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A Case of Simultaneous Primary Gastric Cancer and Bladder Cancer with a Rare Mode of Metastasis

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Abstract A 60-year-old woman presented to our hospital with lower abdominal discomfort. Abdominal computed tomography showed a bladder tumor and a metastatic liver tumor. Gastric cancer was suspected to be the primary tumor for the hepatic metastasis. Biopsy of the gastric tumor revealed adenocarcinoma, biopsy of bladder tumor squamous cell carcinoma mixed with transitional cell carcinoma. The patient was admitted for gastrectomy and biopsy of the metastatic liver tumor. We performed distal partial gastrectomy with D2 dissection and Billroth I reconstruction, with partial resection of the liver tumor in segment 3. Histopathological examination revealed a moderately differentiated tubular adenocarcinoma, subserosa. Metastasis to the No.4d lymph node was adenocarcinoma and that to the No.8a and 9 lymph nodes were squamous cell carcinoma mixed with transitional cell carcinoma from the bladder cancer. The metastatic liver tumor was also found to be from the bladder cancer. The patient had an uneventful post-operative course, and was transferred from the surgical ward to the department of urology for chemotherapy, 14 days postoperatively. She ultimately died of leptomeningial carcinomatosis, 10 months after the operation. It is extremely rare with regional lymph node metastasis of stomach from mixed double gastric and bladder cancers.

Key words: double cancer, metastasis, regional lymph nodes

Introduction

Simultaneous double cancers can differ in clinical stage and principles of treatment. It is necessary to determine the clinical stage of each cancer to accurately diagnose and thereby select the optimal treatment for each tumor. We report a case of simultaneous primary gastric cancer and bladder cancer with a rare mode of metastasis.

Case history

A-60-year-old woman presented to our gynecology department with a chief complaint of lower abdominal discomfort. She had undergone a muscle-preserving radical mastectomy for right breast cancer in 1998. Pathological findings were consistent with a scirrous carcinoma, and the pathological staging was pT2, pN2, pM0, stage IIIa. Postoperative therapy was tamoxifen and doxifluridine, taken orally for five years and six

months after radiotherapy. The patient had undergone total abdominal hysterectomy and salpingo-oophorectomy for a suspected endometrial cancer in 2004. Pathological findings indicated endometrial hyperplasia. The genetic test was not accomplished, but there was not the person infected with cancer to the close relatives, and Li-Fraumeni syndrome was denied. Abdominal computed tomography (CT) and magnetic resonance imaging (MRI) showed bladder, gastric and metastatic liver tumors (Fig. 1A, B) and upper gastrointestinal fiberscopy revealed gastric cancer (Fig. 2A). Tumor markers were elevated (CEA 5.2 ng/ml, CA19-9 186.9 U/ml, and SCC 98.4 ng/ml). Abdominal CT showed an approximately 3 cm gastric tumor in the lower portion of the stomach and swelling of the regional lymph nodes, low density areas in both lobes of the liver, an approximately 5 cm in diameter tumor invading the upper left pelvis of the bladder with swelling of regional lymph nodes, left hydronephrosis, and swelling of para-aortic lymph nodes. Low density areas in both lobes of the liver in the CT were diagnosed as metastatic liver tumor, but the breast cancer, the gastric cancer, any metastasis of the bladder cancer were unknown. Upper gastrointestinal fiberscopy showed an approximately 4 cm type 2 tumor in the lower portion of the greater curvature of the stomach, and biopsy of this tumor revealed an adenocarcinoma. Cystoscopy showed pressure from the left of the bladder wall (Fig. 2B) and that the left ureteric orifice was closed by the tumor. Biopsy of the bladder tumor revealed squamous cell carcinoma mixed with transitional cell carcinoma (Fig. 3A). Bone scintigraphy showed no metastases to bone. The preoperative diagnosis was simultaneous primary gastric and bladder cancers. Chemotherapy rather than surgery was indicated for the bladder cancer because of the pelvic lymph node metastasis. A distal partial gastrectomy was indicated for the gastric cancer as a means of prophylactically treating bleeding and obstruction. Metastatic regional lymph nodes were considered to likely represent metastases from the gastric cancer. Metastases involving the para-aorta

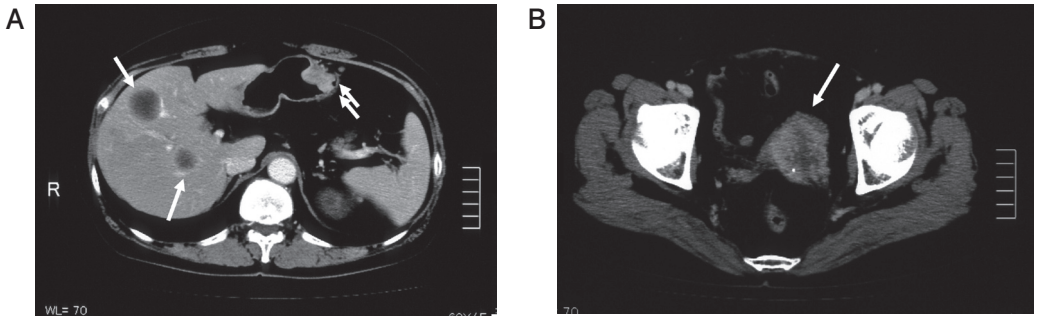

Fig. 1 A: Abdominal CT showing a metastatic liver tumor (↓) and gastric cancer (↓↓). B: Abdominal CT showing a mass approximately 5 cm in diameter in the upper left pelvis of the bladder (↓).

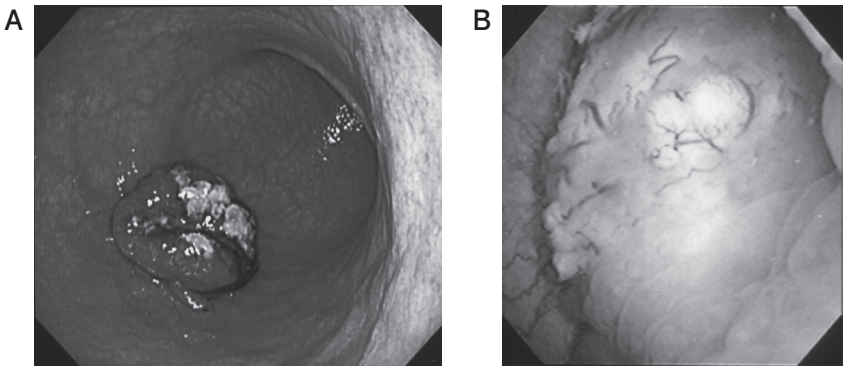

Fig. 2 A: Upper gastrointestinal fiberscopy showed an approximately 4 cm type 2 tumor. B: Cystoscopy showed pressure from the left of the bladder wall.

lymph nodes and liver were of uncertain origin, as the gastric cancer, bladder cancer and even the right breast cancer 11 years earlier, were all possible sources. We performed a distal partial gastrectomy with D2 dissection and Billroth I reconstruction for prevention of bleeding and obstruction, with partial resection of the liver tumor in segment 3 to confirm metastasis of any cancer. Histopathological examination revealed a moderately differentiated tubular adenocarcinoma (Fig. 3B), subserosa (ss). Metastasis to the No. 4d lymph node (greater curvature nodes) was adenocarcinoma (Fig. 4A), that to the No. 8a lymph nodes (common hepatic artery nodes anterosuperior group) and No. 9 lymph nodes (celiac artery nodes) was squamous cell carcinoma mixed with transitional cell carcinoma from the bladder cancer (Fig. 4B). The metastatic liver tumor was also found to be from the bladder cancer (Fig. 4C). We considered the clinical stage to be ss (T2), n1, stage

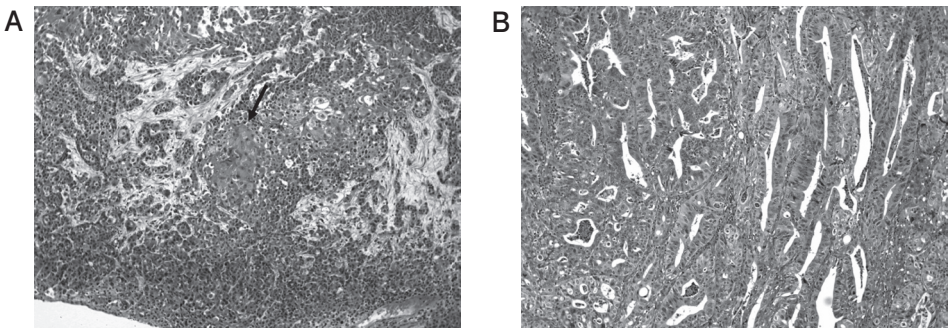

Fig. 3 A: Squamous cell carcinoma (↓) mixed with transitional cell carcinoma was diagnosed by biopsy of the bladder tumor. (H.E. stain × 100.) B: Pathological examination of the gastric cancer revealed moderately differentiated tubular adenocarcinoma. (H.E. stain × 100.)

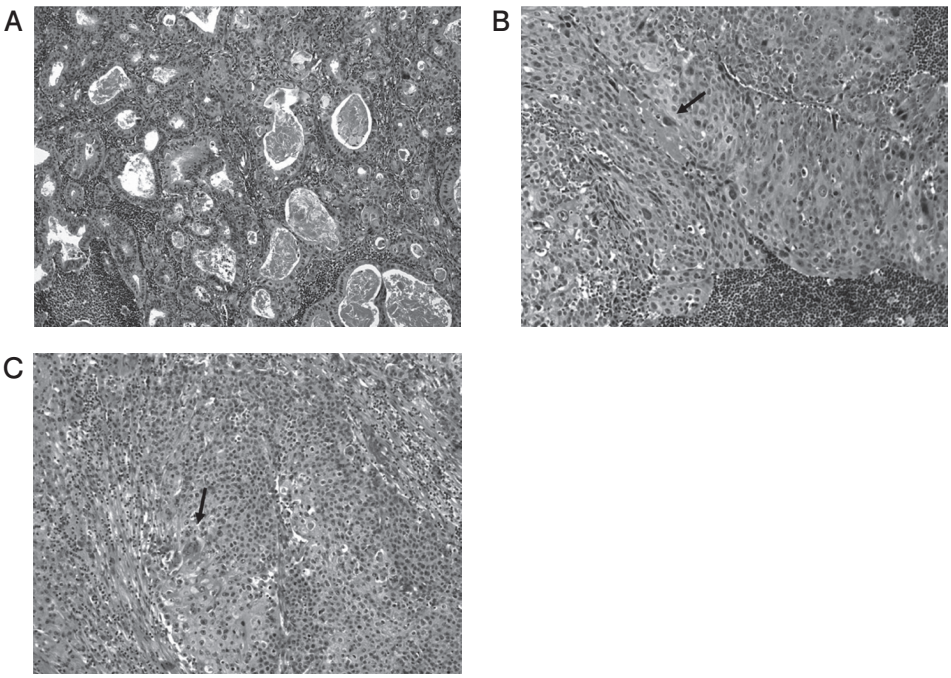

Fig. 4 A: The No.4d lymph node metastasis was adenocarcinoma from the gastric cancer. (H.E. stain × 100.) B: The No. 9 lymph node metastasis was squamous cell carcinoma (↓) mixed with transitional cell carcinoma from the bladder cancer. (H.E. stain × 200.) The No.8a and No. 9 lymph node metastases had the same characteristics. C: The metastatic liver tumor was squamous cell carcinoma (↓) mixed with transitional cell carcinoma from the bladder cancer. (H.E. stain × 200.)

II, and there was curative potential of gastric resection with Resection A for the gastric cancer. We considered the para-aortic lymph node swelling to represent metastasis of the bladder cancer. The postoperative course was uneventful and the patient was transferred from the surgical ward to the department of urology for chemotherapy, 14 days postoperatively. She received cisplatin 100 mg/body on day 1, and gemcitabine hydrochloride 1.6 g/body on days 1 and 8 every 3 weeks. Three courses of this regimen were administered. Next, the patient received epirubicin hydrochloride 80 mg/body on day 1, methotrexate 50 mg/body on day 1, calcium folinate 45 mg/body on day 1 and 75 mg/body on day 2, and nedaplatin 60-80 mg/body on days 2 and 3. Two courses of this regimen were administered. Abdominal CT showed a remarkable reduction of the primary bladder cancer and lymph node metastasis in the abdomen but the liver metastasis was unchanged. The hepatic arterial infusion chemotherapy regimen was carboplatin 360-575 mg/body on day 1, gemcitabine hydrochloride 0.8-1 g/body on day 1, and docetaxel 60-80 mg/body on day 1. Three courses of this regimen were administered. However, abdominal CT showed progression of the primary bladder cancer, the lymph node metastases in the abdomen and the liver metastasis. She was admitted with complaints of gait disturbance and dysarthrosis, 10 days after being discharged following the final chemotherapy. Head MRI showed leptomeningial carcinomatosis in the brain. The patient died 14 days after the final admission, i.e. 10 months after surgery (Fig. 5).

Discussion

Definitions of multiple primary malignant tumors have been widely applied based on the criteria proposed by Warren and Gates, i.e., that each of the tumors must present a definite picture of malignancy, each must be distinct, and the probability of one being a metastasis of the other must be excluded.[1] The double cancers in our case were a gastric tumor found to be a moderately differentiated tubular adenocarcinoma and a bladder cancer showing squamous cell carcinoma mixed with transitional cell carcinoma, and thus met Warren and Gate's criteria.

Surgical resection of gastric cancer is a well established treatment. Guidelines for the diagnosis and treatment of carcinoma of the stomach include the operative method,

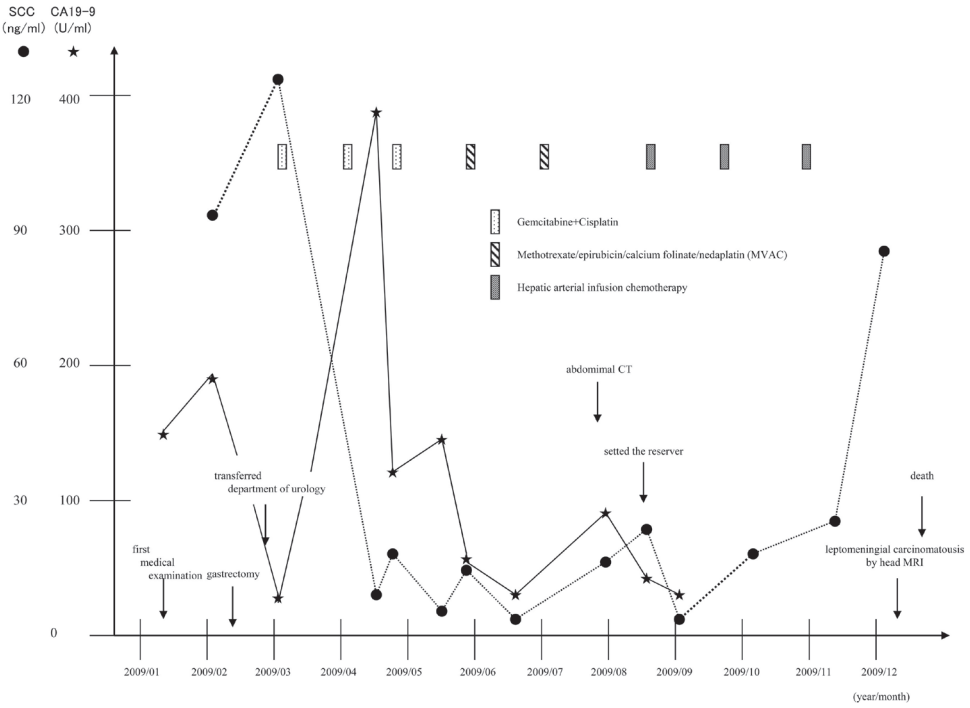

Fig. 5 Clinical course and tumor marker value.

the area of lymph node dissection, and so on, according to clinical stage.[2] The regional lymph nodes of the stomach are classified into station numbers and into three groups, depending upon the location of the primary tumor, in the Japanese classification of gastric carcinoma,[3-6] and the Japanese Classification of Gastric Carcinoma describes lymph node metastasis from a nearby regional lymph node to distant regional lymph nodes, that is, from an n1 lymph node to a para-aortic lymph node via n2 and n3 lymph nodes.

Regional lymph node metastases of bladder cancers are not classified depending upon the location of the primary tumor but rather on the number and/or size of metastatic regional lymph nodes,[7] based on the TNM classification of the international union against cancer.[8] The classifications of regional lymph node metastasis differ between gastric and bladder cancers, because lymph flow associated with the bladder involves various lymph nodes in the pelvis. Lymph from the bladder drains into the internal iliac nodes, though some lymph from the base may pass directly to the internal iliac and common iliac nodes, and some from the neck of the bladder may go directly to the sacral nodes.[9] Lymph node metastasis of bladder cancer reportedly involves the paravesical nodes in 16%, the obturator nodes in 74%, the external iliac nodes in 65%, the presacral nodes in approximately 25%, and juxtaregional lymph nodes in approximately 20% of cases.[10] Thus, bladder cancer can metastasize to several pelvic lymph nodes.

Regional lymph node metastasis due to a mix of gastric and bladder cancers is very rare. An extensive literature search using the key words gastric cancer, bladder cancer, regional lymph node metastasis, metastasis, and/or double cancer, from 1950 to 2010, yielded no reports similar to our case in PubMed. We speculate that the gastric cancer metastases had originated from the primary gastric tumor and reached the No.4d lymph nodes (greater curvature nodes) normogradely, while those of the primary bladder cancer had reached the pelvic and para-aortic lymph nodes and then spread from the para-aortic to the No. 8a lymph nodes (common hepatic artery nodes anterosuperior group) and No. 9 lymph nodes (celiac artery nodes) retrogradely.

More than 90% of bladder cancers are transitional cell carcinomas. Squamous cell carcinoma accounts for only 1% of bladder cancer in England, and 3% to 7% in the United States. Squamous cell carcinoma accounts for 3.2% (9/285) and squamous cell carcinoma mixed with transitional cell carcinoma accounts for 9.1% (26/285) of bladder cancer in Japan.[11] Friedell[10] reported the rate of mixed tumors comprised of both squamous cell carcinoma and transitional cell carcinoma to be 6.0%. Squamous cell carcinomas are usually caused by chronic irritation from urinary calculi, long-term indwelling catheters, chronic urinary infections, or bladder diverticula.[12] Conversely, squamous cell carcinoma accounts for as much as 75% of bladder cancer in Egypt, and approximately 80% of squamous cell carcinomas in Egypt are associated with chronic infection with Schistosoma haematobium.[12]

Distal metastasis from squamous cell carcinoma of the bladder is rare,[13] with metastatic disease being confirmed in only 8.8% of cases.[13] Thus, squamous cell carcinoma of the bladder is considered to be highly invasive at the local level. The prognosis of squamous cell carcinoma of the bladder is reportedly poor; only 23.8% of patients were alive one year after the diagnosis and the 5-year survival rate was 1.9%.[12] In one study, 92.2% of patients with squamous cell carcinoma of the bladder were found to have invasive tumors (T2-T4) at diagnosis,[14] and most patients die after attempts at locoregional tumor control have failed.[13] Takai reported that squamous cell carcinoma mixed with transitional cell carcinoma was the property that resembled transitional cell carcinoma well, and special mention for squamous cell carcinoma mixed with transitional cell carcinoma was not accomplished.[11] Charbit[15] reported that primary squamous cell carcinoma exhibited a faster growth rate, followed by primary adenocarcinomas, and that the growth rate of squamous cell carcinoma was exceeded by the growth rate of its metastases. As noted above, we considered the prognosis of squamous cell carcinoma of the bladder to be poor as it shows marked local invasive-

ness, progresses rapidly with deep invasion, and quickly invades distant organs, i.e., is a highly invasive tumor.

For this patient, we decided to perform resection A (no residual disease with high probability of cure) for the gastric cancer, as the clinical stage was T2 (ss), n1, stage II and the patient underwent D2 dissection (all Group 1 and Group 2 nodes).[3] Thus, adjuvant chemotherapy was not always necessary for the gastric cancer. At present, there is no recommended adjuvant chemotherapy regimen for gastric cancer and a course of 5-FU/CDDP,[16] UFT,[17] or TS-1[18] is administered according to the standard of each institution.

Clinically, the bladder cancer which had metastasized to lymph nodes of the pelvis and to the liver was stage IV, an indication for chemotherapy but not surgery. However, there is no established regimen for squamous cell carcinoma and squamous cell carcinoma mixed with transitional cell carcinoma of the bladder, such that a regimen recommended for transitional cell carcinoma of the bladder was used. The standard regimen for advanced transitional cell carcinoma of the bladder, according to Sternberg, was methotorexate/vinblastine/doxorubicin/cisplatin (M-VAC).[19] Recently, however, a randomized controlled trial revealed gemcitabine/cisplatin (GC) to provide efficacy similar to that of M-VAC with a better safety profile and tolerability.[20][21] GC therapy is anticipated to replace M-VAC as the standard treatment for advanced metastatic bladder cancer.

We experienced a rare case with regional lymph node metastasis of stomach from mixed double gastric and bladder cancers. Thus, in cases with simultaneous double cancers, we must determine the stage and select the most appropriate therapy for each tumor because therapeutic regimens differ among cancers.

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