Renal and ureteral involvement in Erdheim-Chester disease

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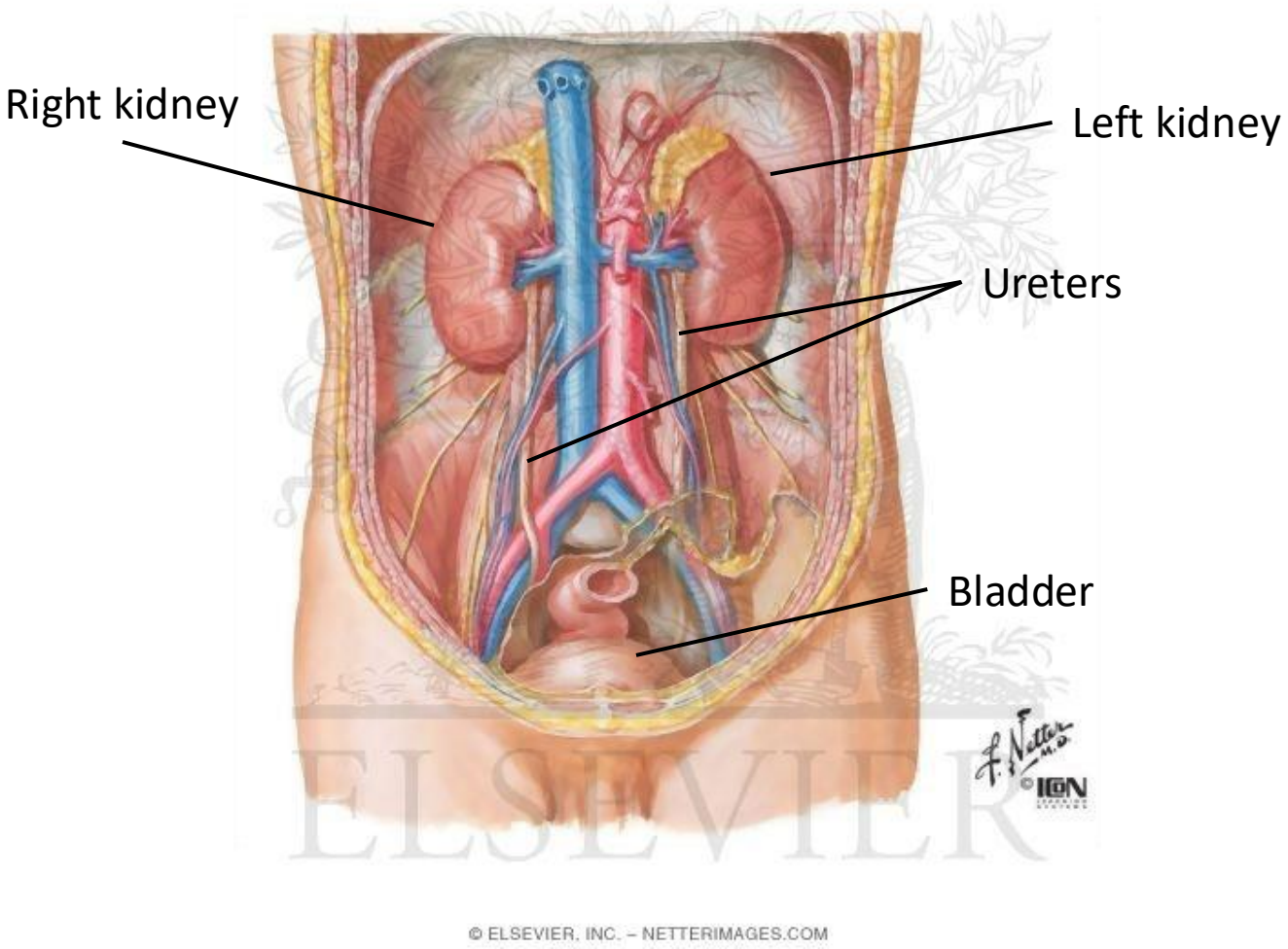
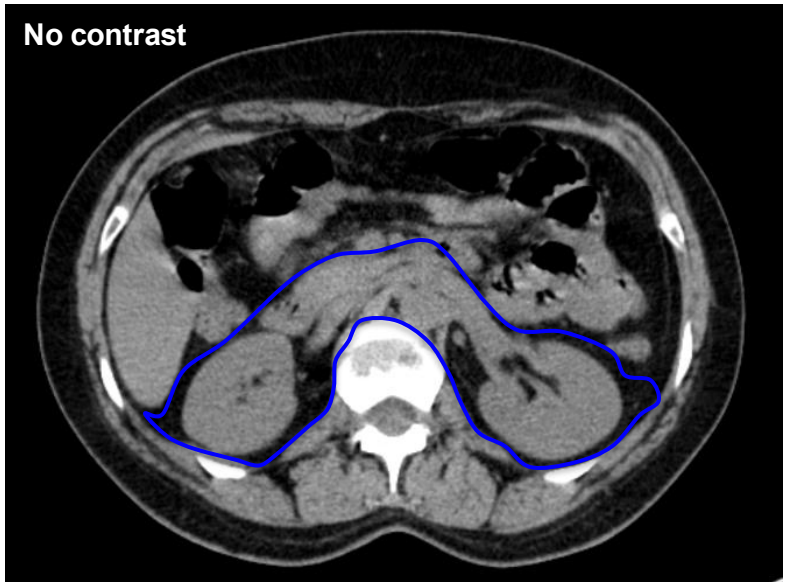
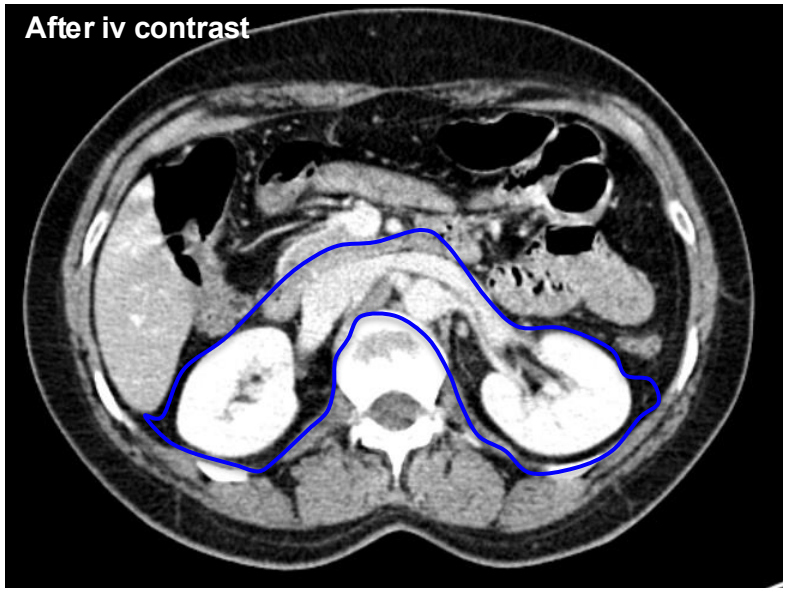
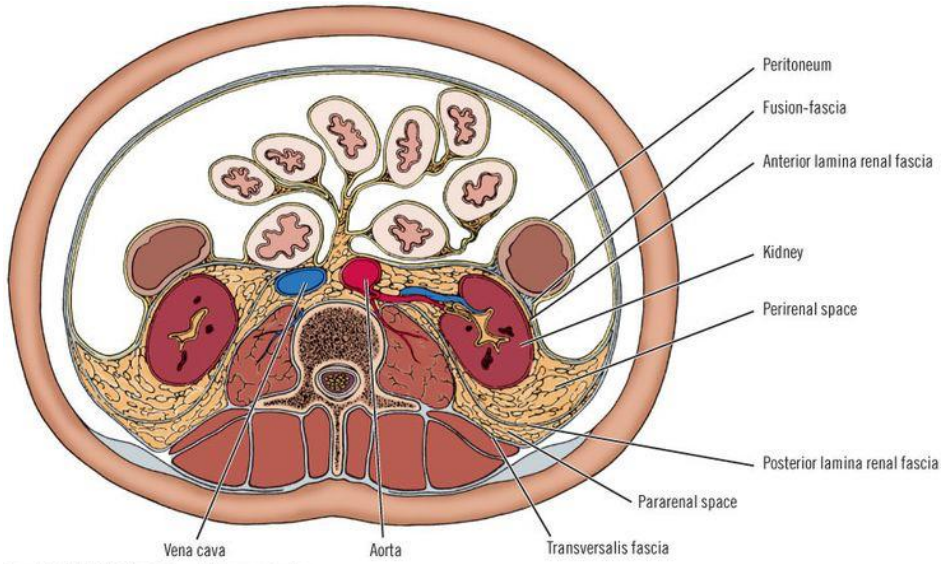
The kidneys and the urinary excretory system



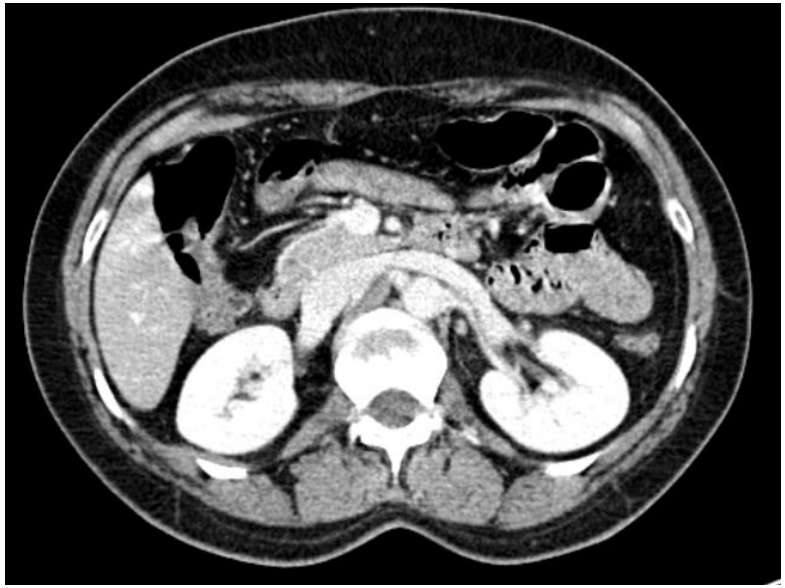
The kidneys and the retroperitoneum



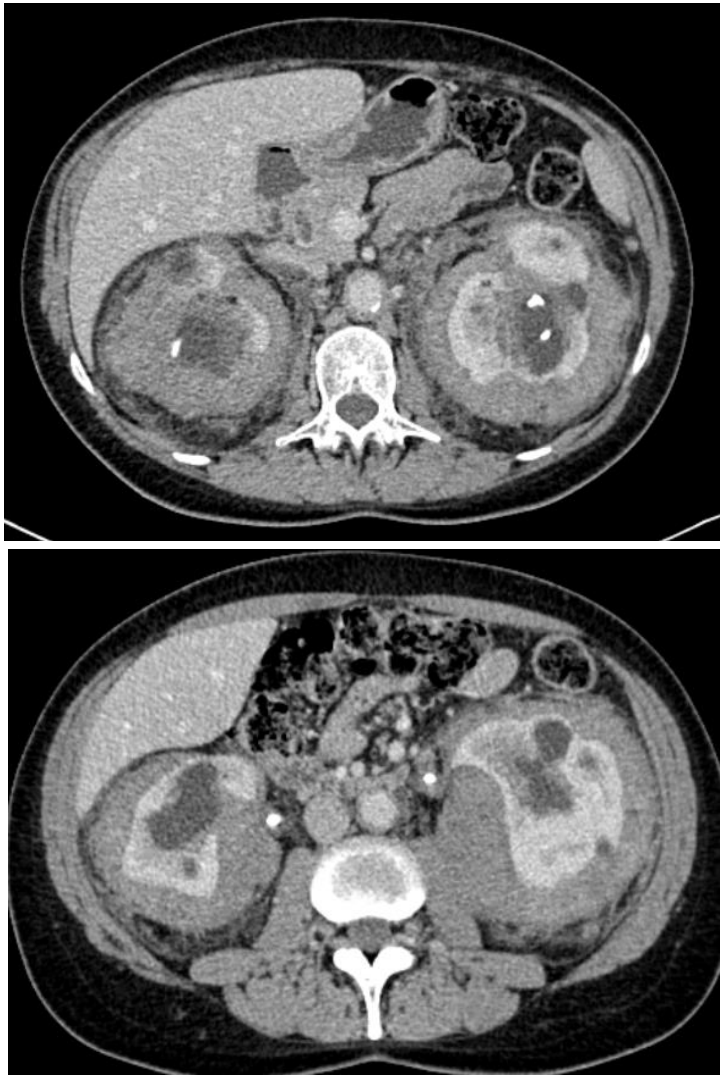




Perirenal infiltration in ECD (*hairy* kidneys)

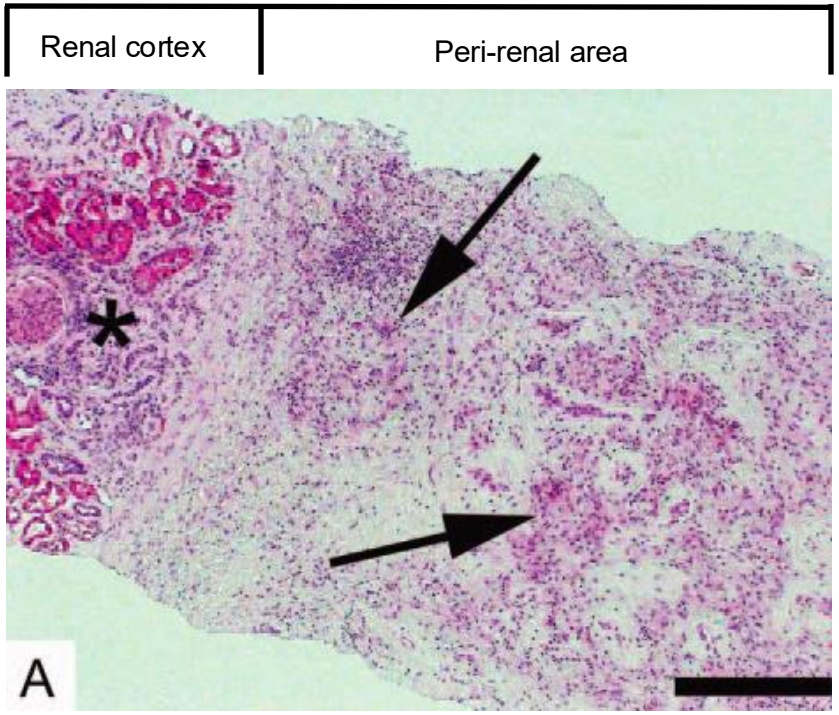


Abdominal CT scan in a healthy 38 yo lady



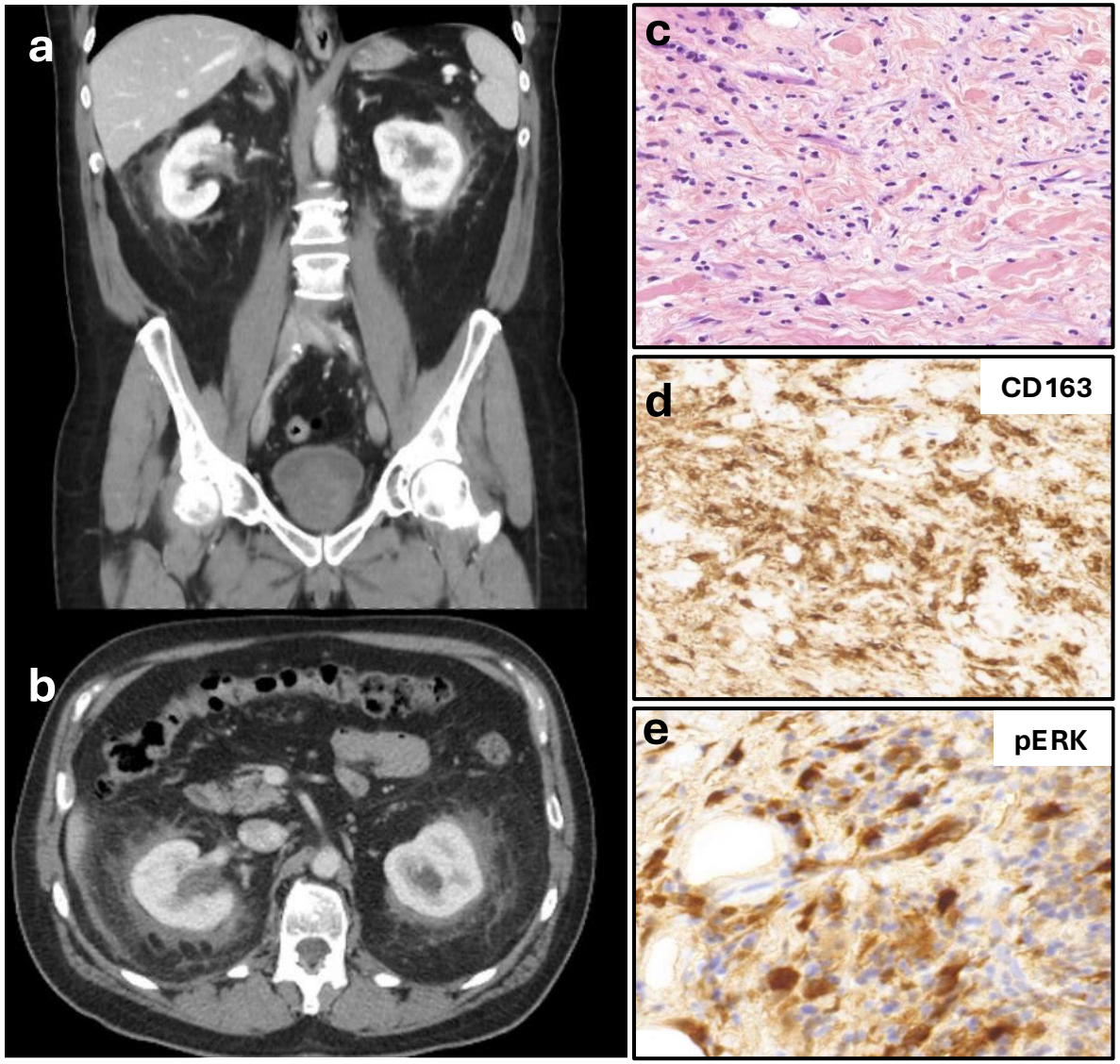
Abdominal CT scan in a 50-yo ECD man

Perirenal infiltration in ECD (*hairy* kidneys)



- Approximately 50-70% of the cases (in our series, 17/28 pts, 62%)
- The infiltration is often limited to the peri-renal space
- It usually extends to the renal hilum (renal artery and vein), the renal pelvis and the proximal ureter
- Peri-renal disease may limit the ability of the kidney to dilate when the ureters are compressed
- Good site for diagnostic biopsy

Perirenal infiltration as an isolated manifestation of ECD



Catamerò F et al., *Kidney Int* in press

Imaging studies for retroperitoneal/perirenal ECD

Imaging technique	**PROs**	**CONs**
Sonography (ultrasound)	Allows visualization of hydronephrosis; non-invasive, no radiation	Poor visualization of peri-renal or peri-ureteral tissue; limited usefulness for peri-renal tissue follow-up; operator-dependent
Computed tomography (CT)	Optimal visualization of all renal and ureteral complications of ECD; non-operator dependent	Radiation; potential nephrotoxicity; contraindicated if allergy to iodinated contrast medium
Magnetic resonance imaging (MRI)	Optimal visualization of all renal and ureteral complications of ECD; non-operator dependent; no radiation	Contraindicated in patients with severe renal failure, allergy to metals, bearing pacemakers or metal prosthesis
Positron emission tomography (PET)-CT	Allows evaluation of metabolic disease activity (active vs inactive); no significant contraindications	Radiation; does not reliably assess dimension of the lesion; high cost

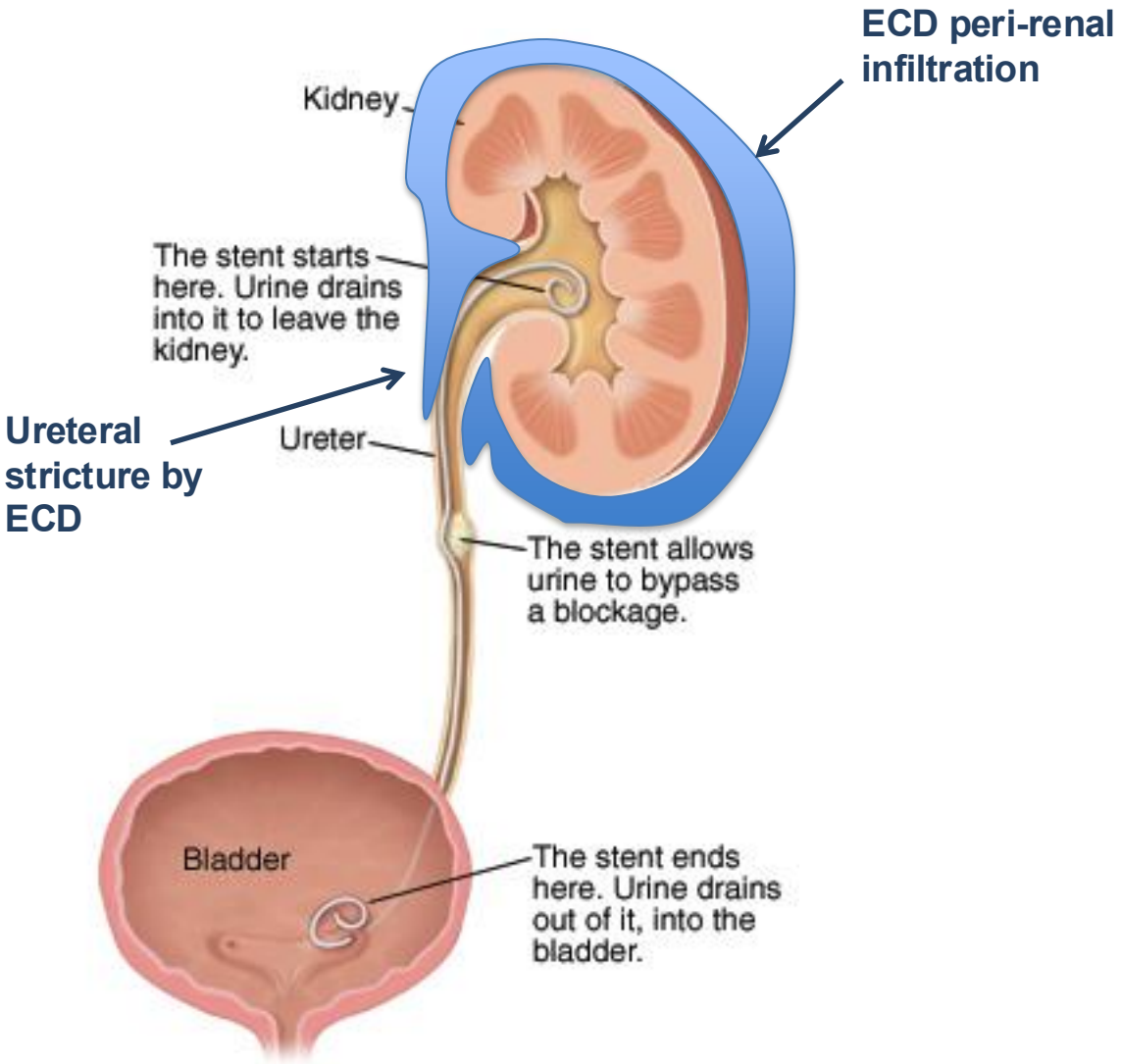
Ureteral obstruction in ECD

- Approximately 20-50% of the cases
- May be unilateral (often bilateral)
- Usually insidious onset, often asymptomatic or with dull back pain
- ECD infiltration usually causes stenosis of the proximal(upper) third of the ureters

How to relieve ureteral obstruction

Double- J ureteral stents

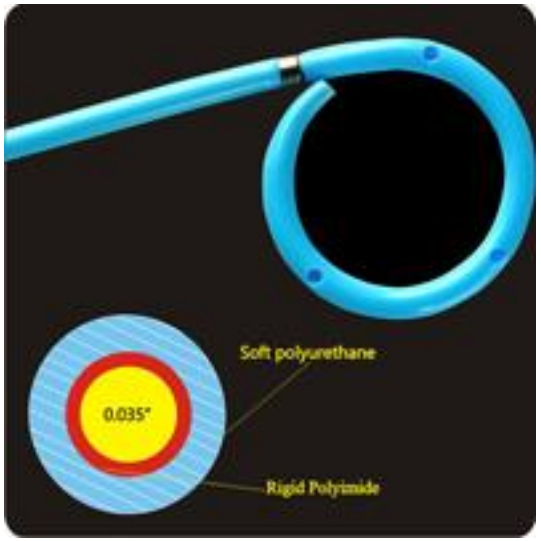
- Placed via cystoscopy
- Duration: 6-12 mths
- Complications: irritation, lower urinary tract symptoms, infections, bleeding
- Allow “internal” renal drainage avoiding external nephrostomy tubes



How to relieve ureteral obstruction

Double-J "tumor" stents

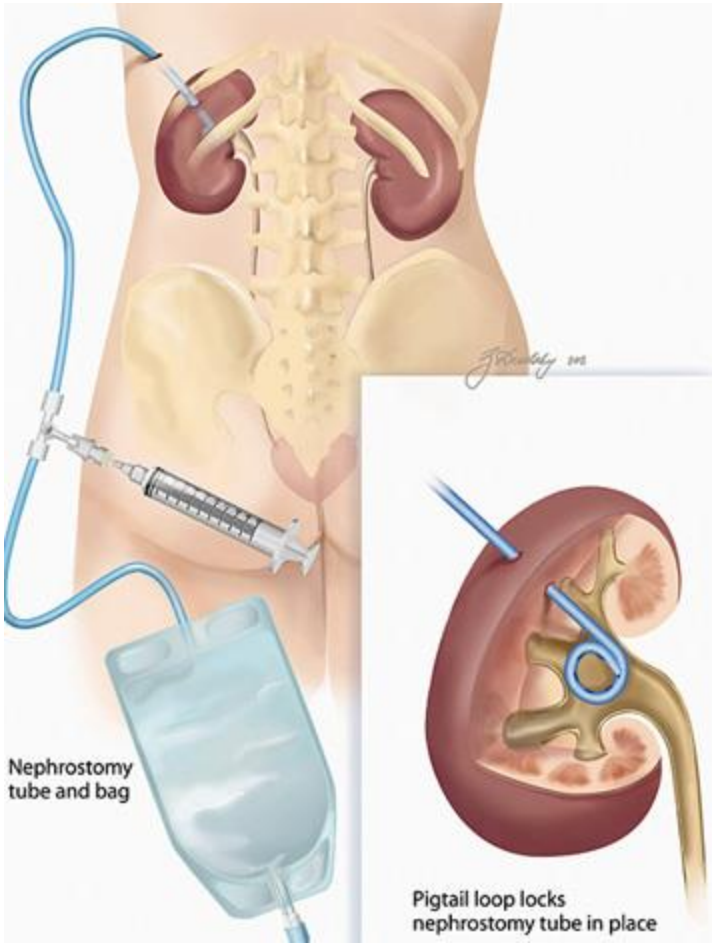
- Placed via cystoscopy
- Duration: 6-12 mths
- Reinforced internal layer for resistance to compression
- Different reinforced segments depending on the site of ureteral obstruction



How to relieve ureteral obstruction

Nephrostomy

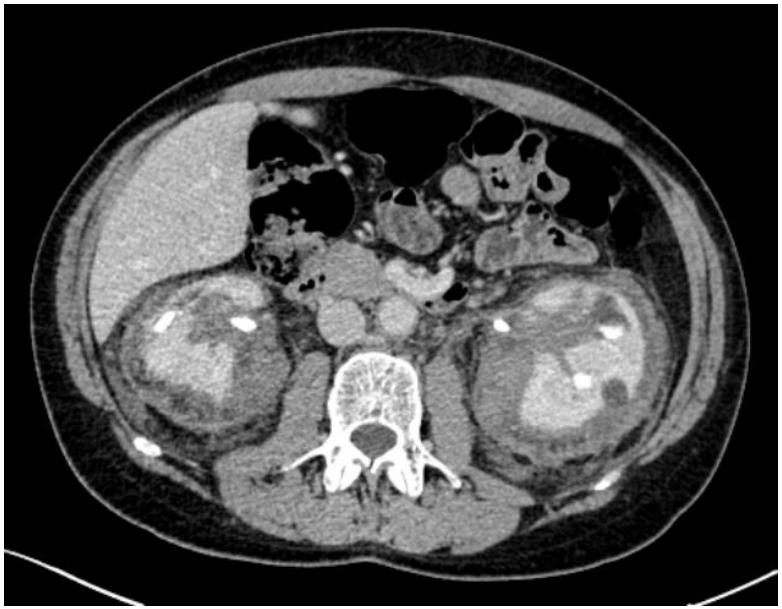
- Placed percutaneously
- Complications: infections, bleeding, poor quality of life
- Allows efficacious drainage of the obstructed kidney(s)



How to relieve ureteral obstruction

Ureteral obstruction must be treated with stents or nephrostomies AND medical therapy.
Although effective, this approach may not completely resolve obstruction and surgical ureterolysis can be performed

With stents, before therapy



With stents, month 6 of Everolimus therapy

Functional consequences of ureteral obstruction in ECD

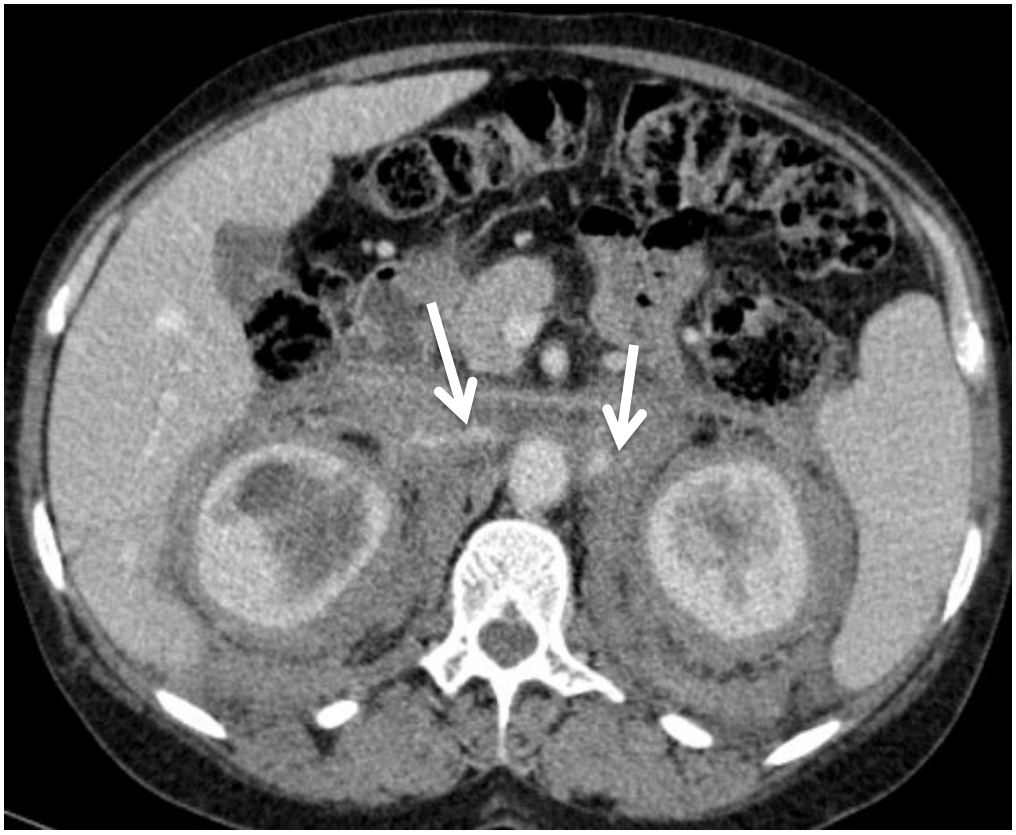
- Acute renal failure (uncommon)
- Chronic renal failure (chronic kidney disease, CKD) of varying degrees → possible progression to *end-stage kidney disease*
- Renal atrophy
- Infection (pyelonephritis)

End stage kidney disease

- Hemodialysis preferred over peritoneal dialysis

47-yo man with ECD and (moderate) chronic renal failure; CT scan shows hydronephrosis and renal hypotrophy/atrophy (right > left)

Renal artery (and vein) stenosis in ECD

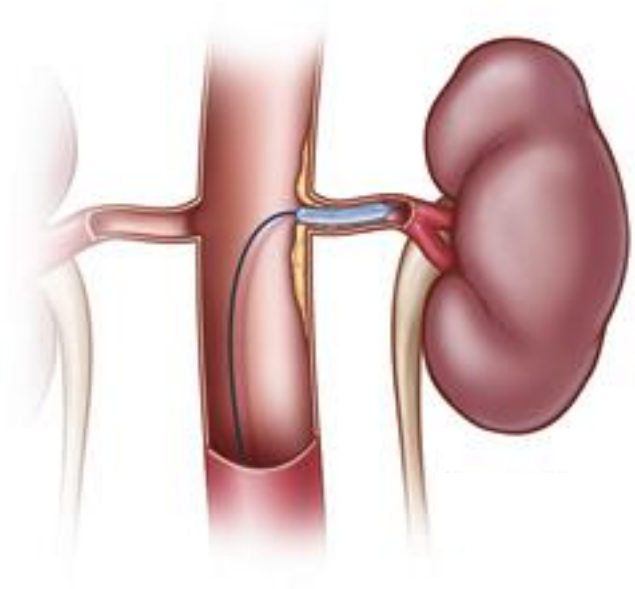


- Compression of the renal arteries causes *reno-vascular hypertension*, a particularly severe form of arterial hypertension
- It may also cause renal atrophy
- When bilateral, it can progressively lead to chronic renal failure
- Diagnosed by angio-CT, angio-MRI and traditional angiography

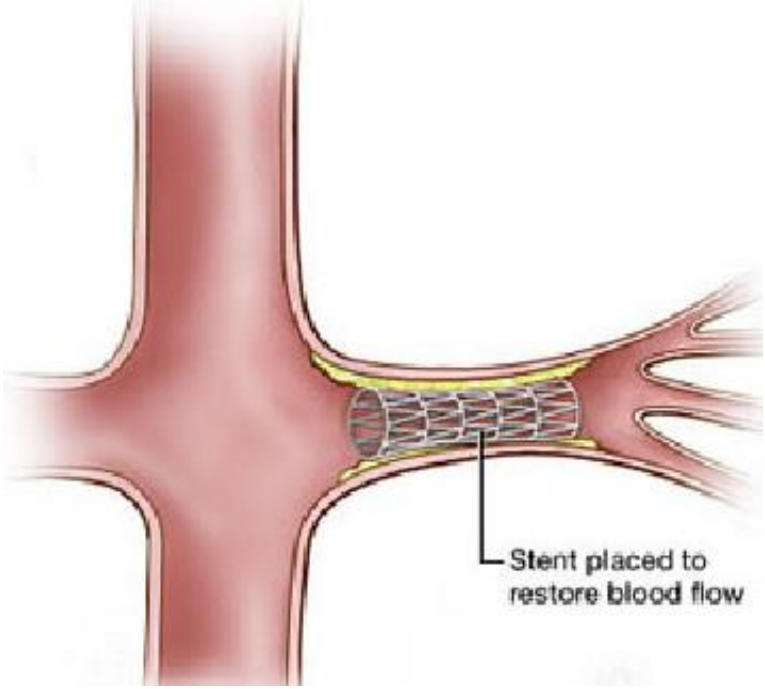
When to suspect renal artery stenosis in ECD

- Worsening hypertension
- Hypertension requiring multiple anti-hypertensive drugs
- Renal asymmetry on imaging studies
- Serological abnormalities
    - Worsening renal function (creatinine increase)
    - Hypokalemia (low K, below 3.5 mEq/L)
    - Increase in renin activity and aldosterone levels
    - Metabolic alkalosis (increase in pH and bicarbonate levels)

How to treat artery stenosis in ECD



Renal artery ANGIOPLASTY



Renal artery STENTING

Clinical phenotypes and long-term outcome of kidney involvement in Erdheim-Chester histiocytosis

Thibaud Chazal[1,2,13], Francesco Pegoraro[3,13], Gaia Manari[4], Alessandra Bettiol[5], Valerio Maniscalco[3], Elena Gelain[6], Frédéric Charlotte[7], Roei D. Mazor[8], Raphaele Renard-Penna[9], Zahir Amoura[1], Fleur Cohen-Aubart[1], Julien Haroche[1], Hassan Izzedine[10,11] and Augusto Vaglio[6,12]

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis that frequently infiltrates the peri-kidney space ("hairy kidney" appearance), kidney pelvis and proximal ureters, leading to obstructive uropathy. Here, we analyzed the clinical characteristics, imaging findings and long-term kidney outcome of a large multicenter cohort comprising 195 consecutive patients with ECD. Retroperitoneal peri-kidney or peri-ureteral involvement was detected at diagnosis in 147 patients. Of them, 70 had hydronephrosis (bilateral in 47), and 16 with kidney atrophy (unilateral in 14). Kidney vascular peduncle infiltration was found in 60 patients, and kidney artery stenosis in 31. The estimated glomerular filtration rate (eGFR) at diagnosis was significantly lower in patients with than in those without peri-kidney involvement (median 74 vs. 98 mL/min/1.73 m^2). Ureteral stenting often failed to achieve kidney function recovery. A total of 181 patients received medical therapies: first-line treatments included interferon-α (61%), BRAF-inhibitors (17%), mTOR-inhibitors (7%), or other drugs (15%). These therapies were efficacious for ECD but rarely induced kidney function improvement (one-year eGFR increase over 25% in under 10% of patients). After a median of 43 months, 19% of patients died and 5% developed kidney failure. Among patients with peri-kidney involvement, 44% developed chronic kidney disease (CKD) 3-5 at five years vs. 5% of those without. Unadjusted predictors of advanced CKD and kidney failure/death were age over 50 years, hypertension, BRAFV600E mutation, and baseline eGFR. At multivariable analysis, cardiovascular comorbidities were associated with advanced CKD, and age over 50 years with kidney failure/death. Thus, kidney involvement is common in ECD and can lead to CKD or kidney failure despite effective medical therapies or urological procedures.

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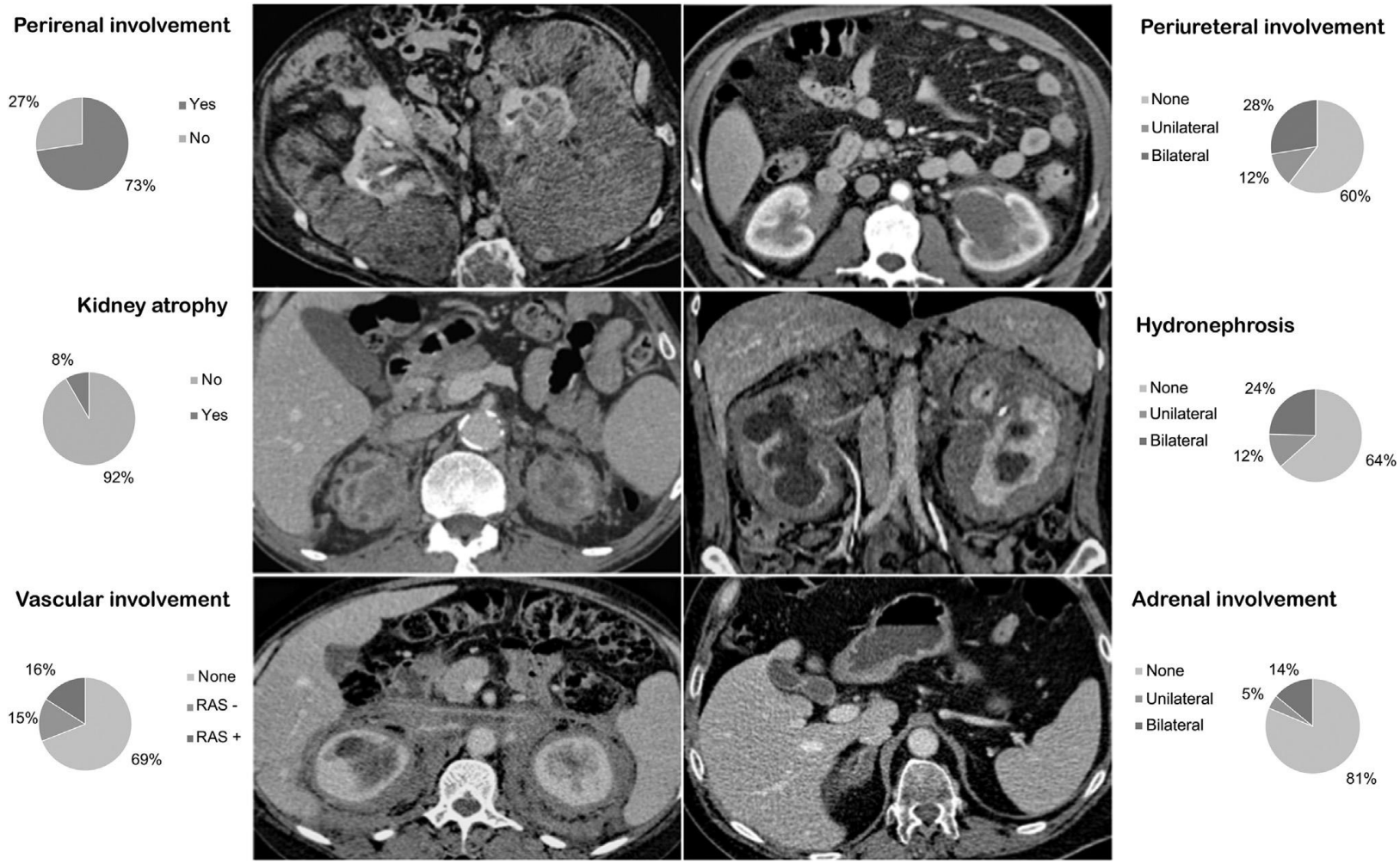
KEYWORDS: BRAF; Erdheim-Chester disease; hairy kidney; histiocytosis; hydronephrosis

Chazal T et al., *Kidney Int* 2023

Kidney outcome in ECD



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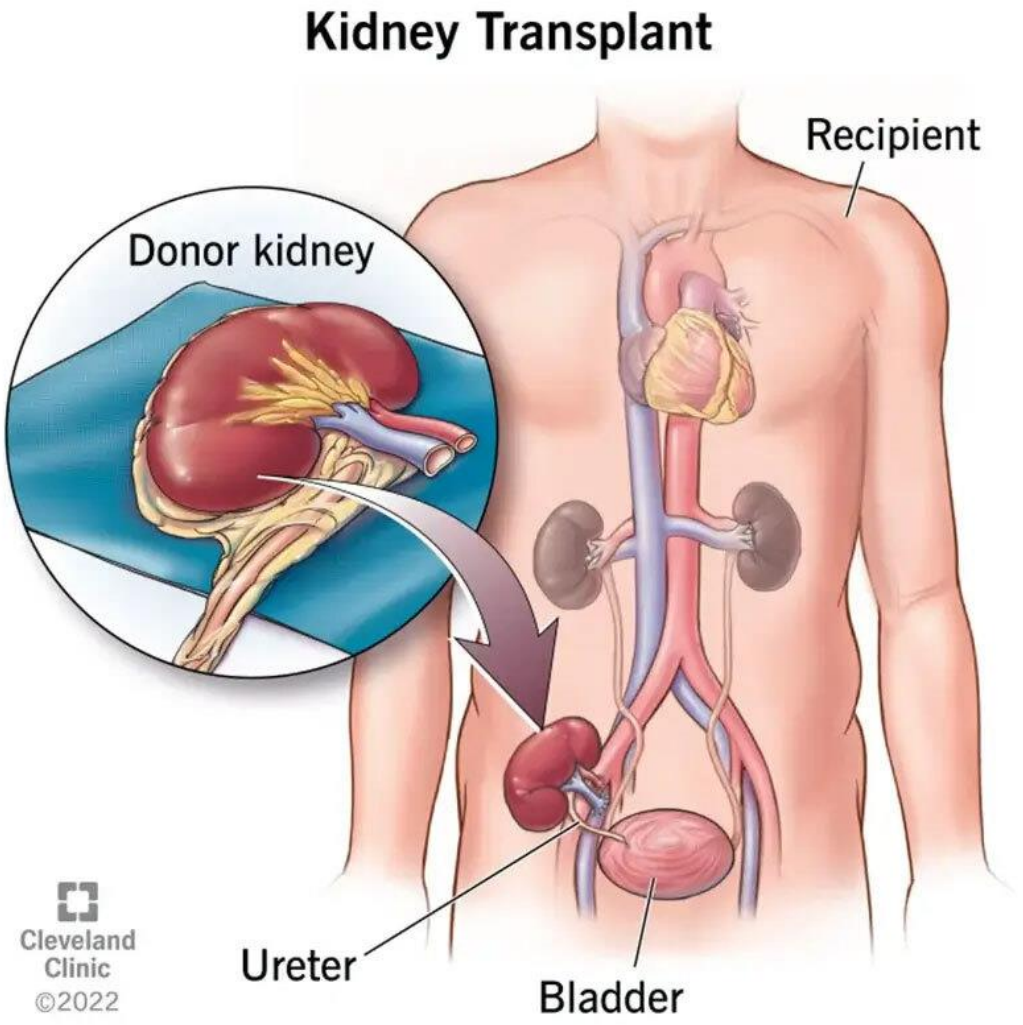
Kidney outcome in ECD

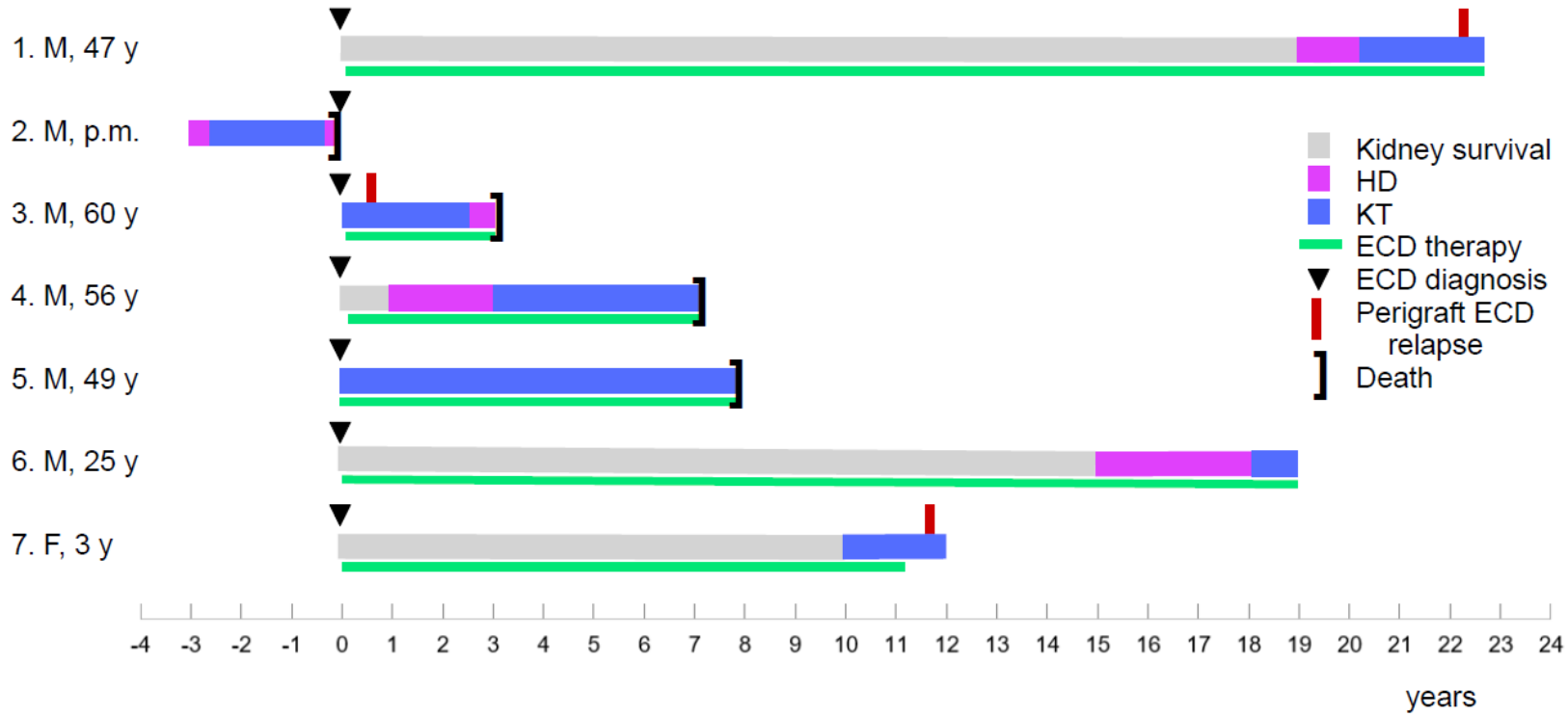
Variable	Risk of CKD 4–5 or eGFR decrease >25%		Risk of kidney failure or death	
	Crude OR (95% CI)	*P* value	Crude HR (95% CI)	*P* value
Female sex	0.81 (0.38–1.75)	0.592	1.30 (0.64–2.66)	0.468
Age at onset >50 yr	2.94 (1.35–6.37)	0.006	3.36 (1.58–7.16)	0.002
Comorbidities				
Hypertension	2.09 (1.06–4.14)	0.034	1.98 (1.03–3.78)	0.039
Diabetes	3.81 (1.86–7.80)	<0.001	1.43 (0.71–2.90)	0.319
Obesity	1.29 (0.55–3.03)	0.556	1.12 (0.47–2.71)	0.796
Hypercholesterolemia	1.94 (0.94–4.01)	0.074	0.75 (0.33–1.70)	0.487
CAD	4.23 (2.09–8.94)	<0.001	1.62 (0.83–3.14)	0.158
Smoking	1.64 (0.81–3.30)	0.169	1.02 (0.51–2.05)	0.947
Involved sites				
>4 Sites involved	2.23 (1.08–4.59)	0.029	1.28 (0.64–2.55)	0.481
Perirenal	2.86 (1.13–7.24)	0.026	1.75 (0.77–3.99)	0.183
Hydronephrosis	1.90 (0.96–3.76)	0.063	0.75 (0.37–1.51)	0.415
Vascular peduncle	1.95 (0.98–3.92)	0.059	0.91 (0.46–1.81)	0.784
CNS	0.81 (0.40–1.67)	0.574	1.06 (0.44–2.06)	0.867
Large vessels	2.37 (1.09–5.15)	0.029	1.18 (0.58–2.38)	0.652
Heart	1.44 (0.73–2.84)	0.287	1.16 (0.60–2.21)	0.660
Lung	1.40 (0.70–2.79)	0.341	1.26 (0.66–2.42)	0.484
Skin/subcutaneous	0.64 (0.31–1.31)	0.221	0.95 (0.49–1.84)	0.871
Bone	1.98 (0.65–6.04)	0.228	2.05 (0.63–6.70)	0.232
Facial/orbit	1.66 (0.85–3.26)	0.141	0.99 (0.52–1.89)	0.979
Hypothalamic/pituitary	1.31 (0.65–2.63)	0.446	0.64 (0.31–1.31)	0.222
Associated LCH	1.59 (0.67–3.78)	0.292	1.01 (0.44–2.30)	0.988
BRAF^{V600E} mutation	2.06 (0.94–4.52)	0.071	2.44 (1.10–5.41)	0.028
Kidney function at baseline				
eGFR, ml/min per 1.73 m^2	0.98 (0.97–0.99)	0.030	0.99 (0.98–0.99)	0.035
sCreatinine, mg/dl	1.73 (1.04–2.87)	0.034	1.28 (0.76–2.16)	0.345
CKD 3–5	1.97 (0.95–4.05)	0.067	1.90 (0.96–3.75)	0.065
First-line treatment				
Targeted (BRAFi/MEKi/mTORi)	0.79 (0.34–1.87)	0.599	2.14 (0.84–5.44)	0.110
IFN-α, others[a]	1.04 (0.48–2.26)	0.912	0.33 (0.14–0.78)	0.012
Ureteral decompression procedures	1.81 (0.86–3.81)	0.121	0.90 (0.43–1.92)	0.795

Chazal T et al., *Kidney Int* 2023

Kidney transplantation



Kidney transplantation in ECD



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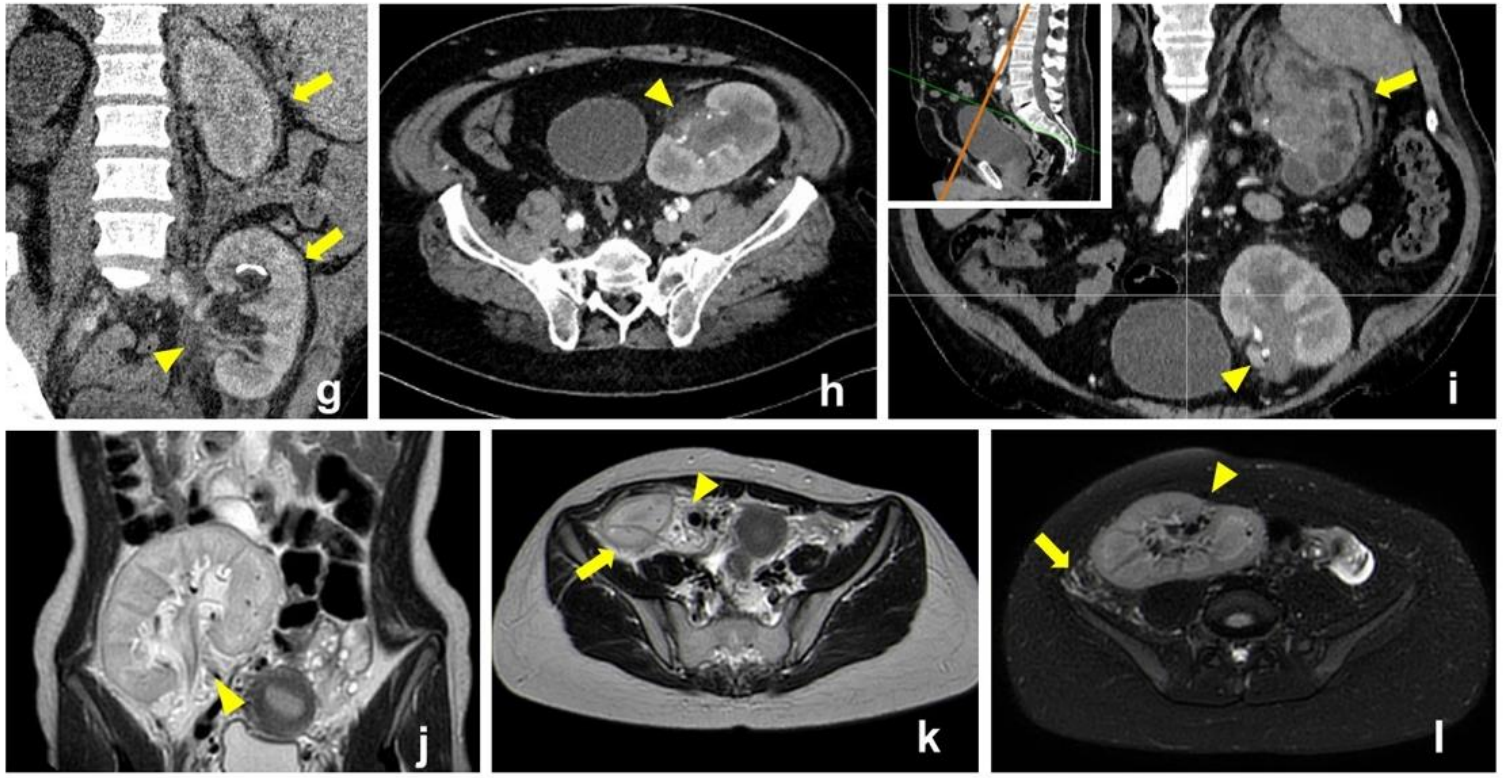
Disease recurrence on the graft?



Palazzini G, Pegoraro F et al, manuscript in preparation

Thank you

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Conclusions

- ECD causes renal/perirenal and ureteral involvement in 50-70% of patients and is often overlooked
- Obstructive uropathy (hydronephrosis) is the most common complication and requires urinary decompression (stents, nephrostomy) + medical therapy
- The management of complications (infections, bleeding, pain) is crucial
- Renal artery stenosis is not uncommon and may cause hypertension and renal failure
- Chronic kidney disease is a common complication whereas end-stage kidney disease is rare
- Kidney transplantation is a feasible option for patients with ECD but needs to be performed in centres of expertise and requires optimal control of ECD and careful follow-up