

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 P5G. 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 (Klatskins 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.

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Inflammatory and tumor-like lesions of the ampulla

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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 ampullary 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. sclerosina 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 ampullary stenosis is "sclerosing cholechochitis" which was described for the first time by Floerchin 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 (EROP) and endoscopic biopsies show an inflammatory reaction with glandular hyperplasia and fibrosis. Despite progress in ERCP and endoultrasonography, 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

Leese *et al.*, six out of 11 patients with inflammatory pseudotumoral lesions of the papilla had gallstones although these were only rarely present in the common bile duct (5). This suggests that most cases of sclerosing odditis, if not all, are related to the passage of calculi through the ampulla resulting in inflammatory changes with pseudotumor formation. Whether primary sclerosing odditis exists remains controversial.

Oddi's sphincter dysfunction

Oddi's sphincter dysfunction is a rare but distinct entity related to a functional disturbance of the motility of Oddi's sphincter. A history of intermittent biliary and pancreatic symptoms is usually present in the absence of any gallstone or biliary lithiasis. Diagnosis relies mostly on radiologic and manometric data although there is controversy about the safety of these procedures (6). Most authors agree that this disease is neither related to sclerosing odditis nor to gallstones. To date there are no consistent reports of the histopathological basis of Oddi's sphincter dysfunction. When intraampullary biopsies have been performed, either no inflammatory lesions, or only mild ones, have been found (7). However, it is noteworthy that, in a significant number of cases, lesions initially considered as Oddi's sphincter dysfunction, after delayed or repeated intraampullary biopsies have been carried out, are revealed to be ampullary carcinoma (7).

The border between Oddi's sphincter dysfunction and sclerosing odditis might be not so clear-cut since some authors suggest that persistent Oddi's sphincter dysfunction might evolve to sclerosing odditis.

Hamartomatous lesions

Symptomatic hamartomatous lesions are rare, composed of a mixture of elements normally found in the papilla. Again, distinction between the normal and pathological features of ampullary mucosa is difficult to make on endoscopic biopsies.

Some cases are sufficiently symptomatic that surgery or endoscopic sphincterotomy must be performed. Hamartomatous lesions may present as sessile or villous polyps or small nodular lesions protruding in the papilla and sometimes covered by an ulcerative mucosa. Endoscopic findings are by no means pathognomonic and conventional forceps biopsies have a low diagnostic yield. Endo-

ultrasonography and large particle biopsy using an electrocautery snare have been shown to increase diagnostic accuracy and to favor conservative therapy.

At light microscopy, the lamina propria contains glands, some lined by mucous-secreting cells and others by absorptive cells and goblet cells. Thick bundles of smooth muscle course through the lamina propria in various directions, some of them forming whorls in which densely packed glandular elements are embedded. The stroma often contain inflammatory elements and dilated vessels. When the smooth muscle component is abundant, the lesion is an adenomyoma. Due to their variable histology, adenomyomas are often confused with different but similar entities, including ectopic pancreatic tissue, fibroadenoma and Brunner's gland hyperplasia. Brunner's gland hyperplasia consists of abundant Brunner's glands with atrophic villi and crypts in the adjacent mucosa. Specimens consisting solely of pancreatic acinar tissue and islet cells in the duodenal muscular wall or the submucosa should be considered as ectopic, aberrant or heterotopic pancreatic tissue.

In conclusion, symptomatic inflammatory and pseudotumoral lesions are relatively rare lesions that are sometimes hard to recognize on endoscopic biopsies, even after endoscopic sphincterotomy. The pathologist must always bear in mind the possible diagnosis of an unrecognized adenocarcinoma.

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