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Case report

Searching for the source: Extraovarian primary peritoneal carcinoma presenting as chest wall masses

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ABSTRACT

Background: Extraovarian primary peritoneal carcinoma (EOPPC) is a rare form of epithelial adenocarcinoma arising from the peritoneal lining with little to no ovarian involvement. To date, very few cases of EOPPC with primary tumors outside of the peritoneum have been described, the majority of which present with a primary tumor in the retroperitoneum. No cases have been reported with primary presentation as a chest wall mass.
Case report: This case describes a 64-year-old woman referred for the evaluation of PAX8 positive chest wall masses. Biopsies of these masses demonstrated tumor architecture that was predominantly micropapillary with rare psammomatous calcifications. Immunohistochemically, the tumor was PAX8, CK7, ER, MOC31, and BerEP4 positive, with a mutational pattern of p53. This was consistent with Mullerian adenocarcinoma markers and suggestive of high-grade serous carcinoma. The patient was diagnosed with a unique presentation of EOPPC and is currently alive at 36 months post initial diagnosis. She has been treated with a combination of diagnostic surgery, chemotherapy and radiation therapy.
Conclusion: To the best of our knowledge, this is the first documented case of EOPPC presenting with a primary tumor of the chest wall. This case highlights the importance of pathology, immunohistology, and interdisciplinary collaboration in diagnosing and treating rare malignancies.

1. Introduction

Extraovarian primary peritoneal carcinoma (EOPPC) is a rare form of epithelial adenocarcinoma arising from the peritoneal lining with little to no ovarian involvement. The age-adjusted incidence rate is 6.78 per million (Goodman and Shvetsov, 2009). EOPPC is a diagnosis of exclusion, with the differential diagnosis including malignant peritoneal mesothelioma, psammocarcinoma, metastatic peritoneal carcinomatosis, and other benign or borderline processes. Key features of EOPPC include primary tumor histology characteristics of serous ovarian adenocarcinoma with limited to no involvement of the ovaries on microscopic analysis, and greater involvement of extraovarian anatomic sites as compared to the ovarian surface (Bloss et al., 1993).

EOPPC does not have a distinct staging system. Instead, it is staged using the FIGO staging system for ovarian cancer. All cases are at least stage III at time of diagnosis due to the degree of peritoneal involvement. To date, very few cases have been described with non-intraperitoneal primary tumors and the majority of these have been retroperitoneal primary (Win et al., 2020). To the best of our knowledge, the case presented here is the first case of EOPPC in a patient presenting with chest wall primary and no intraperitoneal disease.

2. Case

The patient is a 64-year-old postmenopausal woman presenting to an outside institution with 6 months of chest pain and palpable nodules of the chest wall. Biopsy of the nodules demonstrated poorly differentiated carcinoma positive for PAX8, WT1, and CK7, and negative for CDX2. A simultaneously noted right breast nodule was biopsied and negative for malignancy. Given the chest wall mass biopsy demonstrated positivity for PAX8 and WT1, this was suggestive of possible Mullerian primary, and the patient was referred to gynecologic oncology for further workup and evaluation.

On presentation, the patient denied history of smoking, and family

Abbreviations: EOPPC, Extraovarian primary peritoneal carcinoma; FIGO, The International Federation of Gynecology and Obstetrics; EPSPC, Extraovarian peritoneal serous papillary carcinoma; EOC, Epithelial ovarian carcinoma.

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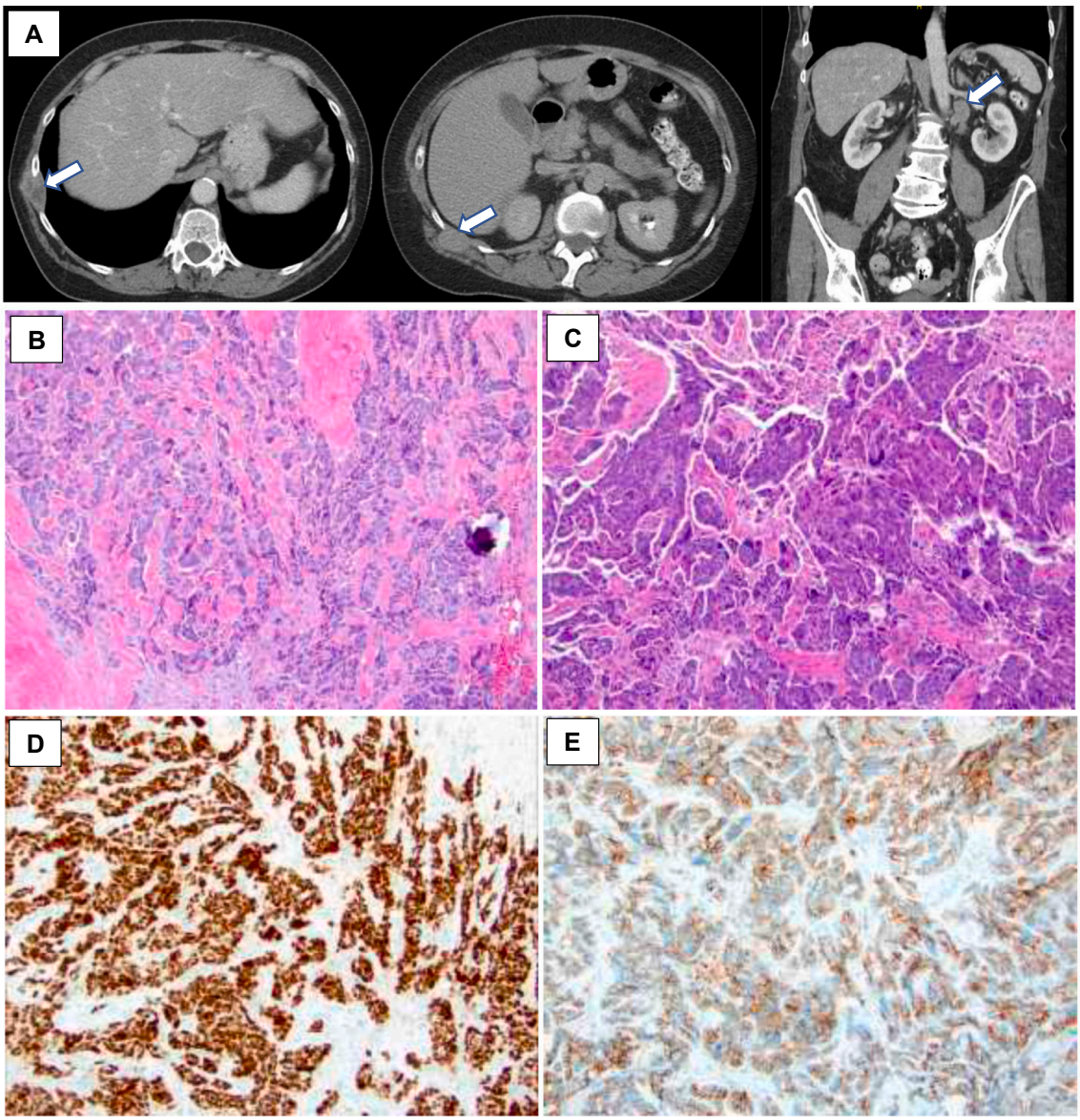

Fig. 1. A: CT images demonstrating right intercostal masses between ribs 9 and 10 (left), and 11 and 12 posteriorly (middle). 2 cm retroperitoneal lymph node at the level of the renal hilum (right). All findings marked with arrows. B: Tumor with psammomatous calcifications. C: High grade nuclear cytology with frequent mitoses and micropapillary growth pattern. D: Diffusely positive PAX8 staining on immunohistochemistry. E: Positive staining for BerEP4.

history was significant for breast cancer in a maternal aunt and cousin and negative for ovarian, and pancreatic cancer. She denied any difficulty breathing, abdominal pain, bloating, unintentional weight loss, or postmenopausal bleeding. Physical exam was normal aside from the previously noted chest wall nodules. CA 125 was elevated to 225 u/ml. CT of the chest, abdomen, and pelvis demonstrated two right-sided intercostal masses, epicardial lymphadenopathy, and several enlarged retroperitoneal lymph nodes, the largest of which was a 2 cm lymph node at the level of the left renal hilum (Fig. 1). No free fluid, abdominopelvic masses, or findings suggestive of peritoneal carcinomatosis were seen.

Given the suspicion, based on molecular testing, for occult carcinoma of Mullerian primary, the patient underwent diagnostic laparoscopy, total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, and cystoscopy. Intraoperative findings were significant for left ovary adhered to the pelvic sidewall, a normal appearing uterus and right adnexa, and smooth abdominal cavity, liver edge, and bilateral diaphragms. Intraoperative survey was negative for any overt lesions, masses, or evidence of intraperitoneal disease. Final pathology was notable only for endometriosis of the right ovary and no evidence of malignancy in the pelvic washings, uterus, endometrium, cervix, bilateral fallopian tubes and ovaries. The patient underwent incisional biopsy of the chest wall masses, with final pathology demonstrating cohesive, infiltrative nests of pleomorphic cells with high nuclear to cytoplasmic ratio, frequent mitotic activity, and predominantly micropapillary architecture with rare psammomatous calcifications (Fig. 1). On immunohistochemical analysis, the tumor was positive for PAX8, CK7, ER, MOC31, BerEp4, and mutational p53 pattern, consistent with high grade serous carcinoma of Mullerian origin (Fig. 1). A diagnosis of mesothelioma or metastatic breast carcinoma were unlikely due to lack of positive staining for WT1, calretinin, CK5/6, and GATA3. Given the lack of pelvic and peritoneal disease, the specimen was sent for molecular classification via CancerType ID (BioTheranostics), which demonstrated 90% probability of ovarian serous adenocarcinoma.

Discussion at multidisciplinary gynecologic oncology and cardiothoracic tumor boards and consultation with multiple outside gynecologic oncologists led to a presumed diagnosis of EOPPC and recommendation for systemic chemotherapy with carboplatin and

Table 1
GOG diagnostic criteria for Extraovarian Primary Peritoneal Carcinoma (EOPPC).

GOG Criteria for the Diagnosis of Extraovarian Primary Peritoneal Carcinoma
1. Both ovaries must be either physiologically normal in size or enlarged by a benign process.
2. The involvement in extraovarian sites must be greater than the involvement on the surface of either ovary.
3. Microscopically, the ovarian component must be one of the following:
A. non existent;
B. confined to ovarian surface epithelium with no evidence of cortical invasion;
C. involving ovarian surface epithelium and underlying cortical stroma but with tumor size less than 5x5mm within ovarian substance with or without surface disease.
4. The histological and cytological characteristics of the tumor must be predominantly of the serous type that is similar or identical to ovarian serous adenocarcinoma of any grade

paclitaxel due to unresectable disease. She underwent palliative radiation to the chest wall due for symptomatic control. Restaging CT after 4 cycles of primary chemotherapy demonstrated persistent disease, which was followed by four additional cycles of carboplatin, paclitaxel, and bevacizumab. Genetic testing was negative for mutations in *BRCA1/2* genes. Profiling of the tumor tissue demonstrated proficient homologous recombination, with no tumor mutation in *BRCA1/2* genes (Myriad). Near-complete response after 8 cycles of primary chemotherapy prompted transition to maintenance bevacizumab for 17 cycles. 17 months after initial diagnosis, PET/CT demonstrated enlarging retroperitoneal lymphadenopathy, for which she underwent external beam radiation therapy.

22 months after diagnosis, PET/CT demonstrated progression of disease and she began second-line therapy with carboplatin and doxorubicin for 6 cycles with good response. Three months after completing second-line chemotherapy, imaging demonstrated progression of disease. In consultation with an outside gynecologic oncologist, the patient was started on third-line chemotherapy with weekly paclitaxel and biweekly bevacizumab.

Biopsy was performed for repeat tumor testing, however once again, no actionable mutations were found. Surveillance imaging after 3 cycles of third-line therapy demonstrated progression of disease, and treatment was transitioned to fourth-line cyclophosphamide, bevacizumab, and pembrolizumab. Progression of disease after 4 cycles led to fifth-line therapy with pemetrexed and bevacizumab. Three years after diagnosis, the patient is alive with persistent disease and continues on fifth-line chemotherapy.

3. Discussion

Extraovarian primary peritoneal carcinoma (EOPPC), first described by Swerdlow in 1959 (Bloss et al., 1993), is an adenocarcinoma arising in the peritoneal lining of the abdomen and pelvis characterized by abdominal carcinomatosis with little to no ovarian involvement, no identifiable primary tumor, and histologic similarities to papillary serous carcinoma of the ovary. EOPPC accounts for approximately 10% of pelvic serous carcinomas (Rothacker and Möbius, 1995). In order to aid in the differentiation of EOPPC from epithelial ovarian cancer (EOC), in 1993 the Gynecologic Oncology Group (GOG) defined the criteria for the diagnosis of EOPPC (Table 1) (Bloss et al., 1993).

Although most cases of EOPPC demonstrate serous histology, other histologic variants of the Mullerian system have been reported, including endometrioid, clear cell, mucinous, Brenner tumors, and mixed Mullerian tumors (Eltabbakh and Piver, 1998). The subset of serous-type EOPPC has been specified as extraovarian peritoneal serous papillary carcinoma (EPSPC) by the GOG. Malignancies arising from the peritoneal epithelium often histologically resemble those from the ovarian surface epithelium. These similarities are proposed to be due to the shared derivation of these tissues from the embryonic coelomic epithelium (Matsuura et al., 2009). As in the case presented here, tumor histology of EOPPC is a predominantly high-grade papillary pattern, usually irregular in size and shape, with psammoma bodies and a prominent number of mitoses, features seen in EOC. Because the immunohistochemical features of EOPPC are indistinguishable from those of EOC, with tumors staining positive for ER, CK7, WT1, and CA 125 (Bloss et al., 1993; McCluggage and Wilkinson, 2005), the two diseases are often thought to arise from the same process. This is supported by the fact that EOPPC and EOC demonstrate similar rates of p53 overexpression, however, distinct molecular changes can be seen in EOPPC, which demonstrated almost double the rate of HER-2/neu overexpression (59% vs 36%) in one study (Kowalski et al., 1997).

The rapid uptake of risk reducing bilateral salpingo-oophorectomy (RRBSO) after cloning of the *BRCA1/2* genes 1990s led to the discovery of serous tubal intraepithelial lesions (STIL) and serous tubal intraepithelial carcinoma (STIC) lesions and resulted in a new paradigm of EOC pathogenesis. Today it is widely accepted that most serous ovarian cancers arise in the fallopian tubes. However, even after RRBSO, there remains a risk of EOPPC, with one prospective study demonstrating an incidence of 1.7% (Dowdy et al., 2004). This provides support for the theory that EOPPC may have a mechanism of pathogenesis distinct from EOC. There are two proposed theories of EOPPC pathogenesis: the first is that embryonic germ cell rests remain along the gonadal embryonic pathway and undergo malignant transformation (Eltabbakh and Piver, 1998). The second theory is that field carcinogenesis initiates a common response in tissues derived from the coelomic epithelium (peritoneum and germinal epithelium of the ovary), eventually resulting in malignant transformation (Eltabbakh and Piver, 1998; Matsuura et al., 2009).

The clinical presentation of EOPPC is similar to that of advanced-stage epithelial ovarian cancer. Symptoms are vague, and commonly include abdominal pain, distension and bloating in addition to gastrointestinal symptoms (e.g. nausea, vomiting, changes in bowel habits) (Mendonca et al., 2021). Laboratory evaluation typically reveals an elevated CA 125 level (Mendonca et al., 2021). Similar to EOC, surgical intervention usually demonstrates widespread intraperitoneal malignancy involving the omentum and upper abdomen, however, is distinguished from EOC due to little or no ovarian involvement. Metastasis typically occurs transperitoneally, though distant metastasis via lymphatic or hematologic routes have been reported (Mendonca et al., 2021). In the current case, there was no intraperitoneal involvement, which highlights the unique pathophysiology of this case.

Non-intraperitoneal occurrences of EOPPC are extremely rare and few cases have been reported in the literature. When presenting with a primary mass outside the peritoneal cavity, EOPPC usually presents with retroperitoneal mass or primary lymphadenopathy, which may occur within cervical, retroperitoneal, or distant lymph nodes (Win et al., 2020; Clare et al., 2020). Other rare presentations reported include a patient with primary abdominal wall tumor without evidence of peritoneal disease (Matsuura et al., 2009), and there have been 5 patients reported who were diagnosed with EOPPC after presenting with malignant pleural effusion (Mendonca et al., 2021). To date, this is the first documented case of EOPPC to present with a mass of the chest wall and retroperitoneal lymphadenopathy without any evidence of intraperitoneal disease.

In this case of a chest wall mass, the differential diagnosis included metastatic breast cancer and mesothelioma. Histologic and immunohistochemical findings were critical for differentiating the diagnosis and determining the optimal treatment course. The papillary architecture with psammoma bodies, high grade appearance, and prominent mitoses was suggestive of serous epithelial ovarian carcinoma, for which these are classic histopathologic findings. Given the atypical clinical presentation, numerous immunohistochemical studies were performed to aid in identifying the origin of the patient's malignancy. Positive PAX8 and BerEP4 straining, along with p53 mutational pattern, were critical to make the diagnosis of EOPPC. BerEP4 is a monoclonal antibody that identifies epithelial cell surface glycoproteins and is used to distinguish

Table 2
Selected clinical presentations and recommended treatments for patients with cancer of unknown primary.

Histologic Type	Clinical Scenario	Treatment
Adenocarcinoma	Female with isolated axillary adenopathy	Treat as stage II breast cancer
	Female with peritoneal carcinomatosis	Treat as stage III ovarian cancer
	Colon cancer profile	Treat as advanced colon cancer
	Non-small cell lung cancer (NSCLC) profile	Treat as advanced NSCLC
Squamous cell carcinoma	Inguinal adenopathy	Inguinal node dissection Consider concurrent chemotherapy/radiation therapy (as in advanced cervical or anal cancer)

metastatic adenocarcinoma from reactive or malignant mesothelial cells (Wang et al., 2014). Studies have shown that staining for the transcription factor PAX8, which is positive in 99% of high grade serous ovarian carcinomas, reliably identifies tumors of Mullerian origin, and can be used to rule out mesothelioma (Laury et al., 2010). In an immunohistochemical comparison of 254 serous ovarian and 50 mesothelial tumors, PAX8 staining was positive in only 9% of peritoneal malignant mesotheliomas and none of the pleural malignant mesotheliomas (Laury et al., 2010). As described earlier, p53 overexpression has been shown in up to 83% of cases of EOPPC (Moll et al., 1997). In this case, the histologic and immunohistochemical findings, along with the absence of any intraperitoneal disease on laparoscopy, which was confirmed on surgical pathology, support the diagnosis of a chest-wall variant of EOPPC with retroperitoneal lymph node metastases.

Identification of the tissue of origin is key in cases such as this, as patients with cancer of unknown primary (CUP) have particularly poor prognosis. Despite advances, diagnostic workup will fail to identify a primary tumor in some patients, and approximately 60% of patients with CUP will not fit into a subgroup that can be used to guide treatment (selected listed in Table 2) (Greco and Pavlidis, 2009). Treatment in such patients typically involves chemotherapy with a platinum agent in combination with other cytotoxic therapies, and results in median survival of 7–10 months, with two-year survival of only 20–25% (Greco and Pavlidis, 2009). In contrast, Bloss et al. previously demonstrated that patients with EOPPC treated with cytoreductive surgery followed by platinum-based chemotherapy have disease-free intervals and overall survival comparable to patients with serous epithelial ovarian cancer, for which five-year survival is 42% (stage III) and 26% (stage IV) (Bloss et al., 1993; Torre et al., 2018). Studies have shown that the primary determinant of EOPPC outcomes is the feasibility of completing cytoreductive surgery (Bloss et al., 1993; Win et al., 2020).

4. Conclusion

This is the first documented case of EOPPC, as defined by the GOG, presenting with chest wall primary tumors. This unique case demonstrates the critical role of pathologic, histologic, and immunohistochemical workup in identifying the tissue of origin in patients with malignancy of unknown primary, and the importance of interdisciplinary collaboration to determine the correct diagnosis and afford the patient the optimal treatment course. Furthermore, this case highlights the utility of radiation therapy for local control and symptomatic improvement in select cases of EOPPC.

Patient Consent Statement:

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Madison Brinker Feng: Writing – original draft, Writing – review & editing. **Nora Badiner:** Writing – original draft, Writing – review & editing. **Linda Hong:** Writing – review & editing. **Yevgeniya Ioffe:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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