Rare disease

Vanishing bile duct syndrome in a HIV patient on HAART therapy

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Summary

Vanishing bile duct syndrome refers to a group of disorders characterised by progressive destruction of the intrahepatic bile ducts resulting in cholestasis. It is a final common pathway for many disorders. The diagnoses is mainly made by histological findings. To consider a diagnosis there should be loss of interlobular bile ducts in more than fifty per cent of small portal tracts provided that the specimen contains at least 10 portal tracts. Here the authors present a case of vanishing bile duct syndrome which developed after initiation of highly active antiretroviral treatment therapy.

CASE PRESENTATION

Our patient is a 43-year-old Hispanic male with a long history of untreated HIV and asthma who was admitted for recurrent headaches secondary to toxoplasmosis and neurosyphilis. He was treated with penicillin and pyrimethamine-sulfadiazine which improved his symptoms. The HIV viral load on admission was 91000 copies/ml and the CD4 count was 15 cells/cu.mm. Patient was started on highly active antiretroviral treatment (HAART) therapy with atazanavir, ritonavir and tenofovir/emtricitabine. Two weeks after initiating HAART therapy he was found to have an acute hepatitis with an alanine transaminase (ALT) of 1058 IU/l, aspartate aminotransferase (AST) of 357 IU/l, alkaline phosphatase (ALP) of 417 IU/l, total bilirubin of 10.5 mg/dl and direct bilirubin of 8.7 mg/dl. His international normalised ratio was 1.0. The renal functions remained normal. The patient was asymptomatic. The hepatitis A, B and C serologies were negative and an ultrasound of the liver and biliary system was normal. His hepatitis was thought to be drug induced and antiretroviral agents were briefly discontinued. Other medication

changes included a switch from sulfadiazine to clindamycin for the toxoplasmosis. His transaminases started to come down but bilirubin levels remained elevated.

INVESTIGATIONS

Three weeks later, after HAART was reinstituted without atazanavir, his bilirubin levels continued to rise without elevation of the transaminases. His ALT was 154 IU/l, AST 96 IU/l, total bilirubin 14.6 mg/dl and direct bilirubin 10.9 mg/dl. His ALP was 403 IU/l. A MRI of the abdomen did not reveal any abnormalities and an endoscopic retrograde cholangiopancreatography (ERCP) was performed. The common bile duct measured 6 mm but otherwise the ERCP did not reveal any evidence of AIDS cholangiopathy. The biopsies and brushings were unremarkable. Additional blood tests including a search for other possible viral causes of hepatitis such as cytomegalovirus were unremarkable.

A month later, the patient was re-admitted to the hospital as his total bilirubin continued to climb and was 23.4 mg/dl while the direct bilirubin was 19.5 mg/dl. His transaminases were in the 60's and ALP was 363 IU/l. A liver biopsy

Figure 1 Histopathological appearance of the liver biopsy. The picture on the left is a H&E stain under lower power and it shows absence of bile ducts. The one on the right is a cytokeratin stain and it shows only one intact bile duct with disruption of others.

was performed to rule out infiltrating disorders. It showed intrahepatic cholestasis with no evidence of inflammation (figure 1). Also there was a notable absence of bile ducts. Cytokeratin 7 stain showed only one intact bile duct in the entire specimen,¹ that confirmed the diagnosis of vanishing bile duct syndrome.

OUTCOME AND FOLLOW-UP

The patient's HAART treatment was discontinued and later restarted with a regimen involving different medications. The bilirubin levels improved and had stayed normal since then. Also his HIV has been well-controlled with the new regimen.

DISCUSSION

The diagnosis of vanishing bile duct syndrome is made by histopathological examination. The disappearance of the bile ducts is a common mechanism for different diseases due to multiple pathologies.² Conditions which initiate this kind of bile duct destruction could be congenital, idiopathic, toxin or drug induced, infectious, neoplastic or immunologic.^{3–5} In our patient, there was no evidence of any infectious or neoplastic process as evidenced by the serological testing, viral amplification methods and the biopsy. He was negative for antibodies that would make us think of autoimmune causes as a reason for the ductopenia.^{6–9} Also there is a strong temporal relationship between initiation of HAART therapy and the elevation of his bilirubins. Although he had other medications which could be hepatotoxic, none of them were given for a time long enough to cause the damage and he continued to show worsening of his liver function despite stopping those drugs. It is well known that atazanavir causes hyperbilirubinemia via competitive inhibition of a key enzyme involved in bilirubin conjugation and patients with Gilbert's syndrome are more likely to develop jaundice and severe hyperbilirubinemia when exposed to atazanavir than those who do not.¹⁰ Our patient did not have evidence for Gilbert's syndrome.

Learning points

- To our knowledge, this is the first case of vanishing bile duct syndrome where it is highly suggestive that one or all of the components of the patients HAART regimen was responsible for the vanishing bile duct syndrome. Though we were not able to narrow down to a single drug, we believe that this case would make clinicians aware of the possibility of vanishing bile duct syndrome in any patient taking HAART therapy and we hope that further experience with antiretroviral therapy would help us in finding the specific drugs.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Nakanuma Y**, Tsuneyama K, Harada K. Pathology and pathogenesis of intrahepatic bile duct loss. *J Hepatobiliary Pancreat Surg* 2001;**8**:303–15.
2. **Woollf GM**, Vierling JM. Disappearing intrahepatic bile ducts: the syndromes and their mechanisms. *Semin Liver Dis* 1993;**13**:261–75.
3. **Ludwig J**, Wiesner RH, LaRusso NF. Idiopathic adulthood ductopenia. A cause of chronic cholestatic liver disease and biliary cirrhosis. *J Hepatol* 1988;**7**:193–9.
4. **DeBenedet AT**, Berg CL, Enfield KB, *et al*. A case of vanishing bile duct syndrome and IBD secondary to Hodgkin's lymphoma. *Nat Clin Pract Gastroenterol Hepatol* 2008;**5**:49–53.
5. **Liangpunsakul S**, Kwo P, Koukoulis GK. Hodgkin's disease presenting as cholestatic hepatitis with prominent ductal injury. *Eur J Gastroenterol Hepatol* 2002;**14**:323–7.
6. **Wee A**, Ludwig J. Pericholangitis in chronic ulcerative colitis: primary sclerosing cholangitis of the small bile ducts? *Ann Intern Med* 1985;**102**:581–7.
7. **Ludwig J**. Small-duct primary sclerosing cholangitis. *Semin Liver Dis* 1991;**11**:11–7.
8. **Murphy JR**, Sjogren MH, Kikendall JW, *et al*. Small bile duct abnormalities in sarcoidosis. *J Clin Gastroenterol* 1990;**12**:555–61.
9. **Agostini C**, Adami F, Semenzato G. New pathogenetic insights into the sarcoid granuloma. *Curr Opin Rheumatol* 2000;**12**:71–6.
10. **Lacerda MA**, Ludwig J, Dickson ER, *et al*. Antimitochondrial antibody-negative primary biliary cirrhosis. *Am J Gastroenterol* 1995;**90**:247–9.

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