Case 45

A 47-year-old woman presented with a 2-week history of abdominal distension. She had an 18-year history of type 2 diabetes, now controlled with insulin. She also had peripheral vascular disease with a left, below-knee amputation. There was no history of myocardial infarction, neuropathy, or retinal disease. Current medications were enalapril, atenolol, aspirin, amlodipine, and insulin. She drank <10 units/week of alcohol and denied ever having been a heavy drinker.

On examination, her pulse was 80bpm, blood pressure 150/80mmHg, and she was apyrexial. There were no stigmata of chronic liver disease. Ascites was present and there was pitting oedema to the sacrum. Her BMI prior to the ascites was 31kg/m^2.

Investigations showed:

- Hb 12.5g/dL, WCC 10.1 x 10^9/L, platelets 100 x 10^9/L
- Na 132mmol/L, K 3.5mmol/L, urea 6.3mmol/L, creatinine 87μmol/L
- Random blood glucose 8.7mmol/L
- Bilirubin 4μmol/L, AST 95 IU/L, ALT 70 IU/L, ALP 434 IU/L, GGT 40 IU/L, albumin 26g/L
- Ferritin 440μg/L
- Prothrombin time 14.0 sec
- Abdominal ultrasound: coarse liver texture, ascites, normal sized spleen
- Ascitic fluid analysis: albumin 4g/L, WCC <250 cells/mL, no malignant cells
- CA125 1052 IU/ml (normal range 0–30)
- CT of the abdomen: enlarged irregular liver, splenomegaly, patent portal vein.

Questions

45a) What is the differential diagnosis and what other serological blood tests are appropriate?

45b) What should be the next investigation?

45c) What is the natural history of this condition?

45d) Which patients should have a liver biopsy?

45e) How could the patient's liver disease have been prevented?

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Answers

45a) **What is the differential diagnosis and what other serological blood tests are appropriate?**

The differential diagnosis of ascites in this patient includes:

- Cirrhosis
  - Non-alcoholic fatty liver disease (NAFLD)
  - Alcoholic liver disease
  - Haemochromatosis
  - Autoimmune liver disease
  - Chronic viral hepatitis (B or C, see Cases 43 and 44)
  - Cryptogenic cirrhosis
- Right heart failure
- Ovarian cancer with peritoneal metastases.

This patient is likely to have **cirrhosis**, because there is thrombocytopaenia, hypoalbuminaemia, an elevated prothrombin time, and an abnormal appearance of the liver on both ultrasound and CT scan. The sensitivity and specificity, however, of ultrasound or CT for the diagnosis of cirrhosis is low. The patient is at particular risk of NAFLD because she has type 2 diabetes, obesity, and hyperlipidaemia. NAFLD is, however, a clinicopathological diagnosis that is made after the exclusion of other liver disorders.

The following aetiologies need to be excluded:

- Significant alcohol consumption (>20g/day ethanol)
- Haemochromatosis (although an elevated ferritin, usually <1000μg/L, is common in NAFLD)
- Chronic viral hepatitis
- Alpha-1 antitrypsin deficiency
- Autoimmune liver disease.

In NAFLD, it is the ALT and GT that are commonly abnormal, although a third of patients have cholestatic liver function tests with an elevated ALP and GT. The ALT is characteristically higher than the AST, in contrast to alcoholic liver disease. A high ALT/AST ratio reverses in the presence of cirrhosis. A low platelet count is common in cirrhosis.

It is important to exclude **right heart failure** as a cause of ascites, by examination (elevated jugular venous pressure, pulsatile liver), and by

echocardiogram. Our patient had no clinical signs of right heart failure and the echocardiogram was normal. It is also prudent to check that the hypoalbuminaemia is not caused by nephrotic syndrome. The patient's 24-hour urinary protein was <1g.

An elevated CA125 can occur in cirrhosis, although it is important to exclude **ovarian cancer**. No malignant cells were seen in the ascitic fluid (sensitivity 60–70%). The coarse liver texture on ultrasound and CT, the splenomegaly and low protein ascites with a serum ascites albumin gradient >11g/L, is characteristic of cirrhosis.

45b) **What should be the next investigation?**

This patient needs a **liver biopsy** (Figs 45.1 and 45.2 in the central colour section). Since the patient had ascites and a BMI >30kg/m^2, this was carried out via the transjugular route. Transjugular liver biopsy is appropriate in the presence of ascites, coagulopathy (PT prolonged >5 sec above the normal upper range) or platelets <60 x 10^9/L. Liver biopsy helps confirm the stage of cirrhosis and establishes the aetiology. The histological features of NAFLD associated with cirrhosis are those of non-alcoholic steatohepatitis (NASH). These include Mallory's hyaline, macrovesicular fat, and a chronic inflammatory portal infiltrate with interface hepatitis and a varying degree of fibrosis. The amount of fat in hepatocytes often declines as cirrhosis develops. The histopathological features are indistinguishable from alcoholic liver disease, so a clinical history is needed to differentiate the two conditions. Many cases of cryptogenic cirrhosis (i.e. unknown cause) are attributable to non-alcoholic fatty liver disease.

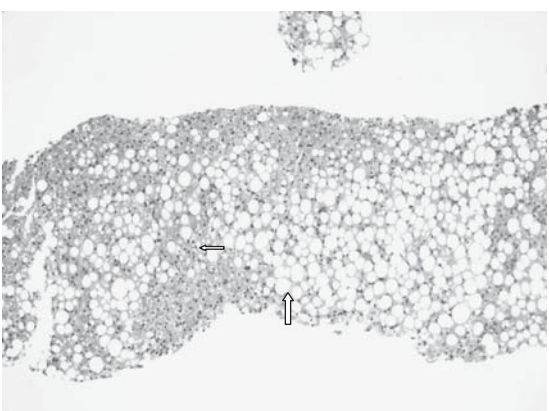

Fig. 45.1 (see colour plate 22) Liver biopsy in non-alcoholic fatty liver disease (low power) showing steatosis (large arrow) and interface hepatitis (small arrow).

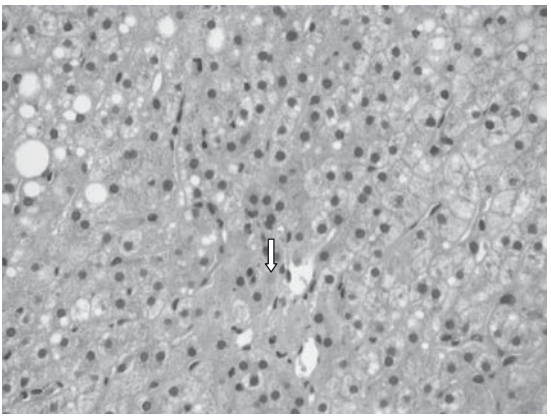

Fig. 45.2 (see colour plate 23) Liver biopsy in non-alcoholic fatty liver disease (high power) showing Mallory's hyaline (arrow).

45c) **What is the natural history of this condition?**

NAFLD can be separated on histopathology into simple steatosis and **non-alcoholic steatohepatitis** (NASH). Only NASH is associated with fibrosis and progression to cirrhosis. It typically presents with asymptomatic abnormal liver function tests. The prevalence of NAFLD is 3–7%. About a third of those with NASH will develop cirrhosis, although this may take several decades. NASH is associated with increased liver-related mortality.

Factors associated with more severe disease include:

- Obesity
- Type 2 diabetes
- Age >45 years
- Hypertriglyceridaemia
- The role of gender is contentious. Some studies suggest that female gender is an independent risk factor for more severe disease.

45d) **Which patients should have a liver biopsy?**

Patients who present with **cirrhosis of unknown cause** should have a liver biopsy. When a patient presents with abnormal liver function tests and NAFLD is suspected, a period of lifestyle modification is generally appropriate before biopsy. This means weight reduction for 3–6 months.

Biopsy is required for patients:

- in whom liver tests fail to correct after lifestyle modification
- >45 years of age

- with a BMI >30kg/m^2
- with type 2 diabetes
- with features suggestive of cirrhosis
- if ALT levels remain persistently above twice the upper level of normal.

45e) **How could the patient's liver disease have been prevented?**

This patient was always at high risk of NAFLD, because she had type 2 diabetes, obesity, and hypercholesterolaemia. She now presents with evidence of decompensated cirrhosis. If NASH had been diagnosed at an earlier stage, progression to cirrhosis would probably have been delayed by:

- **Improved diabetic control**: she is already on insulin and her control should be optimized. Although there is no evidence of a beneficial effect of metformin on hepatic fibrosis, it can be given in the presence of cirrhosis. The thiazolidinediones (such as pioglitazone) act on peroxisome proliferator-activated receptor gamma (PPARγ) to increase insulin receptor expression in adipocytes and hepatocytes. This can improve LFTs but can also increase body weight.
- **Weight loss**, which improves liver fibrosis even when severe.
  - Exercise (difficult in this particular case because of below-knee amputation and peripheral vascular disease)
  - Gastric banding has been shown to improve liver disease.
- **Abstinence** from alcohol, because alcohol aggravates steatosis and contributes to cellular damage.

Further reading

Ali R, Cusi K (2009). New diagnostic and treatment approaches in non-alcoholic fatty liver disease (NAFLD). *Ann Med*; **41**: 265–78.

Dixon JB, Bhathal PS, Hughes NR, O' PE (2004). Non alcoholic fatty liver disease: improvement in liver histological analysis with weight loss. *Hepatology*; **39**: 1647–54.

Garcia-Compean D, Jaquez-Quintana JO, Gonzalez-Gonzalez JA, Maldonado-Garza H (2009). Liver cirrhosis and diabetes: risk factors, pathophysiology, clinical implications and management. *World J Gastroenterol*; **15**: 280–8.