Drug Induced Liver Disease – Role of the Pathologist
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Disclosure
Dr. Saxena has nothing to Disclose

#1
DILI has no specific pattern of injury - it can mimic any and every other pattern

#2
DILI is always in the differential diagnosis

DILI can never be excluded
**Diagnosis of DILI**

- Demonstrate association with the drug
  - temporal relationship of symptoms to drug use
  - resolution on drug removal (recurrence on re-challenge)
- Exclude other potential competing causes

**Diagnosis is challenging**

- Drug history is not always clear
  - Patient’s ability as a historian
  - Patient does not mention herbals (safe natural product, not a drug?!)  
    - Patient taking many meds (polypharmacy)
- No specific clinical pattern
- No specific biochemical pattern
- No specific diagnostic test

**Diagnosis is challenging**

Ever increasing

- use of medications; polypharmacy
- new therapeutic compounds for cancer and autoimmune diseases
- number and use of herbal compounds and nutritional supplements

Propensity for injury and type of injury not known for newer agents

**CIOMS score**

Scores translated into categories of suspicion

- definite or highly probable (score ≥8)
- probable (score 6–8)
- possible (score 3–5)
- unlikely (score 1–2)
- excluded (score 0)

Council for International Organizations of Medical Sciences (Geneva, Switzerland)
What is the role of a pathologist?

Can we make a diagnosis on histology alone?

Two questions

Is this injury due to a drug?
Which drug?

- Centrilobular necrosis with no inflammation
- Acetaminophen
- Ischemia
• Cholestasis with no inflammation, cell damage or ductular reaction – bland cholestasis
  • Anabolic steroids
  • very early obstruction

• Alcoholic steatohepatitis pattern with numerous well defined Mallory hyaline except they are periportal
  • Amiodarone
Drug specific patterns

• Acetaminophen: Zone 3 necrosis
• Androgenic steroids: canicular cholestasis
• Amiodarone: steatohepatitis

• Both questions answered:
  • is this injury due to a drug?
  • which drug?

Cholestatic hepatitis

• Hardly ever seen outside context of DILI
• Amoxicillin clavalunate
  • 10% of all DILI cases in various series
  • second most common drug within DILIN with biopsies
• Floroquinolones
• Several other drugs
"bland" loss of bile ducts

- Hardly ever see outside the context of transplantation
  - Liver transplantation – rejection
  - Bone marrow transplantation - GVHD and DILI
- No consistent association with any drug

Diagnosis of duct loss

- 50% portal tracts without bile ducts (unpaired arterioles) with at least 10 portal tracts in the biopsy
  - 90-95% of portal tracts contain pairs of arterioles and bile ducts
  - A small number (7%) of portal tracts may have unpaired arterioles in normal livers
- Marked cholestasis ± inflammation
Veno-occlusive disease/ sinusoidal obstruction syndrome

- Hardly ever seen outside context of DILI
  - Oxaliplatin
  - Ablative therapies
  - Azathioprine
  - Jamaican bush tea (toxin)

Patterns almost exclusive to DILI

- Cholestatic hepatitis
- Bland loss of bile ducts (outside context of transplantation)
- Veno-occlusive disease

- Is this injury due to drug? – most likely
- Which drug? – not always possible
• 58-year-old obese male, alcohol use
• Fatigue, abdominal pain, pale stools
• Bili 7 (direct 4.1), AP 589, ALT 82, AST 71, leucocytosis (14.9 but no eosinophilia)
• Negative viral and autoimmune markers
• No biliary dilatation
• 3 months earlier had been started on trazadone
• Bili went up to 17.2 when biopsy was done
• Drug stopped; 3 months later came down to 1.9

Trastuzumab emtansine (T-DM1)
• antibody-drug conjugate
  • trastuzumab, a recombinant antiepidermal growth factor receptor 2 (HER2) monoclonal antibody
  • thioether linker
  • mertansine (DM1), a maytansinoid
• trastuzumab moiety binds to HER2 on tumor cell surfaces and on internalization, the DM1 moiety is released and binds to tubulin, thereby disrupting microtubule assembly/disassembly dynamics, resulting in cell-cycle arrest and cell death.

General patterns (also seen with non-DILI injury)
• Diagnosis requires
  • temporal association of injury to drug intake
  • exclusion of competing causes
• Both questions
  • is injury due to drug
  • which drug
  require clinical input (CPC)
Drugs with known general/non-DILI patterns

- Is injury due to drug?
  - requires temporal association and exclusion of other causes
- Which drug? – narrow differential
  - INH: submassive necrosis
  - TNFα inhibitors, nitrofurantoin, α methylldopa: autoimmune hepatitis

Oddball pattern that does not fit

- 24-year-old Ripped Fuel X (body building supplement containing ephedra) for 3-4 months (april – july) followed by Lipo 6 (july –august) 2 weeks later had jaundice
- Nausea, vomiting, headache, dark urine
- Bili 7.6, AP 316, ALT 177, AST 156
- Viral, autoimmune markers negative
- MRCP negative
- Drugs discontinued : bili came down to 1.6 in a month and 4 months later was 0.9
Challenge of herbals and nutritional supplements

- Usage common and increasing
  - Considered safe natural products
- Formulations non-standardized
  - Change over time in purity, potency and concentration
  - Botanical products change with harvest conditions
  - Often contain active drugs
- Establishing causality
  - History not forthcoming (safe natural products)
  - Taken over long periods of time
  - Self-perpetuating

Role of the surgical pathologist

- recognize and identify known patterns of drug injury
  - confirm diagnosis when drug history known
  - diagnose when drug history not known
- suspect drug (and alert) when injury pattern is odd and does not fit
- define pattern of injury of new agents

Drug Induced Liver Injury Network
An NIH Initiative

- High degree of clinical suspicion
- History taking with direct questioning, specifically for supplements (health foods, herbals)
What about eosinophils?
Eosinophils are not specific or sensitive for DILI. They are present in hypersensitivity types of DILI reactions and useful for diagnosis of DILI in the appropriate context. DILI can never be excluded.