CASE REPORT

Non-Hodgkin's lymphoma: a cause of paraneoplastic cholestasis

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SUMMARY

We describe a 79-year-old gentleman with a longstanding history of chronic lymphocytic leukaemia who presented with subacute onset of cholestatic jaundice. Comprehensive review of the patient's data and medications failed to reveal any obvious causes. Exhaustive testing including abdominal CT and magnetic resonance cholangiopancreatography failed to reveal any obstruction. A liver biopsy demonstrated scattered non-caseating granulomas. The patient was diagnosed with granulomatous hepatitis and treated with oral steroids and eventually improved. It was thought to be due to paraneoplastic cholestasis as an extrahepatic manifestation of non-Hodgkin's lymphoma.

BACKGROUND

This case serves to highlight a review of the important considerations to be made in the patient with non-Hodgkin's lymphoma presenting with cholestatic jaundice. In such instances, a comprehensive history in addition to the detailed review of culprit medications and over-the-counter supplements must be performed. Imaging should be obtained to elicit direct or indirect evidence of cholestasis either as demonstrable pathology or biliary dilatation. Where such findings are absent, endoscopic retrograde cholangiopancreatography/magnetic resonance cholangiopancreatography (ERCP/MRCP) has a greater sensitivity in detecting more subtle lesions. Not uncommonly, lymphoma can infiltrate into the liver and a liver biopsy may be warranted to exclude this. In spite of an exhaustive work-up, we were unable to find an obvious cause. In such circumstances, the clinician may be hard pressed to find an explanation. We encountered such a predicament, thus prompting a review of the relevant literature and the entity known as 'idiopathic paraneoplastic cholestasis'.

CASE PRESENTATION

A 79-year-old man with a 30-year history of chronic lymphocytic leukaemia (CLL) presented to the outpatient haematology clinic for a regular surveillance visit. While in the office, his nurse noted that his skin looked yellow. Further history revealed that he had been having generalised pruritus, 'tea-coloured' urine and pale loose stools in the previous week. He was otherwise completely asymptomatic and denied any change in appetite or well-being. His remaining medical problems included diabetes mellitus that was well-controlled on insulin, and a history of kidney stones. His only other medications included low-dose daily aspirin

and losartan for hypertension. His family history was significant for throat cancer in his father and breast cancer in one of his sisters. He was admitted for further evaluation. A comprehensive laboratory testing was performed. The viral hepatitis profile was negative. Initial labs were as follows: aspartate aminotransferase (AST) 137 IU/l, alanine aminotransferase (ALT) 203 IU/l, total bilirubin 13.9 mg/dl, direct bilirubin 11.6 mg/dl and alkaline phosphate (ALP) 458 IU/l. It appeared that his liver synthetic function was doing well as his international normalised ratio (INR) was 1.0. A CT of the abdomen/pelvis with contrast was performed (see figure 1) and showed a lymph node mass in the gastrohepatic ligament, 4.5×3.3 cm, and a paraaortic lymph node, 3.4×2.0 cm, both unchanged from the previous imaging. Importantly, there were no evident hepatic lesions or evidence of biliary dilatation. To further evaluate for biliary obstruction, an MRCP was performed and showed intrahepatic bile and pancreatic ducts that were normal in calibre and appearance. Drug-induced cholestatic liver disease was considered though he did not endorse any recently started medications or herbal supplements. Given the history of CLL, there was interest in seeing if the patient possibly had lymphoma that had spread into the liver. Other infiltrative causes including amyloidosis, sarcoidosis and fungal infections were also considered, prompting a liver biopsy. The biopsy (refer to figure 2) showed cholestasis with mild bile ductule proliferation in addition to occasional non-caseating granulomas. There was no evidence of involvement by a lymphoproliferative disorder, however. Given the persistent diarrhoea, he was prescribed ursodiol for presumed bile salt deficiency from cholestasis. He was started on a low dose of prednisone, and discharged home.

INVESTIGATIONS

Over the next few weeks, the itching resolved, but he remained deeply jaundiced and had unintentionally lost more than 20 pounds in weight. He was treated with steroids and finally tapered for a total of 10 weeks of treatment. Repeat liver function tests (LFTs) remained elevated although he was no longer jaundiced: AST 112 IU/l, ALT 96 IU/l, ALP 536 IU/l, total bilirubin 4 mg/dl, direct bilirubin 3.6 mg/dl, γ -glutamyl transferase 1081 IU/l. Repeat positron emission tomography/CT images were obtained and showed interval increase in size and fluoro-D-glucose (FDG) hypermetabolism of the conglomerate lymph node mass within the portohepatic/gastrohepatic region. In addition, multiple

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Figure 1 The abdominal CT showed no evident focal liver lesions or biliary dilatation. A large conglomerate of lymph nodes in the gastrohepatic region is seen measuring about 4.5×4.3 cm, unchanged from previous imaging.

airspace opacities within the left lung, predominantly at the perihilar region, demonstrating increased FDG hypermetabolism. The patient had not received cytotoxic chemotherapy for the CLL to potentially account for these findings. ACE levels were drawn and found to be elevated, suggesting possible sarcoidosis in light of his other findings. A bronchoscopy with washings and transbronchial biopsies was performed and found to be normal. Over the next few months, his symptoms resolved and he regained the lost weight. Repeat LFTs had normalised completely (refer to graph in figure 3) and repeat PET/CT images showed stability of the previously seen lymph nodes.

DIFFERENTIAL DIAGNOSIS

- ▶ Drug-induced cholestatic liver disease.
- ▶ 'Missed' malignant infiltration within the liver.

Figure 2 In this liver biopsy, normal architecture with mild expansion of the portal triads is noted. Mild proliferation of the interlobar bile ductules is observed, few of which are surrounded by neutrophils. This feature raises a concern for biliary outflow obstruction. The occasional granulomas which are present, are not centered on the bile ducts. These are non-caseating and negative for acid-fast bacteria and fungi.

OUTCOME AND FOLLOW-UP

The patient was followed for over a year and continues to be seen regularly in the haematology clinic. He has not had recurrence of his symptoms or deterioration in his clinical condition with regard to his CLL.

DISCUSSION

Lymphoma may cause jaundice by both infiltration within the liver or by obstruction at the porta hepatis,^{1–3} but there was no evidence on the biopsy of lymphoma within the liver or on imaging. The pathophysiological basis of cholestasis in these circumstances is unknown. A cholestatic form of jaundice has been described in association with lymphoma as an extrahepatic manifestation, presumably related to the release of a cholestatic factor. It is an extremely rare phenomenon, but well described throughout the years in the literature.^{4–8} Given its rarity, we were unable to find any previous cases in which steroids were used for the treatment of lesions.

Learning points

- ▶ To review a rational diagnostic approach in the patient presenting with jaundice.
- ▶ To review the important differential diagnoses in the patient with non-Hodgkin's lymphoma and concomitant jaundice.
- ▶ To recognise the role of liver biopsy in establishing idiopathic paraneoplastic jaundice as an aetiology since it is a diagnosis of exclusion.

Contributors ZA reviewed the literature. HD took care of the patient and collected the relevant information. AA wrote the case. VD supervised the project, proofread the final case report and took care of the patient in clinic.

Figure 3 Changes in patient's liver functions tests over time.

Competing interests None.

Patient consent Obtained.

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