

CASE REPORT

Synchronous primary colonic and early gallbladder carcinomas: report of a rare case

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Abstract

The incidence of multiple primary malignant tumors in the same individual is increasing worldwide. We report a case of a 30 years old female with an adenocarcinoma of the colon in whom a high grade dysplasia/carcinoma in situ of the gallbladder was incidentally discovered in the cholecystectomy specimen resected with the colon for multiple gall stones. Synchronous adenocarcinomas of the colon and the gallbladder are extremely rare with only seven cases reported so far. The link between the colonic and the gall bladder carcinoma may reside in the presence of gall stones rather than a hereditary predisposition to cancer development as may be suggested by a negative family history for colorectal and gallbladder cancers. Because the colon is the organ that is most frequently involved in the setting of multiple primary malignant tumors, thorough preoperative screening and follow up for other cancers, including gallbladder cancer, is recommended for patients presenting with colorectal carcinoma.

Key words

Synchronous, Colorectal, Adenocarcinoma, In situ carcinoma, Dysplasia, Gallbladder, Multiple primary malignant tumors

1 Introduction

The phenomenon of multiple primary malignant tumors (MPMT) in the same individual was first described by Warren and Gates in 1932^[1]. Cancers diagnosed at the same time or within a period of six months after the diagnosis of the initial cancer are described as synchronous while those diagnosed after six months are called metasynchronous^[2]. Autopsy studies on MPMT cases showed the colon to be the organ most frequently involved^[3,4], especially among the aged^[3]. Herein, we report a case of a 30 years old female with an adenocarcinoma of the colon, in whom a high grade dysplasia/carcinoma in situ of the gallbladder was incidentally discovered in the cholecystectomy specimen resected with the colectomy for multiple gall stones. Synchronous adenocarcinomas of the colon and the gallbladder are extremely rare with only seven cases reported so far^[5-11].

2 Case presentation

A 30 years old non-smoker, non-alcoholic female presented with central abdominal pain of six months duration, complicated by bloody diarrhea one week before admission. The pain was associated with anorexia and weight loss and

negative history of vomiting, fever or night sweats. The patient had unremarkable medical, surgical and allergic past history. There was no family history of colorectal or gallbladder cancers. CBC showed: RBCs 2.76 mil/ μ l, Hgb 5.9 g/dl, Hct 20.3%, WBC 17.5 k/ μ l and Platelets 980 k/ μ l. Colonoscopy showed an ulcerating annular mass, 26 cm from the anal verge that was diagnosed by biopsy as invasive moderately differentiated adenocarcinoma.

2.1 Contrast-enhanced CT

Contrast-enhanced CT of the abdomen and pelvis with oral contrast performed after colonoscopy showed marked sigmoid wall thickening with stricture and infiltration of adjacent fat and the posterior bladder wall consistent with the diagnosis of cancer (see Figure 1). There were as well multiple laminated large gallbladder stones (see Figure 1A). The patient underwent exploratory laparotomy with sigmoid resection and end to end anastomosis, with partial cystectomy, salpingo-oophorectomy and cholecystectomy. In a study performed by Juhasz *et al.* [12] on 305 patients it was concluded that unless there are clear contraindications, patients with asymptomatic gall stones who have colorectal surgery should have concomitant cholecystectomy. Earlier experience has also suggested that selected patients who have had adequate bowel preparation have minimal risks associated with additional intra-abdominal surgery performed at the time of colectomy [13].

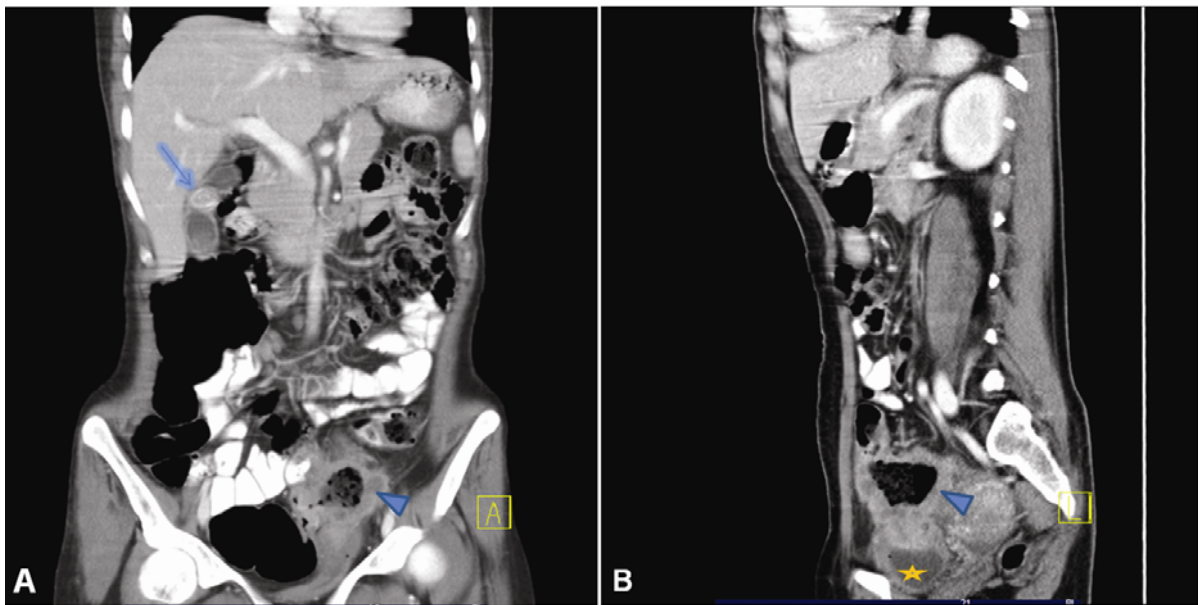


Figure 1. Coronal and sagittal CT reformats of the abdomen and pelvis. (A) Gallbladder with large calcified stone (arrow) and marked sigmoid wall thickening with adjacent mesenteric fat infiltration (arrow head); (B) Sigmoid wall thickening infiltrating urinary bladder wall (star).

2.2 Pathologic findings

The surgical specimen included 14 cm of sigmoid colon and attached part of urinary bladder and jejunal loop with a 6 cm \times 5 cm \times 3.5 cm infiltrating hard tumor invading the urinary bladder and forming a fistula between jejunum and colon (see Figure 2A). The gallbladder specimen was received opened with no grossly identifiable masses or stones (see Figure 2B). Microscopic examination revealed a moderately differentiated adenocarcinoma of the sigmoid colon (see Figure 3) invading the urinary bladder and the jejunum (TNM stage pT4b N1 M0, group stage IIIC) along with acute and chronic cholecystitis with high grade dysplasia/carcinoma in situ extending into Rokitansky-Aschoff sinuses (TNM stage pTis N0 M0, group stage 0, see Figure 4). Immunohistochemically, the colonic cancer was CK20 and CDX2+ve, and CK7-ve, while the gallbladder cancer was CK20 and CK7+ve, and CDX2-ve (see Figure 5 and 6).

Postoperatively, the patient was stable and she was referred to another center for chemotherapy.

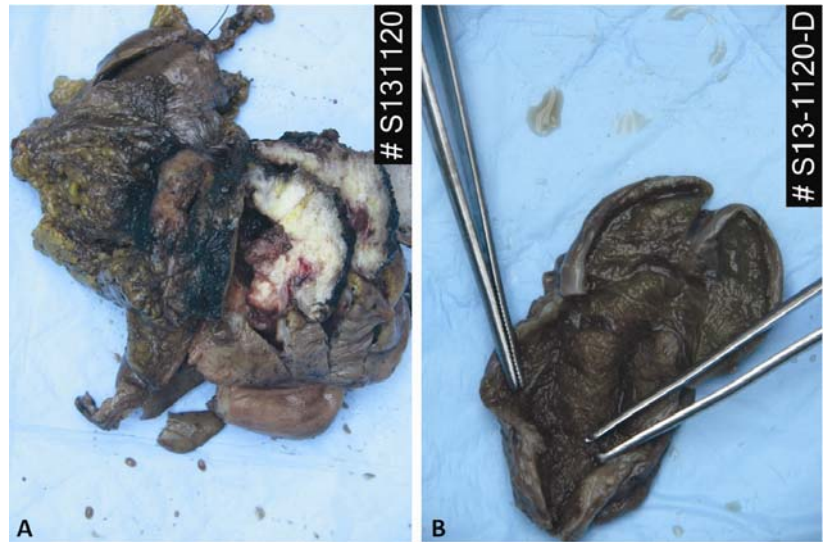


Figure 2. (A) Infiltrating tumor in sigmoid colon; (B) Opened gallbladder with no grossly identifiable tumor

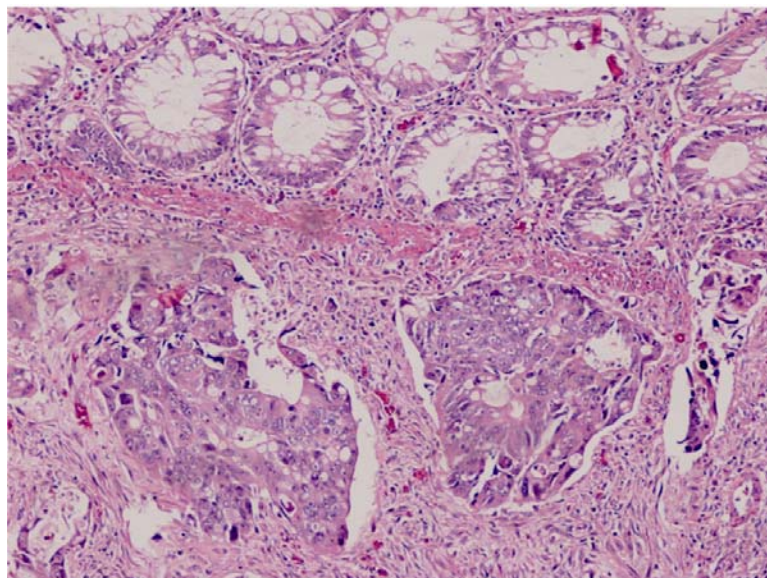


Figure 3. Moderately differentiated adenocarcinoma infiltrating sigmoid submucosa. H & E $\times 200$

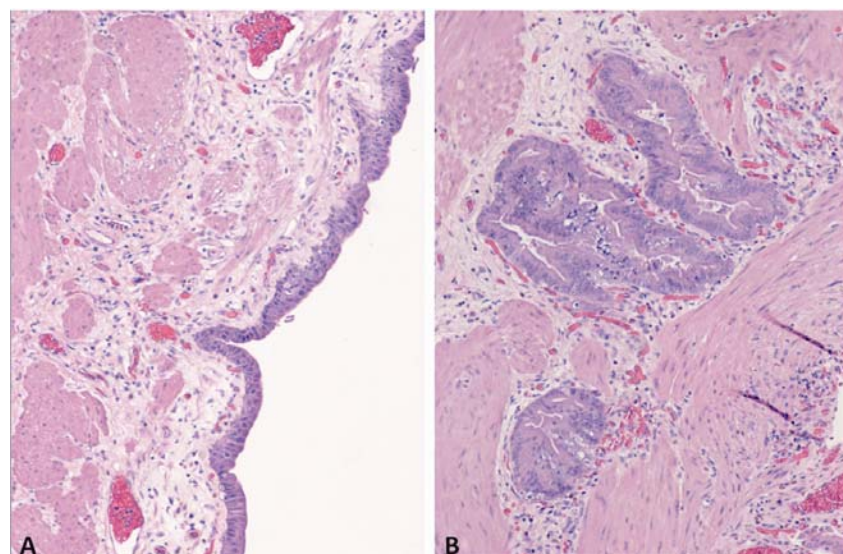


Figure 4. (A) High grade dysplasia/carcinoma in situ involving gallbladder lining. H & E $\times 100$; (B) High grade dysplasia/carcinoma in situ extending into Rokitansky-Aschoff sinuses in gallbladder wall. H & E $\times 100$

Figure 5. (A) Colonic adenocarcinoma showing negative immunoreactivity for CK7. IHC $\times 100$; (B) Gall bladder high grade dysplasia/carcinoma in situ showing positive immunoreactivity for CK7. IHC $\times 100$

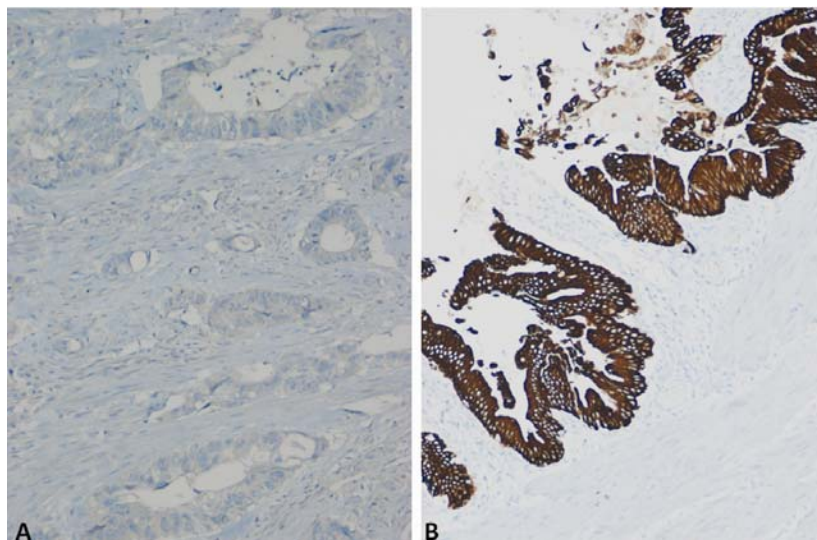
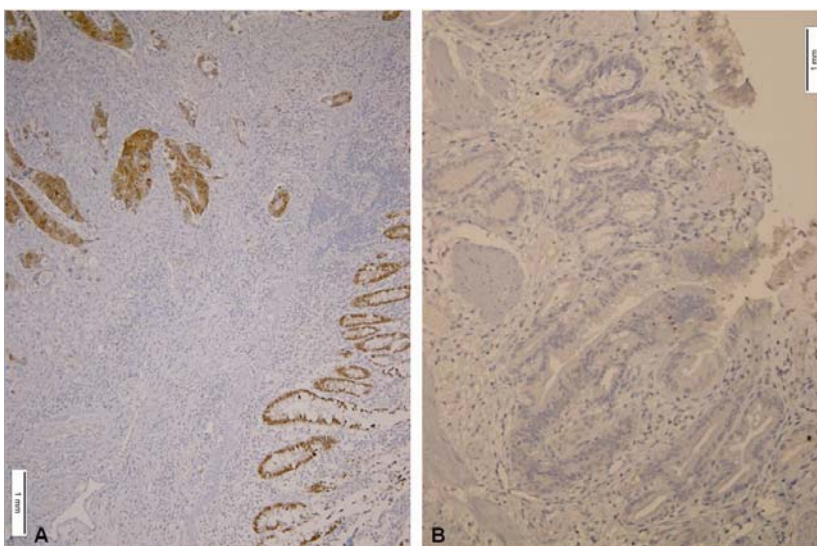


Figure 6. (A) Colonic adenocarcinoma showing positive immunoreactivity for CDX2. IHC $\times 100$; (B) Gall bladder high grade dysplasia/carcinoma in situ showing negative immunoreactivity for CDX2. IHC $\times 100$



3 Discussion

Multiple primary malignant tumors in the same patient is relatively rare with a 0.7%-11.7% overall occurrence ^[14]. However, the incidence is increasing worldwide with increase in the number of cancer survivors due to advances in diagnostic techniques and treatment modalities ^[15, 16]. According to Waren and Gates ^[1], the diagnostic criteria of multiple primary cancers are: first, each tumor should be histopathologically malignant; second, each tumor should be histologically different; and third, the possibility of metastasis of each tumor should be ruled out. These criteria fully apply to the case we are reporting in which the two synchronous cancers showed immunohistochemical differences as outlined above.

The carcinogenic process involved in the development of multiple primary cancers has not been clarified and hereditary and environmental factors, and radiological and anticancer treatments have been implicated ^[16]. Methylene tetrahydrofolate reductase (MTHFR) is an enzyme that takes part in acid metabolism, catalyzes the conversion of 5, 10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate, a co-substrate for homocysteine remethylation to methionine, and plays a major role in DNA methylation ^[17, 18]. Many studies found that genetic variation of MTHFR might influence the susceptibility to colon cancer, and may also affect extracolonic cancers such as breast, ovarian and other cancers ^[19, 20].

Age seems to be an important factor as most of the cases reported in the literature have occurred in elderly patients. In a study of 134 cases of colorectal cancer with synchronous and metachronous cancers, Samadder *et al.* found that the risk for synchronous colorectal cancer was higher in age > 65 years [21]. However, our patient was much younger than 65 (only 30 years old).

Reported MPMTs include variable combinations of colorectal, gastric, breast, gynecologic, prostatic, renal, bladder, thyroid, intracranial, and head and neck cancers [15] with the colon being the organ that is most frequently involved [3]. Thus patients with colon cancers may probably be at increased risk of developing other primary malignancies. Consequently, thorough preoperative screening and follow up for other cancers is recommended for patients presenting with colorectal carcinoma.

Synchronous adenocarcinomas of the colon and the gallbladder are extremely rare. To the best of our knowledge only seven cases have been previously reported. The following table shows the main clinicopathological features of five of those cases as compared to ours.

Table. Clinicopathological features of five previously reported synchronous colon and gall bladder carcinomas, compared to present case

Author	Year	Age/ Sex	Colon cancer			GB Cancer			Other synchronous cancers
			Location	Histology	Stage (TNM)	Location	Histology	Stage (TNM)	
Konodo <i>et al.</i> [6]	1985	60y/M	SC	Well differentiated adenoCa	-	-	In situ adenoCa	pTis	Early, poorly differentiated squamous carcinoma of the esophagus
Schmid <i>et al.</i> [7]	1988	79y/F	TC	Mucinous carcinoma	pT3	No macroscopic evidence	Well differentiated adenoCa	pT2	Early, non invasive adenoCa of the apex of the appendix
Tamura <i>et al.</i> [9]	2003	70y/M	SC	Well differentiated adenoCa	I	Fundus	Papillary adenoCa	I	Well differentiated adenoCa of the stomach, stage II
Sakellaridis <i>et al.</i> [10]	2005	72y/F	R	Moderately differentiated adenoCa	II	Anterior wall	Well to moderately differentiated adenoCa.	II	Absent
Gupta <i>et al.</i> [11]	2013	40y/F	R	Moderately differentiated adenoCa	IIA	Antero medial wall	Moderately differentiated adenoCa	II	Absent
Present case	2014	30y/F	SC	Moderately differentiated adenoCa	IIIC	No macroscopic evidence	In situ adenoCa	pTis	Absent

Note. SC = Sigmoid colon; TC = Transverse colon; R = Rectum; adenoCa = Adenocarcinoma; GB = Gall bladder

The link between the colonic and the gall bladder carcinomas may reside in the presence of gall stones rather than a hereditary predisposition to cancer development as may be suggested by the negative family history for colorectal and gallbladder cancers. Reports of high fecal excretion of bile acids and bile derivatives by patients with colorectal cancer and those with cholecystectomy have intensified research into the relation between gall stones and colorectal cancer [22]. Several studies of gall stone patients have been reported [23-32], most showed a positive association with cancer of the colon, with relative risks of 1.2-2.4. In the studies that showed an effect and provided data on risk by anatomical sub-site, the risk was generally greater for cancer of the proximal colon than for other parts of the colon and rectum [28-32].

Gall bladder cancer is a notoriously rare though lethal malignancy with marked geographic variation. Risk factors for developing gall bladder cancer include ethnicity, female sex, old age, genetic susceptibility, lifestyle, and chronic inflammation which is often a product of gall stones^[33].

4 Conclusion

The incidence of multiple primary malignant tumors in the same individual is increasing worldwide. Because the colon is the organ that is most frequently involved in such a setting, thorough preoperative screening and follow up for other cancers, including gallbladder cancer, is recommended for patients presenting with colorectal carcinoma.

Competing interests

The authors declare that they have no competing interests.

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