Hepatic failure and encephalopathy has many causes, ranging from viral infections to medications to metabolic disorders. Severe primary hypothyroidism as a cause of severe liver failure and encephalopathy is very uncommon and, therefore, may be diagnosed late. The following is a case of severe myxoedematous hepatic failure which improved significantly following thyroxine therapy.

Clinical case report

A 47-year-old woman was presented with a 2-month history of progressive lethargy and malaise. She presented acutely in a semiconscious state and barely rousable following a rapid 2-day deterioration when jaundice was noticed. There was no other significant medical history and she denied taking any medications, prescribed or otherwise. She also denied any alcohol intake, intravenous drug use or recent overseas travel. There was no family history, particularly, of thyroid disease. She had been diagnosed with hypothyroidism 5 years ago, the exact cause was uncertain. She ceased thyroxine herself after her practitioner had left the area and had been without medical care for some time. Clinical examination showed a semicomatose patient, unkempt and delirious but with stable vital signs. Her pulse rate was 96 beats per minute and blood pressure was 180/110 with no postural change. She was jaundiced with fetor hepaticus. There were no peripheral stigmata of chronic liver disease. Her liver span was normal. There was no splenomegaly, no ascites and no peripheral oedema. Her liver function tests showed a mixed pattern with aspartotransferase (AST) 599 U/l [Normal (N), <35], alaninetransferase (ALT) 569 U/l (N, <26), γ-glutamyltransferase (GGT) 121 U/l (N, <35), alkaline phosphatase (ALP) 272 U/l (N, 30–115) and bilirubin 130 μmol/l (N, <15). Albumin was slightly low at 33 g/l (N, 36–48), serum creatinine was 153 μmol/l and coagulation assay levels were increased with INR (international normalized ratio) 1.8 (N, 0.8–1.0) and APTT (activated pro-thrombin time) 38 s (N, 20–30). The initial thyrotropin (TSH) was found to be grossly elevated at 430 mU/l with undetectable free tetra- and tri-iodothyronine levels. Her anti-thyroglobulin and anti-thyroperoxidase levels were 42 (N, <150) and 19 (N, <50), respectively. The α-1-antitrypsin (A1AT) level was depressed at 0.77 g/l (N, 0.84–1.81). Her anti-nuclear antibody, extractable nuclear antigen and double strand DNA levels were negative. Iron studies, copper level, caeruloplasmin level, serum angiotensin converting enzyme activity, hepatitis A, B and C serology were non-diagnostic. Similarly, the liver ultrasound and computerized tomography (CT) scan were not
helpful in arriving at any definitive diagnosis. There was no biliary tree obstruction. The CT scan showed heterogeneity in appearance with evidence of generalized hepatic oedema, some of which surrounded the portal vein. A liver biopsy was equally non-diagnostic, revealing chronic inflammation and fibrosis with some architectural distortion suggestive of a more insidious underlying pathological process. The patient was referred to a tertiary transplant centre where the transjugular liver biopsy showed chronic inflammation and fibrosis with some architectural distortion. Because there was a substantial number of surviving hepatocytes, an urgent transplantation was deemed unnecessary.

Myxoedematous hepatic failure was the provisional diagnosis and thyroxine was initiated at 25 µg escalating over the ensuing 3 months to 125 µg daily. At 6-month follow-up, the patient is symptomatically well with normal TSH level. Her bilirubin has normalized to 13 µmol/l with GGT 88, ALP 188, ALT 87, AST 102, albumin of 30 and total protein of 72 g/l. A second core transhepatic biopsy confirmed the presence of end-stage liver disease with completely distorted liver structure, a predominance of lymphocyte and mononuclear cellular infiltrates and an absence of hepatocytes, the latter is clearly due to random sampling (Figure 1). Overall, this is consistent with a picture of post-hypothyroid hepatic necrosis with fibrotic, scarred and hepatocyte-absent areas. The CT scan also confirmed the cirrhosis with multiple focal regenerative nodules (Figure 2).

Discussion

Myxoedemic hepatic failure is a very uncommon occurrence with unknown frequency. Most incidents are indeed case reports. The presentation of liver failure in relation to hypothyroidism is interesting in that both conditions manifest with similar features. Non-specific and generalized fatigue and alterations in mental status may both be present as in this case. In addition, there is muscle weakness, myalgia, oedema, ascites or pleural effusions. Less commonly, patients may present in a more serious manner with gross ascites, encephalopathy or coma.

In similar presentations to our case, common causes of liver failure needs to be entertained, such as medications, viral infections, metabolic and autoimmune hepatitides. Equally important, however, hypothyroidism needs to be considered as a potential cause because it is readily remediable. Liver function tests alone are unhelpful in determining the aetiology of liver failure, keeping in mind that pre-existing chronic liver disease may be present. Some studies suggest a greater increase in AST than ALT may be seen. Coagulation test abnormalities and low albumin levels further confirm ongoing liver damage, but again these derangements are non-specific. Testing for immune-mediated disorders, although rare, is necessary to rule out conditions that could damage both thyroid and liver. There are associations between the presence of anti-thyroid antibodies and autoimmune hepatitis, primary biliary cirrhosis and chronic hepatitis C.

Figure 1. Core liver biopsy showing end-stage liver damage with a complete absence of hepatocytes, an abundance of mononuclear infiltrates and loss of normal liver architecture.
and in some cases, patients may even present with an autoimmune polyglandular syndrome. Hyperammonaemia might have contributed to the delirious state but was not assessed in this case. Ammonia production has been proposed to increase in hypothyroidism despite the overall reduction in the metabolic rate it commonly induces.

In myxoedemic liver disease, hypothyroidism is usually severe with TSH being drastically elevated and undetectable fT4 and fT3 levels. Several other cases of myxoedema associated with liver dysfunction have been reported in the literature, and all previous cases had normal or fully compensated liver disease. In addition, one study established that hypothyroidism in patients with non-alcoholic cirrhosis is associated with a more rapid deterioration and worse outcomes. This further highlights the importance in investigating for pre-existing liver disease. Unexpectedly, our patient was found to have a low A1AT level, probably reflecting the poor liver synthetic function at the time of the acute illness. This is unlikely to contribute to the patient’s liver failure.

Imaging may reveal findings, such as ascites, enlarged thyroid gland, or pleural or pericardial effusions, as well as results consistent with a degree of cirrhosis. Liver biopsy may not be useful unless the patient is carefully selected. However, if there is a history of liver dysfunction or high clinical suspicion of a new diagnosis then it is recommended.

The possible mechanisms for the development of severe hepatic failure in the myxoedematous state are poorly understood, if at all. There is a dearth of information or understanding at the molecular or biochemistry level. Histopathologically, there is central congestive fibrosis, especially, when ascites has developed. Perhaps this is a reflection of chronic right-sided congestive cardiac failure. Another alternative is that severe hypothyroidism causes enhanced permeability of the vascular endothelium, resulting in generalized oedema throughout the body and in severe cases ascites. Surprisingly, this did not occur in our particular case despite the severe hypothyroidism. Hypothyroidism also results in poor bilirubin excretion, due to decreased Uridine 5’-diphospho-glucuronosyltransferase activity, causing jaundice and hyperbilirubinaemia independent of hepatocellular disease. Repletion with thyroxine is expected to reverse these abnormalities over a number of months.

The treatment of this rare diagnosis includes cautious thyroxine replacement. In most cases, it is recommended to start thyroxine at low dose and escalate the dose to the requirement of 0.5–1.6 μg/kg/day. This is because of the potential issue of undetected coronary atherosclerotic disease when starting with a higher dose of thyroxine. In addition, in the presence of liver failure, binding protein concentrations are low, allowing for more free thyroxine to exert its effect at the tissue site, further aggravating any coronary artery disease. Another concern is intestinal oedema, often present in hepatic failure. With the resolution of the oedema, there may follow a rapid absorption of thyroxine, potentially precipitating or aggravating cardiac complications. The third safety concern with high dose thyroxine replacement therapy is the unmasking of unsuspected adrenal insufficiency. Although this is uncommon and happens in case reports, some clinicians favour the addition of short term glucocorticoid cover.

Following the satisfactory replacement regimen of thyroxine and in the absence of any pre-existing chronic liver dysfunction, treating hypothyroidism produces a gradual and steady normalization of liver function with concomitant clinical improvement. This is supported in our case where it took ~6 months for the liver function tests to significantly
improve following therapy (Figure 3). In the context of background liver disease, the prognosis appears to be better in euthyroid than hypothyroid patients. It remains contentious whether thyroxine and its metabolite, tri-iodothyronine, can be used to assist in liver regeneration following severe hepatic injury without hypothyroidism. In animal models, high dose thyroxine has been shown to induce hepatic proliferation and increase liver mass in normal liver tissue. In our case, the liver unfortunately has progressed to end-stage cirrhotic disease with regenerating nodules which might have been aided by thyroxine supplement.

It is important to consider hypothyroidism as a cause of liver failure despite its low prevalence, given the widespread availability of TSH measurements. This is because the condition is readily treatable with the potential normalization of the liver function.

**Acknowledgement**

We would like to thank Dr Fadia Natali, Consultant Histopathologist, for her assistance with the reproduction of the liver histology slides.

**Conflict of interest:** None declared.

**References**