsases.
- Cell polarity is altered as Na^{+}-K^{+}-ATPase is redistributed from the basolateral membrane to the luminal surface.
- This leads to increased Na^{+} delivery to distal tubules and leads to vasoconstriction through the production of endothelin and decreased production of vasodilators

Acute tubular necrosis ischemic

- Ischemic tubular cells express cytokines (MCAP1) and adhesion molecules (ICAM1)
- Lead to aggregation of tubular cells and luminal obstruction.
- TGF-α, insulin-like growth factor 1, and hepatocyte growth factor key to renal tubular repair.

Acute tubular necrosis ischemic



Necrosis and sloughing of epithelial cells of the proximal convoluted tubules. The glomeruli and distal convoluted tubules are preserved.

https://www.brown.edu/Courses/Digital_Path/systemic_path/renal/atn.html
Accessed 02/20/2020

Acute tubular necrosis nephrotoxic

- Extensive necrosis of tubular cells along proximal tubule
- Carbon tetrachloride:
- Neutral lipid accumulation and fatty change in injured cells
- Ethylene glycol:
- Ballooning and hydropic changes of proximal tubules
- Calcium oxalate crystals in tubular lumina
- Hemoglobin or myoglobin:
- Numerous deeply pigmented, red-brown casts in distal and collecting ducts

Acute tubular necrosis nephrotoxic

- Indinavir:
- Intraluminal clear crystals with mononuclear reaction
- Lead
- Dark intranuclear inclusions
- Mercury
- Large acidophilic inclusions
- Tenofovir
- Proximal tubular eosinophilic inclusions (giant mitochondria)
- Vancomycin
- Acute interstitial nephritis with lymphocytic and eosinophilic infiltrate

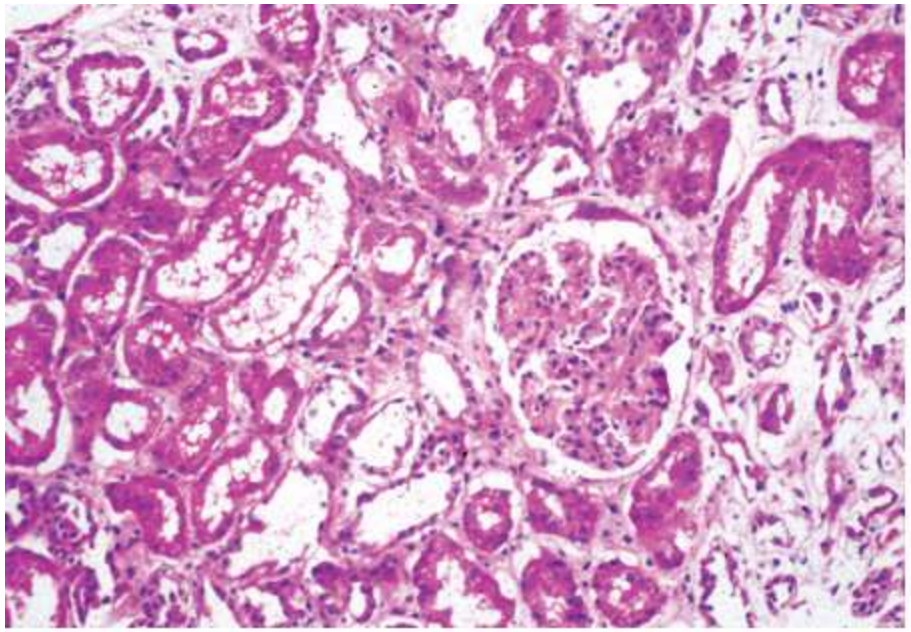
Acute tubular necrosis

- Ultrasound used to exclude obstruction as cause of acute renal failure.
- Once the tubules are damaged (ATN), urinary concentration is lost (urine specific gravity 1.010) and Na^+ is lost in the urine.
- FE_{Na+} >2% (if <1%, hypoperfusion)
- FE_{urea} >50% (<35%, hypoperfusion).
- Not affected by diuretic use.

Acute tubular necrosis

- Urine specific gravity >1.010 and urine osmolality >400 mOsm/kg are associated with hypoperfusion.
- In hospital mortality 37%.
- Final recovery generally occurs over 1-2 weeks in 60% of survivors.
- Dialysis required by the others.

Acute tubular necrosis



Complication of renal artery vasoconstriction coupled with sympathetic stimulation in a response to prolonged fall in blood pressure. There is extensive flattening of the tubular epithelium and loss of the brush border, with mild interstitial edema.

(ABF/Vanderbilt Collection.)

Fig. e9-24 Accessed 03/17/2010

Renal tubular acidosis

- Growth failure and systemic acidosis.
- Type I
- Deficiency in the secretion of H^+ from the distal tubules.
- Unable to acidify urine (urine pH >6).
- Positive urine anion gap without hyperkalemia.
- Secondary disease:
- Sjögren's and SLE
- Sickle cell anemia
- Hyperparathyroidism and hyperthyroidism

Renal tubular acidosis

- Type II
- Deficient bicarbonate absorption in proximal tubules. Urine pH normal
- Negative urine anion gap.
- In Fanconi's syndrome there is also loss of amino acids, glucose, water, and other electrolytes.
- Cystinosis
- Wilson's disease
- Secondary causes include ifosfamide and acetazolamide
- Type III is a combination of types I and II

Renal tubular acidosis

- Type IV
- Associated with aldosterone deficiency or decreased distal tubular responsiveness (particularly in children).
- Hyperkalemic, hypochloremic acidosis.
- Urine pH <5.5.
- Positive urine anion gap with hyperkalemia.
- May be caused by obstructive uropathy.
- Correct any obstruction.

Renal tubular acidosis

- Secondary causes:
- Spironolactone, ACE inhibitors, or angiotensin receptor blockers
- NSAIDs
- Trimethoprim or pentamidine
- Heparin

- Restore normal urinary acidification with administration of citrate or bicarbonate (type II)

End stage renal disease

- Elevated BUN
- Anemia (diminished erythropoietin)
- Platelet dysfunction
- Diminished conversion of vitamin D (1-α hydroxylase)
- Secondary hypoparathyroidism
- Fibrinous pericarditis

End stage renal disease

- Major causes
- Diabetes (40%)
- Hypertension (20%)
- Glomerulonephritis (18%)
- Tubulointerstitial disease (7%)
- Cystic kidney disease (5%).

Dialysis

- Peritoneal dialysis equivalent to a GFR of 10ml/min.
- May be ambulatory, continuous.
- Hemodialysis equivalent to a GFR of 200ml/min. Requires hours, confinement.
- 2 year life span from when dialysis begins;
- 10-20+ year life span (age dependent) if transplanted.

Transplantation

- Recipients of HLA identical allografts from a monozygotic twin usually receive azathioprine and steroids only for three months.
- They are subsequently maintained without immunosuppressive medication given that the allograft and recipient are immunologically identical.

Transplant rejection

- Hyperacute
- Preformed circulating antibodies (usually ABO)
- Type II reaction
- Vessel thrombosis threatens graft
- Higher risk in multiparous women
- ABO mismatch transplant donor and recipient
- Acute
- Antibody mediated post-exposure
- Chronic
- Antibody identified in circulation but not in graft
- Vasculitis

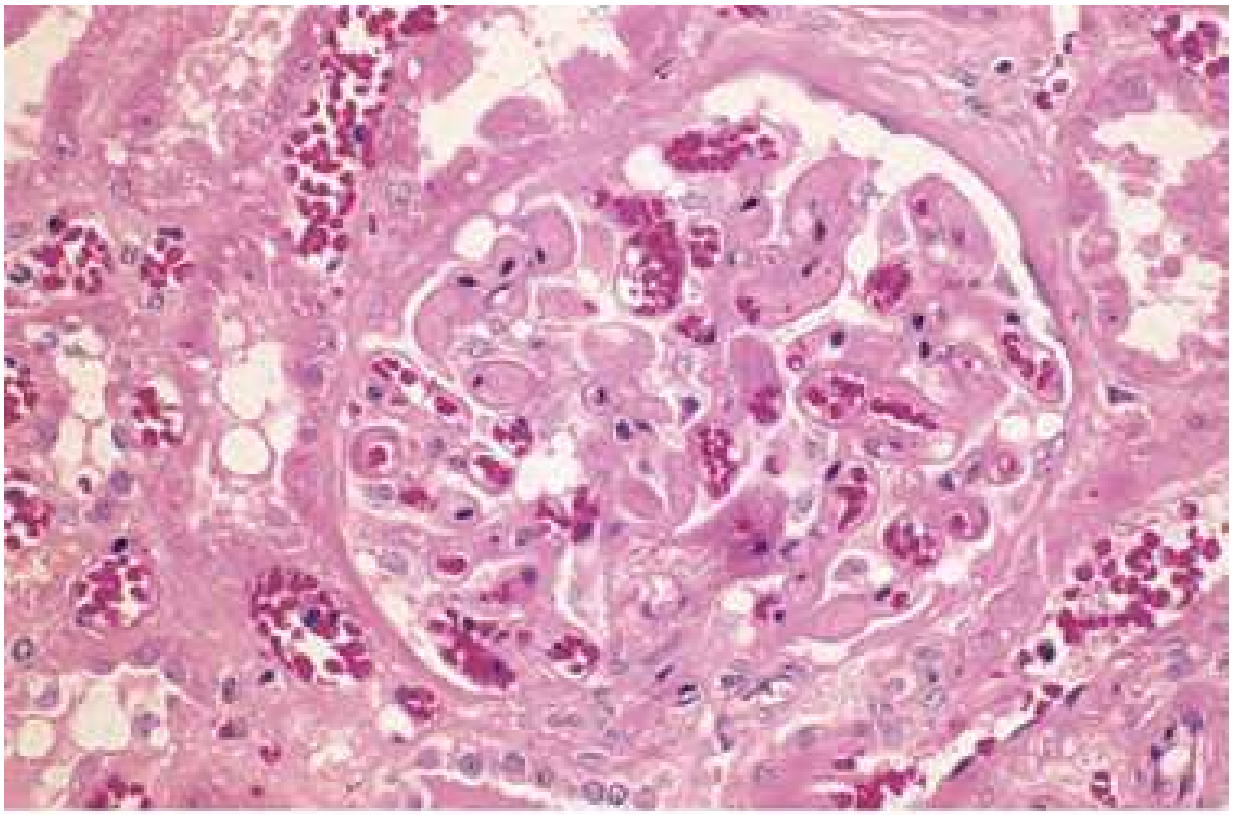
Transplant rejection

- Acute cell-mediated
- Most common
- Type IV reaction
- CD8+, CD4+ cells
- Inflammatory cytokines
- Interstitial and endothelial destruction
- Reversible
- Chronic cell-mediated
- Cytokines that promote fibrosis and endothelial cell proliferation

Hyperacute renal allograft rejection

- Antibody mediated
- Histopathology:
- Intense neutrophil inflammatory infiltrates
- Platelet and fibrin thrombi in glomeruli
- Severe ischemic change
- Immunoglobulin and complement deposited in membranes

Hyperacute rejection

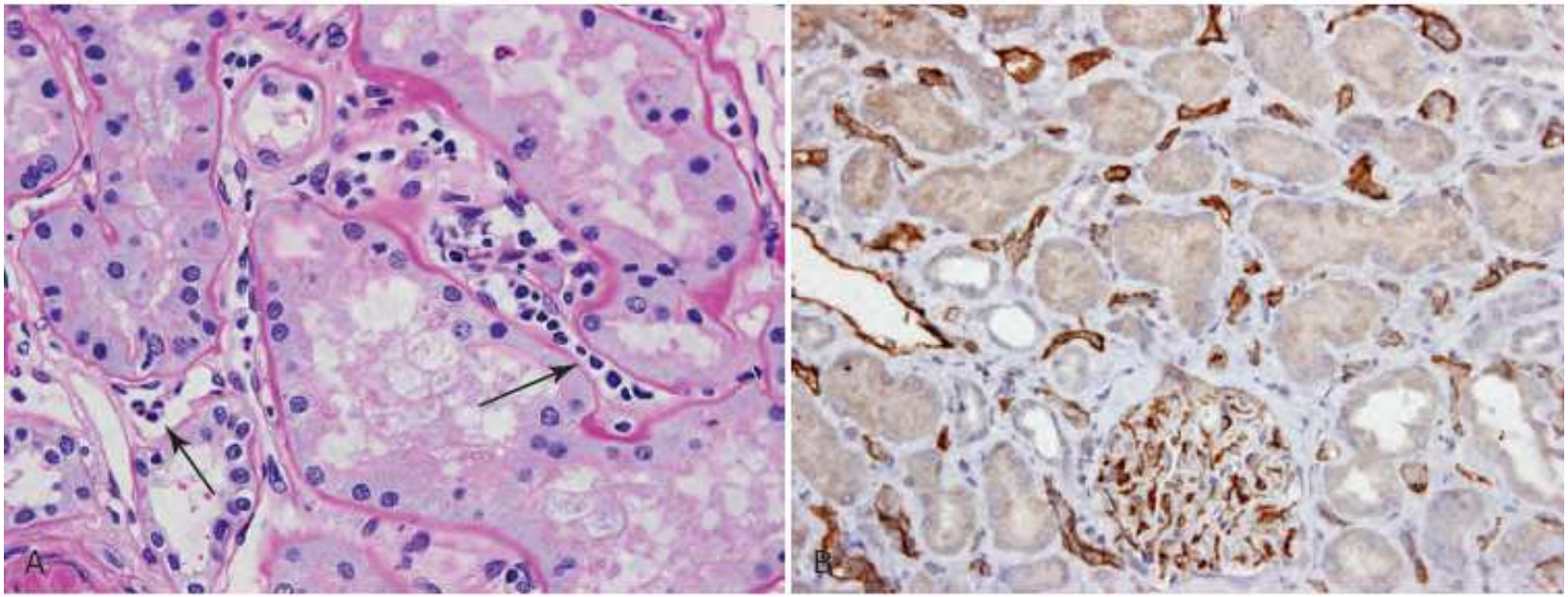


Kumar, V, Abbas, AK, Aster, JC, “Diseases of the immune system,” in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Fig. 6-33
Accessed 12/10/2019

Acute renal allograft rejection

- Antibody mediated
- Histopathology:
- Glomerular and peritubular capillaries pattern
- Inflammation of glomeruli and peritubular capillaries
- C4d deposited

Acute humoral mediated rejection

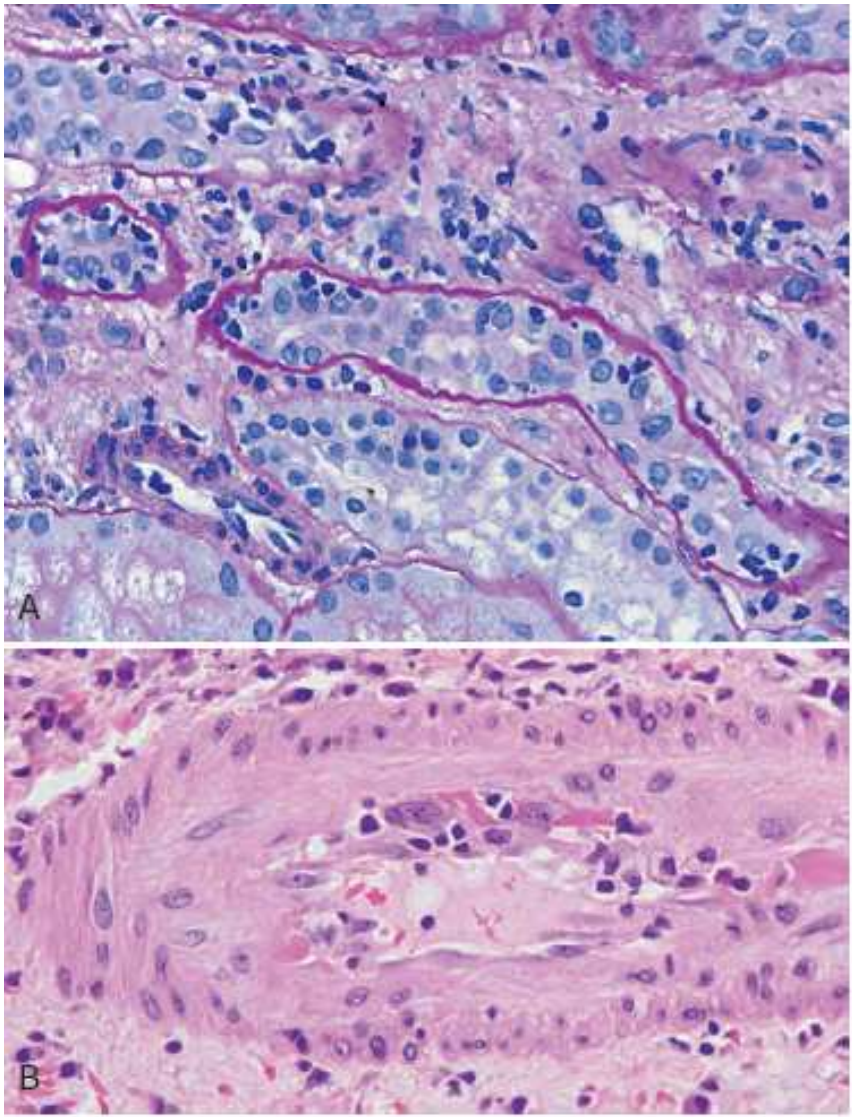


Kumar, V, Abbas, AK, Aster, JC, “Diseases of the immune system,” in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Fig. 6-35 Accessed 12/10/2019

Acute renal allograft rejection

- CD4+, CD8+ mediated
- Histopathology:
- Tubulointerstitial pattern of rejection
- Type I reaction
- Interstitial inflammation with infiltration of tubules
- Type II reaction
- Endothelial inflammation
- Type III reaction
- Necrosis of vessel wall

Acute T-cell mediated rejection

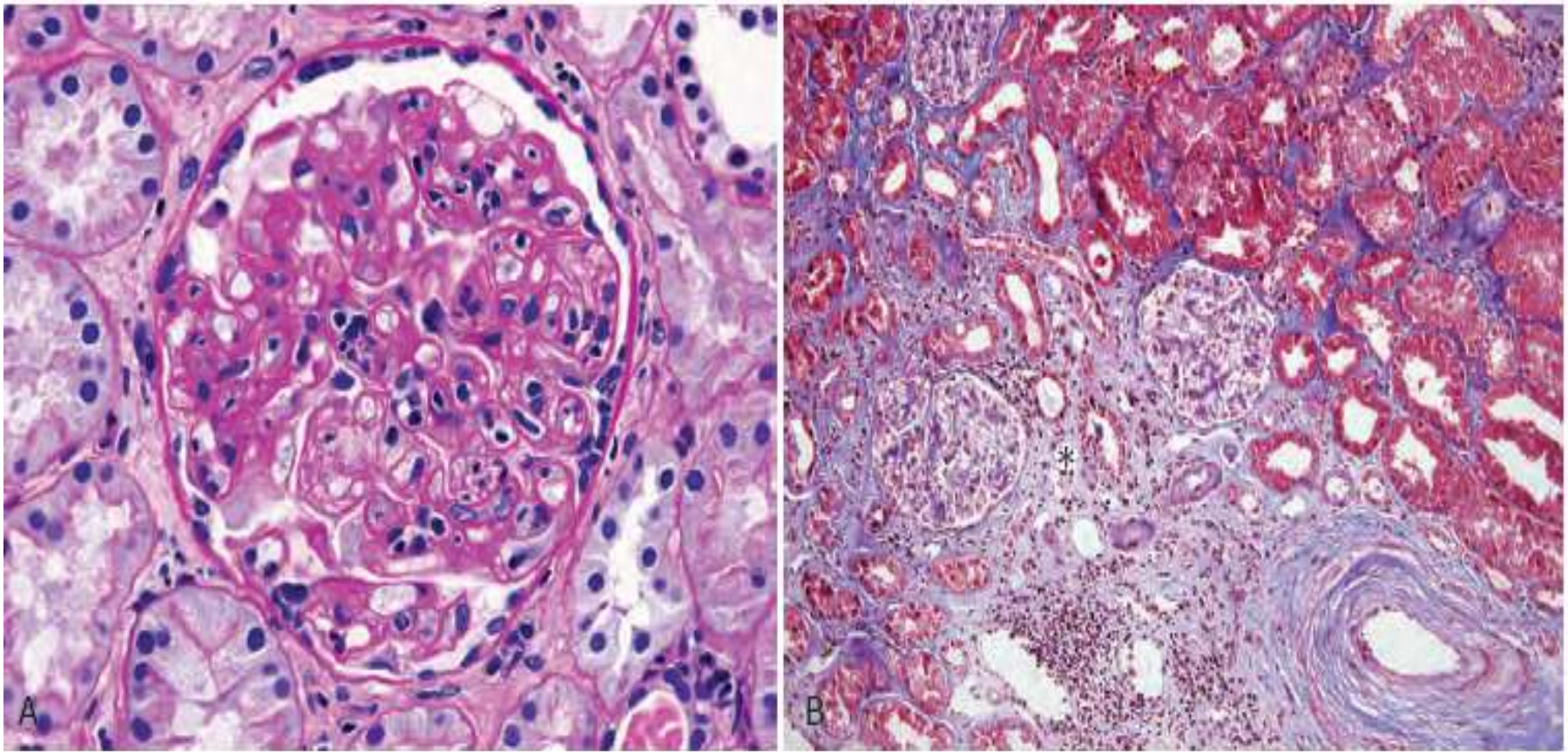


Kumar, V, Abbas, AK, Aster, JC, "Diseases of the immune system," in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Fig. 6-34
Accessed 12/10/2019

Chronic renal allograft rejection

- Histopathology:
- Intimal thickening of vessels
- Reduplication of glomerular basement membrane
- Multilayering of peritubular capillaries
- Intersititial fibrosis
- Mononuclear cell infiltrates including NK and plasma cells

Chronic rejection



Kumar, V, Abbas, AK, Aster, JC, “Diseases of the immune system,” in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Fig. 6-36
Accessed 12/10/2019

Match criteria

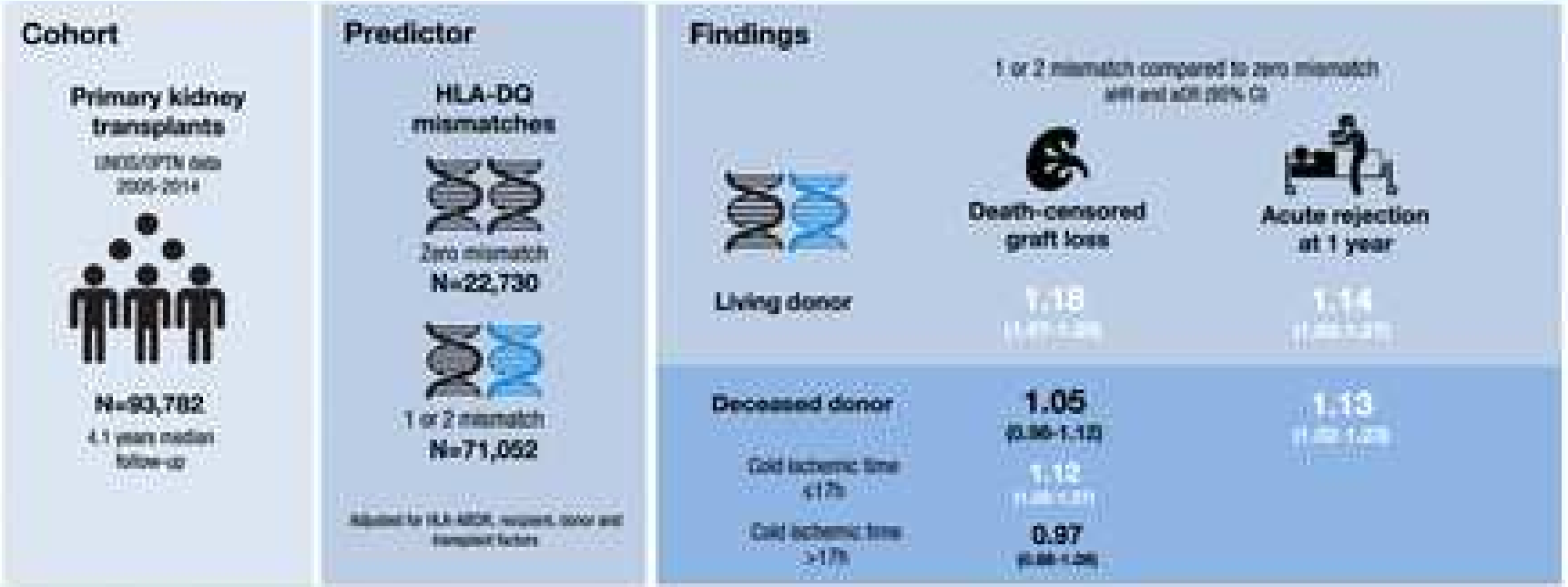
- ABO match is essential as a mismatch would lead to immediate failure of the transplant.
- For kidney transplants
- HLA match is important.
- In addition to the six antigen crossmatch, HLA-DQ is specifically examined as a mismatch at DQ is associated with poorer graft outcomes.
- 24% of transplanted patients will develop antibodies to donor DQ over a 10 year period.

Match criteria

- 1. When the recipient is placed on the transplant list,
- 2. As well as periodically during the wait for a donor,
- 3. And immediately prior to transplant,
- Tthe recipient is again screened for antibodies to HLA antigens that may attack the transplanted organ.

Is HLA-DQ mismatching associated with graft loss and acute rejection?

CJASN



Conclusions HLA-DQ mismatching is associated with graft loss and acute rejection independent of HLA-ABDR. Cold ischemic time >17 hours appears to obviate the benefit of zero HLA-DQ mismatches.

Napat Leaphorn, Jeremy Pena, Natanong Thamcharoen, Eliyahu Khankin, Martha Pavlakis, and Francesca Cardarelli. HLA-DQ Mismatching and Kidney Transplant Outcomes. CJASN doi: 10.2215/10860917.

Accessed 12/10/2019

Match criteria

- A living donor kidney may survive 12-20 years
- A deceased donor kidney may survive 8-12 years
- 93% (1 year), 75% (5 year), 48% (10 year) kidney organ survival post transplant
- 96, 85, 64% patient survivals over same time frame
- 99, 92, 79% if live donor used
- Whites and Asians constitute the largest groups of live donors
- Neither age disparity nor the presence of diabetes mellitus in the recipient affects overall graft survival

Match criteria

- Optimal size match between donor and recipient associated with greater graft survival irrespective of HLA status
- <30 kg difference in weight
- <15 cm difference in height
- Race pairing also affects survival
- Antigen subtypes not yet identified
- As there are racial disparities in kidney transplantation in the US for genetic reasons, the US has largely abandoned strict crossmatch criteria in order to increase the number of kidneys available to Blacks.

Immunosuppression

- Rejection is associated with a lymphocytic infiltrate and necrosis of the target tissue.
- Triple drug therapy with prednisone, azathioprine, and cyclosporine to diminish risk of acute rejection.
- After several months of therapy, maintenance with cyclosporine to diminish risk of chronic rejection.

Immunosuppression

- Prednisone is metabolized in the liver to prednisolone.
- Blocks release of lymphocytes into the circulation.
- Inhibits glucose transport into the cell as well as blocks phosphorylation upstream of NF-κB transcription (regulates genes involved in immune expression).
- Induction of cell death in immature lymphocytes.
- ABC cassette system (p-glycoprotien) resistance leads to increased drug efflux from cell.

Immunosuppression

- Azathioprine is an antimetabolite that antagonizes purine metabolism and may inhibit synthesis of DNA, RNA, and proteins.
- Metabolized in the liver to 6-mercaptopurine (6-MP), by glutathione S-transferase.

Immunosuppression

- Three major pathways for further metabolism of 6-MP in the liver and GI tract:
- (1) Hypoxanthine guanine phosphoribosyl-transferase (to 6-thioguanine-nucleotides, the major metabolites).
- Incorporates into DNA.
- (2) Xanthine oxidase (to 6-thiouric acid, inactive).
- Allopurinol increases toxic metabolites by blocking this pathway.
- (3) Thiopurine methyltransferase (TPMT), which forms 6-methylmercapotpurine (6-MMP).
- Blocks de novo purine synthesis.

Immunosuppression

- Cyclosporine inhibits a nuclear transcription factor that leads to a block of production and release of IL-2 and inhibits IL-2 induced activation of resting T-lymphocytes.
- Widely distributed in the body; crosses the placenta.
- ABC cassette system (p-glycoprotein) resistance leads to increased drug efflux from cell.
- Long latency period (time to which drug adequate levels are achieved).

Immunosuppression

- Mycophenolate mofetil blocks purine biosynthesis (noncompetitive inhibitor of inosine monophosphate dehydrogenase).
- May see Crohn like enterocolitis.
- Contraindicated in pregnancy.
- Rapamycin binds to mTOR.
- Inhibits T-cell response to IL-2.
- Used if calcineurin toxicity.
- OKT3 is a murine antibody that binds to CD3 (ε-chain), blocking cellular interaction with CD3 protein responsible for T-cell signal transduction.

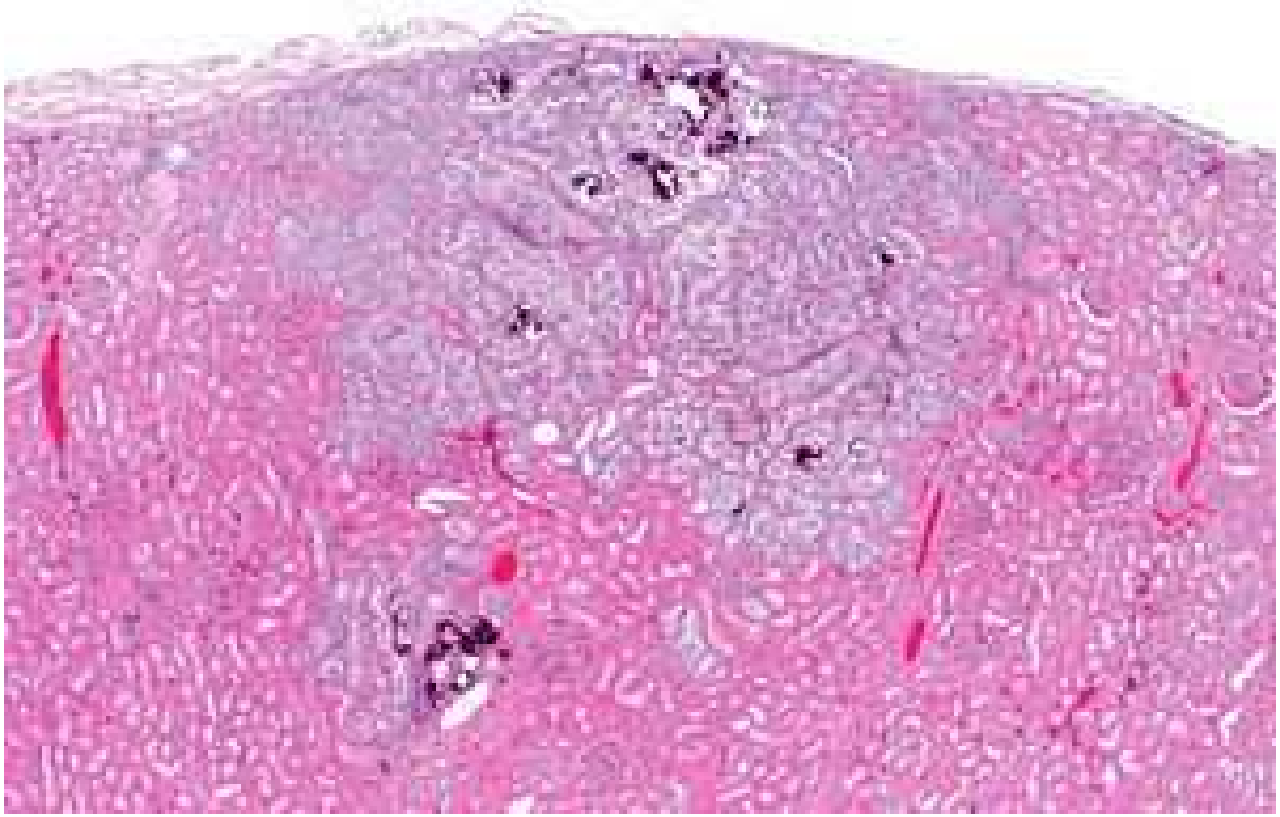
Adenoma

- Arise from renal tubular epithelium
- Usually papillary
- 7-22% of patients
- <1.5 cm in diameter
- Increased risk of metastasis if >3cm in diameter.

Adenoma

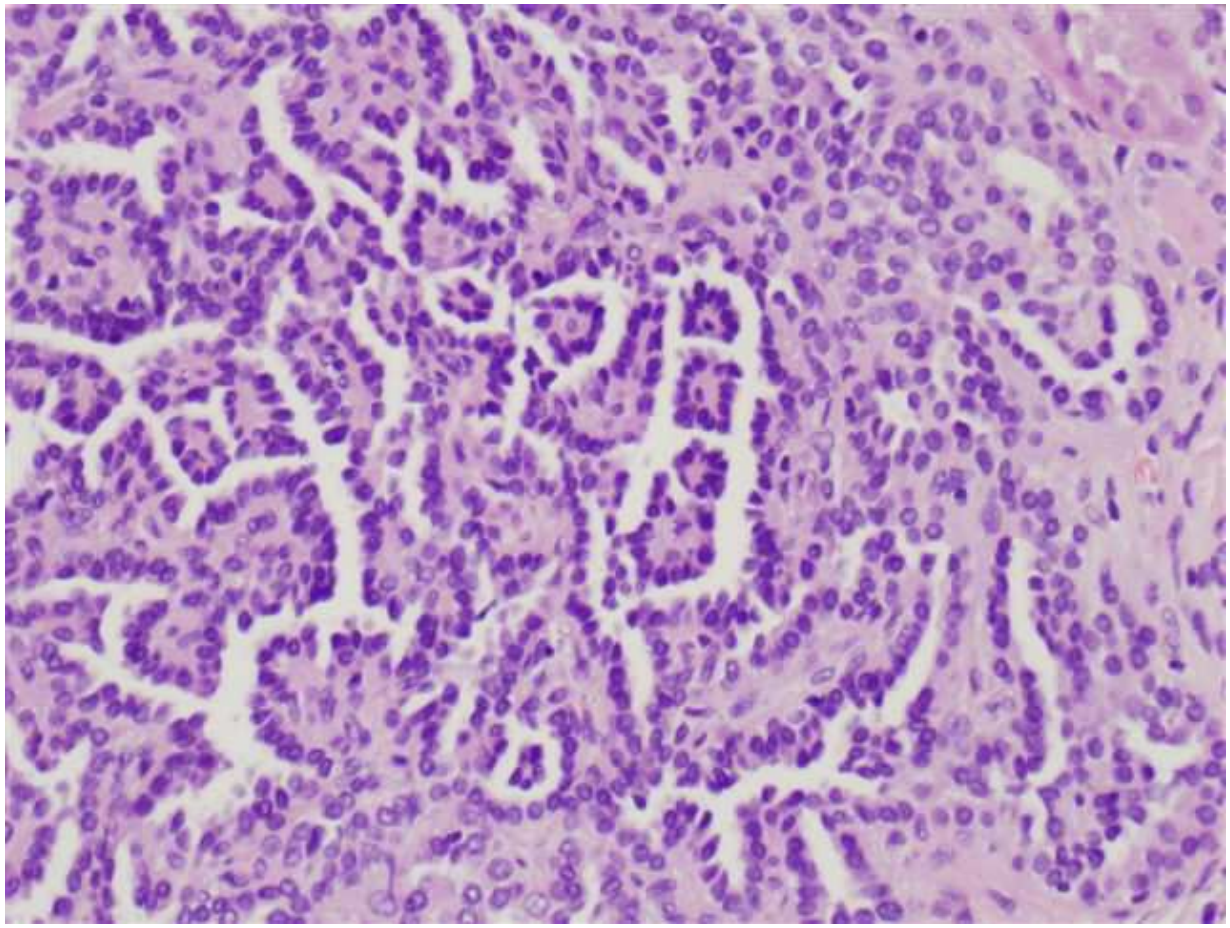
- Pale yellow-gray, discrete, well-circumscribed cortical nodules.
- Composed of complex, branching, papillomatous structures with numerous complex fronds. Cells may also grow as tubules, glands, cords, and sheets of cells.
- The cells are cuboidal to polygonal in shape and have regular, small central nuclei, scanty cytoplasm, and no atypia.

Renal papillary adenoma



https://librepathology.org/w/images/thumb/d/d6/Renal_papillary_adenoma_--_very_low_mag.jpg/300px-Renal_papillary_adenoma_--_very_low_mag.jpg
Accessed 02/20/2020

Renal papillary adenoma

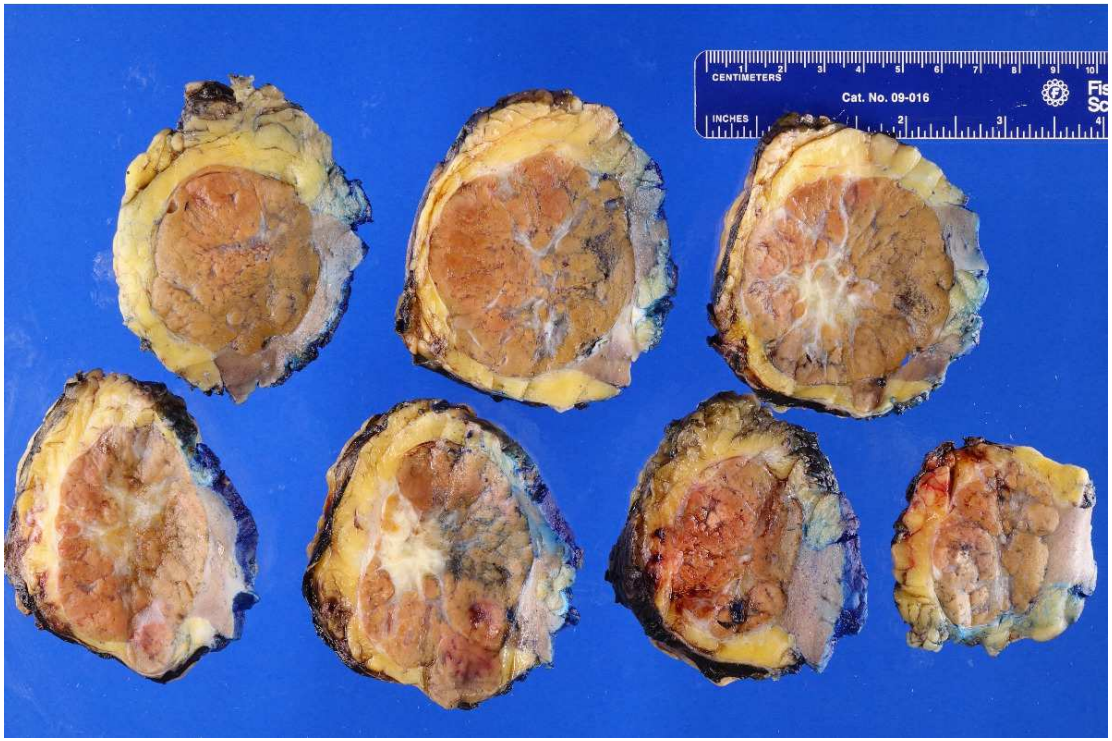


http://www.pathologyoutlines.com/caseofweek/Case200643image2.jpg accessed 02/20/2020

Oncocytoma

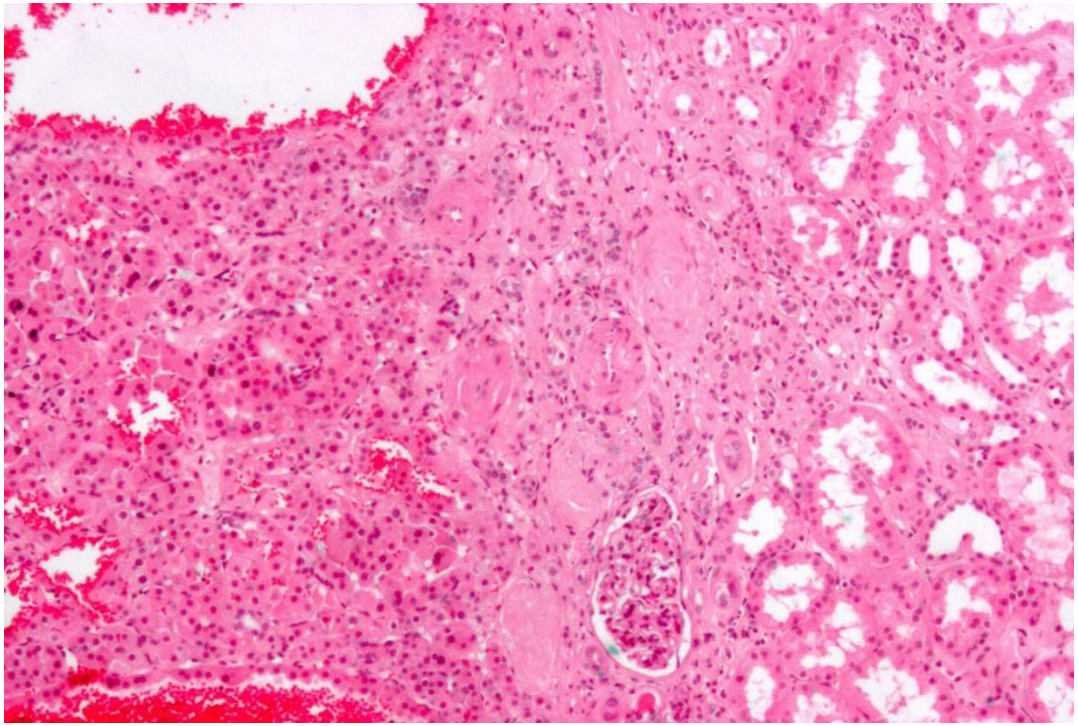
- Composed of large eosinophilic cells having small, round, benign-appearing nuclei that have large nucleoli.
- Arise from the intercalated cells
- Have numerous mitochondria.
- Tan or mahogany brown, relatively homogeneous, and usually well encapsulated with a central scar in one-third of cases.

Renal Oncocytoma



http://www.pathologyoutlines.com/topic/kidneytumoroncocytoma.html Contributed by Debra Zynger, MD
Accessed 02/20/2020

Renal oncocytoma



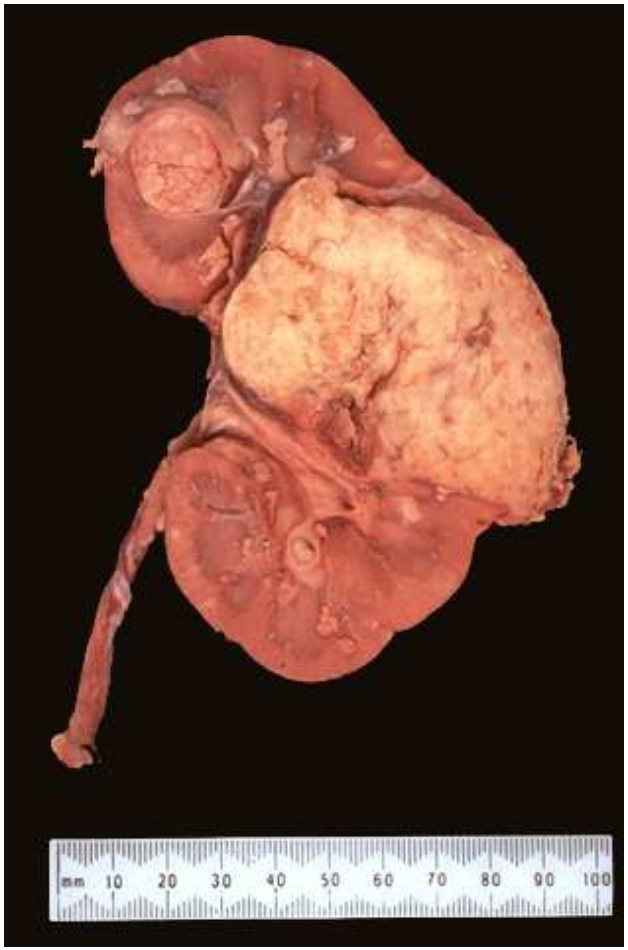
The tumor cells (left of the image) are arranged in nests, have slightly enlarged nuclei and have a more eosinophilic cytoplasm than the normal kidney (right of image). A glomerulus is seen at the bottom-center of the image. Normal renal tubules are seen on the right of the image.

https://upload.wikimedia.org/wikipedia/commons/d/d9/Renal_oncocytoma3.jpg
Accessed 02/20/2020

Angiolipoma

- Vessels, smooth muscle, and fat originating from perivascular epithelioid cells in the cortex
- Up to 50% of patients with tuberous sclerosis
- Loss-of-function mutations in the TSC1 or TSC2 tumor suppressor genes.
- Loss of regulation of mTOR signaling
- Tendency to spontaneous hemorrhage

Angiomyolipoma

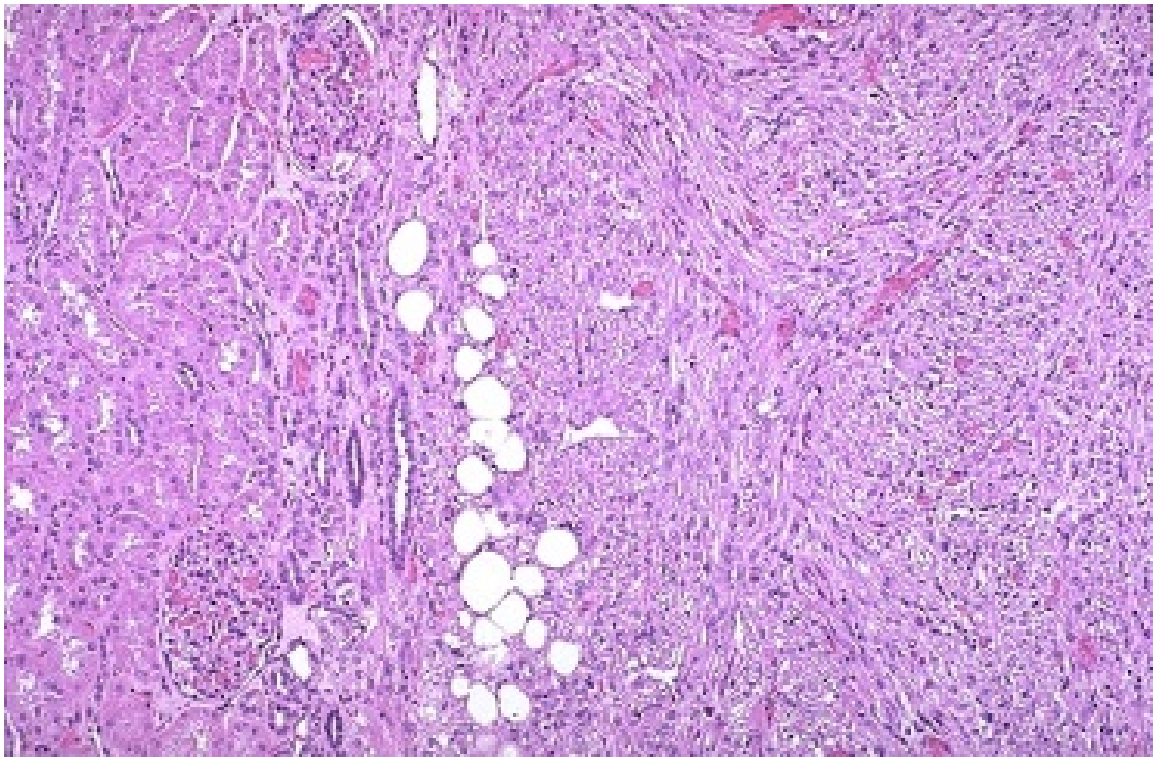


Note that it is solid and has a tan to yellowish-tan cut surface. It is also multifocal. Most of these tumors are incidental findings. Those with tuberous sclerosis often have these tumors. This neoplasm is one form of perivascular epithelioid cell tumor (PEComa) derived from the perivascular epithelioid cell (PEC), and not present in normal tissue.

[Image contributed by John Nicholls, MD, Hong Kong University]

https://webpath.med.utah.edu/RENAHTML/RENAL115.html
Accessed 01/20/2020

Angiomyolipoma



There is normal renal parenchyma at the left. The tumor has a strip of adipose tissue in the center that then blends in with interlacing bundles of smooth muscle in which are scattered vascular spaces.

https://webpath.med.utah.edu/RENAHTML/RENAL106.html
Accessed 01/20/2020

Mesoblastic nephroma

- Most common renal cancer in infancy
- 5% of all pediatric renal cancers
- May present in utero with polyhydramnios
- Classic type presents at 16 days of age
- Mixed type presents at 2 months of age
- Cellular type presents at 5 months of age
- 5-10% recur or metastasize
- Usually by age 1
- Metastases to lung and brain, NOT bone

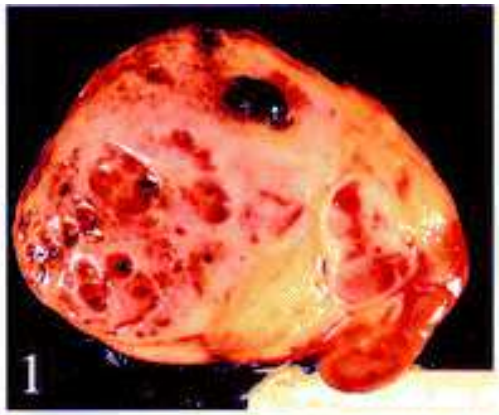
Mesoblastic nephroma

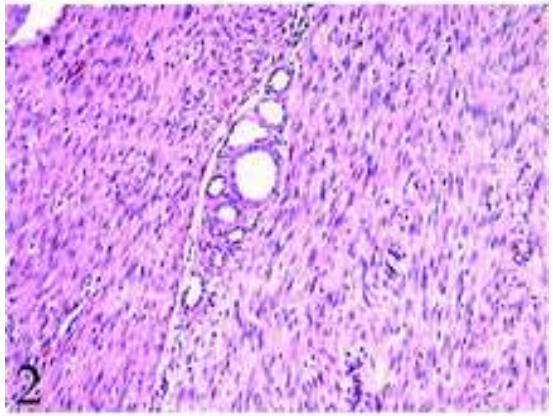
- Classic (25%):
- Resembles infantile fibromatosis or leiomyoma
- Fascicles and whorls of bland spindled myofibroblasts and thin collagen fibers
- No desmoplasia
- Tumor surrounds tubules and glomeruli, has irregular borders
- Chondroid metaplasia or dysplasia of the entrapped tubules is common
- Mitoses are rare
- No recurrent genetic aberration

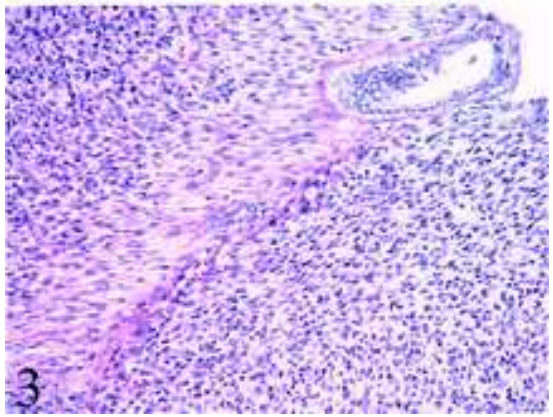
Mesoblastic nephroma

- Cellular (65%):
- Resembles infantile fibrosarcoma
- Sheet-like proliferation of plump, atypical spindle cells with abundant cytoplasm, vesicular nuclei and nucleoli
- Mitoses are common
- Necrosis
- The tumor has a pushing border
- Shares the same translocation with infantile fibrosarcoma: t(12;15) and results in ETV6-NTRK3 fusion protein
- Mixed (10%):
- A combination of classic and cellular features

Mesoblastic Nephroma







Cellular areas have mitotic figures, cystic degeneration, hemorrhage and necrosis.
SMA and Vimentin positive.

https://www.archivesofpathology.org/action/showFullPopup?id=i1543-2165-128-8-929-f01&doi=10.1043%2F1543-2165%282004%29128%3C929%3APQCRMI%3E2.0.CO%3B2

Accessed 02/20/2020

Wilm's tumor (nephroblastoma)

- 6-7% of childhood malignancies.
- Most common pediatric renal tumor.
- 90% diagnosed before age 6
- 90% are sporadic
- 5% present with specific genetic syndromes
- May first present with pain
- Flank or abdominal mass.
- Unilateral in sporadic cases
- Hypertension and hematuria.
- Arises from metanephric blastema.

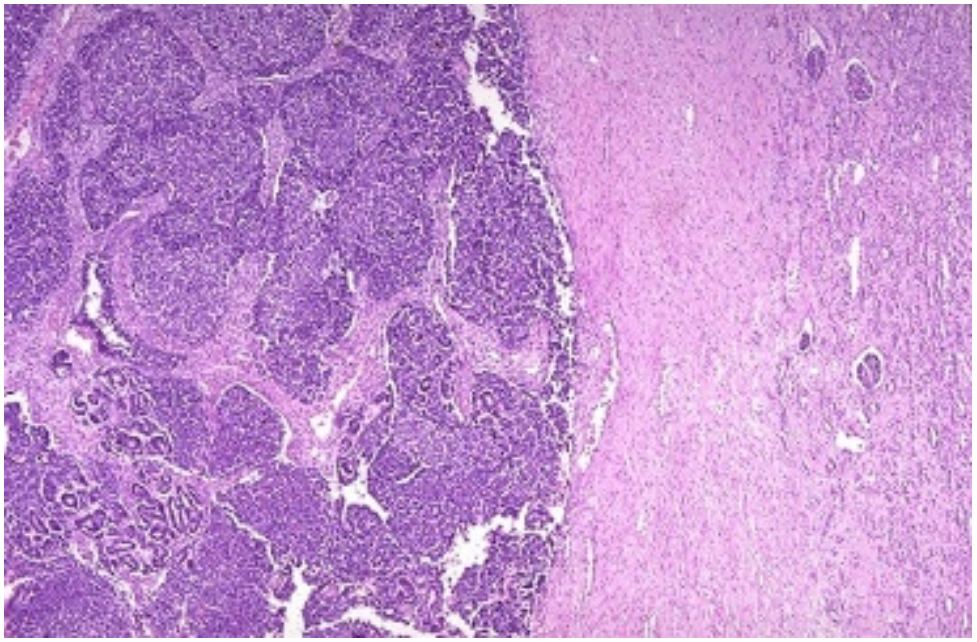
Wilm's tumor

- Triphasic combination of blastemal, stromal, and epithelial cell types
- Sheets of small blue cells with few distinctive features characterize the blastemal component.
- Epithelial differentiation is usually in the form of abortive tubules or glomeruli.
- Stromal cells are usually fibrocytic or myxoid in nature, although skeletal muscle differentiation is not uncommon.
- Rarely, other heterologous elements are identified.
- The presence of nephrogenic rests correlates with high risk of developing contralateral disease

Wilm's tumor

- WT1 gene (zinc finger transcription factor at 11p13) controls blastema development.
- The presence of anaplasia correlates with the presence of p53 mutation and chemotherapy resistance.
- 11q-, 16q-, 1q+ poor prognostic factors.
- Age >2 years poor prognosis
- Liver is most common site of metastasis
- Rarely metastasizes to bone

Wilm's tumor

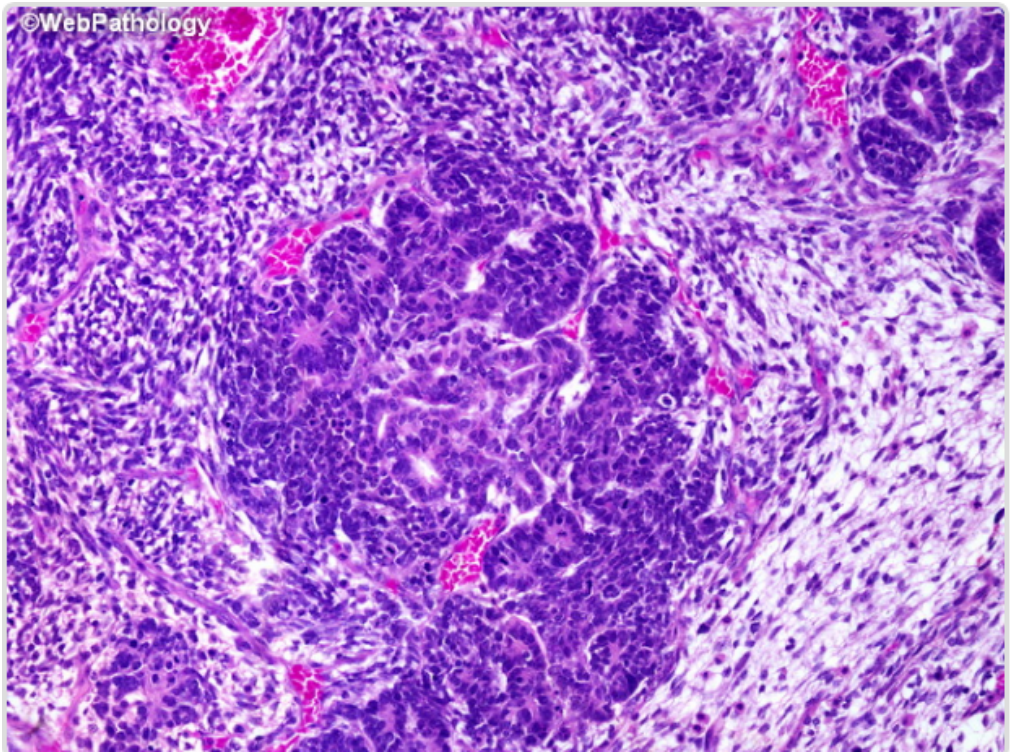


Left. The tumor is a lobulated tan mass. Right: The tumor is comprised of nests and sheets of dark blue cells at the left with compressed normal renal parenchyma at the right.

https://webpath.med.utah.edu/RENAHTML/RENAL057.html and RENAL058.html

Accessed 01/20/2020

Wilm's tumor



http://webpathology.com/image.asp?n=13&Case=73
Accessed 02/20/2020

Classically, Wilms tumor is triphasic and consists of variable proportions of blastema, stroma, and epithelial cells. The blastemal component consists of small poorly differentiated round cells. The epithelial component consists of abortive tubules and glomerular structures. Stroma is usually fibroblastic or myxoid and may contain heterologous elements such as skeletal muscle, smooth muscle, bone, cartilage, adipose tissue, and neuroglial tissue.

CHILDREN'S ONCOLOGY GROUP (COG) STAGING OF WILMS TUMOR[1]

COG Staging of Wilms Tumor	
Stage I	Tumor limited to kidney, completely resected. The renal capsule is intact. The tumor was not ruptured or biopsied prior to removal. The vessels of the renal sinus are not involved. There is no evidence of tumor at or beyond the margins of resection. *Note:* For a tumor to qualify for certain therapeutic protocols as Stage I, regional lymph nodes must be examined microscopically.
Stage II	The tumor is completely resected and there is no evidence of tumor at or beyond the margins of resection. The tumor extends beyond kidney, as is evidenced by any one of the following criteria: • There is regional extension of the tumor (i.e. penetration of the renal capsule, or extensive invasion of the soft tissue of the renal sinus, as discussed below). • Blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor. *Note:* Rupture or spillage confined to the flank, including biopsy of the tumor, is no longer included in Stage II and is now included in Stage III.
Stage III	Residual nonhematogenous tumor present following surgery, and confined to abdomen. Any one of the following may occur: • Lymph nodes within the abdomen or pelvis are involved by tumor. (Lymph node involvement in the thorax, or other extra-abdominal sites is a criterion for Stage IV.) • The tumor has penetrated through the peritoneal surface. • Tumor implants are found on the peritoneal surface. • Gross or microscopic tumor remains postoperatively (e.g., tumor cells are found at the margin of surgical resection on microscopic examination). • The tumor is not completely resectable because of local infiltration into vital structures. • Tumor spillage occurring either before or during surgery. • The tumor was biopsied (whether tru-cut, open or fine needle aspiration) before removal. • Tumor is removed in greater than one piece (e.g. tumor cells are found in a separately excised adrenal gland; a tumor thrombus within the renal vein is removed separately from the nephrectomy specimen). *Note:* Extension of the primary tumor within vena cava into thoracic vena cava and heart is considered Stage III, rather than Stage IV even though outside the abdomen.
Stage IV	Hematogenous metastases (lung, liver, bone, brain, etc.), or lymph node metastases outside the abdominopelvic region are present. (The presence of tumor within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present).
Stage V	Bilateral renal involvement by tumor is present at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of the extent of disease.

[1] Adapted from Wilms Tumor and Other Childhood Kidney Tumors Treatment (PDQ®)–Health Professional Version. National Cancer Institute. Accessed February 3, 2021. Available at: https://www.cancer.gov/types/kidney/hp/wilms-treatment-pdq#_23_toc

https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf
Accessed 03/17/2021

SYNDROMES AND CONGENITAL ANOMALIES ASSOCIATED WITH WILMS TUMOR

- Other Syndromes (cont.)
  - Perlman syndrome[27] (MIM: 614184):
    Inheritance autosomal recessive (AR):
    Gene *DIS3L2*
    Affected children are large at birth, are hypotonic, and show organomegaly, characteristic facial dysmorphisms (inverted V-shaped upper lip, prominent forehead, deep-set eyes, broad and flat nasal bridge, and low-set ears), renal anomalies (nephromegaly and hydronephrosis frequent neurodevelopmental delay, and high neonatal mortality.
  - Bohring-Optiz syndrome[28,29] (MIM: 605039)
    Inheritance AD:
    Gene *ASXL1*
    Malformation syndrome characterized by severe intrauterine growth retardation, poor feeding, profound mental retardation, trigonocephaly, prominent metopic suture, exophthalmos, nevus flammeus of the face, upslanting palpebral fissures, hirsutism, and flexion of the elbow and wrists with deviation of the wrists and metacarpophalangeal joints
  - MULIBREY (MUscle, LIver, BRain, and EYes) Nanism syndrome[30] (MIML 605073, https://omim.org/entry/253250)
    Inheritance AR:
    Gene *TRIM37*
    Growth disorder with prenatal onset, including occasional progressive cardiomyopathy, characteristic facial features, failure of sexual maturation, insulin resistance with type 2 diabetes, and an increased risk for Wilms tumor
- Congenital Anomalies Associated with Predisposition Syndromes
  - Aniridia
  - Cryptorchidism
  - Hemihypertrophy
  - Horseshoe kidney (patients are twice as likely to develop WT)
  - Hypospadias
  - Renal duplication
  - Renal ectopia
  - Renal hypoplasia
  - Mesoblastic nephroma
  - Ureteral duplication
- Surveillance Recommendations for WT Predisposition Syndromes[10,15]
  - The Pediatric Cancer Working Group of the American Association for Cancer Research recommends renal US every 3 mo up to age 8 y

Familial Nephroblastoma

FWT1/FWT2 (Familial WT) gene mutations account for about 1-2% of WT cases. These mutations are autosomal dominant with variable penetrance. They have no association with the *WT1* mutation. *FWT1* is found on chromosome 17q; whereas *FWT2* is found on chromosome 19q.[22,31-33]

References

SYNDROMES AND CONGENITAL ANOMALIES ASSOCIATED WITH WILMS TUMOR

Somatic Genetic Variants

- Most common somatic variants in WT are:
  - *CTNNB1, DROSHA, WT1, WTX, WTX (AMER-1), DGCR8, SIX1, BCORL1, MLLT1, MYCN, SIX2*; TP53 is associated with anaplastic WT[1]
  - *WT1*, a tumor suppressor gene found on chromosome 11p13, is implicated in the development of WT. *WT1* codes a transcription factor crucial for normal kidney/genitourinary function (5%–10% of cases)[2-11]
  - WT2, a tumor suppressor gene found on chromosome 11p15, is also implicated in the development of WT.

- WT predisposition genes by exome sequencing[12-14]
  - *REST, TRIM28, FBXW7, NYNRIN, KDM3B, XPO5, CHEK2, and PALB2*

- Predisposition Syndromes Associated with WT[15]
  - Denys-Drash syndrome[16,17] (MIM: 607102):
    Inheritance Autosomal Dominant (AD):
    Gene *WT1*; locus 11p13
    Disorders of Sexual Development (DSD), mesangial sclerosis, renal failure, usually 46 XY karyotype[18]
  - Frasier syndrome[19] (MIM: 607102)
    Inheritance AD
    Gene *WT1*; locus 11p13
    DSD, progressive glomerular nephropathy, patients present with normal female external genitalia, streak gonads, and XY karyotype, and frequently develop gonadoblastoma
  - Beckwith-Wiedemann syndrome[20,21] (MIM: 616186, 604115, 600856):
    Inheritance complex: AD, Uniparental Disomy, Epimutations involving locus 11p15.5
    Characterized by gigantism, omphalocele, macroglossia, genitourinary abnormalities, ear pits and creases, hypoglycemia, and hemihypertrophy; present in about 5% of children with WT.[22,23]
  - Contiguous Gene Deletion Syndrome or WAGR/WAGR syndrome with obesity (WAGRO)[24] (MIM 194072, 612469)
    Gene *WT1* gene; locus 11p13
    Characterized by aniridia, genitourinary abnormalities, obesity, and hemihypertrophy;
  - Trisomy 18 syndrome[25]

- Other Syndromes
  - Li Fraumeni syndrome[26] (MIM: 191170)
    Inheritance AD:
    Gene *TP53*
    Broad cancer predisposition syndrome associated with anaplastic Wilms tumor in young patients.

General Principles

- The administration of adjuvant, and in some cases neoadjuvant chemotherapy, in combination with surgery ± radiation markedly improves survival for FHWTs.
- Selection of the appropriate chemotherapy regimen is based on tumor histology, stage, tumor weight, the patient's age, response of lung metastases (when present) to chemotherapy, and molecular markers, which together determine the risk group (see Risk Assessment for FHWT [WILMS-F]).
- Adjuvant chemotherapy should be started within 7 to 14 days of up-front nephrectomy and the timing should be coordinated with radiation, if it is required, to avoid co-administration of full doses of dactinomycin or doxorubicin with radiation. Dactinomycin and doxorubicin can be administered at full doses prior to the start of radiation.
- Neoadjuvant chemotherapy is administered for unresectable tumors or tumors for which NSS is indicated (see Principles of Surgery [WILMS-D]) to reduce the size of the tumor(s).
  - Re-image after 6 weeks of neoadjuvant chemotherapy to determine whether the tumor(s) is/are resectable.
  - The postoperative adjuvant chemotherapy regimen is determined by tumor histology, stage, and molecular markers.

Chemotherapy Regimens

- EE4A: 13 doses of vincristine and 7 doses of dactinomycin administered over 18 weeks.[1,2]
- DD4A: 15 doses of vincristine, 5 doses of dactinomycin, and 4 doses of doxorubicin (cumulative dose 150 mg/m²) administered over 24 weeks with alternating doses of dactinomycin and doxorubicin.[1,2]
- VAD: 6–12 doses of vincristine, 2–4 doses of dactinomycin, and 2–4 doses of doxorubicin (cumulative dose 70–140 mg/m²) administered over 6–12 weeks used only in the neoadjuvant setting for patients who are candidates for NSS. In this regimen dactinomycin and doxorubicin are given together.[3]
- Regimen M: 9 doses of vincristine, 5 doses of dactinomycin, 5 doses of doxorubicin (cumulative dose 150 mg/m²), 4 courses of 5 daily doses of cyclophosphamide, and 4 courses of 5 daily doses of etoposide over 24 weeks. Dactinomycin and doxorubicin are given together, and cyclophosphamide and etoposide are given together. This regimen starts at week 7 for tumors requiring augmentation of therapy based on molecular markers or response of lung metastases to 6 weeks of DD4A.[4]
- Regimen I: 9 doses of vincristine, 4 doses of doxorubicin (cumulative dose 180 mg/m²), 7 courses of 3 to 5 daily doses of cyclophosphamide, and 3 courses of 5 daily doses of etoposide. Doxorubicin and 3 daily doses of cyclophosphamide are given together, and 5 daily doses of cyclophosphamide and etoposide are given together. This regimen starts at week 7 for tumors requiring augmentation of therapy based on histology.[3,5,6]

- Initial risk is based on age, clinical, radiographic, surgical. and pathological findings.
- Final risk is based on initial risk plus LOH at 1p and 16q, and response of lung metastases at week 6.

Patient Age	Tumor Weight	Stage	Intital Risk Group	LOH 1p/16q	Lung Metastases Response	Extra-Pulmonary Metastases	Final Risk Group
<2 years	<550 g	I	Very Low	Any	N/A	N/A	Very Low
Any	≥550 g	I	Low	No	N/A	N/A	Low
≥2 years	Any	I	Low	No	N/A	N/A	Low
Any	Any	II	Low	No	N/A	N/A	Low
Any	≥550 g	I	Low	Yes	N/A	N/A	Standard
≥2 years	Any	I	Low	Yes	N/A	N/A	Standard
Any	Any	II	Low	Yes	N/A	N/A	Standard
Any	Any	III	Standard	No	N/A	N/A	Standard
Any	Any	IV	Higher	No	Complete	No	Standard
Any	Any	III	Standard	Yes	N/A	N/A	Higher
Any	Any	IV	Higher	Yes	Any	Any	Higher
Any	Any	IV	Higher	Any	Partial	Any	Higher
Any	Any	IV	Higher	Any	Any	Yes	Higher
Any	Any	V	Bilateral	Any	Any	Any	Bilateral

Prognostic Factors
- Stage (See ST-1)
- Histology (favorable or unfavorable/anaplastic)
- Patient age at diagnosis
- Tumor weight
- Completeness of lung nodule response to therapy at week 6
- LOH of chromosomes 1p, 11p15, and 16q
  - LOI of 11p15
- Chromosome 1q gain[1]

https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf
Accessed 03/17/2021

Genetic syndromes

- WAGR Syndrome
- Wilms tumor
- Aniridia (absence of iris)
- Genitourinary abnormalities
- Retardation (mental)
- Germline WT1 gene deletion occurs near PAX6 gene (also at 11p13)
- 33% lifetime risk for Wilm's tumor

Wilm's tumor

- Denys-Drash syndrome
- Gonadal dysgenesis (male pseudohermaphroditism) and early-onset nephropathy leading to renal failure.
- Diffuse glomerular sclerosis
- Dominant-negative missense mutation in the zinc-finger region of the WT1 protein inactivates wild-type allele
- Leads to gonadal dysgenesis
- At risk for developing gonadoblastoma
- Bi-allelic loss of WT1 associated with Wilm's tumor
- 90% of patients

Wilm's tumor

- Beckwith-Wiedemann syndrome
- Exophthalmos
- Microglossia
- Gigantism
- Hemihypertrophy
- WT2 gene at 11p15.
- This chromosomal region usually contains genes that are normally expressed from only one of the two parental alleles
- Transcriptional silencing (imprinting) of the other gene by methylation of the promoter region.
- Higher risk for hepatoblastoma, adrenal cortical and pancreatic tumors, rhabdomyosarcoma

Therapy

- Primary resection provides necessary biologic information for risk stratification and selection of appropriate therapy.
- Minimize treatment for low-risk patients
- Improve survival in higher risk patients.
- Transabdominal or a thoracoabdominal exposure with transperitoneal approach (preferred surgical approaches) and abdominal exploration, unilateral radical ureteronephrectomy with LN sampling.
- LN sampling MUST be performed for adequate staging; recommend obtaining minimum >5 (nodes) from areas in renal hilum anatomically expected to represent nodes associated with kidney

Therapy

- Contraindications to Primary Resection
- High risk of renal failure for those with germline WT1 mutations (Denys-Drash, WAGR) or bilateral WT.
- Overall risk of long-term renal failure is <1%.
- Unacceptable anesthesia risk due to disease burden
- Massive pulmonary disease
- Very large abdominal tumors causing pulmonary compromise

Therapy

- Contraindications to Primary Resection
- Surgeon judgment:
- Operation would lead to significant morbidity/mortality, tumor spill, or residual tumor
- Solitary kidney
- IVC tumor thrombus above the level of the hepatic veins

Therapy

- Goals of Surgery for Unilateral WT
- Complete clearance of all disease
- Accurate LN staging
- Complete pathologic evaluation
- Resection without rupture of the tumor

Therapy

- Summary of Surgical Approach to Bilateral WT
- Do not biopsy upon presentation of bilateral WT.
- Use of standardized 3-drug neoadjuvant chemotherapy (VAD) followed by bilateral nephron-sparing surgery (NSS) to preserve renal function
- Possible criteria for successful NSS:
- Small tumor size
- Peripheral or polar location of the mass
- Lack of invasion or encasement of renal vessels

Therapy

- Relative contraindications to NSS:
- Central location
- Proximity to the renal vessels

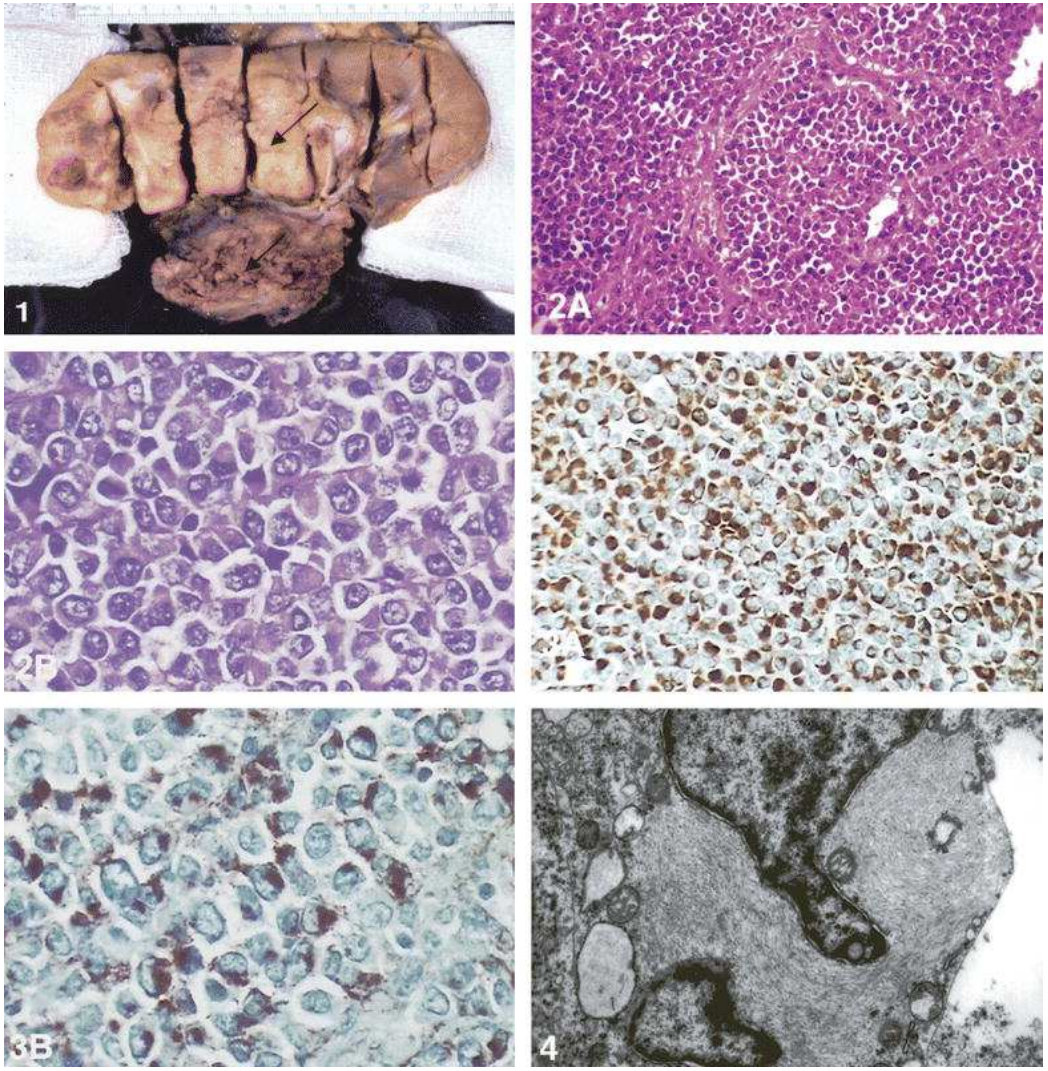
Therapy

- Week 6 re-evaluation
- Perform surgery if bilateral NSS is possible
- For less than a partial response to chemotherapy, consider open biopsy to assess for presence of anaplasia
- Continue chemotherapy if patient has some response but is not a candidate for NSS
- Surgery should be performed within 12 weeks of starting neoadjuvant therapy
- Aim for bilateral NSS, if possible. If operating after chemotherapy, enucleation is safe
- If disease recurrence, repeat NSS

Rhabdoid tumor

- 1-2% of childhood renal tumors
- 60% <1 year old; 30% 1-3 years old
- 15% associated with pineal neuroectodermal tumor in the midline fossa
- 82% present with metastases
- 90% mortality at 2 years
- Gross appearance is that of a fleshy mass.
- Histologically the tumor is composed of small round cells with prominent nuclei and nucleoli, growing in a sheath like pattern separated by thin fibrovascular septa.
- INI1 deletion

Rhabdoid tumor



3A, Most of the cells stain positively for vimentin (original magnification ×125). B, Focally, tumor cells also stain positively for epithelial membrane antigen (original magnification ×500).
4. Large swirls of cytoplasmic intermediate filaments with some entrapped organelles (original magnification ×22400)

https://www.archivesofpathology.org/na101/home/literatum/publisher/pinnacle/journals/content/arpa/2003/15432165-127.9/1543-2165%282003%29127%3Ce371%3Amrtotk%3E2.0.co%3B2/production/images/large/i1543-2165-127-9-e371-f01.jpeg

Renal cell carcinoma

- 85% of renal cancers
- 50-60 years old
- 2:1 men
- 15% present with metastases
- Risk factors include tobacco, obesity, unopposed estrogen therapy, and hypertension
- Asbestos, petroleum products, heavy metals as other risk factors
- Higher risk in ESRD as well as tuberous sclerosis
- Adult polycystic disease also predisposes (30x greater risk)
- Sporadic

Renal cell carcinoma

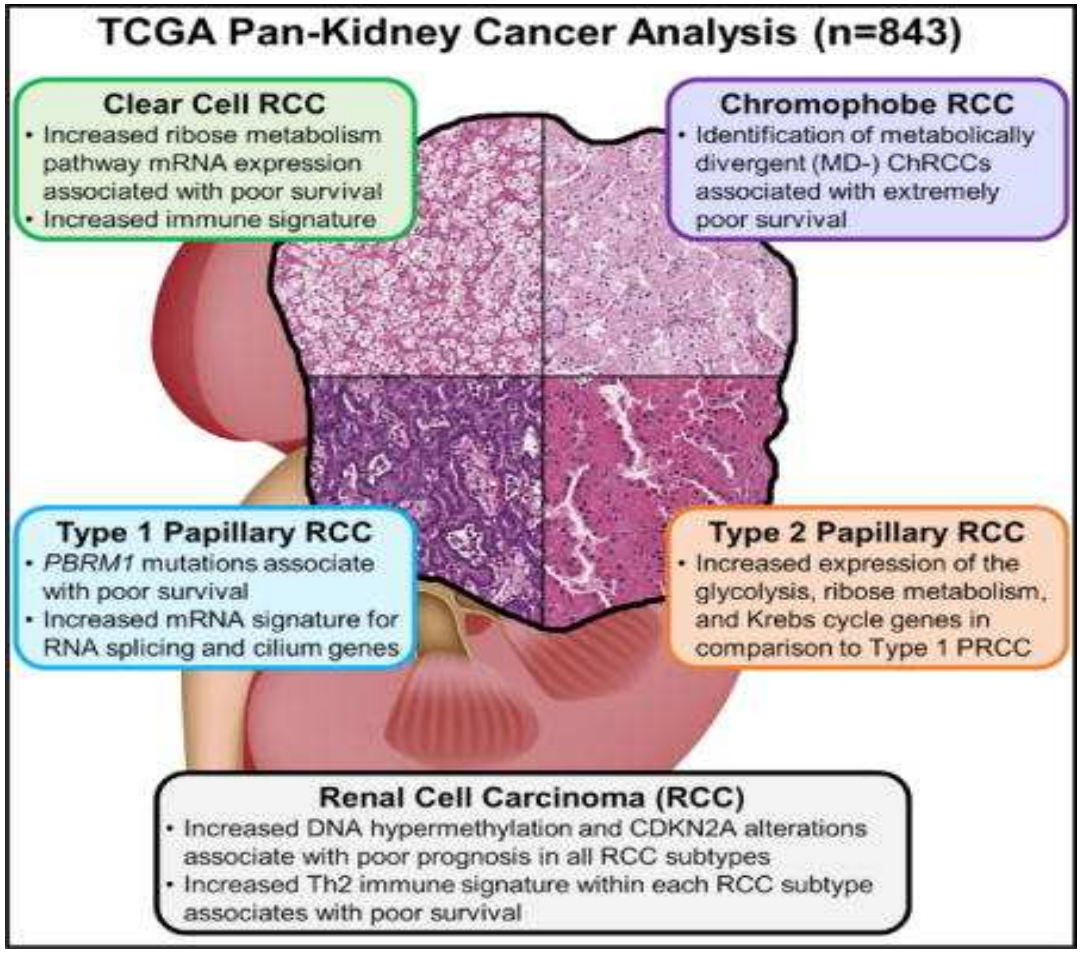
- Often in the upper pole of the kidney
- Usually present with hematuria
- Flank mass and pain may also be present
- Invade along renal vein
- Lungs (50%) and bones (33%) most common sites of metastasis
- “Cannon ball” appearance on lung x-ray
- Osteolytic bone metastases
- Hemorrhagic metastatic nodules in skin
- Highly vascular lesion

Renal cell carcinoma

- Left renal kidney involvement may be associated with left varicocele
- Left renal vein involvement blocks drainage of left spermatic vein
- As right spermatic vein drains directly into the inferior vena cava, no development of varicocele in right sided kidney involvement

Renal cell carcinoma

- Ectopic hormone production secondary to abnormalities with Hypoxia induction factor (HIF)
- May produce erythropoietin
- Secondary polycythemia
- May produce parathyroid hormone related peptide
- Hypercalcemia
- Renin overproduction
- Hypertension



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6075733/

Renal cell carcinoma

- Somatic alteration of BAP1 (3p21.1), PBRM1 (3p21.1), and PTEN (10q23.21) and altered metabolic pathways correlate with subtype-specific decreased survival
- BAP1 produces a deubiquinating enzyme
- Inactivating mutations in the BAP1 gene are associated with poor prognosis in clear cell renal cell carcinoma (CC-RCC) and type 1 papillary renal cell carcinoma (PRCC1)
- PBRM1 is an integral component of complexes necessary for ligand-dependent transcriptional activation by nuclear hormone receptors

Renal cell carcinoma

- PTEN is a tumor suppressor in the PI3K/AKT/mTOR pathway
- Inactivation of TP53 or the CDKN2A tumor suppressors or a CpG island hypermethylation phenotype (CIMP) increases in the immune-related Th_2 gene expression signature correlate with decreased survival within all major histologic subtypes.

Renal cell carcinoma

- CpG island methylator phenotype subtype of clear cell renal cell carcinoma (CIMP-RCC) demonstrates an increased immune signature, including the Th_2 gene
- A uniform and distinct metabolic expression pattern identifies a subset of metabolically divergent (MD) chromophobe renal cell carcinoma (ChRCC) that is associated with extremely poor survival.

Renal cell carcinoma

- Increased expression of pyruvate dehydrogenase activation genes in and ChRCC
- Oxidative phosphorylation
- Decreased expression of pyruvate dehydrogenase activation genes in and CC-RCC and PRCC2
- Glycolysis dependent energy production

Molecular alterations

- Clear cell renal cell carcinoma demonstrates significant loss of chromosome 3p and gain of 5q
- Type 1 papillary renal cell carcinoma demonstrates gains of chromosomes 7 and 17
- Chromophobe renal cell carcinoma demonstrates a pattern of CIMP-RCC or the type 2 papillary renal cell carcinoma (PRCC2)
- Both demonstrated an increased loss of chromosome 22 that encodes NF2 from the HIPPO pathway and SMARCB1, a fundamental component of the SWI/SNF complex

Molecular alterations

- The CIMP-renal cell carcinoma had loss of chromosome 13q at a similar rate to ChRCC (60% versus 61.3%) that encodes RB1 and BRCA2 chromosomal losses that included 1, 2, 6, 10, 13, and 17
- CA IX abundantly expressed
- Inversely regulated by VHL wt

Molecular alterations

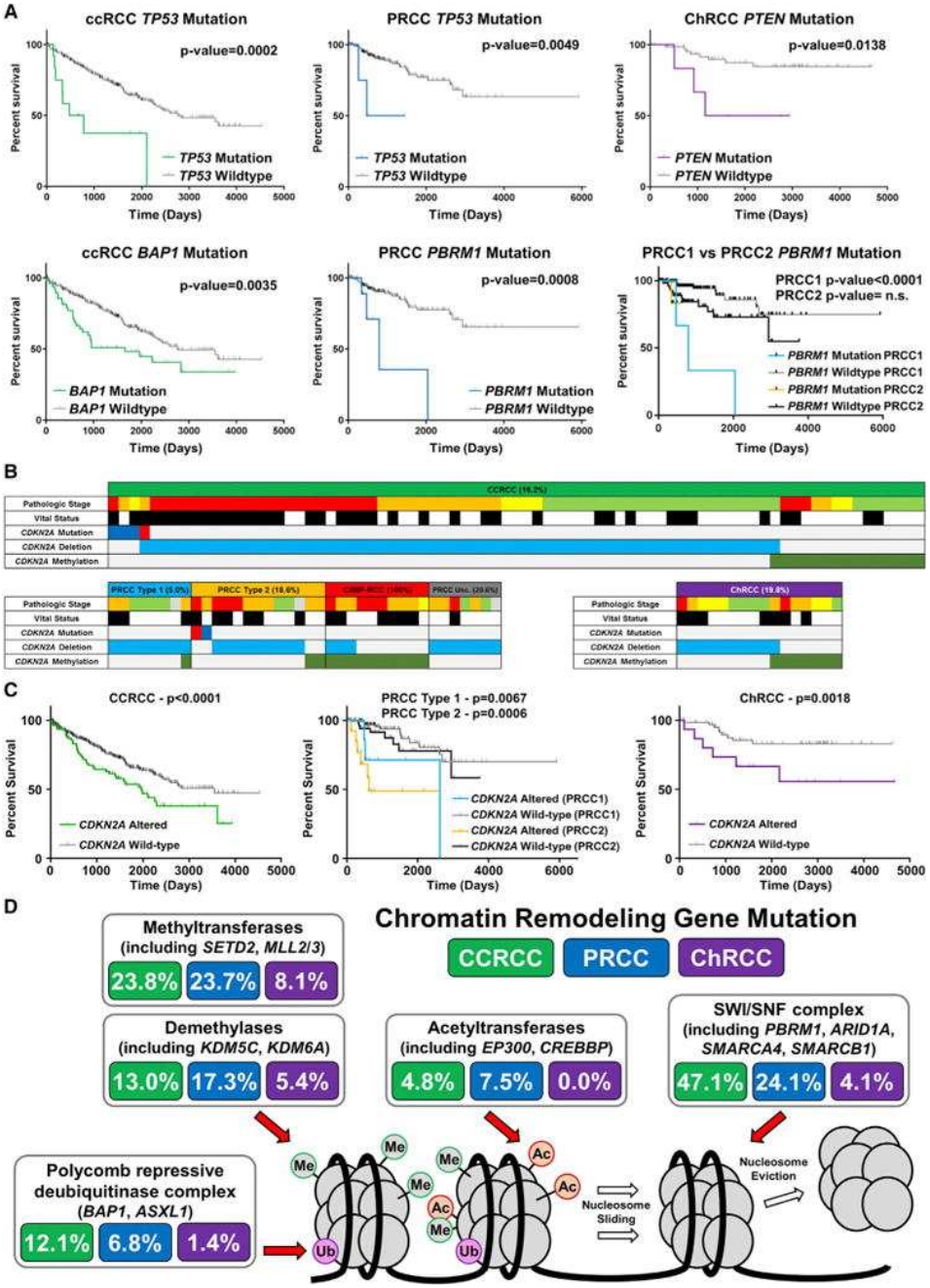
- Sarcomatoid and rhabdoid features may develop in any underlying Renal Cell carcinoma histology (papillary, clear cell, chromophobe) and have distinct molecular features such as BAP1 (3p21) and CDKN2A (9p21) mutations as well as heightened MYC transcriptional programs.
- Resistant to VEGF and mTTOR inhibitors, but respond to nivolumab plus ipilimumab
- Benefit regardless of PDL1 status
- CD8+ PD-1+ TIM3- LAG3-
- TILs stronest predictive biomarker
- Inhibition of PD-1 on Tregs may support immune suppression
- LOF mutation in PBMR1 in VEGF-TKI refractory setting has been linked to enhanced response to nivolumab

Molecular alterations

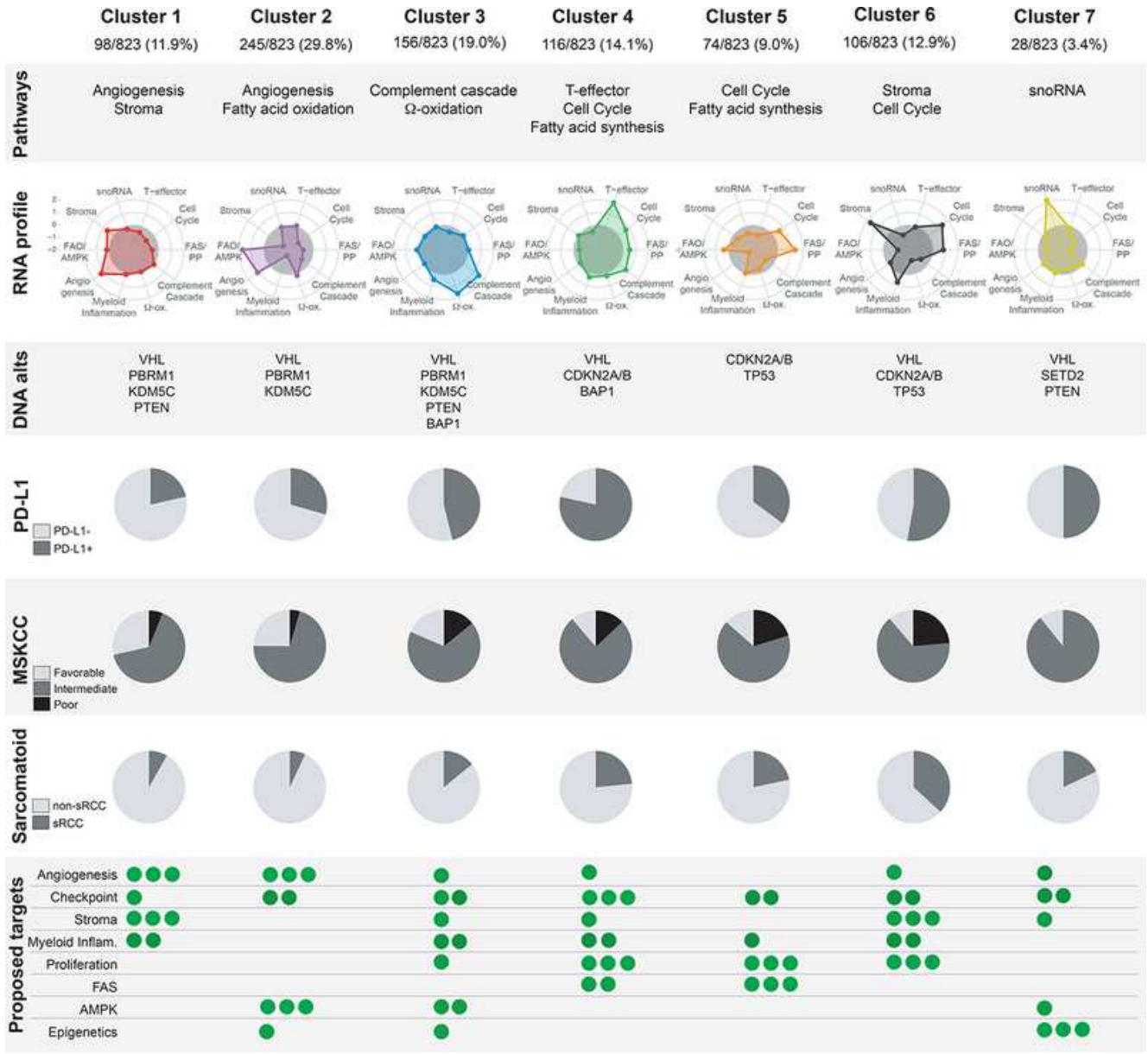
- 9p and 14q losses are drivers of metastatic spread
- 9p loss poor prognosis in urothelial cancer, not renal cell
- TREM2+ APOE+ C1Q+ macrophages as risk factor for disease recurrence following nephrectomy
- HLA-A*03 carriage respond better to TKI

Molecular alterations

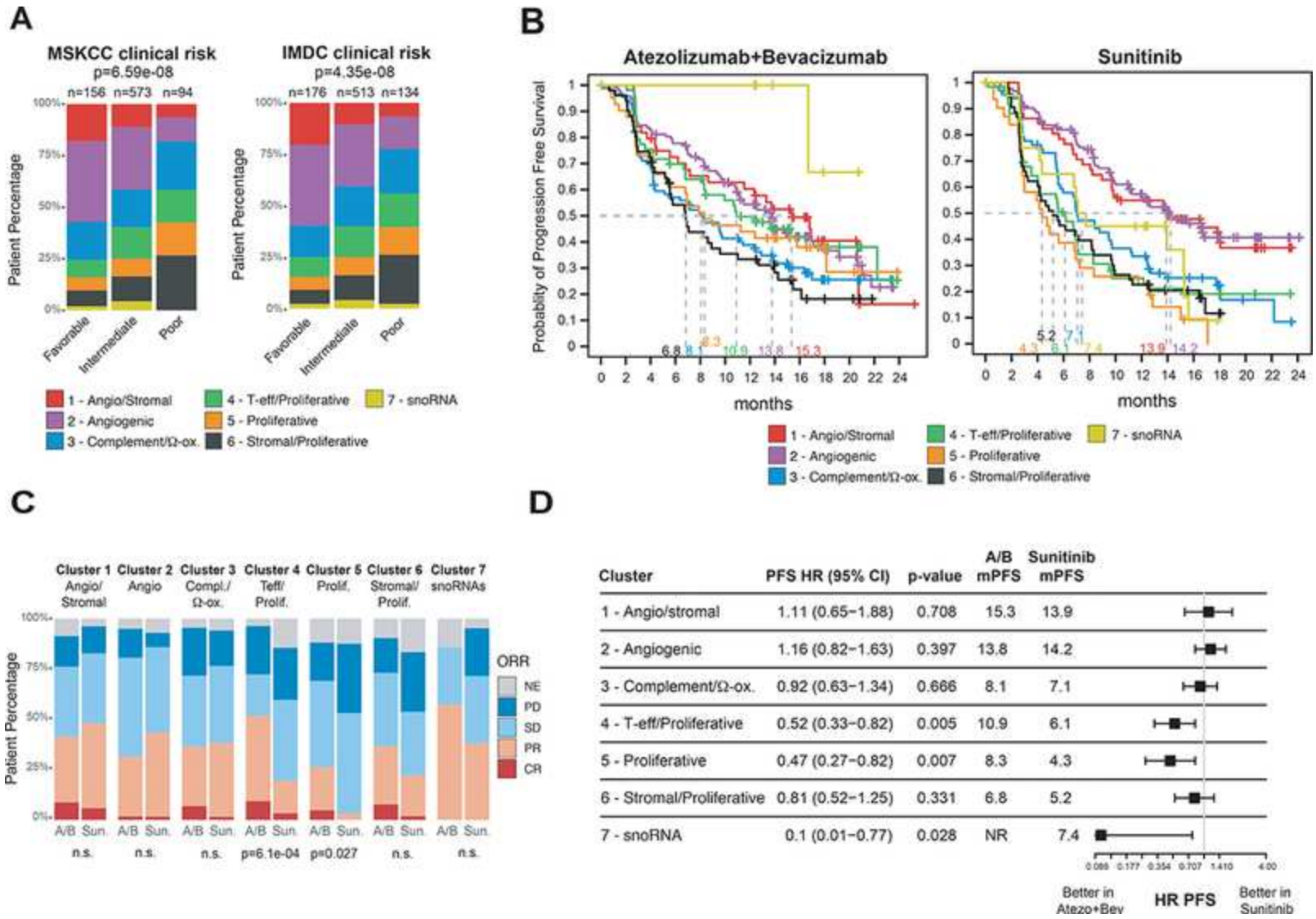
- Genes associated with kidney morphogenesis and angiogenesis respond to nivolumab
- Genes associated with metabolic processes do not respond to nivolumab
- SLAMF7+PD-1+CD8+ population that expresses residency markers (ZNF683/HOBIT and ITGAE/CD103) resistant to nivolumab
- SMP in IL7 intron associated with adverse events in immune therapy



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6075733/



10.1016/j.ccell.2020.10.011



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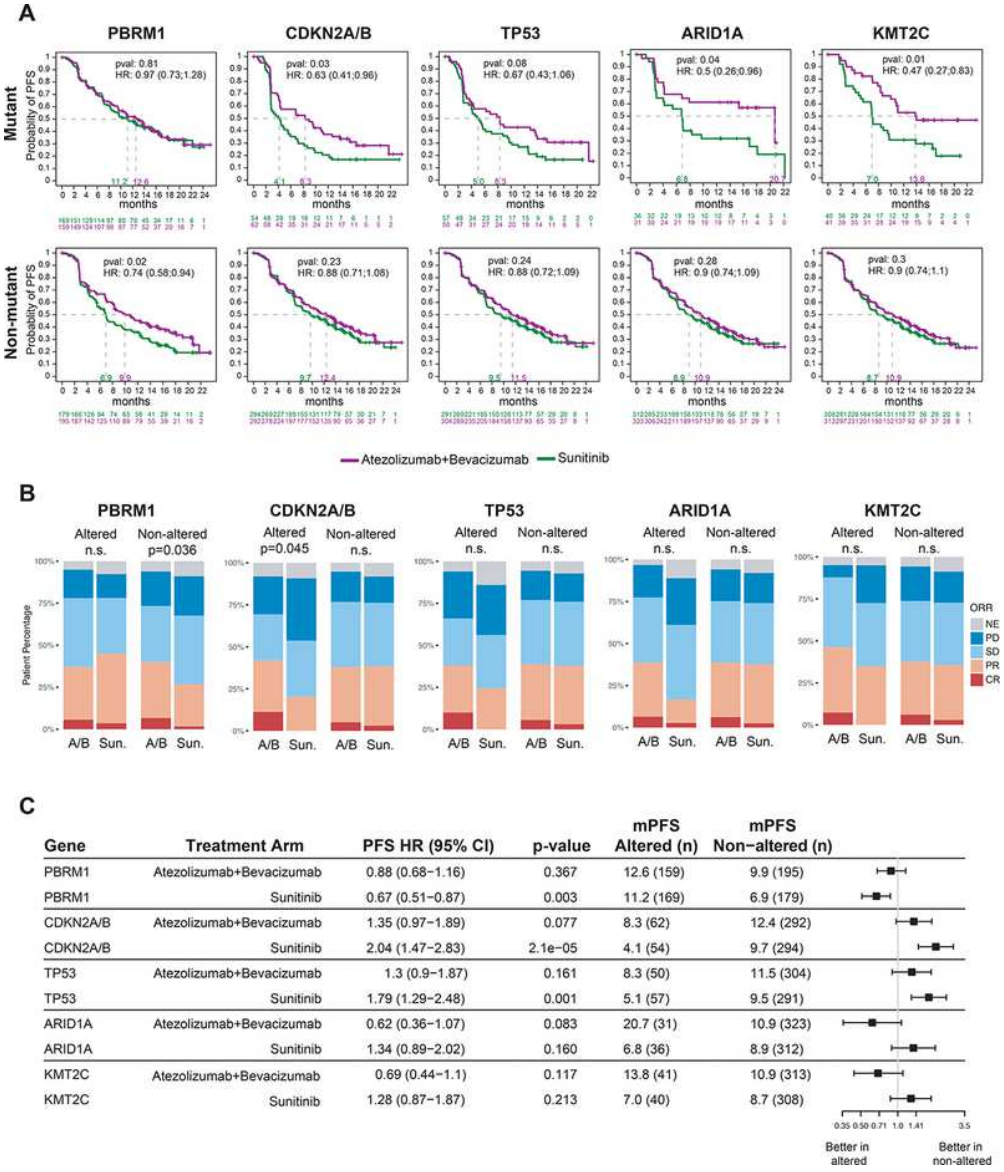


C

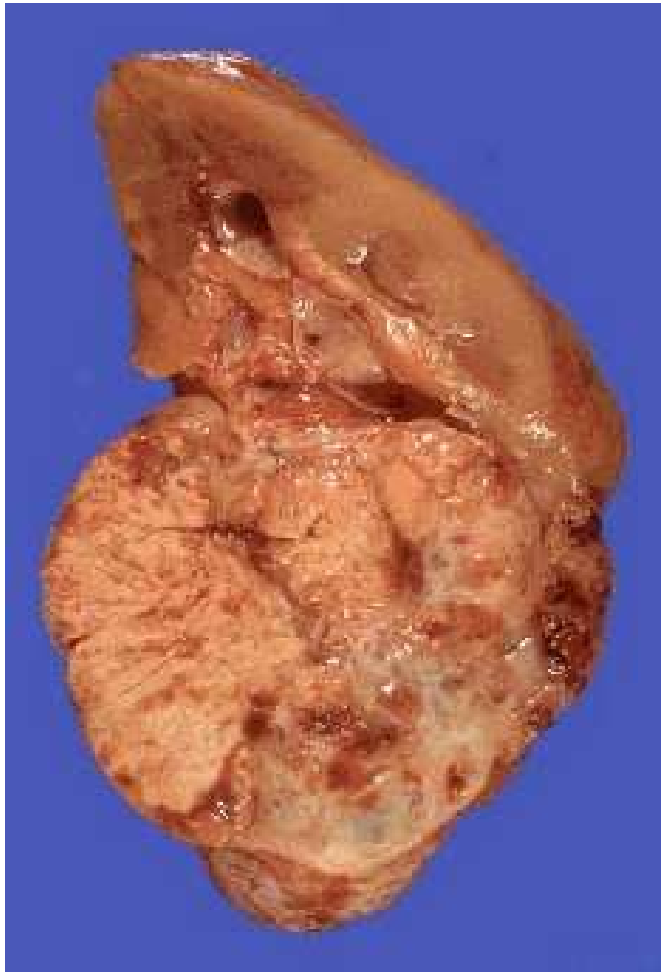
Gene	Treatment Arm	PFS HR (95% CI)	p-value	mPFS Altered (n)	mPFS Non−altered (n)
PBRM1	Atezolizumab+Bevacizumab	0.88 (0.68−1.16)	0.367	12.6 (159)	9.9 (195)
PBRM1	Sunitinib	0.67 (0.51−0.87)	0.003	11.2 (169)	6.9 (179)
CDKN2A/B	Atezolizumab+Bevacizumab	1.35 (0.97−1.89)	0.077	8.3 (62)	12.4 (292)
CDKN2A/B	Sunitinib	2.04 (1.47−2.83)	2.1e−05	4.1 (54)	9.7 (294)
TP53	Atezolizumab+Bevacizumab	1.3 (0.9−1.87)	0.161	8.3 (50)	11.5 (304)
TP53	Sunitinib	1.79 (1.29−2.48)	0.001	5.1 (57)	9.5 (291)
ARID1A	Atezolizumab+Bevacizumab	0.62 (0.36−1.07)	0.083	20.7 (31)	10.9 (323)
ARID1A	Sunitinib	1.34 (0.89−2.02)	0.160	6.8 (36)	8.9 (312)
KMT2C	Atezolizumab+Bevacizumab	0.69 (0.44−1.1)	0.117	13.8 (41)	10.9 (313)
KMT2C	Sunitinib	1.28 (0.87−1.87)	0.213	7.0 (40)	8.7 (308)

10.1016/j.ccell.2020.10.011

Renal cell carcinoma

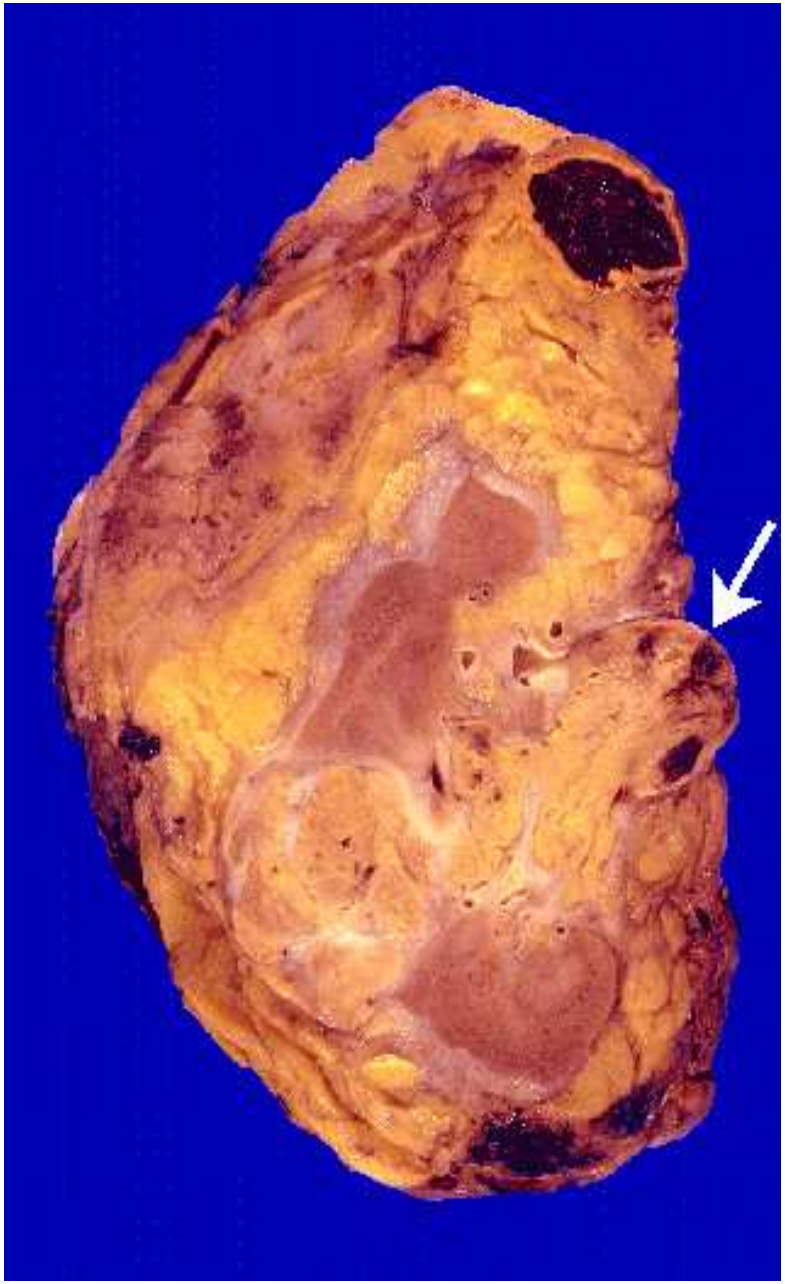
- Tumor is bright yellow as is rich in glycogen and lipids
- Larger tumors have areas of hemorrhage and necrosis
- Histology:
- Principal type is clear cell
- Round or polygonal cells with clear cytoplasm containing glycogen or lipid
- Transitional cell carcinoma 50% of cases in renal pelvis or ureter
- Squamous carcinoma is rare

Renal cell carcinoma



The tumor is fairly circumscribed. The cut surface demonstrates a variegated appearance with yellowish areas.

https://webpath.med.utah.edu/RENAHTML/RENAL062.html
Accessed 01/20/2020



Renal cell carcinoma

Renal vein invasion is shown here at the white arrow in a resected kidney surrounded by adipose tissue.

Renal cell carcinomas may invade through the renal capsule. Renal cell carcinomas may metastasize to odd locations, and about a fourth of them first present as metastatic lesions.

https://webpath.med.utah.edu/RENAHTML/RENAL054.html

Accessed 01/20/2020

Renal cell carcinoma

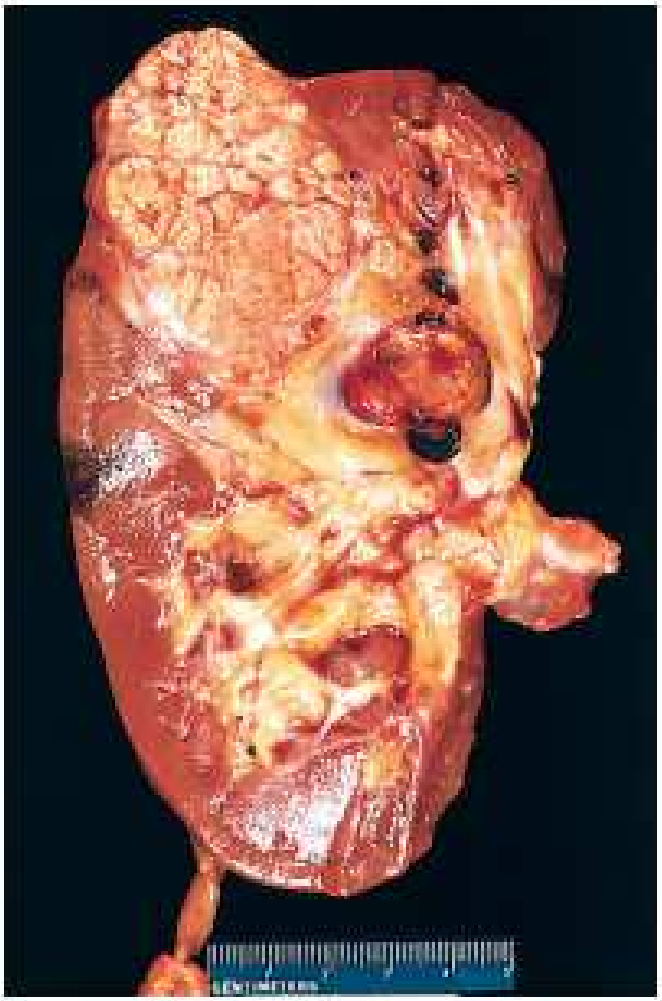


Figure 20.50 Renal cell carcinoma. Typical cross-section of yellowish, spherical neoplasm in one pole of the kidney. Note the tumor in the dilated thrombosed renal vein.

Renal cell carcinoma

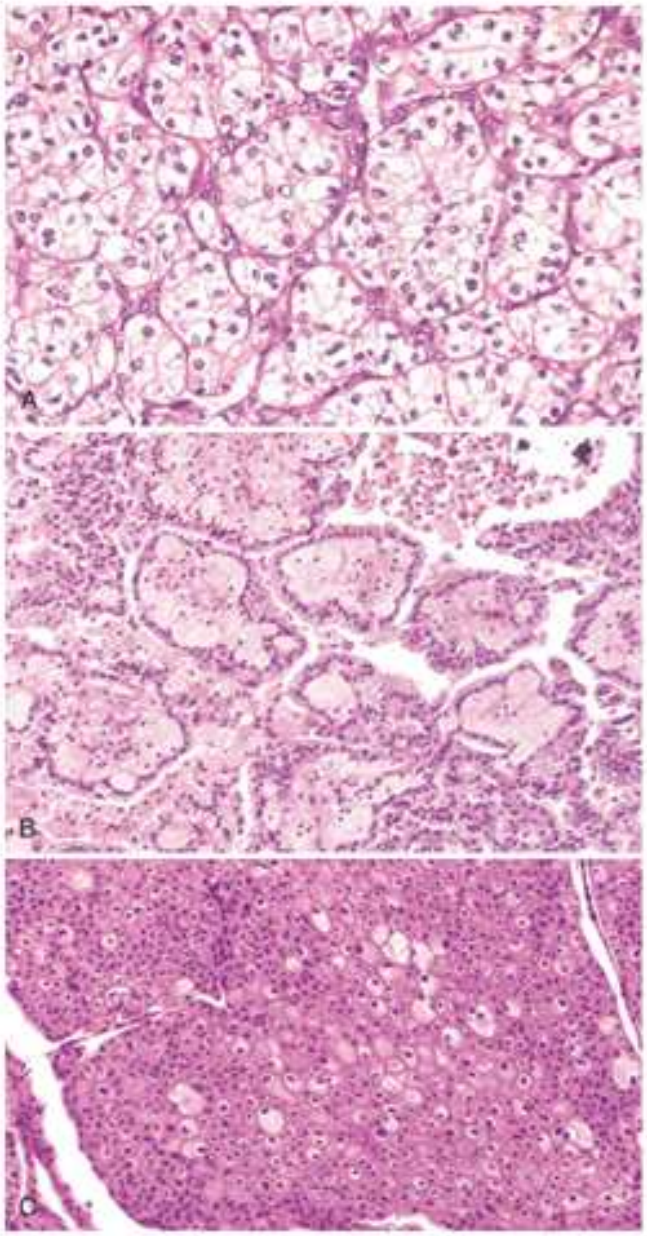
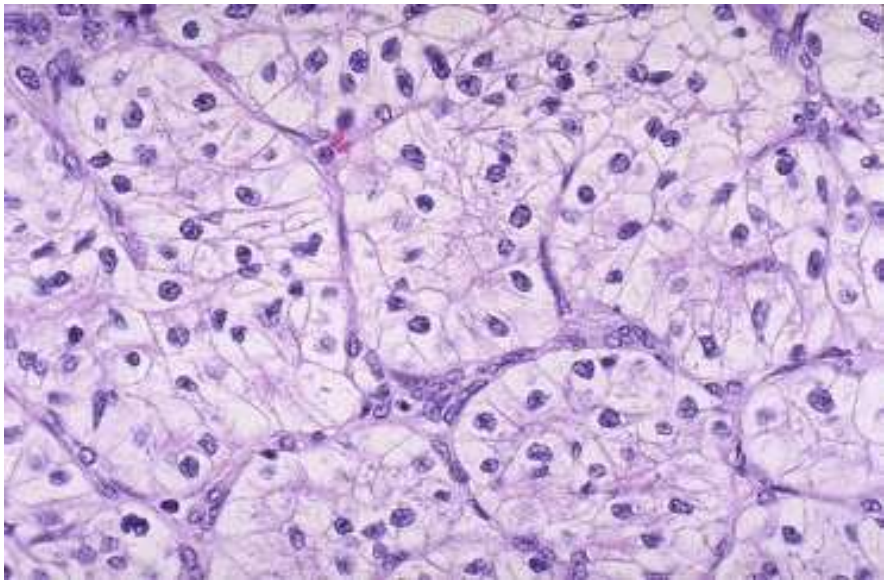
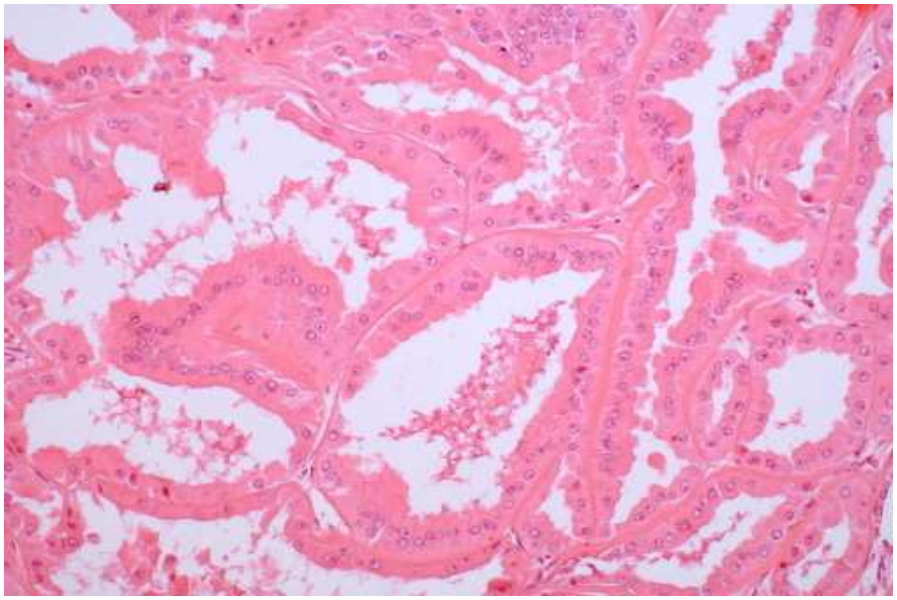


Figure 20.51 Renal cell carcinoma. (A) Clear cell type. (B) Papillary type. Note the papillae and foamy macrophages in the stalk. (C) Chromophobe type. (Courtesy Dr. A. Renshaw, Baptist Hospital, Miami, Fla.)

Renal cell carcinoma





Left: This is the classic clear cell histologic appearance of a renal cell carcinoma (clear cell carcinoma). The neoplastic cells have clear cytoplasm and are arranged in nests with intervening blood vessels. Mutation of the VHL gene may be found.

Right: The less common papillary variant of renal cell carcinoma is shown below. Note the eosinophilic cytoplasm. Mutation of the MET gene may be present.

https://webpath.med.utah.edu/RENAHTML/RENAL055.html Accessed 01/20/2020

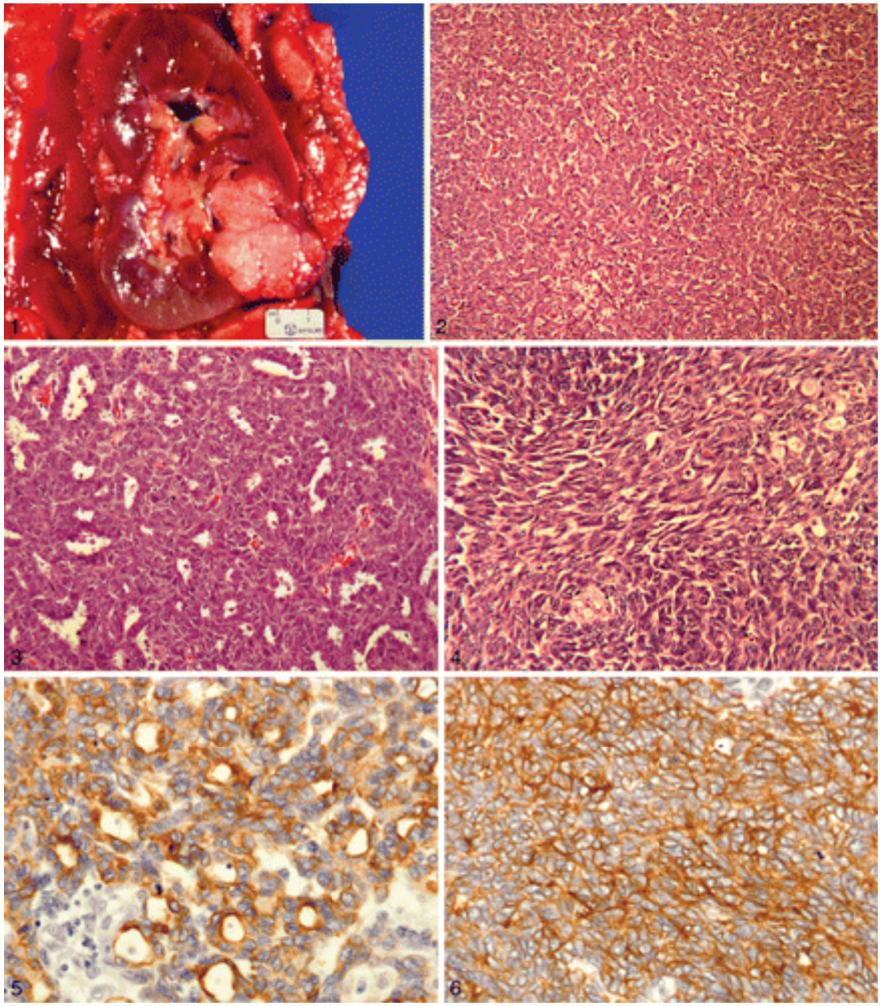
Renal cell carcinoma
solid variant

- 3% of renal cell carcinomas
- Morphologically similar to Type 1 papillary renal carcinoma but lack true papillae containing fibrovascular cores
- Solid sheets of cells, often with distinct micronodules resembling abortive papillae or glomeruloid bodies
- Surrounded by a pseudocapsule

Renal cell carcinoma
solid variant

- Cells have scant to abundant clear, basophilic or eosinophilic cytoplasm
- Nuclei may have nucleoli or nuclear grooves
- May have compact areas of low grade spindle cells lining thin, angulated tubules
- No mucinous stroma
- May have foamy macrophages, psammoma bodies

Renal cell carcinoma solid variant



https://www.archivesofpathology.org/action/showFullPopup?id=i1543-2165-134-8-1210-f01&doi=10.1043%2F2009-0464-CR.1

Accessed 02/20/2020

Figure 1. Gross photograph showing a solid, firm, tan tumor protruding from the renal cortex as a solitary, rounded mass. The tumor interface is well demarcated; the tumor abuts the renal pelvis.

Figure 2. Solid sheets of cells (hematoxylin-eosin, original magnification ×100).

Figure 3. An ill-defined tubular pattern, while in Figure 4, a spindle cell component is seen. (hematoxylin-eosin, original magnification ×400).

Figure 5 and Figure 6. Spindled neoplastic cells are diffusely immunoreactive to cytokeratin 8/18. (original magnification ×400).

Renal cell carcinoma

- Collecting duct neoplasms are rare
- 80% are clear cell carcinomas
- Arise from proximal tubular epithelium
- Sporadic
- LOH 1q, 6p, 13q, 14, 15, 21q, and 22
- del 9 has poor prognosis.
- Consequence of loss of VHL gene (3p25) is disruption of ubiquitin ligase complex.
- Second VHL allele hyper-methylated in 80% of cases of renal carcinoma.

Renal cell carcinoma

- Most common type
- Bright yellow-gray-white masses
- Rounded or polygonal cells with clear or granular cytoplasm which contains glycogen and lipids
- Tend to invade renal vein

Renal cell carcinoma

- Chromophobe tumors account for fewer than 5% of renal neoplasms
- Arise from intercalated cells of collecting ducts
- Composed of cells with prominent cell membranes and pale eosinophilic cytoplasm
- Perinuclear halo common
- Largest cells found arranged about vessels
- Hypodiploid
- 11% bilateral, 22% multifocal

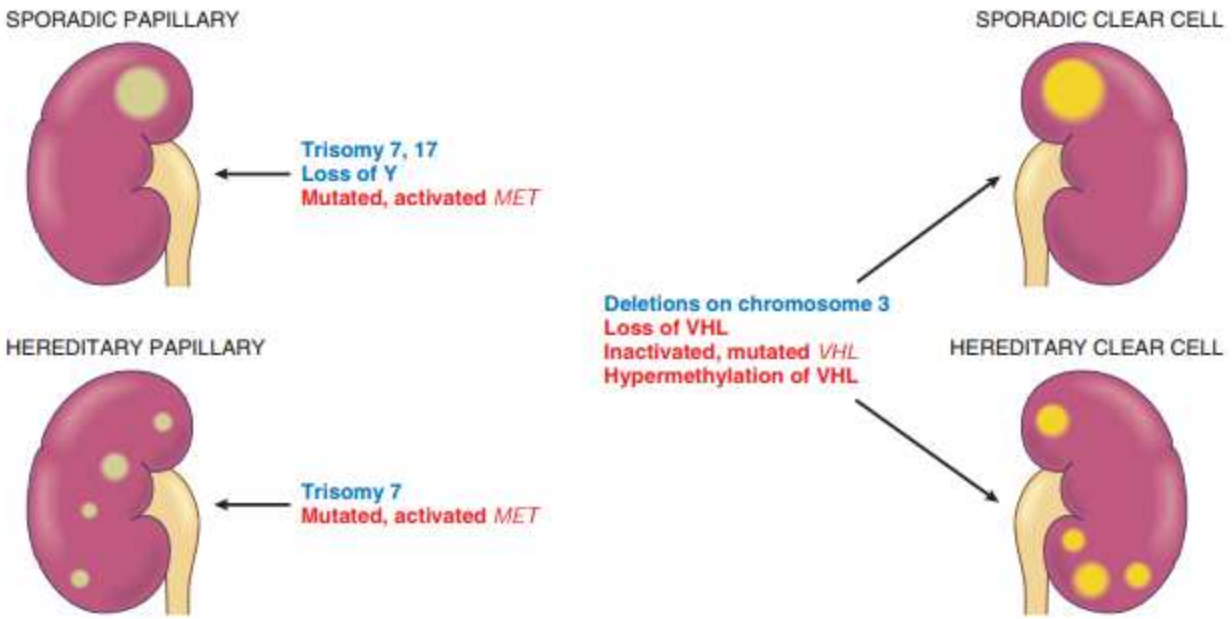


Figure 20.49 Cytogenetics *(blue)* and genetics *(red)* of clear cell versus papillary renal cell carcinoma. (Courtesy Dr. Keith Ligon, Brigham and Women's Hospital, Boston, Mass.)

Other cancers

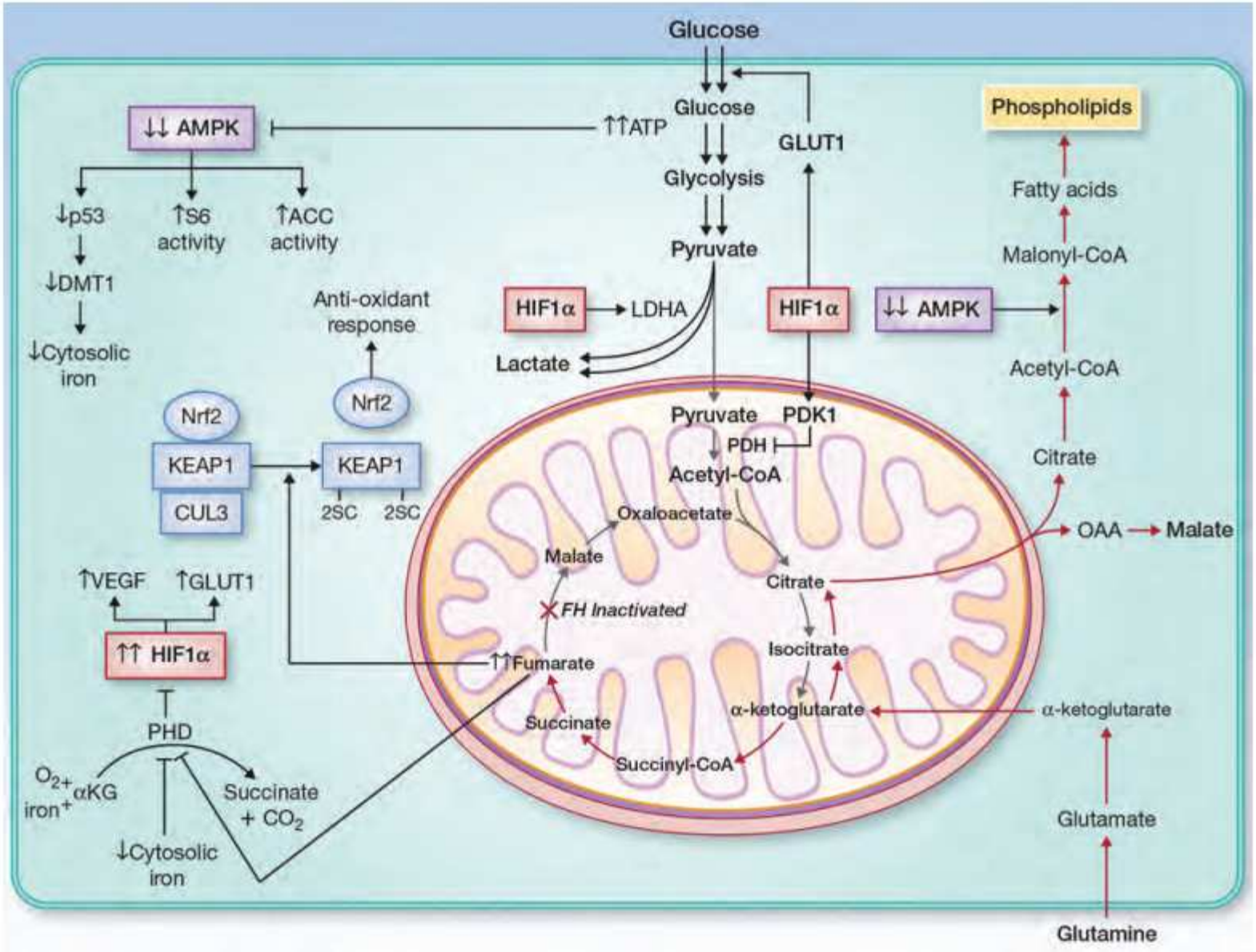
- Xp11 translocation carcinoma
- Young patients
- TFE3 translocations at Xp11.2
- Leucine zipper transcription factor
- Five fusion factors identified
- Clear cytoplasm with a papillary architecture
- Bellini (collecting duct) carcinoma
- 1% of cancers
- Arise from medullary collecting duct cells
- Irregular channels lined by atypical epithelium with hobnail pattern enmeshed in fibrous stroma
- Sarcomatous change is poor prognostic sign

Renal cell carcinoma

- Von Hippel-Lindau disease
- Bilateral
- Younger adults
- Autosomal dominant
- Inactivation of VHL gene
- Increased risk of developing hemangioblastoma
- Increased risk of developing pheochromocytoma
- Not in papillary cancer

Renal carcinoma

- HIF accumulates as under normal oxygen conditions.
- The VHL complex targets these factors for ubiquination:
- HIF-1α, poor prognosis
- HIF-2α, more favorable prognosis
- IL-4 and IL-13 share IL-4R chain in their structure.
- Stimulate IgE production
- Mediate antigen stimulated T-cell activity.
- Mutation associated with propensity to renal cancer.


Glucose
Glucose
↓↓ AMPK
↑↑ATP
GLUT1
Glycolysis
Pyruvate
Phospholipids
Fatty acids
Malonyl-CoA
↓p53
↑S6 activity
↑ACC activity
↓DMT1
↓Cytosolic iron
Anti-oxidant response
HIF1α
LDHA
Lactate
HIF1α
↓↓ AMPK
Acetyl-CoA
Nrf2
Nrf2
KEAP1
KEAP1
CUL3
2SC
2SC
Pyruvate
PDK1
PDH
Acetyl-CoA
Citrate
Oxaloacetate
OAA
Malate
Malate
Citrate
FH Inactivated
↑VEGF
↑GLUT1
↑↑ HIF1α
↑↑Fumarate
Isocitrate
α-ketoglutarate
α-ketoglutarate
PHD
Succinate
Succinyl-CoA
O2+ iron+ αKG
Succinate + CO2
↓Cytosolic iron
Glutamate
Glutamine

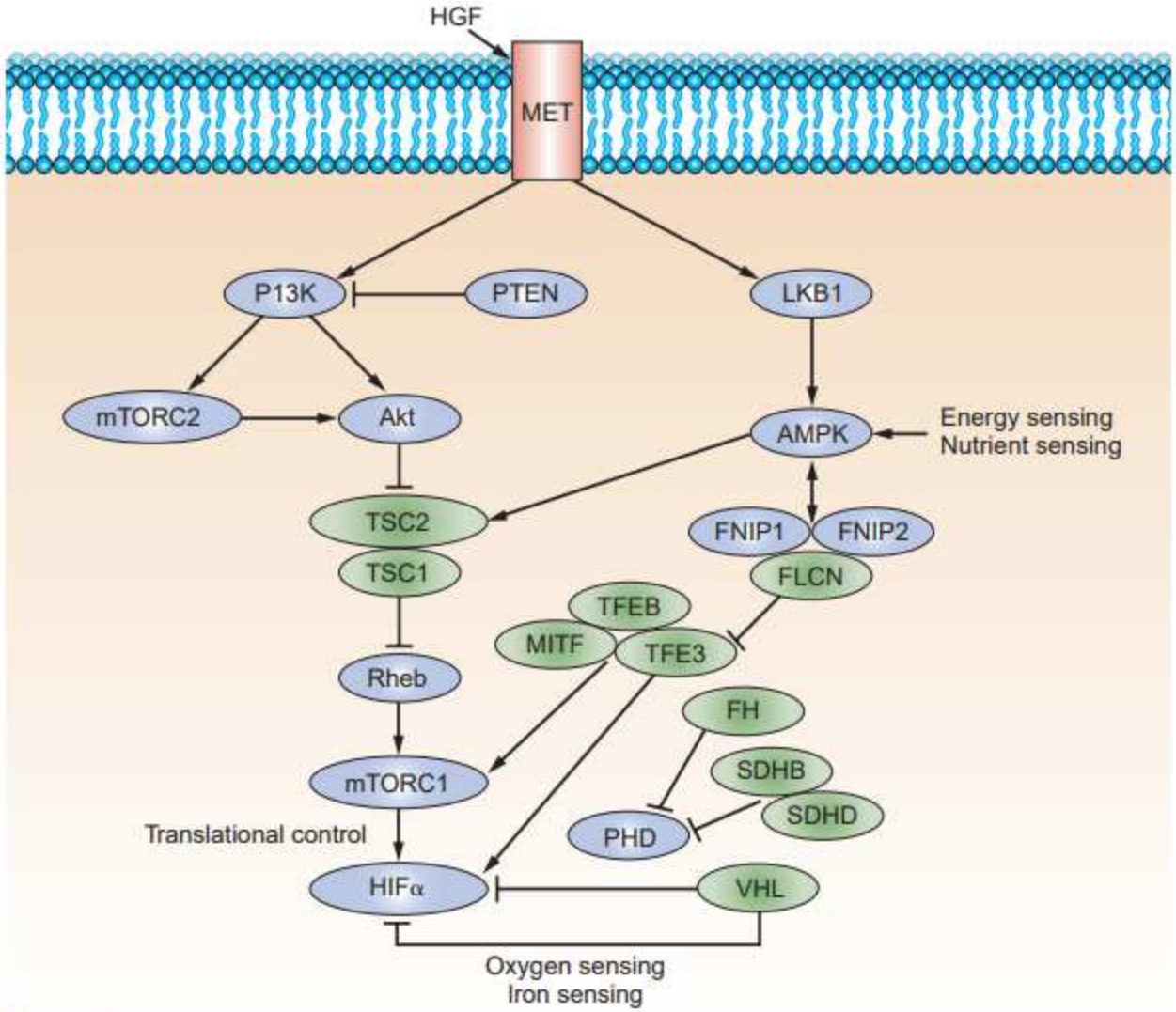


Figure 62.4 The genetic basis of kidney cancer. Twelve renal cancer predisposing genes—*VHL, MET, FLCN, TFE3, TFEB, MITF, TSC1, TSC2, PTEN, FH, SDHB,* and *SDHD*— have been identified mainly through studies of inherited kidney cancer syndromes. These genes interact through common oxygen, iron, nutrient, and energy sensing pathways and demonstrate that kidney cancer is fundamentally a metabolic disease. Our understanding of the molecular mechanisms by which these genes interact in these pathways has enabled the development of targeted therapeutic agents to benefit kidney cancer patients. (From Linehan WM, Ricketts CJ. The metabolic basis of kidney cancer. *Semin Cancer Biol* 2013;23:46–55.)

Renal cell carcinoma

- VEGFα (6p12), PDGFβ (5q33) production stimulated (angiogenesis);
- CAIX (9p12), CAXII (15q22) stimulated (pH regulation through carbonic anhydrase);
- Erythropoietin (7q22), glut-1 (1p34) stimulated;
- TGF-α (2p13), TGF-β (19p13), IGF1 (12q23), EFGR (7p12) stimulated, leading to autocrine growth;
- CXRC4 (2q21) stimulated (associated with metastatic potential).
- All are downstream targets of HIF.

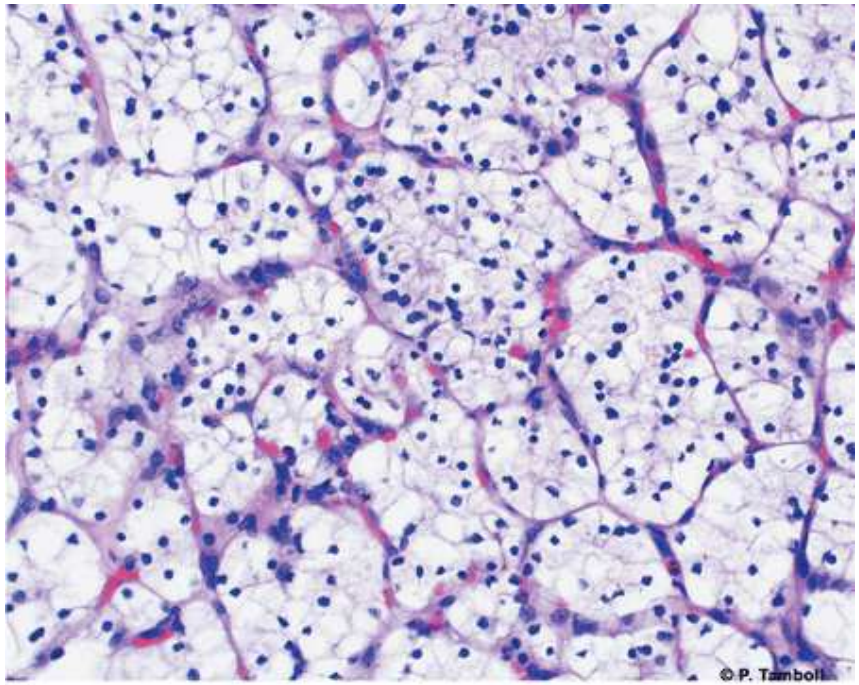
Papillary carcinoma

- 10-15% of renal cancers
- Frequently multifocal in origin
- Arise from distal collecting tubules
- Cuboidal or columnar cells in papillary configuration. Interstitial foam cells common in papillary cores. May find Psammoma bodie.
- Trisomy 7 or 17 or loss of Y chromosome in sporadic cases
- Trisomy 7 in familial cases
- MET activation (Hepatocyte growth factor)

Renal carcinoma

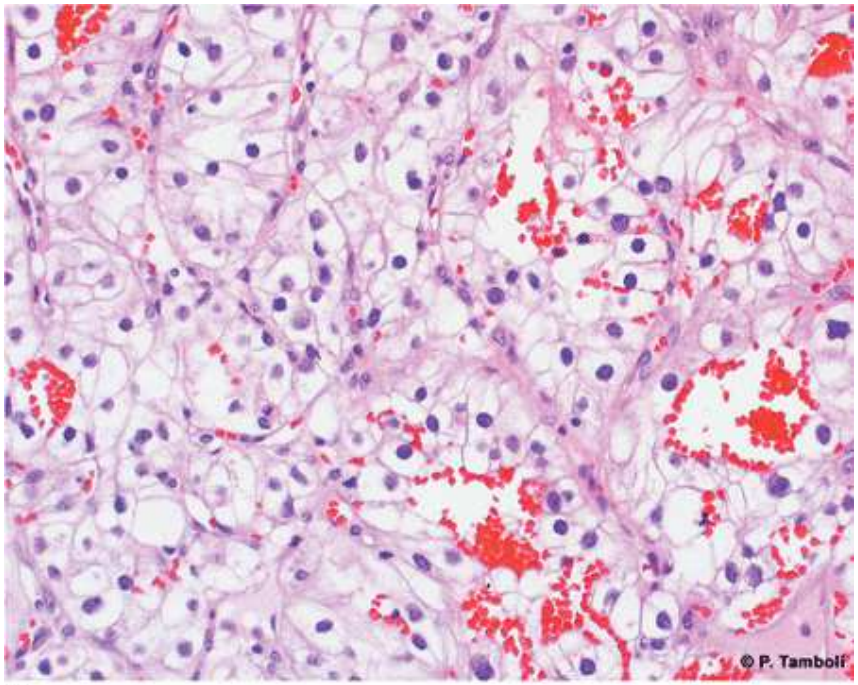
- Papillary adenocarcinomas constitute 10% of renal cancers.
- Arise from intercalated cells of ductal cells.
- Bilateral, multifocal papillary tumors type I
- Associated with:
- Trisomy 7 (familial form)
- C-MET gene (7q31) encodes tyrosine kinase receptor for hepatocyte growth factor.
- (Hypoxia upregulates MET gene normally.)
- del Y (male associated)
- Trisomy 16
- Trisomy 17.

Renal cell papillary carcinoma Type 1



A

Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com



B

Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Photomicrographs of clear cell (conventional) RCC with low-grade nuclear features (A) and high-grade nuclear features (B).

(Reprinted by permission from Pheroze Tamboli, MD.)

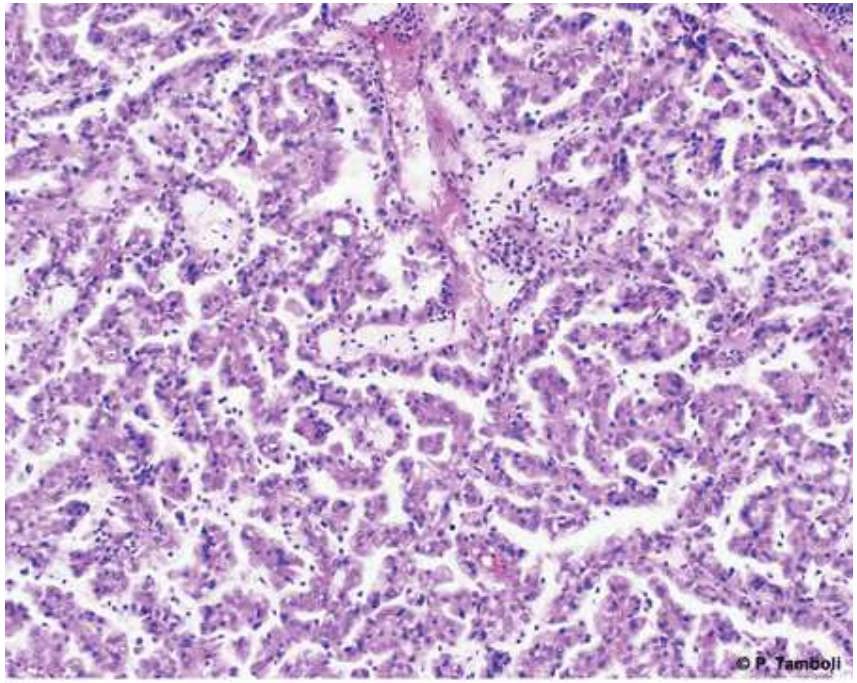
Fig. 29-1 Accessed 08/01/2010

Renal carcinoma

- Bilateral, multifocal papillary tumors type II
- Mutation in fumarate hydratase gene (1q42)
- Deranges mitochondrial conversion of fumarate to malate.
- Hypoxia results (HIF upregulated).
- Papillae lined by tall columnar cells found in tumor.

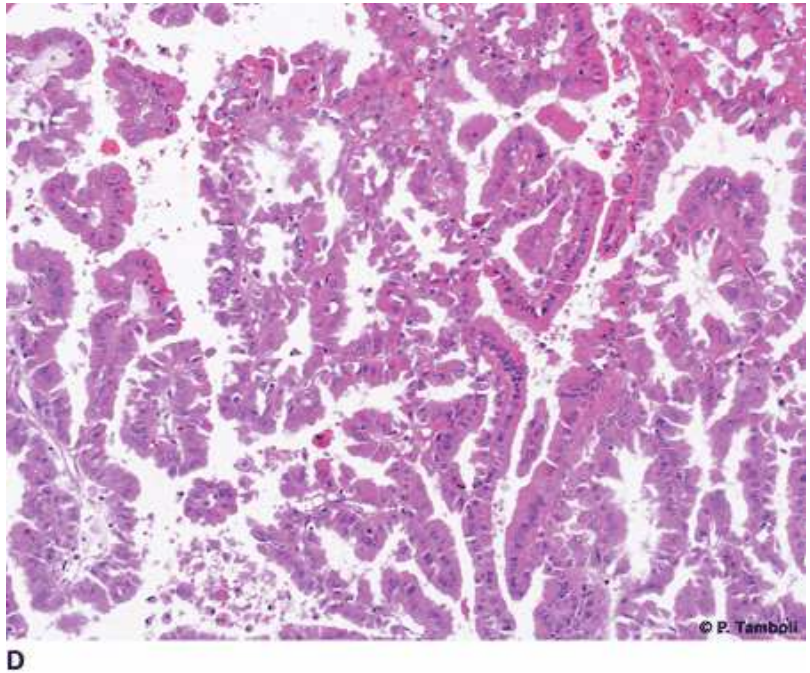
- Spindle cell renal cell carcinoma is not associated with leiomyoma, rhabdomyoma, or squamous differentiation.

Renal cell carcinoma



C

Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com



D

Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Photomicrographs of clear cell (conventional) RCC showing papillae lined by short cuboidal cells (C), and type 2 papillary RCC showing papillae lined by tall columnar cells, with eosinophilic cytoplasm and high grade nuclear features (D).

(Reprinted by permission from Pheroze Tamboli, MD.) Fig. 29-1 Accessed 08/01/2010

TABLE 63.1

2004 World Health Organization Classification of Sporadic Renal Cell Carcinoma with Genetic and Clinical Correlates

Type	Genetics	Clinical
ccRCC (70% to 80%)	Deletion, mutation or methylation of 3p25-26 (*VHL*)	Most common variant Prognosis predicted by stage and grade
Multilocular cystic ccRCC (uncommon)	Deletion, mutation, or methylation of 3p25-26 (*VHL*)	Variant of ccRCC Distant metastases uncommon
Papillary RCC (10% to 15%)	Gain of 7 or 17 (trisomy or tetrasomy), loss of Y, deletion of 9p. Mutations of 7q31 when associated with hereditary papillary RCC	10% to 15% of RCC 95%+ 5-year cancer-specific survival in type I papillary RCC Response to tyrosine-kinase inhibitors less robust
Chromophobe RCC (3% to 5%)	Extensive chromosomal loss of Y, 1, 2, 6, 10, 13, 17, 21 Mutations of 17p11.2 when associated with BHD	5% of RCC Affects men and women equally with overall excellent prognosis
Collecting duct carcinoma (Bellini tumor) (<1%)	Highly variable Losses of 1q, 6p, 8p, 9p, 13q, 19q, 21q	Male preponderance (2:1) Mean age 55 Microscopically high grade, may resemble urothelial spectrum of cancers, Overall poor prognosis
Renal medullary carcinoma (rare)	Not defined	Associated with sickle cell trait Aggressive and lethal within 12 mo Mean age 19 y Male>female
Xp11 translocation carcinoma (rare)	Translocation of TFE3 gene on XP11.2	Children and young adults May present at advanced state and act more aggressively in adults
Renal carcinoma associated with neuroblastoma (rare)	Not defined	Morphologically and microscopically similar to ccRCC
Mucinous tubular and spindle cell carcinoma (rare)	Not defined	Female preponderance (4:1) Rarely metastasize
Unclassified RCC (1% to 3%)	Varied	Generally poor prognosis

ccRCC, clear cell renal cell carcinoma; RCC, renal cell carcinoma.

Adapted from Deng FM, Melamed J, Zhou M. Pathology of renal cell carcinoma. In: Libertino JA, ed. In *Renal Cancer: Contemporary Management*. New York: Springer; 2013:51–69.

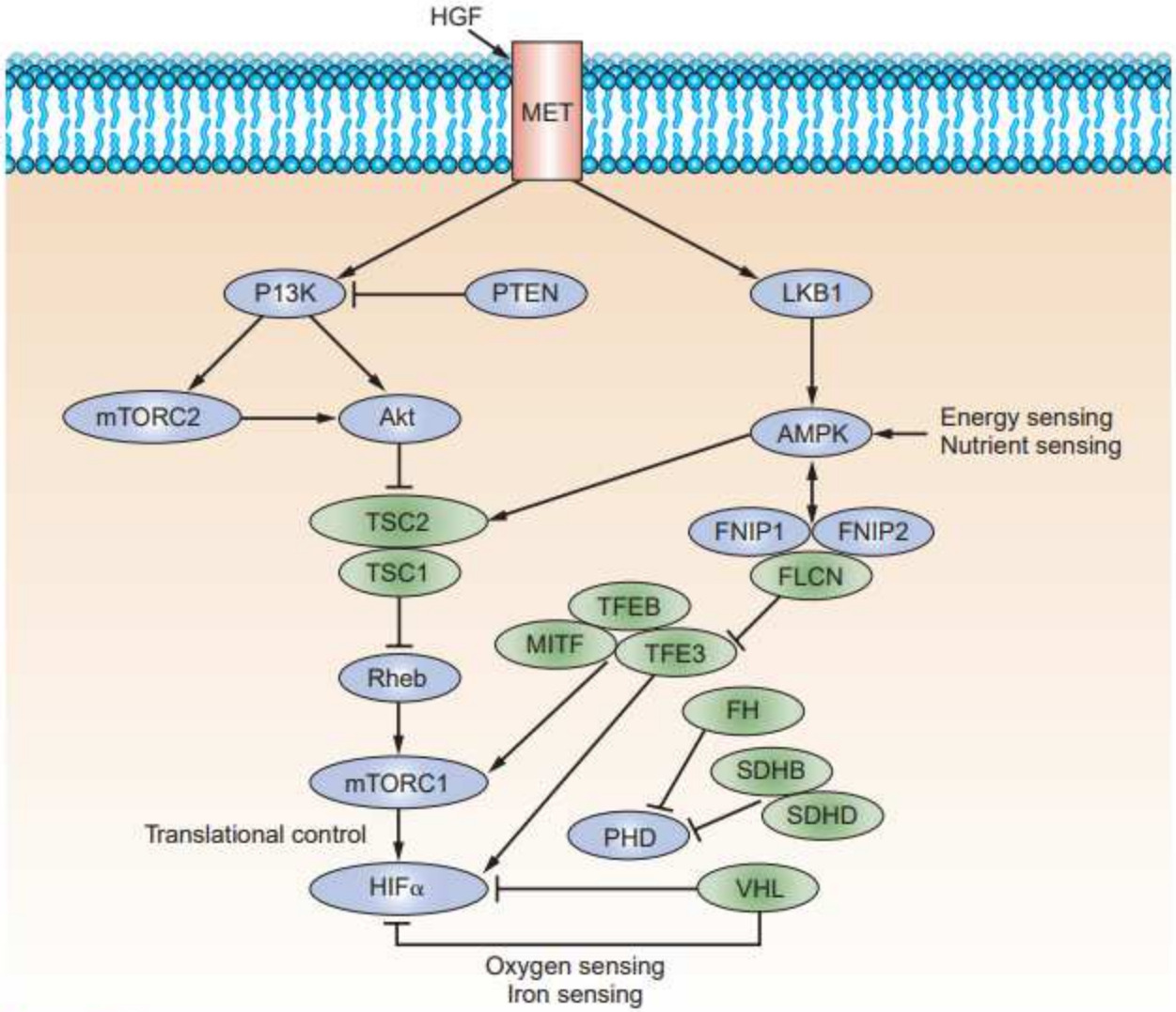


Figure 62.4 The genetic basis of kidney cancer. Twelve renal cancer predisposing genes—*VHL, MET, FLCN, TFE3, TFEB, MITF, TSC1, TSC2, PTEN, FH, SDHB,* and *SDHD*— have been identified mainly through studies of inherited kidney cancer syndromes. These genes interact through common oxygen, iron, nutrient, and energy sensing pathways and demonstrate that kidney cancer is fundamentally a metabolic disease. Our understanding of the molecular mechanisms by which these genes interact in these pathways has enabled the development of targeted therapeutic agents to benefit kidney cancer patients. (From Linehan WM, Ricketts CJ. The metabolic basis of kidney cancer. *Semin Cancer Biol* 2013;23:46–55.)

TABLE 62.1

Hereditary Renal Cancer Syndromes

Syndrome	Chromosome Location	Predisposing Gene	Histology	Frequency of Gene Mutations	
				Germ Line	Sporadic RCC
Von Hippel-Lindau (VHL) disease	3p25	*VHL*	Clear cell	100%[14]	92%[22]
Hereditary papillary renal carcinoma type 1 (HPRC)	7q31	*MET*	Type 1 papillary	100%[6,41,42]	13%[45]
Birt-Hogg-Dubé syndrome (BHD)	17p11.2	*FLCN*	Chromophobe, hybrid	90%[65]	11%[76]
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)	1q42–43	*FH*	Type 2 papillary	93%[105]	TBD
Succinate dehydrogenase (SDH)–associated familial renal cancer	1p35–36 1q23.3 11q23	*SDHB* *SDHC* *SDHD*	Clear cell, chromophobe, oncocytic neoplasm	TBD	TBD
Tuberous sclerosis complex (TSC)	9q34 16p13.3	*TSC1* *TSC2*	Angiomyolipoma, all histologies	80%–90%	TBD

TBD, to be determined.

- An individual with a close blood relative[b] with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene

- An individual with RCC with any of the following criteria:
  - Diagnosed at age ≤46 y
  - Bilateral or multifocal tumors
  - ≥1 first- or second-degree relative[b] with RCC

- An individual whose tumors have the following histologic characteristics:
  - Multifocal papillary histology
  - Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated RCC, RCC with fumarate hydratase (FH) deficiency or other histologic features associated with HLRCC
  - Birt-Hogg-Dubé syndrome (BHDS)-related histology (multiple chromophobe, oncocytoma, or oncocytic hybrid)
  - Angiomyolipomas of the kidney and one additional tuberous sclerosis complex criterion in the same person (See Table 1)
  - Succinate dehydrogenase (SDH)-deficient RCC histology[c]

https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf
Accessed 03/17/2021

TABLE 63.3

Familial Renal Cell Carcinoma Syndromes

Syndrome	Gene (Chromosome)	Major Clinical Manifestations
von Hippel-Lindau	*VHL* gene (3p25-26)	Clear cell RCC Retinal angiomas Central nervous system hemangioblastomas Pheochromocytoma Other tumors
Hereditary papillary RCC	*c-met* proto-oncogene (7q31)	Multiple, bilateral type 1 papillary RCCs
Familial leiomyomatosis and RCC	*Fumarate hydratase* (1q42-43)	Type 2 papillary RCC Collecting duct RCC Leiomyomas of skin or uterus Uterine leiomyosarcomas
Birt-Hogg-Dubé	*Folliculin* (17p11)	Multiple chromophobe RCC, hybrid oncocytic tumor, oncocytomas Occasional clear cell (occasionally) Papillary RCC (occasionally) Facial fibrofolliculomas Lung cysts Spontaneous pneumothorax
Succinate dehydrogenase RCC	Succinate dehydrogenase complex subunits: *SDHB* (1p36.1-35) or *SDHD* (11q23)	Chromophobe, clear cell, type 2 papillary RCC, oncocytoma Paragangliomas (benign and malignant) Papillary thyroid carcinoma
Tuberous sclerosis	*TSC1* (9q34) or *TSC2* (16p13)	Multiple renal angiomyolipomas Clear cell RCC (occasionally) Renal cysts/polycystic kidney disease Cutaneous angiofibromas Pulmonary lymphangiomyomatosis
PTEN hamartoma tumor syndrome (Cowden syndrome)	*PTEN* (10q23)	Breast tumors (malignant and benign) Epithelial thyroid carcinoma Papillary RCC or other histology

PTEN, phosphatase and tensin homolog; RCC, renal cell carcinoma.
Adapted from Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. *J Urol* 2003; 170(6 Pt 1):2163-2172. and Linehan WM, Ricketts CJ. The metabolic basis of kidney cancer. *Semin Cancer Biol* 2013;23:46–55.

HEREDITARY RCC SYNDROMES OVERVIEW

Syndrome/Gene	Histology	Inheritance Pattern Major Clinical Manifestations
von Hippel-Lindau (VHL)/ *VHL* gene	Clear cell	• Autosomal dominant • See Table 2
Hereditary papillary renal carcinoma (HPRC)/*MET* gene	Type 1 papillary	• Autosomal dominant • Multifocal, bilateral renal cell tumors
Birt-Hogg-Dubé syndrome (BHDS)/*FLCN* gene[d,e]	Chromophobe, hybrid oncocytoma	• Autosomal dominant • Cutaneous fibrofolliculoma or trichodiscoma, pulmonary cysts, and spontaneous pneumothorax
Tuberous sclerosis complex (TSC)/*TSC1*, *TSC2* genes	Angiomyolipoma, clear cell	• Autosomal dominant • See Table 1
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)/*FH* gene	HLRCC or FH-associated RCC/ type 2 papillary	• Autosomal dominant • Leiomyomas of skin and uterus, unilateral, solitary, and aggressive renal cell tumors. PET-positive adrenal adenomas
BAP1 tumor predisposition syndrome (TPDS)/*BAP1* gene[f,g]	Clear cell, chromophobe	• Autosomal dominant • Melanoma (uveal and cutaneous), kidney cancer, mesothelioma
Hereditary paraganglioma/ pheochromocytoma (PGL/ PCC) syndrome/*SDHA/B/ C/D* genes	Clear cell (not usually *SDHB*), chromophobe, papillary type 2, renal oncocytoma, oncocytic neoplasm	• Autosomal dominant • Head and neck paraganglioma and adrenal or extra-adrenal pheochromocytomas, benign lung lesions, GIST tumors

https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf
Accessed 03/17/2021

Table 1: Features of Tuberous Sclerosis (TSC)

Major Features	Minor Features
• Renal angiomyolipoma (AML)[1,2] • Cardiac rhabdomyoma • Cortical dysplasias, including tubers and cerebral white matter migration lines • Angiofibromas (≥3) or fibrous cephalic plaque • Hypomelanotic macules (3 to >5 mm in diameter) • Lymphangioleiomyomatosis (LAM)[1] • Multiple retinal nodular hamartomas • Shagreen patch • Subependymal giant cell astrocytoma (SEGA) • Subependymal nodules (SENs) • Ungual fibromas (≥2)	• Multiple renal cysts • "Confetti" skin lesions (numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs) • Dental enamel pits (>3) • Intraoral fibromas (≥2) • Nonrenal hamartomas • Retinal achromic patch

Table 2: Features of Von Hippel-Lindau (VHL) Disease

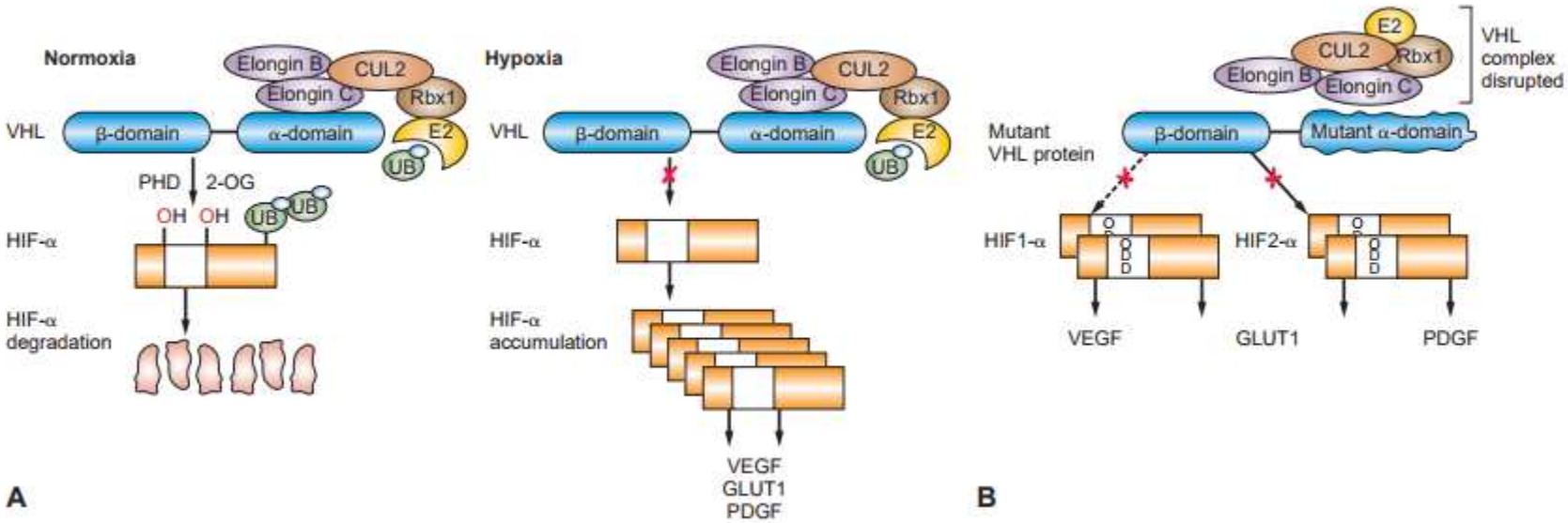
Major Features	Minor Features
• Hemangioblastomas of the retina, spine, or brain • Clear cell RCC (ccRCC) diagnosed <40 years of age or multiple/bilateral ccRCC tumors diagnosed at any age • Adrenal or paraganglioma • Paraganglioma of abdomen, thorax, or neck • Retinal angiomas	• Endolymphatic sac tumors • Papillary cystadenomas of the epididymis or broad ligament • Pancreatic serous cystadenoma (>1) • Pancreatic neuroendocrine tumor or multiple pancreatic cysts (>1)

[1] The combination of AML and LAM does not meet criteria for definite diagnosis.
[2] Multiple AMLs are a major feature.

https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf
Accessed 03/17/2021

Familial variants

- Von-Hippel Lindau syndrome
- VHL gene at 3p25.3 is lost
- Encodes E3 ubiquitin ligase
- HIF elevated in normoxic conditions
- Promotes angiogenesis
- With MYC, promotes cell growth
- Renal cysts and multiple renal cell carcinomas
- Nearly all will develop carcinomas over time


Normoxia
Elongin B
CUL2
Elongin C
Rbx1
VHL
β-domain
α-domain
E2
UB
PHD
2-OG
OH
OH
UB
UB
HIF-α
HIF-α
degradation
Hypoxia
Elongin B
CUL2
Elongin C
Rbx1
VHL
β-domain
α-domain
E2
UB
HIF-α
HIF-α
accumulation
VEGF
GLUT1
PDGF
A
E2
CUL2
Rbx1
Elongin B
Elongin C
VHL
complex
disrupted
Mutant
VHL protein
β-domain
Mutant α-domain
HIF1-α
HIF2-α
O
D
D
VEGF
GLUT1
PDGF
B

Familial variants

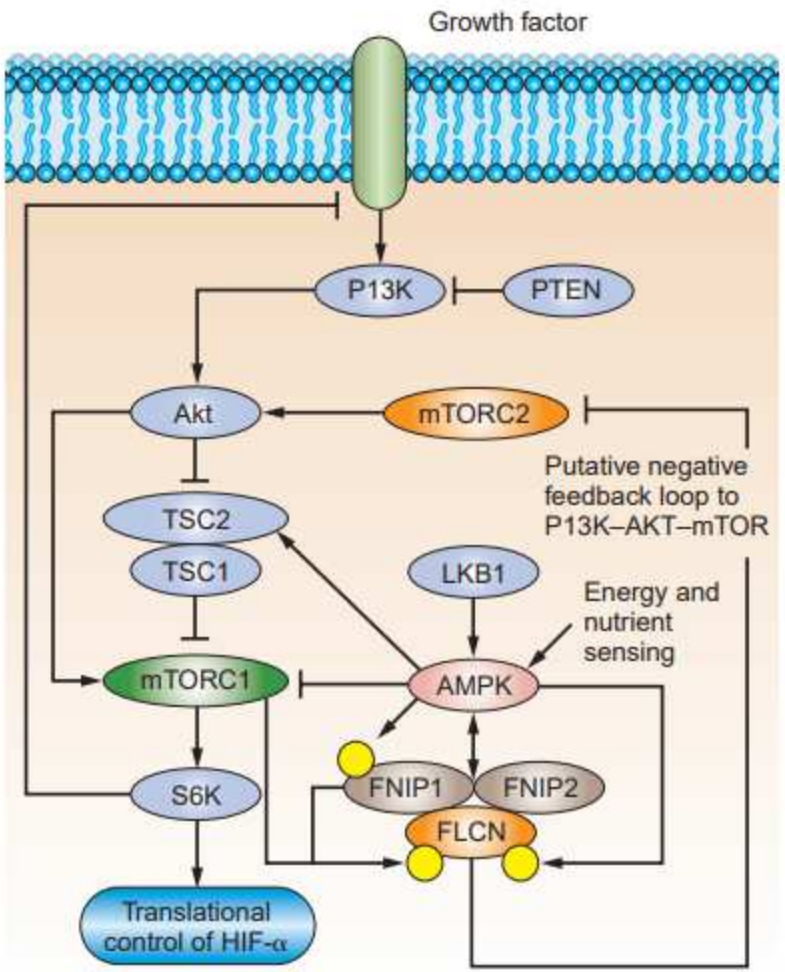
- Hereditary leiomyomatosis and renal cancer syndrome
- Fumarate hydrase (FH) gene at 1q42-43
- Accumulation of fumarate and succinate lead to HIF activation
- Cutaneous and uterine leiomyomata and papillary carcinoma
- High metastatic potential
- Rare to survive 5 years
- Succinate dehydrogenase B and D mutations also lead to accumulation of succinate and HIF activation

Familial variants

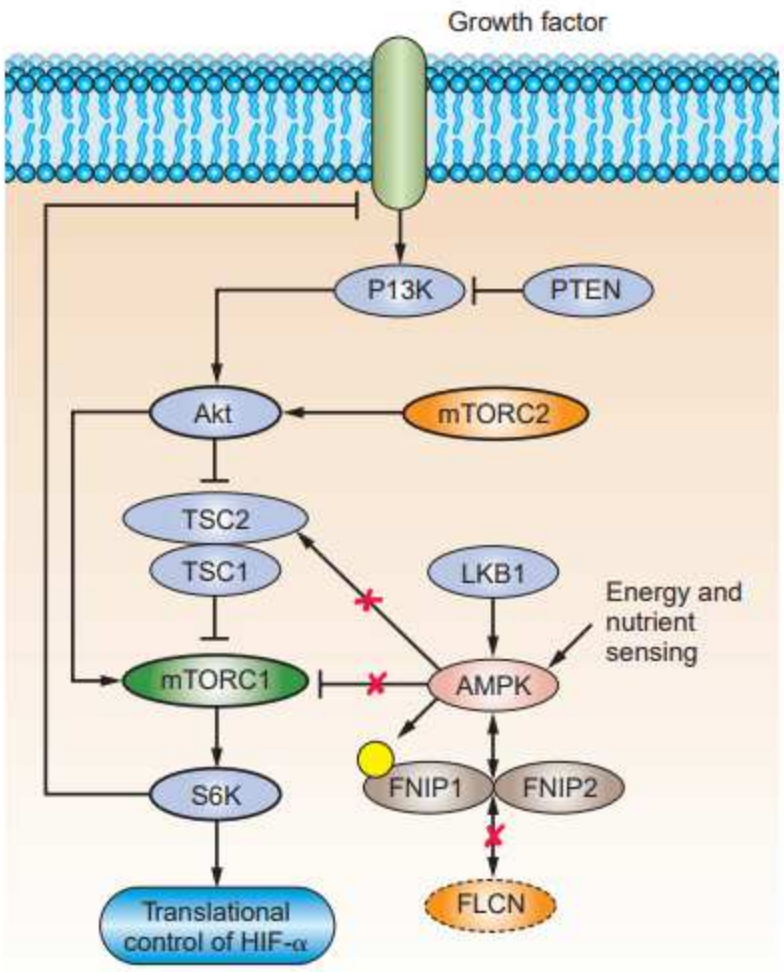
- Hereditary papillary carcinoma
- Bilateral tumors
- Autosomal dominant
- Trisomy 7
- MET gene at 7q31 activated

Familial variants

- Birt-Hogg-Dubé syndrome
- Fibrofolliculomas and lung cysts in 85% of patients
- Autosomal dominant
- FLCN gene at 7q (expresses folliculin)
- LOH mutations in both alleles
- Negative feedback on PI3K-AKT-mTOR
- Translational control of HIF


Growth factor
P13K
PTEN
Akt
mTORC2
Putative negative
feedback loop to
P13K–AKT–mTOR
TSC2
TSC1
LKB1
Energy and
nutrient
sensing
mTORC1
AMPK
FNIP1
FNIP2
S6K
FLCN
Translational
control of HIF-α

A


Growth factor
P13K
PTEN
Akt
mTORC2
TSC2
TSC1
LKB1
Energy and
nutrient
sensing
mTORC1
AMPK
FNIP1
FNIP2
S6K
FLCN
Translational
control of HIF-α

B

TABLE 63.2

International Tumor, Node, Metastasis Staging System for Renal Cell Carcinoma and Survival Rates

T: Primary Tumor				**Five-Year Survival (%)**
TX	Primary tumor cannot be assessed			
T0	No evidence of primary tumor			
T1a	Tumor ≤4 cm and confined to the kidney			90–100
T1b	Tumor >4 cm and ≤7 cm and confined to the kidney			80–90
T2a	Tumor >7 cm and ≤10 cm and confined to the kidney			65–80
T2b	Tumor >10 cm and confined to the kidney			50–70
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota fascia			40–65
T3b	Tumor grossly extends into the vena cava below the diaphragm			30–50
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava			20–40
T4	Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)			0–20
N: Regional Lymph Nodes				
NX	Regional lymph nodes cannot be assessed			
N0	No regional lymph nodes metastasis			
N1	Metastasis in regional lymph node(s)			0–20
M: Distant Metastases				
MX	Distant metastasis cannot be assessed			
M0	No distant metastasis			
M1	Distant metastasis present			0–10
Stage Grouping				
Stage I	T1	N0	M0	
Stage II	T2	N0	M0	
Stage III	T3	Any N	M0	
	T1 or T2	N1	M0	
Stage IV	T4	Any N	M0	
	Any T	Any N	M1	

Prognostic and surgical staging systems of IVC tumor thrombus

Anatomic landmark	Staging systems				
	TNM	Neves	Novick	Hinman	Robson
RV	T3b	0	I	I	IIIa
IVC <2 cm above RV		I	II		
IVC >2 cm above RV and below hepatic veins		II			
IVC above hepatic veins and below diaphragm		III	III	II	
IVC above diaphragm	T3c	IV	IV	III	

Figure 63.5 Classification of renal cell carcinoma venous tumor thrombi. Level 0 (*green*): Thrombus within main renal vein (RV) or its branches and not reaching into the inferior vena cava (IVC). Level I (*yellow*): IVC thrombus is present within the IVC, <2 cm above renal vein. Level II (*orange*): IVC thrombus extends along the IVC, but not to the level of the main hepatic veins. Level III (*purple*): IVC thrombus extends within the IVC above the level of the main hepatic veins, but below the diaphragm. Level IV (*red*): IVC thrombus extends above the diaphragm, near to or into the right atrium and occasionally beyond. TNM, tumor, node, metastasis. (Reproduced with permission from Pouliot F, Shuch B, Larochelle JC, et al. Contemporary management of renal tumors with venous tumor thrombus. *J Urol* 2010;184:833–841.)

TABLE 63.7

Prognostic System in Metastatic Renal Cell Carcinoma

Schema	Factors	Comments
MSKCC[215]	■ Low Karnofsky performance status ■ High lactate dehydrogenase ■ Low serum hemoglobin ■ High corrected serum calcium ■ Time from initial RCC diagnosis to start of therapy <1 y	Developed from patients with metastatic RCC patients treated with IFN-based therapy on clinical trials at MSKCC
Heng et al.[187]	■ Low Karnofsky performance status ■ Low serum hemoglobin ■ High corrected serum calcium ■ Time from initial RCC diagnosis to start of therapy <1 y ■ Elevated neutrophils ■ Elevated platelets	Developed from retrospective data for a global multicenter consortium of patients receiving targeted therapy for metastatic RCC

MSKCC, Memorial Sloan-Kettering Cancer Center; RCC, renal cell carcinoma; IFN, interferon.

Treatment

- Tumors <4cm show 1% yearly progression to metastatic disease
- 5% progress to be symptomatic.
- Partial nephrectomy may be utilized.
- Nephrectomy curative only for localized disease.
- Lymphadenectomy if retroperitoneal lymphadenopathy present.
- Ipsilateral adrenalectomy reserved for patients with large upper pole disease.

Treatment

- If patient has retroperitoneal lymphadenopathy and metastasis, nephrectomy and retroperitoneal lymphadenectomy indicated.
- Do not respond as well to adjuvant therapy as those patients without retroperitoneal lymphadenopathy but with metastasis.
- Solitary metastasis may be resected.

Treatment

- Stage I T1a cancer is treated with partial nephrectomy or nephron-sparing total nephrectomy.
- Stage I T1b cancer is treated with partial nephrectomy or radical nephrectomy.
- No adjuvant therapy follows for Stage I cancers.
- There is no uniform treatment for Stage II cancers following partial nephrectomy or radical nephrectomy.

Treatment

- Sunitinib is recommended for systemic adjuvant therapy following nephrectomy only for clear cell histology as well as high-risk renal cell carcinoma.
- The presence of sarcomatoid or rhabdoid histology is associated with a more aggressive disease course and a low likelihood of response to TKI monotherapy

Treatment

- 87% are PD-L1 positive
- Ipilimumab and nivolumab if intermediate or poor prognosis in clear cell type
- Axitinib (blocks VEGF 1,2,3) and pembrolizumab are the better choice across all histologic types
- Sunitinib and cabozantib (tyrosine kinase inhibitors) prolong time to disease progression.
- PD1/PDL-1 and CTLA-4 or VEGFR inhibitors are the standard of care in metastatic renal cell carcinoma

See Evidence Blocks on KID-C (EB-1)

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	Preferred regimens	Other recommended regimens	Useful in certain circumstances
Favorable[a]	• Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Pazopanib • Sunitinib	• Ipilimumab + nivolumab[b] • Axitinib + avelumab[b] • Cabozantinib (category 2B)	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d]
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Ipilimumab + nivolumab[b] (category 1) • Cabozantinib + nivolumab[b] • Cabozantinib	• Pazopanib • Sunitinib • Axitinib + avelumab[b]	• Axitinib (category 2B) • High-dose IL-2[d] • Temsirolimus[e]

See Evidence Blocks on KID-C (EB-2)

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY		
Preferred regimens	Other recommended regimens	Useful in certain circumstances
• Cabozantinib (category 1) • Nivolumab[b] (category 1) • Ipilimumab + nivolumab[b]	• Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab[b] • Everolimus • Pazopanib • Sunitinib • Axitinib + avelumab[b] (category 3)	• Bevacizumab[f] (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B)

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY[g]		
Preferred regimens	Other recommended regimens	Useful in certain circumstances
• Clinical trial • Sunitinib	• Cabozantinib • Everolimus • Lenvatinib + everolimus	• Axitinib • Bevacizumab[f] • Erlotinib • Nivolumab[b] • Pazopanib • Bevacizumab[f] + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC) • Bevacizumab[f] + everolimus • Temsirolimus[e] (category 1 for poor-prognosis risk group; category 2A for other risk groups)

Treatment

- Under some circumstances and if not poor risk, bevacizumab (anti-VEGF antibody) may be useful
- Hypertension, bleeding common with bevacizumab, particularly in elderly.
- Those who develop hypertension have better outcomes.

EVIDENCE BLOCKS FOR SYSTEMIC THERAPIES FOR NON-CLEAR CELL CARCINOMA

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY	
Preferred regimen	
Sunitinib	
Other recommended regimens	
Cabozantinib	
Everolimus	
Lenvatinib/everolimus	
Useful under certain circumstances	
Axitinib	
Bevacizumab	
Erlotinib	
Nivolumab	
Pazopanib	
Bevacizumab/erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC)	
Bevacizumab/everolimus	
Temsirolimus (poor-prognosis risk)	
Temsirolimus (risk groups other than poor-risk)	

https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf
Accessed 03/17/2021

KIDNEY-SPECIFIC SURGICAL RECOMMENDATIONS FOR PATIENTS WITH CONFIRMED HEREDITARY RCC

- Preoperative alert: Patients with a suspected or known diagnosis of PGL/PCC or VHL are at increased risk of pheochromocytomas and should have blood and/or urine screening for this prior to any surgical procedure.

BAP1-TPDS
- No specific guidelines in surgical management for this syndrome (See KID-A).

BHDS
- Nephron-sparing surgery is the treatment of choice for renal tumors whenever possible, with consideration that an individual may have multiple tumors during their lifetime.[1]
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

HLRCC
- As these tumors can be aggressive, surveillance of renal tumors is not recommended, and total radical nephrectomy should be considered.[2]

HPRC
- Nephron-sparing surgery is the treatment of choice for renal tumors whenever possible, with consideration that an individual may have multiple tumors during their lifetime.
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

PGL/PCC
- Malignant tumors absent aggressive histology and early stage should undergo surgical resection; partial nephrectomy can be considered.
- For larger tumors and those with aggressive histology (eg, high grade, sarcomatoid), radical nephrectomy should be considered.[3]

TSC
- AML is a benign lesion associated with TSC and managed separately.[4,5,6]
- Nephron-sparing surgery is the treatment of choice for malignant renal tumors whenever possible, with consideration that an individual may have multiple tumors during their lifetime.[7]
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

VHL
- Management of localized renal masses in patients with VHL are typically guided under the "3 cm rule."[7]
- The idea is to intervene at a time point of maximal benefit to the patient to limit the chance of development of metastatic disease but also to consider the recurrent and multiple resections many of these patients will have over the course of their lifetime with subsequent development of chronic and progressive renal failure.[7,8]
- Patient should undergo partial nephrectomy if at all possible and consider referral to centers with surgical expertise in complex partial nephrectomies and management of VHL patients.[8]
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf
Accessed 03/17/2021

KIDNEY-SPECIFIC SYSTEMIC THERAPY FOR PATIENTS WITH CONFIRMED HEREDITARY RCC

HLRCC

- There are no specific FDA-approved therapies for HLRCC. Treatment with erlotinib plus bevacizumab[1] demonstrated benefit in patients with metastatic RCC from HLRCC (See KID-C).[2]

TSC

- Everolimus is an FDA-approved therapy for asymptomatic, growing angiomyolipoma measuring >3 cm in diameter.[3]

VHL Disease

- At this time there are no FDA-approved therapies for nonmetastatic RCC arising in VHL disease. However, pazopanib was associated with a >50 % objective response rate in renal lesions in a 31-patient phase II study.[4]

https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf
Accessed 03/17/2021