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28 Tweets • 2022-11-10 • [See on Twitter](#)

rattibha.com 

1/ Want to continue the learning streak of #Kidneywk ?
#MedTwitter #NephTwitter, we bring another
#ASPNOFOAM group tweetorial based on pathology
webinar @ASPNePh on T-cell mediated
rejection(TCMR) in kidney transplant (Tx)



2/

Let's start with a vignette! 13 yr M with CAKUT s/p DDKT 6mo ago, p/w with doubling of Cr from 0.7 to 1.5 mg/dl, normal vitals and PE. UA normal. A lot of recent stressors and concern for non-adherence. Sounds like a familiar scenario?

What is the potential cause of graft dysfunction in this patient?

3/ ⚡ Likely REJECTION!

Check out this awesome #tweetorial by @miketurk6 on “SCARI” causes of kidney graft dysfunction 🎃 👻




4/

📌 Kidney transplant rejection remains an independent risk factor for long term graft survival.

📌 Despite robust immunosuppression regimen, TCMR and antibody mediated rejection (ABMR) is a concerning cause for graft loss

<https://pubmed.ncbi.nlm.nih.gov/32066593>

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- Rejection can lead to increased risk of interstitial fibrosis/tubular atrophy (IF/TA)
 - (Previously known as chronic allograft nephropathy)
 - Two main types: (sometimes patients can have both!)
 - Acute T cell-mediated (cellular) rejection (TCMR)
 - Lymphocytic infiltration mostly of the tubules and interstitium
 - Active antibody-mediated rejection (ABMR)
 - Acute tissue injury, donor specific antibodies, and antibody-endothelial cell interaction (ie. C4d staining)
 - Subclinical rejection
 - Evidence of rejection of biopsy without rise in serum creatinine
 - Usually found in protocol kidney biopsies
- 

5/

TCMR typically occurs in 1st yr post Tx.

ABMR is the most common cause of late kidney allograft failure.

<https://pubmed.ncbi.nlm.nih.gov/34507254/>

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What are some risk factors for kidney Tx rejection?

6/

🧐 Let's look into histopathology of TCMR

😊 This is a pathology webinar, duh!!!

Off we go to heavenly Banff 🧳 🏕️



abc The Banff lingo

Banff Lesion Score

► Interstitial inflammation

-mononuclear infiltrates involving unscarred cortical parenchyma

► Tubulitis

-mononuclear infiltrates in tubular basement membrane

► Arteritis

- inflammatory cells beneath the endothelial cells

i0—No inflammation or in less than 10% of unscarred cortical parenchyma.

i1—Inflammation in 10 to 25% of unscarred cortical parenchyma.

i2—Inflammation in 26 to 50% of unscarred cortical parenchyma.

i3—Inflammation in more than 50% of unscarred cortical parenchyma.¹¹

Banff Lesion Score *i*

Interstitial inflammation

Banff Lesion Score *t*

Tubulitis

t0—No mononuclear cells in tubules or single focus of tubulitis only.

t1—Foci with 1 to 4 mononuclear cells/tubular cross section (or 10 tubular cells).

t2—Foci with 5 to 10 mononuclear cells/tubular cross section (or 10 tubular cells).

t3—Foci with >10 mononuclear cells/tubular cross section or the presence of ≥2 areas of tubular basement membrane destruction accompanied by *i2/i3* inflammation and *t2* elsewhere.¹²

v0—No arteritis.

v1—Mild to moderate intimal arteritis in at least 1 arterial cross section.

v2—Severe intimal arteritis with at least 25% luminal area lost in at least 1 arterial cross section.

v3—Transmural arteritis and/or arterial fibrinoid change and medial smooth muscle necrosis with lymphocytic infiltrate in vessel.¹¹

Banff Lesion Score *a*

Arteritis

8/

Banff classification

- ◆ Borderline rejection added 2005
 - ◆ < 10-25% inflammation
 - ◆ foci of tubulitis + minor interstitial inflammation
(Banff i0 or i1)
 - ◆ interstitial inflammation (i2 or i3) with minor tubulitis
(t1)
- i0(t1-t3), i1(t1-t3), i2t1 and i2t3

<https://tinyurl.com/yc29smb6>

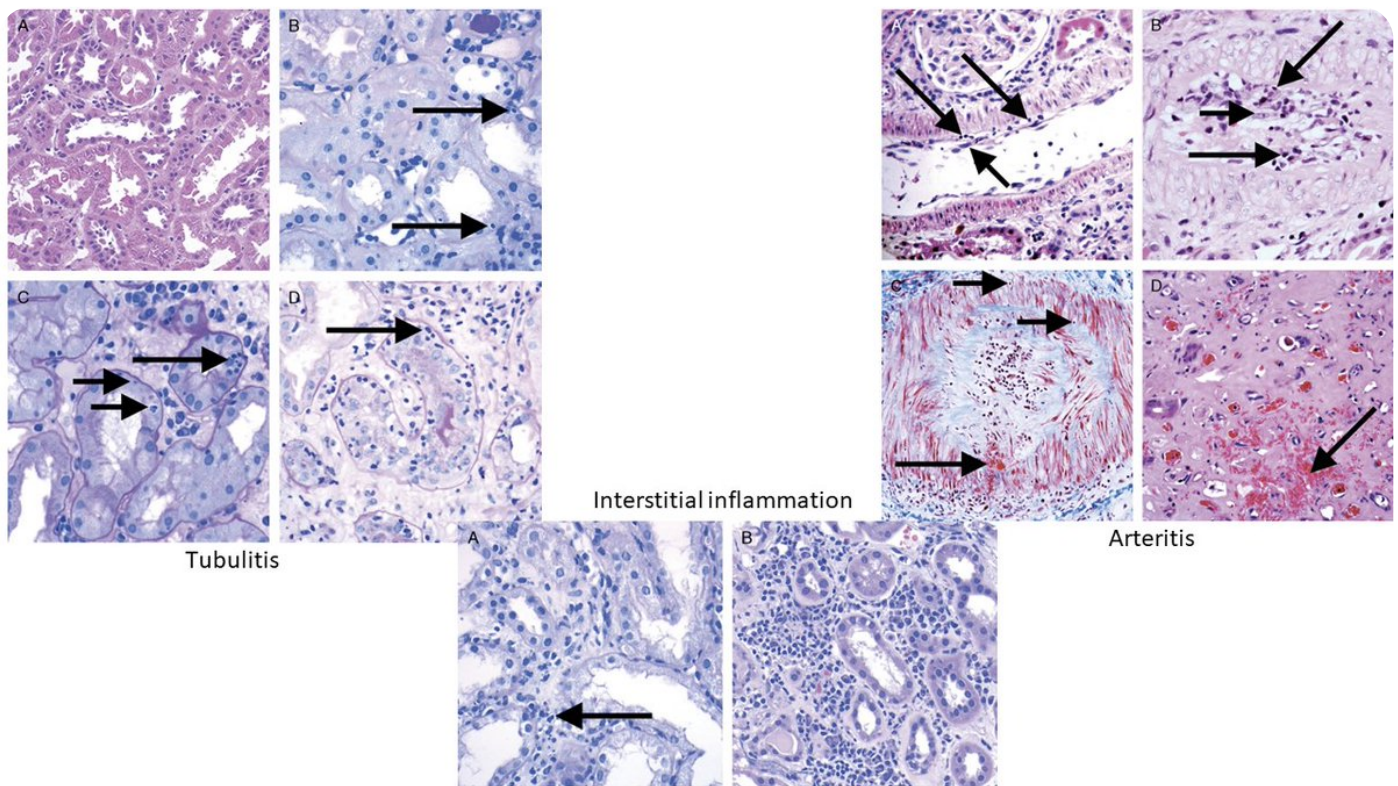
Description		Banff scores
Acute TCMR		
Type IA	Moderate tubulitis and at least moderate interstitial inflammation	t2i2 or t2i3
Type IB	Severe tubulitis and at least moderate interstitial inflammation	t3i2 or t3i3
Type IIA	Mild to moderate intimal arteritis	v1
Type IIB	Severe intimal arteritis (> 25% of the luminal area)	v2
Type III	'Transmural' arteritis and/or fibrinoid necrosis	v3
Chronic active TCMR		
Grade IA	Moderate tubulitis and at least moderate total cortical inflammation and at least moderate scarred cortical inflammation and other known causes ruled out	t2, ti ≥ 2, and i-IFTA ≥ 2
Grade IB	Severe tubulitis and at least moderate total cortical inflammation and at least moderate scarred cortical inflammation and other known causes ruled out	t3, ti ≥ 2, and i-IFTA ≥ 2
Grade II	Arterial intimal fibrosis with mononuclear cell inflammation, formation of neointima	cv1, cv2, or cv3

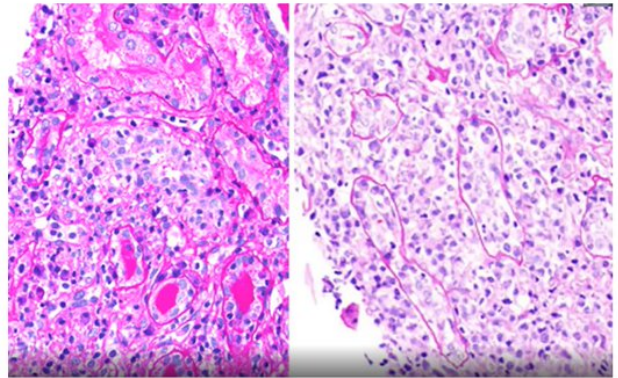
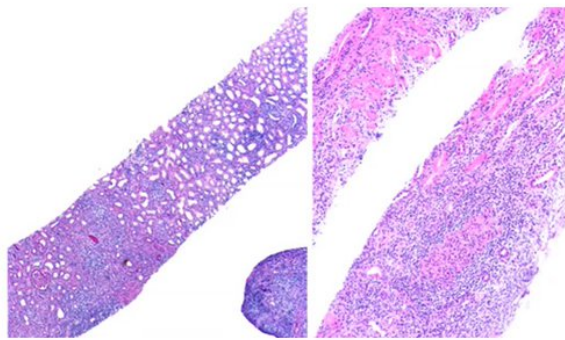
cv, arterial fibrous intimal thickening; i, interstitial inflammation; i-IFTA, tubulointerstitial inflammation (inflammation in areas of interstitial fibrosis and tubular atrophy); t, tubulitis; TCMR, T cell-mediated rejection; ti, tubulointerstitial inflammation (inflammation in total parenchyma, including scarred and non-scarred cortex); v, intimal arteritis.

9/

◆ Image shows mononuclear infiltrates in the interstitium, tubules and arteritis

◆ Light microscopy shows significant lymphocytic infiltrates





10/

🪡 Protocol biopsy done for early detection before change in GFR/proteinuria

🛑 Pitfalls of biopsy(bx)

- Cost
- Invasive, potential complication
- Sampling error
- Labor intensive

@RenalFellowNtwk @jadav_md

<https://www.renalfellow.org/2021/07/01/donor-derived-cell-free-dna-in-kidney-tra>

nsplantation-the-next-frontier/

What are the barriers to early diagnosis of kidney Tx rejection?

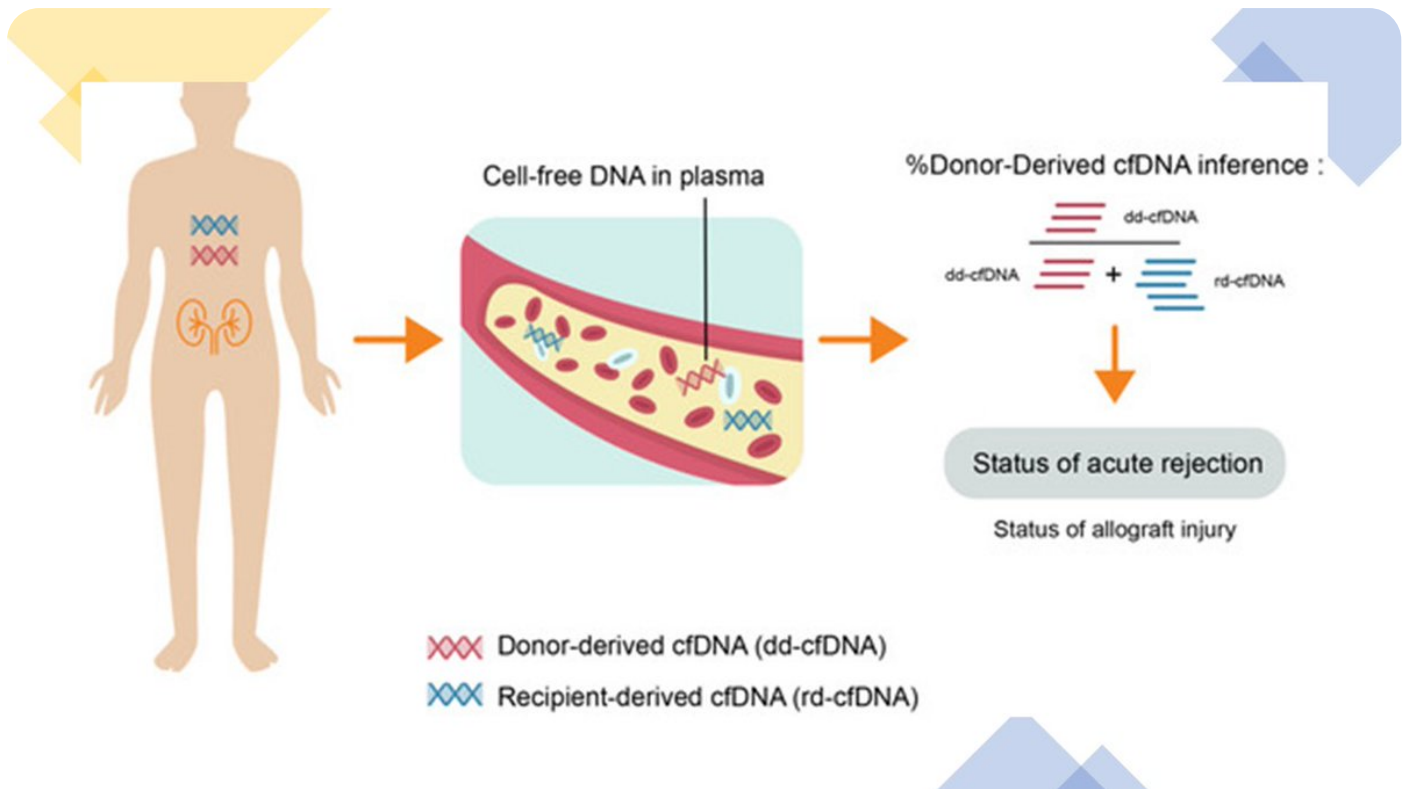
12/

★ This calls for non-invasive bio-marker!!!

❖ One such biomarker recently studied is donor derived cell free DNA

❖ % or total amount DNA released from injured donor kidney tissue (DD cf-DNA)

<https://www.mdpi.com/2077-0383/9/5/1480/>
htm





13/


dd-cf-DNA clinical assay uses Single nucleotide polymorphism (SNP) for donor and recipient identification

Check out this article with beautiful cartoons
@NatRevNeph

<https://www.nature.com/articles/s41581-021-00428-0>

Approach	Technology	Genotyping required	Assay
Random ^a	Ligation-based	Donor and recipient	Not commercially available
		Recipient	TRAC
Targeted ^a	PCR-based with ddPCR read-out	Recipient	TheraSure
	PCR-based with NGS read-out	Not required	AlloSure
			Prospera



14/ Lets review few big studies on DD-cf-DNA

🎯 DART-> Allosure testing platform

◆ Median dd-cfDNA in ABMR 2.9%;

◆ 1.2% in TCMR grade 1B or worse

◆ 0.2% for TCMR 1A

◆ 1% cut-off used for test positivity

☞ Better for predicting ABMR (AUC 0.87) than TCMR

PMID # 28280140

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◆ Initial Prospera study

◆ median cf-DNA for ABMR (2.2%), TCMR(2.7%) and mixed rejection(2.6%) did not differ significantly.

<https://pubmed.ncbi.nlm.nih.gov/30583588/>

16/

🧬 Viracor Transplant Rejection Allograft Check(TRAC) analyzes 70,000 SNP's, initial study promising with AUC for detection ~ 0.85

🧬 Ongoing TRULO study looks at gene expression assay TruGraf and TRAC dd-cfDNA

<https://tinyurl.com/52uva58f>

17/

Meta-analysis of cf-DNA in TCMR, the median level did not differ between pts with TCMR and those without rejection, thus limiting its utility

<https://pubmed.ncbi.nlm.nih.gov/32981117/>

18/

❓ Why was cf-DNA not high in TCMR in these studies?

- ⚡ No direct endothelial injury
- ⚡ Mostly tubulointerstitial damage
- ⚡ Classifying TCMR into mixed rejection

19/

▶ Borderline TCMR/1A rejection makes up $\frac{3}{4}$ of all ACR

▶ Does affect long term graft function

▶ cf-DNA could differentiate although at lower detection levels ($<1\%$)

<https://pubmed.ncbi.nlm.nih.gov/32056331/>

20/

◆ Improvement in cf-DNA after IV pulse steroids for TCMR



Could be used to guide therapy



Recent studies showed effectiveness of using cfDNA in ped kidney Tx



PMID #

●36302566

●33217125

●35340104

What the potential confounders of DD-cf-DNA?

21/



Trifecta study in 300 kidney bx ->relationships b/w dd-cfDNA(%) at the time of indication biopsy and the genome-wide molecular findings assessed by microarrays




Molecular rejection correlated with elevated cf-DNA better than histologic changes

<https://tinyurl.com/4ef72pwm>

22/

Treatment TCMR

 Banff BL, IA, IB → Steroid pulse 10 mg/kg q daily x 3 doses OR oral steroid cycle over 3mo

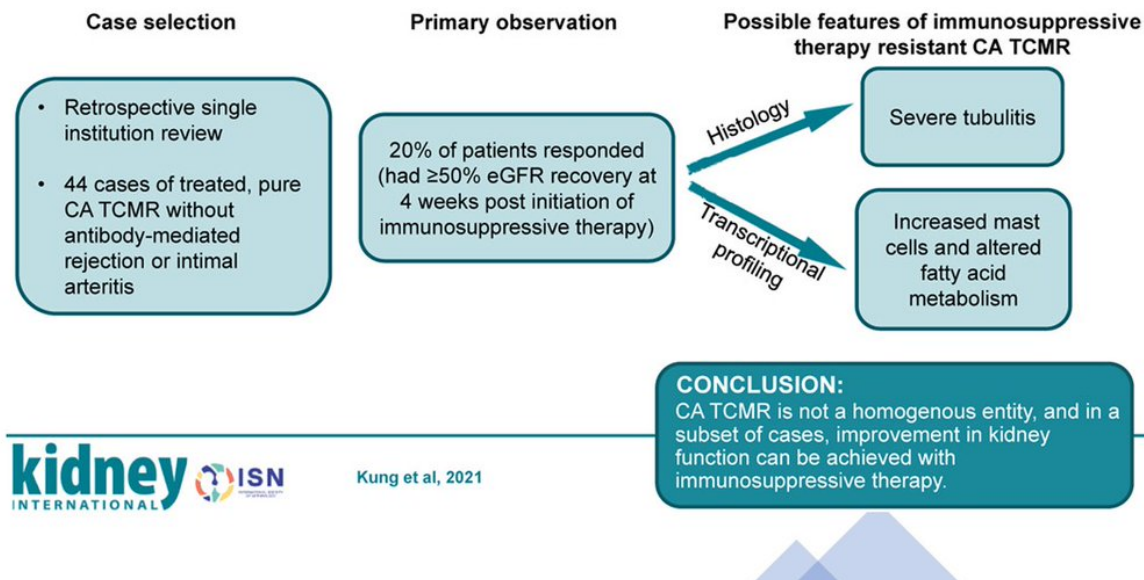
 Banff IIA, IIB, III → Rabbit ATG 3-5 doses

23/

Chronic active TCMR is newly described entity with long term graft loss and variable treatment response

<https://www.sciencedirect.com/science/article/pii/S0085253821003628>

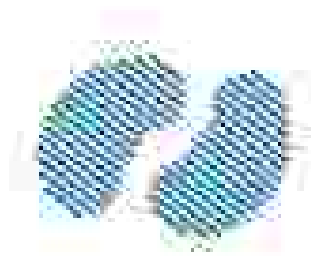
Chronic active T cell-mediated rejection is variably responsive to immunosuppressive therapy.



For a case-based clinical discussion on #TCMR with an expert - login to @ASPNeph website, Sept 2022 webinar #Membereducation

Special thanks to #ASPNFOAM group members @drM_sudha @CatherineJ20 for reviewing!

<https://www.aspneph.org/committees/member-education-committee/aspn-renal-pathology-webinar-series-2/>



American Society of
Pediatric Nephrology

@threadreaderapp please unroll

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