Spilling The Tea: A Case Of Acute Liver Failure Secondary To Green Tea Extract

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Disclosure of Relevant Financial Relationships

No relevant financial relationships.

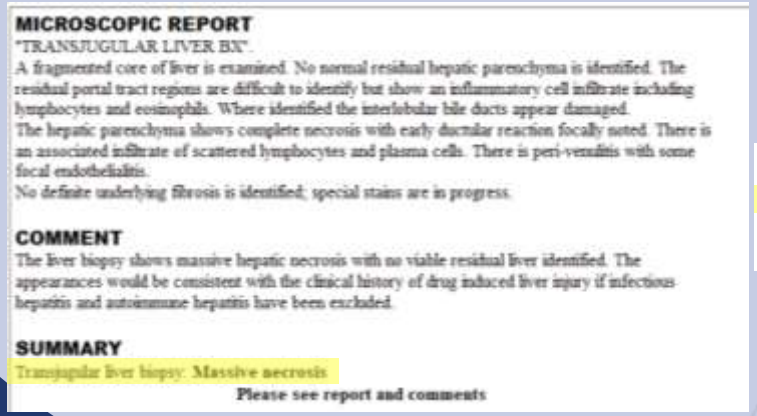
Our case

- 58F presents to ED with worsening reflux, malaise and jaundice
- Initial investigations consistent with acute liver failure
- Hx: Chronic alcohol consumption, plus 6/12 hx of weight-loss formulation containing green tea extract
- Ddx: Alcohol vs. DILI
- Transferred to Royal Prince Alfred Hospital (RPAH) for consideration of orthotopic liver transplant (OLTx)

Investigations	Patient results	Reference range
ALT	**1086 U/L**	< 35 U/L
AST	**1149 U/L**	< 40 U/L
INR	**2.5**	~1.0
Albumin	**27 g/L**	32-45 g/L
Bilirubin (total)	**269 µmol/L**	< 20 µmol/L

Our case (cont.)

- Transjugular liver biopsy – massive hepatic necrosis with no viable residual liver or features of chronic liver disease
- Bilirubin 386 → development of Grade 2 encephalopathy on D10 of admission
- OLTx 3 days later
- Unremarkable recovery, discharged from ICU 2 days post-operatively



MICROSCOPIC REPORT

"TRANSJUGULAR LIVER BX".

A fragmented core of liver is examined. No normal residual hepatic parenchyma is identified. The residual portal tract regions are difficult to identify but show an inflammatory cell infiltrate including lymphocytes and eosinophils. Where identified the interlobular bile ducts appear damaged.

The hepatic parenchyma shows complete necrosis with early ductular reaction focally noted. There is an associated infiltrate of scattered lymphocytes and plasma cells. There is peri-venulitis with some focal endothelialitis.

No definite underlying fibrosis is identified; special stains are in progress.

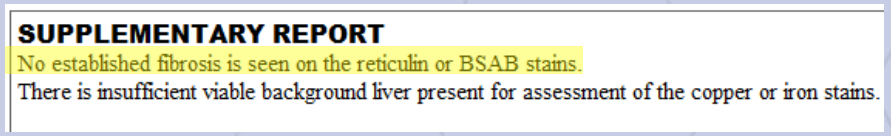
COMMENT

The liver biopsy shows massive hepatic necrosis with no viable residual liver identified. The appearances would be consistent with the clinical history of drug induced liver injury if infectious hepatitis and autoimmune hepatitis have been excluded.

SUMMARY

Transjugular liver biopsy: **Massive necrosis**

Please see report and comments

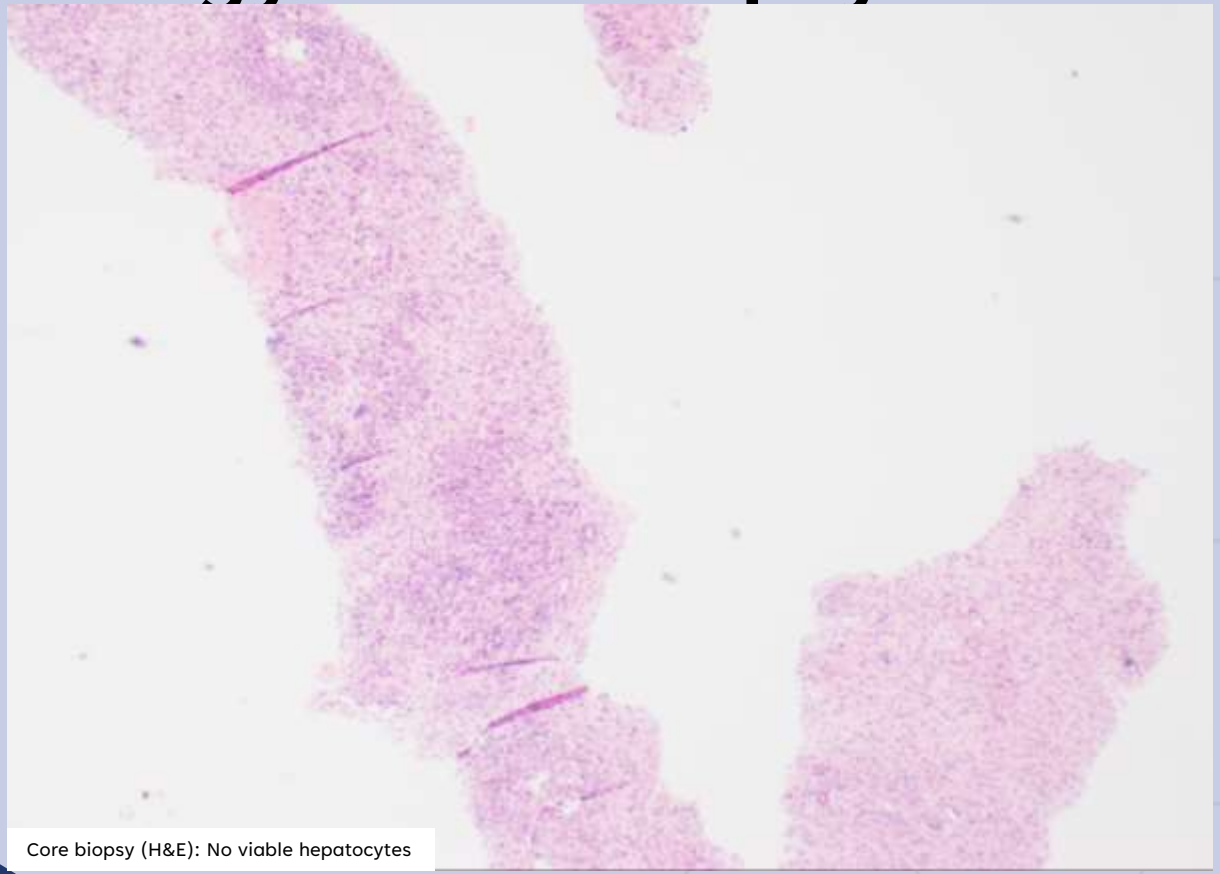


SUPPLEMENTARY REPORT

No established fibrosis is seen on the reticulin or BSAB stains.

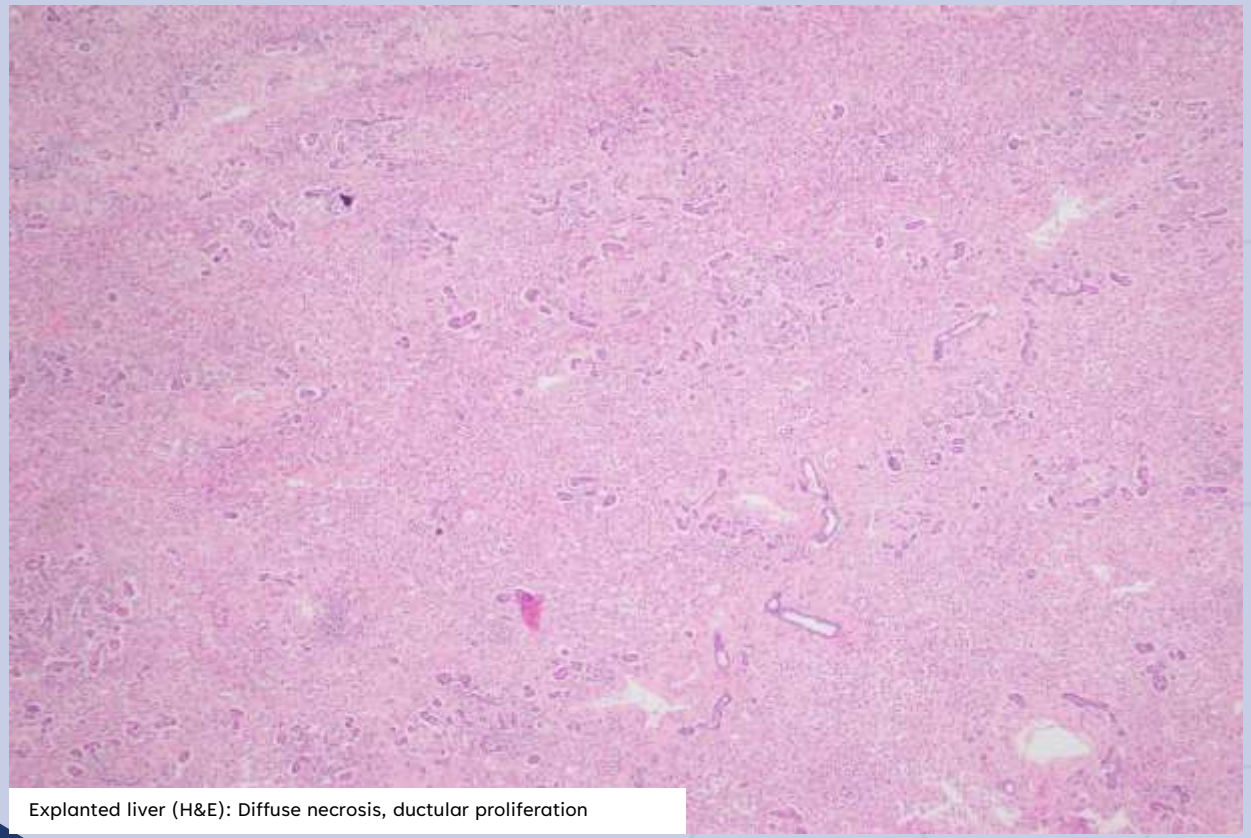
There is insufficient viable background liver present for assessment of the copper or iron stains.

Histology – core biopsy



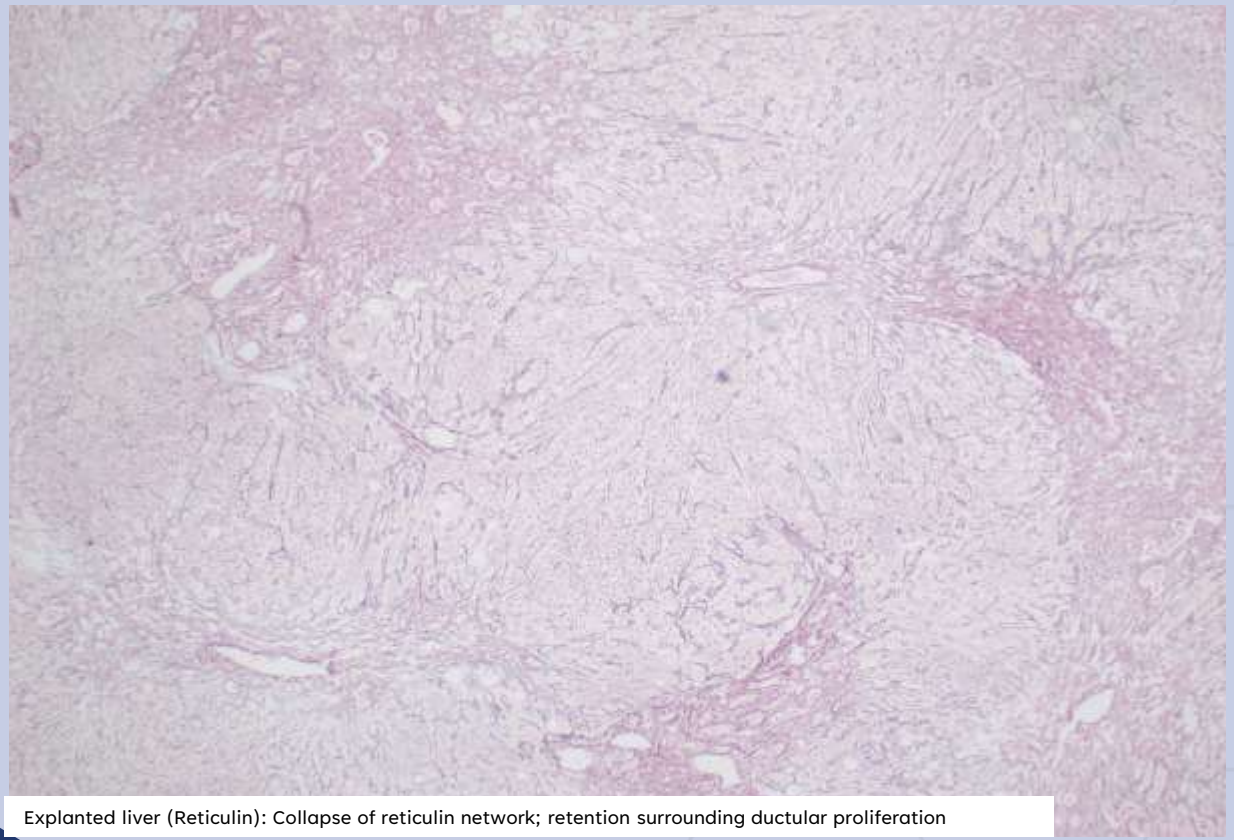
Core biopsy (H&E): No viable hepatocytes

Histology – explanted liver



Explanted liver (H&E): Diffuse necrosis, ductular proliferation

Histology – explanted liver



Explanted liver (Reticulin): Collapse of reticulin network; retention surrounding ductular proliferation

Explanted liver report

3. "RECIPIENT LIVER".
The medication history, including history of herbal supplement intake, is noted.

Sections of liver show some distortion of the architecture by extensive necrosis and collapse.

The portal tract regions show a mild inflammatory cell infiltrate predominantly composed of lymphocytes. Small numbers of plasma cells are noted. Interobular bile ducts are identified. Endothelialitis is noted in some portal veins.

The hepatic parenchyma shows extensive necrosis which varies in severity, with approximately 10% viable liver remaining. The remaining hepatic parenchyma shows extensive ductular proliferation and focal cholestasis. Multiple foci of perivenulitis with endothelialitis are identified. No definite steatosis is identified although there is minimal normal residual liver present for examination. No viral inclusions are identified. The cysts in segment 5 and 8 noted radiologically have been identified macroscopically. Microscopy shows these to be simple hepatic cysts lined by attenuated cuboidal to flattened epithelium, with no evidence of atypia or malignancy.

BSAB and reticulin stains are difficult to interpret in the presence of extensive necrosis. Some immature fibrous tissue is identified on the BSAB stain but no established fibrosis is seen. Reticulin stain shows collapse of the reticulin fibre network in areas of necrosis. No increase in the stainable iron or copper is identified, although minimal residual hepatocytes are present for assessment. PAS/diastase shows no evidence of intracytoplasmic inclusions.
The gallbladder is largely autolysed with minimal viable mucosa present, making histological assessment difficult.

Features of this case are consistent with DILI secondary to GTE, in consideration of the literature, patient serology and temporal correlation

Analysis of case reports

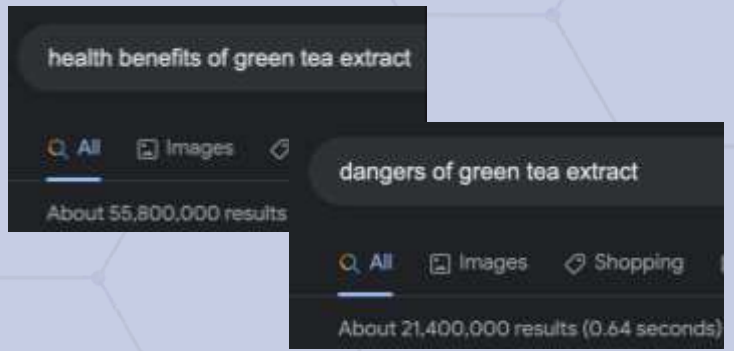
- We identified 66 cases of GTE-associated hepatotoxicity, 63 of which were suitable for analysis
- Most cases of hepatotoxicity were self-limiting, resolving with supportive care
- 8 cases necessitated OLTx, including the other Australian case[1]

- Where classifiable histopathology reports were available, the most common patterns of DILI[2] were:
  - Zonal necrosis (n = 8), Acute hepatitis (n = 6), Submassive or massive necrosis (n = 5), Cholestatic hepatitis (n = 3), Mixed (n = 2)
- Mild fibrosis was only noted in 1 case, reflecting the acuity of the pathological process

	Age (years) (n = 62)	Gender (F : M) (n = 62)	Duration of use (weeks) (n = 44)	Type of green tea formulation (n = 63)	Liver biopsy performed (n = 54)	Pattern of DILI (n = 24)	Required transplant (n = 58)
Total cases (n = 63)	Range: 2 – 81 Mean: 40.6	3.5 : 1	Range: 0.7 – 260 Mean: 22	Green tea extract (n = 48) Other, including brewed green tea (n = 15)	Yes (n = 35) No (n = 19)	Zonal necrosis (n = 8) Acute hepatitis (n = 6) Sub/massive necrosis (n = 5) Cholestatic hepatitis (n = 3) Mixed (n = 2) Mild fibrosis (n = 1)	Yes (n = 8) No (n = 50)

What is green tea extract (GTE)?

- Green tea comes from the stems and leaves of the tea plant (*Camellia sinensis*)
- It is processed immediately without fermentation, which polymerises catechins (the main active ingredient in tea) to form polyphenols, resulting in a much higher concentration compared to black teas[3]
- GTE is a compound commonly found in weight-loss formulations has been touted for the following properties:
  - Antioxidant, anticancer, anti-inflammatory, anti-immune, anti-obesity, anti-diabetogenic, and anti-aging
- These have only been observed in-vitro and in animal studies[3]; they have not been replicated in human studies
- Google search → 55mil results espousing the virtues of GTE



Popularity of GTE

- From 1995 – 2017, herbal and dietary supplement consumption by Australians increased from 49% to 70%[4]
- By 2030, Australians are projected to spend $9.81b on herbal and dietary supplements[5]

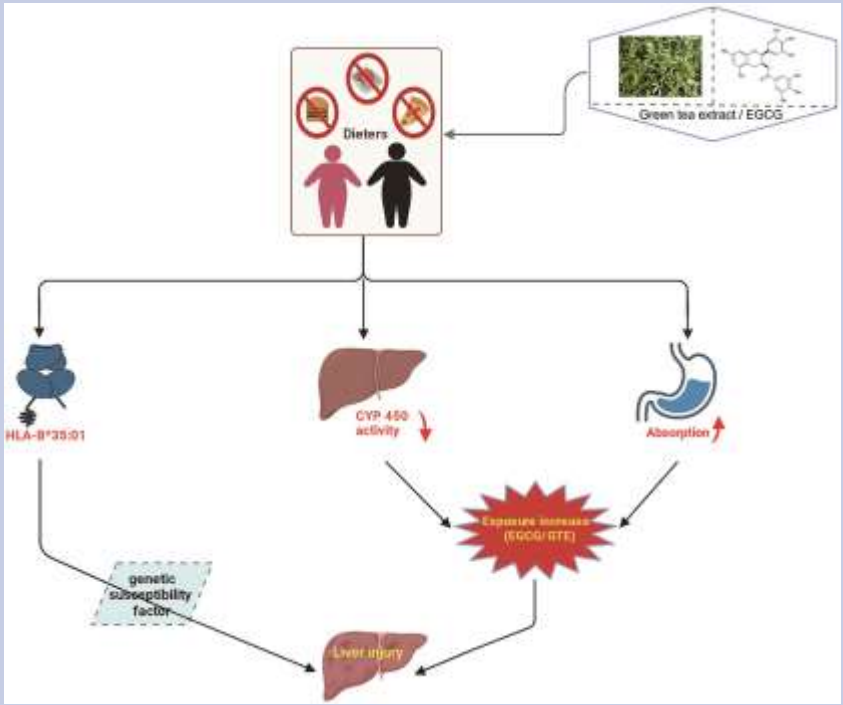
- The Australian Therapeutic Goods Administration (TGA) lists 267 medicines containing *Camellia sinensis*, many of which are “used to assist with weight management and as source of antioxidants.”[6]
- Herbal and dietary supplements ordered online may bypass TGA scrutiny

How much is too much?

- Maximum tolerated dose of GTE in humans is 9.9g per day
  - ~Equal to 24 cups of brewed green tea[7]
- Susceptible individuals who are in a fasted state can show a 5x increase in serum levels[8]
- Additionally, chronic intake of GTE (longer than 4 weeks) increases systemic bioavailability by approximately 60%[9,10]

One formulation that has been removed by the TGA is *Camsen 6000* (containing 6000mg GTE per tablet), which had a dosage frequency of 3 tablets per day!

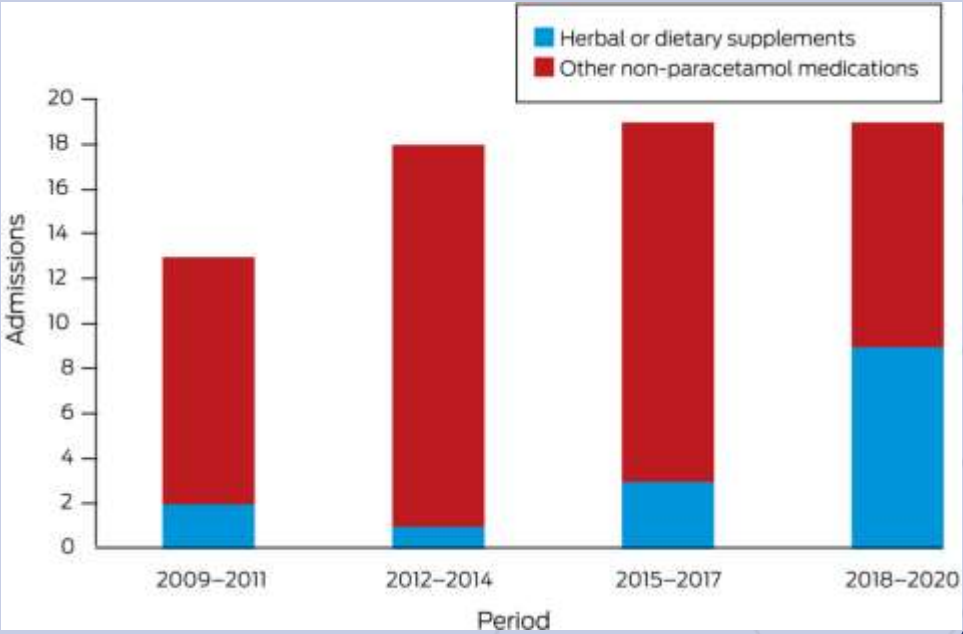
Mechanism of injury:



- Hepatotoxicity has been attributed to the effects of the main catechin in GTE, epigallocatechin-3-gallate (EGCG)
- Re-exposure to EGCG in susceptible individuals bearing the HLA allele B*35:01 results in rapid recurrence of liver injury, suggesting an immunologic aetiology[11]

DILI and GTE

- Commonest cause of acute liver failure in Australia is drug-induced liver injury (DILI)[12]
- Top 3 causes of DILI:
  1. Paracetamol
  2. Antimicrobials
  3. Herbal and dietary supplements



Numbers of admissions with non-paracetamol-related DILI to the A.W. Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, January 2009 – August 2020[12]

Take-home messages

- Higher risk for GTE-associated DILI in fasted states and chronic consumption
- Internationally, weight-loss formulations containing GTE have been removed from the market
- There are minimal published Australian case reports of GTE-associated DILI
- Clinicians should have a high index of suspicion for DILI with unexplained deranged LFTs
- Clinicians should report cases of GTE-associated DILI to the TGA and/or their local public health unit

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