

The etiology of adnexal masses in women with a history of non-gynaecological malignancy: recurrence, second, primary or none?

Harika Yumru Çeliksoy, Hamdullah Sözen, Merve Baktıroğlu, Samet Topuz, Yavuz Salihoğlu

Department of Gynecological Oncology, İstanbul University-İstanbul University Faculty of Medicine, İstanbul, Turkey

Abstract

Objective: The occurrence of adnexal masses in patients with a history of non-gynaecological malignancy (NGM) raises concerns for malignancy, either primary or metastasis. Subsequent treatment and prognosis depends on the etiology. Our aim was to investigate the characteristics and results of the patients with suspicious adnexal masses, who had a history of NGM.

Material and Methods: The records of 61 patients with a history of NGM were analyzed, who were operated for an adnexal mass. Complex adnexal masses were included in the analysis while simple cysts were excluded.

Results: The most common NGM origins were gastrointestinal (gastric and colorectal) tract and breast. Of all adnexal masses, four were benign (6.5%), 22 were primary ovarian malignancy (36.1%) and 35 were metastasis (57.4%). Two of the 22 primary cases were borderline ovarian tumor. Among the characteristics of primary and metastatic groups, laterality in pathology results and serum CA125 levels were statistically different ($p < 0.05$). Among the patients with history of gastrointestinal cancers, the percentage of ovarian metastasis was 81%. Primary ovarian malignancy was most frequently (64%) observed among the patients with history of breast cancers.

Conclusion: For patients with a history of gastrointestinal cancer, recurrence of the cancer in the form of ovarian metastasis was more likely, rather than a second primary cancer. The risk of primary ovarian cancer (POC) was remarkable in those with history of a breast cancer. A multidisciplinary strategy, including a gynaecological oncologist, plays an important role in managing these cases, regardless of whether or not it is a POC. (J Turk Ger Gynecol Assoc 2022; 23: 263-7)

Keywords: Ovarian neoplasms, metastasis, Krukenberg tumor

Received: 12 February, 2021 **Accepted:** 30 July, 2021

Introduction

Adnexal masses are usually incidentally diagnosed during the follow-up of patients with a history of non-gynaecological malignancy (NGM). For these patients, the occurrence of an adnexal mass raises concerns for malignancy, either primary or metastatic, 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. In contrast, 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 an ovarian metastasis of NGM, laparoscopy can be performed for the diagnosis, thereby avoiding more invasive routes. However, for early stage POC, this procedure carries the risk of POC cells spilling into the abdomen (1). Furthermore, surgical exploration and debulking cannot be performed at advanced stages by laparoscopy. 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 preoperative assessment, and magnetic resonance



Address for Correspondence: Harika Yumru Çeliksoy

e-mail: harika.yumru@istanbul.edu.tr ORCID: orcid.org/0000-0002-8936-5211

©Copyright 2022 by the Turkish-German Gynecological Education and Research Foundation - Available online at www.jtgga.org

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.

DOI: 10.4274/jtgga.galenos.2021.2021-0031

imaging (MRI) should be used as a second imaging study if further information is needed for surgical decision making. Tumor markers are also helpful for identifying 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 NGM are investigated in this study, and our aim was to clarify the differential diagnosis of adnexal masses in these patients.

Material and Methods

The study protocol was approved by the Local Ethics Committee of the İstanbul University (approval number: 2019/539). It was not applicable for informed consent.

We analysed the files of patients with a history of NGM, who attended for investigation of an adnexal mass in the gynaecological oncology department between 2006-2020. Patients who were under 18 or above 85 years, had a pregnancy, or 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 other NGM-related tumor markers, including CA19-9, CA15-3 and carcinoembryonic antigen (CEA), were measured preoperatively. Patients, in whom adnexal masses were suspected because of a combination of USG findings and/or CA125 level and/or 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 considered for statistical analysis. Tumors were classified and staged according to World Health Organization and International Federation of Gynaecology and Obstetrics classifications. A 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, version 21.0 was used for statistical analysis (IBM Inc., Armonk, NY, USA). Data were written as mean \pm standard deviation or median and interquartile range. Categorical values were expressed as absolute numbers and percentages. Non-

parametric tests included Mann-Whitney U and chi-square test and the parametric test was Independent-samples t-test, which were used as appropriate. A p-value <0.05 was considered statistically significant.

Results

Fifty-nine patients with an adnexal mass and a history of NGM were identified, of whom 48 (81.4%) 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) while there were a small number with 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 a history of a gastrointestinal cancer, while primary ovarian malignancy was most frequently (64%) observed among the patients with a history of breast cancer.

Ten (16.9%) of all patients with an adnexal mass had a recent diagnosis of NGM within the preceding six months, nine of these masses were metastases to ovaries and one 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 (67.8%) had a history of undergoing chemotherapy. Only one patient had received pelvic radiotherapy (due to colorectal cancer), and no second primary cancer was diagnosed, but she had 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 histological subtypes were either serous (n=17) or endometrioid (n=3) adenocarcinoma. Eight of the 20 (40%) POCs were at early stage (stage 1-2) and the remaining twelve were at stage 3. One of the 21 primary cases was BOT which was serous type at stage 1.

Table 2 shows a comparison of 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 exhibited significant differences.

High CA125 levels (>35 IU/mL) were present in 14 (40%) of the metastatic cases. Eleven (78.6%) of these 14 patients also had high levels of the NGM-related tumor marker, such as CA19-9, CA15-3 and CEA. Of three remaining cases whose CA125 levels were high but NGM-related markers were misleadingly normal,

one had breast and two had gastric cancer. Twenty-one (60%) of the metastatic cases had normal CA125 levels. Seven (4 colorectal, 1 gastric, 1 breast, 1 renal cell cancer) had normal levels of other tumor markers while twelve 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 also had 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%) ($p=0.7$). In contrast, histopathologically, 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 frequently the site of metastasis from

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 (years)	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	4 (19.0)	13 (37.1)	0.231
Postmenopausal	17 (81.0)	22 (62.9)	
Tumor diameter, cm	8.1±5.8	9.6±4.5	0.264
USG findings, n (%)			
Solid	10 (47.6)	21 (60)	0.251
Multiloculate	3 (14.3)	1 (2.9)	
Solid + multiloculate	8 (38.1)	13 (37.1)	
Laterality (USG), n (%)			
Unilaterally	15 (71.4)	22 (62.9)	0.716
Bilaterally	6 (28.6)	13 (37.1)	
Laterality (microscopic), n (%)			
Unilaterally	10 (47.6)	6 (17.1)	0.019
Bilaterally	11 (52.4)	29 (82.9)	
Ascites, n (%)	3 (14.3)	3 (8.6)	0.661
CA125, U/mL	205 (33-262)	27 (14-70.5)	0.001

BMI: Body mass index, USG: Ultrasonography

NGM, women with a history of NGM may also be at increased risk of developing a POC. In Europe, it was estimated that 66,693 new ovarian cancers would 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 the present study, colorectal cancer was the most common NGM resulting in metastasis to the ovaries and the rate of POC was extremely low (13.6%). Despite the low overall rate of POCs, in those with a history of breast cancer presenting with a suspicious adnexal mass this was as high as 64%. A recent study that included one hundred and seventy-seven patients with ovarian metastasis from non-gynecological primary sites found that the colorectum (n=68) and stomach (n=61) were the two most common non-gynecological primary sites of ovarian metastasis (8). These authors also reported that more than 70% of synchronous ovarian metastases were misdiagnosed as POC prior to surgery. Juretzka et al. (9) operated on two hundred and sixty-two patients with an adnexal mass and a history of NGM and 202 (77.1%) 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%) 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). In contrast to the study of Juretzka et al. (9), the overall malignancy rate in our series was 95%, which was higher, possibly because we did not include probable benign cysts. The second major difference was that we found the POC/metastasis ratio approximately twice as high 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 the 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 etiology 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 analyzed 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 (11). A ratio of CA125: CEA >25 was an effective and convenient method to distinguish POC from metastatic colorectal cancer. Thus it is apparent that one marker is not sufficient for an accurate prediction and it would be wise to combine markers. Human epididymis protein 4 (HE4), which is a relatively new marker, rises in POC. However, NGM, including invasive ductal carcinoma of breast, endometrial, pancreaticobiliary, and renal cell carcinoma, can also express HE4 proteins or genes (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 to be helpful to discriminate metastatic tumors to the ovary (3). In 2004, Moore et al. (4) 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 different. However, bilaterality by microscopic evaluation was found significantly different. These results suggest that USG findings did not help preoperatively and were deceptive for laterality.

In our 59 patients, the frozen-section and final histopathological results had >95% correlation, which was similar to previous reports. 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).

Study Limitations

In terms of limitations, although the number of cases appears low, it should be remembered that we only included complex adnexal masses.

Conclusion

Recurrence of prior malignancy is more likely than POC, but especially in 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 the involvement of a gynaecological oncologist is necessary, in our opinion, to evaluate these challenging cases.

Acknowledgments: We would like to thank our Gynecological Oncology Clinic Secretary Sultan Uskan Öz for helping to collect data.

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee of the İstanbul University (approval number: 2019/539).

Informed Consent: It was not applicable for informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices: S.T., H.S.; Concept: Y.S.; Design: H.Y.Ç.; Data Collection or Processing: H.Y.Ç., M.B.; Analysis or Interpretation: M.B.; Literature Search: H.Y.Ç.; Writing: H.Y.Ç.

Conflict of Interest: No conflict of interest is declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

- Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, et al; ESMO-ESGO Ovarian Cancer Consensus Conference Working Group. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†. *Ann Oncol* 2019; 30: 672-705.
- Reinert T, Rodrigues AN, Kestelman FP, Prolla PA, Graudenz MS, Bines J. The challenge of evaluating adnexal masses in patients with breast cancer. *Clin Breast Cancer*. 2018; 18: e587-94.
- de Waal YR, Thomas CM, Oei AL, Sweep FC, Massuger LF. Secondary ovarian malignancies: frequency, origin, and characteristics. *Int J Gynecol Cancer* 2009; 19: 1160-5.
- Moore RG, Chung M, Granai CO, Gajewski W, Steinhoff MM. Incidence of metastasis to the ovaries from nongenital tract primary tumors. *Gynecol Oncol* 2004; 93: 87-91.
- Skírnisdóttir I, Garmo H, Holmberg L. Non-genital tract metastases to the ovaries presented as ovarian tumors in Sweden 1990-2003: occurrence, origin and survival compared to ovarian cancer. *Gynecol Oncol* 2007; 105: 166-71.
- <https://ecis.jrc.ec.europa.eu/?%20Cancer=27&Gender=2>
- Molina-Montes E, Requena M, Sánchez-Cantalejo E, Fernández MF, Arroyo-Morales M, Espín J, et al. Risk of second cancers cancer after a first primary breast cancer: a systematic review and meta-analysis. *Gynecol Oncol*.2015; 136: 158-71.
- Zhang JJ, Cao DY, Yang JX, Shen K. Ovarian metastasis from nongynecologic primary sites: a retrospective analysis of 177 cases and 13-year experience. *J Ovarian Res* 2020; 13: 128.
- Juretzka MM, Crawford CL, Lee C, Wilton A, Schuman S, Chi DS, et al. Laparoscopic findings during adnexal surgery in women with a history of nongynecologic malignancy. *Gynecol Oncol* 2006; 101: 327-30.
- Geng B LM, Ye XB, Zhao WY. Association of CA 15-3 and CEA with clinicopathological parameters in patients with metastatic breast cancer. *Mol Clin Oncol* 2015; 3: 232-6.
- NCCN Clinical Practice Guidelines in Oncology. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 1.2020 - March 11, 2020.
- Galgano MT, Hampton GM, Frierson HF Jr. Comprehensive analysis of HE4 expression in normal and malignant human tissues. *Mod Pathol* 2006; 19: 847-53.
- Abu-Rustum NR, Rhee EH, Chi DS, Sonoda Y, Gemignani M, Barakat RR. Subcutaneous tumor implantation after laparoscopic procedures in women with malignant disease. *Obstet Gynecol* 2004; 103: 480-7.