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CASE REPORT - PATHOLOGY

Renal pelvic plasmacytoid subtype urothelial carcinoma accompanied with solitary mammary metastasis

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Abstract

A 72-year-old female was referred to our institution for further evaluation of right renal tumor detected during work-up for macroscopic hematuria in other hospital. CT urography performed at our institution suggested renal pelvic tumor. Voiding cytology was atypical. CT also revealed a small mass in the right mammary gland. Percutaneous needle biopsies were performed on the right mammary gland and renal mass, leading to a pathological diagnosis of UC with plasmacytoid subtype, suggesting metastasis from the renal pelvic UC to the mammary gland. She had a favorable response to four cycles of dose-dense MVAC therapy; therefore, we performed nephroureterectomy. One month after nephroureterectomy, new intraperitoneal metastatic lesions were observed and pembrolizumab therapy was started. After seven doses of pembrolizumab, CT revealed a marked size reduction of intraperitoneal metastases and the mammary metastasis remained small.

Keywords Urothelial carcinoma · Plasmacytoid subtype · Solitary mammary metastasis · Renal pelvic cancer

Introduction

Mammary metastasis from extra-mammary cancer is rare, with reported incidences ranging from 0.3 to 2.7% of all breast malignancies [1]. Furthermore, mammary metastasis from urinary tract is extremely rare with few reports [2, 3]. On the other hand, the pathological features of infiltrating lobular breast cancer (ILBC) and plasmacytoid urothelial carcinoma (UC) mimic each other, making differential diagnosis important in daily clinical practice [4].

Herein, we describe the first case of solitary mammary metastasis showing plasmacytoid UC, which was difficult to diagnose because of its specific pathological features.

Case report

A 72 year-old female was referred to our institution for further evaluation of right renal tumor detected during work-up for macroscopic hematuria in other hospital. Computed tomography (CT) urography performed at our institution detected filling defects in the renal calices in the excretory phases, suggesting renal pelvic tumor. Voiding cytology was atypical. In addition, chest CT revealed a small mass in the right mammary gland (Fig. 1A). Breast ultrasonography revealed a hypoechoic mass measuring 27 × 26 × 23 mm in the upper-inner section of the nipple of the right breast, suggesting primary breast cancer. Percutaneous needle biopsies of right mammary gland and renal mass were performed. The mammary tumor specimens revealed signet ring cell-like tumor cells with eccentrically placed nuclei and abundant eosinophilic cytoplasm (arrowhead) (Fig. 2A, B). Immunohistochemical evaluation of the mammary gland tumor was negative for estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2), and positive for GATA3 (Fig. 2C). E-cadherin staining showed distinct positive and negative areas (Fig. 2D). Pathological diagnosis of mammary gland tumor suggested the specific type of ILBC or plasmacytoid UC. Pathological findings of renal tumor revealed mostly necrotic tissue with few

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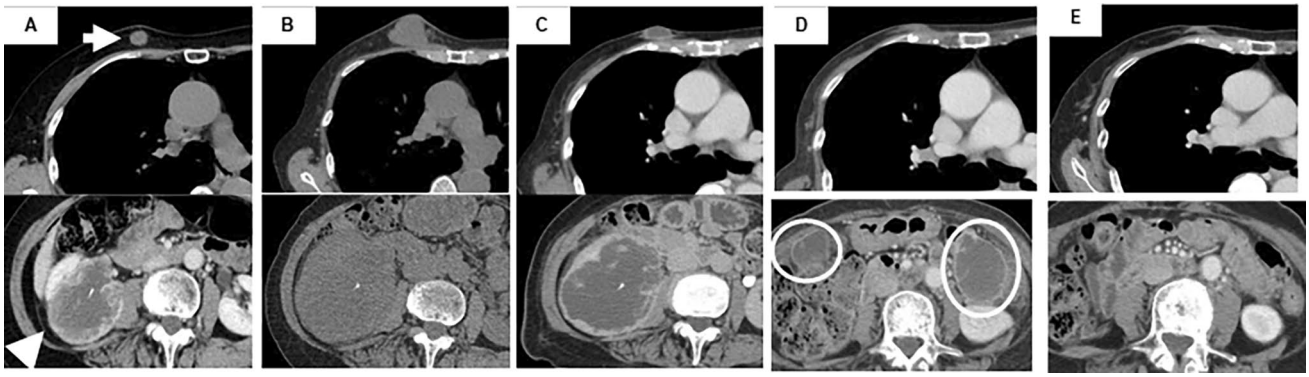

Fig. 1 CT findings **A** Contrast-enhanced CT showing renal pelvic tumor extensively invading the renal parenchyma (arrowhead), and plain CT revealing solitary mammary small tumor (arrow). **B** Plain CT showing the mammary tumor and renal pelvic tumor markedly growing during the 3-month period. **C** Contrast-enhanced CT showing the mammary tumor markedly decreasing in size and renal pelvic tumor slightly decreasing in size after chemotherapy. **D** Contrast-enhanced CT showing the mammary tumor maintaining shrinkage and new onset of multiple intraperitoneal metastatic lesions (circles) one month after surgery. **E** Contrast-enhanced CT showing the mammary tumor maintaining shrinkage and the multiple intraperitoneal metastatic lesions disappearing after seven doses of pembrolizumab therapy

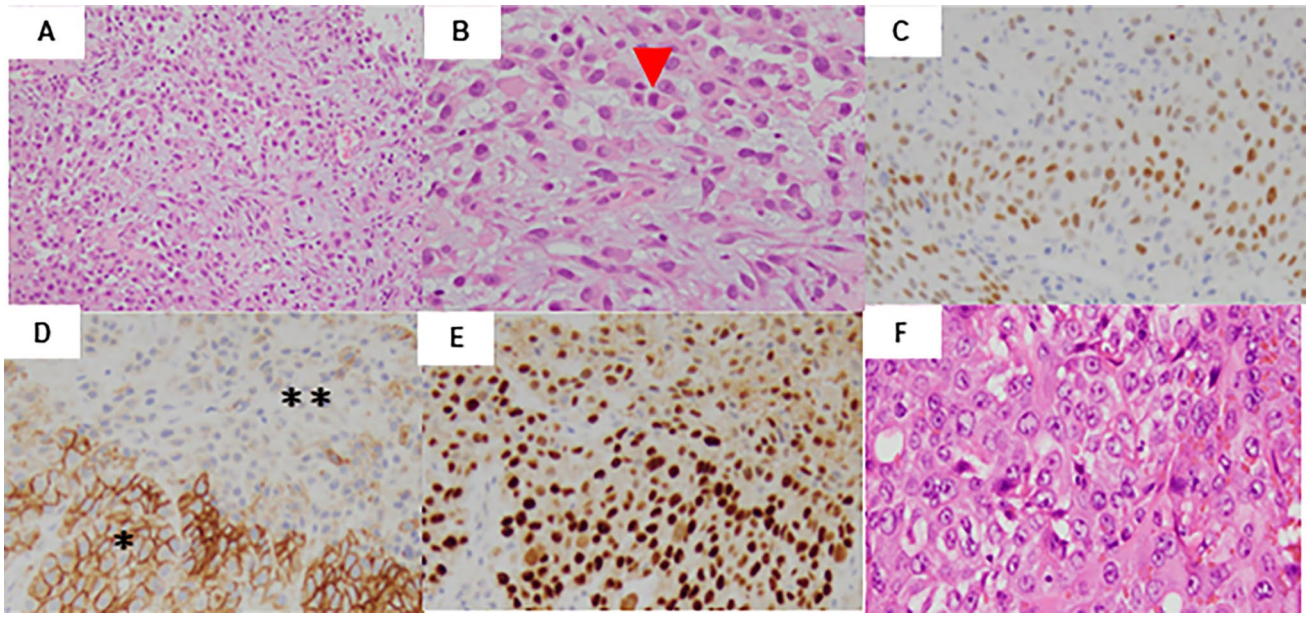

Fig. 2 Pathological findings (**A** ×40, **B**–**F** ×200) Hematoxylin and eosin staining of mammary tumor revealed discohesive tumor cells with eccentrically placed nuclei (arrowhead) and abundant eosinophilic cytoplasm (**A**, **B**). Immunohistostaining was negative for ER, PgR, and HER2 (not shown) but positive for GATA3 (**C**). E-cadherin staining showed distinct positive (*) and negative (**) areas (**D**). Additional immunohistostaining was positive for p63 (**E**). An obvious plasmacytoid subtype component was not observed in the nephroureterectomy UC specimens (**F**)

cancer cells and immunohistochemical evaluation was positive for cytokeratin (CK)7, CK5/6, and GATA3, indicating UC. Additional immunohistochemical examination was performed to determine whether the breast tumor was primary breast cancer or metastatic tumor from the renal pelvic UC. The mammary biopsy specimens were positive for CK5/6 and negative for uroplakin II and mammaglobin. The renal biopsy specimen was also negative for uroplakin II. As both right mammary gland tumor and renal pelvic mass showed positive for p63 (Fig. 2E), the final diagnosis was renal pelvic UC with plasmacytoid subtype metastatic to the mammary gland. Moreover, as there were no distinct differences in the immunohistochemical staining of both GATA3 and p63 between the E-cadherin-positive and -negative areas, we determined that the E-cadherin-positive area was consistent with UC

and the E-cadherin-negative area represented plasmacytoid subtype UC. The size of the right mammary gland tumor and renal pelvic mass rapidly increased three months after the initial CT (Fig. 1B). The TNM classification of this urinary pelvic cancer was cT3N0M1. Therefore, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) therapy was started immediately after the evaluation. CT scan taken after four cycles of dose-dense MVAC revealed a slight decrease in the size of the renal pelvic mass and a dramatic decrease in the size of the right mammary gland mass (Fig. 1C). Because of the good response to chemotherapy of the solitary metastatic lesion of the right mammary gland and no increase in the size of the primary renal pelvic tumor, surgical resections of these tumors were planned. We initially performed an open nephroureterectomy. The resected specimen showed high-grade tumor remained in renal parenchyma (pT3) and partially necrotic tissue. However, the surgical specimens of UC did not reveal the presence of the plasmacytoid subtype component (Fig. 2F). CT one month after nephroureterectomy showed the mammary metastatic site was still small; however, new intraperitoneal metastatic lesions invading the colon wall were observed (Fig. 1D). Pembrolizumab therapy was started. After seven doses of pembrolizumab, follow-up CT revealed a marked size reduction of intraperitoneal metastases and the mammary metastasis remained small (Fig. 1E). The patient's general condition had greatly improved. She continued to receive pembrolizumab therapy and after 17 doses, tumor shrinkage was maintained.

Discussion

Upper tract urothelial carcinoma (UTUC) is relatively uncommon, accounting for only approximately 5% of total urothelial malignancies [5]. Lymph nodes are commonly the initial site for UTUC metastasis and the most common sites of visceral metastasis are the lung, followed by the liver and bone [6]. On the other hand, mammary metastasis from extra-mammary cancer is rare, reported to range from 0.3 to 2.7% of all breast malignancies [1]. Common malignancies that metastasize to breast include melanoma, lung cancer, gynecological cancers, and hematologic malignancies [7]. There are few literatures reporting mammary metastasis from urinary tract cancer, almost all of which were cases of bladder cancer (Table 1). To the best of our knowledge, our study is the first to describe a solitary mammary tumor with histological features of plasmacytoid UC metastasizing from renal pelvic cancer.

Histology of the metastatic site revealed plasmacytoid subtype UC, making diagnosis difficult. Plasmacytoid UC is a rare subtype with an incidence of around 1–5% of all UC; however, it is associated with locally aggressive nature and poor prognosis [8, 9]. Plasmacytoid UC can also variably display rhabdoid and signet ring cell morphology along with cells that are difficult to distinguish from ILBC [4]. These histologic features make distinguishing between the metastasis of plasmacytoid UC and ILBC difficult as in this case.

Initially we, urologists and breast surgeons suspected that the patient had two primary cancers: renal pelvic tumor and mammary cancer. We performed percutaneous biopsies

Table 1 Summary of cases reports of mammary metastasis from urothelial carcinoma

References	Age	Sex	Primary location	Metastasis in other sites	Treatment for mammary metastasis	Follow-up periods from detection of mammary metastasis	Outcome
Ishikawa et al. [3]	74	Male	Ureter	None	Metastatectomy	5 months	DOD
Kai et al. [20]	68	Female	Bladder	Para-aortic, axillary, clavicle lymph node	Chemotherapy	5 months	DOD
Kamio et al. [21]	29	Female	Bladder	Brain	Chemotherapy, endocrinotherapy	19 months	DOD
Kobayashi et al. [22]	81	Male	Bladder	Liver, pelvic and axillary lymph node	Metastatectomy	–	–
Lievore et al. [2]	66	Female	Bladder	Iliac lymph node	Metastatectomy	10 months	AWD
Belton et al. [23]	57	Female	Bladder	Skin	Metastatectomy, chemotherapy	8 months	DOD
Yoon et al. [24]	59	Male	Bladder	Periureteral, peritoneum, inguinal lymph node	–	–	–
Laraqui et al. [25]	64	Male	Bladder	None	Metastatectomy	6 months	AWD
Current patient	72	Female	Renal pelvis	None	Chemotherapy	19 months	AWD

DOD dead of disease, *AWD* alive with disease

of the two lesions to confirm the histological findings. The pathological features of the mammary tumor biopsy specimen suggested either triple-negative ILBC, which is a rare type of breast cancer, or plasmacytoid UC. The immunohistochemical features of the mammary tumor, such as ER(−), PgR(−), HER2(−), GATA3(+), and E-cadherin(−), were applicable to both plasmacytoid UC and ILBC. As ER and PgR positivity has been reported in approximately > 95% and 75% in ILBC, and 0–20% and 13% in plasmacytoid UC, respectively, the ER and PgR expression could be useful in differential diagnosis between plasmacytoid UC and ILBC [4, 10]. On the other hand, Plasilova et al. evaluated 38628 triple-negative breast cancer patients identified from the National Cancer Database and reported that triple-negative ILBC was found in only 2% of ILBC [11]. The loss of membranous E-cadherin in plasmacytoid UC was reported as 57–100%; however, it is not specific for distinguishing plasmacytoid UC from other UC [12]. On the other hand, the loss of E-cadherin is specific in ILBC and has been used to distinguish it from invasive ductal carcinoma [13]. GATA3 is a general sensitive marker for UC and positivity in the plasmacytoid subtype is reported to be 44–100%; furthermore, it is expressed in breast cancer patients [4, 14]. Interestingly in our present case, UC and plasmacytoid UC components were found to coexist in the mammary gland metastatic site, suggesting that metastases do not always proliferate from a single tumor cell. CK5/6 is less frequently expressed in triple negative ILBC [15], but its positivity rate in UC is not significantly high, ranging 20–35% [16, 17]. Borhan et al. evaluated 45 plasmacytoid UC patients and reported that no one showed positive mammaglobin[4]. So, the immunochemical findings of mammary biopsy, showing CK5/6 (+) and mammaglobin (−), strongly suggested the metastasis of UC. Ultimately, we used p63 staining to distinguish plasmacytoid UC from ILBC, because the rate of p63 positivity in plasmacytoid UC has be reported as approximately 50% [14], whereas p63 expression is usually not observed in ILBC [18].

We found that the biopsy specimen consisted mostly of necrotic tissue and could not confirm the presence of the plasmacytoid subtype. However, we believe the primary renal pelvic tumor consisted of both conventional and plasmacytoid subtype UC, and these two types simultaneously metastasized to breast. The chemosensitivity of plasmacytoid UC has not been adequately verified yet because of its rarity, with the various rate of yT0N0, which is 7–60% [9, 19]. In our case, we speculate that the dose-dense MVAC might contribute to the absence of plasmacytoid subtype in the resected specimens.

In the present case, if breast and renal pelvic cancers were both primary tumors, the breast cancer would have been indicated for surgical resection; however, as the final diagnosis was primary renal pelvic UC with mammary metastasis, the patient was treated with systemic cisplatin-based chemotherapy. We were unable to shrink the primary lesion of renal pelvic tumor, but we did find a decrease in the size of the mammary metastatic lesion. At the time, no other new onset metastatic lesions were observed. Therefore, we planned surgical removal of both tumors; however, as the intraperitoneal metastases appeared just after nephroureterectomy, pembrolizumab therapy was initiated instead of mammary lesion resection. Intraperitoneal metastases disappeared and shrinkage of the mammary lesion was maintained by pembrolizumab therapy.

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Data availability All data supporting the findings of this study are available within the paper.

Declarations

Conflict of interest N. Hayakawa received honorarium for lectures from DAIICHI SANKYO Company Ltd.; Merck & Company Inc.; Takeda Pharmaceuticals; and Astellas Pharma Inc. K. Aida received honorarium for lectures from Nippon Kayaku Co. Ltd.; Takeda Pharmaceuticals; Eisai Co., Ltd. E. Kikuchi received honorarium for lectures Merck & Company Inc.; Astellas Pharma Inc.; Bristol Meyers Squibb. The other authors have no conflicts of interest to declare.

Informed consent Written informed consent has been obtained from the patient.

Statement of human rights, and on the welfare of animals This article does not contain any studies with human participants or animals performed by any of the authors.

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