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Case report

Isolated recurrence of ovarian serous adenocarcinoma to adrenal gland

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ABSTRACT

Objectives: The purpose of this report was to present the diagnosis and management of an unusual case of a woman with ovarian carcinoma who developed an isolated recurrence to the adrenal gland six years after initial diagnosis.

Case: A 79-year-old woman was diagnosed with stage IVa high-grade serous carcinoma of the ovary with malignant pleural effusion in January 2014. She received six cycles of carboplatin and paclitaxel and underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and optimal tumor debulking in May 2014. After developing new liver implants in August 2015 and peritoneal carcinomatosis in April 2016, she received 5 cycles of carboplatin and paclitaxel and 6 cycles of doxorubicin, respectively, after which she had no evidence of disease. In March 2020, a surveillance computed tomography (CT) scan showed a 1-cm interval thickening of the left adrenal gland suspicious for metastasis. Positron emission tomography (PET) scan revealed an adrenal mass that was intensely fluorodeoxyglucose (FDG) avid with subsequent fine-needle aspiration (FNA) consistent with metastatic serous carcinoma. She was treated with laparoscopic left adrenalectomy in October 2020 and underwent 4 cycles of adjuvant carboplatin and paclitaxel. Follow-up CT imaging revealed stable post-adrenalectomy status with no interval thickening of the gland and post-operative Ca-125 level of 11.2 from 26.1 pre-operatively.

Conclusions: Interval adrenal thickening detected on surveillance CT was the most important initial indicator of adrenal metastasis in this case of ovarian carcinoma. The adrenal mass was further evaluated using PET CT and FNA for pathology diagnosis. As this new recurrence occurred in a patient with no evidence of disease, we suggested an aggressive management approach consisting of surgical excision in combination with chemotherapy to eliminate visible disease and optimize survival.

1. Introduction

Ovarian cancer is the most common cause of death amongst women with gynecologic malignancies and presents as stage III or IV disease in approximately 75% of cases (Lheureux et al., 2019). Among this group of women with advanced-stage disease, as many as 70% will develop recurrent or progressive disease after initial treatment (Ushijima, 2010). The median time to recurrence in patients with ovarian cancer is 18–24 months after completion of initial therapy (Ushijima, 2010).

The primary mechanism of spread in ovarian carcinoma, unlike other cancers, is classically thought to be through intraperitoneal exfoliation or "seeding" of cancer cells within the abdominopelvic cavity. Other less common mechanisms of metastasis occur through hematogenous and lymphatic dissemination as well as transdiaphragmatic passage. The most common sites of metastases outside the pelvis include the omentum, peritoneum, diaphragm, liver, and lymph nodes (Sehouli et al., 2009; Lengyel, 2010).

The adrenal gland is a rare site of metastasis in those with ovarian carcinoma. Although autopsy studies reveal evidence of adrenal gland metastases in 15–20% of these women (Dvoretsky et al., 1988; Rose et al., 1989), there are only isolated case reports of adrenal gland metastases diagnosed *in vivo*. Thus, there are currently no clear guidelines for the management of these lesions in the setting of recurrent ovarian cancer. We therefore present a case of ovarian serous carcinoma with

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recurrence to the adrenal gland and aim to highlight potential diagnosis and treatment strategies of this clinically rare site of metastasis.

2. Case presentation

A 79-year-old woman with a remote history of breast cancer (treated with lumpectomy in 1990) was diagnosed with stage IVa high grade serous carcinoma of the ovary with malignant pleural effusion in January 2014. Her initial burden of disease included perivascular and cardiophrenic lymphadenopathy, peritoneal carcinomatosis, and heterogeneous ovarian enlargement seen on CT imaging. She was initially treated with four cycles of neoadjuvant carboplatin and paclitaxel which resulted in decreased pleural effusions and peritoneal carcinomatosis evident on CT scan. She underwent a total abdominal hysterectomy, bilateral salpingoopherectomy, and omentectomy with optimal tumor debulking in May 2014 followed by two more cycles of adjuvant carboplatin and paclitaxel. Subsequent genetic testing was negative for BRCA1/BRCA2 mutation or other germline or somatic mutation. In August 2015, the patient was found to have recurrence with development of serosal implants along the liver and spleen. She was treated with five cycles of carboplatin and paclitaxel, with therapy discontinued due to bone marrow toxicity in December 2015. At this point, the patient had stable disease and traveled back to her home country for several months. Surveillance CT in April 2016 unfortunately showed worsening peritoneal carcinomatosis and she elected to start 6 cycles of doxorubicin that was given from September 2016 to February 2017. Her Ca-125 count fell from 31.1 to 6.7 after completion of therapy.

The patient had no evidence of disease until she underwent a CT in March 2020 that was performed for monitoring of a small peritoneal nodule and several small lung nodules that had been stable for a 2-year period. The CT scan showed thickening of the left adrenal gland suspicious for metastasis. The thickening measured approximately 1.4 × 0.7 cm in trans axial dimensions as compared to 3 mm in width on the previous study (Fig. 1). There was no right adrenal mass or any other site of disease found on the imaging study. Follow up positron emission tomography (PET) CT revealed a left adrenal gland lesion 20 × 11 mm in size that was intensely fluorodeoxyglucose (FDG) avid. Of note, there was no associated rise in Ca-125 count (Ca-125 of 13 in November 2019 and Ca-125 of 12 in March 2020). The patient was referred to a surgical oncologist for follow up and evaluation of adrenal mass.

The patient was evaluated for symptoms or laboratory evidence of adrenal disease. She denied headache, changes in vision, palpitations, abdominal pain, nausea, vomiting or other complaints at the time. All electrolytes were found to be normal. Cortisol level was < 1.0 (range 4.0–20.0 ug/dL), dehydroepiandrosterone sulfate level was 18 (range 35–430 ug/dL), adrenocorticotropic hormone was 6 (range 6–50 pg/mL), total metanephrines level was 109 (range < 205 pg/mL), free metanephrine was < 25 (range < 57 pg/mL), free normetanephrine level was 109 (range < 148 pg/mL) and renin activity was 0.48 (range 0.25–5.82 ng/mL/h). As there was no evidence of hormone hypersecretion, there was low clinical suspicion for a functional or primary adrenal adenoma. Her diagnostic workup ultimately led to fine needle aspiration of the gland, which revealed clusters of pleomorphic epithelial cells with an immunoprofile consistent with metastatic serous carcinoma (Fig. 2).

After multidisciplinary discussion regarding surgical and medical treatment options, the patient was treated with laparoscopic left adrenalectomy in October 2020. Her pre-operative Ca-125 count in September 2020 was 26.1 and fell to 15.8 post-operatively in December 2020. The surgical pathology revealed serous carcinoma that extended into the *peri*-adrenal adipose tissue. Resection margins were focally narrowly negative for involvement. The surgery was well tolerated and 4 cycles of carboplatin and paclitaxel were initiated for adjuvant therapy. Genetic testing of the adrenal tissue was performed and genes associated with Homologous recombination deficiency (HRD) were not present. Follow up imaging revealed stable post-adrenalectomy status with no interval thickening of the gland.

The patient continues to follow up regularly and her most recent Ca-125 count was stable at 10.6 in October 2021. She remains asymptomatic and has not developed any new sites of disease.

3. Discussion

This report presents a case of recurrent ovarian cancer with metastasis to the adrenal gland diagnosed on routine CT surveillance nearly six years after initial cancer diagnosis. The detection of adrenal gland metastasis amongst cancer patients is rare; in fact, a 30-year retrospective study by Lam and Lo (2002) found that 94% of cancer patients who had metastases to the adrenal gland were detected postmortem. Because the diagnosis of an adrenal gland metastasis is such a rare event, our case raises several considerations regarding the identification of potentially suspicious adrenal masses as well as potential management strategies of these lesions.

The incidental finding of an adrenal nodule is present on up to 4% of abdominal imaging studies (Mclean et al., 2011). The vast majority of these tumors are benign, with 2.5% representing metastatic disease (Lee and Duh, 2009). Weighing the risks and benefits of aggressive workup of adrenal lesions can therefore be a clinical dilemma, as invasive testing can pose a risk to patients and can utilize medical resources unnecessarily. Features that typically raise suspicion of a malignant lesion include large diameter (>4–6 cm), irregular border, inhomogeneity, calcifications, radiologic evidence of invasion into local structures, interval growth detected on follow-up imaging, and patient history of cancer (Mclean et al., 2011; Nieman, 2010). Malignant lesions are typically asymptomatic, but can present with adrenal insufficiency (especially if bilateral) or back pain from local expansion or hemorrhage into the retroperitoneal space.

In the setting of recurrent ovarian cancer, we suggest that the first

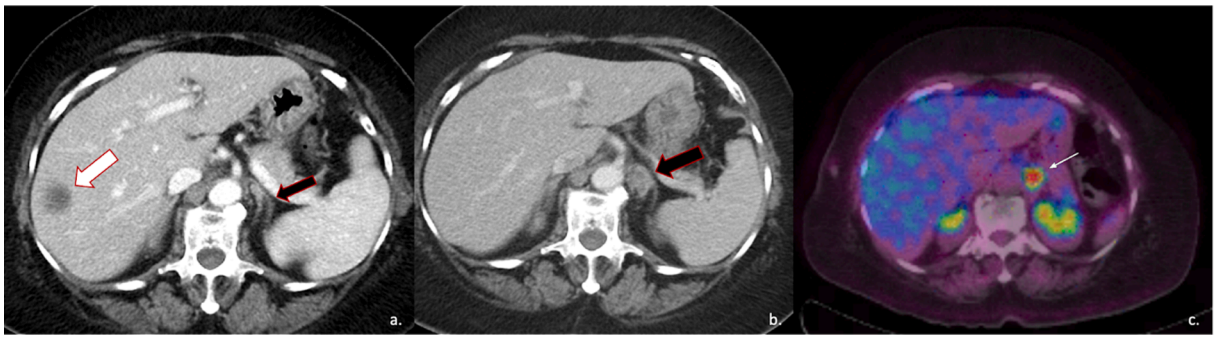

Fig. 1. a. Black arrow - CT axial image demonstrates a normal appearing left adrenal gland and a cyst in the liver (white arrow); b. Black arrow - CT axial image demonstrates development of a new heterogeneous nodule in the left adrenal gland; c. White arrow – PET/CT axial fused image demonstrates FDG uptake in the left adrenal gland lesion with standard uptake value of 6.7.

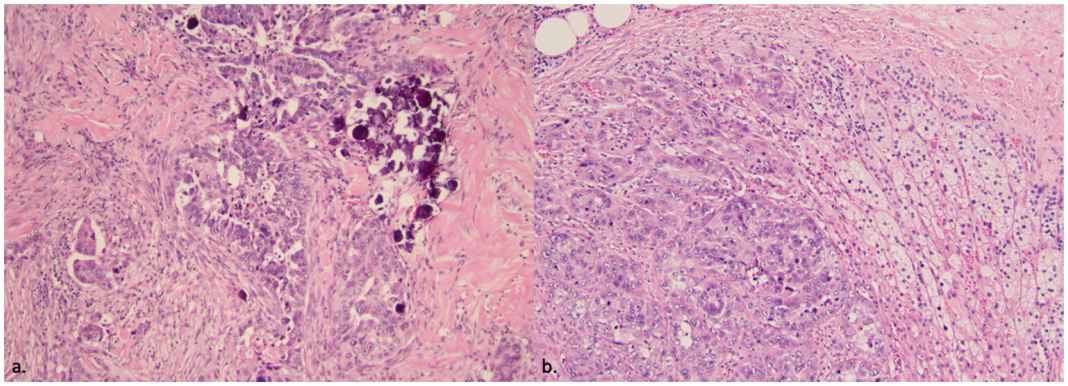

Fig. 2. a. Medium power view (10x/100x) view of adrenal gland with metastatic carcinoma with micropapillary architecture (left) and psammomatous calcification (right); b. Medium power view (10x/100x) shows metastatic carcinoma (left aspect) within the adrenal gland (right aspect). The carcinoma displays scant eosinophilic cytoplasm, nuclei with vesicular chromatin and prominent nuclear membrane and nuceolus, along with mitotic activity and single cell necrosis/apoptosis, in a glandular architecture. The adrenal cortex demonstrates is usual appearance of three layers, with a outermost thin zona glomerulosa, middle layer of the usually prominent zona fasciculata (larger cells with small nucleus, and abundant cytoplasm with small lipid vacuoles) and the innermost zona reticularis.

step in evaluation of an adrenal mass is to compare with prior imaging studies, even in the context of small diameter and the presence of reassuring features. In the present case, the diameter of the adrenal lesion was 1.4 cm and was described as "thickening" rather than a discreet mass. Our suspicion for malignancy remained high, however, as the thickening had increased from 3 mm on prior imaging. Recognition of this interval growth was essential to the diagnosis of metastatic lesion in this patient.

Left adrenalectomy was then performed followed by adjuvant chemotherapy with intent to resect a suspected single site of metastatic disease and achieve a state of no residual disease. Secondary cytoreductive surgery in patients with small-volume isolated disease has been shown to achieve a survival benefit in patients with recurrent ovarian cancer, and we therefore suggest surgical intervention for patients who are appropriate surgical candidates (Harrison et al., 2021). Furthermore, laparoscopic adrenalectomy has been shown to be a safe procedure associated with survival benefits in cancer patients with metastatic adrenal gland tumors (Muth et al., 2010; Sarela et al., 2003). (Howell et al., 2013) found that the overall median survival of patients with adrenal metastasectomy in a single-centered retrospective review was 30 months in those with isolated adrenal metastasis and 25 months in those with oligometastatic disease (Howell et al., 2013). A study comparing survival outcomes of adrenalectomy versus chemotherapy treatment alone in patients with non-squamous cell lung cancer with adrenal metastases found a similar median survival of 31 months in the adrenalectomy group versus 8.5 months in the chemotherapy-only group (Luketich and Burt, 1994).

To the best of our knowledge, adjuvant chemotherapy post-adrenalectomy has not yet been documented as a treatment strategy for adrenal metastasis in women with recurrent ovarian cancer. The present case is unique in that the patient's adrenal metastasis represented the only interval change in disease burden over a course of nearly 4 years. As such, this clinical scenario interestingly resembles that of an isolated adrenal metastasis. Our treatment strategy therefore utilized surgery in combination with chemotherapy to target any micrometastatic disease associated with the lesion. The patient had not received platinum-based chemotherapy (PBC) since December 2015 and was considered to have platinum-sensitive disease (progression of disease noted 6 months after completion of therapy). In patients with epithelial ovarian cancer, PBC is the first-line treatment of platinum sensitive disease, and longer platinum-free intervals are associated with higher response rates and longer durations of disease control (Gupta et al., 2019). PBC was therefore initiated which resulted in continued to downtrend of Ca-125 over the following several months.

4. Conclusions

In this case, interval adrenal thickening of the adrenal gland detected on CT scan was the most important initial diagnostic indicator of adrenal metastasis in our patient with recurrent ovarian cancer. Further diagnostic confirmation was attained using a combination of PET CT imaging and FNA for pathology diagnosis. As this new recurrence was isolated to the adrenal gland, we suggested an aggressive management approach consisting of surgical excision in combination with chemotherapy to eliminate visible disease and optimize survival.

Consent

Written informed consent was obtained from the patient for publication of this case report.

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.

References

Dvoretsky, P.M., Richards, K.A., Angel, C., Rabinowitz, L., Stoler, M.H., Beecham, J.B., Bonfiglio, T.A., 1988. Distribution of disease at autopsy in 100 women with ovarian cancer. Hum. Pathol. 19 (1), 57–63. https://doi.org/10.1016/s0046-8177(88)80316-2.

Gupta, S., Nag, S., Aggarwal, S., Rauthan, A., Warrier, N., 2019. Maintenance therapy for recurrent epithelial ovarian cancer: Current therapies and future perspectives – a review. J. Ovarian Res. 12 (1) https://doi.org/10.1186/s13048-019-0579-0.

Harrison, R., Zighelboim, I., Cloven, N.G., Marcus, J.Z., Coleman, R.L., Karam, A., 2021. Secondary cytoreductive surgery for recurrent ovarian cancer: An SGO clinical practice statement. Gynecol. Oncol. 163 (3), 448–452. https://doi.org/10.1016/j.ygyno.2021.10.008.

Howell, G.M., Carty, S.E., Armstrong, M.J., Stang, M.T., McCoy, K.L., Bartlett, D.L., Yip, L., 2013. Outcome and prognostic factors after adrenalectomy for patients with distant adrenal metastasis. Ann. Surg. Oncol. 20 (11), 3491–3496. https://doi.org/10.1245/s10434-013-3050-2.

Lee, J.A., Duh, Q., 2009. Functioning and non-functioning adrenal tumors. General Surg. 1687–1698. https://doi.org/10.1007/978-1-84628-833-3_167.

Lengyel, E., 2010. Ovarian cancer development and metastasis. Am. J. Pathol. 177 (3), 1053–1064. https://doi.org/10.2353/ajpath.2010.100105.

Lheureux, S., Gourley, C., Vergote, I., Oza, A.M., 2019. Epithelial ovarian cancer. The Lancet 393 (10177), 1240–1253. https://doi.org/10.1016/s0140-6736(18)32552-2.

Luketich, J., Burt, M., 1994. Does resection of isolated adrenal metastases in non-small cell lung Cancer (nsclc) improve survival? Lung Cancer 11, 153. https://doi.org/10.1016/0169-5002(94)94362-1.

Mclean, K., Lilienfeld, H., Caracciolo, J.T., Hoffe, S., Tourtelot, J.B., Carter, W.B., 2011. Management of ISOLATED Adrenal lesions in cancer patients. Cancer Control 18 (2), 113–126. https://doi.org/10.1177/107327481101800206.

Muth, A., Persson, F., Jansson, S., Johanson, V., Ahlman, H., Wängberg, B., 2010. Prognostic factors for survival after surgery for adrenal metastasis. Europ. J. Surg. Oncol. (EJSO) 36 (7), 699–704. https://doi.org/10.1016/j.ejso.2010.04.002.

Nieman, L.K., 2010. Approach to the patient with an adrenal incidentaloma. J. Clin. Endocrinol. Metabolism 95 (9), 4106–4113. https://doi.org/10.1210/jc.2010-0457.

Rose, P.G., Piver, M.S., Tsukada, Y., Lau, T., 1989. Metastatic patterns in histologic variants of ovarian cancer. An autopsy study. Cancer 64 (7), 1508–1513. https://doi.org/10.1002/1097-0142(19891001)64:73.0.co;2-v.

Sarela, A.I., Murphy, I., Coit, D.G., 2003. Metastasis to the adrenal gland: The emerging role of laparoscopic surgery. Ann. Surg. Oncol. 10 (10), 1191–1196. https://doi.org/10.1245/aso.2003.04.020.

Sehouli, J., Senyuva, F., Fotopoulou, C., Neumann, U., Denkert, C., Werner, L., Gülten, O., 2009. Intra-abdominal tumor dissemination pattern and Surgical outcome in 214 patients with PRIMARY ovarian cancer. J. Surg. Oncol. 99 (7), 424–427. https://doi.org/10.1002/jso.21288.

Ushijima, K., 2010. Treatment for recurrent ovarianc cancer-at first relapse. J. Oncol. 2010, 497429 https://doi.org/10.1155/2010/497429.