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CASE REPORT

Bone metastasis as a recurrence of early papillary adenocarcinoma of the stomach

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Abstract
Papillary adenocarcinomas of the stomach are rare and associated with a high rate of lymphovascular invasion and distant metastasis. However, the association between papillary adenocarcinoma and bone metastasis in gastric cancer remains largely unexplored. We report a rare case of bone metastasis as a recurrence of early papillary adenocarcinoma of the stomach after curative surgery. A 75-year-old man with a pedunculated polyp at the pylorus of the stomach was diagnosed with papillary adenocarcinoma after biopsy of the lesion, and the polyp was surgically resected. Pathohistological examination revealed intramucosal cancer without lymphovascular invasion or lymph node metastasis. Eight months after surgery, imaging studies showed osteolysis in the right sacrum, and the lesion was diagnosed as a bone metastasis after biopsy. The patient received palliative chemotherapy and radiotherapy for the bone metastasis, which resulted in relief of his leg pain. Subsequently, he was provided supportive care when his condition deteriorated, and he died 8 months after the diagnosis of bone metastasis. Our case shows that bone metastasis should not be overlooked, even though it is rare in gastric cancer patients. Papillary adenocarcinoma of the stomach should be carefully followed up through imaging examinations, even after curative resection.

Keywords Early gastric carcinoma · Papillary adenocarcinoma · Bone metastasis

Introduction

Early gastric carcinoma (EGC) is curatively treated through surgical or endoscopic resection [1]. Recent studies have reported that the recurrence rate of EGC after curative surgical resection is 2–3% [2, 3]. Further, studies have also shown that the 5-year overall survival rate after surgical or endoscopic resection in EGC is more than 90% [4, 5]. Old age (≥ 65 years), male sex, undifferentiated tumors, submucosal invasion, and venous invasion have all been found to be risk factors for tumor recurrence in pT1N0M0 gastric cancer after curative surgical resection [6].

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Papillary adenocarcinomas of the stomach are a rare histologic tumor type that account for only 6–11% of all gastric carcinoma cases [7]. Relative to tubular adenocarcinoma patients, early papillary adenocarcinoma patients have a comparatively poor prognosis with a 5-year overall survival rate of 80.5% versus 96.8%. Papillary adenocarcinomas of the stomach have been reported to be associated with high rates of deep invasion into the submucosal layer, micropapillary component, and lymphovascular invasion, all of which contribute to poor prognosis [8]. Furthermore, gastric carcinomas with micropapillary components are associated with lymphovascular invasion and lymph node metastasis (LNM) [9]. A previous study showed that high-grade nuclear atypia in papillary gastric adenocarcinoma was correlated with higher rates of deep invasion beyond the submucosal layer, lymphovascular invasion, LNM, and poor prognosis [10]. The rate of distant metastasis after curative resection has been reported to be higher in papillary adenocarcinoma (11.8%) than in tubular adenocarcinoma (3.7%) [8]. Previous studies have also reported that distant metastasis to the liver is more common in patients with papillary adenocarcinoma than in patients with non-papillary adenocarcinoma [7].

Bone metastasis, which contributes to skeletal-related events (SREs), such as chronic pain, pathological fractures, and hypercalcemia, directly contribute to the deterioration of patient quality of life [11]. Bone metastasis after curative resection of EGC is very rare and has been reported in 0.2–0.4% of cases [3, 12]. Bone metastases have been noted in patients with depressed-type carcinomas, signet-ring cell carcinomas, poorly differentiated carcinomas, and lymph node involvement [13].

Although the distant metastasis rate in early papillary adenocarcinomas of the stomach is not very high, it has important clinical consequences. Data on the association between papillary adenocarcinomas and bone metastases in gastric cancer are limited. Here, we report a rare case of a patient with intramucosal papillary adenocarcinoma who was treated with curative resection but subsequently showed bone metastasis 8 months later, despite careful observation.

Case report

A 75-year-old man presenting with lightheadedness was transferred from another hospital for gastric tumor treatment. Blood tests showed hypochromic anemia and normal alkaline phosphatase, Ca, carcinoembryonic antigen, carbohydrate antigen 19-9, and cancer antigen 125 levels on admission. Esophagogastroduodenoscopy revealed a pedunculated polyp around the pylorus of the stomach (Fig. 1). Since preoperative examination showed that the tumor was large (2.5 cm) and had an expanding appearance, we determined that submucosal invasion had occurred. Tumor biopsy was performed, and a diagnosis of papillary adenocarcinoma was made. The tumor around the pylorus of the stomach was clearly noted on computed tomography (CT) but did not show any apparent distant metastasis or LNM. No cancerous lesions were found in other organs, including the thyroid, kidney, lung, and digestive tract. The tumor was staged at cT1bN0M0 (7th Union for International Cancer Control staging system), and surgery was performed. The tumor was a papillary adenocarcinoma with a grossly pedunculated lesion, 2.5 cm in diameter. The lesion was confined to the mucosal layer, lymphovascular invasion was found to be negative, micropapillary components were not identified, and low-grade nuclear atypia was observed. No lymph node metastases were found. Mucin immunohistochemical staining revealed that the lesion was positive for MUC5AC and MUC6 and negative for CD10 and MUC2 (Fig. 2). Subsequently, the lesion was determined to be a gastric-type differentiated adenocarcinoma and was completely resected. Although the patient did not experience any related symptoms, CT performed 8 months after surgery showed osteolysis in the right sacrum, and high tracer uptake on 18F-fluorodeoxyglucose positron emission tomography/CT was noted in the right sacrum, left pedicle of the third thoracic vertebra (T3), and fifth right rib (Figs. 3, 4). Suspecting multiple myeloma, a bone biopsy was performed. The findings were consistent with metastasis of gastric adenocarcinoma, as papillary structures similar to those noted in the histopathological specimen of the gastric cancer were detected. Low-grade nuclear atypia was also observed in the bone metastasis specimen. The metastatic bone lesion did not have either gastric or intestinal phenotypic expression (Fig. 5). The patient began to experience chronic pain in the right buttock and thigh 9 months after surgery. He was transferred to our hospital for administration of palliative chemotherapy and radiotherapy for bone metastasis. However, on admission, CT scans also revealed liver metastases. Extracorporeal radiotherapy (45 Gy) was administered to the right sacrum, and the patient was also treated with denosumab and analgesics. This relieved the pain, and pathological fractures did not occur. Chemotherapy with tegafur, gimeracil, oteracil potassium, and cisplatin was started but withdrawn 5 days later due to severe adverse effects. We recommended second-line chemotherapy with ramucirumab and paclitaxel following improvement of the patient's general condition. However, paclitaxel administration was rejected by the patient due to low emetic risk associations. Following further discussion with the patient, only ramucirumab, which had minimal emetic risk, was administered.

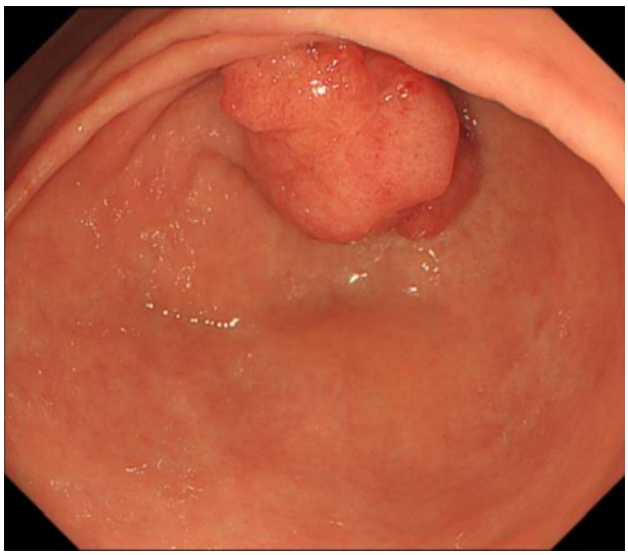

Fig. 1 Esophagogastroduodenoscopy revealing a pedunculated polyp around the pylorus of the stomach

The patient then received second-line palliative chemotherapy with ramucirumab. Three months after therapy initiation, disease progression was noted in the pre-existing bone and liver metastatic lesions, and new lumbar bone metastases (L1, L3) were noted. Due to the symptoms of right lower limb pain and upper back pain, palliative radiotherapy

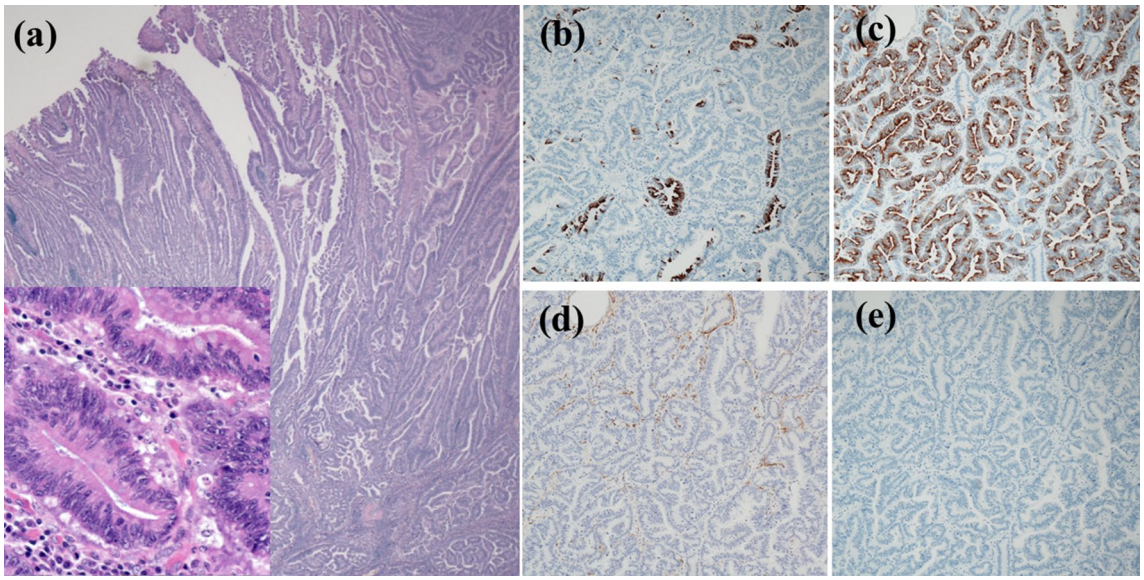

Fig. 2 Histopathological examination revealing papillary adenocarcinoma with low-grade nuclear atypia (**a**); the carcinoma glands are immunoreactive for MUC5AC (**b**) (from 5 to 10%) and MUC6 (**c**) (approximately 30%) and show negative staining for CD10 (**d**) and MUC2 (**e**)

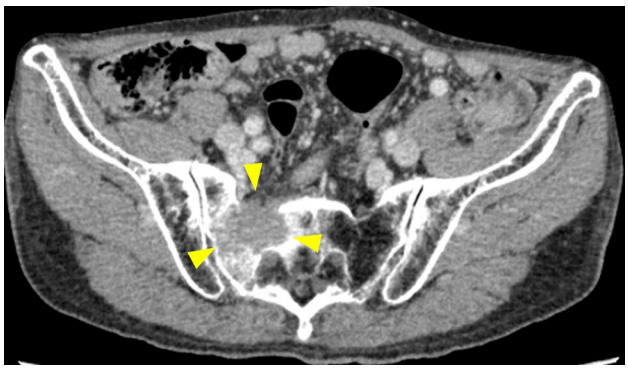

Fig. 3 Computed tomography showing osteolysis in the right sacrum

(36 Gy) targeting T3, L1, and L3 was re-administered. The patient developed esophagitis following radiotherapy, which caused decreased oral intake and deterioration in performance status. Following this, the patient received supportive care and died 8 months after the initial diagnosis of bone metastasis.

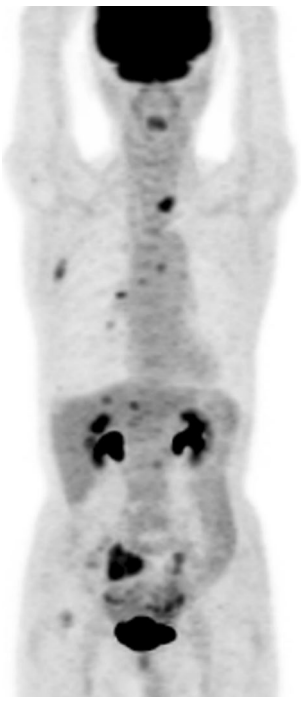

Fig. 4 18F-fluorodeoxyglucose positron emission tomography/computed tomography revealing high tracer uptake in the right sacrum, left pedicle of the third thoracic vertebra, and fifth right rib

Discussion

We report a case of early papillary adenocarcinoma of the stomach that was treated with curative resection, but the patient subsequently showed bone metastasis after 8 months. Metastasis was detected via CT prior to the patient's complaints of chronic right leg pain. This case demonstrated that early papillary adenocarcinoma of the stomach without any LNM can recur with bone metastasis.

Old age and male sex were possible contributing risk factors for tumor recurrence in our case, as has been suggested by a previous study [6]. However, we did not observe deep

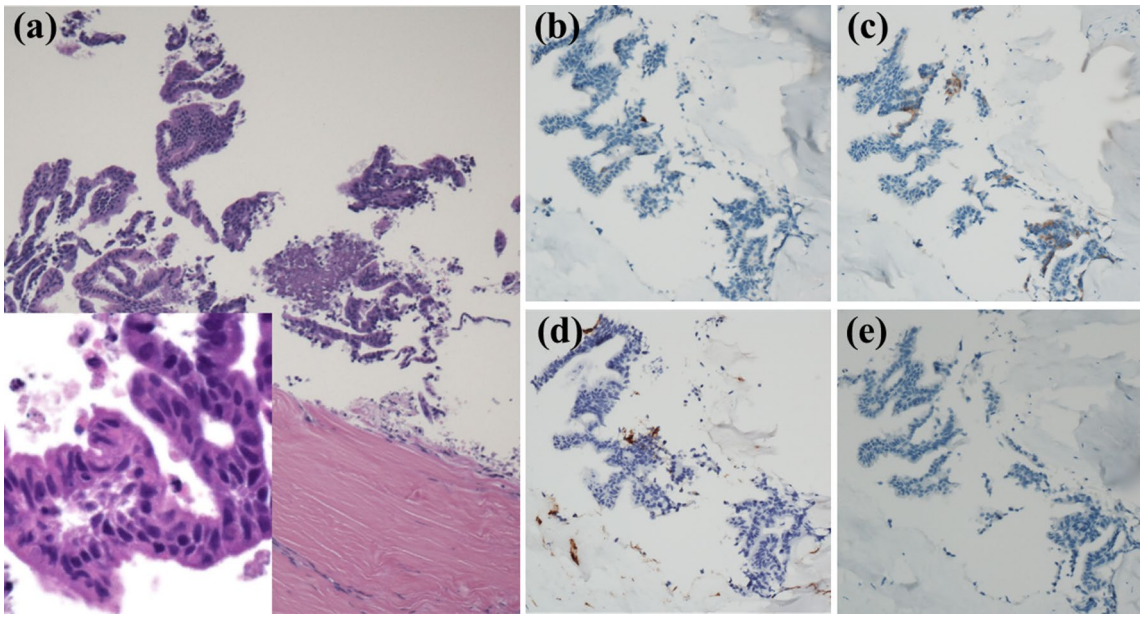

Fig. 5 Bone biopsy revealing papillary adenocarcinoma, consistent with metastasis of gastric cancer; the bone metastasis specimen shows low-grade nuclear atypia (**a**) and the carcinoma glands are not immunoreactive for MUC5AC (**b**), CD10 (**d**) and MUC2 (**e**). Few MUC6 (**c**) positive cells are observed

invasion into the submucosal layer or lymphovascular invasion. Micropapillary component, which is associated with poor prognosis of gastric papillary adenocarcinoma, was also not identified [8]. Mucin immunohistochemical staining revealed that the primary lesion had gastric-type mucin expression, which has been suggested to be strongly associated with lymphatic invasion and lymph node metastasis [14]. This case suggests that gastric-type mucin expression is also associated with bone metastasis. The bone metastatic lesion in this patient lost its phenotypic expression and was not classified as having gastric or intestinal type mucin expression. This loss of phenotypic expression was consistent with a previous report suggesting that loss of phenotypic expression was associated with tumor progression [15]. Surprisingly, the metastatic lesion revealed low-grade nuclear atypia, which was similar to that of the primary gastric lesion. Although bone metastasis has been considered to occur through hematogenous metastasis, in our case, pathological examination did not reveal vascular invasion [16]. Even though this case involved a lesion confined to the intramucosal layer, low-grade nuclear atypia, and no lymphovascular invasion or micropapillary component, bone metastasis was detected only 8 months after curative surgical resection.

The metastasis documented in this case may have been brought about through another mechanism. It is possible that tumor cells were present in the peripheral blood or had disseminated into the bone marrow as a previous report showed that circulating tumor cells (CTCs) were detected in peripheral blood of metastatic cancer patients [17]. The amount of CTCs is relatively high in gastric cancers with diffuse bone metastasis, as suggested by a previous study [18]. While CTCs were not examined in this case, they may have been present in peripheral blood, consequently finding a niche and residing in the bone marrow. Further research on the possible mechanisms of metastasis, including CTCs, is needed as it can be used to predict distant metastasis and help prevent abrupt recurrences as was demonstrated in this case.

Early treatment following detection of bone metastasis is important. Radiation therapy and denosumab administration are beneficial for reducing SREs [19, 20]. According to a previous report, the median time to bone metastasis detection after EGC diagnosis is 65 months [21]. In our case, the time taken for detecting bone metastasis (via follow-up CT) after gastrectomy was only 8 months, and metastasis was detected before the patient complained of chronic right leg pain. Even though recurrence occurred within a short time period, prompt treatment of SREs was possible after biopsy-based diagnosis of bone metastasis as this prevented adverse effects in terms of daily living activities. Early treatment following discovery of bone metastases can be beneficial with this regard.

In conclusion, this case demonstrated the possible risk of bone metastasis in patients with early papillary adenocarcinoma of the stomach, even after curative resection. Papillary adenocarcinomas of the stomach should be carefully followed with imaging examinations to detect possible bone metastasis in a timely manner.

Compliance with ethical standards

Conflict of interest Nobukazu Agatsuma, Yoshitaka Nishikawa, Takahiro Horimatsu, Yasuki Nakatani, Noriko Juri, Takuji Akamatsu, Takeshi Seta, Sachiko Minamiguchi and Yukitaka Yamashita declare that they have no conflict of interest.

Human rights All the procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all patients for being included in the study.

References

1. Gotoda T, Jung H-Y. Endoscopic resection (endoscopic mucosal resection/endoscopic submucosal dissection) for early gastric cancer. Dig Endosc. 2013;25(Suppl 1):55–63.
2. Lai JF, Kim S, Kim K, et al. Prediction of recurrence of early gastric cancer after curative resection. Ann Surg Oncol. 2009;16:1896–902.
3. Youn HG, An JY, Choi MG, et al. Recurrence after curative resection of early gastric cancer. Ann Surg Oncol. 2010;17:448–54.
4. Suzuki H, Oda I, Abe S, et al. High rate of 5-year survival among patients with early gastric cancer undergoing curative endoscopic submucosal dissection. Gastric Cancer. 2016;19:198–205.
5. Sun W, Han X, Wu S, et al. Endoscopic resection versus surgical resection for early gastric cancer. Medicine (Baltimore). 2015;94:e1649.
6. Choi HJ, Kim SM, An JY, et al. Risk factors and tumor recurrence in pT1N0M0 gastric cancer after surgical treatment. J Gastric Cancer. 2016;16:215–20.
7. Yasuda K, Adachi Y, Shiraishi N, et al. Papillary adenocarcinoma of the stomach. Gastric Cancer. 2000;3:33–8.
8. Yu H, Fang C, Chen L, et al. Worse prognosis in papillary, compared to tubular early gastric carcinoma. J Cancer. 2017;8:117–23.
9. Fujita T, Gotohda N, Kato Y, et al. Clinicopathological features of stomach cancer with invasive micropapillary component. Gastric Cancer. 2012;15:179–87.
10. Nakashima Y, Yao T, Hirahashi M, et al. Nuclear atypia grading score is a useful prognostic factor in papillary gastric adenocarcinoma. Histopathology. 2011;59:841–9.
11. Mundy GR. Metastasis to bone: causes, consequences and therapeutic opportunities. Nat Rev Cancer. 2002;2:584–93.
12. Park JM, Song KY, Kim WC, et al. Bone recurrence after curative resection of gastric cancer. Gastric Cancer. 2013;16:362–9.
13. Kobayashi M, Okabayashi T, Sano T, et al. Metastatic bone cancer as a recurrence of early gastric cancer—characteristics and possible mechanisms. World J Gastroenterol. 2005;11:5587–91.
14. Koseki K, Takizawa T, Koike M, et al. Distinction of differentiated type early gastric carcinoma with gastric type mucin expression. Cancer. 2000;89:724–32.
15. Nakamura T, Yao T, Kabashima A, et al. Loss of phenotypic expression is related to tumour progression in early gastric differentiated adenocarcinoma. Histopathology. 2005;47:357–67.
16. Kelly PJ, Peterson LFA, Pease DC, Zamboni L. Circulation of Bone. In: Abramson DI, editor. Blood vessels and lymphatics. 1st ed. New York: Academic Press; 1962. p. 531–556.
17. Takeuchi H, Kitagawa Y. Circulating tumor cells in gastrointestinal cancer. J Hepatobiliary Pancreat Sci. 2010;17:577–82.
18. Shimazu K, Fukuda K, Yoshida T, et al. High circulating tumor cell concentrations in a specific subtype of gastric cancer with diffuse bone metastasis at diagnosis. World J Gastroenterol. 2016;22:6083–8.
19. De Felice F, Piccioli A, Musio D, et al. The role of radiation therapy in bone metastases management. Oncotarget. 2017;8:25691–9.
20. Body J-J. Denosumab for the management of bone disease in patients with solid tumors. Expert Rev Anticancer Ther. 2012;12:307–22.
21. Silvestris N, Pantano F, Ibrahim T, et al. Natural history of malignant bone disease in gastric cancer: final results of a multicenter bone metastasis survey. PLoS ONE. 2013;8:e74402.