A diagnosis fifteen years in the making
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ABSTRACT
A 52-year-old male with a diagnosis of non-alcoholic fatty liver disease re-engages with the medical system and is found to have an unexpected diagnosis.

Case report

A 52-year-old male was reviewed in the hepatology outpatient clinic with chronically elevated cholestatic liver enzymes. Dating back twelve years, gamma-glutamyl transferase (GGT) was elevated at $\times 3–5$ upper limit of normal and alkaline phosphatase (ALP) $\times 2–3$ the upper limit of normal. Liver synthetic function was normal. Medical history was relevant for type 2 diabetes mellitus treated with metformin.

A review by Gastroenterology in 2016 showed his serologic liver screen was unremarkable, with no evidence of viral hepatitis; including chronic hepatitis B and C, and no evidence of autoimmune hepatitis or an inherited liver condition. Abdominal ultrasound revealed diffuse hepatic steatosis. The gastroenterology opinion was of non-alcoholic fatty liver disease (NAFLD) based the patient's history of type 2 diabetes, hepatic steatosis on ultrasonography and a negative serological liver screen. A FibroScan performed in 2017 showed an elevated liver stiffness of $14.0\text{kPa}$, consistent with advanced fibrosis or early cirrhosis. A liver biopsy was considered but the patient was lost to follow-up.

In 2020, the patient re-engaged with his general practitioner and was referred to hepatology. He reported chronic right upper quadrant pain. The pain was constant and worse at night. It was not associated with meals and was managed with regular tramadol. He was otherwise systemically well with a stable weight and a BMI of 25.5. There were no features of metabolic syndrome other than type 2 diabetes. He did not drink alcohol or use illicit drugs.

On examination there was no peripheral stigmata of chronic liver disease. Abdominal examination revealed mild right upper quadrant tenderness with no hepatosplenomegaly, ascites or peripheral oedema. The GGT and ALP were persistently elevated, while the remaining liver enzymes were unremarkable. A repeat non-invasive liver screen was negative. An abdominal ultrasound revealed a liver of mildly patchy echotexture with no focal lesions or signs of portal hypertension. FibroScan showed a liver stiffness of $10.3\text{kPa}$, consistent with moderate to severe fibrosis.

Due to the elevated hepatic stiffness with a clinical diagnosis of non-alcoholic fatty liver disease a liver biopsy was performed to determine whether he would need surveillance for hepatocellular carcinoma, as there were no other clinical features to suggest the patient had cirrhosis. The histology showed non-caseating, epithelioid granulomas. There was mild steatosis and Metavir stage 3–4 fibrosis. There were no specific features to identify the aetiology of the granulomatous hepatitis.

Full blood count and extended electrolytes were unremarkable. Human immunodeficiency virus serology and QuantiFERON-TB gold were negative. Serum angiotensin converting enzyme was within normal range. Brucellosis serology was negative. Stool examination did not reveal ova, cysts or parasites. Computer tomography scan demonstrated heterogeneity of liver attenuation however no other abnormality was seen within the chest, abdomen or pelvis.

The patient was born in Ethiopia before immigrating to New Zealand 15 years prior to the review. He was raised near Lake Tana; this was his family's water source in which they swam and bathed. He recalled episodes of rectal bleeding as a child and an episode of “liver pain”, which was treated with traditional remedies. In 2008, a year after arriving in New Zealand, he presented to hospital with a chronic perianal fistula. This was managed with incision and drainage and antibiotics.

Considering the new clinical information, the liver biopsy was re-examined. Deeper levels of the tissue revealed numerous eosinophils within the granuloma, as well as a small amount of central...
necrotic debris (Figure 1). A Ziehl-Neelsen stain was repeated on the deeper levels of tissue, and this highlighted parasitic remnants within the granuloma (Figure 2).

Schistosomal antibodies were strongly positive at titres greater than 2,560. This test was performed with the Fumouze IHA assay which has a 76% sensitivity, and 95% specificity for *Schistosoma mansoni*.

The patient received eradication treatment with praziquantel to treat his hepatic schistosomiasis. He has been referred for upper gastrointestinal endoscopy to investigate for varices.

**Discussion**

Schistosomiasis causes considerable morbidity and mortality. It is estimated that more than 200 million people are infected, most of whom live in Africa.¹

The acute manifestations of infection are Swimmer’s Itch and acute schistosomiasis or “Katayama’s fever”; however, the main burden of disease is due to chronic infection involving either the gastrointestinal or genitourinary system, depending on which species of the flat worm the patient is infected with. In rare instances embolisation of eggs and worms can cause neurologic and pul-

**Figure 1:** The image on the left shows a liver core biopsy containing a lobular granuloma (x100). The image on the right shows the granuloma with numerous eosinophils present and central necrotic debris (x400).

**Figure 2:** Ziehl-Neelsen stain showing parasitic remnants present in the centre of the granuloma (x400).
monary disease, and glomerulopathy can occur from immune complex deposition in the kidney. Adult worms evade the host immune system, and instead, it is the eggs which cause pathological damage by inducing a Th-2 immunogenic response leading to formation of eosinophilic granulomas. Clinical disease depends on several factors including the number of eggs trapped in tissue, their anatomical location, the duration of infection, and the intensity if the host immune response.3

Hepatic schistosomiasis is one of the most common causes of non-cirrhotic portal hypertension worldwide.4 S. mansoni is responsible for most cases in Africa and South America, and S. japonicum, in Asia. Eggs are laid in the mesenteric veins lodge in the intestine causing luminal disease, or they are carried into the portal veins and become trapped in the portal venules. Liver injury results from a granulomatous reaction around trapped eggs in the presinusoidal space. Classically, patients develop “pipestem” portal fibrosis with presinusoidal portal hypertension.5 Liver synthetic function is typically preserved, and patients present with complications of portal hypertension rather than hepatocellular failure. Heavily infected individuals may develop advanced periportal fibrosis at a young age, while focal portal granulomas may be the only abnormality in older patients with lighter infection,4 as was the case with our patient.

Twenty-one point nine percent of refugees arriving in New Zealand between 1995–1999 had positive schistosomal serology.6 These numbers have fallen to 3.2% between 2010–2014,7 reflecting the different infection rates in refugee country of origin. Ethiopia has high rates of schistosomiasis with approximately 5 million people1 or 8% of the population infected. Our patient’s wife was given refugee status, and our patient travelled to New Zealand on a family reunification visa to join her. He had a medical examination in Ethiopia before departure but unlike his wife, he was not seen in the New Zealand refugee clinic. Non-refugee migrants from endemic areas are not routinely screened for schistosomiasis, and the cost of medical care in the primary care setting may be prohibitive. The patient was not evaluated for schistosomiasis during the admission in 2008, but S. mansoni resides in the gastrointestinal system and perianal fistulae are well-documented complications of anorectal infection.

Our patient was diagnosed with hepatic schistosomiasis 15 years after immigrating to New Zealand. Active hepatic schistosomiasis has been reported in a Portuguese soldier 34 years after returning from Angola.7 Tropical diseases like schistosomiasis are rarely seen in New Zealand, and the necessary pathological examination is often not performed without the pathologist being aware of the travel history.

Our patient did not have the classic features of hepatic schistosomiasis and the diagnosis remained elusive until liver biopsy was performed. Unrecognised schistosomiasis can lead to significant morbidity, mortality and healthcare expense. This case raises the question about whether New Zealand should implement universal schistosomal screening in new immigrants from countries with endemic infection.

Liver biopsy is not usually performed in patients with metabolic risk factors who meet the diagnostic criteria for NAFLD. However, in patients with abnormal liver function tests and a normal serological liver screen, liver biopsy has been shown to make an alternative diagnosis to NAFLD in 25.3% of patients with or without an abnormal echo pattern on abdominal ultrasound.8 While histological examination is not required to make a diagnosis of NAFLD, it is the only investigation which confirms the diagnosis. This case highlights the role of liver biopsy in NAFLD. Liver biopsy can be used to accurately stage the degree of liver fibrosis and should be considered in cases of diagnostic uncertainty.9
COMPETING INTERESTS
Nil.

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