

## Juvenile DOIVDOSIS

Juvenile polyps of the duodenum are rare and nearly always occur in the context of a more widespread gastrointestinal juvenile polyposis. Clinical features and neoplastic risk are less significant, although there is a case report of a duodenal carcinoma occurring in a patient with familial juvenile polyposis. Most of the polyps resemble the more common sporadic juvenile polyp of the colon, being round and smooth-surfaced pedunculated lesions. They consist of cystically dilated, small intestinal-type glands, lined by unremarkable goblet cells, absorptive cells, endocrine cells and Paneth cells. The background is an exuberant, rather inflamed lamina propria, devoid of smooth muscle (7).

## Cronkhite-Canada syndrome

Cronkhite-Canada syndrome is characterized by multiple polyps of the entire gastrointestinal tract in association with characteristic skin and nail changes. It is an extremely rare acquired sporadic condition. Gastrointestinal involvement is often revealed by protein and electrolyte loss. Duodenal polyps are found in 75% of patients and tend to be smaller in number and size than those of the stomach. They show superficial similarities to JP polyps but are usually small and more diffuse and can be differentiated easily by the associated ectodermal changes.

Microscopy shows normal villi but also flat areas with prominent crypt openings. There is flattening of the epithelial surface cells. The crypts can be elongated, irregular and cystic. The cysts are lined by attenuated epithelium. A mixed inflammatory infiltrate can be observed in the lamina propria which is edematous and thickened (9).

## Malignant lymphomatous (lymphoid) Polyposis and benign lymphoid polyposis

Lymphomatous polyposis (Mantle cell type malignant lymphoma) is an uncommon disease which may affect any part of the gastrointestinal tract. Macroscopically the mucosa shows multiple, fleshy polyps of variable size. The smallest lesions consist of a single mucosal lymphoid nodule, diffusely replaced by lymphoma sometimes with preservation of the reactive follicle center. It must be distinguished from reactive lymphoid hyperplasia.

## References

1. Sew-Choen E, HoJMS, Won9 J et al. Gross and histologic abnormalities of the foregut in familial adenomatous polyposis. *Colorect Dis* 1992; 7:177-183.
2. Sarre AG, Frost AG, Jagelman DG et al. Gastric and duodenal polyps in familial adenomatous polyposis: A prospective study of the nature and prevalence of upper gastrointestinal polyps. *Gut* 1987; 28: 306-314.
3. Spigelman AD, Williams GB, Talbot IC et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. *Lancet* 1989; ii: 783-785.
4. Vasan HFA, Bijlow M, Myrhoi T et al. Decision analysis in the management of duodenal adenomatosis in familial adenomatous polyposis. *Gut* 1997; 40: 716-719.
5. Kashiwagi H, Spigelman AD, Talbot IC et al. Overexpression of p53 in duodenal tumours in patients with familial adenomatous polyposis. *Br J Surg* 1996; 83: 225-228.
6. Attanoos A, Williams GT. Epithelial and neuroendocrine tumors of the duodenum. *Sam in Diagnostic Pathology* 1991; 8:149-162.
7. Jasa JA, Williams GB, Bussey HJR. Juvenile polyposis: A precancerous condition. *Histopathology* 1988; 13: 619-630.
8. Marth T, Schmitt Gräff A, Zimmer T et al. Gastrale hamartome und schildrüsenkarzinom mit folliculärer und neuroendokriner Differenzierung bei Cowden-Syndrom. *Z Gastroenterol* 1996; 34: 30-35.
9. Jenkins D, Stephenson PM, Scott SB. The Cronkhite-Canada syndrome: An ultrastructural study of pathogenesis. *J Clin Pathol* 1985; 38: 271-276.

## Extrahepatic biliary lesions

### G. Cathomas

Dept. of Pathology, University Hospital, Zürich, Switzerland.

### Gross anatomy and histology

The extrahepatic biliary tree includes the common hepatic duct emerging from the combined right and left hepatic ducts and continuing in the common hepatic duct after the fusion with the cystic duct. The common hepatic duct is about 5-6 cm long and drains through the papilla into the duodenum. The gallbladder is about 10 cm long and shows considerable variation in size, depending on the amount of bile present. The surface epithelium of the gallbladder is composed of a single layer of tall columnar cells with basal oriented nuclei. In addition, "pencil-like" and basal cells can be observed. The muscular layer is composed of loosely arranged bundles of smooth muscle fibers that do not show a well-formed layer. The muscle bundles are separated by fibrovascular connective tissue. Herniation of the mucosa into the smooth muscle or the subserosal tissue is common and named Rokitansky-Aschoff sinuses. The adventitia, composed of connective and fatty tissue, vessels and nerves, is covered by serosa on the abdominal side. On the hepatic side, bile ducts (Luschka's ducts) are present in the subserosal connective tissue. The extrahepatic biliary tracts are lined by a single layer of tall epithelia similar to the gallbladder. The epithelium invaginates into the stroma forming the sacculi of Beale, which are surrounded by mucinous glands. The dense subepithelial stroma of the common bile duct usually shows no muscle fibers except in the intrahepatic and intraduodenal portion.

### Malformations

Malformations of the gallbladder are relatively rare and include the angulation of the fundus (Phrygian cap), septations, hourglass gallbladder, cysts, congenital diverticula and hypoplasia. Agenesis, with and without concomitant extrahepatic biliary atresia, as well as duplication or triplication, can occur. Although many of these malformations are clinically irrelevant, they are more often associated with gallstones. A variety of different types of bile duct cysts have been described, which occur either as solitary extrahepatic cysts, especially in the common bile duct, or as multiple intra- and extrahepatic cysts.

### Congenital extrahepatic biliary atresia

Congenital extrahepatic biliary atresia is a serious digestive disease in infants, defined by a localized obliteration of the extrahepatic bile duct at any point from the porta hepatis to the duodenum. The obstruction of bile flow leads to chronic cholestasis with rapidly progressive fibrosis and cirrhosis associated with common complications, including portal hypertension and even hepatocellular carcinoma. The incidence of biliary atresia has been estimated as one in 10,000 live births worldwide. However, epidemiological differences have suggested that environmental as well as genetic factors may be involved in the pathogenesis of the disease, including infections with cytomegalovirus and Reovirus 3. None of these have, however, been unequivocally associated with biliary atresia and it has been suggested that this disease may have several causes. Two forms have been distinguished. The postnatal form

accounts for about 65-90% of the cases and progresses after birth. The infants develop a progressive cholestatic disease after the resolution of the physiological jaundice. In the congenital form, present in 35-10%, an intrauterine onset has been suggested and there is basically an absence of bile duct remnants. In addition, many of these patients have associated congenital anomalies of the heart, digestive tract and spleen. Morphologically, granulation tissue, lymphocytic infiltrates and fibrosis are present in the bile duct remnants. Satisfactory postoperative bile drainage has been associated with the presence of a duct of more than 150 mm at the resection margin. However, this correlation has not been confirmed by all the studies. Liver biopsies reveal cholestasis, marginal bile duct proliferation, bile ductal cholestasis and multinucleated giant cells. Biopsies taken prior to 6 weeks, however, may only show unspecific, nondiagnostic features. Without surgical treatment, progressive portal fibrosis, nodular regeneration and complete cirrhosis develop within 6-18 months. However, following surgical treatment with Kasai portoenterostomy, long-term survival is about 60% at 5 years and 30% at 10 years, respectively and liver transplantation may be necessary.

### **Gallstones and cholecystitis**

Gallstones are extremely common with an estimated prevalence of 10% in the Western world. The main risk factors, which have been known for a long time, have recently been confirmed and include age, heredity, obesity, weight loss and diabetes mellitus. In addition, patients with liver cirrhosis have an increased risk of developing gallstones. The pathogenesis is complex and includes multiple factors, such as impaired gallbladder function, cholesterol hypersecretion, crystallization promoting factors and an increase in deoxycholate conjugates and the recycling rate of enterohepatic circulation. The primary defect, however, remains to be elucidated. Recently, the *Helicobacter* species has been detected in the bile and gallbladder tissue of patients with chronic cholecystitis. Although the *H. pylori*/bacteria species cannot be detected in all tissue samples of patients with gallstones, the concept that chronic infection may play a role in the development of gallstones is intriguing. The most common morphological finding in patients with gallstones is chronic cholecystitis; however, there is little correlation between the size and amount of stones and the inflammatory reaction. The inflammatory infiltrates, consisting primarily of mononuclear cells sometimes admixed with eosinophils, can be surprisingly mild. There is an increased thickness in the bladder wall by hypertrophied muscle and an increase of fibrous connective tissue. In addition, metaplasia of the mucosa can be observed, including the pyloric, and less commonly, the intestinal type.

A special form of chronic inflammation of the gallbladder is xanthogranulomatous cholecystitis, which sometimes clinically and macroscopically mimics malignancy. Morphologically, this type of inflammation is characterized by varying amounts of foamy histiocytes, plasma cells, lymphocytes cholesterol clefts and a giant cell reaction.

Acute cholecystitis is usually associated with gallstones. Although bacteria can be detected in the bile early in the clinical course in over 80% of patients, the primary event is thought to be a combination of increased intraluminal pressure with edema of the wall and secondary ischemia of the mucosa. The histology reveals an acute inflammatory reaction including edema, vascular congestion, hemorrhage and variable neutrophilic infiltrates.

Acalculous acute cholecystitis is found after trauma, severe burns and (nonbiliary) surgical procedures. Finally, a variety of

infectious agents and inflammatory processes can involve the gallbladder, including parasitic infections with *Ascaris lumbricoides*, *Schistosomiasis*, *Echinococcus*, *Malakoplakia* or *Cryptosporidium*, microsporidia and cytomegalovirus in AIDS patients.

### **Cholangitis**

Acute cholangitis, either in a nonsuppurative or suppurative form, is usually associated with biliary obstruction by either choledocholithiasis, tumors or extrabiliary processes. For the development of cholangitis, however, the combination of obstruction, bile stasis and bacterial infections seems to be necessary. Microscopically, the bile duct shows edema, neutrophil infiltrates and degenerative changes of duct epithelia. A special form of cholangitis is recurrent pyogenic cholangitis, described in the Far East and associated with parasitic infections, such as *Clonorchis sinensis*, and with an increased risk of developing cholangiocarcinoma.

Primary sclerosing cholangitis (PSC) is an idiopathic chronic inflammatory disease of the intra- and extrahepatic bile ducts. The disease is associated with inflammatory bowel disease in 50-70%, mainly with ulcerative colitis but also with Crohn's disease. There is a male predominance and the patients are usually between 25-45 years of age, although PSC has been described in children. Histologically, the extrahepatic ducts show, in a segmental way, nonspecific inflammatory changes and fibrosis. It is well established that PSC is associated with an increased risk for cholangiocellular carcinoma.

### **Biliary stricture**

Biliary obstruction, not associated with malignant tumors or PSC, is often caused by injury to the common bile duct. The most common type of trauma is previous surgery of the biliary tract, especially cholecystectomy. The wall of the duct involved is thickened and the lumen narrowed or occluded. The mucosa is often ulcerated with considerable inflammation and reveals major reactive epithelial atypia. The resulting biliary obstruction may lead to cholangitis and biliary cirrhosis.

### **Neoplastic lesions of the gallbladder**

Polyps of the gallbladder, generally defined as a protruding mass, include morphologically a variety of lesions. The most common are cholesterol polyps and adenomas. Cholesterol polyps are part of the manifestations of cholesterolemia, a condition characterized by lipid-containing macrophages in the lamina propria, known as strawberry gallbladder. This lesion has little clinical relevance except that it is often associated with gallstones and the two lesions may share a common pathogenesis. Adenomas are found in less than 0.5% of surgically removed gallbladders and are usually less than 2 cm in size. Microscopically, tubular and papillary adenomas of the pyloric, intestinal and biliary type are described and goblet cells, Paneth cells and squamous metaplastic changes can be present. Although, in analogy with colon cancer, an adenoma-to-carcinoma sequence has been proposed for the gallbladder, recent data do not support this concept. In practical terms, polyps of less than 10 mm are usually benign and progression to carcinoma has rarely been observed.

The incidence of carcinomas of the gallbladder shows considerable variation in different regions in the world, with the highest incidence reported in Latin American countries such as Chile, Mexico and Bolivia. In addition, cancer of the gallbladder is more

common in females and is clearly associated with gallstones. On the molecular level, gallbladder cancer and bile duct cancers frequently show overexpression of p53 and *bcl-2*, the latter being associated with resistance to apoptosis. In cholecystectomy specimens, carcinoma is found in 1-2%. Grossly, the tumor may be either infiltrating, sometimes barely visible, or polypoid. The most common type of carcinoma is a well to moderately differentiated adenocarcinoma and, as in the biliary tree, a variety of other histological types have been described.

The depth of tumor invasion is crucial for postoperative survival. pT1 tumors rarely show lymph node metastasis and the 5-year survival is 100%. In contrast, lymph node metastasis is present in 50% of pT2 tumors and the 3-year survival is 56% in pT2 tumors and 22% in pT3 tumors.

### **Extrahepatic bile duct carcinoma**

Extrahepatic bile duct carcinoma is less common than carcinoma of the gallbladder. An increased risk has clearly been associated in patients with inflammatory bowel disease and primary sclerosing cholangitis and up to 30% of patients with PSC have been reported to develop cholangiocellular carcinoma. Interestingly, smoking has recently been associated with a further increased risk for cholangiocarcinoma in patients with PSC. An increased risk has further been observed in patients with choledochal cysts and in those infected with flukes, such as *Clonorchis* and *Opisthorchis*, although the parasites more often cause intrahepatic cholangiocarcinoma. Finally, previous radiation therapy has been associated with cholangiocarcinoma. Grossly, the tumors can be classified into diffuse, polypoid and nodular types. Tumors located in the upper third of extrahepatic bile duct at the hilar region (Klatskin's tumor) were originally associated with a better prognosis, a view that is not shared by all authors. Microscopically, most tumors of the biliary tract are well to moderately differentiated adenocarcinomas. Other histological types, including signet ring cell, clear cell and mucinous adenocarcinomas, as well as adenosquamous and small cell carcinoma, have been described. Neuroendocrine markers can also be detected but the clinical significance of this finding remains to be elucidated.

### **References**

- Jessurun J, Albores-Sasvadra J. *Gallbladder and extrahepatic biliary ducts*. In: Damisov I, Linder J (Eds.). *Anderson's Pathology*, 10th ed., Mosby, St. Louis 1996; 1859-1890.
- Berquist A, Olaumann H, Persson B, Brooks U. *Risk factors and clinical presentation of hepatobiliary carcinoma in patients with primary sclerosing cholangitis: A case-control study*. Hepatology 1998; 27: 311-316.
- Fox GJ, Dewhirst FE, Shen Z et al. *Hepatic helicobacter species identified in bile and gallblader tissue from Chilean with chronic cholecystitis*. Gastroenterology 1998; 114: 755-763.
- Letkowitch JH. *Biliary atresia*. Mayo Clin Proc 1998; 73: 90-95.
- Holzhuch TR. *Newer pathogenetic concepts in cholesterol gallstone formation: A unitary hypothesis*. Digestion 1997; 58(Suppl. I): 29-32.
- Bates MD, Bucuvalas JO, Alonso MH, Ryckman PC. *Biliary atresia: Pathogenesis and treatment*. Semin Liver Dis 1998; 18: 281-293.
- Attili AF, Oapoccacia R, Cadrucci N et al. *Factors associated with gallstone disease in the MICOL experience*. Hepatology 1997; 26: 809-818.
- Boulton RA, Adams OH. *Gallbladder polyps: When to wait and when to act*. Lancet 1997; 349: 817.
- Moriguchi H, Tazawa J, Hayashi Y et al. *Natural history of polypoid lesions in the gallbladder*. Gut 1996; 39: 860-862.

## **Inflammatory and tumor-like lesions of the ampulla**

**R Bedossa**

Service d'Anatomie Pathologique, Hôpital Bicêtre, Le Kremlin-Bicêtre, France.

Although a wide variety of neoplastic lesions may involve Vater's ampulla, nontumoral lesions are relatively rare and mostly asymptomatic. However, when clinical symptoms occur, the diagnosis of tumor-like lesions of the ampulla can create a difficult challenge. Although malignant tumors have a relatively favorable prognosis after extensive surgical resection, such an approach is unnecessary in patients with tumor-like lesions of the ampulla. Therefore, an accurate tissue diagnosis is essential for the appropriate management of these patients. Endoscopic ultrasonography may help but it is generally considered that differentiation between a small ampillary localized tumor and an inflammatory process is difficult with endoscopic ultrasonography.

Inflammatory and tumor-like lesions of the ampulla include sclerosing odditis, probably the least controversial entity among inflammatory lesions of the papilla, Oddi's sphincter dysfunction and various hamartomatous lesions.

### **Odditis, scierosina odditis, Oddi's sphincter dysfunction**

Whether odditis is a myth or a reality has been debated (1). Data in the literature are scarce and controversial, coming essentially from Europe and South America. In most of these reports histopathological lesions are poorly described or even not illustrated.

The least controversial, albeit uncommon cause, of inflammatory ampillary stenosis is "sclerosing choledochitis" which was described for the first time by Floerchen in 1912. Similar lesions have subsequently been reported under various names, such as sclerosing odditis, stenosing odditis and papillitis. The histological basis of sclerosing odditis is rather confusing. Several authors have studied their histopathological features through papillary biopsies but their findings have been criticized because similar lesions have been described in papillae coming the autopsies of patients without any symptoms (2). In a personal series of 109 autopsies, 18 cases showed histological lesions of the ampulla consistent with the diagnosis of "odditis" but all of these cases were clinically silent and not significantly associated with pancreatic or biliary symptoms (3).

However, symptomatic cases of sclerosing odditis exist in which the clinical history and endoscopic appearance may show considerable overlap with a nonulcerating tumor (4). These patients complain of recurrent biliary and pancreatitis symptoms which generally need to be cured by an endoscopic or surgical approach. Papilla is usually normal but, in some cases, a prominent infundibulum or an enlarged inflammatory orifice might create suspicion. Dilatation of the common bile duct or the main pancreatic duct is usually observed by endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic biopsies show an inflammatory reaction with glandular hyperplasia and fibrosis. Despite progress in ERCP and endoultrasoundography, features and evolution are sometimes sufficiently disturbing that extensive surgery may be carried out.

It is now recognized that most of these cases of sclerosing odditis are secondary lesions related to biliary lithiasis. In a study by