



**Figure 18-64** Chronic cholecystitis. **A**, The gallbladder mucosa is infiltrated by inflammatory cells. **B**, Outpouching of the mucosa through the wall forms Rokitansky-Aschoff sinus (contains bile).

cells, and macrophages are found in the mucosa and in the subserosal fibrous tissue (Fig. 18-64A). In more advanced cases there is marked subepithelial and subserosal fibrosis, accompanied by mononuclear cell infiltration. Reactive proliferation of the mucosa and fusion of the mucosal folds may give rise to buried crypts of epithelium within the gallbladder wall. Outpouchings of the mucosal epithelium through the wall (**Rokitansky-Aschoff sinuses**) may be quite prominent (Fig. 18-64B). Presence of acute inflammatory changes implies acute exacerbation of an already chronically injured gallbladder.

In rare instances extensive dystrophic calcification within the gallbladder wall may yield a **porcelain gallbladder**, notable for a markedly increased incidence of associated cancer. In **xanthogranulomatous cholecystitis**, the gallbladder has a massively thickened wall and is shrunken, nodular, and chronically inflamed with foci of necrosis and hemorrhage. It is triggered by rupture of Rokitansky-Aschoff sinuses into the wall of the gall bladder followed by an accumulation of macrophages that have ingested biliary phospholipids. Such lipid containing cells with foamy cytoplasm are called xanthoma cells and hence the name of this condition. Finally, an atrophic, chronically obstructed, often dilated gallbladder, may contain only clear secretions, a condition known as **hydrops of the gallbladder**.

**Clinical Features.** Chronic cholecystitis does not have the striking manifestations of the acute forms and is usually characterized by recurrent attacks of either steady epigastric or right upper quadrant pain. Nausea, vomiting, and intolerance for fatty foods are frequent accompaniments.

Diagnosis of both acute and chronic cholecystitis is important because of the following complications:

- Bacterial superinfection with cholangitis or sepsis
- Gallbladder perforation and local abscess formation
- Gallbladder rupture with diffuse peritonitis
- Biliary enteric (cholecystenteric) fistula, with drainage of bile into adjacent organs, entry of air and bacteria into the biliary tree, and potentially, gallstone-induced intestinal obstruction (ileus)

- Aggravation of preexisting medical illness, with cardiac, pulmonary, renal, or liver decompensation
- Porcelain gallbladder, with increased risk of cancer, although surveys of this risk have yielded widely discrepant frequencies

## Carcinoma

**Carcinoma of the gallbladder is the most common malignancy of the extrahepatic biliary tract.** Approximately 6,000 new cases of gallbladder cancer are diagnosed each year in the United States. There are wide variations in the incidence of gallbladder cancer worldwide, with some regions such as Chile, Bolivia and Northern India, harboring the highest numbers of cases. Even within the United States, areas with large numbers of Native American or Hispanic populations, such as the southwest, have a higher incidence of gallbladder cancer than the rest of the country. *Gallbladder cancer is at least twice as common in women than in men; this gender disparity can be several fold greater in regions of highest incidence.* The overwhelming majority of patients are diagnosed at an advanced, surgically unresectable, stage, and the mean 5-year survival for these patients remains at less than 10%.

**Pathogenesis.** *The most important risk factor for gallbladder cancer (besides gender and ethnicity) is gallstones which are present in 95% of cases. However, it should be noted that only 1-2% of patients with gallstones develop gallbladder cancer.* In Asia, chronic bacterial or parasitic infections have been implicated as risk factors, and the coexistence of gallstones with gallbladder cancer is much lower. Nonetheless, the common thread that ties gallstones or chronic infections together with gallbladder cancer is chronic inflammation. Gallbladder cancers harbor recurrent molecular alterations that might be “actionable” targets of therapy. One example is the oncoprotein ERBB2 (Her-2/neu) that is overexpressed in a third to two-thirds of cases, and therefore might be targeted with small molecule inhibitors or monoclonal antibodies. Recent deep sequencing of gallbladder cancers has revealed mutations