Original Investigation

The Etiology of Adnexal Masses in Women with a History of Non-Gynaecologic Malignancy: Recurrence, Second Primary or None?

Celiksoy et al. Adnexal Masses After Non-Gynaecologic Malignancy

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Introduction

Adnexal masses are incidentally diagnosed during the follow-up of patients with a history of non-gynaecologic malignancy (NGM). For these patients, the occurrence of an adnexal mass raises concerns for malignancy, either primary or metastasis, but the overall risk is not clearly defined. The prognosis and treatment depend on the etiology. Ovarian metastasis is usually associated with an advanced incurable disease and needs only palliative systemic therapy. On the other hand, primary ovarian cancer (POC) is a potentially curable disease and the standard treatment is surgery followed by systemic chemotherapy. The definitive diagnosis must be made by histopathology. If it is likely ovarian metastasis of NGM, laparoscopy can be performed for the diagnosis, thereby avoiding more invasive routes. However, for early stage POC, it carries the risk of POC cells spilling into the abdomen (1). Furthermore, the exploration and debulking could not be performed at advanced stage by laparoscopically. The primary purpose of evaluating a suspected adnexal mass with a history of NGM is to clarify the most likely etiology of the mass and subsequent management. This specification does not have any clear rules. Ultrasonography (USG) remains the standard tool for the preoperative assessment, and magnetic resonance imaging (MRI) should be used as a second imaging study if further information is needed for surgery decision. Tumor markers are also helpful for revealing the underlying disease. Compared with POC, lower serum CA125 levels and higher levels of the other markers have been reported in metastatic cases (2). Ovarian metastases tend to be bilateral (3), and are mostly caused by gastrointestinal tract and breast carcinomas (4).

The characteristics of adnexal masses in patients with a history of nongynecological malignancies are investigated in this manuscript, and our aim was to to clarify the differential diagnosis of the adnexal masses in these patients.

Material and Methods

We analysed the files of 59 patients with a history of NGM, who were for an adnexal mass in the gynaecological oncology department between 2006-2020. Patients who were under 18 or

above 85 years, had a pregnancy, had a history of genital sourced malignancy, were excluded from the study. All patients underwent transvaginal or transrectal and transabdominal 2D-USG by a consultant gynaecological oncologist. The presence of solid areas, multilocular cysts and bilateral lesions were noted. Simple cysts were not included. Tumour size was based on the largest diameter on USG. Serum CA125 levels and the other NGM-related tumor markers (CA19-9, CA15-3, carcinoembryonic antigen (CEA)) were measured preoperatively. Patients, whom adnexal masses were suspected by USG findings, CA125 level and menopausal status, underwent MRI and were evaluated at our tumor board meeting. For presumed malignancy, patients underwent laparotomy with midline incision and masses were sent for frozen-section. Surgical procedure was performed according to the results of perioperative frozen-section, considering age and fertility requirements. The final histopathological diagnosis was taken into account for statistical analysis. Tumors were classified and staged according to World Health Organization (WHO) and International Federation of Gynaecology and Obstetrics (FIGO) classifications. The patient was accepted as postmenopausal, if she was amenorrhoeic for more than a year or had undergone hysterectomy and was 50 years or older. Borderline ovarian tumor (BOT) was accepted as a primary ovarian malignancy.

Statistical analysis

SPSS (Statistics Package for Social Sciences) 21.0 version was used. Mann-Whitney U and chi-square test as nonparametric methods and independent-samples t test as parametric method were done. P value <0.05 was considered statistically significant. Data were written as mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical values were expressed as absolute numbers and percentages.

Results

Fifty-nine patients with an adnexal mass and a history of NGM were identified. 48 patients had no symptoms and were diagnosed during their routine follow-up. The other patients had abdominal bloating and/or pain. The majority of patients had a history of gastrointestinal tract (colorectal (n=22) and gastric (n=9)) and breast cancer(n=25); the others had renal cancer (n=2) and pancreas cancer (n=1) (Table 1). Of all adnexal masses, three were benign (5 %), 21 were primary ovarian malignancy (36%) and 35 were metastatic disease (59 %). Ovarian metastasis was most frequently (81%) observed among the patients with history of a gastrointestinal cancer, while primary ovarian malignancy was most frequently (64%) observed among the patients with a history of breast cancer.

Ten of all patients with an adnexal mass had a recent diagnosis of NGM (in 6 months), 9 of these masses were metastases to ovaries and one of them was diagnosed with a primary ovarian malignancy. Of the 35 metastatic cases, two had relapsed before without ovarian metastasis, while 33 patients first relapsed with ovarian metastasis.

Forty patients had a chemotherapy history. Only one patient had received pelvic radiotherapy (due to colorectal cancer), and no second primary cancer was diagnosed, but ovarian metastasis of colorectal cancer.

One patient with ovarian carcinoma underwent second surgery for re-staging, because frozen-section diagnosis was consistent with breast cancer metastasis to ovary, but final diagnosis confirmed a primary ovarian malignancy. Strikingly, the frozen-section accuracy rate was 96.6%.

All of the POCs were epithelial and histologic subtypes were serous (n=17) and endometrioid (n=3) adenocarcinoma. Eight of the 20 POCs were at early stage (stage 1-2) and twelve were at stage 3. One of the 21 primary cases was BOT which was serous type at stage 1.

Table 2 compared the characteristics of patients who had primary ovarian malignancy or metastatic carcinoma to the adnexa. Among these features, the laterality in pathology specimens and serum CA125 levels had statistically significant difference.

When examined in detail, high CA125 levels (>35 IU/mL) were present in 14 (40%) of the metastatic cases: Eleven of these 14 patients had also high levels of the NGM-related tumor markers like CA19-9, CA15-3, CEA. Of three remaining cases whose CA125 levels high but NGM-related markers were misleadingly normal, one was breast and two were gastric cancer. 21 (60%) of the metastatic cases had normal CA125 levels: Seven of them (4 colorectal, 1 gastric,1 breast,1 renal cell cancer) had normal levels of the other markers, twelve of them had high levels of CA19-9 and/or CEA with gastrointestinal cancer metastasis to adnexa, the other two patients with breast cancer had high level of CA15-3.

Five (24%) of the primary cases had normal CA125 levels. The levels of NGM-related markers of the other five cases (3 gastrointestinal and 2 breast cancer) were also normal. High CA125 levels were present in 16 (76%) of the primary cases and half of them had also high levels of other NGM-related markers.

The rate of bilaterality observed with preoperative USG did not differ significantly between metastatic cases (37%) and primary ovarian malignancies (29%) (p=0.7). On the other hand, according to pathology results, the percentage of microscopic bilaterality in metastatic (83%) and primary cases (52%) was significantly different (p=0.019).

Discussion

Metastasis comprises 5-20% of all ovarian neoplasms and the most common non-gynecological source is gastrointestinal tract cancer (57%), followed by breast cancer (30%) (5). Although the ovaries are frequent site of the metastasis from NGM, women with a history of NGM may also be at increased risk of developing a POC. In Europe, 66693 new ovarian cancers were estimated to be diagnosed in 2020 (6). This risk is doubled after a diagnosis of breast cancer (7). Although there are many studies on ovarian metastasis rates in other types of cancer, there is no precise data on the rate of POCs and their discrimination. In our study design, colorectal cancer was the most common NGM resulting in metastasis to the ovaries and the rate of POC was extremely low (13.6%). On the other hand, the rate of POC was as high as 64% in those with a history of breast cancer presenting with a suspicious adnexal mass. A recent study included one hundred seventy-seven patients with ovarian metastasis from non-gynecological primary sites. The colorectum (n=68) and stomach (n=61) were the two most common non-gynecological primary sites of ovarian metastasis. They also discovered that more than 70% of synchronous ovarian metastases were misdiagnosed as primary ovarian cancer prior to surgery(8). Juretzka et al. operated two hundred sixty-two patients with an adnexal mass and a history of NGM and 202 of them had a history of breast cancer. In all, 49 patients (18.7%) had malignancy, including 19 (38.8%) patients with a new POC and 30 (60.2%) patients with a metastatic malignancy to the ovary. Of the 202 patients with a history of breast cancer, thirty-seven had adnexal malignancy and 18 (48.6%) of them had POC. Of the twelve patients with a history of gastrointestinal tract cancer, seven had adnexal malignancy and 6 (85.7%) of them had metastasis to adnexa (9). Unlike their study, the overall malignancy rate in our series was 95 % which was quite high, because we did not include probable benign cysts. And the second major difference was that we found the POC/metastasis ratio approximately two times higher in patients with breast cancer.

Serum tumor markers may aid as part of the evaluation of these patients. We found CA125 useful in identifying the type of ovarian malignancy, primary or metastasis. The other NGM-related markers were also useful, but a statistical comparison could not be made in present study, because there were different markers regarding different NGM with a small number of samples. These NGM-related markers including CEA, CA19-9 and CA15-3 might be useful in identifying the reason of adnexal mass, but they might also be elevated at a POC. In a series of 284 metastatic breast cancer cases, elevated serum levels of CA15-3 and CEA were found significantly associated with breast cancer subtypes. While elevated CEA levels did not differ between patients with a single and those with multiple metastatic sites, increased CA15-

3 tend to correlate with a larger number of metastatic sites and might also be more commonly associated with hormone receptor-positive disease (10). CA19-9 is a useful marker for tumors of gastrointestinal origin, including the pancreas. A study which analysed preoperative findings in NGM metastasizing to the ovaries, reported that CEA was a useful marker to distinguish NGM from POC and the CEA levels were significantly higher in colorectal cancer than in gastric cancer. The ratio of CA125: CEA >25 is effective and convenient method to distinguish POC from metastatic colorectal cancer (11). It seems that one marker is not sufficient for an accurate prediction and it would be wise to combine markers. HE4 (human epididymis protein 4), which is a new marker compared to others, rises in POC. However, NGM, including invasive ductal carcinoma of breast, endometrial, pancreaticobiliary, and renal cell carcinoma, can express HE4 proteins or genes, too (12). Further research is needed to investigate the utility of HE4 in discriminating NGM from POC.

In the literature, bilaterality and lesser ovarian enlargement were found helpful to discriminate the metastatic tumors to the ovary (3). In 2004, Moore et al. reported bilateral ovarian metastasis was demonstrated in 39 (66%) patients and unilateral ovarian metastasis in 20 (34%) patients (4). In our analysis, both tumor size and laterality, monitored by USG, were not statistically different. However, bilaterality at microscopic evaluation was found statistically different. According to these results, USG findings did not help us preoperatively and it were deceptive for laterality.

In our 59 patients, the frozen-section and final pathologic results had more than 95% correlation, which was similar to the literature. We performed laparotomy in all cases, but laparoscopy is recommended by most authors. However, if the frozen-section diagnosis suggests a POC at advanced stage or if an ovarian mass cannot be dissected safely, laparotomy should be performed (9,13).

In our study design, although the number of cases seems to be low, it is not bad considering that we only conducted complex adnexal masses.

Conclusion

Recurrence of prior malignancy is more likely than POC, but especially for patients with a history of breast cancer the risk of POC should not be disregarded. Given the high rates of metastasis, it would be reasonable to start with laparoscopy in patients with a history of a gastrointestinal cancer presenting with an adnexal mass. A multidisciplinary team with involvement of a gynaecological oncologist would be necessary to evaluate these challenging cases.

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Table 1. Histopathologic results of patients

Prior cancer history	Primary ovarian malignancy, n(%)	Metastatic carcinoma to the adnexa, n(%)	Benign, n(%)
Breast (n=25)	16(1 BOT) (64)	8 (32)	1 (4)
Colorectal (n=22)	3 (13.6)	18 (81.8)	1 (4.6)
Gastric (n=9)	2 (22.2)	7 (77.8)	0
Renal (n=2)	0	1 (50)	1(50)
Pancreas (n=1)	0	1 (100)	0
BOT: Borderline ovarian tumor			

Table 2. Characteristics of patients

Prognostic factors	Primary ovarian malignancy (n=21, 1 borderline)	Metastatic carcinoma to the adnexa(n=35)	p

Age(y)	56,2±9,2	52,4±12,0	0.216
Interval time (month)	48 (24-156)	24 (12-54)	0.184
BMI, kg/m^2	30,0±5,8	27,4±6,2	0.15
Active treatment/recent diagnosis, n (%)	1 (4,8)	9 (25,7)	0.072
Chemotherapy history, n (%)	12 (57,1)	29 (82,9)	0.073
Menopause status, n (%) Premenopausal Postmenopausal	 4 (19,0) 17 (81,0)	 13 (37,1) 22 (62,9)	 0.231
Tumor diameter, cm	8,1±5,8	9,6±4,5	0.264
USG findings, n (%) Solid Multiloculate Solid + multiloculate	 10 (47,6) 3 (14,3) 8 (38,1)	 21 (60) 1 (2,9) 13 (37,1)	 0.251
Laterality (USG), n (%) Unilaterally Bilaterally	 15 (71,4) 6 (28,6)	 22 (62,9) 13 (37,1)	 0.716
Laterality (microscopic), n (%) Unilaterally Bilaterally	 10 (47,6) 11 (52,4)	 6 (17,1) 29 (82,9)	 0.019
Ascites, n (%)	3 (14,3)	3 (8,6)	0.661
CA125, U/mL	205 (33-262)	27 (14-70,5)	0.001