Metastatic pancreatic tumors from lung cancer and Malignant adenomyoepithelioma of the breast with cystic changes resembling intraductal papillary mucinous neoplasm: a case report

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Abstract

Background: Adenomyoepithelioma (AME) of the breast is a very rare tumor and is generally considered to be benign and Metastatic pancreatic tumors from lung cancer (MPTLC) constitute 3% of all metastatic pancreatic tumors. We present an extremely rare case of cystic MPTLC that was difficult to distinguish from intraductal papillary mucinous neoplasm (IPMN).However, some show malignant transformation, which results in local recurrences or distant metastases. The morphological features of AME that might predict malignant potential have not been elucidated. Moreover, there is also no established multidisciplinary treatment for malignant AME aside from complete excision at an early stage.

Case presentation: The patient was a 74-year-old woman who underwent lobectomy of lung cancer 2 years before presentation to our hospital and A 64-year-old female diagnosed with AME of the left breast underwent lumpectomy. The surgical margins were negative. Six months after the operation, however, malignant AME recurred locally in the left breast. MRI showed multiple masses, which invaded the skin. A left mastectomy with axillary lymph node dissection was performed. Additional areas of AME were found in about one third of the entire breast. Eight months after the mastectomy, lung metastases were detected. She underwent chemotherapy with fluorouracil, epirubicin, and cyclophosphamide (FEC) for 9 cycles with little response. Lung metastasectomy was performed. Nine months after lung metastasectomy, the metastases were widespread to the brain, heart, and kidney; she subsequently died 2 months later. She was referred to our department for resection of cystic pancreatic tumors, which were diagnosed as IPMN with high-risk stigmata. Abdominal computed tomography (CT) showed a 37-mm-wide cystic tumor with a contrasted solid nodule in the pancreatic head and a 17-mm-wide cystic tumor in the pancreatic tail. We performed a total pancreatectomy for these lesions. According to histopathological and immunohistochemical findings, the tumors were diagnosed as metastatic pancreatic tumors from lung cancer.

Conclusion: In this case, the cystic morphology was formed by eosinophilic secretions from tumor cells, and it was difficult to distinguish from IPMN with high-risk stigmata. We consider this case, based on the variable clinical findings, an extremely rare variant of MPTLC and Malignant AME has various morphological features, and in this report, we characterize new findings from both imaging and pathology/autopsy. Malignant potency is related to the tumor size, tumor appearance, and mitoses, even if only a few. Given that ductal spread is one of the morphological features of malignant AME, it is of paramount importance to assess the surgical margins.

Keywords: Adenomyoepithelioma; metastatic pancreatic tumors; papillary mucinous neoplasm.

MPTLC: Metastatic pancreatic tumor from lung cancer

IPMN: Intraductal papillary mucinous neoplasm

EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration

FDG-PET: 18F-Fluorodeoxyglucose positron-emission tomography

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CT: Computed tomography

MRI: Magnetic resonance imaging Adenomyoepithelioma

CT: Computed tomography

FEC: Fluorouracil, epirubicin, and cyclophosphamide

Ki-67: Ki-67 labeling index

MRI: Magnetic resonance imaging

SMA: α-Smooth muscle actin

US: Ultrasonography

VATS: Video-assisted thoracic surgery

Introduction

Adenomyoepithelioma (AME) of the breast is a rare disease characterized by a bicellular pattern consisting of both ductal and myoepithelial cells [1, 2]. While most of AMEs of the breast are benign with good prognosis, some have shown malignant transformation. Malignant AME is difficult to differentiate from other benign diseases such as intraductal papilloma, tubular adenoma, and sclerosing adenosis. Moreover, malignant AME has a strong potential for local recurrence and distant metastasis to sites including the lungs, thyroid gland, bone, and brain [3].

Metastatic pancreatic tumors from lung cancer (MPTLC) constitute 3% of all metastatic pancreatic tumors. Although MPTLC is mainly treated with chemotherapy, pancreatectomy is sometimes performed in cases of solitary or metachronal metastasis. MPTLC is reported to present as hypo vascular or ring-enhancing lesions on imaging findings, but it is difficult to distinguish from primary pancreatic cancer. Because MPTLC typically forms solid tumors, cystic changes of MPTLC are extremely rare. Herein, we reported a case of cystic MPTLC, which was difficult to distinguish from intraductal papillary mucinous neoplasm (IPMN).

Since the morphological features of AME that could predict the malignant potency have not been elucidated, the tumors which seem to be benign have the possibility of changing into malignant tumors. Our case is atypical in that we describe new morphological features not previously reported. Thus, our case of malignant AME is of interest not only for its rarity, but also for the aspects of the morphological features.

Case presentation

A 64-year-old female with no significant past medical history was referred to our institution after new micro calcifications were identified in the left breast on screening mammography. Diagnostic ultrasonography (US) showed a 4.9 × 5.1 × 4.2 mm low echoic mass on the left between external-inferior and internal-inferior quadrants (Figure 1). Only duct papillomatosis was found on core needle biopsy. This was found to be concordant, and she was treated with observation.

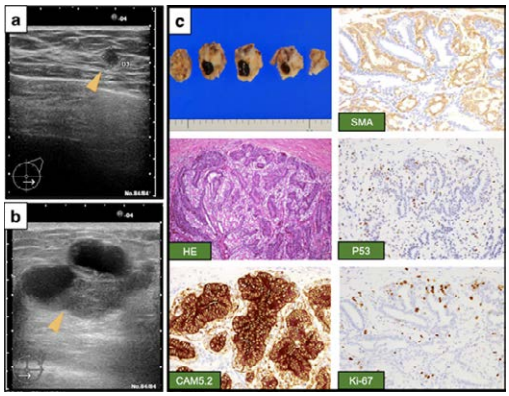

Figure 1: The cystic tumor on the pancreatic head gradually increased from 20 to 37 mm in 1 year and showed a contrasted solid nodule inside the cystic tumor.

The patient was a 74-year-old female who underwent left lower lobectomy for lung cancer 2 years before presenting to our institution. The histological type was adenocarcinoma, with a pathological staging of T4N1M0 stage IIIA (Union for International Cancer Control: UICC 8th Ed). One year after lobectomy, cystic lesions appeared on the head and tail of the pancreas, diagnosed as IPMN. The cystic tumor on the pancreatic head gradually increased from 20 to 37 mm in 1 year and showed a contrasted solid nodule inside the cystic tumor. The patient was referred to our department for surgery because the tumor was considered IPMN with high-risk stigmata. Her blood test results were as follows: carcinoembryonic antigen, 2.4 ng/mL (normal range, < 5.0 ng/mL); carbohydrate antigen 19-9, 38 U/mL (normal range, < 15 U/mL); DUPAN-2, 39 U/mL (normal range, < 150 U/mL); and SPAN-1, 29.8 U/mL (normal range, < 30 U/mL). Abdominal computed tomography (CT) showed a 37-mm cystic tumor with a contrasted solid nodule at the pancreatic head and a 17-mm cystic tumor at the pancreatic tail. Endoscopic ultrasonography (EUS) revealed that the cystic tumor at the head was a 35-mm solitary cyst with a 24-mm mural nodule, and the cystic tumor at the tail was a 20-mm solitary cyst with a 10-mm mural nodule. The main pancreatic duct had no extension. Although we had confirmed that the cystic tumor and main pancreatic duct were close, we could not define the link between the main pancreatic duct and the cyst (Figure 2). 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET) showed FDG uptake (SUV max 1.9) at the lesion in the pancreatic head. No evidence of metastasis from other organs was observed (Figure 3). Magnetic resonance imaging (MRI) could not be performed because of a cardiac pacemaker. The patient developed jaundice because the pancreatic head tumor excluded the common bile duct. From these results, we diagnosed the tumors as IPMN with high-risk stigmata because of jaundice and a contrasted mural nodule. We performed a total pancreatectomy for the two lesions after bile duct drainage by endoscopic retrograde cholangiopancreatography (ERCP). Because we performed ERCP on emergency, we could not perform

brushing cytology or pancreatic juice cytology for food residue in the stomach and duodenum. The tumors were solitary cysts with papillary lesions at the pancreatic head and tail. Histopathological findings showed that tumor cells had papillary components without mucus production (Figure 4). Moreover, a small tumor lesion was also microscopically detected at the pancreatic tail. Immunohistochemical analysis showed positive results for TTF-1, Napsin A, and CK7, but CK20 did not present significant staining, and these findings indicated this tumor to be lung cancer metastasis rather than IPMN. The histological findings were similar to those of the existing lung adenocarcinoma resected 2 years before now (Figure 5). According to these findings, we diagnosed the patient with metastatic pancreatic carcinoma from lung cancer. The postoperative course was good, and the patient was discharged 21 days after the operation. The patient did not receive adjuvant therapy and had no recurrence for 6 months after pacreatectomy.

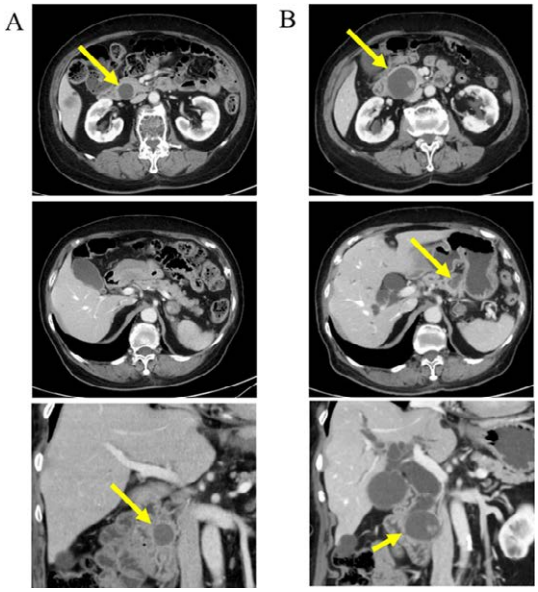

Figure 2: The main pancreatic duct had no extension. Although we had confirmed that the cystic tumor and main pancreatic duct were close, we could not define the link between the main pancreatic duct and the cyst.

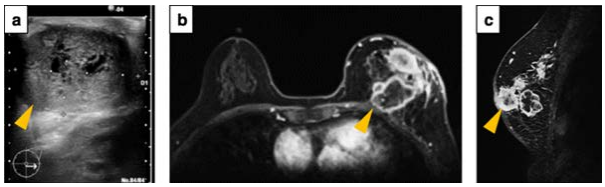

Figure 3: 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET) showed FDG uptake (SUV max 1.9) at the lesion in the pancreatic head. No evidence of metastasis from other organs was observed.

Two and a half years after the first consultation, she palpated a mass at the same location. A new US highlighted a larger 26.1 × 22.6 × 26.8 mm low echoic mass. Benign adenomyoepithelioma (AME) was identified on core needle biopsy. As the patient was a candidate for breast conservation, lumpectomy was performed. The histological analysis revealed a benign AME with few mitotic figures measuring 31 × 27 × 21 mm. All surgical margins were negative. The tumor consisted of both epithelial cells positive for CAM 5.2 and myoepithelial cells positive for α-smooth muscle actin (SMA)

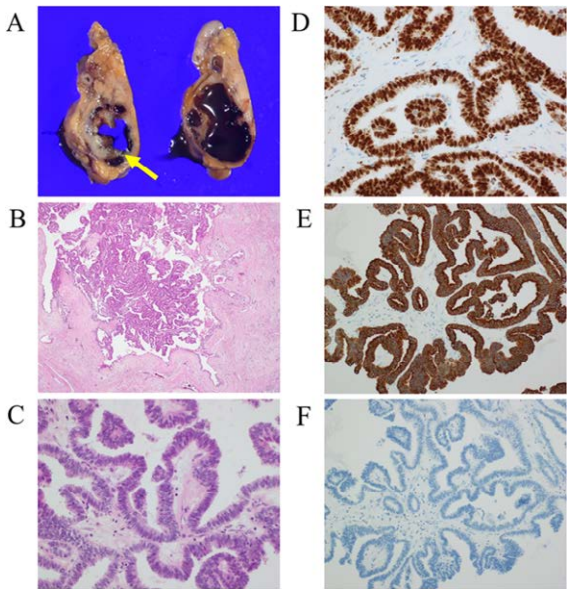

Figure 4: Histopathological findings showed that tumor cells had papillary components without mucus production.

Six months after the primary operation, she noticed a mass at the same location again. Diagnostic US highlighted a 34 × 26 mm hypoechoic mass along the left lumpectomy cavity. A computed tomography (CT) scan of the chest, abdomen, and pelvis showed no signs of distant metastasis. MRI showed multiple masses, which invaded the skin. Pectoralis muscle invasion was also suspected.

Discussion

The definition of malignant AME is not clearly defined. Nadelman et al. described 2 cases of metastases of histologically "benign" AME of the breast to the lung. Some AME tumors appear benign but may contain cellular atypia or mitotic figures. Although morphological features of malignant transformation include nuclear atypia, increased mitotic activity, necrosis, and infiltrative growth pattern, there is no established reference to differentiate between benign and malignant AMEs. In our case, mitotic figures were present in the tumor at the primary operation. Considering the patient's course, this may have provided a clue as to the malignant potential of her primary tumor. Tumor size is also one of the characteristics that may be related to potential malignancy. Patients with a primary tumor of ≥16 mm often presented with metastases. Some papers have concluded that AMEs over 2 cm should be treated as malignant. In our case, the size of the tumor at the primary operation was 31 mm, leading to poor prognosis. In addition to the tumor size, tumor appearance is an important factor in prognosis. Generally, malignant AME has been described as a large stable mass, but our case of malignant

AME showed multimodality within the breast. To the best of our knowledge, this represents an unusual presentation of AME. Other factors including mitotic figures, tumor size, and tumor appearance are also indicators of the malignant potential.

Metastatic pancreatic tumors are reported to consist of renal cell carcinoma, breast cancer or colorectal cancer, and lung cancer, which accounts for 3% of all cases. On the other hand, lung cancer metastasizes to the pancreas at a frequency of 13.8%, and small cell carcinoma is the most frequent histological type [4].

In imaging diagnosis, metastatic pancreatic tumors are reported to reflect the features of primary lesions, and pancreatic metastases of renal cell carcinoma are relatively easy to diagnose as they are hypervascular tumors, like the primary tumor [5]. MPTLC is reported to have several features, such as excluding stenosis and semilunar disruption of the main pancreatic duct by endoscopic retrograde cholangiopancreatography or hypovascular tumors and ring-enhancing images by enhanced CT/MRI. Rumancik et al. have argued that it is difficult to distinguish MPTLC from primary pancreatic cancer in diagnostic imaging [6]. Recently, several studies reported the feasibility of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) to confirm diagnoses. Cystic MPTLC is extremely rare, with few reports in the literature. Ramirez et al. reported cystic MPTLC cases that showed metastasis 2 years after lobectomy for undifferentiated large-cell lung carcinoma.

IPMN is defined as a pancreatic tumor producing mucus with a papillary epithelial structure. IPMN is classified as having worrisome features or high-risk stigmata from several malignant risk factors. The 2017 revision of the International Association of Pancreatology consensus guidelines suggested that high-risk stigmata were obstructive jaundice, an enhancing mural nodule $\geq$ 5 mm, and dilation of the main pancreatic duct to a diameter of $\geq$ 10 mm. Because our case had features of enlargement, obstructive jaundice, and papillary nodules inside cystic lesions, it was difficult to distinguish MPTLC from IPMN with high-risk stigmata. Moreover, EUS-FNA was difficult to perform in this case due to cystic changes. In this patient, the case findings suggested a chronologically increasing cyst with the appearance of an enhancing mural nodule, and these were the basis for considering it IPMN with high-risk stigmata. On the other hand, it was untypical of IPMN that dilation of the main pancreatic duct was not observed with the increase in cyst size.

Reddy and Wolfgang proposed the following surgical indications for metastatic pancreatic tumors: (i) a relatively better prognosis of the primary lesion, (ii) a controlled primary lesion, (iii) absence of multiple metastases, (iv) a resectable metastatic lesion, and (v) an operable condition of the patient. A standard pancreatectomy with lymph node dissection is recommended to prevent recurrence. Although the resection of MPTLC was not recommended because of poor improvements in prognosis, Dietzek et al. reported good surgical indications for MPTLC with long intervals between initial therapy and recurrence. Masetti et al. evaluated the prognoses of 234 pancreatic metastasis cases, and poor prognostic factors included being symptomatic, having multiple metastases, and incomplete resection in univariate analysis, and incomplete resection and melanoma in multivariate analysis. Pancreatic metastasis of renal cell carcinoma had a significantly better prognosis than other cancers. MPTLCs have been treated with surgical resection in cases of metastases from adenocarcinoma or squamous cell carcinoma, but metastases from small cell carcinoma were mostly treated with chemotherapy.

In general, the biological behavior of tumors developing in mammary glands ranges from benign to malignant transformation of either the epithelial or the myoepithelial component or both. As portrayed by our case, the biological behavior of tumors is different between primary and recurrent lesions. Although all of the lesions consisted of both the epithelial component and the myoepithelial component, the proportions of the two components were different. The epithelial component was most abundant in the primary site followed by the brain metastases, and least in secondary site, which was diagnosed as malignant AME. Moreover, the proportions of epithelial and myoepithelial cells were different among the brain metastases. Recognizing that heterogeneity between the proportions of epithelial and myoepithelial cells impacts treatment resistance, the increased proportion of the myoepithelial component compared to the epithelial component likely contributes to worse prognosis.

The treatment of malignant AME is not established except for complete excision at an early stage. Kihara et al. concluded that a complete local excision remains the only way to reduce the chance of local recurrence and distant metastases. On the other hand, it remains unknown whether axillary lymph node sampling is necessary. Similar to surgical treatment, there is no effective adjuvant chemotherapy at present. Chemotherapy has been used in some malignant cases, but the majority of them are not effective. Lee et al. reported that eribulin had a beneficial effect on malignant AME of the breast with multiple hepatic, pleural, and abdominal wall metastases. Neither complete resection of lung metastases nor chemotherapy including FEC and eribulin could control the malignant AME in our case.

Malignant AME can progress very aggressively as it did in the current case. Even if AME presents in a benign manner, it is important to assess the extent of the primary lesion by MRI and to consider wide surgical margins at the primary operation to perform complete resection as this may be the only potential option for a favorable outcome.

In this case, adenocarcinoma was diagnosed as the primary lesion, which showed eosinophilic secretions pathologically. In the pancreatic lesions, no mucus was found in the cyst components or tumor cells, suggesting the accumulation of eosinophilic secretions in the tumor as in the primary lesion. These eosinophilic secretions and papillary nodules in the cyst exhibited a morphology that resembled that of IPMN with high-risk stigmata. Regarding the diagnosis, the histological and immunohistonchemical similarities (TTF-1, Napsin A, and CK7 were positive) with lung cancer were comprehensively evaluated, and this tumor could be diagnosed as an MPTLC. Several pathways have been reported for metastatic pancreatic tumors, including direct invasion from surrounding organs, lymphatic metastasis to the peri-pancreatic lymph node, or hematogenous metastasis. Because this case had no metastasis in 53 pieces of dissected lymph node, hematogenous metastasis is most likely the implicated pathway. As a characteristic clinical course of this case, the progression rate was rapid for IPMN. This case was labeled as metachronous metastasis, and radical resection was performed due to multiple lesions in the pancreas. Therefore, it is necessary to monitor for recurrence in the future carefully. Malignant AME has various morphological features, and we demonstrated unique findings from both imaging and pathology/autopsy.

Conclusion

In this case, the cystic morphology was formed by eosinophilic secretions from tumor cells, and it was difficult to distinguish from IPMN with high-risk stigmata. We consider this case, based on the variable clinical findings, an extremely rare variant of MPTLC. Even only a few mitotic figures should raise caution regarding the malignant potential of the tumor in addition to the size and appearance of AME. Considering that ductal spread is one of the more aggressive morphological features of malignant AME, it is of paramount importance to assess the surgical margin before resection and obtain widely negative surgical margins.

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