HUGH A. EDMONDSON, M.D.



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ARMED FORCES INSTITUTE OF PATHOLOGY

ATLAS OF TUMOR PATHOLOGY

Section VII—Fascicle 26

TUMORS OF THE GALLBLADDER AND EXTRAHEPATIC BILE DUCTS

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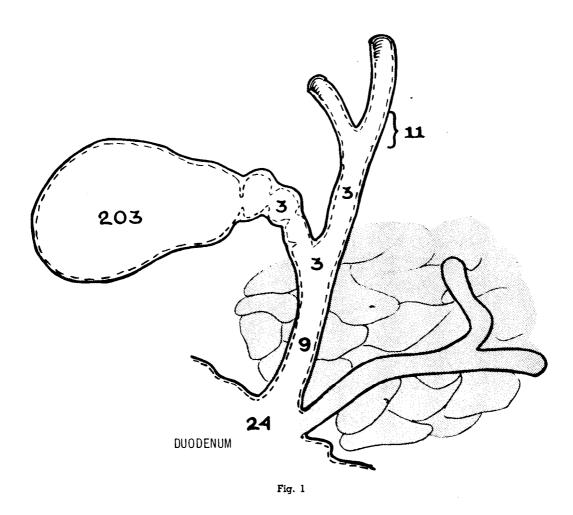


Figure 1. Frequency of carcinoma of the gallbladder and extrahepatic bile ducts in 56,000 autopsies performed at the Los Angeles County Hospital between 1918 and 1956. A.F.I.P. Acc. No. 219929-1.

INTRODUCTION

There are many difficult problems related to the etiology, diagnosis, and treatment of tumors of the gallbladder and extrahepatic bile ducts. Unlike most neoplasms, carcinoma of the gallbladder commonly arises in association with a curable disease, cholelithiasis. The frequency of cholelithiasis varies widely among various racial groups and between the sexes. Furthermore, in individuals with cholelithiasis there is a difference in susceptibility to carcinoma that is apparently related to race and sex. Neoplasms of the extrahepatic bile ducts, on the contrary, are rarely associated with choledocholithiasis. While a few attempts have been made to produce carcinoma of the gallbladder in experimental animals, similar studies on the extrahepatic ducts are almost nonexistent.

Carcinoma of the gallbladder is a frequent cause of death in the seventh and eighth decades. Thus, as the number of older people increases, so can an increase in gallbladder carcinoma be expected. Even though carcinomas of the extrahepatic bile ducts are encountered less frequently than those of the gallbladder, the differential diagnosis of these obstructive lesions from stones and pancreatic carcinoma is frequently difficult. Yet their recognition is important because many of them, especially those of the intraduodenal bile duct and papilla of Vater, produce jaundice at a time when they are small and still resectable.

It is hoped that this fascicle will aid in the morphologic diagnosis and a better understanding of these tumors and of their etiology. Better means of prevention and treatment remain a challenge both to clinician and to pathologist.

The material for the present fascicle was furnished chiefly by the autopsy and surgical pathology services of the Los Angeles County Hospital. Among 56,000 autopsies, there were 216 cases of primary carcinoma of the gallbladder; a histologic diagnosis was possible on 203 of them. In this same series, there were 53 carcinomas of the extrahepatic and intraduodenal bile ducts and papilla of Vater. Comparison of the frequency of carcinoma of the gallbladder and carcinomas of the extrahepatic bile ducts among 56,000 autopsies is shown in figure 1.



TUMORS AND TUMOR-LIKE LESIONS OF THE GALLBLADDER NORMAL ANATOMY

The gallbladder mucosa has a layer of simple columnar epithelium covering an intricate pattern of folds (fig. 2) that increase or decrease in height with the corresponding emptying or filling of the viscus. These folds have a polygonal configuration that is easily seen macroscopically. Minor folds may traverse the floor of polygonal compartments. The normal epithelium functions as an absorptive surface and shows little mucin-secreting activity. Mucinous glands are present only in the neck of the gallbladder.

The subepithelial area is composed of moderately cellular, loose, connective tissue. The muscle layer consists of bundles of smooth muscle in loose arrangement but it is without a well defined circular or longitudinal layer. A subserosal layer of connective tissue contains nerves, blood vessels, and the lymphatic system. In the gallbladder fossa, the connective tissue of the wall is continuous with the periportal spaces of the liver.

The differential diagnosis of lesions of the gallbladder that may be observed on cholecystograms includes tumor-like lesions such as adenomyomatous hyperplasia, cholesterol polyps, and inflammatory polyps, as well as benign neoplasms. Because the roentgenologist, clinician, and pathologist may have to consult one another in the management of the patient, it is deemed desirable to discuss these various polypoid and other benign lesions as a group.

CHANGES IN CHOLELITHIASIS AND CHOLECYSTITIS

In gallbladder disease associated with gallstones, a series of changes may occur in the mucosa that may be confused with, or may possibly be the forerunner of, neoplasms. In the normal gallbladder, mucous glands are present only in the neck of the viscus, while in chronic gallbladder disease, newly formed mucous glands may be derived from the epithelium of the depths of the folds and may thicken the mucosa (fig. 3). Occasionally, the mucous membrane becomes markedly hyperplastic and the glandular pattern becomes more complex (fig. 4). In chronic cholecystitis accompanied by hyperplasia, inflammatory polyps may develop.

In addition to the epithelial changes that affect the mucosa, herniations of the mucosa through the muscularis to the subserosal layer form the so-called Rokitansky-Aschoff sinuses (fig. 5). It is not unusual for the mucosa in these sinuses to form glands. The sinuses may also be observed in noncalculous gallbladders of adults. A critical review of the literature has been made by Robertson and Ferguson.

NORMAL GALLBLADDER

Figure 2. In the mucosa of a normal gallbladder, irregular folds of uneven size are covered by columnar epithelium. The cytoplasm is slightly granular. The nuclei occupy a position near the base of the cell. Goblet cells are not seen. The subepithelial connective tissue has a loose arrangement, is moderately cellular, and the capillaries are not outstanding. Hematoxylin and eosin stain. × 150. L.A.C.H.* 52–1418; A.F.I.P. Acc. No. 219929–2.

HYPERPLASIA

Figure 3. Hyperplastic glands arranged around the depths of the mucosal folds. The connective tissue stroma is rather scanty. The patient, α 68-year-old white woman, had had a long history of gallbladder disease. The gallbladder, removed at surgery, contained one large green-black stone and several smaller stones. The wall of the gallbladder was thickened and opaque. Hematoxylin and eosin stain. × 125. L.A.C.H. 53–1402; A.F.I.P. Acc. No. 219929–3.

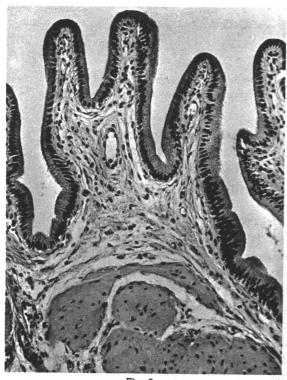
Figure 4. An unusual type of localized papillary hyperplasia of the gallbladder mucosa is shown. The histologic section was taken from an annular sessile lesion, 5 mm. in width and 3 mm. in height, located in the fundus of the gallbladder.

The gallbladder, which was removed from a 29-year-old woman who had symptoms indicative of gallbladder colic, contained 8 pigmented calculi measuring up to 1 cm. in diameter. Hematoxylin and eosin stain. \times 75. (Courtesy of Dr. H. W. Jones, Seattle, Wash.) A.F.I.P. Acc. No. 219929-4.

ROKITANSKY-ASCHOFF SINUS

Figure 5. The mucosa in the Rokitansky-Aschoff sinus has herniated through the muscularis into the subserosa. Hematoxylin and eosin stain. × 35. L.A.C.H. 59–1441; A.F.I.P. Acc. No. 219929–5.

^{*}In this and following legends, L.A.C.H. stands for the Los Angeles County Hospital, Los Angeles, California.



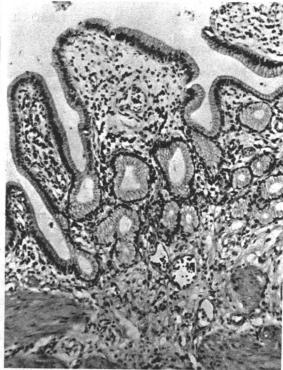


Fig. 2

Fig. 3





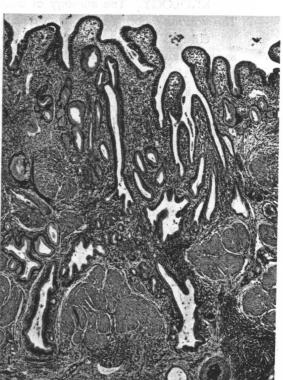


Fig. 5

TUMOR-LIKE LESIONS

Adenomyomatous Hyperplasia

SYNONYMS AND RELATED TERMS: Adenoma; adenomyoma; cholecystitis cystica; cholecystitis glandularis proliferans; cystadenoma; fibromyoadenoma; hamartoma; intramural diverticulosis; myo-epithelial anomalies; myoma.

DEFINITION. A circumscribed or an extensive intramural, or intramural and subserosal, structure composed of glands and ducts lined with columnar epithelium. These epithelial structures are intimately associated with irregular masses of smooth muscle that often encircle the glandular elements. The ducts empty into the gallbladder.

CLINICAL DATA. Shepard and associates noted that adenomyomas occur most often in women whose average age is 48.9 years. The lesions usually cause no specific symptoms. If they are associated with gallstones, which now seems rare, symptoms of cholecystitis may supervene. According to LeQuesne and Ranger, the diagnosis of "cholecystitis glandularis proliferans" is suggested when there is a fundal filling-defect, a stricture, or dye-filled spaces around the periphery of the greater or lesser part of the gallbladder shadow. Fotopoulos and Crampton distinguish between diffuse, segmental, and fundal types of adenomyomatosis. These authors made a radiologic diagnosis of the disease in 62 (4.6 percent) of 1,333 cholecystograms.

ETIOLOGY. The etiology of adenomyomatous hyperplasia is unknown. The various theories have been discussed by Fotopoulos and Crampton.

GROSS. Usually, adenomyomatous hyperplasia is a single lesion located in the fundus of the gallbladder (fig. 6). When a larger portion of the gallbladder is diseased, the change usually affects the distal segment (fig. 7). Rarely is the entire gallbladder involved. The majority of adenomyomatous hyperplasias are 1 cm. or less in diameter; a few attain a diameter of 2 cm. or more. When sectioned, they are found to be sharply demarcated from the normal gallbladder wall, to be yellow-white to gray-red, and to have a honeycombed appearance. A central pit or dimple is present on the mucosal aspect. In two patients of LeQuesne and Ranger, there was, in addition to the fundal nodule, a circumferential band of similar change near the neck, the intervening body of the gallbladder being normal.

Rarely, intramural abscesses or intramural stones may complicate the disease. In one study of surgical material, stones were present in the lumen of the gallbladder in 60 percent of the 103 patients (Shepard et al.).

MICROSCOPIC. Adenomyomatous hyperplasias of the fundus are composed of multiple tubular and glandular structures that form a rather complex pattern in the wall of the gallbladder (fig. 8). The ducts are part of a branching system that arises at a central opening in the mucosa of the gallbladder. Around some of the ducts are small subsidiary glands, many of which are mucus

secreting. The center of the lesion appears to be the area of the most active growth and hyperplasia. In the periphery, the ducts may become cystic, and intramural calculi may form. It is not unusual for some of the dilated ductular structures to have papillary ingrowths of varying size and complexity.

There is proliferation of smooth muscle (fig. 9) and often a considerable amount of cellular connective tissue immediately subjacent to the epithelium. The smooth muscle fibers are sometimes concentrically arranged around the tubules. In the subserosa, tiny ducts, associated with irregularly arranged smooth muscle, indicate that during development these two elements proliferate simultaneously. Infiltration by lymphocytes is frequent. Intramural abscesses have been observed. In the diffuse form, the cystic glands are abundant, especially in the muscularis and serosa (fig. 10), and intramural calculi are more likely to form. The proliferation of ducts and connective tissue does not seem to be quite as exuberant as in the fundal type.

TREATMENT. Symptomless adenomyomatous hyperplasias are usually left alone. If they produce symptoms or are associated with calculi, cholecystectomy is indicated.

DIFFERENTIAL DIAGNOSIS. Adenomyomatous hyperplasias are distinguished from Rokitansky-Aschoff sinuses by their size and by the interrelationship of the tubules to smooth muscle and connective tissue. The proliferation of the latter elements in the subserosa is characteristic. Rokitansky-Aschoff sinuses are more general in distribution and usually consist of only a hernialike outpouching of the mucosa through the muscularis.

Cholesterol Polyp

Cholesterol polyps are yellow, soft, and usually pedunculated (fig. 11). They are solitary or multiple innocent lesions which result in some manner from the faulty metabolism of cholesterol. Their surface is irregularly nodular or berry-like. They are most often about 0.5 cm. in length; rarely are they more than 1 centimeter. They are composed of cholesterol-filled macrophages. A few strands of connective tissue and blood vessels are also noted (fig. 12). Actually, many polyps appear to be composed of several greatly enlarged villi. With enlargement, adjacent villi are displaced and appear alongside. Sometimes, these adjacent villi also contain cholesterol. The epithelium of the polyps differs little from that of the surrounding mucosa.

Heterotopia

When glandular elements in the gallbladder have a histologic structure similar to that of the stomach, pancreas, or liver, they are designated as heterotopias.

Several cases of gastric heterotopia have been reported (Williams and Humm). Some of the patients had symptoms suggestive of gallbladder disease,