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Case report

Axillary lymph node metastasis in ovarian carcinoma: Two case reports and review of literature

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1. Introduction

Among gynecologic cancers, ovarian carcinoma is associated with the poorest prognosis (WEIDLE et al., 2016). High grade serous carcinoma is the most common type of ovarian cancer and most patients have advanced disseminated disease upon presentation (Hennessy et al., 2009). Although intraperitoneal dissemination is the most common route of spread, lymphatic metastasis is not uncommon (Hynninen et al., 2012) and hematogenous spread has also been documented (Rose et al., 1989). However, extra-peritoneal metastasis is rather rare, and the most common extra-peritoneal metastatic sites are lung, pleura, skin and brain (Cheng et al., 2009; Cormio and Rossi, 2003). Extra-peritoneal lymph node metastasis to the groin, supra-clavicular nodes, and paracardiac nodes has been well documented (Cormio and Rossi, 2003; Uzan et al., 2004; Raban et al., 2015). Although very rare, few case reports have documented axillary lymph node metastasis in ovarian serous carcinoma (Patel et al., 2014; Aydin et al., 2009). As the axillary lymph nodes are not an apparent site of drainage from the abdomen, the presentation of women with primary ovarian cancer with axillary lymph node metastasis is of interest.

Here we present two cases of high grade ovarian serous carcinoma metastasizing to axillary lymph nodes at presentation, in patients without history of breast cancer or other malignancy. We discuss the literature and attempt to explain the route of spread to these nodes.

1.1. Case 1

A 70-year-old woman presented with abdominal bloating. Medical and family history are noncontributory.

Initial work-up included serum levels of CA-125 and CT scan of chest-abdomen-pelvis. Levels of CA-125 were 4758. CT scan demonstrated large volume ascites, significant omental involvement, enlarged bilateral iliac and retroperitoneal para-aortic lymph nodes in addition to enlarged right axillary lymph node measuring 1.5 cm (Fig. 1). Cytologic findings from ascites revealed malignant cells with papillary structures. On immunohistochemistry (IHC), the tumor cells were positive for cytokeratin 7 and CA-125 – of likely gynecologic origin.

A tru-cut biopsy from right axillary lymph node demonstrated poorly differentiated adenocarcinoma with papillary pattern. On IHC, tumor cells were positive for ER, P53, P16, CA125, PAX8, KER, cytokeratin 7. Some of the cells were positive for WT-1and negative for GATA-1. The pathology report concluded that the lymph node pathology was similar to that of the ascites and consistent with metastasis of high grade ovarian serous carcinoma.

Since a diagnosis of stage IV, high grade ovarian carcinoma was made, the patient was referred for neoadjuvant chemotherapy (NACT) and received four courses of carboplatin and paclitaxel with partial response. PET-CT performed after NACT showed a significant decrease in the dimensions of the axillary lymph node. Serum levels of CA-125 dropped to 439.

Patient underwent interval cytoreduction with optimal debulking. Final pathology reports foci of high grade serous carcinoma involving both ovaries, uterus, omentum and biopsy from small intestine. In addition, right fallopian tube was involved with foci of high grade serous carcinoma compatible with serous tubal intraepithelial carcinoma.

Onco-genetic testing was negative for BRCA1 and BRCA2 common Ashkenazi Jewish mutations.

The patient went on to receive adjuvant chemotherapy with three courses of carboplatin and paclitaxel, along with bevacizumab followed by maintenance therapy with bevacizumab. PET-CT performed after

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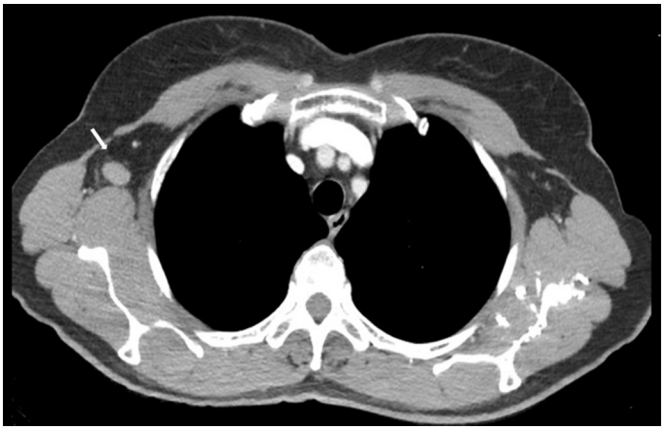

Fig. 1. CT scan demonstrating right axillary lymph node enlargement (white arrow) in case one prior to NACT treatment.

end of adjuvant chemotherapy demonstrated complete response, and serum levels of CA-125 were normal. Six months later, after five courses of maintenance bevacizumab, levels of CA-125 had risen. PET-CT demonstrated recurrent disease in axillary lymph nodes bilaterally, mediastinum, retroperitoneal lymph nodes and with few peritoneal implants.

1.2. Case 2

A 51-year-old woman presented with a 6 week history of umbilical purulent discharge unresponsive to antibiotic treatment. Due to abdominal pain, an abdominal CT was performed which demonstrated an enlarged uterus with multiple cysts, bilateral ovarian masses, and omental cake. No ascites or liver involvement were documented. Medical and family history are noncontributory. Uterine curettage revealed no signs of carcinoma, hyperplasia or atypia. Skin biopsy from the umbilicus showed metastatic carcinoma compatible with ovarian high grade serous carcinoma. On IHC, tumor cells were positive for CK7 and partially positive for ER. Serum levels of CA-125 upon first presentation were 327.

On physical examination prior to starting NACT treatment for stage IV ovarian carcinoma, an enlarged left axillary left node was palpated. This lymph node was demonstrated on CT scan as well. Core biopsy under ultrasound guidance was performed. Pathology revealed metastatic carcinoma with extensive necrosis, compatible with metastatic high grade serous carcinoma. Tumor cells were positive for cytokeratin 7. Some cells were positive for PAX8. ER partially positive and cells were negative for PR. Tumor cells were negative for CK20, P53, P40, TTF1, GATA3.

Patient received four courses of NACT with carboplatin and paclitaxel. Serum levels of CA-125 prior to treatment were 1675 and dropped to 91 prior to surgical intervention.

Patient underwent interval cytoreduction with optimal debulking. During surgery, biopsy from sub-cutis area in the umbilicus was taken. Final pathology reports foci of high grade serous carcinoma involving both ovaries. In addition, foci of metastatic carcinoma involving bilateral fallopian tubes, omentum, uterus, and biopsy from umbilicus.

Axillary metastasis was not surgically removed due to complete imaging response after NACT.

Onco-genetic testing was positive for a mutation in BRCA1 (5382insC).

After surgery the patient received four courses of chemotherapy with carboplatin and paclitaxel along with bevacizumab. Levels of CA-125 were normal at the end of adjuvant therapy. PET-CT performed routinely after adjuvant chemotherapy, prior to continuing maintenance therapy with bevacizumab, demonstrated a new pelvic mass and peritoneal carcinomatosis. Axillary lymph node involvement was not demonstrated.

2. Discussion

We describe two cases of ovarian serous carcinoma with axillary lymph node metastasis at initial diagnosis. Metastasis to the breast in cases of ovarian carcinoma is an unusual finding, but in up to 67% of these cases axillary lymph node involvement is also documented (Recine et al., 2004). However, isolated axillary lymph node metastasis without breast involvement is rare and has been reported only in few case reports (Patel et al., 2014; Aydin et al., 2009). All of these case reports included patients with advanced stage (IIIC and IV) serous ovarian carcinoma.

A study conducted by Cormio and Rossi (2003) reported an incidence of 8% of distant metastasis at time of diagnosis in stage IV epithelial ovarian carcinoma (EOC). The most common sites of distant metastasis were liver, pleura, lung, central nervous system and skin. Only five cases out of the 162 reviewed, had extra-abdominal lymphatic spread. In this study, risk factors for distant metastasis included stage, grade and lymph node involvement. Moreover, long interval time between diagnosis of ovarian carcinoma and documentation of distant metastasis was associated with poor prognosis.

Extra-peritoneal lymphatic spread in EOC has been well described by Hynninen et al. (2012). Since EOC often presents with carcinomatosis and ascites, the trans-diaphragmal invasion of cancer cells to the supra-diaphragmatic lymphatic system is logical. Once it reaches the superior diaphragmatic lymph nodes, this system divides into two routes, the anterior and the posterior route. The anterior route consists of prepericardial lymph nodes which are located behind the sternum and between the diaphragm and the heart and their afferents drain either to the internal jugular and subclavian vein or to the subclavian trunk and thoracic duct which could lead eventually to axillary lymph nodes. The posterior route includes drainage from deep lymphatic vessels inferior to the diaphragm and superficial lymphatic vessels inferior to the level of the umbilicus. These vessels unite to form the cisterna chyli and the thoracic duct which eventually drains to the junction of the left subclavian and internal jugular vein. This later rout could explain the left axillary lymph node metastasis in case 2 presented earlier.

An issue that should be addressed in patients with isolated axillary lymph node metastasis is the role of surgical resection. In general, surgical cytoreduction followed by adjuvant chemotherapy is the accepted management for most cases of advanced stage ovarian carcinoma. It has been shown to improve overall survival especially when optimal cytoreduction (residual disease < 1 cm) is achieved (Chang et al., 2013). Therefore, there might be a role of axillary lymph node resection as part of primary cytoreductive surgery.

In cases with advanced EOC, which are deemed to be non-optimally resected during primary surgery, NACT is offered as primary treatment followed by interval cytoreduction and adjuvant chemotherapy (Wright et al., 2016). Should distant lymph nodes, proven positive prior to NACT, be resected or sampled during interval cytoreduction remains questionable. In the two cases presented earlier, where axillary lymph nodes responded to NACT and they were not grossly apparent prior to surgery, removing them during interval cytoreduction would not have changed the surgical result as it will remain to be optimal debulking, and probably would not change adjuvant treatment. However, positive distant lymph nodes after NACT might change prognosis.

Since axillary lymph node metastasis in EOC is rare and only few case reports published, it is hard to tell whether this finding has an adverse impact on prognosis compared to counterpart patients with stage IV ovarian carcinoma.

Axillary metastasis can mimic primary breast cancer metastasis, especially when metastasis to breast is also involved. Clinical and radiological appearance can be very challenging for clinicians (Susini et al., 2010). The role of pathology in these cases is extremely

important. IHC staining suggesting ovarian origin of the axillary metastasis, such as was found in our cases, are cytokeratin 7, WT-1, PAX8 and CA-125 with negative staining for GATA-3. Given the possibility of synchronous breast and ovarian cancer often noted in this patient population, identifying the origin of the axillary metastasis using pathology and IHC staining is of great clinical significance and may well impact on both prognosis and management.

In addition, radiologic assessment of suspected second primary breast carcinoma as the origin of axillary metastasis should be performed using mammography or magnetic resonance imaging.

As for genetic testing, case 2 was positive for BRCA1 mutation. Previous studies have shown different patterns of spread and response to chemotherapy in BRCA1 and BRCA2 carriers (Pinto et al., 2016), it is important to identify these cases, not only for tailoring the treatment for the patient, but for counseling and screening her family members.

In conclusion, we presented two cases of axillary lymph node metastasis upon presentation of high grade ovarian serous carcinoma. Full body imaging and thorough physical examination is crucial when planning treatment for patients with advanced ovarian carcinoma in the abdomen, as extra-abdominal disease may alter treatment decisions. Physicians should be aware of this rare entity, second primary breast cancer should be ruled out by imaging or IHC, especially when there is questionable suspicion of ovarian carcinoma.

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