Primary Fallopian Tube Carcinomas In Patients With Multiple Malignancies: Utility Of Tissue Of Origin Testing

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Citation

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Abstract

Context: The diagnosis of primary fallopian tube carcinoma (PFTC) may be difficult and require ancillary tests in patients who are genetically susceptible to cancer or have more than one malignant tumor. Objective: Usage of ancillary tests for definite diagnosis of PFTC. Design: Two occult PFTC with unusual morphology and a third case with morphologic features of serous carcinoma with clear cell changes were studied by immunohistochemistry and the molecular tissue-of-origin test (TOO).Results: The first two patients had histories of breast carcinoma; the latter was also a carrier of a BRCA1 mutation. ER immunostain was positive in both cases with WT-1 co-expressed in the latter. A third patient with metastatic papillary serous carcinoma received neoadjuvant chemotherapy prior to surgical treatment. TOO identified the malignancies as ovarian carcinomas with similarity scores of 89.5, 95.7, and 96.6. Conclusion: While TOO cannot distinguish PFTC from ovarian carcinoma, it can be useful in cases where the morphology, immunohistochemistry and comparison with previous tumors from the other sites are equivocal.

INTRODUCTION

Primary fallopian tube carcinoma (PFTC) is an uncommon gynecologic malignancy. The incidence of the disease ranges between 0.18-1.6% of all female genital tract cancers (1, 2). In the largest series to date, serous adenocarcinoma is the most common type followed by endometrioid adenocarcinoma (3). Transitional, clear cell, and squamous cell carcinoma, malignant mixed mullerian tumor, leiomyosarcoma and synovial sarcoma have each been reported as primary malignancies in the Fallopian tube (FT) (4, 5, 6, 7, 8, 9, 10). Hu established the diagnostic criteria for PFTC that were later modified by Sedlis (11,12). These include the presence of the main tumor in the endosalpinx, transition from benign to malignant tubal epithelium and either normal ovaries and endometrium or smaller tumors in these sites.

The introduction of risk-reducing salpingo-oopherectomy (RRSO) and new protocols requiring the histologic examination of the entire FT have increased the detection of early disease, particularly serous tubal intraepithelial carcinoma (TIC) in patients with BRCA mutations (13,14). PFTC has been reported to metastasize to the ovaries, omentum, breast and pericardium (15, 16,17). Reports of synchronous or metachronous presentations of PFTC with other malignancies in the genital tract or elsewhere complicate the identification of the primary site (18,19).

In the presence of multiple tumors particularly in patients genetically prone to multiple cancers, the diagnosis of PFTC can be challenging. This distinction can have important implications for clinical management. We report two occult PFTC with unusual morphology and an additional PFTC consisting of serous carcinoma with clear cell change, studied by immunohistochemistry and molecular tissue of origin test (TOO) (Pathwork Diagnostics, Redwood City, CA)

CASES

Patient #1 was a 70-year-old female who presented with a 7 cm right pelvic mass. Two years earlier she underwent lumpectomy and radiation therapy for a moderately differentiated infiltrating duct carcinoma (IDC) of the breast. A right ovarian serous cystadenofibroma was identified during intraoperative examination and she underwent a total hysterectomy with bilateral salpingo-oopherectomy (TAH/BSO). The entire bilateral FT were submitted for microscopic examination.

Patient #2 was a 63-year-old woman with a BRCA1 mutation. She had previously undergone a right lumpectomy and radiation treatment for IDC in 1997, followed by a right mastectomy in 2009 for a local recurrence. She underwent RRSO two years after the mastectomy, where an incidental nodule was discovered on the serosal aspect of the right FT.

Intraoperative (frozen section) evaluation confirmed the nodule as carcinoma in favor of a metastatic lesion. A TAH/BSO and omentectomy was performed. The bilateral FT were entirely submitted for histologic examination.

Patient #3 was a 58-year-old female with a long history of smoking who presented with bleeding from the umbilicus. Computerized tomography revealed a 12x10x10 cm pelvic tumor and two metastatic lesions over the dome of the liver, measuring 1.5 and 2.7 cm preoperatively. A biopsy of the umbilical mass was consistent with a metastatic serous carcinoma. The patient was treated with six cycles of neoadjuvant carboplatin and taxol, followed by TAH/BSO, pelvic and periaortic lymphadenectomy, omentectomy and resection of the intraperitoneal masses.

RESULTS

Patient #1: In addition to the ovarian serous cystadenoma, the right FT contained a 0.6 cm sub-mucosal poorly differentiated carcinoma with spindle cell features and foci of necrosis (Figure 1). There was minimal muscle invasion. The fimbriated end of the FT was uninvolved. Immunostains for AE1/AE3 and EMA were strongly positive in the tumor cells. ER showed (2+) nuclear staining in 70% of the tumor cells. Immunostain for p16 was focally positive, while WT-1, vimentin, desmin, CD10, calretinin, CK7, CK20, CK5/6, p63, PR, chromogranin and synoptaphysin immunostains were negative. The similarity score (SS) by TOO was 89.5 in favor of primary ovarian carcinoma (OC), whereas the SS was only 1.3 for breast cancer.

Patient #2: A well-circumscribed 1.7 cm mass involved serosal and muscular layers of the right FT. No evidence of invasive or in-situ carcinoma was seen in the tubal fimbria. The tumor cells were arranged as solid sheets with alternating areas of necrosis, focally mimicking comedo-type necrosis of breast carcinoma. Immunostains for mammoglobin and GCDFP15 were negative; ER, p16 and WT-1 were positive in the tumor cells. The morphology of the prior IDC was distinct from that of the FT lesion. The same immunohistochemical panel performed on the prior breast cancer showed that mammoglobin was focally positive while the stains for WT-1, ER and GCDFP-15 were negative. As the location and morphology of the carcinoma was unusual for PFTC, the tumor was sent for TOO testing. The SS score was 95.7 in favor of OC. The SS for the breast cancer was 2.

Patient #3: FT sections from the third patient showed bilateral tumors (right: 0.8 cm left: 3.1 cm) with involvement of the fimbriated end only on the left side. Both lesions demonstrated serous carcinoma with clear cell features (Figure 2). The ovaries were uninvolved by tumor. The right diaphragm and omentum were involved by foci of the tumor. Endometriosis was seen in the right ovary and uterine serosa. The myometrium showed adenomyosis. All regional lymph nodes were negative for carcinoma. Postoperatively, the patient received an additional three cycles of carboplatin and taxol. At the time of last follow up, the CA125 level was 8 unit/ml and there were no clinical signs of residual disease 17 months post-operatively.

Figure 1

Figure 1: 1 and 3: Case 1; Submucosal nodule. Spindle-cell features in high power picture. 2 and 4: Case 2; Subserosal nodule. Solid cell proliferation with intervening necrosis mimicking comedo-type necrosis.

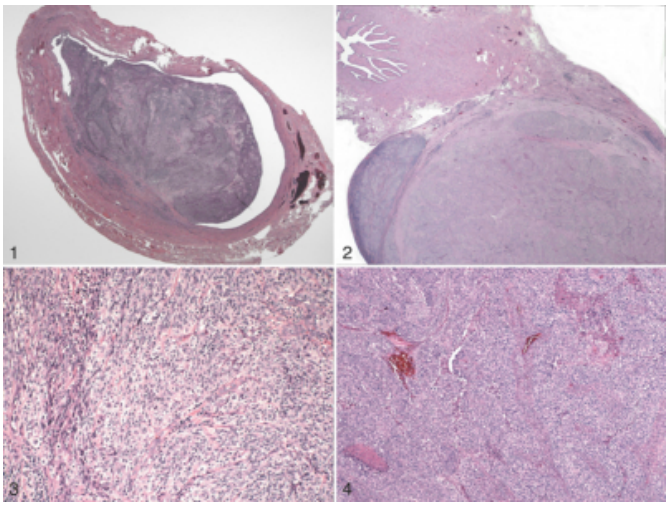
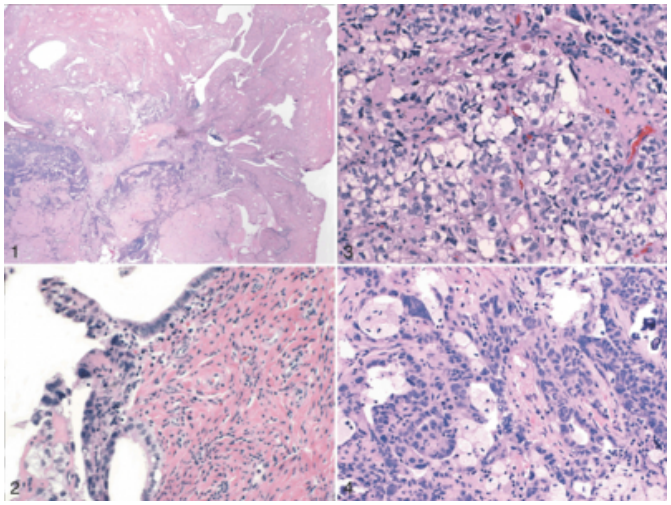


Figure 2

Figure 2: Case 3 1: Serous carcinoma of fallopian tube with clear cell features 2. Tubal intraepithelial carcinoma 3: Areas with clear cell changes 4: Serous adenocarcinoma, high power



DISCUSSION

During laparoscopic procedures for adnexal mass lesions, the chance of detecting PFTC is extremely low (0.028%) (20). Only 4% of PFTC are correctly diagnosed before surgery (21). Recent changes in the management of female carriers of BRCA mutations have provided an opportunity to increase our understanding of primary FT, ovary and peritoneal carcinomas (22). The prevalence of occult ovarian/FT cancers at the time of RRSO has varied widely among several studies. In one prospective multicenter study, the incidence of occult ovarian/FT cancer was 2.5% in BRCA1/2 mutation carriers (23). This contrasts with a report from a single institution where 10 of 111 BRCA carriers had 14 sites of occult neoplasia (9.1%) (24). As RRSO becomes standard therapy in BRCA + patients, the prevalence of early stage PFTC is likely to increase.

In patients with BRCA mutations, early serous carcinoma is reported to arise from in-situ disease at the fimbriated end of the FT (25). In our case # 2, despite having a known BRCA mutation, the tumor entirely spared the fimbria. It has been suggested that tubal carcinomas without involvement of the fimbria may arise from Walthard rests, paratubal cysts, paramesonephric remnants or directly from the tubal serosa (6). Hwang, for example, reported a clear cell adenocarcinoma arising in a paratubal cyst (26).

Both patients #1 and 2 had previous IDC of the breast. The distinction between metastatic breast cancer and a second gynecologic primary is clinically important, but not always straightforward. Immunostains for ER, PR, HER2 and p53 are not uncommonly seen in carcinomas from either breast or gynecologic sites. While staining with antibodies to GCDFP-15 or mammaglobin favor a breast primary, they have relatively low sensitivity (23% and 55% of cases, respectively) (27). WT-1 and p16 expression are more commonly seen in gynecologic primaries, but have also been reported in the breast carcinoma (28, 29). In cases where the diagnosis remains unclear, TOO testing may be useful. TOO compares the RNA expression of an unknown tumor with that of available tissue libraries, generating a similarity score (SS). The SS ranges from 0 (very low similarity) to 100 (very high similarity) and sum to 100 across all 15 tissues on the panel. The highest SS indicates the most likely tissue of origin. An SS ≤ 5 essentially rules out that tissue type as the tissue of origin (30). The TOO result is automatically generated by a computer algorithm with no consideration of the reference diagnosis. As currently constructed, the test cannot discriminate PFTC from OC. Such a distinction may have prognostic significance. In a recent series, early stage PFTC (17 cases) had a worse prognosis than staged-matched OC (31). This contrasts with older studies where stage for stage FT primaries appeared to have an improved prognosis (32). As the authors of the latter study note, there was no central review of pathology, and at least for advanced stage disease, some cases of FT carcinoma were likely misclassified as ovarian primaries skewing results.

In our two occult PFTC cases, the bilateral FT were entirely submitted for histologic evaluation. The main differential in our occult PFTC cases was with metastatic breast carcinoma. In each case, the TOO effectively excluded breast carcinomas a consideration. In unknown primary cases, integration of all available data, including immunohistochemistry and direct comparison with any previous tumor is sufficient for diagnosis in most situations. In those cases that remain equivocal, TOO may allow a definitive diagnosis.

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