Case report

Serous borderline tumor with distant mediastinal metastasis? An Exceptional presentation of ovarian tumor

Julia M. Sołek[1], Aleksandra Zielińska[1], Magdalena Sobczak[2], Urszula Czernek[2], Robert Kubiak[3], Radzisław Kordek[1], Dorota Jesionek-Kupnicka[1]

[1]Department of Pathology, Medical University of Lodz, Lodz, Poland
[2]Department of Chemotherapy, Chair of Oncology, Medical University of Lodz, Poland
[3]Department of Pathology, SYNEVO, Lodz, Poland

Borderline ovarian tumor is a non-invasive lesion with an excellent prognosis. Here we report a case of 48-year-old woman with distinctive clinical presentation of metastasis of ovarian adenocarcinoma, which was an microinvasive component of a serous borderline tumor. On initial diagnosis patient did not present any clinical manifestation of ovarian tumor. Histological examination of resected ovary showed typical features of the serous borderline tumor with one very diminutive focus of invasive serous adenocarcinoma 4mm in diameter. This exceptional case shows that borderline tumors of ovary with any features of invasion could present an aggressive course with distant metastases.

Key words: borderline tumor, ovary, serous adenocarcinoma, metastasis, microinvasion.

Introduction

Ovarian cancer is a leading cause cancer-related death in woman with a 5-years survival below 50% [1]. Historically, it is called "silent killer" because more than 62% of the disease occurs in IV stage with distant metastasis without previous warning symptoms [2]. According to the Surveillance, Epidemiology, and End Results (SEER) database, 10-year survival for patients with IV stage of disease with distant metastasis is 15%, whereas 10-year survival for patients with early stage is 55%. This fact presents a high need to find an effective screening test and also calls for deeper understanding molecular mechanism of metastasis. Here we present an unusual presentation of distant metastasis during very early clinical stage of ovarian cancer i.e. borderline tumor with microinvasion which constituted a huge diagnostic dilemma and required profound diagnostic workup with large panel of immunohistochemistry and molecular study. The comprehensive analyses provided here gives us a deeper insight in enigmatic mechanism of ovarian distant metastasis.

Case presentation

The 48-year-old Caucasian women presented in Department of Oncology with 12-weeks history of shortness of breath and reduced exercised tolerance. She had no significant past medical history. Due to the breathing problems, pulmonary function test and imaging study were performed. In spirometry all values fell within the normal range. Radiography imaging showed enlarged lung hilum what suggested that suspicious lesion is localized in lymph nodes. Subsequent surgical biopsy of affected lymph nodes around tracheal bifurcation was performed. On high magnification an adenocarcinoma

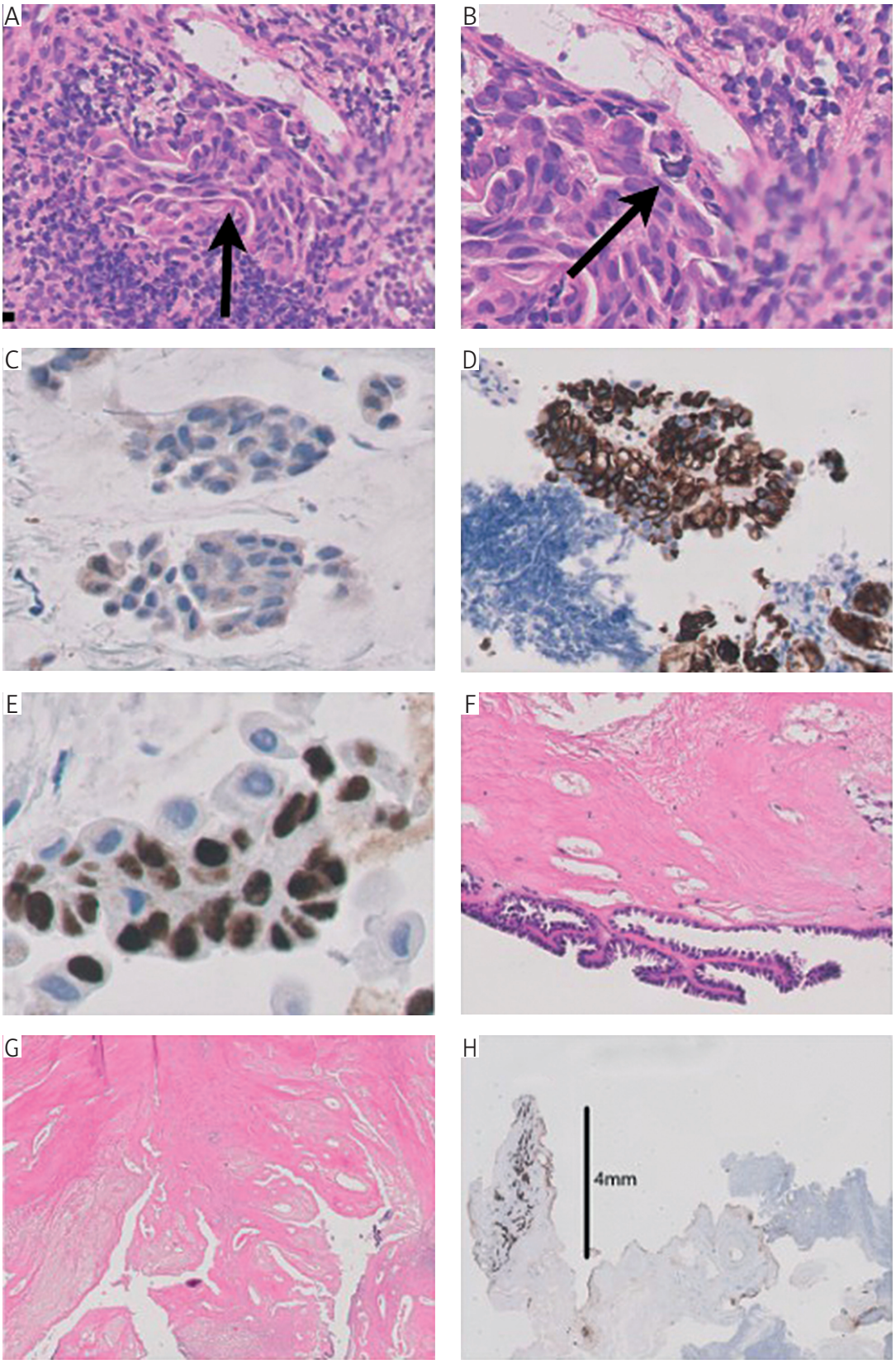

Fig. 1. Pathology evaluation of mediastinal lymph node biopsy, 100× magnification (A-E). Papillary structures (arrow) (A); psammoma body (arrow) (B); negative IHC staining for thyroid transcription factor 1 (TTF1), thyroglobulin, gross cystic disease fluid protein (GCDFP-15) and mammaglobulin (C); positive staining for: cytokeratin 7(CK7) (D); estrogen receptor (ER), progesterone receptor (PR); paired box 8 (PAX8), thyroid transcription factor 1 (TTF1) (E); Pathology evaluation of resected ovarian tumor, 40× magnification (F-H). Papillae covered by single- or multi-layered, non-atypical epithelium (F); area of necrosis (G) IHC staging for cytokeratin AE1/AE3 showing area of invasion 4 mm in diameter

Table I. Summary of all examinations during the process of diagnosis

Immunohistochemical study	Molecular study	Diagnostic imaging	Blood test
TTF-1	BRAF	PET/CT	CA-125
Thyroglobulin	EGFR	RTG	
Mammaglobulin	ALK		
CK7	ROS1		
ER			
PR			
WT-1			
PAX8			
PD-L1			
Pan Type Cytokeratin (AE1/AE3)			
GCDFP-15			

CK7 – cytokeratin 7; ER – estrogen receptor; PR - progesterone receptor; WT1 – Wilms' tumor 1; PAX8 – paired box 8; TTF1 – thyroid transcription factor 1; GCDFP-15 – gross cystic disease fluid protein; PET/CT – positron emission tomography–computed tomography; RTG – radiography; CA-125 – cancer antigen 125

papillary structures and psammoma bodies were seen (Fig.1 A, B). The immunohistochemical (IHC) study showed positive expression for cytokeratin 7 (CK7), estrogen receptor (ER), progesterone receptor (PR), Wilms' tumor 1 (WT1) and paired box 8 (PAX8) by tumor cells and negative expression for thyroid transcription factor 1 (TTF1), thyroglobulin, gross cystic disease fluid protein (GCDFP-15), and mammaglobulin (Fig.1 C-E). The differential diagnosis included: primary lung papillary adenocarcinoma as well as metastatic tumors – breast carcinoma metastasis, papillary thyroid carcinoma metastasis and eventually very rare presentation of ovarian tumor metastasis. Molecular examination gave positive results for *BRAF* mutation, whereas negative for *EGFR, ALK, ROS1* mutations. Additional pharmacodiagnostic test found a negative PD-L1 expression. Most molecular studies were performed in National Research Institute of Oncology in Warsaw. Increased concentration of cancer antigen 125 (CA-125) was detected (124,0 U/ml; cut off value 35,0 U/ml) what together with analysis of IHC and molecular study results strongly suggested ovarian tumour as a most probable metastatic tumor source. All results of performed diagnostic examinations are visible in Table I. Finally, positron emission tomography-computed tomography (PET/CT) scan showed approximately 20 mm in diameter mass of increased metabolic activity in right ovary (SUV_{max} = 5,4) and surgical resection of ovary was performed (Fig.2). Surprisingly, histopathological analysis of resected ovary mass displayed features typical for serous borderline tumour: papillae covered by single- or multi-layered, non-atypical epithelium (Fig. 1F). Within tumour tissue there were a large areas of necrosis (Fig. 1G). Detailed pathological diagnosis and positive immunohistochemical staining for pan type cytokeratin AE1/AE3 shown a diminutive, 4 mm in diameter, focus of invasion, what, according to WHO recommendation confirmed the final diagnosis of ovarian serous borderline tumor with microinvasion (Fig. 1H). Moreover negative staining for P53 highly suggests a non-mutational *TP53* "wild type"– pattern. The patient was referred for palliative chemotherapy recommended for IVth stage of invasive ovarian carcinoma with 6 cycles of carboplatin, paclitaxel and bevacizumab and 1 consisting only bevacizumab. During therapy patient showed gradual decrease in CA-125 level (Fig. 3). After seven cycles of combined chemotherapy and immunotherapy tumor mediastinal mass disappeared as well as patient's breathing disturbances were resolved.

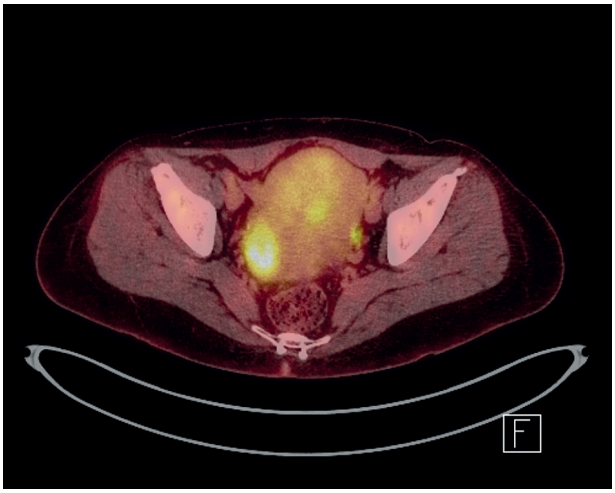

Fig. 2. Positron emission tomography-computed tomography (PET/CT) scan showed approximately 20 mm in diameter mass of increased metabolic activity in right ovary (SUV_{max} = 5.4)

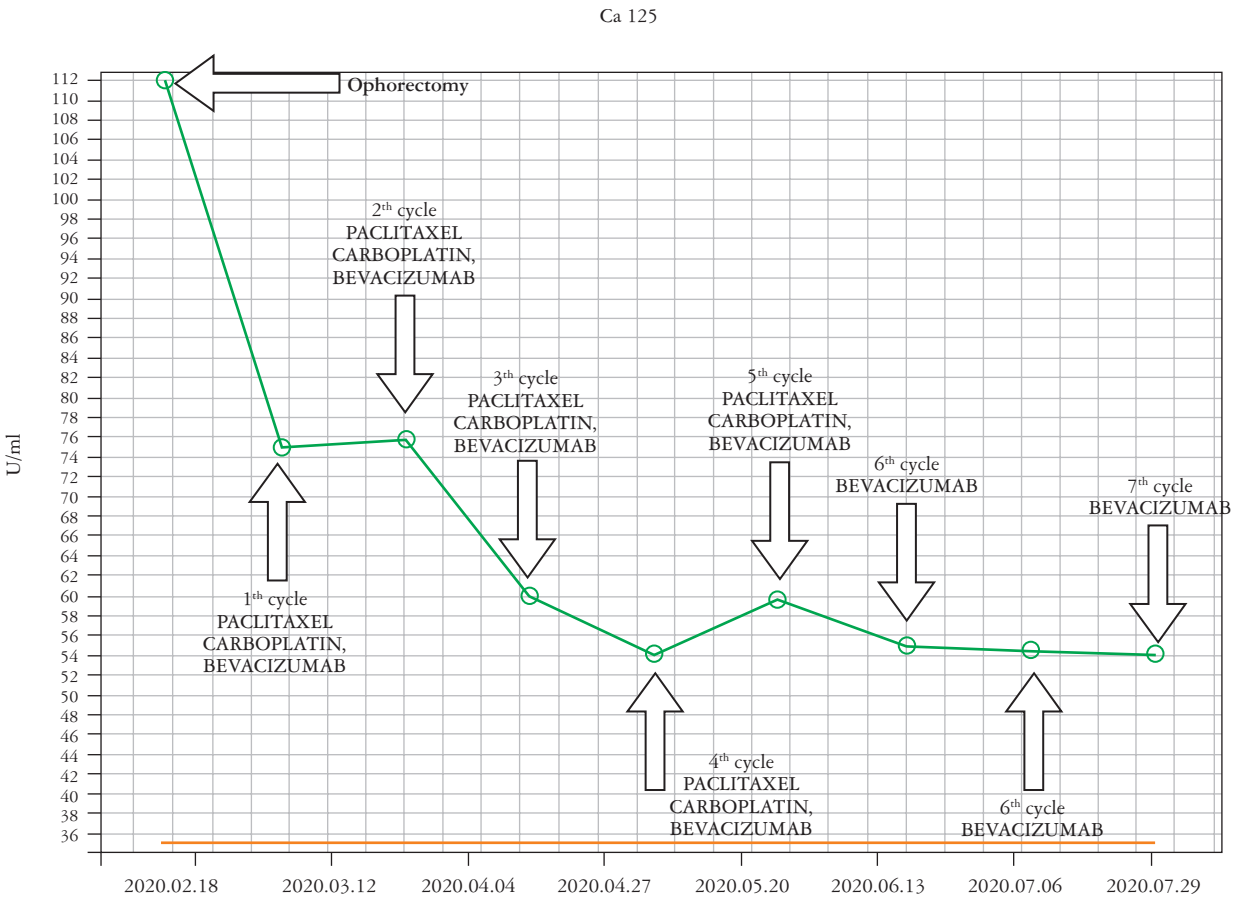

Fig. 3. Dynamic of cancer protein 125 (CA-125) concentration during the therapeutic process

Discussion

Recent classification of serous ovarian carcinoma is based on molecular biology and distinguishes two types of serous ovarian carcinoma: low-grade and high-grade. Low grade carcinoma arises from benign or borderline lesion and progresses slowly in stepwise manner to become an invasive carcinoma. These tumors are associated with certain mutation pattern which involves *EGFR* signaling pathway (*BRAF, KRAS, ERBB2* gene) and are characterized by young age at diagnosis and prolonged overall survival time (median 82 months). High grade tumors are characterized by aggressive behavior, shorter time of overall survival (30 months) and lack of precursor lesion [3, 5]. *TP53* mutation are virtually ubiquitous in high-grade serous cancers, being present in over 95% of cases [6]. Other frequently mutated genes include the tumor suppressors *NF1* and *RB*, as well as *BRCA1* and *BRCA2* in familiar ovarian cancers [3]. Here we present an unusual case of borderline tumor with distant metastasis to mediastinum in which only the microinvasion was detected. On molecular level, it showed *BRAF* mutation and lack of P53 staining what is characterized for low grade pathway. However, clinically it presented an aggressive course with distant metastasis from very diminutive site of invasion and very good response to chemotherapy what is more characteristic for high-grade lesion. Dehari *et al.* have shown that it is a possible for high grade carcinoma to come from low grade pathway. They presented that *BRAF* mutation is shared between low and high grade tumor what indicates clonal relationship. Moreover, in those tumors which arose from low grade lesion, P53 mutation was undetectable what allows the possibility that some of the high-grade serous carcinomas could have a different molecular pathogenesis compared with conventional high-grade carcinomas that develop along the type II pathway [18].

The biological behavior of ovarian carcinoma is unique, markedly different from hematogenous metastasis found in most other cancers. Most of ovarian metastases are found within peritoneal cavity [3]. Once the cancer cells have detached as single cells or clusters from the primary ovarian tumor, they metastasize through a passive mechanism, carried by the physiological movement of peritoneal fluid to the peritoneum and omentum and invade the mesothelial cell layers. Metastases outside the peritoneum, through the vasculature are less common in ovarian cancer (16%)

and are related with IV stage of disease and poor prognosis [1, 4]. Most common sites of distant metastasis are liver (12.6%), pleura (6.6%) and lungs (4.6%) [7]. Here we present a case where distant mediastinal metastases was the only metastatic site without accompanying peritoneal involvement. Moreover, according to the previous research, site of distant metastasis is an independent prognostic factor and lung metastases are associated with the worst overall survival compared to the other sites [2]. Patient in our case presented complete response to the treatment with resolution of breathing symptoms and regression of tumor mass.

The stromal invasion is a hallmark that distinguishes a serous invasive carcinoma from a serous borderline tumor. A standardized quantitative criteria for distinguishing microinvasion from frankly invasive carcinoma within borderline tumor has not been established and varying definitions have been used in different studies including 1 mm, 2 mm, 3 mm, 5 mm, 10 mm [8, 9, 10, 11, 12]. Current WHO Classification suggests a cut-off of 5 mm [12]. However, according to the literature, neither a presence nor the size of microinvasion should alter the outcome [12, 19]. Here we present a focus of microinvasion 4mm in diameter which was found only in one section. This could be perceived as a limitation of the histopathological examination. However, the tumor was carefully examined with numerous sections and the borderline lesion was dominant. This case strongly suggests that even small diameter of invasion could influence the clinical behavior and should be considered as a very important prognostic factor.

There are only single cases of metastatic borderline tumor reported in the literature with sites of metastasis in brain, bone marrow and internal mammary lymph nodes [13, 14, 15, 16, 17]. To our knowledge, this is the first reported case of borderline tumor with microinvasion and mediastinal metastasis with such a distinct clinical presentation. Unforeseen course of the borderline tumor presented here brings us to an important conclusion that the very diminutive focus of invasion has a possibility to give a distant metastasis characteristic for IV stage of disease what indicates that there is a huge gap in knowledge about mechanism of ovarian cancer metastasis. The lesson learned from this case is that the borderline tumors of ovary with any features of invasion could present an aggressive course and metastasize to parenchymal organs in an occult fashion what the clinicians and pathologists should bear in mind.

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Address for correspondence

Julia M. Sołek
Department of Pathology
Medical University of Lodz
Pomorska 251
92-213 Lodz, Poland
e-mail: julia.solek@gmail.com