Turk J Gastroenterol *2014; 25 (Suppl.-1): 234-6*

Pyloric gland type adenoma including intramucosal carcinoma focus of gallbladder

To the Editor,

Gallbladder adenomas (GAs) are rare primary neoplasms of gallbladder. They are determined in 0.1-10% of cholecystectomy performed due to cholelithiasis (1,2). Female predominance and localization of corpus/fundus are noted. Polyps in 10% of cases are multiple. There are 3 histological type of GAs; tubulary, papillary and tubulopapillary. Histogenetically, GAs are classified as types of pyloric gland, intestinal and biliary. Pyloric gland type adenomas (PGAs) are the most common form (3).

A 37 year female patient with dyspeptic complaints at last one year was admitted. Ultrasonography revealed a polypoid lesion with high vascularity. A polypoid lesion with ulcerated surface was determined during the intraoperative pathology consultation (IPC) (Figure 1a). The pedunculated polypoid lesion was 20x10x7 mm in dimensions and length of peduncle was 5 mm. Polypwas localized in the neck of the gallbladder and composed of numerous tubular glands by lined columnar cells with atypical nuclei (Figure 1b). IPC was resulted as "paraffine" because of atypical architecture and cytology. Gallbladder and polyp were totally sampled. Polyp was composed of pyloric type glands and sparsely mild /moderate dilated tubular glands (Figure 1b). Epithelial lining of some tubular glands were in columnar shaped. Squamoid cell morules were focally present (Figure 1c). Foci of crowded tubular glands with atypical architecture/cytology and relatively high mitoses were determined on the surface. These areas were reminiscent of intestinal cryptsand some crypts had goblet and Paneth cells. A focus had an infiltrative appearance with severe atypical changes and minute necrosis foci, hence this focus was accepted as intramucosal carcinoma (IC) (Figure 1d, e). Other epithelial areas did not show metaplastic and dysplastic changes. Pyloric glands showed no staining withPAS/alcian blue pH 2.5. Luminal edges of surface and cryptic epithelium were positive for acidic mucin. Only one crypt had goblet cells including acidic mucin (Figure 1f). Cholesterolosis and cholesterol polyps were noted in other mucosal areas of gallbladder. Focus of IC showed relatively higher p53 (Labvision, Fremont, USA) and Ki67 (Labvision, Fremont, USA) immunostaining. Severe/diffuse immunostainings of CK19 (Labvision, Fremont, USA), AE1/AE3 (Labvision, Fremont, USA), AE1(Labvision, Fremont, USA) and CK5-6(Labvision, Fremont, USA) were seen while focal expression of CK17 (Labvision, Fremont, USA) and multifocal immunostainings of CD10 (Labvision, Fremont, USA) and CK7 (Labvision, Fremont, USA) were present on glandular and surface epithelium (Figure g and h). Expressions of CK20 (Labvision, Fremont, USA) and CEA (Labvision, Fremont, USA) were not seen. Histopathological and immunohistochemical findings pointed to PGA including IC focus. Differentiation areas of biliary, intestinal and pyloric gland were present in the polyp. Thereupon, whole gastrointestinal tract of the patient was investigated for synchronous/metachronous lesions. Any lesion was determined. Our patient have no a complaint in postoperative fifth years.

Nagata et al analyzed 78 PGA of 59 cases in their study (4). The mean age and male/female ratio were 64 year and 0.5, respectively. Corpus and neck were predominant localization areas and 24% of cases had multiple polypoid lesions. The mean diameter of polyps was 9.8 mm (ranged from 10 to 40 mm). Most adenomas were with peduncle (73%). Only two cases had polyps including carcinomatous foci and diameters of their polyps were longer than 30 mm (4). Our case's polyp was located in the neck region and its longest diameter was 20 mm in length. Her age was lower than the mean age in the study of Nagata et al. (4).

Heterotopic gastric mucosa (HGM) and metaplastic epithelial changes (MEC) are also encountered in gallbladder. In the literature, we determined 23 cases of HGM of

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Received: September 26, 2012 **Accepted:** February 22, 2013

Turk J Gastroenterol 2014; 25 (Suppl.-1): 234-6

gallbladder. Hamazaki and Fujiwara analyzed 19 cases of HGM in their study (5). We also determined three other publications which 4 cases of HGM were analyzed in these reports (6-8). In these studies, the mean age and male/female ratio were 40.4 year (age interval; 16-78) and 2, respectively. Discrimination of HGM from normal mucosa is usually difficult. Some HGM may show polypoid or intramural growing. Corpus, fundus and neck regions are areas of common localization . Cystic duct localization is rare. In these studies, most lesions showed a polypoid growing pattern and the mean diameter was 1.6 mm. These lesions were composed of fundic and pyloric glands (5-8).

Pyloric/pseudopyloric gland metaplasia is the most common form of MEC in gallbladder. Its frequency is 66-84%. Frequency of intestinal MEC is 12-52% and they are frequently related with pyloric metaplasia (7). MEC are different from HGM. MEC may include gland types of intestinal, pyloric, and mucous with goblet and Paneth cells. Fundic glands are not seen. (5-8). MEC may be congenital or secondary to cholecystitis, cholelithiasis, or a tumoral growing (8). MEC, especially intestinal type epithelium has a risk of malign transformation (7).

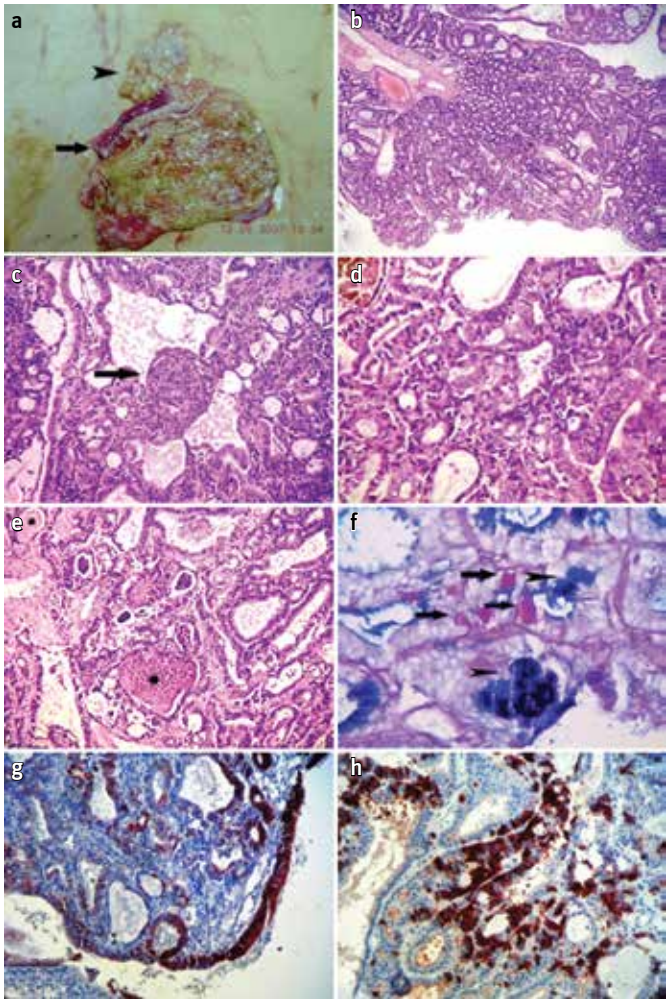

Figure 1. a-h. Polypoid lesion (arrowhead) on cholecystectomy material. Residual part of the peduncule on neck region of gallbladder (a). A panaromic histological view of PGA (HE, X5) (b). Squamoid morule formation (arrow) in the PGA (HE, X25) (c). Intramucosal carcinoma focus characterized by glandular crowding and cytological atypia in PGA (HE, X40) (d). Areas of focal necrosis (asterisks) in the PGA (HE, X20) (e). The presence of sparse neutral mucin (arrow) and intensive sialomucin (arrowhead) in goblet cells and on luminal edges of cyript epithelium (PAS-Alcian blue pH 2.5, X40) (f). CK7 expression on surface and glandular epithelium of PGA (AEC, X30) (g). Strong CD10 expression on glandular epithelium of PGA (AEC, X30) (h).

Age and gender are clinical parameters for discrimination between adenomas and metaplasia/heterotopia. If a polypoid lesion is determined in gallbladder of a young male patient (younger than 30-40 years) with symptoms of cholecystitis / cholelithiasis, this polypoid lesion is likely HGM rather than PGA. PGAs are usually encountered in older female patients than 40-50 years. In histomorphological discrimination, proliferation degree, macroscopical discernibility, composition of glands and cells, restriction from normal mucosa are important criteria for PGA. Anatomical localization, mean diameter and growing patterns are similar in PGA and HGM. These 3 criteria have no any significance in the discrimination. But PGAs have usually larger dimensions than those of HGM at the diagnosis. If the longest diameter of a gallbladder polyp is more than 25-30 mm, this polyp is probably a PGA.

The lining epithelium of polypoid lesion in our case was reminiscent of biliary epithelium. Acidic mucin positivity at cytoplasmic luminal edges supported to biliary epithelial differentiation. However, the presence of goblet and Paneth cells in a few crypts were an evidence of intestinal differentiation. Immunohistochemistry pointed out to biliary epithelial immunophenotype by multifocal expression of CD10 and CK7. CK20 expression was not seen. Glanduler, surface lining epithelium and squamoid morules were diffusely positive for CK19, AE1/AE3, AE1 and CK5-6. These findings supported a PGA with multifocal biliary and focal intestinal epithelial differentiation. Nagata et al reported that PGAs had a similar immunophenotype to those of pyloric gland, gastric foveolar and biliary epithelium excluding intestinal epithelium (4). However, Wani et al suggested that intestinal differentiation could be also seen in PGAs on the basis of their series (9). GAs, especially intestinal types, may include foci of dysplasia or in situ carcinoma. Severe dysplasia and/or in situ carcinoma are extremely rare in PGAs (3). Although dysplastic and metaplastic epithelium do not show p53 overexpression, in situ and invasive carcinomas prone to show p53 overexpression (7). Nagata et al. (4) reported that two cases of adenoma with carcinomatous foci were negative for p53, whereas with relatively high Ki67i. In our case, the focus of IC showed expression for both of p53 and Ki67 but these expressions were not a level of overexpression. A careful histological examination in PGAs is very important to discriminate they from HGM and MEC, moreover not to overlook a probable focus of carcinoma in especially large PGAs.

Conflict of Interest: No conflict of interest was declared by the authors.

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