J Korean Med Sci 1998; 13: 295-8
ISSN 1011-8934

Copyright © The Korean Academy of Medical Sciences

Tubular Adenoma of the Gallbladder with Spindle Cell Metaplasia

We report four cases of tubular adenoma of the gallbladder with spindle cell metaplasia. Three patients had solitary polyps in the gallbladder and the fourth had multiple (three) polyps. Only one patient who had a polyp of larger size had abdominal pain. Histologically, these tubular adenomas had characteristic morular foci composed of short spindle cells. These spindle cell components lacked intercellular bridges or cytoplasmic keratinization. Immunohistochemically, the spindle cells stained positively for one or more cytokeratins and negatively for vimentin, muscle actin and S-100 protein. Spindle cells are considered to represent the metaplastic component of the adenoma cells.

Key Words : *Gallbladder; Adenoma; Adenocarcinoma metaplasia, spindle cell*

Hyunee Yim, Yoon Mi Jin, Chull Shim

Department of Pathology,
Ajou University School of Medicine

Received : September 10, 1997
Accepted : January 26, 1998

Address for correspondence
Hyunee Yim, M.D.
Department of Pathology, Ajou University Hospital, San 5, Wonchon-dong, Paldal-gu, Suwon, Kyongki 442-749, Korea
Tel : (0331) 219-5926, Fax : (0331) 219-5934
E-mail : ajoupath@soback.kornet21.nm.kr

INTRODUCTION

Adenoma of the gallbladder is a benign glandular tumor composed of cells resembling biliary tract epithelium (1, 2). It is usually classified into three types: tubular, papillary and mixed. Various metaplastic epithelia, such as goblet cells, Paneth cells, and gastric pyloric type cells can be found within this neoplasm. Spindle or squamous cell components in tubular adenomas of the gallbladder have rarely been reported (3). Squamous metaplasia, however, has been reported in adenomas of other organs such as the colon (4, 5, 6).

We herein report four cases of tubular adenoma of the gallbladder with spindle cell metaplasia.

MATERIALS AND METHODS

The files of cholecystectomy cases from June 1994 to July 1997 in the Department of Pathology of Ajou University Hospital were searched. Twelve cases of adenoma and twelve cases of adenocarcinoma of the gallbladder were found among 620 cholecystectomy cases. One to four H&E stained sections of formalin fixed, paraffin embedded tissue from each case of neoplasm were reviewed with the clinical data. Four cases of adenoma were found to have foci of spindle cell metaplasia of the neoplastic glands. To clarify its nature, immunohistochemical stains were performed with various monoclonal antibodies: pankeratin (Novocastra, UK), low molecular weight cytokeratin (AE1) (DAKO, Carpinteria, USA), high molecular weight cytokeratin (AE3) (DAKO, Carpinteria, USA), vimentin (DAKO, Carpinteria, USA), muscle actin (HHF 35) (DAKO, Carpinteria, USA), and S-100 protein (DAKO, Carpinteria, USA).

RESULTS

Four cases of adenoma with spindle cell metaplasia were found among twelve cases of adenoma of the gallbladder. None of the adenocarcinoma cases showed spindle cell metaplasia. The clinical and pathological details of these four cases are summarized in Table 1 and 2.

Table 1. Clinical findings of gallbladder adenomas with spindle cell metaplasia

Patient No.	Age / Sex	Symptom	Associated condition	Location of adenoma	Number	Size (cm)
1	36 / M	Incidental*	None	Body	One	1.2×1.0
2	47 / M	RUQ pain	GB stone	Body	One	2.5×2.0
3	72 / F	Incidental*	GB stone	Body	One	1.0×0.8
4	44 / F	Incidental*	Rectal cancer	Fundus/body	Three	2.5×2.0, 0.7, 0.5

* Incidentally detected by ultrasonography or computed tomography
RUQ: right upper quadrant, GB: gallbladder

Table 2. Microscopic findings of glandular epithelium of gallbladder adenomas with spindle cell metaplasia

Patient No.	Pyloric glands	Goblet cells	Paneth cells	Cellular atypia
1	+	+	−	−
2	−	−	−	+
3	+	−	−	−
4	+	+	−	+

The age of these four patients with adenoma with spindle cell metaplasia ranged from 36 to 72 years. Both sexes were represented equally. Three cases had no related symptoms and adenomas were found incidentally by ultrasonography or computed tomography. Only one patient who had an adenoma of larger size complained of right upper quadrant pain. Gallstones were associated in two cases. One who was incidentally found to have three separate adenomas was a patient undergoing work-up for his known rectal cancer.

Grossly, these adenomas were polypoid, ranging from 0.5 cm to 2.5 cm in diameter (Fig. 1). Histologically, all of them were tubular type adenomas; they were composed of closely packed tubules of variable size arranged in lobules. Each of the tubules was lined by cuboidal to columnar cells. Pyloric metaplasia with mucin secreting cuboidal cells was observed in three cases. Two larger adenomas (2.5 cm) had intestinal metaplasia with goblet cells, but without Paneth cells. In two cases, atypical cellular features, such as nuclear enlargement, nuclear

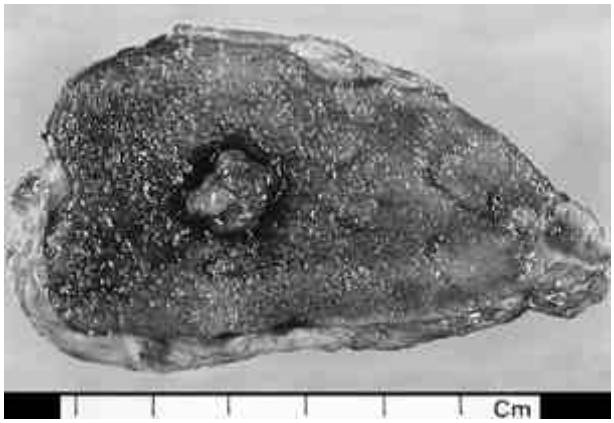

Fig. 1. Gross photo of case 1, showing polypoid tumor with lobulated surface.

stratification and prominent nucleoli were identified. Stromal edema, capillary proliferation and infiltration of polymorphonuclear leukocytes, lymphocytes and plasma cells were also identified in these adenomas. The spindle cell metaplasia was characterized by solid morular foci of short spindle cells, which did not show definite squamoid features such as intercellular bridge or cytoplasmic keratinization and glandular lumen (Fig. 2). These hypercellular nests were randomly scattered in lamina propria and often associated with glands. Occasional foci of whirling arrangements of spindle cells were noted. The latter had eosinophilic cytoplasm with partly fibrillary features. The cell borders of these spindle cells were poorly defined. In one case (No. 4), cells forming a few morular foci

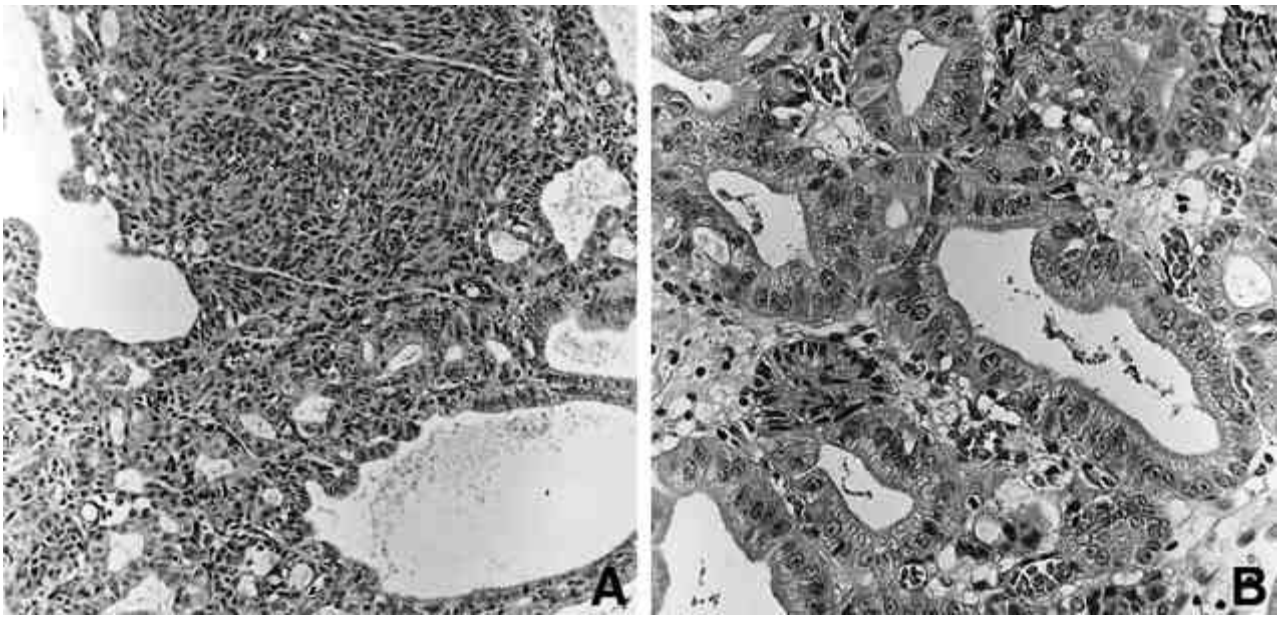

Fig. 2. A: The spindle cell nest of whirling arrangment shows no intercellular bridge or evidence of keratinization (H&E, ×100). B: The short spindle cells are closely associated with adenoma glands (H&E, ×200).

Table 3. Immunohistochemical findings of spindle cell metaplasia of GB adenomas

Patient No.	Pankeratin	Low M.W. cytokeratin	High M.W. cytokeratin	Vimentin	Actin	S-100
1	+*	−	+*	−	−	−
2	+	−	+	−	−	−
3	−	−	+*	−	−	−
4	+	+*	+*	−	−	−

* focal weak positivity

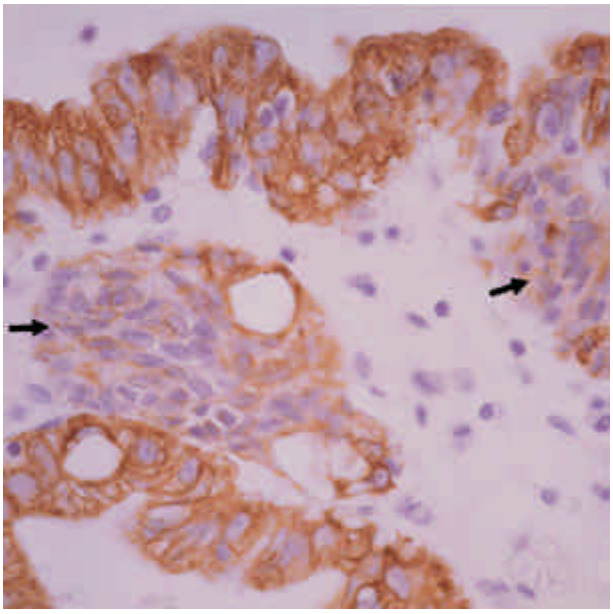

Fig. 3. The spindle cells (arrows) are stained positive for pankeratin (immunostaining, ×400).

became polygonal in shape with abundant eosinophilic or partly clear cytoplasm with a well defined cytoplasmic border. No mitotic figures or nuclear atypia were identified among the spindle cells. Immunohistochemically, these spindle cells were positive for one or more cytokeratin. High molecular weight cytokeratin was positive in all cases, but low molecular weight cytokeratin was positive in only one case (Fig. 3). However, the low molecular weight cytokeratin negative cases revealed positivity for pankeratin (Table 3). The cells of spindle cell metaplasia were negative for vimentin, actin and S-100 protein.

DISCUSSION

Adenoma of the gallbladder is a rare tumor with a reported incidence from 0.1 to 10% of cholecystectomy cases (7, 8). This tumor is usually discovered incidentally during cholecystectomy or presents with radiolucent defects on cholecystograms (1). It rarely causes symptoms unless it obstructs the gallbladder neck or cystic duct (9). However, signs and symptoms can result from stones or inflammation. Just as Shepard et al. (10) had stressed the etiologic importance of injury from inflammation or stones in adenoma, chronic inflammation was found in all of our four cases and stones in two.

Spindle cell metaplasia of benign neoplasms is rare (4, 5, 6), although it is not unusual in malignant neoplasms of several organs, such as the anus, esophagus, and larynx (11). There has been a report of three cases with spindle cell metaplasia in gallbladder adenoma by Nishihara et al. (3). The incidence of spindle cell metaplasia in adenomas of the gallbladder in our files was four out of twelve (33.3%) in contrast to Nishihara's 5.3%, so we can assume that this type of morphologic change is not as rare as previously thought. Since none of the cases of gallbladder adenocarcinoma in our study showed spindle cell metaplasia, we assume that it is a unique finding among the cases of adenoma of the gallbladder. Morular foci similar to our cases are well known in endometrial adenocarcinoma (12).

Nishihara's description of spindle cell nests was quite similar to that of our cases, except that pyloric or goblet cell metaplasia seen in our cases was not mentioned in their cases (3). In addition, cellular atypia was not described in that report. The differentiation of atypical changes from in situ or invasive carcinoma can be difficult; the histologic criteria for differentiation are similar to those used for tumors arising in the intestine (1, 7). We agree with the notion that adenoma with marked cellular atypia may be premalignant lesion in the adenoma-adenocarcinoma sequence of the gallbladder as suggested by Kozuka on the basis of the fact that a few adenomas have shown malignant change, and transformation from benign adenoma into carcinoma was traceable in invasive carcinomas (7). He also described a positive correlation between the size of a lesion and malignant change.

Although there was no intercellular bridge or keratin formation, Nishihara considered that spindle cell change was a type of squamoid metaplasia of adenoma cells on the basis that spindle cells stained positive for high molecular weight cytokeratin, considered to be a marker of squamous differentiation. In present study, we confirmed the positivity for high molecular weight cytokeratin in all four adenoma cases with spindle cell metaplasia. We

also observed that spindle cell metaplasia stained positive for pankeratin. So, we consider that spindle cell metaplasia of the gallbladder does not represent the mesenchymal cells but metaplasia of epithelial cells. However, the possibility of multipotential reserve cell origin cannot be excluded.

In summary, we investigated 4 cases of gallbladder adenomas with spindle cell metaplasia, which are not as rare as previously thought. The spindle cell component is interpreted as metaplasia of adenoma cells on the basis of positive staining results for various cytokeratins. The presence of solid foci of spindle cells in adenoma of the gallbladder should not be misinterpreted as malignancy.

REFERENCES

1. Albores-Saavedra J, Henson DE. *Tumor of the gallbladder and extrahepatic bile ducts (Atlas of Tumor Pathology, 2nd Series, Fascicle 22). Armed Forces Institute of Pathology, Washington, D.C., 1986: 17-25.*
2. Yamaguchi K, Enjoji M. *Gallbladder polyps. Inflammatory, hyperplastic and neoplastic types. Surg Pathol 1988; 1: 203-13.*
3. Nishihara K, Yamaguchi K, Hashimoto H, Enjoji M. *Tubular adenoma of the gallbladder with squamoid spindle cell metaplasia. Report of three cases with immunohistochemical study. Acta Pathol Jpn 1991; 41: 41-5.*
4. Chen KTK. *Colonic adenomatous polyp with focal squamous metaplasia. Human Pathol 1981; 12: 848-9.*
5. Bansal M, Fenglio CM, Robboy SJ, King DW. *Are metaplasia in colorectal adenomas truly metaplasia? Am J Pathol 1984; 115: 253-65.*
6. Gramer SF, Velasco ME, Whitlatch SP, Graney MF. *Squamous differentiation in colorectal adenomas. Literature review, histogenesis and clinical significance. Dis Colon Rectum 1986; 29: 87-91.*
7. Kozuka S, Tsubone M, Yasui A, Hachisuka K. *Relation of adenoma to carcinoma in the gallbladder. Cancer 1982; 50: 2226-34.*
8. Kimura W, Muto T, Esaki Y. *Incidence and pathogenesis of villous tumors of the gallbladder and their relation to cancer. J Gastroenterol 1994; 29: 61-5.*
9. McGregor JC, Cordiner JW. *Papilloma of the gallbladder. Br J Surg 1974; 61: 356-8.*
10. Shepard VD, Walters W, Dockerty MB. *Benign neoplasms of the gallbladder. Arch Surg 1942; 45: 1-8.*
11. Iezzoni J, Mills SF. *Sarcomatoid carcinoma (carcinosarcomas) of the gastrointestinal tract. A review. Semin Diagn Pathol 1993; 10: 176-87.*
12. Dutra FR. *Intraglandular morules of the endometrium. Am J Clin Pathol 1959; 31: 60-5.*