

## Introduction

### Definition:

The term cholangitis means localized or diffuse inflammatory changes of different aetiology, affecting the intrahepatic and extrahepatic bile ducts. Cholangitis can be acute or chronic; it may originate as a primary disease in the bile ducts or develop as secondary concomitant cholangitis in the course of another underlying disease. Forms of cholangitis which exclusively affect the intrahepatic bile ducts generally give rise to the clinical picture of liver disease (*Chan F.K.L. et al., 2000*).

### Aetiology:

The bile is sterile under physiological conditions. Pathophysiological events can cause asymptomatic bacteriocholia, which is of no clinical importance. Microorganisms are verifiable in bile in 75-100 % of patients with obstruction of the large bile ducts where as this applies only to 0-10 % of patients with obstruction due to pancreatic carcinoma (*Chan F.K.L. et al., 2000*).

Diagnostic or therapeutic endoscopic interventions in the bile ducts are often followed by bacterial cholangitis, attributable to the importation of microorganisms, particularly as a result of a (usually temporary) hindrance of bile flow (*Carpenter H.A., 1998*).

Cholangitis caused by infection is not a separate entity. Initially, ascending cholangitis has to be considered on account of its pathogenetic development. This condition originates in the gallbladder, duodenum or pancreas (*Thompson J. et al., 1994*).

Moreover, the bile ducts are liable to infection by bacteria or parasites as a consequence of cholestasis (*O'Connor M.J. et al., 1982*), (*Sung J.Y. et al 1992*).

Descending cholangitis is considered to be less frequent, with the infection descending from a chronically infected gallbladder or from a primary infection of the liver, for example in the case of salmonellosis (*Csendes A. et al., 1992*).

An infection of the bile ducts may cause pyogenic cholangitis, which can take an acute, relapsing or chronic course, the later mainly being caused by a hindrance of bile flow (*Davis J.J. et al., 1987*), (*Teixidor H.S. et al., 1991*).

Depending on the time taken for an obstruction to develop, obstructive cholangitis manifests as either acute or chronic disease. In the case of obstruction, the increase in intraductal pressure ( $> 15\text{-}20\text{ cm H}_2\text{O}$ ) causes a cholangiovenous or cholangiolymphatic reflux of bacteria or endotoxins into the blood circulation. As a result, signs of systemic and, in severe cases, septic disease appear. Toxic cholangitis may be triggered by chemicals, medicaments or toxins. Furthermore, there is also the clinical picture of immunological cholangitis. This form includes (1.) primary biliary cholangitis, (2.) primary sclerosing cholangitis, (3.) autoimmune cholangitis, and (4.) overlap syndromes (*Arnold J.C. et al., 1992*), (*Lim J., 1991*), (*Chan F.k.L. et al., 1989*).

## **Cholangitis**

### **1-Infectious cholangitis**

#### **A-Bacterial cholangitis**

Based on the number of reported cases, bacterial cholangitis is by far the most frequent type. It can take an acute, relapsing or chronic

course, and it may have a purulent (pyogenic, suppurative) or non suppurative form. There are four routes for bacteria, and hence infection, to spread: (1.) ascending, (2.) descending, (3.) periductular lymphogenetic, and (4.) in the case of sepsis, via the hepatic artery. In general, bacteriocholia only results in cholangitis in the case of disrupted bile flow (*Rush O. et al., 1980*), (*Gigot J.F. et al., 1989*), (*Lo C.M. et al., 1996*), (*Thompson J. et al., 1994*).

### **B-Parasitic cholangitis**

*Ascaris lumbricoides*, *Clonorchis sinensis*, *Lambliia intestinalis*, *Fasciola hepatica*, *Opisthorchis felinus* and *viverrini*, *Lymnaea trunculata*, *Cryptosporidium*, etc. have been identified as parasitic causes of cholangitis. The development of cholangitis is mainly due to a hindrance of bile drainage. During their migration into the biliary tree, parasites may physically introduce bacteria into the bile ducts, which often lead to secondary bacterial cholangitis (*Carpenter H.A., 1998*), (*Danilewitz M. et al., 1996*).

### **C-Mycotic cholangitis**

Various fungi have also been found to cause (obstructive) cholangitis, e.g. *Cryptococcus neoformans*, *Candida* *Microsporidium* (*Carstensen H. et al., 1986*), *Blastomyces* (*Ryan M.E. et al., 1989*).

### **D-Viral cholangitis**

Viral cholangitis is less common and less discussed than viral hepatitis. This does not diminish the importance of bile duct damage in the diagnosis, treatment, and understanding of viral liver disease. Hepatotropic viruses (A, B, C, and E) are generally regarded as hepatocellular pathogens, yet cholangitic manifestations are now well described as part of 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. These situations will be discussed in terms of histologic diagnosis and disease biology (*Nouri-Aria K.T. et al., 1995*), (*Bucuvalas J.C. et al., 1985*).

### **Cholangitis Associated with Hepatotropic Viruses:-**

*Poulsen* and *Christoffersen* in 1969 described histologic bile duct lesions in liver biopsy samples that otherwise had morphologic changes of viral hepatitis, Although their patient population no doubt contained cases of autoimmune hepatitis, the observation of cholangitic lesions in viral hepatitis has been consistently reaffirmed in patients serologically confirmed to have a hepatotropic viral infection. As with immune-mediated cholangitic lesions, it is bile ducts of 50- to 70- $\mu$ m diameter that appear to be targeted (*Poulsen H. et al., 1969*).

*Ludwig* and associates divided nonsuppurative cholangitic lesions into four morphologic types (granulomatous, lymphoid, fibrous, and pleomorphic) and looked at each in terms of sensitivity and specificity as to disease type. Their work demonstrated a 6 to 9% prevalence of lymphoid aggregates or follicles in both chronic biliary disease and chronic hepatitis, including viral and autoimmune hepatitis. Pleomorphic (lymphocytic) hepatitis without lymphoid aggregates was present with much higher incidence in primary biliary cirrhosis and primary sclerosing cholangitis but was still noted in a minority of chronic hepatitis biopsy specimens. Although fibromatous cholangitis was noted in chronic hepatitis samples described by *Ludwig* and

colleagues, fibro-obliterative or granulomatous lesions were present only in biliary disease. Therefore, although granulomatous and fibro-obliterative cholangitis are specific for chronic biliary disease, lymphocytic cholangitis occurs across the spectrum of liver disease (*Ludwig J. et al., 1984*), (*Pol S. et al., 1993*).

### **Hepatitis C**

Hepatitis C has become the prototypic viral hepatitis with cholangitic lesions. Approximately a third of biopsy specimens from patients with hepatitis C show bile duct damage, usually with intraepithelial lymphocytic infiltration. Up to half the hepatitis C biopsy samples show portal lymphoid aggregates or follicles, obviously without duct damage in some cases. The duct lesions have been shown to be 30 to 60  $\mu\text{m}$  in length although usually much larger in girth. These viral-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. Prognosis and response to therapy are not associated with the presence of biliary lesions (*Lefkowitz J.H. et al., 1993*).

### **Hepatitis B**

Hepatitis B is the focus of much less attention than hepatitis C with respect to biliary lesions. The histologic lesions are essentially indistinguishable from those described in hepatitis C but are present in a smaller percentage of studied cases. Approximately a quarter of hepatitis B biopsy samples show portal lymphoid aggregates or follicles, and less than 10% reveal bile duct damage. Hepatitis B surface and core antigens have also been demonstrated in cholangiocytes in a small minority of cases. Zone I hepatocytes

sustaining severe necroinflammatory damage may undergo ductular metaplasia, retaining viral particle antigenicity while assuming the morphology of ductules. This metaplasia complicates immunophenotypic studies of cholangiocyte viral load (*Delladetsima J.K. et al., 1994*).

### **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 (*Bouche H. et al., 1993*).

## **CHOLANGITIS ASSOCIATED WITH SYSTEMIC VIRUSES:-**

### **Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome:**

HIV with resultant acquired immunodeficiency syndrome (AIDS) serves as the prototype for hepatobiliary disease in immunocompromised patients. Although hepatitis is present with high frequency in AIDS, biliary disease is uncommon but recognized with increasing frequency (*Teixidor H.S. et al., 1991*), (*Davis J.J. et al., 1987*), (*Schneiderman D.J. et al., 1987*).

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. Secondary infections have been implicated etiologically in a third to a half of the investigated cases. The most commonly identified pathogens are Cytomegalovirus, Cryptosporidia, and Microsporidia. 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 (*Lou H.Y. et al., 2003*), (*Pol S. et al., 1993*).

### **Orthotopic Liver Transplantation**

Patients who undergo orthotopic liver transplantation suffer biliary stricturing that is predominantly noninfectious. These patients are at risk for opportunistic infections in general, but not to the degree of patients with AIDS because of less severe immunosuppression. Cytomegalovirus (CMV) hepatitis is by far the most common infectious complication. Several investigators have reported a possible link between CMV hepatitis and ductopenic chronic orthotopic liver transplant rejection (vanishing bile duct syndrome) (*O'Grady J.G. et al., 1988*), (*Paya C.V. et al., 1992*).

### **Immunocompetent Subjects**

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 sign of hepatitis. The histology typically shows hepatocellular damage, and bile duct damage is unusual (*Burgart L.G., 1998*), (*Ludwig J. et al., 1984*).

An exception to the rule is congenital or perinatal CMV hepatitis. Unlike immunocompetent adults, these infants have characteristic viral inclusion bodies; the remainder of the histology ranges from neonatal hepatitis to portal hepatitis with ductal damage and ductular proliferation. These histologic changes can simulate biliary atresia (*Ko W.F. et al., 2003*), (*Pol S. et al., 1993*). In fact, there has been conjecture that CMV may be involved in true cases of infantile cholestasis with paucity of bile ducts (*Einsele H. et al., 1994*), (*Finegold M.J. et al., 1982*).

Other viruses suggested as potential etiologic agents in biliary atresia include reovirus type 3 and rotavirus (groups A and C). These associations do not appear simple or unifactorial. Enrichment of specific HLA haplotypes in patients with biliary atresia strongly suggests immune predisposition. Although viruses are suspected to have a pathogenetic role in biliary atresia, the problem remains complex (*Bouche H. et al., 1993*), (*Castiella A. et al., 1998*), (*Da-Silva F. et al., 1993*).

## ***2-Obstructive cholangitis***

An obstruction in the bile ducts does not always result in cholangitis; however, a disorder of bile drainage is considered to be a



prerequisite for the manifestation of cholangitis (*Danilewitz M. et al., 1996*), (*Kawada N. et al., 1996*), (*Yoon H.K. et al., 1997*).

Oriental cholangiohepatitis:

This particular type of cholangitis was first described by *K.DIGBY* in 1930. It develops from the formation of calcium bilirubinate stones, especially with intrahepatic localization. It is mainly found in China, Japan, Malaysia and Taiwan. (*Harris H.W. et al., 1998*), (*Khuroo M.S. et al., 1993*), (*Stain S.C. et al., 1995*).

### **3- Toxic cholangitis**

Toxic (especially sclerosing) cholangitis has been attributed to the effects of aromatic amines. Likewise, this condition can be caused by lithocholic acid (*Fukuzumi S. et al., 1990*), (*Pokorny C.S. et al., 1992*), (*Schmitt M. et al., 1997*), (*Sebagh M. et al., 1995*).

It may also be triggered by various medications acting as facultative toxins, e.g. allopurinol, antibiotics, carbamazepine, phenylbutazone, tolbutamide. Such a type sometimes occurs after intra-arterial administration of cytostatics and as a result of burn injuries. (*Fukuzumi S. et al., 1990*), (*Hohn D. et al., 1985*).

## **Clinical aspects**

### **Acute cholangitis:**

The acute course is initially diagnosed clinically. It is characterized by **Charcot's triad**: (1.) sudden onset of pain (epigastric, right sided), (2.) fever (also with shivers), and (3.) jaundice (*J.M. Chacot, 1877*: "intermittent gall fever"). This triad was expanded by *B.M. Renold et al. (1959)* to a pentad, which points to septic cholangitis: (4.) confusion, and (5.) coagulation disorder, occasionally with the development of disseminated intravascular coagulopathy

(DIC) (*Lo C.M. et al., 1996*), (*O'Connor M.J. et al., 1982*), (*Thompson J. et al., 1994*).

Suppurative cholangitis:

Pyogenic (suppurative) cholangitis has the most severe course with a very poor prognosis (*Lee C.S. et al., 1993*), (*Leung J.W.C. et al., 1989*).

**Chronic cholangitis:**

The symptomatology is bland particularly in older people. Younger people mostly suffer from a chronic relapsing course. Clinical symptoms include pain in the right upper abdomen, possibly also inappetence and nausea as well as occasionally verifiable hepatomegaly (*Chan F.K.L. et al., 2000*), (*Csendes A. et al., 1992*), (*Gogel H.K. et al., 1987*).

## Morphology

**Acute cholangitis:**

Thickened bile-duct walls with inflammatory infiltration as well as focal ulcerations are found histologically. The portal fields are expanded by oedema and reveal pericholangiolar and intracholangiolar infiltrations from leucocytes (*Pokorny C.S. et al., 1992*), (*Takada T. et al., 1996*).

**Chronic cholangitis:**

This disease shows dilated, proliferated, peripherally located ductules, which contain concentrated bile with degenerative epithelial changes. Large numbers of polymorphonuclear leucocytes are verifiable in the lumen and in the bile-duct wall; leucocytic infiltrations spread to the neighbouring parenchyma (*Ramalho L.N.Z. et al., 2002*), (*Schneiderman D.J. et al., 1987*).

## **AIM OF THE WORK**

To collect recent data about viral infection and their effect on bile ducts.

To show that both hepatotropic and non hepatotropic viral infections can induce cholangitis.