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Case Report

Metachronous Second Primary Colorectal Cancer in Patients with Gastric Cancer: Two Cases Report and Literature Review

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Abstract **Although it remains a topic of debate as to whether the presence of gastric cancer implies a general increase in susceptibility to colorectal cancer, the recognition of such an association is important as it provides surgeons with an unusual opportunity to detect colorectal cancer at an early stage in patients with gastric cancer. CT colonography after gastric cancer surgery may be helpful to evaluate postoperative metastases as well as to find second primary colorectal cancer. Early detective of these lesions, based on an awareness of the possibility of metachronous colorectal cancer, will increase the survival of these patients. The authors reported two cases of metachronous primary colorectal cancer in patients with gastric cancer and the literature was reviewed.**

INTRODUCTION

Multiple primary cancers are defined by the International Association of Cancer Registries as the occurrence of two or more primary cancers, where each cancer originates in a separate primary site and is neither extension, recurrence or metastasis.[1] Cancer-bearing patients are susceptible to an increased risk of developing cancer in other organs.[2,3] Multiple primary cancers are more likely to develop in organs of the same system than in those of different system.[4]

Since Billroth firstly described multiple primary cancers in 1889[5], it is crucial to recognize the characteristic of multiple cancers in order to detect the second cancer early enough to treat it for cure. The prevalence of second primary cancer in the gastric cancer patients was higher than the prevalence in the general population, and the most common second primary cancer was colorectal.[6-10] Herein, the authors reported two cases of gastric cancer who developed metachronous colorectal cancer and reviewed the literatures.

CASE 1

A 77-year-old presented with rectal bleeding for one month. Physical examination revealed no abnormality. Laboratory evaluations including CEA were unremarkable. Colonoscopy showed an ulcerative mass at 15 cm from anal verge. Biopsy showed moderately differentiated adenocarcinoma. He was the known case of gastric cancer. Radical subtotal gastrectomy with D2 lymph node dissection and Billroth II anastomosis were performed $2\frac{1}{2}$ years ago. The

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pathologic diagnosis was poorly differentiated adenocarcinoma and lymph node metastases in 3 of 49. Pathologic staging was stage IIIA ($T_3N_1 M_0$). He denied any postoperative adjuvant therapy. He was well with regular follow-up until this illness. Laparotomy was done with the diagnosis of second primary colorectal cancer. No recurrent lesion of gastric cancer was found. Low anterior resection was performed with double stapler technique. The pathologic evaluation showed moderately differentiated adenocarcinoma with angiolymphatic invasion and positive lymph nodes in 2 of 20. Pathologic staging was stage IIIA ($T_3N_1 M_0$). The patient had an uneventful postoperative recovery. He still denied postoperative adjuvant therapy. He is now symptom-free with no recurrent tumor $5\frac{1}{2}$ years after the first operation (for gastric cancer) and 3 years after the second operation (for colorectal cancer).

Case 2

A 49-year-old man complained of abdominal pain and bowel habit change for one month. Physical examination revealed no abnormality except a circumferential lesion at distal rectum from per anal examination. Colonoscopy showed circumferential ulcer 4 cm from anal verge with nearly occluded lumen. Biopsy showed moderately differentiated adenocarcinoma. CT scan of the whole abdomen revealed newly seen circumferential thickening of upper rectum with perirectal invasion causing obstruction. No liver metastasis was seen. Locally advanced rectal cancer which was most likely than metastatic carcinoma was reported. The patient was the known case of gastric cancer. Radical total gastrectomy with D2 lymph node dissection and Roux-en-Y esophago-jejunostomy was performed two year ago. The pathologic diagnosis was signet ring cell carcinoma with angiolymphatic invasion and positive lymph nodes 21 in 38. Pathologic staging was stage IIIB ($T_3N_2M_0$). He received postoperative adjuvant chemotherapy completely. Seven months ago (17 months after gastrectomy), he presented with abdominal wall recurrence. En bloc resection of abdominal wall mass with wedge resection of liver segment 4B was performed. No recurrent lesion in other area in the abdominal cavity was found. Pathologic examination showed metastatic signet ring cell carcinoma involving abdominal wall muscle, soft tissue and superficial surface of liver. He was well until this illness. Exploratory laparotomy was performed for the diagnosis of advanced rectal cancer with partial obstruction. At laparotomy, frozen pelvis and generalized peritoneal dissemination was found. Proximal diversion with loop transverse colostomy was performed. During the 2-month follow-up period after colostomy, the patient received only symptomatic and supportive treatment.

Discussion

During the last two decades, the survival rate of the patients with gastric cancer has improved due to both early detection and the performance of extensive lymph node dissection.[7,11-13] The first study of second primary cancer in patient with gastric cancer was reported by Yoshino et al from Japan in 1985[14]. In that study, the incidence was 2%.[14] Since then, other studies have reported an incidence of 1.1% to 4.7%.[7-8,10,15-19] The most common second primary cancer was colorectal cancer.[6,8,17,20-23]

The close combination of gastric and colorectal cancer was reported in many institutes with a large number of cases in Japan.[2,24-26] Saito et al in 2008[27] reported the prevalence of synchronous colorectal cancer in patients with gastric cancer was 4% (18/466). All these patients were older than 50 years. Ikeda et al in 2003[7] analyzed 2,250 gastric cancer patients and reported 95 (4.2%) patients had second primary cancer with colorectal cancer most prevalently occurring (32.5%). In Korea, Park et al in 2010[28] reported the prevalence of colorectal cancer, using colonoscopic surveillance, in a cohort of patients with gastric cancer (n = 543) matched with controls (n = 1,086). The odds ratio of developing colorectal cancer was higher in the presence of gastric cancer (OR = 3.46; 95%CI 1.51-7.91). Kim et al in 2009[21] reported the result of preoperative colonoscopy for patients with gastric cancer (n = 205). Synchronous colorectal cancer was detected in 4 (2%) patients. Multivariate analysis showed that age > 50 years was the only risk factor. In asymptomatic average-risk Koreans, the prevalence of colorectal cancer was 0.3% in the subjects > 50 years.[29] In an additional study in asymptomatic Asian multinational subjects (n = 860), the prevalence of colorectal cancer was 1%.[30] Oh et al in 2006[31] reported the risk of colorectal cancer was 9.5% in the gastric

cancer patients (n = 105) and 0.7% in age-sex-match patients without gastric cancer (n = 269). Lee et al in 2006[8] analyzed 3,291 gastric cancer patients and reported 3.4% had synchronous cancer with colorectal cancer most prevalently occurring (37.2%). Yoo et al in 2006[32] performed prospective multicenter trial, 723 gastric cancer patients had colonoscopy and the incidence rate of colorectal cancer was 2.4%, meaning it was 2.5 times that of healthy people (0.97%).

In China, Dong et al in 2010[20] reported the incidence of 1.7% second primary cancer (synchronous 0.2%, metachronous 1.5%) in patients with gastric cancer (n = 4,426) with colorectal cancer most prevalently occurring. This association has been observed not only in Japan, Korea and China, but also in Australia and Portugal. Heard et al 2005[33] reported multiple primary cancer combination from South Australia Cancer Registry. They identified new cancer association including colorectal cancer following gastric cancer. They had no explanation for this finding. Dinis-Ribeiro et al from Portugal in 2002[34] reported the prevalence of associated primary cancer in patients with gastric cancer. Of 2,668 gastric cancer patients, 3.4% (78/2,668) had second primary cancer, 27% of which were synchronous and 73% metachronous, mostly were colorectal cancer. On the contrary, gastric cancer was the most common second primary cancer among colorectal cancer patients, the incidence varied from 0.2% to 2.9%.[2,8,26,35-40]

In case of second primary colorectal cancer associated with gastric cancer, the diagnostic criteria according to Warren and Gates[41] were used to diagnose multiple primary cancers: 1) each tumor must be clearly malignant as determined by a histologic evaluation, 2) each tumor must be geographically separate and distinct, and 3) the probability that one was metastatic from the other should be ruled out. Patients were classified into two groups according to the date of colorectal cancer detection. Synchronous cancer was defined as those diagnosed at the same time or within six months of gastric cancer diagnosis. Colorectal cancer diagnosed more than six months before or after gastric cancer was defined as metachronous[35-36,40], as in our cases.

Two cases of metachronous colorectal cancer in the patients with gastric cancer were reported. During the same period of this study ($5\frac{1}{2}$ years from January 2005 to June 2010), 133 gastric cancer (24 cases/year) and 289 colorectal cancer (52 cases/year) were operated by the author (C.E.). As a result, in the single author experience, metachronous colorectal cancer was presented in 1.5% (2/133). Both cases were males. The age at an onset of gastric cancer was 74 and 49 years, respectively. The interval between the diagnosis of gastric and colorectal cancer was $2\frac{1}{2}$ and 2 years, respectively. As in our cases, many studies reported that the risk factor of second primary colorectal cancer is gastric cancer in elderly male patients.[6-8,21] The prevalence of colorectal cancer in asymptomatic average-risk in Thai population is not available for comparison.

Although we were not able to establish the mechanism underlying the association between colorectal and gastric cancer, both cancers might be closely related. This finding may be attributed to the fact that gastric and colorectal cancer share the same risk factors, such as environmental factors or genetic abnormalities[7,14,21,27,34] including the p53[42,43], APC (adenomatous polyposis coli)[42], DCC (deleted in colorectal cancer)[44], and K-ras gene.[45] In addition, microsatellite instability (MSI) is thought to play an important role in the development of multiple primary cancers of the GI tract.[21,22,37,46,47] The dysfunction of mismatch repair (MMR) genes, known to cause microsatellite instability, has been identified in gastric cancer as well as in colorectal cancer.

However, this might be a false assumption. The association of colorectal cancer with gastric cancer may be incidental as they are common tumors.[8] The prevalence of gastric cancer in the Korean and Japanese population was high, whereas that of colorectal cancer was lower than in the Western countries. If gastric cancer was a significant risk factor of colorectal cancer, the prevalence of colorectal cancer would have been as high as that of gastric cancer during the same period.

The incidence of colorectal cancer is higher than gastric cancer in Thailand, but we think that the occurrence of metachronous colorectal cancer in gastric cancer patients is not merely a chance phenomenon. However, we are not able to establish the fact that gastric cancer is directly related to colorectal cancer. The reason for this association needs further investigation. The frequency of second primary colorectal cancer seems to be higher in gastric cancer patients. This cannot be ignored in clinical practice.

For many years, colonoscopy has been the only

diagnostic method for evaluating colorectal neoplasms. A consensus guidelines for surveillance after colorectal resection in 2006 by the American Cancer Society and the US Multi-Society Task Force on colorectal cancer addressed only the use of endoscopy in the surveillance for colorectal cancer.[48] However, colonoscopy is difficult to perform after gastric cancer surgery, because most patients are old and generally have low body mass index due to surgery and affects the completion rate in colonoscopy.[21,42,49] In addition, a history of abdominal surgery has been associated with difficulties in colonoscopy.[50]

In 2008, CTC (CT colonography or virtual colonoscopy) has been recommended as a less-invasive alternative to conventional colonoscopy for colorectal cancer screening.[51] However, controversial results have been reported by different authors.[52-58] CTC fared poorly in detecting individual lesion ≤ 5 min.[42] However, the prevalence of malignancy in diminutive polyp is extremely small, approximately 0.25%.[59] CTC is highly specific, but the sensitivity varied widely. The use of CTC in routine screening should be subject to quality control.[42,52] In addition to detection of colorectal neoplasms, CTC allows detection of recurrent lesions of gastric cancer. Lim et al from Korea in 2010[15] reported the use of CTC as a substitute for routine follow-up CT scan for detection of recurrent lesion in 700 patients who underwent curative resection for gastric cancer. Recurrent gastric cancer was identified in 1.1%. Colorectal polyps measuring ≥ 6 mm were also detected in 14.9%. The diagnostic yield for second primary colorectal cancer was 1.6%. The prevalence of colorectal cancer was higher than the 0.4% reported in a similar population of asymptomatic average-risk Korean adults[60], and higher than the diagnostic yield of a large Western screening trial using CTC (0.4%)[61], despite the fact that the prevalence of primary colorectal cancer is higher in Western countries.

Most colorectal cancer, identified after gastric cancer surgery, were detected within five years.[2,16] But in some study, about half of the cases of metachronous colorectal cancer were identified more than five years after gastric cancer surgery.[40] To better classify the need for surveillance for colorectal cancer and adequate follow-up duration in patients who underwent gastric cancer surgery, further research is needed. Colorectal cancer screening in gastric cancer patients is not routinely performed in our institute. A good surveillance program should be cost-effectiveness, so that unnecessary examination can be avoided. We think that colorectal cancer fulfils the conditions required for screening in this situation. It is one of the major public health problems in Thailand. Colorectal cancer is the third in frequency in males and the fifth in females.[62] And also it can be cured by detection at early stage and even prevented by the removal of adenomas.

Conclusion

As the number of patients treated for gastric cancer and the survival rate of this disease has increased, clarification of both recurrences and second primary cancer is important for the development of effective postoperative follow-up programs. The present study cautions that surgeons should be aware of metachronous colorectal cancer in patients with gastric cancer in order to detect these lesions as early as possible to prolong survival and achieve a possible cure of disease. If colorectal cancer screening is needed, CTC is suggested.

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