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, pyloric gland type, and intestinal metaplasia with dysplastic changes in the gall bladder. As heterotopic tissue may promote carcinogenesis of the gall bladder, close attention should be paid to any occurrence of such lesions in this anatomical region.

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.

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**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).
Heterotopic gastric mucosa in the gall bladder is extremely unusual. It was first described by Egyedi in 1934. Since then it has been reported in various organs and sites in the gastrointestinal tract, including the tongue, esophagus, 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 a slight female preponderance, with an age range of 6–77 years (most patients being less than 25 years). Most patients have upper quadrant abdominal pain, often of a colicky type, or vomiting or, in some cases, obstructive symptoms with jaundice. In younger patients (that is, those less than 25 years), ectopic gastric mucosa tends to be the only pathological finding and clinical symptoms seem to be relatively short or even absent, while in older patients this may be an incidental finding together with chronic cholecystitis and/or cholelithiasis. Gall stones are present in almost one third of cases. Intraoperative findings comprise a normal, checkered, nodular, or multiloculated gall bladder, or adherent to other organs, with localised or diffuse thickening of the wall. The heterotopic tissue usually protrudes into the lumen or is sessile, ranging in size from 0.5 to 2.0 cm, and is often situated in the neck or fundus of the gall bladder.

The characteristic feature of heterotopic gastric mucosa is the histological presence of fundic glands with both parietal and chief cells as well as pyloric glands, and most investigators have reported that heterotopic gastric mucosa involves all of these components (fundic type). APUD cells have been demonstrated in five cases, thyroid tissue in one, and pancreatic tissue in two. In three cases there was peptic ulceration of the wall of the gall bladder.

Embryologically, the gall bladder arises from the hepatic primordium. The latter originates from the ventral surface of the foregut in the 2.5 mm embryo, some distance caudal to the developing stomach. Both are in close proximity to the septum transversum during the later stage of development. It seems therefore that heterotopia could result either by entrapment of primitive gastric tissue, by heterotopic differentiation within the primitive gall bladder, or by metastatic differentiation. Recently, the correct diagnosis of gastric heterotopia was made preoperatively, with detection of gastric mucosa in a Meckel’s diverticulum by the use of pertechnetate scintigraphy, associated with H2 receptor blocking agent. The differential diagnosis of gastric heterotopia in general includes fixed gall stone or (rarely) a neoplasm, and for the pathologist intestinal metaplasia that sometimes also has a polyoid configuration, and pyloric gland metaplasia.

In our first case, ectopic gastric mucosa with body type epithelium was found together with pyloric type gastric mucosa and colonic type intestinal metaplasia. In the latter, foci of dysplastic changes—that is, crowding and hyperchromasia of nuclei with little to moderate pseudostratification and mitotic figures—were evident while in the remaining mucosa, histological features of chronic cholecystitis were obvious. As expected, the heterotopic gastric type mucosa stained red with Alcian blue-periodic acid-Schiff (PAS), indicating that neutral mucins were present, whereas the acidic mucins of intestinal metaplasia reacted strongly with Alcian blue (figs 1A, B, 2A).

It is well established that there is a strong association between gall bladder carcinoma, premalignant epithelial or metaplastic inflammatory lesions, and cholelithiasis, the incidence 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 cholelithiasis is present. Interestingly, none of our patients had cholelithiasis. Also, the extent of metaplasia 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 metastatic 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 metaplastic 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 metaplastic type carcinomas seem to be more frequent in females and the survival rate is better than in non-metaplastic 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). These
metaplastic and low to moderately dysplastic
lesions should be undertaken to better under-
molecular biology of gall bladder precancerous
develop and progress under induction of gastric
and/or intestinal type di
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munohistochemically and morphologically—
and the first demonstrating a wide spectrum of
normal or metaplastic gall bladder
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 epithelial lesions → 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.”

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