limited available data suggest that RCCLMS has indolent biological behaviour and this readily assessable morphological feature may prove useful in distinguishing RCCLMS from other clear cell renal neoplasms.

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The dangers of herbal weight loss supplements: a case report of drug-induced liver injury secondary to *Garcinia cambogia* ingestion

Sir,

Drug-induced liver injury (DILI) should be suspected in patients presenting with unexplained liver disease. Recent data from the US Drug Induced Liver Injury Network reports 16% of acute liver failure cases are causally related to dietary supplements.[1] Up to 50% of the Australian adult population take dietary supplements.[2] *Garcinia cambogia* (hydroxycitric acid) is a herbal extract from the fruit rind of the *Garcinia cambogia* tree found in South East Asia, India and Africa. It is a commercially available, over the counter weight loss supplement claiming to suppress fatty acid synthesis and appetite, although several small randomised trials report nil efficacy for these purposes.[3] *Garcinia cambogia* has been implicated in causing acute liver injury in several recent case reports.

We present a case of a 54-year-old woman presenting to her local hospital with acute liver failure requiring transplantation after consuming *G. cambogia* for two months. Her initial complaints included malaise, jaundice and dark urine. She reported consuming four to six standard alcoholic drinks per day on a background of binge drinking since age 20. Liver function tests showed ALT 714 U/L (10–35 U/L), AST 644 U/L (10–U/L), ALP 103 U/L (30–110 U/L), bilirubin 666 μmol/L (0–9 μmol/L) and INR >12.0. Routine viral serology and autoantibodies were negative. The progressive nature of the patient's acute liver failure with consistently high serum bilirubin >300 μmol/L and a prothrombin time >100 s deemed urgent liver transplantation necessary to ensure survival. Post-liver transplantation the patient progressed well with improving graft function and normal liver function tests.

Macroscopically the explanted liver showed extensive necrosis with small residual islands of hepatic parenchyma seen. Microscopically, the liver showed submassive necrosis (Fig 1). The islands of surviving hepatocytes showed non-specific changes including extensive ballooning and cholestasis with adjacent extensive ductular reaction (Fig. 2). Portal tract regions showed a moderately heavy inflammatory cell infiltrate predominantly composed of lymphocytes. No diagnostic evidence of underlying chronic liver disease was identified; in particular, features of alcoholic liver disease including steatosis, Mallory–Denk bodies and perivenular fibrosis were not identified.

The findings were regarded as consistent with DILI secondary to *G. cambogia* in view of the close temporal correlation with the supplement ingestion and absence of other possible causes on clinical history and serology. The histopathological features seen were consistent with the biopsy findings in previous published case reports of *G. cambogia* liver toxicity.[4–7]

A literature review using PubMed was performed to identify similar cases using search terms 'liver failure', 'hepatitis', 'DILI', 'herbal supplement', 'weight loss supplement' and 'G.

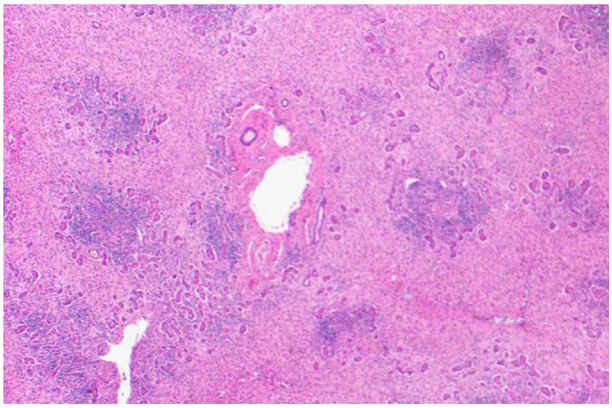

Fig. 1 Low power view showing extensive necrosis present.

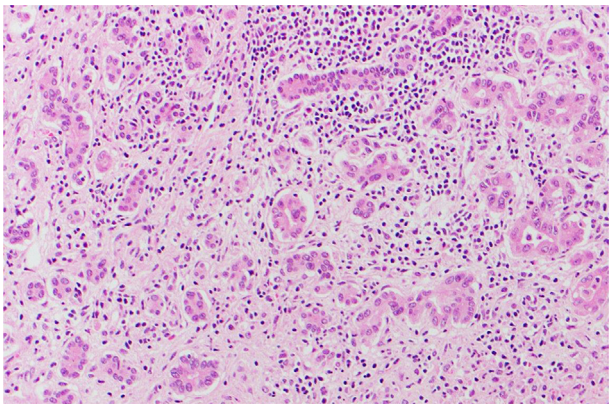

Fig. 2 High power view with extensive necrosis and ductular reaction.

cambogia' or 'Garcinia cambogia'. A review of the literature found 20 published articles containing 34 individual case reports of *G. cambogia* implicated liver injury, with six cases requiring liver transplantation (Table 1). Seventy-five percent of published articles were from the USA (15/20). Twenty-six case reports stated the gender of the patient, of which 14 were female and 12 were male. The duration of supplement ingestion was most commonly 2−7 months (28/34 cases) before hospital presentation, but usage up to 2 years was noted in five cases. In four cases, pure *G. cambogia* was ingested and in 21 cases Hydroxycut with the main active ingredient *G. cambogia* was implicated. The nine other cases noted the patient had ingested another type of weight loss formulation with *G. cambogia* as the main ingredient.

There has only been one previous case report in Australia of *G. cambogia* hepatoxicity.[6] It is likely that there are further unreported cases. In several Australian studies the majority of adverse drug reactions to dietary supplements were found to be unreported, as fewer than 50% of patients discuss their use of herbal preparations with health professionals. Furthermore, these medicines are rarely recorded on hospital admission forms.[8,9]

In 2009, the US Food and Drug Administration issued a recall of Hydroxycut products containing *G. cambogia* due to its implication in liver failure in several case reports, including one death.[4] Although *G. cambogia* was asserted as the putative cause of the banned supplement's hepatotoxic effects, the ingredient has never been banned due to lack of definitive evidence. Most cases of *G. cambogia* associated hepatotoxicity have been from mixed supplements or formulaic variations, making evaluation of the causal ingredient of supplement induced hepatotoxicity difficult.[5] *Garcinia cambogia* is considered safe for ingestion by the Therapeutic Goods Administration (TGA) in Australia in lower risk medicines. However, the TGA notes that it did not specifically evaluate whether or not the ingredient works.[10]

Table 1 Published case reports of *G. cambogia* implicated liver failure

Case	Age/Sex	Duration of *G. cambogia* use	Pure *G. cambogia* or formulation?	Required transplant?	Year of publication
1	57/F	1 month	Pure	N	2018
2	61/F	2 months	Super Anas Slim formulation	N	2018
3	39/F	1 month	Obless formulation	N	2018
4	47/F	1 month	Thermo Giallo formulation	N	2018
5	52/F	1 month	Jill Cooper be slim formulation	N	2018
6	34/M	5 months	Swanson Premium Brand G Cambogia 5:1 Extract	Y	2016
7	52/F	1 month	Pure	Y	2016
8	45/F	1 week	TOPLINE formulation	Died[a]	2007
9	26/M	1 week (10 weeks prior to presentation)	Whey protein powder; 70% *G. cambogia*	Y	2016
10	51/F	Unspecified	Unspecified; main ingredient *G. cambogia*	N	2018
11	36/F	1 month	Pure	N	2018
12	Age range 17−54[b]	1 year	Hydroxycut	Y	2010
13	Age range 17−54[b]	2 months	Hydroxycut	Y	2010
14	Age range 17−54[b]	1.5 months	Hydroxycut	N	2010
15	Age range 17−54[b]	1 month	Hydroxycut	N	2010
16	Age range 17−54[b]	2 years	Hydroxycut	N	2010
17	Age range 17−54[b]	2 months	Hydroxycut	N	2010
18	Age range 17−54[b]	2 months	Hydroxycut	N	2010
19	Age range 17−54[b]	1 month	Hydroxycut	Y	2010
20	27/M	5 weeks	Hydroxycut	N	2005
21	30/M	5 days (11 days prior to presentation)	Hydroxycut	N	2005
22	28/M	3 months	Hydroxcut	N	2008
23	39/F	12 days	Unspecified powder; *G. cambogia* main	N	2014
24	19/M	1 week	Hydroxycut	N	2010
25	40/F	1 week	Hydroxycut	N	2008
26	33/F	2 weeks (1 month prior to admission)	Hydroxycut	N	2008
27	27/M	Not specified	Hydroxycut	N	2014
28	19/M	4 months	Hydroxycut	N	200
29	31/F	1 year	Hydroxycut	N	2010
30	23/M	Months	Hydroxycut[c]	N	2015
31	23/M	60−90 days	Hydroxycut	N	2008
32	25/M	60−90 days (intermittent periods over 2−3 years)	Hydroxycut	N	2008
33	25/M	60−90 days	Hydroxycut	N	2008
34	42/F	7 days	Pure	N	2015

[a] Died of renal/respiratory failure.
[b] Article does not specify ages in the cases: 6 males, 2 females.
[c] Aetiology of the liver failure was determined to be due to hereditary coprophorphyria (HCP). The inciting event was the use of Hydroxycut.

Many consumers believe herbal supplements are safe, however, our case highlights the risks of herbal supplementation and the variation between nations in their regulation. Consideration should be given to raising public awareness about the lack of effective regulation of supplements. Furthermore, health professionals should ensure to question patients presenting with unexplained deranged liver function tests or acute liver failure about dietary supplement usage to aid accurate diagnosis and clinical management.

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Case report of low-grade neuroepithelial tumour with oligodendroglioma-like components and CD34 expression

Sir,

Low-grade neuroepithelial tumours (LGNT) encompass a heterogeneous group of neoplasms, which differ from more common central nervous system neoplasms in their clinical behaviour as well as their histopathology. Oligodendroglioma-like LGNT is a recently recognised epileptogenic tumour, affecting children and young adults, characterised by strong CD34 immunoreactivity and genetic alterations in the MAP kinase pathway, called polymorphous low-grade neuroepithelial tumour of the young (PLNTY).[1] In this report, we illustrate this rare tumour with its clinical behaviour and histopathology.

A 25-year-old woman presented with a 5-year history of intractable complex seizures. The patient suffered epileptic seizures every 6 months, and absence seizure lasting for 10 seconds once a day, often in the morning. The seizures were relieved by antiepileptic drugs. In the previous 2 months, the patient's symptoms had become significantly aggravated and had increased in frequency. Magnetic resonance imaging (MRI) showed a partially cystic, unifocal lesion on a T1-weighted image, mixed intensity with calcifications on a T2-weighted image, within the subcortical white matter of the left temporal lobe (Fig. 1A). Low grade glioma or dysembryoplastic neuroepithelioma tumour (DNET) was preliminarily considered by MRI. The patient underwent resection of left temporal lobe lesions. During the operation a solid cystic tumour was found to invade the lateral fissure of the left temporal lobe, with waxy yellow colour, soft texture and a size of 2.0×1.5×1.0 cm. Post-surgical MRI revealed complete resection of the temporal lobe lesion. The patient recovered without complications and is free of seizures 6 months following surgery.

The surgical specimen consisted of greyish-red and friable fragments, the largest of which measured 0.7 cm in greatest dimension. On haematoxylin and eosin staining, the tumour showed diffuse growth and infiltrated the overlying cortex, admixed with areas of extensive calcifications. The neoplasm was composed of well differentiated oligodendrocyte-like cells featuring small, round nuclei and perinuclear halos (Fig. 1B), with interspersed thin walled capillaries. No necrosis, microvascular proliferation, or mitotic activity was seen. No Rosenthal fibres, eosinophilic granular bodies or conspicuously pleomorphic astrocytes were identified.

Immunohistochemical analysis revealed the tumour to be positive for glial fibrillary acidic protein (GFAP) and oligodendrocyte transcription factor 2 (OLIG2), with retained α-thalassaemia X-linked mental retardation syndrome (ATRX) and integrase interactor 1 (INI1/SMARCB1). The tumour cells exhibited diffuse and intense positivity for CD34 (Fig. 2A) with ramified, CD34-expressing neuroepithelial elements (Fig. 2B) in cortical tissue adjacent to the neoplasm, and negativity for isocitrate dehydrogenase 1 (IDH1) (R132H), epithelial membrane antigen (EMA), AE1/AE3, neuronal nuclear antigen (NeuN), synaptophysin, somatostatin receptor-2 (SSTR2) and thyroid transcription factor 1 (TTF 1). p53 showed only weak focal positivity. Ki-67 (MIB-1) labelling index was less than 2%. *BRAF* V600E mutation was identified by amplification refractory mutation system polymerase chain reaction (ARMS-PCR). Mutational analysis of *IDH1/IDH2* was negative, and chromosomal 1p/19q co-deletion was not detected by fluorescence *in situ* hybridisation (FISH).

The differential diagnosis included oligodendroglioma, metastatic carcinoma, clear cell meningioma, clear cell ependymoma and polymorphous neuroepithelial tumour such as PLNTY. Metastatic carcinoma and clear cell ependymoma