Hello #Nephtwitter #Medtwitter, @ASPNeph Pathology webinar topic for Jan 2022 is Tubulointerstitial Nephritis with Uveitis or #TINU

#ASPNFOAM #pedneph #Renalpath #Nephpath

But first let’s have a poll. Which of the following is true about #TINU?

All the above.

#TINU is a multisystem autoimmune disorder initially described in 2 adolescent girls in 1975 by Dobrin et al. Since then ~600 cases reported.


What are some of the risk factors for #TINU?

1. Age: most common in adolescent 💆‍♀️ but affects all ages
2. Triggers: Infection & drugs
3. Genetic: HLA risk alleles identified: esp HLA-DRB1*01
4. No geographic or racial predilection

What is the pathogenesis of #TINU?

#TINU is thought to be an auto-immune inflammatory response to an inciting trigger.

Both cellular & humoral immunity pathways activated.

Lead to cascade of inflammation in kidney & uvea in genetically susceptible patient.


Modified CRP (mCRP) may be a target autoantigen in TINU and anti-mCRP antibodies high in # TINU.

Kidney involvement can be:
- Asymptomatic
- Interstitial Nephritis (IN)
- Fanconi syndrome
- Nephrogenic diabetes insipidus
- AKI & CKD

Abnormal urine analysis: ↑ β2M, tubular proteinuria/pyuria/haematuria/glycosuria/white cell casts


Uveitis is
- B/L in 80%
- 2 mo prior to 12 mo post kidney involvement
- In 52% pts, uveitis after nephritis with an av. delay of 3 mo
- 80% non-granulomatous anterior uveitis
- Presents with redness, pain & photophobia
- 20% posterior or pan uveitis

What other systems may be also involved? #TINU can lead to:

- Thyroiditis
- Hearing loss & vestibular failure
- Lymphocytic pulmonary alveolitis
- Other: rash, flu like symptoms, arthritis


#TINU is a diagnosis of exclusion
Mandeville et al proposed the diagnostic criteria

Box 1  Clinical criteria of acute tubulointerstitial nephritis\textsuperscript{3}

1. Abnormal serum renal function
   Increased serum creatinine or decreased creatinine clearance.
2. Abnormal urinalysis
   Increased urinary β2-microglobulin, low-grade proteinuria, presence of urinary eosinophils, pyuria or haematuria without infection, urinary white cell casts or normoglycaemic glycosuria.
3. Systemic illness lasting ≥2 weeks
   i.  \textit{Signs and symptoms}: Fever, weight loss, anorexia, malaise, fatigue, rash, abdominal or flank pain, arthralgia or myalgia.
   ii. \textit{Laboratory findings}: Anaemia, eosinophilia, abnormal liver function or erythrocyte sedimentation rate >40 mm/hour.

\textcolor{red}{https://pubmed.ncbi.nlm.nih.gov/31719109/}

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Diagnostic criteria of tubulointerstitial nephritis and uveitis syndrome\textsuperscript{3}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite diagnostic</td>
<td>Typical (bilateral anterior) uveitis \textit{and} interstitial nephritis (renal biopsy \textit{or} TIN clinical criteria)</td>
</tr>
<tr>
<td>Probable diagnostic</td>
<td>Atypical uveitis \textit{and} positive renal biopsy \textit{or} typical uveitis \textit{and} incomplete TIN criteria</td>
</tr>
<tr>
<td>Possible diagnostic</td>
<td>Atypical uveitis \textit{and} incomplete TIN clinical criteria</td>
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TIN, tubulointerstitial nephritis.

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\#TINU may be under-recognised due to:

- Absence/asynchrony of eye and kidney symptoms
- Kidney symptoms commonly come 1st \textit{and} may resolve before uveitis
- Uveitis may be asymptomatic
- Steroids used to treat kidney disease may mask uveitis
Recent standardization of nomenclature (SUN): using 1083 cases of anterior uveitis, including 94 cases of TINU, evaluated by machine learning may be helpful.

Some other differential diagnosis to consider for multisystem kidney & eye disease

1. Autoimmune: Sjogren, JIA, Behcet’s
2. Vasculitis: SLE, granulomatous polyangiitis
3. Infection: TB, Syphilis
4. Other: Sarcoidosis
Kidney Biopsy in #TINU shows
- Interstitial oedema
- Inflammatory infiltrate composed mostly of lymphocytes
- Tubular injury


Treatment of #TINU?

- Topical steroids & cycloplegic agents in eye
- Systemic steroids: 1mg/kg/day for 3-6 mo in most studies
- Evidence for IMT (immunomodulatory Rx) in TIN is limited: may include AZA, MMF, CNI, Biologics

https://iovs.arvojournals.org/article.aspx?articleid=2270915

Prognosis of TIN
- AKI & CKD more common in adults
  - ~10% children and ~40% adults develop CKD
  - Can recur post-transplant
  - Urine β2M levels may help in therapeutic decisions


Prognosis of uveitis
- Relapses and chronicity in 50%
- Children have more severe eye disease and relapses
- Can lead to reduced visual acuity
- Complications in ~ 20%: post synechiae, macular & disc oedema, chorioretinal scarring

http://EyeRounds.org/cases/226-TINU.htm
Here is the summary of our discussion so far..

**TUBULOINTERSTITIAL NEPHRITIS WITH UVEITIS #TINU**

A multisystem autoimmune inflammatory disorder of unknown etiology

### Risk Factors
- More common in adolescent females but can occur at any age
- No geographic or racial predilection
- Genetic: HLA risk alleles identified: particularly HLA-DRB1*01
- Triggers: infection & drugs (NSAID’s, antibiotics, Chinese herbal medicines)

### Clinical Features
- Uveitis: Painful red eyes, often bilateral, 2 mo prior to 12 mo post kidney involvement
- Kidneys: TIN, AKI, CKD
- Other: anorexia, weight loss, rash, arthralgia, thyroiditis, SN hearing loss, alveolitis

### Diagnosis
- Blood tests: elevated creatinine, anaemia, raised ESR
- Urine: sterile pyuria, increased 82 microglobulin. Kidney Biopsy: definitive: lymphocytic TIN
- Rule out other causes of kidney & eye disease: Sjogren, SLE, Sarcoidosis

### Treatment & Prognosis
- Corticosteroids. Second line: Methotrexate, azathioprine, MMF, biologics
- ~10% children and ~40% adults develop CKD
- Relapses of uveitis more common in children and can lead to permanent damage

For a case-based clinical discussion with a pathology expert, login to @ASPNeph website, Jan webinar #Membereducation

Special thanks to #ASPNFOAM @drM_sudha @nefron1310
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