CASE REPORT

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Synchronous bilateral primary ovarian carcinoma – case presentation

CRÎNGU ANTONIU IONESCU[1,2], SIMONA VLĂDĂREANU[1,3], LIANA PLEŞ[1,4], MIHAI CORNEL TRAIAN DIMITRIU[1,2], GHEORGHE OTO FURĂU[5], TEODORA CAMELIA VLĂDESCU[6], ALINA MIHAELA CĂLIN[7], NUŢI DANIELA OPRESCU[1,8]

[1] *Department of Obstetrics–Gynecology and Neonatology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[2] *Department of Obstetrics and Gynecology, "St. Pantelimon" Emergency Clinical Hospital, Bucharest, Romania*

[3] *Department of Obstetrics and Gynecology, "Elias" Emergency Clinical Hospital, Bucharest, Romania*

[4] *Department of Obstetrics and Gynecology, "St. John" Emergency Clinical Hospital, Bucharest, Romania*

[5] *Department of Obstetrics–Gynecology, "Vasile Goldiş" Western University of Arad, Romania*

[6] *Department of Pathology, "St. Pantelimon" Emergency Clinical Hospital, Bucharest, Romania*

[7] *Department of Surgery, Faculty of Medicine, "Lower Danube" University of Galaţi, Romania; Department of Obstetrics and Gynecology, "St. Apostle Andrew" Emergency County Hospital, Galaţi, Romania*

[8] *Department of Obstetrics and Gynecology, "Polizu" Clinical Hospital, Bucharest, Romania*

Abstract

Bilateral synchronous primary ovarian carcinoma, histopathologically identical or different is a rare entity encountered in clinical practice. We present the case of a 38-year-old patient who is admitted with the presence of a massive pelvic abdominal tumor formation of 45/35/25 cm occupying the lower pelvic and upper abdominal floor, reaching halfway distance between the umbilicus and sternum and lateral bilaterally in the two abdominal flanks until iliac wing. The mixed transabdominal/transvaginal ultrasound and computed tomography (CT), establish the diagnosis of bilateral ovarian tumor. The CA-125 level is 1822 IU/mL. The exploratory laparotomy identifies two distinct bilateral ovarian tumors, ascites liquid and pelvic and lumbo-aortic lymphadenopathy, thus the surgery involves hysterectomy with bilateral ovariectomy, pelvic and paraaortic lymphadenectomy and omentectomy. Histopathological and immunohistochemistry (IHC) diagnosis highlights a well-differentiated serous carcinoma on the left ovary and right ovary. The six-month check after surgery as well as the one-year check showed the efficiency of postsurgery chemotherapy and did not signal the presence of relapses. The particularity of this case lies in the presence of bilateral synchronous primary ovarian carcinoma, histopathologically and IHC indicated serous carcinoma present with a difficult differential diagnosis including clear cell carcinoma at a young patient.

Keywords: well-differentiated serous carcinoma, clear cell carcinoma, synchronous carcinoma, immunohistochemistry.

Introduction

Ovarian cancer is the second most common malignancy of the genital tract after endometrial carcinoma but prior to cervical carcinoma. The incidence of ovarian cancer increases with age being more frequent with patients aged between 50 and 55. At present, there is an increase in the age group 40–50 years [1]. Malignant epithelial tumors represent almost 2/3 of ovarian probably resulting from inclusion cysts localized at the boundary between the ovarian surface epithelium and the adjacent stroma [2].

The frequency of bilateral ovarian malignant tumors is variable: serous cystadenocarcinoma (33–66%), mucinous cystadenocarcinoma (10–20%), endometrioid carcinomas (13–30%), immature trachoma (2–5%) [3]. Bilateral synchronous primary ovarian carcinoma, at a young age, histopathologically serous cystadenocarcinoma is very rarely encountered in clinical practice with only a few cases described in the literature.

The widely used classification of the different primary ovarian carcinoma is that of *World Health Organization* (WHO), which consist of epithelial stromal tumors, germ cell tumors, sex cord tumors, lipoid cell tumors, gonadoblastoma, soft tissue tumors [1, 3]. From the five cell types of epithelial ovarian tumor that are encountered, serous, mucinous, endometrioid, clear cell, Brenner, the clear cell carcinoma has a relative frequency of 5% from ovarian cancers [3]. Histologically serous carcinoma of the ovary consists of epithelial cells, with the micropapillae that are long, thin tufts of tumor cells growing into the cystic spaces. Molecular investigation of genetic changes can generate a reclassification of serous ovarian cancer in low grade and high-grade serous carcinoma [2, 3].

Our case refers to a patient, aged 38, who came in Department of Obstetrics Gynecology, "St. Pantelimon" Emergency Clinical Hospital, Bucharest, Romania, with a pelvic-abdominal tumor formation for which the clinical and laboratory diagnosis (transvaginal/transabdominal ultrasound, computed tomography) could not establish accurately the bilateral ovarian carcinoma. The exploratory laparotomy identified two separate primary bilateral ovarian tumors and the histopathological and immunohistochemistry (IHC) examination established the diagnosis of ovarian serous carcinoma of a high degree on the right ovary and in the left ovary, but with a difficult pathological differential diagnosis.

This case highlights the importance of the IHC tests in differentiating various types of ovarian carcinoma and for the prognosis.

Case presentation

Patient CF, aged 38, was hospitalized in Department Obstetrics Gynecology, "St. Pantelimon" Emergency Clinical Hospital, Bucharest, in October 2015, for pelvic-abdominal diffuse pain occurring for about three weeks, which increased in intensity one week prior to hospitalization, sensation of fullness, exacerbated by the increase in abdominal volume, weight loss of 5–6 kg in the last eight weeks. Antecedents of the patient include two births by Caesarean section, in 1997 and 2001, smoker and menstrual cycle present. The clinical examination of the abdomen shows a tumor formation in hypogastric area, occupying the left abdominal flank and also reaching up to the right iliac fossa, upper extremity of the tumor being halfway distance between the umbilicus and the xiphoid appendix. The tumor surface is irregular, firm, with reduced mobility, causing pain on palpation. The gynecological examination cannot identify the uterus due to tumor formation, but revealed a tumor with irregular surface, localized in the whole pelvis, approximately 25 cm longitudinal diameter and 35 cm transversal diameter, with pain on palpation. The hematological investigations reveal mild anemia hemoglobin (Hb) 11.4 mg/dL (normal 11.7 mg/dL), white blood cells (WBC) count with neutrophilia (Neu) 76% (normal 20–60%). The other biochemical investigations are within normal limits. Serum levels of CA-125 are greatly increased with a value of 1822 IU/mL (normal values 0–35 IU/mL). Abdominal and transvaginal ultrasound show a tumor formation, multicystic, multiseptate with vascularized septa, of 45/35/25 cm localized in the lower right abdominal level, reaching to the midway between the umbilicus and the xiphoid appendix, and in the left flank reaching 4 cm below the costal margin, with the uterus being normal in size but rather difficult to individualize and without ascites in the pelvis. Computed tomography (CT) with contrast substance identifies three tumors formations of which the first mass formation is localized in the left abdominal flank and the left iliac fossa, reaching close to the costal margin and measuring 14/9 cm, a second mass formation at the level of the right iliac fossa and lateral-pelvic right abdomen, of 10.9/8.7 cm, and a third one present on the median line with the dimensions of 13/10 cm; there is a limit boundary between them, they outline polycyclic formations with internal septa, with tissue heterogeneous densities polyglobular structure and with many fluid areas; there also appear to exist cleavage plan between the mass formation and the bladder, sigmoid colon and rectum, with pelvic lymph nodes adenopaties and no ascites liquid. Therefore, CT establishes the diagnosis of ovarian carcinoma (Figures 1 and 2).

After obtained informed consent, exploratory surgery through laparotomy was performed under general anesthesia, and followed by total hysterectomy with salpingo-ovarectomy, bilateral pelvic lymphadenectomy and lumbo-aortic omentectomy. Extemporaneous cytological examination reveals serous carcinoma cells.

During surgery, there is noticed the presence of ascites fluid (approximately 100 mL), two tumor formations (although the CT describe three tumoral mass), the first belonging to the left ovary measuring 20/10/15 cm, with areas of solid and cystic nodular with papillary vegetations, hemorrhagic surface and necrotic areas, the second on the right ovary, measuring 15/9/8 cm, with spongy appearance, with prominent nodules caused by uneven surface. Both large bilateral ovarian tumors consisting of serous fluid filled cysts with papillary projections. The solid regions were tan-white with extensive necrosis and hemorrhage. The uterus 7.5/5.5/4.5 cm with regular surface is covered by the two large masses.

There were taken tumoral fragments from different areas and the final histopathological examination on common histochemical staining sections, Hematoxylin–Eosin (HE) stained, highlights the following: the presence of typical serous ovarian carcinoma aspects on the left ovary, tumors composed of macro- and micro-gland-like papillae with associated gland-like structures; solid masses of cells with slit-like spaces and necrosis were also present. Large nuclei, hyperchromatic and pleomorphic with atypical mitoses and prominent nucleoli. The micro-papillae have long, thin tufts of tumor cells growing into the cystic spaces (Figures 3 and 4).

Other areas on the right ovary with tubular structures with endometrioid-like pattern and clear cell like pattern outlining also serous carcinoma histological characteristics, but with some small areas with tubulopapillary short sheets of homogenous pattern and hyalinized septae and with small hyperchromatic nuclei with clear cytoplasm which can rise the differential diagnosis with clear cell carcinoma. There are also present some areas of necrosis (Figures 5 and 6).

For IHC studies, there were used the antibodies: monoclonal mouse anti-human p53 protein (clone DO-7, 1:50 dilution), monoclonal mouse anti-human Ki-67 antigen (clone MIB-1, 1:50 dilution), monoclonal mouse anti-human progesterone receptor (clone PGR, 1:50 dilution), monoclonal mouse anti-human estrogen receptor (ER) (clone 1D5, 1:50 dilution), monoclonal mouse anti-human cytokeratin 7 (CK7) (clone OV-TL, 1:50 dilution) were tested. The results for the left ovary were the following: p53 immunostaining diffuse nuclear positivity confirming the diagnosis of serous ovarian tumor (Figure 7).

Nuclear expression of Ki67 proliferation index was detected in 60% in the nuclei of tumoral cells (Figures 8 and 9). The difference with borderline tumor, in which the Ki67 is positive in less than 2%. The hormone markers for progesterone receptors staining focally positive in tumoral cells and for estrogen receptors were also positive. CK7 diffuse positive membrane marker indicates the origin of the tumor (Figure 10).

The results for the right ovary were the same as for the left ovary. For the differential diagnosis with clear cell variant of serous carcinoma, the IHC was very useful because in such a case the p53 must be negative, positive for CK7, positive for Ki67, and negative for estrogen receptors. The correlation between the histopathological diagnosis with IHC results establish the diagnosis of synchronous serous carcinoma of the ovary excluding the clear cell carcinoma in the right ovary.

Adjuvant chemotherapy treatment in this case was based on four cycles of chemotherapy. Postoperative evaluation of this patient at six months and one year after surgery revealed no presence of recurrence.

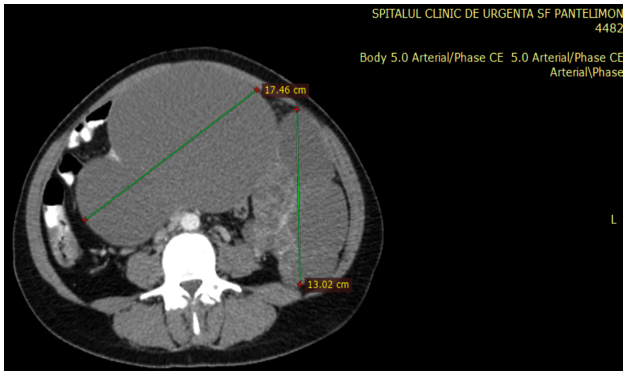

Figure 1 – ***Computerized tomography reveal two bilateral ovarian mass, median and left paravertebral 17.46 cm longitudinal diameter, right paravertebral 13.02 cm longitudinal diameter.***

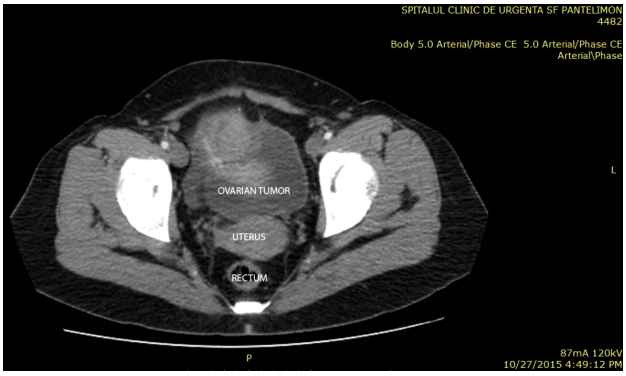

Figure 2 – ***Computerized tomography reveal the two bilateral ovarian masses with polylobular contour, bounded each by its own wall.***

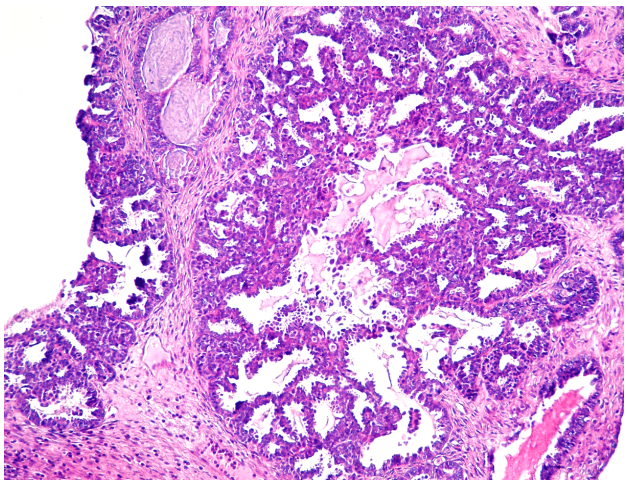

Figure 3 – ***Serous carcinoma composed of macro- and micro-papillae associated with gland-like structures. Stromal invasion and atypical cytocores and papillar outbreaks. Solid masses of cells with slit-like spaces and necrosis. HE staining, ×200.***

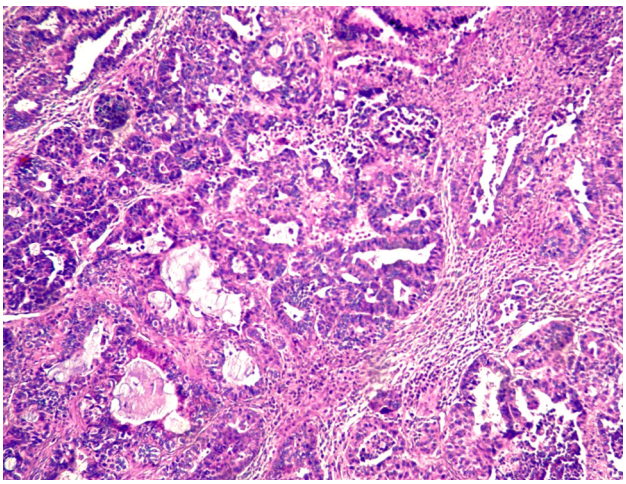

Figure 4 – ***Serous carcinoma: tubular pattern. Epithelium resembles that of Fallopian tube with cytonuclear atypia, hyperchromatic and pleomorphic large nuclei with atypical mitoses and prominent nucleoli. HE staining, ×200.***

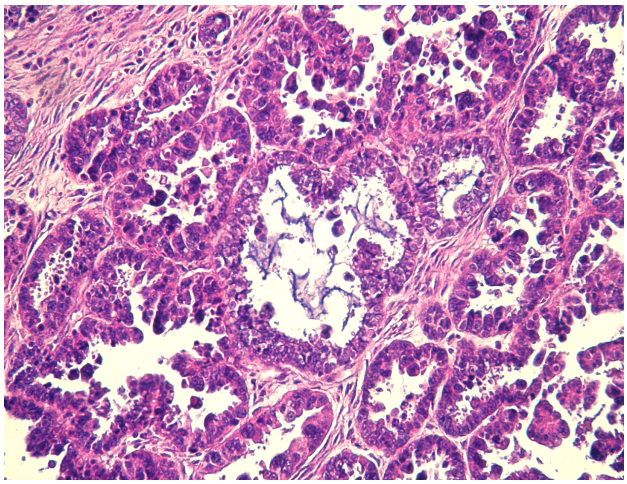

Figure 5 – ***Serous carcinoma. The micro-papillae are long, thin tufts of tumor cells growing into the cystic spaces; stroma and acute inflammatory infiltrate and papillary outbreaks with cytoplasmic nuclear atypia. HE staining, ×200.***

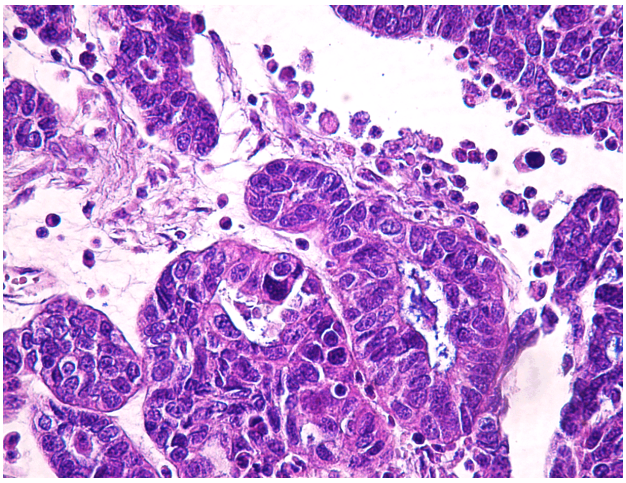

Figure 6 – ***Fragment of ovary with areas witch contain tubular structures pattern like with polyhedral cells with abundant cytoplasm, clear cell pattern, with protruding nuclei line which shows tubules. HE staining, ×400.***

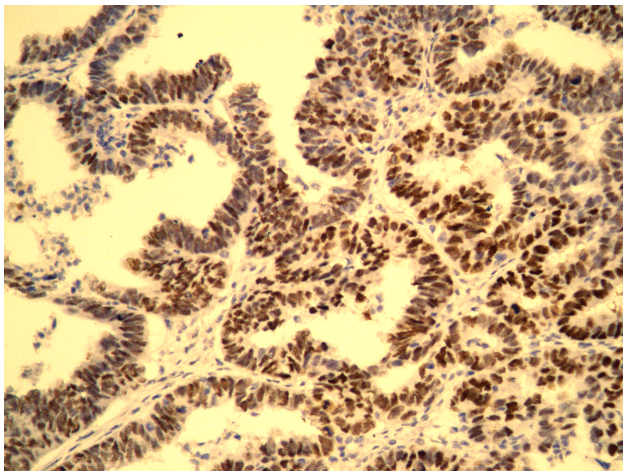

Figure 7 – ***Areas with clear cell pattern, cysts lined by flattened tumor cells, with edematous stroma and papillary outbreaks. p53 antibody immunostaining, ×200.***

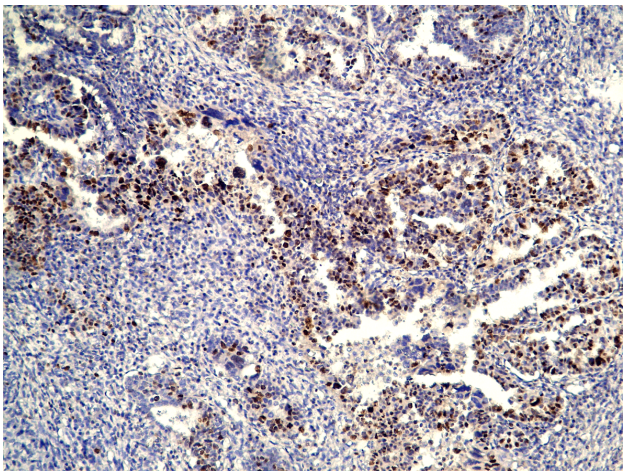

Figure 8 – ***Serous carcinoma with Ki67 diffuse nuclear positivity in branched papilla, confirming the diagnosis of high-grade tumor. Ki67 antibody immunostaining, ×100.***

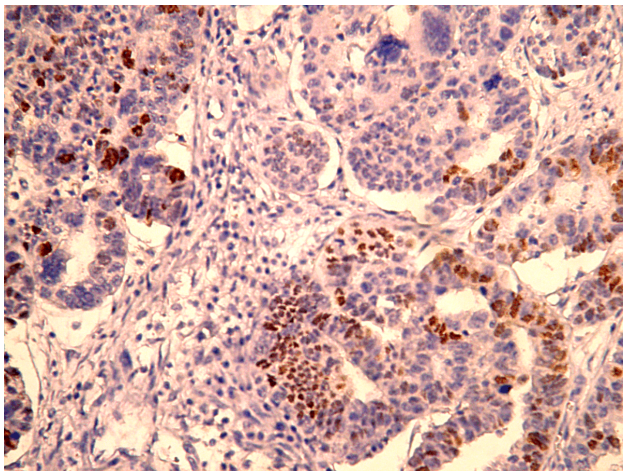

Figure 9 – ***Fragments of tumor with nuclear expression of Ki67 proliferation index, which was detected in 60% in the nuclei of tumoral cells. Ki67 antibody immunostaining, ×200.***

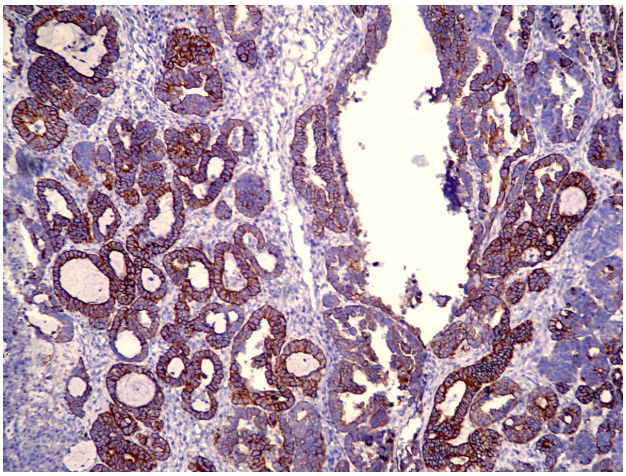

Figure 10 – ***Fragments of epithelial tumor with CK7 focally positive in tumoral cells. CK7 antibody immunostaining, ×100.***

Discussion

The presence of synchronous primary ovarian malignancies is very rare, with an incidence ranging between 0.7% and 1.5% [4]. Synchronous primary ovarian malignancies are even rarer. Serous ovarian carcinoma is an entity with an incidence of 35–40%. Serous carcinoma classifies molecular investigations into high and low grade. One theory, which is discussed in literature today, is that high-grade serous carcinoma has its origin in tubal epithelium [5, 6]. Poorly differentiated serous carcinomas represent 6–10% of all serous carcinoma, and comparing poorly differentiated carcinoma with the well differentiated serous carcinoma, there can be observed that the first appears at younger ages (45–50 years), the rate of progression of the free range is the same of 19.5 months, with a longer rate of survival (average of 80–99 months) [4, 5]. Clear cell carcinoma has an incidence of 5% [5]. The differential diagnosis in HE-stained between serous carcinoma and clear cell variant of serous carcinoma, contained that papillary structure with macro- and micropapillae associated with gland-like structures, solid masses of cells with slit-like spaces and necrosis present, large nuclei, hyperchromatic and pleomorphic with atypical mitosis and prominent nucleoli, the micro-papillae are long, thin tufts of tumor cells growing into the cystic spaces, are specific for serous carcinoma. Clear cell carcinoma contains cells with a high content of glycogen that prevail into the lumen of glandular cell nuclei. The nuclei are small and are eccentrically placed. Molecular investigations in case of the latter suggest a similar renal pathology [7]. HE examination of the left and right ovary highlights the serous carcinoma.

Primary ovarian carcinoma usually has CK7 positive and CK20 negative. Generally, diagnosis markers for clear cell carcinoma show carcinoembryonic antigen (CEA), CD15, epithelial membrane antigen (EMA), hepatic nuclear factor-1 (HNF-1), CA-125, PAX8 and WT1 negative and ER [8]. Serous ovarian carcinoma is generally associated with WT1, p53, CK5/6, CK8, EMA, CK18, PAX8 [9]. IHC for serous carcinoma of the ovary in our case was noted positive for CK7 membrane and for p53, ER and PG receptors. WT1 is useful in differentiating squamous cell carcinoma clear to mixed serous/clear cells. To the left and right ovary, the p53 expression was strongly positive.

Usually, clear cell carcinoma contains nuclei predominant into the glandular lumen. Tumors of the same histological aspect are also found in the endometrium,

vagina, cervix and analysis of these tumors suggests the presence of similar items with renal pathology [10]. They occur mostly between 40 and 70 years and are very aggressive [11]. Genes have been identified that are the signature of clear cell carcinoma [12]. There are 437 genes that belong to the following three categories – the genes involved in the response to stress, in carbohydrate metabolism and coagulation. They are responsible for the appearance of clear cell carcinoma. Clear cell carcinoma can also occur within a cyst endometriosis, benign or atypical endometriosis lesions or endometriosis can be found along with serous carcinoma [12, 13]. Clear cell carcinoma is considered to be a highly differentiated carcinoma.

Regarding serous carcinoma, a recent study showed that using combined expression of p53 and CDKN2A may differentiate between, poorly differentiated serous carcinoma from well-differentiated serous carcinoma. At the same time, determining the PR and ER expression, it was found that the PR and ER expression is greater for weakly differentiated serous carcinoma against well-differentiated serous carcinoma [13, 14]. Synchronous development of ovarian cancer can occur in both ovaries. There may be similar histopathological type in both ovaries or it may be two different primary ovarian carcinomas that develop at the same time or may be phenotypic differentiation of tumor from one of the ovaries and which has a metastatic on the contralateral ovary. Immunohistochemical study is one that can determine the difference between types of ovarian neoplasia and may set the primary independent nature.

The five histological types of epithelial ovarian carcinoma (poorly differentiated serous, serous well-differentiated, clear cell, endometrioid, mucinous), are distinct entities in terms of biology, clinical behavior and response to chemotherapy. It seems that weak differentiated serous neoplasms respond less well than the well-differentiated ones to neoadjuvant postoperative therapy [14, 15]. Cytoreductive surgery remains the gold standard in ovarian carcinoma.

Conclusions

We presented a rare case of bilateral synchronous primary ovarian serous carcinoma on the ovaries at a young age. The patient age, the significant size of tumor formation, the clinical as well as the histological type were important and significant elements. It was a difficult histopathological differential diagnosis, but immunohistochemistry was able to distinguish between different forms of ovarian malignancies, in our case serous and clear cell.

Conflict of interests

The authors declare no conflict of interests.

References

[1] Yancik R, Ries LG, Yates JW. Ovarian cancer in the elderly: an analysis of Surveillance, Epidemiology, and End Results Program data. Am J Obstet Gynecol, 1986, 154(3):639–647.

[2] Gershenson DM, Bodurka DC, Lu KH, Nathan LC, Milojevic L, Wong KK, Malpica A, Sun CC. Impact of age and primary disease site on outcome in women with low-grade serous carcinoma of the ovary or peritoneum: results of a large single-institution registry of a rare tumor. J Clin Oncol, 2015, 33(24):2675–2682.

[3] Coleman RL, Ramirez PT, Gershenson DM. Neoplastic disease of the ovary: screening, benign and malignant epithelial and germ cell neoplasms, sex-cord stromal tumors. In: Lobo RA, Gershenson DM, Lents GM, Valea FA (eds). Comprehensive gynecology. 7th edition, Elsevier, 2017, 733–780.

[4] Eser S, Gulhan I, Özdemir R, Dicle N, Hanhan M, Baloglu A, Ozsaran A, Saygili U. Synchronous primary cancers of the female reproductive tract in Turkish women. Asian Pac J Cancer Prev, 2011, 12(4):857–859.

[5] Soslow RA. Histologic subtypes of ovarian carcinoma: an overview. Int J Gynecol Pathol, 2008, 27(2):161–174.

[6] Gershenson DM, Sun CC, Iyer RB, Malpica AL, Kavanagh JJ, Bodurka DC, Schmeler K, Deavers M. Hormonal therapy for recurrent low-grade serous carcinoma of the ovary or peritoneum. Gynecol Oncol, 2012, 125(3):661–666.

[7] Quattrocchi L, Sisson M, Green A, Martin SG, Durrant L, Deen S. Expression of angiogenic chemokines in ovarian clear cell carcinoma. J Obstet Gynaecol Res, 2013, 39(1):297–304.

[8] Ueda H, Watanabe Y, Nakai H, Hemmi H, Koi M, Hoshiai H. Microsatellite status and immunohistochemical features of ovarian clear-cell carcinoma. Anticancer Res, 2005, 25(4):2785–2788.

[9] Acs G, Pasha T, Zhang PJ. WT1 is differentially expressed in serous, endometrioid, clear cell, and mucinous carcinomas of the peritoneum, fallopian tube, ovary, and endometrium. Int J Gynecol Pathol, 2004, 23(2):110–118.

[10] Okamoto A, Glasspool RM, Mabuchi S, Matsumura N, Nomura H, Itamochi H, Takano M, Takano T, Susumu N, Aoki D, Konishi I, Covens A, Ledermann J, Mezzanzanica D, Steer C, Millan D, McNeish IA, Pfisterer J, Kang S, Gladieff L, Bryce J, Oza A. Gynecologic Cancer InterGroup (GCIG) consensus review for clear cell carcinoma of the ovary. Int J Gynecol Cancer, 2014, 24(9 Suppl 3):S20–S25.

[11] Mackay HJ, Brady MF, Oza AM, Reuss A, Pujade-Lauraine E, Swart AM, Siddiqui N, Colombo N, Bookman MA, Pfisterer J, du Bois A; Gynecologic Cancer InterGroup. Prognostic relevance of uncommon ovarian histology in women with stage III/IV epithelial ovarian cancer. Int J Gynecol Cancer, 2010, 20(6):945–952.

[12] Yamaguchi K, Mandai M, Oura T, Matsumura N, Hamanishi J, Baba T, Matsui S, Murphy SK, Konishi I. Identification of an ovarian clear cell carcinoma gene signature that reflects inherent disease biology and the carcinogenic processes. Oncogene, 2010, 29(12):1741–1752.

[13] Altman AD, Nelson GS, Ghatage P, McIntyre JB, Capper D, Chu P, Nation JG, Karnezis AN, Han G, Kalloger SE, Köbel M. The diagnostic utility of TP53 and CDKN2A to distinguish ovarian high-grade serous carcinoma from low-grade serous ovarian tumors. Mod Pathol, 2013, 26(9):1255–1263.

[14] Escobar J, Klimowicz AC, Dean M, Chu P, Nation JG, Nelson GS, Ghatage P, Kalloger SE, Köbel M. Quantification of ER/PR expression in ovarian low-grade serous carcinoma. Gynecol Oncol, 2013, 128(2):371–376.

[15] Hoskins WJ, Bundy BN, Thigpen JT, Omura GA. The influence of cytoreductive surgery on recurrence-free interval and survival in small-volume stage III epithelial ovarian cancer: a Gynecologic Oncology Group study. Gynecol Oncol, 1992, 47(2):159–166.

Corresponding author

Simona Vlădăreanu, Associate Professor, MD, PhD, Department of Obstetrics–Gynecology and Neonatology, "Carol Davila" University of Medicine and Pharmacy; Department of Obstetrics and Gynecology, "Elias" Emergency Clinical Hospital, 17 Mărăşti Avenue, Sector 1, 011461 Bucharest, Romania; Phone +40721–200 461, e-mail: simconst69@gmail.com

Received: March 15, 2016 *Accepted: May 13, 2017*