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Isolated splenic high-grade serous carcinoma: A case report

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ABSTRACT

We present a unique case of high-grade serous carcinoma isolated to the spleen at the time of diagnosis, without any tumor present in the ovary, fallopian tubes, omentum or uterus, which was pathologically consistent with metastatic Mullerian carcinoma. Tumor sequencing with the MSK-IMPACT (Memorial Sloan Kettering–Integrated Mutation Profiling of Actionable Cancer Targets) multigene tumor panel test was performed, which revealed somatic mutations in PALB2 and in ARID1, as well as a TP53 hotspot mutation.

1. Introduction

Ovarian cancer is the second most common gynecologic malignancy and the leading cause of death from gynecologic cancer in the United States (Siegel and Miller, 2020). The majority of patients are diagnosed at advanced stage, have disease of high-grade serous histology, and unfortunately, are not cured despite surgical debulking and chemotherapy. The splenic hilum or surface can be involved by disease at the time of diagnosis, and a splenectomy is often required in order to achieve complete gross resection during cytoreductive surgery. In the recurrent setting, the spleen can be the single site of recurrence (Yasuda et al., 2018; LV et al., 2014; Furukawa, 2007; Ushijima et al., 1999; Lauro et al., 2002; Roque et al., 2007; Dawoud et al., 2013; Izuishi et al., 2010).

Primary neoplasms of the spleen are rare and are typically lymphomas, angiosarcomas, hemangiomas, or hamartomas (Chou and Chou, 2017). A prior case of isolated serous carcinoma was described by Chou et al. The authors theorized that non-malignant tissue from either the ovary, stomach, colon, or pancreas was incidentally implanted on the spleen during a total abdominal hysterectomy/bilateral salpingo-oophorectomy 9.5 years earlier after torsion of the right fallopian tube (Chou and Chou, 2017). Here, we present a unique case of high-grade serous carcinoma isolated to the spleen at the time of diagnosis, without any tumor in the ovary, fallopian tubes, omentum, or uterus. The tumor was pathologically consistent with metastatic Mullerian carcinoma.

2. Case report

The patient was a 62-year-old woman who presented as a referral from her general gynecologist for evaluation of a large splenic mass. The patient initially presented to an urgent care center for left-sided abdominal pain. A computerized tomography (CT) scan showed an enlarged spleen with extensive calcifications. Her reproductive organs did not exhibit any abnormality on CT (Fig. 1). The patient subsequently underwent an esophagogastroduodenoscopy and endoscopic ultrasound, which also revealed an enlarged spleen with extensive calcifications. A magnetic resonance cholangiopancreatography (MRCP) showed a splenic lesion that was $9.4 \times 8.7 \times 9.8$ cm. A positron emission tomography (PET) scan showed an FDG-avid (SUV 13.3) splenic mass consistent with malignancy. The patient subsequently underwent an ultrasound-guided splenic mass biopsy that revealed metastatic poorly differentiated carcinoma consistent with Mullerian or peritoneal origin.

The patient subsequently underwent repeat imaging with CT of the chest, abdomen, and pelvis, which also showed a large centrally necrotic splenic mass with scattered calcifications measuring $9.2 \times 8.8 \times 10.5$ cm (Fig. 2), and a PET/CT scan (Fig. 3), which was consistent with previously performed PET CT that showed a hypermetabolic necrotic splenic mass suspicious for malignancy. The uterus, cervix, fallopian tubes, and ovaries were normal on imaging. The patient had a CA 19-9 level of 9

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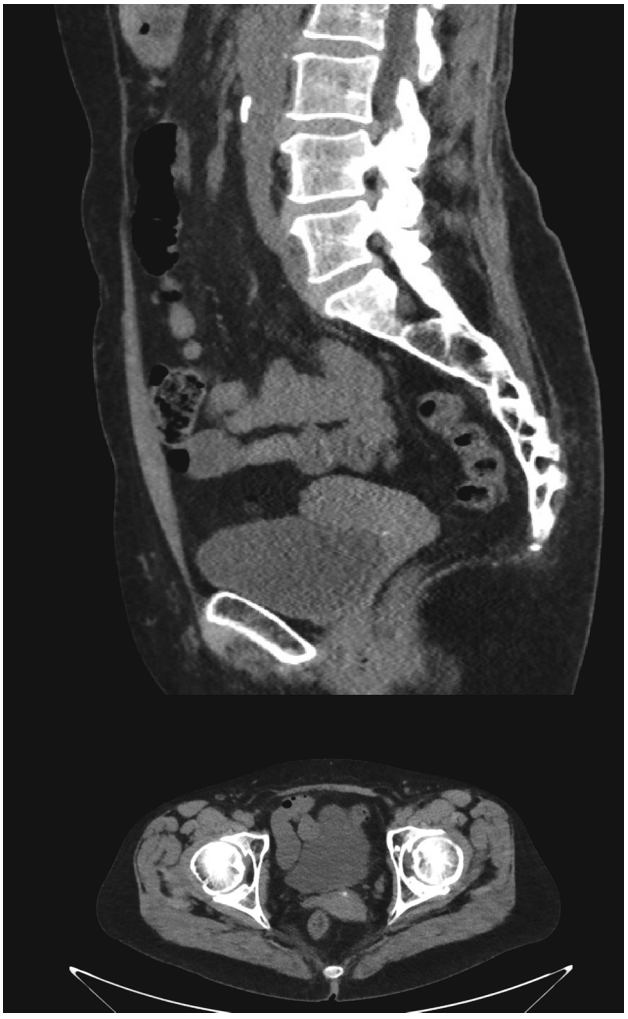

Fig. 1. CT scan showing normal reproductive organs.

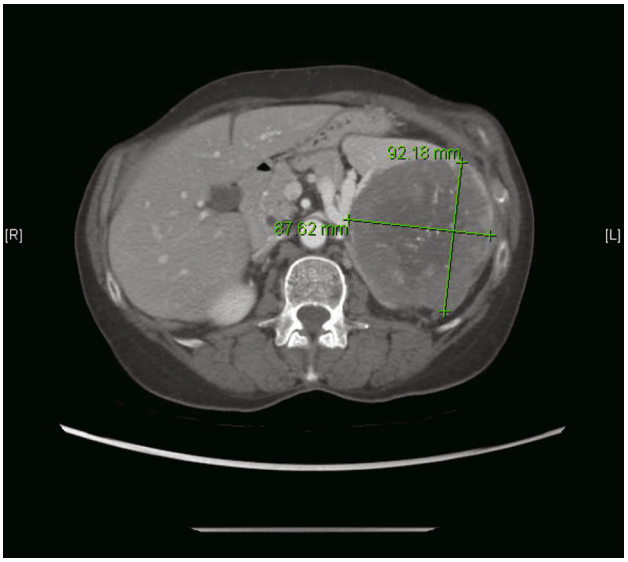

Fig. 2. CT scan showing splenic mass.

units/mL (within normal limits), a CA-125 level of 1605 units/mL (elevated; normal ≤35), and a CEA level of 3.3 ng/mL (within normal limits). The patient was thought to have a primary fallopian tube/ovarian carcinoma, which was not evident on preoperative imaging, with a large metastatic lesion to the spleen.

The patient ultimately underwent exploratory laparotomy and radical tumor debulking, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, splenectomy, distal pancreatectomy, and full-thickness partial left diaphragm resection with primary repair. Complete gross resection was achieved. Intraoperative findings noted an isolated large splenic mass adherent to the pancreas, Gerota's fascia of the left kidney, and diaphragm. Pathology showed high-grade serous carcinoma involving the splenic surface and peri-pancreatic soft tissue, with margins that were free of tumor. The omentum, falciform ligament, uterus, cervix, bilateral fallopian tubes, ovaries, and left diaphragm were all free of malignancy. Germline panel testing demonstrated no variants of clinical significance, including BRCA1/2. The patient's tumor underwent sequencing with the MSK-IMPACT (Memorial Sloan Kettering–Integrated Mutation Profiling of Actionable Cancer Targets) multigene tumor panel test, which revealed somatic mutations in PALB2 and in ARID1, as well as a TP53 hotspot mutation. After surgery, the patient received intravenous dual agent chemotherapy with carboplatin AUC (area under the curve) of 6 and paclitaxel 175 mg/m^2 every 3 weeks for a planned treatment duration of 6 cycles. The patient tolerated 6 cycles of chemotherapy well, with minimal toxicity aside from some mild fatigue. Furthermore, her post-treatment chest/abdomen/pelvis CT showed no evidence of disease, and her CA-125 normalized.

3. Discussion

Both primary splenic tumors and metastatic splenic lesions are rare. In the setting of high-grade serous carcinoma, the majority of tumors are typically metastatic disease, isolated splenic metastasis, or recurrence of ovarian carcinoma following treatment for known ovarian carcinoma. This case represents a unique presentation of isolated splenic Mullerian high-grade serous carcinoma.

Serous ovarian carcinoma is known to metastasize to the spleen in the setting of widely disseminated disease (in one autopsy study of 70 women who died of ovarian cancer, the spleen was involved 47% of the time) (Kataoka et al., 1994) and has been found to recur after treatment isolated to the spleen. Parenchymal splenic metastasis is less common (approximately 1% of metastatic tumors (Sauer et al., 2009)). Splenic metastasis is uncommon possibly due to several anatomic factors, which include the sharp angle made by the splenic artery (which theoretically makes it difficult for tumor to embolize to the spleen), the rhythmic contractile nature of the spleen, which may squeeze tumor deposits from the spleen, the spleen's lack of afferent lymphatics to bring metastatic tumor to the spleen, and the spleen's antitumor activity secondary to high concentrations of lymphoid tissue (Compérat et al., 2007). In all cases of isolated splenic serous/metastatic Mullerian lesions reviewed, there was a known primary tumor for which the patient was treated. In most cases, an isolated splenic lesion was found in the setting of recurrent ovarian carcinoma years after primary surgery/chemotherapy (Yasuda et al., 2018; LV et al., 2014; Furukawa, 2007; Ushijima et al., 1999; Lauro et al., 2002; Roque et al., 2007; Dawoud et al., 2013; Izuishi et al., 2010).

By contrast, this is a case of high-grade serous carcinoma (pathologically consistent with Mullerian origin) isolated to the spleen on initial presentation, without a prior surgery or known diagnosis of Mullerian carcinoma. The pathophysiology of this disease is not entirely clear. It is possible that the primary site of disease was missed at the initial surgery, and that this was a metastatic primary peritoneal carcinoma. It is also possible that this carcinoma arose in pluripotent or multipotent splenic stem cells that transformed into a Mullerian serous carcinoma. Pluripotent/multipotent stem cells have been described in the spleen and are known to differentiate into a multitude of tissue types. They are thought to have a low oncogenic potential (Faustman and Davis, 2010). The patient was found to have seven somatic

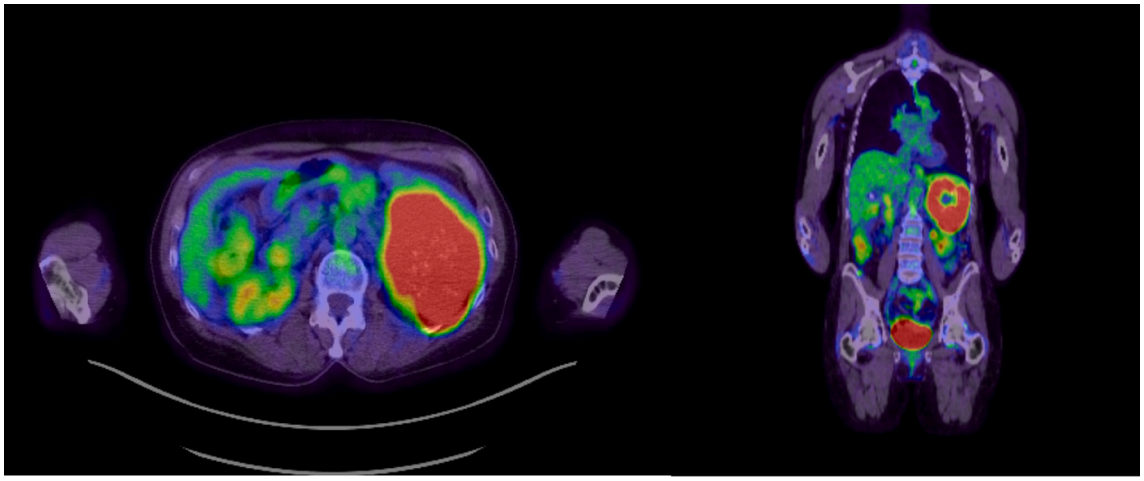

Fig. 3. PET-CT scan showing splenic mass.

mutations, including a frameshift deletion of PALB2, a TP53 hotspot missense mutation, and a missense mutation in ARID1A. In their study, Pennington et al. (2014) found that 9% of the ovarian carcinomas they assessed had somatic mutations including PALB2. The presence of homologous recombinant mutations (such as PALB2) was associated with improved response to poly (ADP-ribose) polymerase (PARP) inhibitor therapy. In the same study, 290 patients (79%) with ovarian cancer had deleterious somatic mutations in TP53. ARID1A somatic mutations are notably more common in ovarian clear cell carcinomas (>50% in one study) (Jones et al., 2010) and endometrioid ovarian carcinomas (30% in one study) (Wiegand et al., 2010).

This case illustrates a unique presentation and provides clinicians insight into the potential metastatic patterns of Mullerian carcinoma. It serves as an example of the possibility of isolated metastatic disease in peritoneal carcinoma. Ultimately, this case can be classified as a metastatic primary peritoneal carcinoma. For clinicians working up isolated abdominal masses, it represents the importance of including atypical metastatic patterns of Mullerian carcinomas in the differential diagnosis.

In conclusion, our case represents a unique presentation of a Mullerian high-grade serous carcinoma isolated to the spleen. The pathophysiology of the origin of this tumor is not known; however, there is the possibility of a splenic pluripotent cell leading to serous carcinoma or some form of microscopic metastasis that was not previously identified. Given the unique nature of this patient's presentation, the isolated site of her disease may confer a favorable prognosis.

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CRediT authorship contribution statement

Ralph Rogers: Conceptualization, Writing - original draft, Writing - review & editing. **Sarah Ehmann:** Conceptualization, Supervision, Writing - review & editing. **William P. Tew:** Supervision, Writing - review & editing. **Vance Broach:** Supervision, 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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