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T Adrian and others

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Incidental finding of non-alcoholic steatohepatitis-cirrhosis

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Summary

A 72-year-old man with type 2 diabetes volunteered to participate in the control group of a clinical study. The study evaluated non-alcoholic fatty liver disease in patients with kidney disease. The patient was followed at a gastroenterology department due to Crohn's disease and post-operative bile acid malabsorption. The patient had no symptoms or biochemical findings suggesting liver disease. Surprisingly, a transient elastography (FibroScan®) suggested advanced fibrosis with a median of 16.1 kPa. A liver biopsy showed non-alcoholic steatohepatitis (NASH)-cirrhosis. The diagnosis was only made incidentally and highlights how NASH-cirrhosis may be overlooked due to the lack of symptoms.

Learning points

- Clinicians treating high-risk populations, including patients with type 2 diabetes and/or components of the metabolic syndrome, should be aware of the frequently occurring co-existence with non-alcoholic fatty liver disease (NAFLD) and especially non-alcoholic steatohepatitis (NASH).
- Liver enzymes may be in the normal range even in people with steatosis, NASH, or even cirrhosis.
- The diagnosis of NAFLD should include evaluation of hepatic fibrosis as this is the most important prognostic factor for liver-related complications and mortality.
- Guidelines about systematic screening for NAFLD in patients with type 2 diabetes are incongruent.

Background

Non-alcoholic fatty liver disease (NAFLD) is threatening to become a major global health burden and is now affecting one in four of the general population. With an increasing prevalence, NAFLD is currently the most frequent liver disorder in many nations. As NAFLD is closely associated with obesity and insulin resistance, it is often regarded as the hepatic manifestation of the metabolic syndrome. NAFLD is defined as lipid accumulation in >5% of the hepatocytes with the absence of excessive alcohol intake (>20 g/day for women and >30 g/day for men) and other causes of steatosis such as viral or autoimmune hepatitis. The disease comprises a large spectrum from benign simple steatosis to non-alcoholic steatohepatitis (NASH) with inflammation and liver cell damage with or without fibrosis which may progress to cirrhosis and hepatocellular carcinoma (1, 2).

NAFLD is generally asymptomatic, and the disease may therefore go unnoticed for several years until decompensated cirrhosis is developed. People with type 2 diabetes constitute a large high-risk population, and

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it is estimated that about 55% and 37% of people with type 2 diabetes have NAFLD and NASH, respectively (3). Accordingly, it is important to identify patients with advanced fibrosis. The diagnosis of NASH requires a liver biopsy, but there are non-invasive tests which may be used to identify patients with fibrosis (1, 2, 4).

We present a case of a man in his early 70s who by chance was found to have NASH-cirrhosis.

Case presentation

A 72-year-old man participated as a control person in a clinical study (ClinicalTrials.gov/NCT03826381). The study evaluated the prevalence of NAFLD in patients with type 2 diabetes and chronic kidney disease. The patient exercised regularly, had a low intake of alcohol, and reported no liver-related symptoms. None of his family members had known liver disease or type 2 diabetes. In addition to type 2 diabetes, he had three other components of the metabolic syndrome: central obesity (waist circumference 100 cm), raised triglycerides (1.8 mmol/L), and raised blood pressure (systolic pressure 144 mm Hg). His BMI was 26.1 kg/m^2. A 4-day continuous glucose monitoring assessed using iPro2® (Medtronic, Northridge, CA, USA) showed a mean sensor glucose of 8.0 mmol/L and glucose levels within the time-in-target-range (3.9–10 mmol/L) 96% of the time. The patient had previously undergone ileocecal resection for Crohn's disease and developed post-operative bile acid malabsorption. Two years before inclusion in the study, the patient underwent CT of the abdomen, which showed no liver abnormalities.

Due to the incidental finding of possible cirrhosis, he was referred to a hepatologist for further investigations.

Investigation

On physical examination, no cirrhosis stigmata were observed. Initial investigations showed modestly elevated levels of alanine aminotransferase (ALT): 78 U/L (reference 10–70 U/L); alkaline phosphate: 108 U/L (reference 35–105 U/L); and gamma-glutamyl-transferase: 159 U/L (reference 15–115). Aspartate aminotransferase (AST), bilirubin, platelets, and albumin were within the normal range. Transient elastography (FibroScan®) assessed liver stiffness and showed a median of 16.1 kPa suggesting advanced fibrosis. Fibrosis 4 (Fib-4) score was 1.56 (4) (Table 1).

A fasting FibroScan® was repeated showing a median of 19.8 kPa, and a percutaneous liver biopsy was therefore performed. The histology showed mild steatosis, inflammation, ballooning, and fibrosis grade 4 (Fig. 1).

Alcoholic cirrhosis was ruled out based on three interviews and the use of the Alcohol Use Disorder Identification Test–Consumption test resulting in a score of three points corresponding to low risk (5). Other liver diseases than NASH including viral hepatitis B and C, hemochromatosis, autoimmune liver diseases, primary biliary cholangitis, celiac disease and thyroid disease as well as other liver diseases associated with steatosis were ruled out based on blood tests and the histological assessment (1).

Treatment

Lifestyle intervention is the treatment of choice for NASH. Advice regarding diet, physical activity, and alcohol intake was given. The patient did not smoke.

The pharmacological treatment of type 2 diabetes prior to inclusion in the clinical study was semaglutide, a glucagon-like-peptide 1 receptor agonist. In addition, atorvastatin was given as primary prevention of cardiovascular disease which also may have a beneficial effect on the full spectrum of liver damage related to NAFLD. The patient was maintained on both treatments.

Treatment with the sodium-glucose transport protein 2 inhibitor (SGLT2 inhibitor) empagliflozin was added to improve metabolic control.

Outcome and follow-up

Twenty-one months after the initial investigation, the patient had a decrease in BMI from 26.1 kg/m^2 to 24.7 kg/m^2 as shown in Table 1. Moreover, there was a modest decrease in some of the metabolic parameters including $HbA1_c$ (decreased by 1 mmol/mol) and circulating levels of total cholesterol (decreased by 0.2 mmol/L), low-density lipoprotein (LDL) (decreased by 0.3 mmol/L), and triglycerides (decreased by 0.35 mmol/L). In addition, a decrease in ALT (61 U/L), AST (37 U/L), and liver stiffness (12.2 kPa) was observed. No signs of hepatic decompensation were observed.

Discussion

This case describes a 72-year-old man with type 2 diabetes who was identified with NASH-cirrhosis when he participated as a control person in a clinical study. He had no symptoms suggesting liver disease and no clear evidence of cirrhosis in the initial assessment. Thus, it is very likely that the patient would not have been diagnosed if he had not participated in the study.

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Table 1 Clinical characteristics and laboratory parameters.

Characteristics	March 2020	March 2021	December 2021	Reference
BMI (kg/m^2)	26.1	24.7	23.4	18.5–25
Blood pressure (mm Hg)	144/83	-	-	130/80
Waist circumference (cm)	100	-	-	<94
Waist–hip ratio	0.99	-	-	<0.9
Biochemistry				
Hemoglobin (mmol/L)	10.0	10.8	10.4	8.3–10.5
Leucocytes (109/L)	7.4	6.1	6.5	3.5–8.8
Platelet count (109/L)	226	209	190	145–390
Creatinine (µmol/L)	79	67	65	60–105
eGFR (mL/min/1.73 m^2)	85	91	>90	>60
Albumin (g/L)	39	40	39	34–45
Ferritin (µg/L)	157	168	86	12–300
INR	1.1	1.1	1.1	<1.2
ALAT (units/L)	78	63	61	10–70
ASAT (units/L)	43	41	37	15–45
Bilirubin (µmol/L)	8	8	10	5–25
Alkaline phosphatase (units/L)	108	103	94	35–105
UACR (mg/g)	9	15	-	≤300
Metabolic parameters				
Glucose (mmol/L)	7.4	5.9	-	4.2–6.3
$HbA1_c$ (mmol/mol)	45	43	44	<48
Total cholesterol (mmol/L)	3.3	2.9	3.1	<5.0
HDL cholesterol (mmol/L)	1.52	1.6	1.6	>1.0
LDL cholesterol (mmol/L)	1.1	0.6	0.8	<3.0
Triglycerides (mmol/L)	1.8	1.5	1.45	<2.0
Liver parameters				
Fib-4-score	1.56	1.80	1.85	<1.45
FibroScan (kPa)	16.1/19.8 (M)	18.1 (M)	12.2 (XL)	<8

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; eGFR; estimated glomerular filtration rate; Fib-4 score, Fibrosis-4 score; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; UACR, urinary albumin-creatinine ratio.

The association between NASH and metabolic syndrome is well known as is the lack of accurate biomarkers. People with type 2 diabetes have a two-fold higher risk for NAFLD compared with people without type 2 diabetes (3). The co-existence of NAFLD and type 2 diabetes is frequently occurring and the strong association between these two conditions seems to be bidirectional. Insulin resistance results in increased liver fat accumulation due to suppressed insulin-stimulated glycogen synthesis as well as insufficient suppression of hepatic gluconeogenesis. Although the exact underlying mechanisms are not fully understood, evidence shows that people with type 2 diabetes are more likely to develop NAFLD with advanced fibrosis, which is the most important prognostic factor for liver-related complications and mortality (6). Hepatic steatosis may also be associated with intestinal inflammation and small bowel surgery and could affect the development and progression of NASH (7).

To date, there are no approved medical interventions for NASH-cirrhosis. However, a placebo-controlled phase 2 trial recently showed that treatment with 0.4 mg semaglutide daily improved NASH resolution without worsening of fibrosis compared with placebo (8). This is currently being investigated in the ongoing ESSENCE trial: a randomized double-blind phase 3 study in patients with NASH (ClinicalTrials.gov/NCT04822181). It is also possible that treatment with SGLT2 inhibitor could further improve NAFLD (9). Although no pharmacological treatment is approved for NASH, early diagnosis is vital not only to identify and treat the underlying cause, if possible, but also to diagnose and initiate treatment for cirrhosis-related complications. The earlier the diagnosis of cirrhosis is made, the higher the potential for preventing and minimizing further damage to the liver. Thus, patients with cirrhosis should undergo screening for possible complications: ascites, esophageal varices, and hepatic encephalopathy.

A liver biopsy is the gold standard method for diagnosing and grading NAFLD. Non-invasive methods are used in the evaluation of fibrosis and steatosis. Ultrasound is often used as a first-line imaging technique for steatosis due to its availability, though magnetic resonance

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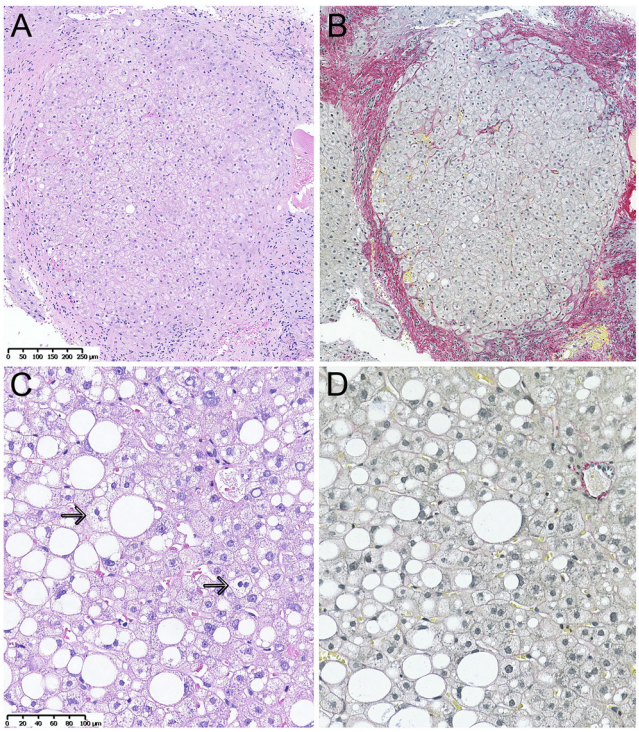

Figure 1
Serial sections of the patient's liver biopsy revealing cirrhosis and steatohepatitis. A: Cirrhotic liver, parenchymal nodule (hematoxylin and eosin). B: Same field as in A showing fibrotic fibers encircling the nodule (hematoxylin and picro sirius red). C: Another area in the cirrhotic liver showing pronounced macrovesicular steatosis and few cells with ballooning (arrows) (hematoxylin and eosin). D: Same field as in C, showing absence of perisinusoidal fibrosis (hematoxylin and picro sirius red). The sections are scanned with Hamamatsu Nanozoomer. A and B zoom factor ×7, C and D zoom factor ×20.

spectroscopy and MRI proton density fat fraction are considered more accurate (10). The FibroScan® is used for the evaluation of fibrosis and has the potential to be used as a screening tool in high-risk individuals in combination with blood tests to evaluate fibrosis such as the Fib-4 score and NAFLD fibrosis score (1).

Current guidelines from the European Association for the Study of the Liver, the European Association for the Study of Diabetes, and the European Association for the Study of Obesity recommend screening for NAFLD in patients with either type 2 diabetes or other components of the metabolic syndrome (1). It is suggested to begin with abdominal ultrasound in combination with liver enzymes. In case of abnormal biochemistry or fibrosis markers, referral to a hepatologist may be considered. In contrast, the American Association for the Study of Liver Diseases does not recommend routine screening due to concerns regarding the lack of effective approved treatments and diagnostic methods combined with uncertainties regarding the long-term benefits and costs (2).

The accuracy of diagnostic tests is a concern. Liver enzymes are often within the normal ranges in patients with NAFLD and the sensitivity of abdominal ultrasound is low (10). Consequently, more reliable methods when screening for NAFLD in high-risk populations are needed. The Fib-4 score and FibroScan® have a high negative predictive value (>90%), but both tests may be false positive and many patients, including the presented case, have values in the gray-zone area (4). The use of these methods as screening tools in primary care and specialist departments is yet unproven. Thus, finding individuals who would benefit from lifestyle intervention and screening for possible complications without overloading the healthcare system with too many false-positive findings is still a huge challenge.

In summary, this case emphasizes the challenges with identifying NASH with fibrosis in people with type 2 diabetes. As even the more severe stages of NAFLD might be masked due to medical treatment, normal biochemistry, or lack of symptoms, we believe that this case addresses a common but unnoticed problem. Thus, NASH-cirrhosis could most likely be diagnosed incidentally in many people – it is just all about how to find them at the right time.

Patient's perspective

'I participated in the clinical study about NAFLD and kidney function in patients with type 2 diabetes because I wanted to encourage and contribute to science. Given that my kidney function was normal I was told that I took part in the control group. Prior to inclusion, I was told a lot about the project, but as I did not have any symptoms related to the liver, I had no expectations that there was something wrong with my liver when I signed up for the study. Then, I had a FibroScan® performed, repeated three times. All pointing the same: there was scarring on my liver and they suspected that I had cirrhosis. Of course, I was really taken by surprise!

I was then referred to the hepatologists for some supplementary investigations. As the results from the FibroScan®, again, suggested that I had scar on the liver, I had a liver biopsy performed. This went well without any complications. Although I was prepared for it, it was still a bit surprising to hear what the biopsy had shown: that my liver was cirrhotic. Many questions ran through my head. What does this mean? Could I, or should I, have reacted before? Are my family members affected too? My questions were answered, and I was overwhelmed with thankfulness when the doctor invited not only my two grown-up children but also my own brother and sister for investigations, and luckily, none of them had any signs of liver disease. Then, my anxiety turned into curiosity instead and I now try to learn more about the disease every time I see my doctor.

I had no idea that the liver could be so damaged without giving any signs. So, although I still feel very well, being told that I have cirrhosis has definitely had an influence on me. I am much more aware of what I eat and drink, I try to keep a good balance between energy intake and energy expenditure, and I follow my doctors´ advice. Lastly, I am thankful and happy for being invited to the study which I enjoyed being part of. I have felt that I have been in the best hands through the whole process. I had never imagined that I could enter a study feeling that I helped others by contributing to science and then ending up being treated of superb specialists within the field'.

Declaration of interest

T A and M H have nothing to declare. F K K has served on scientific advisory panels and/or been part of speaker's bureaus for, served as a consultant to and/or received research support from the following companies producing and/or developing SGLT2 inhibitors and/or GLP-1RAs mentioned in the manuscript: AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD/Merck, Novo Nordisk and Sanofi. L.L.G, has received honoraria for lectures and/or presentations, and/or received payments for expert testimony, and/or served on advisory board, and/or received financial support for research from the following companies: Alexion, Gilead, Norgine, Novo Nordisk, Pfizer and Sobi Interntational.

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Patient consent

Written informed consent for publication of the patient´s clinical details and clinical images was obtained from the patient.

Author contribution statement

T A recruited the patient to the clinical study, performed examinations in the clinical study and wrote the first draft of the manuscript. M H was responsible for the clinical study. F K. K was responsible for the clinical management of the patient. L L G was responsible for the clinical management of the patient and critically supervised the draft manuscript. All authors critically revised and provided intellectual content to the case report described and approved the final version of the manuscript to be published.

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