Heterotopic gastric mucosa together with intestinal metaplasia and moderate dysplasia in the gall bladder: report of two clinically unusual cases with literature review

N Xeropotamos, A S Skopelitou, Ch Batsis, A M Kappas

Abstract
We report the clinicopathological findings of two patients with ectopic gastric mucosa within the gall bladder. The first patient, a 78 year old man, was asymptomatic. He was admitted to hospital for a colon adenocarcinoma. Intraoperatively, a firm nodule was palpable in the gall bladder. Histological examination of the resected specimen revealed a body type gastric mucosa in the submucosa, adjacent to which were extensive pyloric gland and intestinal metaplasia with mild to moderate dysplasia. The remaining gall bladder mucosa demonstrated changes of chronic cholecystitis. The second patient was a 62 year old woman with symptoms of chronic cholecystitis. The preoperative diagnosis was consistent with this diagnosis with a “polyp” at the junction of the neck and cystic duct. Cholecystectomy was performed and the histological examination of the resected specimen showed that the “polyp” consisted of heterotopic gastric mucosa with glands of body and fundus type. In the remaining mucosa, chronic cholecystitis was evident. To the best of our knowledge, this is the first report of a clinicopathological presentation of heterotopic gastric mucosa together with pyloric gland and intestinal metaplasia followed by dysplasia. In the second case, ectopic gastric mucosa was preoperatively interpreted as a benign gall bladder polyp. To date, in three other cases, ectopic gastric mucosa presented as an intraluminal polypoid lesion.

Keywords: heterotopic gastric mucosa; gall bladder; intestinal metaplasia; dysplasia; precancerous lesion

Heterotopia, from the Greek “heteros” (different) and “topos” (location), is defined as the occurrence of normal tissue in an abnormal location. Synonymously, the term “choristoma”, from the Greek “choristos” (separated), has also been used.

Gastric (body type) mucosa has been described in almost every part of the gastrointestinal tract, from the oral cavity to the rectum, including the gall bladder and liver. Pseudopyloric or pyloric gland metaplastic epithelium in the gall bladder is most common, being found in 66–84% of cholecystectomy specimens, while intestinal metaplastic epithelium has been reported in 12–52% of gall bladders and is frequently associated with pyloric metaplasia. Heterotopic gastric mucosa, as well as intestinal metaplasia in the gall bladder, may be one of the causes of gall bladder cancer. We present two unusual cases of gastric heterotopia in the gall bladder and review the literature.

In the first case, the asymptomatic presence of heterotopic gastric mucosa, together with pyloric gland and intestinal metaplasia followed by dysplasia, occurred at the same time as colon adenocarcinoma. In the second case, ectopic gastric mucosa was preoperatively interpreted as a benign gall bladder polyp. To date, in three other cases, ectopic gastric mucosa presented as an intraluminal polypoid lesion.

Case reports

PATIENT NO 1
A 78 year old man was admitted to our hospital for colon carcinoma. At operation, palpation of the gall bladder revealed an intramural firm nodule. Cholecystectomy was carried out together with colectomy. On gross examination the gall bladder specimen measured 3×1.3×0.8 cm and had a smooth and glistening serosa. After opening the specimen, at the body of the gall bladder, a firm nodular thickening of the wall was noticed, measuring 0.7 cm at its largest diameter. Histological examination revealed that the nodule was within the lamina propria and consisted of heterotopic gastric mucosa, with both body type and pyloric type gastric glands. The overlying mucosa was hyperplastic. In close proximity to this heterotopic mucosa, extensive pyloric gland and

Abbreviations used in this paper: PAS, periodic acid-Schiff.
intestinal metaplasia (fig 1A, B) together with mild to focally moderate dysplastic changes in the metaplastic epithelium were observed (fig 2 A–C). In the remaining mucosa, typical features of chronic cholecystitis were obvious. Cholelithiasis was not found.

PATIENT NO 2
A 62 year old woman presented to our hospital with vague dyspeptic symptoms and intermittent postprandial right upper quadrant abdominal discomfort that was described as dull-aching, radiating sometimes through the back, and associated with nausea. She only rarely experienced vomiting. Physical examination revealed a positive Murphy’s sign. Oral cholangiogram showed abnormal gall bladder function with a filling defect suggesting a polyp at the junction of the neck and cystic duct. A sonogram clearly demonstrated a polyp at the same junction. Cholecystectomy was carried out for cholecystitis and gall bladder polyp.

The cholecystectomy specimen measured 8×2×0.9 cm with a smooth gray-whitish glistening serosa. On opening, a smooth velvety green mucosa was found, measuring 0.4 cm in thickness, except at the region of the neck and the orifice of the cystic duct where a polypoid nodule of red-grayish colour was noticed measuring 0.8 cm at its greatest diameter. Gall stones were not observed.

Histological examination revealed that the polypoid lesion consisted of gastric heterotopic mucosa with parietal and columnar mucous secreting cells, almost identical to those observed in the previous case (fig 1B, C). The adjacent gall bladder mucosa showed typical features of chronic cholecystitis.

**Figure 1** (A) Alcian blue-periodic acid-Schiff (PAS) stain in normal (arrowheads) and metaplastic gall bladder epithelium. The acid mucins of intestinal metaplasia are blue whereas neutral mucins of gastric metaplasia (pyloric type) are red (×320). (B) Heterotopic gastric mucosa of body type in the gall bladder; parietal cells (top) have a large pyramidal shape and plump eosinophilic cytoplasm (haematoxylin-eosin ×480); same area (bottom) stained with Alcian blue-PAS (×480). (C) Polyp of the gall bladder consisting of heterotopic gastric mucosa (haematoxylin-eosin ×180).

**Figure 2** (A) Mild and focally moderately dysplastic epithelium (arrow), occurring in intestinal metaplasia (arrowheads) (Alcian blue-periodic acid-Schiff (PAS) stain ×320) (inset: mild dysplasia developing in pyloric type metaplastic epithelium (haematoxylin-eosin ×320). (B) In this field the transition between normal (arrowhead) and metaplastic epithelium (arrow) can be seen (haematoxylin-eosin ×320); mild dysplasia is focally well discerned (inset: haematoxylin-eosin ×850). (C) Intestinal metaplasia of a tubule (arrowheads) in close proximity to the normal gall bladder epithelium (haematoxylin-eosin ×540).
Discussion

Heterotopic gastric mucosa in the gall bladder is extremely unusual. It was first described by Egeved in 1954. Since then it has been reported in various organs and sites in the gastrointestinal tract, including the tongue, oesophagus, epi-glottis, small bowel, vermiform appendix, rectum, and gall bladder. A survey of the world literature revealed 45 reports, including the present cases, and interestingly none shared the broad spectrum of clinical and histological findings of our cases.

There is a wide range in patient age, clinical presentation and symptoms, and roentgenographic and pathological findings. From the six extended reviews, it is apparent that the sex distribution is approximately equal with the following prevalence varying among different ethnic groups. Acute and xanthogranulomatous cholecystitis, adenomyomatosis, pseudopyloric and intestinal metaplasia, hyperplastic polyps, dysplasia, tubular adenomas, and in situ and invasive carcinoma appear to be more frequent when the gallbladder is removed. In older patients, the extent of the disease seems to depend in part on the age of the patient. Antral type and intestinal metaplasia seem to be more extensive and more severe in patients older than 50 years of age, as in our cases. Also, hyperplasia of metaphlastic pyloric type glands is often seen in the vicinity of gall bladder carcinoma.

A heteroplastic pathway rather than a developmental defect could explain the coexistence of gastric heterotopia together with metaphlastic and dysplastic changes of the gall bladder mucosa with complete absence of clinical symptoms in our first case. The metaplastic changes in chronically inflamed epithelia are well established. The close relationship between early gall bladder cancer and metaplasia, in the setting of chronic inflammation, has been emphasised many times.

However, pyloric type metaplasia has less of a relationship with the bases of carcinogenesis than with those of intestinal metaplasia. But Kijima and colleagues have shown that gastric mucosa metaplasia gives rise to early and microinvasive carcinomas of the gall bladder. In such cases, the metastatic potential seems to be more frequent in females and the survival rate is better than in non-metaphlastic type carcinomas.

Because of the importance of p53 protein in gall bladder cancer and its precursor lesions and that our patient (first case) was operated on for colon carcinoma, we performed immuno-histochemistry in both lesions. We used a monoclonal antibody (DO-7; Dako M7001) at an optimal dilution of 1:50. Immunohistochemical staining was performed using the streptavidin-biotin peroxidase method, as previously described. p53 nuclear immunoreactivity was found only in colon adenocarcinoma (well differentiated, Duke's A stage).
results are expected as it is well known that p53 immunoreactivity is detected in approximately 47–50% of colorectal carcinomas, tends to increase with tumour stage, and seems to be a late event in colon carcinogenesis.57

p53 protein expression was absent in both cases of gall bladder metaplastic and dysplastic epithelium. Wee and colleagues40 have reported that significant p53 immunostaining was less common in dysplastic gall bladder epithelium (28%) compared with either carcinoma in situ or invasive carcinoma but most of these premalignant lesions were associated with invasive carcinomas. In fact, only one of seven carcinomas in situ and six of 18 dysplasias corresponded to lesions not found adjacent to invasive carcinoma. Furthermore, no evidence of p53 overexpression has been found in normal or metaplastic gall bladder epithelium.36–40 Concerning both our cases, the absence of p53 protein expression from metaplastic and low to moderately dysplastic lesions should be undertaken to better understand its pathogenesis.

In contrast, the histological changes observed in our cases could be explained by the multidirectional differentiation of gall bladder epithelium during inflammation. Metaplasia could progress to dysplasia and hence to adenocarcinoma via a multistep process which may result from accumulation of genetic abnormalities. It is interesting that the opposite has also been observed—that is, most gall bladder adenocarcinomas in the series studied by Kusima and colleagues38 displayed gastric and/or intestinal type differentiation, both immunohistochemically and morphologically—suggesting that gall bladder adenocarcinomas develop and progress under induction of gastric and intestinal differentiation. Numerous studies on this subject have appeared in the literature. We believe that further investigations of the molecular biology of gall bladder precancerous lesions should be undertaken to better understand its pathogenesis.

To the best of our knowledge, this is the fourth incidentally found case in the literature,25 and the first demonstrating a wide spectrum of epithelial changes, including metaplasia and dysplasia.

Our second patient was not symptomatic until signs and late symptoms, was challenging and led us to hypothesise that this ectopic gastric mucosa could represent a heteroplastic or metaplastic process, due to a developmental error of multipotential/multidirectional mesenchymal cells, rather than a congenital defect.

In conclusion, we have presented the first report of asymptomatic heterotopic gastric mucosa in the gall bladder accompanied by pyloric and intestinal metaplasia together with dysplasia, and the first clinically silent, probably of metaplastic origin, gastric mucosa in the gall bladder, presenting as a polyp. Both conditions emphasise the role of inflammation in the sequence metaplasia → hyperplasia → dysplasia → carcinogenesis of the gall bladder. Furthermore, we propose that the term choristoma, in its etymological sense, could also be applied to lesions derived through a heteroplastic process, and not only to congenital tissue development error.59


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