Viral Infections of the Biliary Tract

Ekta Gupta, Anita Chakravarti

Department of Microbiology, Maulana Azad Medical College (MAMC), New Delhi, India

Address:
Dr. Ekta Gupta, Department of Microbiology, Maulana Azad Medical College (MAMC), Bhadur Shah Zafar Marg, New Delhi - 110 002, India.
E-mail: ektagaurisha@gmail.com

ABSTRACT

Bacterial infections of the biliary tract are often considered to be an important cause of acute cholangitis. Viral infections of the biliary tract however, are very often mistaken as viral hepatitis. This article highlights various viral causes of common biliary tract infections. Viral cholangitis is both less common and less discussed than viral hepatitis. Hepatotropic viruses (A, B, C, and E) are generally regarded as hepatocellular pathogens, yet cholangitic manifestations are now well described in association with these diseases. Systemic viral diseases also lead to cholangitis in varying proportion to hepatitis. Human immunodeficiency virus is associated with protean hepatic complications, including cholangitis due to several causes. Other systemic viruses, most notably those of the herpes virus family, also cause hepatic disease including cholangitis and possibly ductopenia in both immunocompromised and immunocompetent patients.

Key Words: Biliary tract, viral infections, review, cholangitis, cholangiopathy, hepatitis, infection, virus

Received 22.01.2008, Accepted 21.02.2008
The Saudi Journal of Gastroenterology 2008 14(3): 158-60

Biliary tract infections are characterized by acute cholecystitis - an acute inflammation of the gall bladder wall, and cholangitis - an inflammation of the bile ducts. Infection is generally secondary to predisposing factors. Ascending cholangitis is usually due to bacterial infection of the biliary tract. It results from bile stasis due to chronic obstruction, usually by stones. Biliary obstruction due to gallstones causes up to 80% of all cases of acute cholangitis. Not all obstructing lesions are followed by biliary infection. For example, only about 15% of patients with neoplastic obstruction develop cholangitis. The likelihood of infection seems greatest when the duct has acquired a resident bacterial population. Obstruction causes an increase in the ductal pressure. The bacteria proliferate and escape into the systemic circulation via the hepatic sinusoids. The manifestations of sepsis may overshadow those of hepatobiliary disease, causing acute suppurative cholangitis.[1] Viral cholangitis is less common and less discussed than bacterial cholangitis. Hepatotropic viruses (A, B, C, and E) are generally regarded as hepatocellular pathogens, yet cholangitic manifestations are now well described in association with these diseases. Systemic viral diseases also lead to cholangitis in varying proportion to hepatitis. Human immunodeficiency virus (HIV) is associated with protean hepatic complications, including cholangitis of several causes. Other systemic viruses, most notably those of the herpes virus family, also cause hepatic disease including cholangitis and possibly ductopenia in both immunocompromised and immunocompetent patients. This review highlights various viral causes of biliary tract disease.

PATHOPHYSIOLOGY

The main factors in the pathogenesis of bacterial cholangitis are biliary tract obstruction, elevated intraluminal pressure, and infection of the bile. Biliary obstruction diminishes host antibacterial defenses, causes immune dysfunction, and subsequently increases small bowel bacterial colonization. Although the exact mechanism is unclear, it is believed that bacteria gain access to the biliary tree by retrograde ascent from the duodenum or from portal venous blood. As a result, infection ascends into the hepatic ducts, causing serious infection. Increased biliary pressure pushes the infection into the biliary canaliculi, hepatic veins, and perihepatic lymphatics, leading to bacteremia (25-40%). The infection can be suppurative in the biliary tract.[2] These infections are mostly polymicrobial, i.e., involving more than one pathogenic organism. Gram-negative enteric organisms such as *Escherichia coli*, *Enterobacter* spp., *Klebsiella* spp., and *Pseudomonas* spp are commonly encountered; gram-positive bacteria (e.g., *Enterococcus* spp.) are less common.[3,4]

In viral cholangitis, inflammation of the biliary tract is either due to direct tissue invasion especially by hepatotropic viruses or due to immune complex-mediated cell destruction or as a result of secondary bacterial infection. Fungal infections are rare and usually secondary to biliary instrumentation or are observed in immunocompromised patients.[5]

INFECTION OF THE BILIARY TRACT BY HEPATOTROPIC VIRUSES

Among hepatotropic viruses, hepatitis C is more frequently associated with cholangitis. In both hepatitis B and C, the lymphocytic cholangitis duct damage is reversible and does not adversely influence the course of disease or response to

therapy. Despite causing clinical cholestasis, hepatitis A and E do not result in severe cholangitis.

Hepatitis C Virus Infections

Hepatitis C has become the prototypic viral hepatitis with cholangitic lesions, which are mostly intraepithelial lymphocytic infiltrations[6] and lymphoid aggregates or follicle formations usually without duct damage. These virus-associated cholangitic lesions are reversible and do not lead to permanent destruction or ductopenia. Despite this reversibility, structural damage including inflammation-associated diverticula formation, has been demonstrated. Clinically, these patients do not usually have increased serum alkaline phosphatase levels. Prognosis and response to therapy are not associated with the presence of biliary lesions. Hepatitis C viral particles have been reported within a small number of cholangiocytes in a minority of the cases.[7] It is unclear whether hepatitis C-associated cholangitis results from direct viral invasion or is an immune-mediated, hepatitis-associated phenomenon.[8]

Hepatitis B

In hepatitis B infection, the histologic lesions are essentially indistinguishable from those described in hepatitis C but are present in a smaller percentage of the cases. Approximately a quarter of hepatitis B biopsy samples show portal lymphoid aggregates or follicles and <10% reveal bile duct damage. Hepatitis B surface and core antigens have also been demonstrated in cholangiocytes in a minority of the cases.[9]

Hepatitis A and E

Hepatitis A and E do not lead to chronic hepatitis. Although biopsy specimens are not commonly obtained, lymphocytic cholangitis is not typically seen with these viruses. Canalicular cholestasis is seen with both of these infections but is secondary to physiologic bile flow impairment without anatomic or morphologic correlations.

CHOLANGITIS ASSOCIATED WITH SYSTEMIC VIRUSES

Human immunodeficiency virus

Human immunodeficiency virus-related cholangitis/cholangiopathy (also termed acquired immunodeficiency syndrome (AIDS) cholangitis or AIDS-related sclerosing cholangitis) is a well-recognized late complication of AIDS. Sixty percent of the cases can be attributed to infectious causes, while the remaining 40% have no identifiable cause.[10] Many infectious agents including Cytomegalovirus (CMV), *Cryptosporidium*, *Campylobacter*, *Candida albicans*, *Klebsiella pneumoniae*, *Microsporidia*, and Reovirus type 3, have been reported to cause cholangitis in AIDS patients.[11,12] Cytomegalovirus and *Cryptosporidium* are the most frequently reported pathogens.[13] Various pathogenic mechanisms have been postulated, including opportunistic organisms directly producing the biliary lesions, development of biliary lesions due to immune deficiency phenomenon, and direct cytopathic effects of the HIV on the biliary tract mucosa. HIV with resultant AIDS serves as the prototype for hepatobiliary disease in immunocompromised patients. Although hepatitis is very frequently present along with AIDS, biliary disease has typically been uncommon but is being recognized with increasing frequency. Characteristic biliary changes include common bile duct papillary stenosis, sclerosing cholangitis, long extrahepatic bile duct strictures, and combinations of these findings. Clinical findings accompanying AIDS-related biliary disease include abdominal pain, cholestasis without jaundice, and intestinal cryptosporidiosis. Radiographic changes are more characteristic than the histologic changes in AIDS cholangiopathy. The possibility of primary HIV cholangitis remains unconfirmed. In light of the high incidence of secondary infections and the lack of evidence for HIV localization to biliary epithelium, primary HIV cholangitis seems less likely than a role for yet-to-be-described secondary infectious agents. AIDS-related cholangiopathy is a harbinger of late-stage disease and portends a poor prognosis.

VIRAL CHOLANGITITS IN IMMUNOCOMPETENT INDIVIDUALS

Immunocompetent patients experience hepatitis with numerous systemic viral illnesses, particularly CMV and Epstein-Barr virus. Liver involvement in these systemic viral infections is typically asymptomatic or clinically mild, and liver enzyme abnormalities including elevated serum alkaline phosphatase or bilirubin, represent the only clinical signs of hepatitis. The histology typically shows hepatocellular damage and bile duct damage is unusual. However, in congenital or perinatal CMV hepatitis, ductal damage and ductular proliferation may be seen. These histologic changes can simulate biliary atresia. Other viruses suggested as potential etiologic agents in biliary atresia, include Reovirus type 3 and Rotavirus (groups A and C). Although viruses are suspected to have pathogenic roles in biliary atresia, the problem remains to be investigated in detail.

CONCLUSION

Viral infections of the biliary tract are less common and less discussed as compared to bacterial infections. Viral infections are usually secondary to the infection either of the liver or as a part of the systemic viral illness. Primary infection of the liver by viruses is rare. Cholangitis, i.e., the inflammation of the bile duct, is a common manifestation. Viral cholangitis occurs in several distinct settings, including chronic viral hepatitis caused by hepatitis B and C, in association with systemic viral infection in immunocompromised patients and direct invasion by systemic viruses in neonates. Identification of systemic viruses in immunocompromised patients allows the consideration of appropriate intervention

and exclusion of surgically curable biliary obstruction. Viral (CMV) cholangitis in neonates is important in terms of possible therapeutic intervention and understanding the pathogenesis of infantile ductopenic syndromes.

REFERENCES

1. Rosh A, Manko J. Cholangitis. *eMedicine.com*. 2006.
2. Kinney TP. Management of ascending cholangitis. Gastrointest Endosc Clin North Am 2007;17:289-306.
3. Shivaprakasha S, Harish R, Dinesh KR, Karim PM. Aerobic bacterial isolates from choledochal bile at a tertiary hospital. Indian J Pathol Microbiol 2006;49:464-7.
4. Flores C, Maguilnik I, Hadlich E, Goldani LZ. Microbiology of choledochal bile in patients with choledocholithiasis admitted to a tertiary hospital. J Gastroenterol Hepatol 2003;18:333-6.
5. Kulaksiz H, Rudolph G, Kloeters-Plachky P, Sauer P, Geiss H, Stiehl A. Biliary candida infections in primary sclerosing cholangitis. J Hepatol 2006;45:711-6.
6. Lefkowitch JH, Schiff ER, Davis GL, Perrillo RP, Lindsay K, Bodenheimer HC Jr, *et al.* Pathological diagnosis of chronic hepatitis C: A multicenter comparative study with chronic hepatitis B. Gastroenterology 1993;104:595-603.
7. Nouri-Aria KT, Sallie R, Mizokami M, Portmann BC, Williams R. Intrahepatic expression of hepatitis C virus antigens in chronic liver disease. J Pathol 1995.175:77-83.
8. Kim SR, Imoto S, Taniguchi M, Kim KI, Sasase N, Matsuoka T, *et al.* Primary sclerosing cholangitis and hepatitis C virus infection. Intervirology 2005;48:268-72.
9. Delladetsima JK, Vafiadis I, Tassopoulos NC, Kyriakou V, Apostolaki A. HBcAg and HBsAg expression in ductular cells in chronic hepatitis B. Liver 1994;14:71-5.
10. Keaveny AP, Karasik MS. Hepatobiliary and pancreatic infections in AIDS: Part one. AIDS Patient Care STDS 1998;12:347-57.
11. Bouche H, Housset C, Dumont JL, Carnot F, Menu Y, Aveline B, *et al.* AIDS-related cholangitis: Diagnostic features and course in 15 patients. J Hepatol 1993;17:34-9.
12. Kumar M, Murthy A, Duggal L, Sud R. AIDS associated cholangiopathy. Trop Gastroenterol 1998;19:155-6.
13. Lizardi-Cervera J, Luis E, Ramírez S, Luis Poo J, Uribe M. Hepatobiliary diseases in patients with human immunodeficiency virus (HIV) treated with non highly active anti-retroviral therapy: Frequency and clinical manifestations. Ann Hepatol 2005;4:188-91.

Source of Support: Nil, **Conflict of Interest:** None declared.