Case studies

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Abstract
These four case studies were presented by Professor Sheila Sherlock to a panel of four expert hepatologists and a mixed audience of specialists. The response of the audience to a number of questions was monitored using an interactive key pad system. This response is presented in the form of bar graphs and is accompanied by comments from the expert panel.

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Case study number 1

BACKGROUND
A 50 year old business man had no serious illnesses until 1970, when he had a difficult cholecystectomy. The common bile duct was intubated. He was uncertain whether he had had a blood transfusion. In 1980, he had been in an automobile accident, when the spleen was said to be damaged. He thinks he did not receive a transfusion, or a splenectomy. In 1988, routine biochemical tests showed increases in serum transaminase activities and these have fluctuated since. He has no symptoms, there are no abnormal physical signs, and he has consumed only social quantities of alcohol.

Serum biochemistry tests in July 1990 were: aspartate aminotransferase (AST): 145 IU/L (40=upper limit of normal range (ULN)); alanine aminotransferase (ALT): 200 IU/L (40=ULN); albumin: 42 g/l (normal); gammaglobulolin: 25 g/l (slightly high). Other routine biochemical tests were normal.

The platelet count was 152 000 cumm, and the prothrombin time was normal. Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) were all negative. The anti-hepatitis C virus (HCV) c-100 (first generation ELISA) test was, however, positive.

QUESTION
If available, which diagnostic test(s) would you choose initially?

COMMENT
Professor Hadziyannis: I would have chosen a confirmatory test for anti-HCV positivity. The positive predictive value of the HCV test in this setting would be quite high.

QUESTION
If a second choice was available, what would you choose?

COMMENT
ProfessorHadziyannis: I would also carry out a test for autoantibodies routinely, particularly in this group of patients who have a highly increased gammaglobulin. The chances that this particular patient has autoimmune hepatitis are not very high, because of his age and sex, but type I autoimmune liver disease must be excluded with certainty on the grounds of serological testing for autoantibodies.
heavy infiltration in the portal tract which is the typical appearance of chronic hepatitis C. If I look 'inside' the lobule, I can see lobular inflammation in the centre and a little fat. This is clearly compatible with chronic hepatitis C.

**QUESTION**
Which treatment would you give this patient? Figure 3 – audience response.

**COMMENT**

*Professor Sherlock:* There is an overwhelming agreement for the use of interferon, but the real question is one of dose. Which dose of interferon would you prescribe, and for how long? Figures 4 and 5 – audience response.

*Professor Hadziyannis:* I would prescribe interferon 3 million units (MU) three times weekly for one year. In our experience, 3 MU for only six months has been associated with a very high number of relapses.

*Professor Trepo:* In France, regulations state that we have to start with 3 MU for six months, but I would follow this up with 2 MU for another six months, and then 1 MU for a further six months.

**Dr Perrillo:** I would treat with 3 MU interferon three times weekly for six months. In general, I am not convinced by the data advocating higher doses or a long term approach. I would like to mention, however, that in this case, the biopsy examination does not warrant a great need for treatment.

*Professor Nishioka:* I would give 3 MU interferon three times weekly for six months.

**FURTHER INFORMATION**
The patient received 3 MU three times weekly for one year. Transaminase activities fell within two months and remained normal for another five months (Fig 6). The patient had modest side effects after treatment with interferon. For the first two months he was tired and a little febrile.

**QUESTION**
How would you treat or prevent these side effects?

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**Figure 2** Liver biopsy specimen from case study number 1.

**Figure 3** Audience response.

**Figure 4** Audience response.

**Figure 5** Audience response.

**Figure 6** Changes in AST and ALT for case study number 1.
Comment

Professor Nishioka: We have tried giving interferon before bed time, and have used paracetamol for the flu like symptoms. In most people, the side effects disappear within a few weeks of treatment. In others, however, the side effects continue, and this is a real problem in practice. It is interesting to note that of the people who experience side effects, many suffer if the interval between doses is longer (for example, after the weekend). It may be better, therefore, to give interferon on alternate days rather than three times weekly.

Question

The transaminase activities rose eight months after treatment finished. The AST was 80 IU/l, and the ALT was 120 IU/l. What would you do, even though the patient is still symptom free?

Comment

Professor Nishioka: I would confirm the findings by at least three assays within 20–30 days apart. If there was a continuous increase, I would begin a new course of treatment of 3 MU three times weekly for one year.

Professor Trepo: I would negotiate long term treatment with the patient, given that he may experience more side effects.

Dr Perrillo: I would induce again his response with 3 MU three times weekly and attempt to control his ALT with a reduced dose for at least one year.

Professor Nishioka: I would repeat a three month course of treatment and, if there was no response, consider another course of treatment.

Professor Schiff: I would monitor throughout the course of treatment with HCV-RNA, and use this as my guide as to when to stop treatment.

Case study number 2

Background

A 30 year old dentist had felt generally unwell for four months. His appetite was poor, and he rested as much as possible. He was not on any particular treatment, did not abuse drugs, he was heterosexual, and did not travel abroad. He had not had a blood transfusion, and had not had a hepatitis B virus (HBV) vaccination. There was no family history of liver disease or hepatitis.

Biochemical tests showed the following: AST: 320 IU/l (40); ALT: 360 IU/l (40); bilirubin: 2mg/dl (34 SI units); alkaline phosphatase: 190 IU/l (130); albumin: 40 g/l; prothrombin time: normal. Serological tests showed the following: HBeAg +ve; hepatitis B e antigen (HBeAg) –ve; IgM HBcAb +ve; HBsAb –ve; IgA anti hepatitis A virus (HAV) +ve; IgM anti HAV –ve.

Question

Would you perform abdominal ultrasound or a computed tomography (CT) scan?

Comment

Professor Sherlock: I would prefer to use a CT scan, and would have put this before ultrasound. Which do you prefer?

Professor Nishioka: I prefer to use ultrasound.

Professor Schiff: If you are looking for chronic liver disease, then the CT scan is very useful because you can often see the subtle nodularity on the liver surface, an enlarged spleen, and even evidence of portal hypertension.

Question

Would you measure serum α fetoprotein?

Comment

Professor Hadziyannis: The α fetoprotein may be useful but could give misleading information. In this case, it would be useful as a baseline measurement, but high values should not lead to a diagnosis of hepatocellular carcinoma as they may also reflect liver cell regeneration.

Question

Would you measure the erythrocyte sedimentation rate (ESR)?

Comment

Professor Sherlock: Many patients can become very alarmed about the height of their ESR. In my opinion this test can create unnecessary anxiety.

Dr Perrillo: I can see no value in carrying out an ESR test in a patient who obviously has inflammatory liver disease.

Question

Would you measure the platelet count?

Figure 8 – audience response.
COMMENT
Professor Sherlock: If this patient had a low platelet count, would it change your use of interferon?
Dr Perrillo: I would assume that this patient might have some acute changes superimposed on chronic disease, and would monitor and wait a little longer before prescribing interferon.
Professor Triep: I would check the delta markers before proceeding. Whatever the results of these tests, I would consider interferon treatment.
Professor Hadziyannis: I would like to know the exact values of anti-HBc IgM.
Professor Sherlock: I would not perform an upper endoscopy as this may alarm the patient. What would you do?
Professor Nishioka: I recommend upper endoscopy as 60–70% of patients with active liver disease experience changes in the gastrointestinal tract (for example, gastric or duodenal ulcer, gastritis).
Professor Hadziyannis: I would not carry out upper endoscopy and would prefer to rely on good ultrasonography combined with the Doppler technique.
Professor Schiff: If I thought the patient had cirrhosis and established portal hypertension I would probably carry out upper endoscopy.

FURTHER INFORMATION
The results of the serological tests were as follows: IgM anti-delta –ve; anti-HCV (second generation ELISA) –ve; HBV-DNA +ve; HIV –ve; autoantibodies –ve. The diagnosis was chronic HBV (pre-core mutant).

QUESTION
Which dosage regimen of interferon would you give, and for how long? Figures 9 and 10 – audience response.

COMMENT
Dr Perrillo: Our standard regimen has been 5 MU daily, but I am not sure how this patient would react, so I would probably start on a three times weekly regimen and gradually increase to daily treatment. I would treat for a minimum of four and a maximum of six months. The DNA value could act as a guide to treatment. If the value of viraemia is high, the patient will probably require higher dosage.
Professor Triep: I would aim at 5 MU daily or 10 MU three times weekly.
Professor Hadziyannis: I would use an intermediate dose of 5 MU three times weekly. The data for six months’ treatment are associated with a high rate of relapse, so I would treat for 12 months or repeat the cycle.
Professor Nishioka: I would treat for six months using 5 MU daily, even though the six month regimen is still under consideration in Japan.

RESULTS AND CONCLUSIONS
Professor Sherlock: The patient was actually given 5 MU interferon three times weekly for three months after which the serum transaminase activities showed a satisfactory rise to 500 IU/l and then fell to 120 IU/l. The liver biopsy showed resolution of the acute changes, and the HBV-DNA became negative. Recent results in Hepatology^1 report the beneficial effects of interferon in HBc antigen negative, HBV-DNA positive chronic hepatitis. At 18 months, the HBV-DNA became negative and the transaminase activities returned to normal in 53% of patients treated with interferon, and 17% of the controls. This shows, therefore, that this pre-core mutant responds to interferon.

CASE STUDY NUMBER 3

BACKGROUND
A housewife, aged 52, was a carrier of haemophilia A (16 µ/dl factor VIII normal 50–250). Her son also had haemophilia. In 1984 she injured her knee. She had a very marked prepatellar haematoma and was given 200 donor units of cryoprecipitate. After eight weeks her serum transaminase activities started to rise (AST 90 IU/l, previously normal), and after nine weeks she had jaundice with a very high transaminase activity (AST 1930 IU/l), and a bilirubin of 7 mg/dl. HBV, HAV, Epstein-Barr virus and cytomegalovirus markers were all negative. She became encephalopathic with confusion, EEG slowing,
and a prothrombin time of 50 seconds, but recovered with conservative treatment. Transaminase activities, however, continued to fluctuate over the next six years. The patient was diagnosed as having non-A/non-B hepatitis, and subsequently she was found to be second generation ELISA HCV positive.

**QUESTION**

Would you perform a liver biopsy, yes or no? Figure 11 – audience response.

**COMMENT**

*Professor Triño*: I would perform a jugular vein liver biopsy, not the usual biopsy, and would take advice from a coagulation consultant.

**FURTHER INFORMATION**

The biopsy showed a mild chronic active hepatitis compatible with NANB. The changes in liver function tests are shown in Fig 12. In 1987 she was symptomatic with a transaminase activity of 150 IU/l, and was again found to be anti-HCV positive. She was given interferon and the results are shown in Fig 13.

**QUESTION**

ALT activities rose to 379 IU/l when treatment with interferon was stopped. What would you do now? Figure 14 – audience response.

**RESULTS AND CONCLUSIONS**

The interferon was, in fact, stopped. The patient was still symptomatic and still had fluctuating transaminase activities, so interferon was given again (5 MU three times weekly) in August 1990. Treatment with low dose interferon has been almost continuous between August 1990 and March 1992. The transaminase activities are normal.

**Case study number 4**

**BACKGROUND**

A housewife born in September 1928, complained of insomnia, fatigue, and weight loss (3 kg in six months). She did not experience pain or itching, and was not receiving any treatment. She had had a goitre when she was 25, a hysterectomy when she was 55, but has not had a blood transfusion. In June 1991, she complained of insomnia, and biochemical tests showed an increase in serum cholesterol. On examination, she did not have a goitre, was clinically euthyroid, and the liver and spleen were not palpable.

The serum biochemistry was as follows: bilirubin: 0.5 mg/dl (normal); alkaline phosphatase: 179 IU/l (130); AST: 47 IU/l (40); gamma GT: 948 IU/l (48); gammaglobulin: 10.6 g/l; cholesterol: 320 mg/dl. HAV, HBV, and HCV markers were all negative, and serum mitochondrial antibodies and thyroid antibodies were absent.

**QUESTION**

Which of the following would you perform initially? Figure 15 – audience response.
COMMENT

Dr Perrillo: I would opt for biopsy rather than ultrasound, given that this patient does not have evidence of obstructive disease in the biliary tree.

Professor Sherlock: We did, in fact, carry out a biopsy which showed the following appearance (Fig 16).

Dr Perrillo: The bile duct epithelium is not perfectly regular, and suggests primary biliary cirrhosis rather than chronic active hepatitis.

FURTHER DETAILS

The pathologist’s report of the biopsy specimen listed portal inflammation, lymphocytes, histiocytes, bile duct damage, and foci of piecemeal necrosis, which suggested early primary biliary cirrhosis. Lymphoma and chronic HCV were excluded. The patient was treated with ursodeoxycholic acid (600 mg daily) from August until November 1991. Her transaminase activities rose appreciably, gamma GT remained very high, and alkaline phosphatase values increased slightly. Her ANA was positive (1:2560), anti-actin smooth muscle was positive (1:1280), and M2 antibody specific for primary biliary cirrhosis was negative.

QUESTION

What would be your first choice of treatment at this point? Figure 17 – audience response.

Dr Perrillo: I would assume that the patient had received suitable treatment for primary biliary cirrhosis, presume that some autoimmune process was present, and begin treatment with corticosteroids.

FURTHER DETAILS

Prednisolone (10 mg daily) was started in December 1991, and the serum biochemistry is seen in the Table.

RESULTS AND CONCLUSIONS

The diagnosis was one of autoimmune cholangiopathy, an entity that has rarely been described. It is marked by the histological evidence of primary biliary cirrhosis, but the serology of active chronic hepatitis.
