Question 89
A 45 year-old man with a family history of ischaemic heart disease is diagnosed with hypertension and hypercholesterolaemia. He is started on aspirin 150 mg daily, atorvastatin 20 mg nocte and atenolol 50 mg daily. Eight weeks later, he is reviewed and complains of some lethargy and itching. His blood pressure is 120/70 mmHg. He is noted to be icteric. There are no other findings on physical examination.

Blood investigations show:

- white cell count 5.6 x 10⁹/L [4.0-9.0]
- haemoglobin 142 g/L [130-175]
- platelet count 468 x 10⁹/L [150-450]
- prothrombin time-international normalised ratio (PT-INR) 1.0 [0.9-1.1]
- bilirubin 103 μmol/L [3-21]
- alanine transaminase (ALT) 610 U/L [5-40]
- aspartate transaminase (AST) 358 U/L [5-40]
- alkaline phosphatase (ALP) 540 U/L [30-115]
- gamma glutamyltranspeptidase (GGT) 746 U/L [<65]
- albumin 40 g/L [38-50]
- sodium 145 mmol/L [139-145]
- potassium 4.5 mmol/L [3.8-4.8]
- urea 3.8 mmol/L [2.5-5.6]
- creatinine 0.10 mmol/L [0.06-0.11]
- hepatitis B surface antigen negative
- hepatitis C antibody negative
- ferritin 356 μg/L [25-200]
- anti-nuclear antibody negative
- anti-mitochondrial antibody negative
- anti-smooth-muscle antibody negative

An abdominal ultrasound shows non-dilated bile ducts. The gall bladder is normal with no calculi. A liver biopsy is performed and two representative sections are shown over.

The most likely explanation for the abnormal liver function test results is:

A. atenolol.
B. atorvastatin.
C. non-alcoholic steatohepatitis (NASH).
D. autoimmune hepatitis.
E. primary biliary cirrhosis.
Clinical Presentation
This man has
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- abnormal LFTs with a mixed picture including raised bilirubin
- no radiological evidence of obstruction
- no evidence of other common causes of hepatitis, viral, autoimmune
- ferritin raised - ?significance acute phase reaction
- platelets slightly raised
- normal INR
- liver biopsy looks like an infiltrative process, similar to that seen in autoimmune hepatitis - non specific changes

A. atenolol. - incorrect

ADVERSE REACTIONS SIGNIFICANT
1% to 10%:
Cardiovascular: Persistent bradycardia, hypotension, chest pain, edema, heart failure, second- or third-degree AV block, Raynaud's phenomenon
Central nervous system: Dizziness, fatigue, insomnia, lethargy, confusion, mental impairment, depression, headache, nightmares
Gastrointestinal: Constipation, diarrhea, nausea
Genitourinary: Impotence
Miscellaneous: Cold extremities
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<1% (Limited to important or life-threatening): Alopecia, dyspnea (especially with large doses), hallucinations, impotence, liver enzymes increased, lupus syndrome, Peyronie's disease, positive ANA, psoriaform rash, psychosis, thrombocytopenia, wheezing

B. atorvastatin. – correct answer

ADVERSE REACTIONS SIGNIFICANT
>10%: Central nervous system: Headache (3% to 17%)

2% to 10%:
Cardiovascular: Chest pain, peripheral edema
Central nervous system: Insomnia, dizziness
Dermatologic: Rash (1% to 4%)
Gastrointestinal: Abdominal pain (up to 4%), constipation (up to 3%), diarrhea (up to 4%), dyspepsia (1% to 3%), flatulence (1% to 3%), nausea
Genitourinary: Urinary tract infection
Hepatic: Transaminases increased (2% to 3% with 80 mg/day dosing)
Neuromuscular & skeletal: Arthralgia (up to 5%), arthritis, back pain (up to 4%), myalgia (up to 6%), weakness (up to 4%)
Respiratory: Sinusitis (up to 6%), pharyngitis (up to 3%), bronchitis, rhinitis
Miscellaneous: Infection (3% to 10%), flu-like syndrome (up to 3%), allergic reaction (up to 3%)

C. non-alcoholic steatohepatitis (NASH). – Incorrect

- Nonalcoholic steatohepatitis (NASH) is the term used to describe the distinct clinical entity in which patients lack a history of significant alcohol consumption but have liver biopsy findings indistinguishable from alcoholic hepatitis
- Serum AST and ALT are elevated in almost 90 percent of patients. The AST/ALT ratio is usually less than 1
- A liver biopsy showing moderate to gross macrovesicular fatty change with inflammation (lobular or portal) and with or without Mallory bodies, fibrosis, or cirrhosis

Histologic changes in nonalcoholic steatohepatitis (NASH). Left panel: The hepatocyte in the center contains a large vacuole of fat and deeply staining eosinophilic strands of cytoplasmic hyalin. Numerous neutrophils and phagocytic cells containing golden brown pigmented material (bile components and cellular debris) are present in the sinusoids. Right panel: NASH with cirrhosis. Trichrome stain shows regenerating nodules with fat surrounded by fibrous tissue.

D. autoimmune hepatitis. – incorrect

- Autoimmune hepatitis is a chronic hepatitis of unknown etiology characterized by immunologic and autoimmunologic features, generally including the presence of circulating autoantibodies and a high serum globulin concentration
- Circulating autoantibodies commonly seen in type 1 autoimmune hepatitis are antinuclear, anti-smooth muscle, and/or antiactin antibodies.
In type 2 autoimmune hepatitis, ALKM-1 antibodies occur alone or accompanied by ALC-1 (LC1) antibodies or rarely ANA.

Autoimmune hepatitis is a chronic necroinflammatory disorder, with nonspecific biopsy findings.

Liver biopsy in autoimmune hepatitis showing portal and periportal mononuclear cell infiltration.

The portal tract is expanded by a mononuclear infiltrate; the limiting plate is disrupted; and the inflammatory process extends into the acinus. Staining by hematoxylin-eosin; original magnification x 200

E. primary biliary cirrhosis. - incorrect
  • Classic clinical picture, pruritus, hyperpigmentation
of the skin, and hepatomegaly in a woman with a cholestatic pattern of liver function tests are common in PBC but unusual in other liver disorders such as acute and chronic hepatitis and alcoholic liver disease.

- Antimitochondrial antibodies are the serologic hallmark of PBC. They are present in more about 95 percent of patients with PBC.
- Antinuclear antibodies (ANA) are found in up to 70 percent of patients with PBC.
- Classic liver biopsy

![Liver biopsy in primary biliary cirrhosis](image)

Low power view of liver biopsy in primary biliary cirrhosis. A damaged bile duct is visible in the center of an intense inflammatory cell reaction in an enlarged portal triad. The bile duct appears to be the target of this inflammatory reaction. Courtesy of Sanjiv Chopra, MD.
High power view of liver biopsy in primary biliary cirrhosis in the same patient showing a marked mononuclear cell infiltrate surrounding and destroying a bile duct. Courtesy of Sanjiv Chopra, MD.