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CASE REPORT

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Diagnostic benefit of cytological and histopathological examinations for recurrent vaginal cancer metastasizing to the duodenum: A case report

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Abstract

This is the first case report of a vaginal squamous cell carcinoma that metastasized to the duodenum. Cytological and histopathological examinations are useful for the diagnosis of a duodenal metastasis.

KEYWORDS

cytological diagnosis, duodenal neoplasm, immunohistochemistry, metastatic neoplasm, recurrence, vaginal neoplasm

1 | INTRODUCTION

Metastatic disease from a primary malignancy to the duodenum is extremely rare. Here, we report the first case of a recurrent vaginal squamous cell carcinoma that metastasized to the duodenum. Cytological and histopathological examinations were useful for the diagnosis of a recurrent vaginal cancer metastasizing to the duodenum.

Primary vaginal cancer is a rare tumor, making up approximately 1%–2% of all gynecologic cancers and only 10% of all malignant neoplasms involving the vagina.[1] According to *Cancer Statistics in Japan-2019*, of 157,800 deaths due to female malignant neoplasms, 139 deaths (0.09%) were due to vaginal cancer.[2] Approximately 6,230 new cases of vaginal cancer associated with 1,450 deaths have been estimated for 2020 in the United States.[3] Squamous cell carcinoma (SCC) is the most common histopathological type (85%) followed by adenocarcinoma (10%-15%).[4] A population-based study from Denmark reported that 89% of women with vaginal SCC were positive for high-risk human papillomavirus (HPV).[5]

Though vaginal cancer may invade locally and disseminate by hematogenous and lymphatic routes,[4] a metastasis to the duodenum is extremely rare. Only 1 case report of vaginal malignant melanoma with metastasis to the papilla of Vater can be found on PubMed.[6] Herein, we report a case of recurrent vaginal cancer metastasizing to the duodenum, for which cytological and histopathological examinations were useful for obtaining a diagnosis.

2 | CASE PRESENTATION

The patient was a 76-year-old woman, gravida 4, para 2. Her medical history included stage II rectal cancer at 60 years of age and uterine cervical dysplasia at 64 years of age. Her family and social history were unremarkable. At 68 years of age, she was initially diagnosed with stage IA squamous cell carcinoma (SCC) based on the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system, for a vaginal cancer that was located at 8 o'clock in the upper third of her vagina. The level of the serum tumor marker SCC antigen was increased to 2.1 ng/mL (upper normal range: 1.5 ng/mL). The patient underwent external radiation (51.4 Gy) and intracavitary brachytherapy (30 Gy). Computed tomography (CT) at 21 months after completion of the initial treatment revealed a metastatic para-aortic lymph node with an elevated serum SCC antigen level of 1.8 ng/mL, and she underwent chemoradiation therapy (external radiation 45 Gy and 5 courses of cisplatin 40 mg/m^2 administered intravenously). At 27 months after treatment for her first relapse, CT revealed multiple enlarged lymph nodes from her neck to her pelvis and a swollen para-aortic lymph node adjacent to her duodenum. The serum SCC antigen level had increased to 5.7 ng/mL. The patient was administered 10 courses of paclitaxel and carboplatin.

At 23 months after the end of treatment for her second recurrence, the patient complained of chills and fever. Laboratory data indicated inflammation, liver dysfunction, and an elevated serum amylase and elevated serum SCC antigen level of 12.9 ng/mL (Table 1). The patient was found to be negative for infection with hepatitis B and C virus. CT, MRI (T2WI), and endoscopy showed severe edema of the descending duodenum and marked dilatation of the intra- and extrahepatic biliary trees (Figure 1). However, no cancerous lesion on the duodenal mucosa was seen on endoscopy. No other cancerous lesions were detected in other organs or lymph nodes. The patient underwent endoscopic retrograde cholangiopancreatography (ERCP) and was diagnosed with obstructive jaundice due to bile duct stricture.

Cytological specimens of bile and the biliary tract were collected via ERCP. Cytological examination found atypical keratinized epithelial cells with enlarged nuclei and increased chromatin (Figure 2). Histopathological examination of a duodenal biopsy specimen showed findings similar to those from the previously resected specimen of vaginal SCC (Figure 3). The duodenal specimen was immunohistochemically positive for p40 and cytokeratin (CK) 5/6 and negative for CDX2 expression. In addition, the duodenal tumors were strongly and focally positive for p16 and p53 with a staining pattern identical to that of the primary vaginal SCC.

After undergoing percutaneous transhepatic cholangial drainage, the patient received 1 course of nedaplatin monotherapy, but chemotherapy could not be continued because of severe cholangitis. She was transferred to best supportive care and died of the disease 10 months after the diagnosis of duodenal metastasis. She was maintained in stable condition and was able to receive adequate oral nutrition after undergoing endoscopic biliary and duodenal stenting.

3 | DISCUSSION

Primary vaginal carcinoma was first reported in 1826 by Cruveilhier.[7] Most vaginal cancers are diagnosed in postmenopausal or elderly women. However, vaginal cancers are etiologically correlated with cervical dysplasia and are seen in younger women because of increased numbers of high-risk HPV infections.[8] Cervical dysplasia was diagnosed in our patient 4 years before her diagnosis of vaginal cancer.

Treatment should be based on the clinicopathological variables of the patient. Young age, good performance status, early-stage cancer, small-sized tumor, previous hysterectomy, and normal hemoglobin level were reported to be associated with good clinical outcomes. Although surgery yields good local control and survival for patients with early-stage vaginal cancer, radiation is the principle treatment.[9] Intensity-modulated radiation therapy can deliver high dosages of radiation to the cancer, and concurrent chemotherapy is thought to improve patient outcomes. Guerri et al reported five-year overall survival rates of 35%-78%, with severe late complication rates of 9%–23% for patients with SCC treated by radiotherapy.[10] Although no data from prospective trials are available, Miyamoto and Viswanathan reviewed retrospective studies and reported that chemoradiation therapy provided significantly better overall survival and disease-free survival compared with radiation alone (respective three-year overall survival rates of 79% versus 56% and three-year disease-free survival rates of 73% vs 43%).[11] Nashiro et al claimed that chemoradiation therapy was effective for primary vaginal SCC and should be considered for patients with high-risk disease.[12] However, vaginal cancer primarily affects elderly women, and therefore, possible adverse effects should be carefully considered.

Although multimodal treatments have been performed, the prognosis of vaginal cancer is very poor, with a 5-year overall survival of approximately 50%.[4] Our patient developed 3 recurrences after her initial radiotherapy treatment. Chemoradiation therapy and platinum-based double-agent chemotherapy were performed for her first and second episodes of recurrent disease, respectively. She was found to have obtained complete response after each treatment, but she finally succumbed to a third recurrence 9 years after her initial diagnosis of vaginal cancer. Although she could not receive a complete course of anticancer therapy, she was maintained in stable condition for 10 months. Best supportive care might be effective at maintaining a patient's condition.[13]

TABLE 1 Laboratory findings on admission

Examination items	Values	Reference
Complete blood count		
White blood cells	7800/μL	3300-8600
Neutrophils	90.0%	42.4%-75.0%
Lymphocytes	4.4%	18.2%-47.7%
Monocytes	4.7%	3.3%-9.0%
Eosinophils	0.8%	0.4%-8.6%
Basophils	0.1%	0.2%-1.4%
Red blood cells	$422x10^4$/μL	386-492 $x10^4$
Hemoglobin	12.7 g/dL	11.6-14.8
Hematocrit	37.2%	35.1%-44.4%
Platelet	38.8×10^4/μL	$158\text{-}348 \times 10^4$
Blood chemistry		
Total protein	5.4 g/dL	6.6-8.1
Albumin	2.1 g/dL	4.1-5.1
Total bilirubin	8.6 mg/dL	0.4-1.5
Direct bilirubin	6.9 mg/dL	0.1-0.4
Indirect bilirubin	1.7 mg/dL	0.2-0.8
AST	182 U/L	13-30
ALT	166 U/L	7-23
LDH	223 U/L	124-222
ALP	2535 U/L	106-322
γ-GTP	596 U/L	9-32
ChE	188 U/L	201-421
Total cholesterol	216 mg/dL	142-248
Triglycerides	71 mg/dL	30-117
Urea nitrogen	10.6 mg/dL	8-20
Creatinine	0.55 mg/dL	0.46-0.79
Uric acid	4.2 mg/dL	2.6-5.5
Sodium	138 mmol/L	138-145
Potassium	3.9 mmol/L	3.6-4.8
Chloride	105 mmol/L	101-108
Calcium	10.0 mg/dL	8.8-10.1
Pancreatic-amylase	388 U/L	16-52
Salivary-amylase	66 U/L	8-68
Creatine kinase	95 U/L	41-153
HbA1c	6.0%	4.9%-6.0%
CRP	17.27 mg/dL	0-0.14
Immunology		
IgG	1034 mg/dL	861-1747
IgA	169 mg/dL	93-393
IgM	95 mg/dL	50-269
IgG4	42.2 mg/dL	4.5-117
Antinuclear antibody	×40	<40
Rheumatoid factor	71 U/mL	<15
Virus Marker		
HBs antigen	Negative	Negative
HBc antigen	Negative	Negative
HCV antigen	Negative	Negative
Tumor marker		
SCC ag	12.9 ng/mL	<1.5
CEA	5.6 ng/mL	<5.0
CA19-9	15 U/mL	<37

Abbreviations: ALP, alkaline Phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ChE, cholinesterase; CRP, C-reactive protein; HB, hepatitis B virus; HbA1c, hemoglobin A1c; HCV, hepatitis C virus; Ig, immunoglobulin; LDH, lactate dehydrogenase; SCC ag, squamous cell carcinoma antigen; γ-GTP, glutamyl transpeptidase.

Because of its anatomical location and its extensive interconnecting cardiovascular and lymphatic systems, vaginal cancer is prone to invade adjacent sites and metastasize to other organs. The lymphatic drainage of the vagina is complex. The upper vaginal lymphatics drain to the pelvis, and spread to the para-aortic lymph nodes is rare. Hematogenous dissemination to other organs, including lung, liver, and bone, is usually a late manifestation.[9]

Duodenal SCCs have been reported to be more likely metastases from other sites,[14] but determining whether the duodenal SCC is a primary or metastatic tumor is necessary. Primary duodenal SCC is exceedingly rare, with only a few cases reported in the literature.[15,16] Most of these cases were tumors in the descending duodenum near the ampulla of Vater. Distinguishing between metastatic SCC and primary duodenal SCC on the basis of symptoms and imaging findings is difficult, because the major findings of the 2 conditions are similar.[17] Immunohistochemistry is helpful for the differential diagnosis. Kanthan et al reported a case of duodenal metastasis from uterine cervical SCC.[18] They used the immunohistochemical markers CK5, p63, and p16 to confirm the diagnosis of duodenal metastasis. The duodenal tumor of our patient was strongly and focally positive for p16 and p53, with a staining pattern identical to that of the primary vaginal SCC.

The diagnostic usefulness of brush cytology obtained during ERCP has also been reported. Kyriazi et al diagnosed a pancreatic metastasis from lung SCC by a cytological examination that showed abnormal epithelial cells with squamoid features.[19]

Endoscopically, metastatic tumors were reported to present as submucosal structures with bridging folds and small ulcerations called volcano-like ulcers at the top.[20] In our case, the duodenal mucosa was severely edematous, but no cancerous lesions suggesting metastatic tumors were detected.

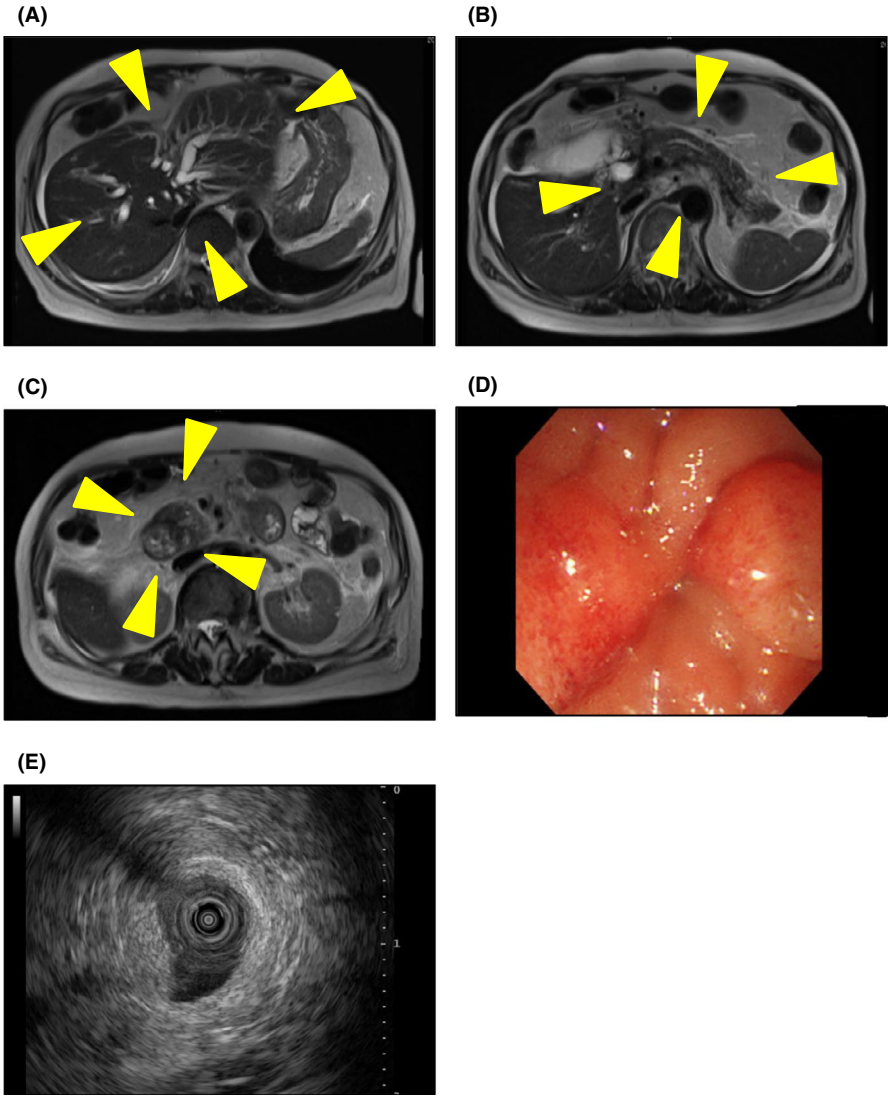

FIGURE 1 Duodenal edema and dilated bile ducts. MRI (T2WI): A, liver, B, pancreas, C, duodenum. Endoscopic view: D, edematous duodenal mucosa. Endoscopic ultrasonography image: E, bile duct stricture

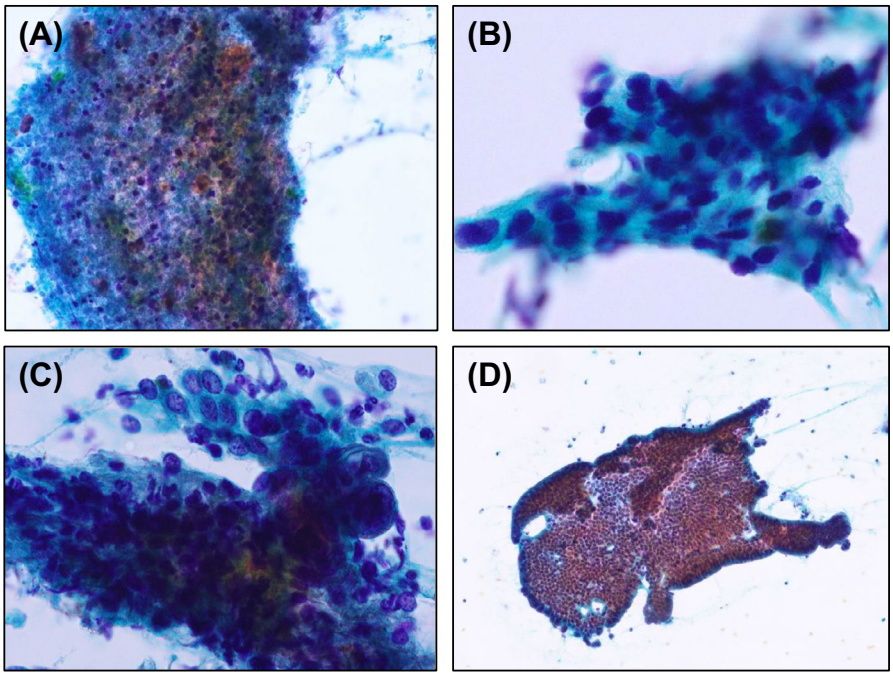

FIGURE 2 Cytological examination revealed atypical keratinized epithelial cells. Papanicolaou staining (magnification: A and D ×40; B and C ×100): A, bile, B, C, bile duct, D, normal bile duct epithelium

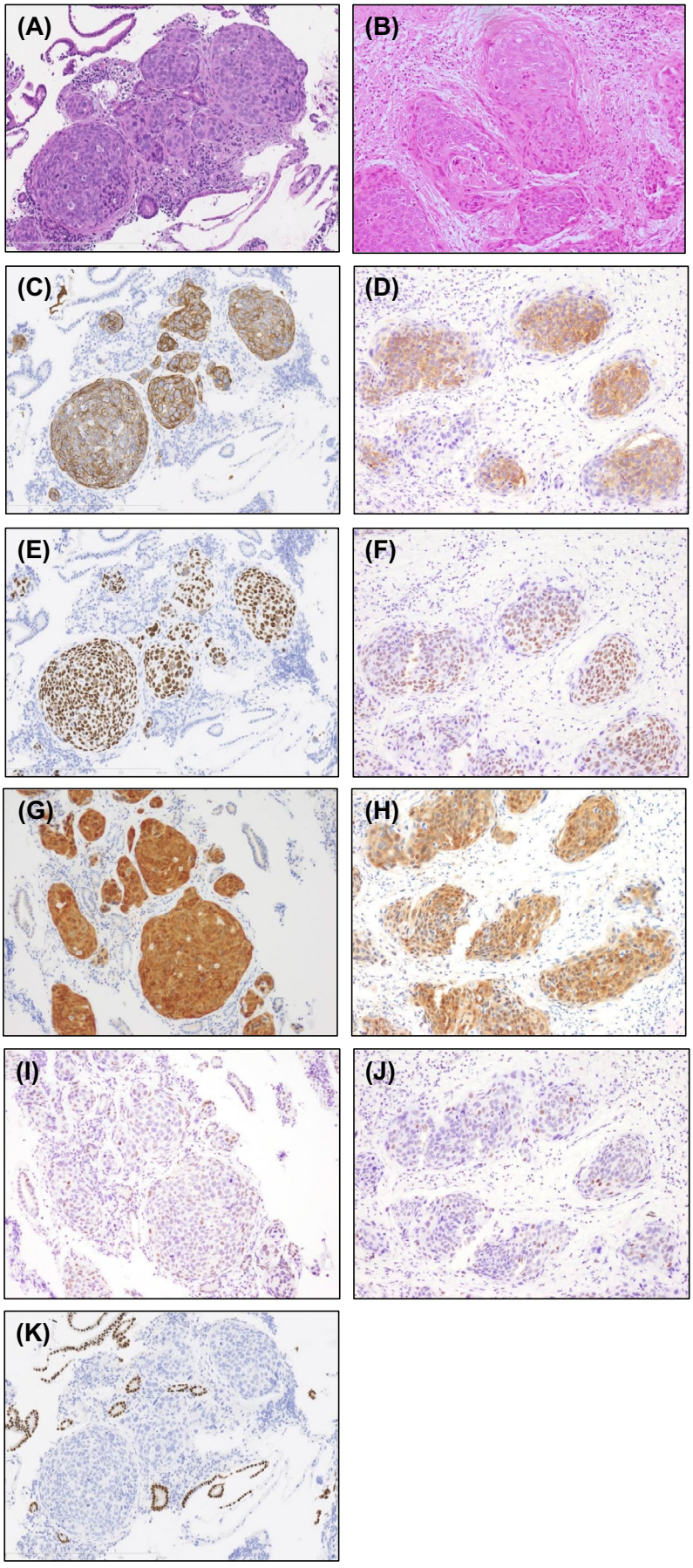

FIGURE 3 Histopathological and immunohistochemical examinations revealed a duodenal metastasis of vaginal cancer. Hematoxylin and eosin staining (magnification: ×100): A, duodenal tumor, B, primary vaginal cancer. Immunohistochemistry of duodenal specimen (magnification: ×100): C, CK5/6, E, p40, G, p16, I, p53, K, CDX2. Immunohistochemistry of vaginal specimen (magnification: ×100): D, CK5/6, F, p40, H, p16, J, p53

We can only speculate on the metastatic route of our patient's tumor from her vagina to her duodenum. Kanthan et al reviewed metastases to the small bowel from WHERE? and claimed that the spread was considered to occur more commonly through the lymphatics, usually via the para-aortic or mesenteric lymph nodes, and less often through hematogenous dissemination.[18] Our patient had a metastatic para-aortic lymph node and multiple metastatic lymph nodes from her neck to her pelvis at her first and second recurrences, respectively. With her third recurrence, she only had a duodenal tumor, and diagnostic imaging did not reveal other cancerous lesions. The mechanisms involved in the establishment of her duodenal metastasis remain unclear, although retrograde lymphatic spread from the para-aortic lymph nodes is suspected.

4 | CONCLUSION

Metastatic disease from a primary malignancy to the duodenum is uncommon. To the best of our knowledge, this is the first case report of a vaginal SCC that metastasized to the duodenum. We think that cytological and histopathological examinations are useful for the diagnosis of duodenal metastasis.

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CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
Dr Sonoda: contributed to data collection, data analysis and interpretation, and the writing of the manuscript. Dr Fujimoto and Dr Taguchi: contributed to cytological and histological diagnosis, immunohistochemistry, and the revision of the manuscript. Dr Sugimoto: contributed to the treatment of obstructive jaundice and the revision of the manuscript. Dr Okadome and Dr Saito: contributed to data analysis and interpretation, and the revision of the manuscript. All authors: contributed intellectually and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
All procedures in the current case report were in accordance with the ethical standards of the Institutional Research Committee of National Hospital Organization Kyushu Cancer Center, the ethical guidelines of the Ministry of Health, Labour, and Welfare of Japan, and the 1964 Helsinki Declaration and its later amendments. We only analyzed the data and medical or radiological images for which the patient gave permission at her first consultation at our hospital. No patient-identifiable data were reported, and no direct interaction with the patient was necessary.

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