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Acute Hepatitis in an Asthmatic Patient

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CASE DISCUSSION

History: A 26-year-old man presented to his family physician with a 5-day history of lethargy, anorexia and tea-coloured urine. He was referred to the Accident and Emergency Department of Singapore General Hospital for further evaluation.

This patient has a past history of childhood asthma but he has been well for the past 12 years. Four weeks prior to admission, he had symptoms of upper respiratory tract infection fever, cough and sorethroat, for which he was given tab paracetamol, tab vitamin C and syrup cough mixture. He returned to his family physician at the end of the week with complaints of persistent cough and dyspnoea which worsened in the nights. He was afebrile by then, but was found to have scattered rhonchi on auscultation. He was given a 5-day course of tab erythromycin and was put on regular treatment with sulbutamol inhaler. In addition, he was given prednisolone 30 mg every morning for his acute bronchial asthma. His dyspnoea and cough improved over the following week.

There was no history of recent travel, sexual exposure, blood transfusion or intravenous abuse. He did not consume any Chinese medicine or alcohol.

On examination, the patient was conscious and rational. He was jaundiced and lethargic. Two to three spider naevi were found on his chest. He was not in respiratory distress; no rhonchi was heard on auscultation; the breath sound was normal; the liver and the spleen were not palpable and there was no ascites, ankle oedema or asterixis.

Question: What are your differential diagnoses?
Answer: The most likely diagnosis is acute viral hepatitis. The differential diagnosis that one should consider is drug-induced liver disease. In this case, erythromycin is a possible culprit as it is known to cause jaundice and hepatitis. However, with the use of newer preparation (eg erythromycin stearate), the incidence of erythromycin-induced liver disease has decreased. We should check with the family physician to find out which formulation was prescribed.

Question: What appropriate investigation would you order?
Answer: Full blood count, liver function test and prothrombin time and viral markers for acute viral hepatitis A and B, namely, anti-HAV IgM, HBs Ag, anti-HBc IgM. Other viral markers, hepatitis C (anti-HCV IgG), hepatitis E (anti-HEV IgG and IgM), CMV (anti-CMV IgM) and Epstein-Barr virus (anti-EBV IgM), may be considered at a later stage should the markers for viral hepatitis A and B be negative.

Hepatitis A and E are transmitted by oro-faecal route, usually via ingestion of uncooked shellfish or contaminated water. Hepatitis B and C usually occur post-blood transfusion. CMV and EBV hepatitis normally manifest as part of a systemic infectious mononucleosis-like illness with lymphadenopathy and splenomegaly. Drug-induced jaundice would be likely if there was associated eosinophilia and the viral markers were negative.
Question: Could you comment on these results?

Total protein	68 g/L
Albumin	35 g/L
Bilirubin	85 μmol/L(N < 21)
Alkaline phosphatase	142 U/L(N < 103)
Alanine transaminase	784 U/L(N < 36)
Aspartate transaminase	564 U/L(N < 33)
Haemoglobin	14 g/L
Anti-HAV IgM	negative
HBs Ag	positive
Anti-HBc IgM	negative
Reticulocyte count	normal
White cell count	5400 x 10^6 /L (eosinophil count normal)
Platelet count	160 x 10^6 /L
Prothrombin time	14.0 secs (control 12.2 secs)
Alpha-fetoprotein	48 μg/L(N < 10)

Answer: The results indicate that the patient's hepatitis could be related to hepatitis B infection. However, the absence of anti-HBc IgM antibody would indicate that this patient did not have acute hepatitis B and he is probably a hepatitis B carrier. The cause of the acute hepatitis in this patient could be due to:
(1) superinfection by other viral hepatitides; or
(2) exacerbation of his underlying hepatitis B infection. The patient was given prednisolone prior to the acute exacerbation of hepatitis, this is a well-known cause of exacerbation of chronic hepatitis B, especially when given at high dose followed by a sudden withdrawal of treatment; or

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(3) a superimposed drug-hepatitis such as that caused by erythromycin. There was no eosinophilia (present in 50% of cases) in this case and the ALT was much too elevated than what one would expect. In addition, erythromycin-induced hepatitis usually occurs during treatment and improves after cessation of treatment; or

(4) an unrelated liver disease, such as Wilson's disease (rare). This may be associated with haemolysis which is absent in this case (normal haemoglobin and reticulocyte count). Low caeruloplasmin level and the presence of Kayser-Fleisher ring (to be examined under slit-lamp by the ophthalmologist) will support the diagnosis (Table I).

Table I – Causes of acute hepatitis in a hepatitis B carrier

1.	Superimposed viral hepatitis	– acute hepatitis A, C, D, E
		– acute CMV and EBV hepatitis
2.	Reactivation of underlying hepatitis B viral infection	
3.	HBe Antigen to anti-HBe IgG seroconversion event (immunological clearance)	
4.	Other causes of hepatitis (alcohol, drugs, Wilson's disease, etc)	

Raised alpha-fetoprotein may occur during hepatitis, but one should rule out the development of hepatocellular carcinoma, especially keeping in mind the patient's background of chronic hepatitis B. We have also observed that the alpha-fetoprotein level tends to rise during HBeAg to anti-HBe IgG seroconversion in a hepatitis B carrier.

Question: What are the other tests which would help to establish the diagnosis in this case?
Answer: (1) HBeAg, anti-HBe IgG, HBV DNA, other viral markers; (2) an ultrasonographic examination should be carried out to rule out the presence of any space-occupying lesion in the liver; and (3) a liver biopsy at a later stage, if all the above investigation results were negative. This will be the definitive investigation to distinguish between erythromycin-induced hepatitis and hepatitis B. There will be evidence of cholestasis, mild centrilobular (zone 3) parenchymal necro-inflammation and portal hepatitis in the former, whereas marked parenchymal necro-inflammation, ground-glass hepatocytes and positive staining of HBcAg will be seen in the latter.

Patient's progress: The patient had initial deterioration of his liver function with further elevation of his ALT and prolongation of his prothrombin time, but subsequently improved over the following 3 – 4 weeks with supportive treatment. The prothrombin time normalised. On subsequent follow-up, his ALT fluctuates between 2 – 3 times the normal range and he remains positive for HBsAg, HBeAg and HBV DNA.

Final diagnosis: Chronic hepatitis B with acute exacerbation post-withdrawal of steroid therapy (prednisolone).

Question: What is the subsequent management for this patient?

Answer: The patient has chronic hepatitis B. In view of his persistently elevated transaminase levels and the presence of positive HBeAg, anti-viral treatment such as interferon or alpha-1 thymosin should be offered to the patient with the objective of achieving anti-HBe seroconversion and normalising the transaminase level.

DISCUSSION

Treatment with corticosteroids followed by its withdrawal is well-known to give rise to exacerbation of chronic hepatitis B caused by heightened immunological activity in an attempt of immunoclearance of the virus[1,2]. This is associated with potentially fatal outcome[3]. In Singapore where we have a hepatitis B carrier rate of approximately 6%, it is important that we are aware of such consequence in the use of steroids in hepatitis B carriers.

Corticosteroids may be prescribed for an appropriate cause in our day-to-day clinical practice. We should make it a routine to enquire for past and family history of hepatitis B whenever the indication for the use of steroids arise. As most of our hepatitis B carriers acquire their infection perinatally by vertical transmission, a positive family history of hepatitis B is frequent among our hepatitis B carriers. A baseline HBs Ag should be done before or at the time of steroid therapy. While steroid therapy should not be withheld for the treatment of life-threatening conditions despite the presence of positive HBsAg, gradual withdrawal of steroid therapy with close monitoring of the hepatic function should be carried out in these cases. Unnecessary use of systemic corticosteroids should be avoided in hepatitis B carriers.

Erythromycin is a relatively benign drug. Its association with hepatic complications is uncommon with the currently available preparations. Nevertheless, one should be aware of its side-effects which is probably immune-mediated[4]. It usually gives rise to cholestatic type of hepatitis. Treatment is expectant. Resolution of hepatitis usually follows cessation of treatment. Diagnosis can be made based on history with appropriate time-course relationship. Liver biopsy is usually not required for diagnosis except in complicated cases, as in this case.

This case is used to illustrate the work-up of a case of hepatitis in a young man, and to remind us of the risk of exacerbation of hepatitis in a hepatitis B carrier by rapid withdrawal of steroid therapy.

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