CASE REPORT

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# A rare case of synchronous ovarian tumors: clinical case report and literature review

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## Abstract

Epithelial ovarian carcinoma makes up 90–95% of all ovarian malignancies, taking into account also low-malignant-potential tumors. The Krukenberg tumor is a rare metastatic adenocarcinoma (ADK) in the ovary, representing 1–2% of ovarian tumors. Multiple primary malignant neoplasms may exist when more than one cancerous tumor is diagnosed in the same or a different organ. The incidence of multiple primary cancers among malignancies is between 2.4% to 8%. The aim of this paper is to report the case of a 47-year-old patient with two synchronous malignant tumors involving both ovaries, one diagnosed as primary papillary serous cystadenocarcinoma and the other one diagnosed as ovarian metastasis (Krukenberg tumor) of a synchronous colorectal ADK, and the complex diagnostic and therapeutic challenges that such a rare case poses. Histopathological (HP) examination and especially the immunohistochemical analysis had a determining role in differentiating between an ovarian primary tumor and a metastasis from a gastrointestinal tract cancer. The tumors examination for somatic mutations of Kirsten rat sarcoma viral oncogene homolog (*KRAS*) and neuroblastoma *RAS* viral oncogene homolog (*NRAS*) genes was performed in order to individualize the chemotherapic treatment in this difficult case. The conclusion of this case is that, although synchronous multiple primary cancers in a young patient are a rare condition, this situation should be taken into account in the differential diagnosis when we encounter clinical and HP diagnostic challenges.

***Keywords***: synchronous cancer, papillary serous cystadenocarcinoma, Krukenberg tumor, immunohistochemistry.

## Introduction

The epithelial ovarian carcinoma makes up 90–95% of ovarian malignancies, taking into account also low-malignant-potential tumors (borderline tumors) [1]. There are no screening programs for ovarian cancer and in the early stages only few clinical signs [2]. Thus, two-thirds of patients have advanced disease by the time they are diagnosed [2]. Ovarian cancer is surgically staged and stage is assigned according to findings before tumor removal and debulking. Approximately one-third of patients have surgical stage I or II disease [2]. If the tumor appears macroscopically confined to the ovary, surgical removal and comprehensive staging is performed [2]. For early-stage ovarian cancer, the recommended surgical management should include collection of peritoneal washings after opening the peritoneal cavity, extrafascial hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, multiple peritoneal biopsies, pelvic and infrarenal para-aortic lymphadenectomy [2]. After the surgery is completed, the surgical removed tissues are submitted for extensive histopathological (HP) and immunohistochemical (IHC) analysis. The management of early-stage ovarian cancer includes chemotherapy in addition to surgery [3–5]. In case of advanced ovarian cancer, the sequenced multimodality therapy offers the most successful outcomes [6]. If possible, surgical cytoreduction is ideally initially performed to remove all macroscopic disease and is followed by six courses of platinum-based chemotherapy [2]. To effectively balance all clinical factors each patient is individually assessed before initiating treatment [2].

Krukenberg tumors are rare metastatic tumors at the level of the ovary, representing up to 1–2% of ovarian tumors [7]. The stomach represents in over 70% of cases the primary site of the tumor [7–9]. Carcinomas of colon, appendix, and mammary gland can be also common primary sites [8–10]. Krukenberg tumors are found more often in younger patients, patients in their fifties, with an average age of 45 years [7–10]. The most common clinical signs that are present, are those related to ovarian involvement, particularly abdominal pain and bloating. The primary tumor can be diagnosed anytime in relationship with the Krukenberg tumor diagnosis, either preoperatively, at the time of ovarian tumor surgery or in the early or late postoperative period [8–11]. IHC staining can be helpful in differentiating between ovarian metastases and primary

ovarian neoplasms [12–14]. The most frequent utilized markers are cytokeratins 7 and 20 (CK7 and CK20) immunophenotyping [15, 16]. Primary ovarian tumors follow a relative constant pattern and are usually positive for CK7 (90–100%), but are negative for CK20 [13, 14, 17]. In comparison, most malignant tumors of the large intestine follow a different pattern and are immunoreactive to CK20, but non-reactive to CK7 immunostaining [7, 12–16]. IHC markers are very important in differentiating between different tumor subtypes and can influence the management and prognosis, because treatment options (surgery, radiotherapy, chemotherapy) can vary depending on the specific IHC characteristics and not only the stage of the disease [18, 19]. Also, tumor serum markers are very important in establishing the diagnosis, prognosis and treatment response, although most of them are not very specific and can have high levels both in malign and benign conditions [20, 21].

Multiple primary malignant neoplasms may coexist when more than one cancerous tumors are diagnosed in the same or a different organs and/or are of a distinct morphology or histology cluster [22]. The definition used in many studies for multiple primaries is "more than one metachronous or synchronous cancer in the same individual" [22, 23]. The incidence of multiple primaries among malignancies is between 2.4% and 8%, up to 17% within 20 years of follow-up [22, 24, 25]. Among the risk factors for multiple primaries are: genetic inherited predisposition; lifestyle, hormonal and environmental factors that may be cancer-promoting; treatment of a previous malignancy and prolonged surveillance of cancer patients [26, 27]. The diagnosis at young age of multiple primary malignant neoplasms, in one or more family members, should make a physician take in consideration the possibility of an underlying cancer predisposition [23]. For example, colon cancer in a young woman with a family history of endometrial or colon cancer may suggest the diagnosis of Lynch syndrome (LS). People with LS are predisposed a wide variety of cancers involving the colon, ovaries, endometrium, stomach, liver, small intestine or urinary tract [28–31].

### Aim

We report the case of a 47-year-old patient with two synchronous malignant tumors involving both ovaries, one diagnosed as primary papillary serous cystadenocarcinoma and the other one diagnosed as ovarian metastasis of a synchronous colorectal adenocarcinoma (ADK), and the complex diagnostic and therapeutic challenges that such a rare case poses.

## Case presentation

A 47-year-old patient was admitted to the Emergency County Hospital of Arad, Romania, with complaints of lower abdominal pain, slow intestinal transit, menstrual irregularities and stress urinary incontinence. The patient was known with chronic hypertension (diagnosed in 2002 and treated with angiotensin-converting-enzyme inhibitor and diuretics) and an appendectomy (2003). She had two vaginal births and no abortion or curettage. From her family history, we noted that her mother suffered from chronic arterial hypertension and diabetes mellitus and her father was known with chronic arterial hypertension.

The clinical examination of the abdomen shows abdominal bloating and lower abdominal pain at palpation. The gynecological examination identifies the following aspects: a slightly enlarged uterus, with irregular outline and high consistency, with preserved mobility and without pain on palpation, right adnexa enlarged, approximately 4/5 cm, solid consistency, with pain on palpation and left adnexa moderately enlarged, approximately 5/7 cm, cystic consistency, with pain on palpation. The transvaginal ultrasound shows an intramural uterine leiomyoma, approximately 4 cm in diameter, located into the anterior uterine wall; right ovary, approximately 4/5 cm, with a cyst, 3.5 cm in diameter, with thick walls, septated, with solid components and highly vascularized; left ovary, approximately 6/8 cm, with three cysts, the largest one being 4.5 cm in diameter, multilocular, with four papillary projections and high vascularization; thin layer of fluid in the pouch of Douglas.

We performed a computed tomography (CT) scan examination, which revealed the following details: five hepatic hemangiomas; a subserosa uterine leiomyoma located into the anterior uterine wall; a tumor in the projection area of the right adnexa – in contact with the uterus – probably a uterine leiomyoma or and adnexal tumor.

The risk of ovarian malignancy algorithm (ROMA) index was 15.9% with a cancer antigen 125 (CA125) value of 36.30 IU/mL. A value over 11.4% of the ROMA index suggests a high risk of epithelial ovarian cancer. Also, the CA125 level is a little bit above the cut off level of 35 IU/mL recommended by many laboratories. The routine blood tests were in normal range.

After obtained informed consent, exploratory laparotomy was performed. After pubic-xyphoidian laparotomy, the following aspects were found: a tumor located in the sigmoid colon, which almost obliterated the colonic lumen, with malignant characteristics, a small subserosa uterine leiomyoma on the anterior uterine wall, the right ovary with hard structure and intact capsule, the left ovary with mixed consistency and the epiploon adherent to the sigmoid colon. After we performed a total hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy, we also carried out a sigmoidectomy with side-to-side anastomosis. The surgical removed tissues were submitted for pathological examination. The total duration of the intervention was seven hours and 45 minutes. The postoperative course was favorable under antibiotherapy, anticoagulant thromboprophylaxis, analgesics, antioxidants, probiotics, 6 units of fresh frozen plasma, one unit of packed red blood cells, parenteral nutrition until day 14 post-operative, followed by enteral nutrition (Figures 1 and 2).

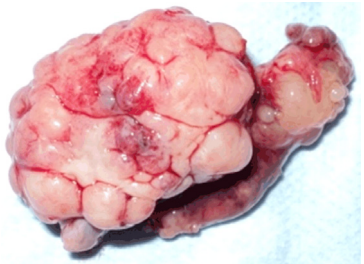

**Figure 1 –** ***Macroscopic aspect of the left ovary.***

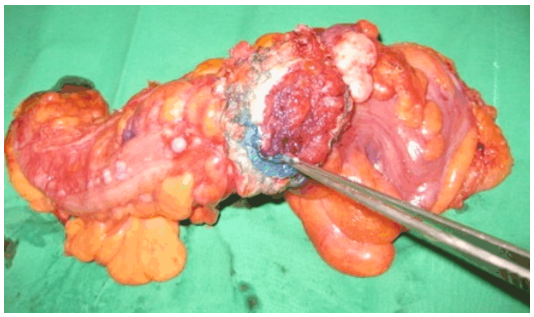

**Figure 2** – ***Macroscopic aspect of the resected sigmoid colon.***

There were taken tumoral fragments from the different structures and sent for HP examination. Using histochemically stained sections, Hematoxylin–Eosin (HE) staining, the following tumor characteristics were revealed: papillary serous cystadenocarcinoma, moderately differentiated G2, probably primary tumor, in the left ovary; primary sigmoid tubular ADK, moderately differentiated G3, with serosal infiltration (T3); carcinomatous involvement of the greater omentum and of the right ovary (metastatic ovarian tumor – Krukenberg tumor) – stage T3 N0 M1 (Figure 3; Figure 4, A and B).

A comprehensive IHC analysis was performed. For IHC studies, the following antibodies were used: monoclonal mouse anti-human p53 protein (clone DO-7, 1:50 dilution), monoclonal mouse anti-human CK7 (clone OV-TL, 1:50 dilution), monoclonal mouse anti-human CK20 (clone Ks 20.8, 1:50 dilution), monoclonal mouse anti-human caudal-type homeobox 2 (CDX2) (clone ZC007, 1:50 dilution), monoclonal mouse anti-human RhCE (clone BRIC69, 1:50 dilution). Those studies had the following results: colorectal ADK with metastasis to the greater omentum and right ovary – pT4b Nx M1b L1 V0 (sections of colonic wall, ovarian parenchyma and epiploon, which show tumoral infiltration from an tubular ADK moderately differentiated G3, with following immunoprofile: CDX2 negative, CK20 positive, CK7 negative, p53 negative – consistent with the colorectal origin of the tumor); papillary serous cystadenocarcinoma of the ovary – pTx Nx Mx L0 V0 (sections of ovarian parenchyma with tumoral infiltration from an papillary serous ADK, poorly differentiated G3, with following immunoprofile: RhCE 30% positive, RhP 30% positive, CK7 positive, p53 positive, CK20 negative, CDX2 negative – consistent with the ovarian origin of the tumor) (Figure 5; Figure 6, A and B).

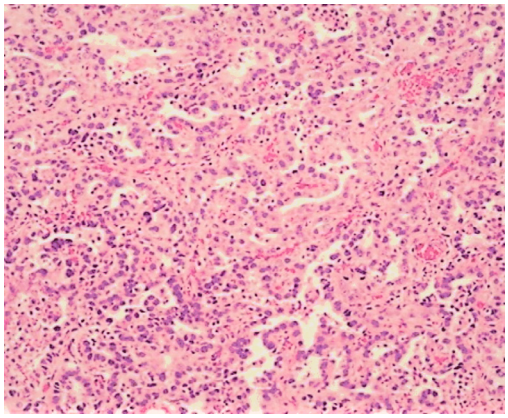

**Figure 3** – ***Papillary serous cystadenocarcinoma, left ovary. HE staining of ovarian serous carcinoma (×200).***

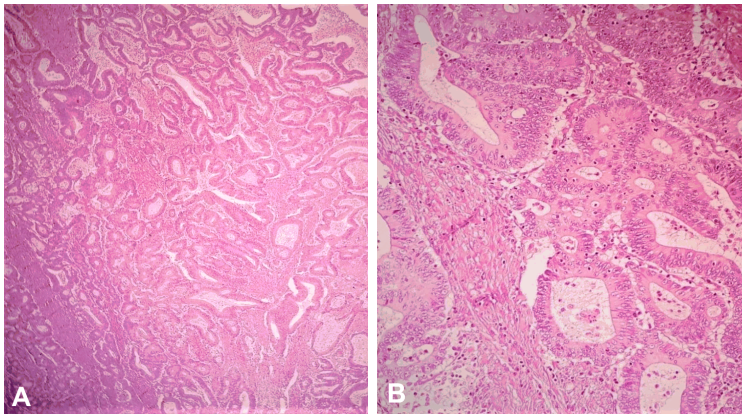


**Figure 4** – ***(A and B) Moderately differentiated adenocarcinoma of the colon showing complicated glandular structures in a desmoplastic stroma. HE staining: (A) ×40; (B) ×200.***

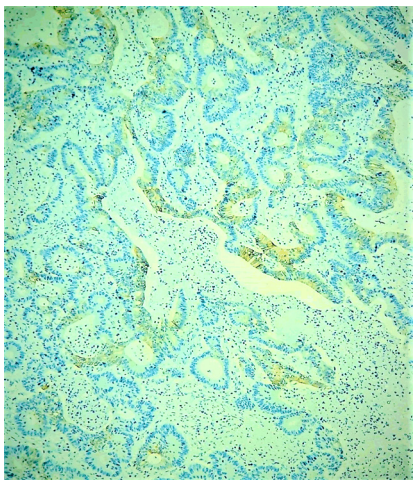

**Figure 5** – ***Diffuse CK20 positive immunostaining in the colonic adenocarcinoma (×100). CK20: Cytokeratin 20.***

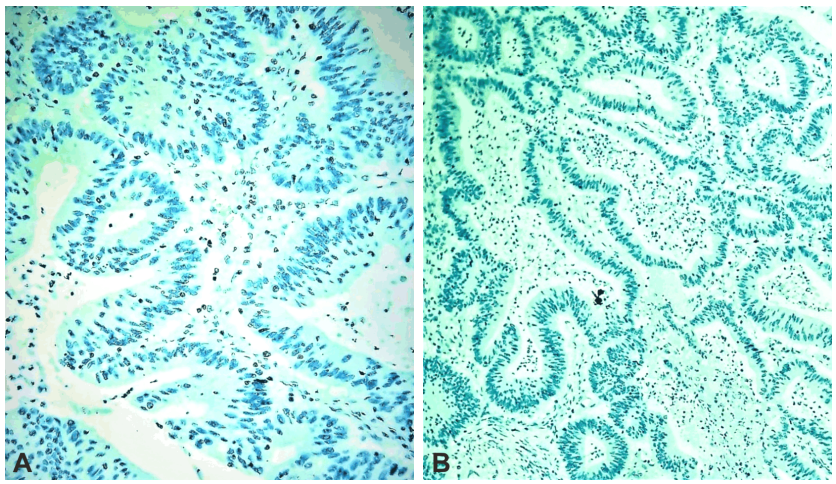


**Figure 6** – ***Immunohistochemistry of metastatic colorectal adenocarcinoma: (A) CDX2 negative (×200); (B) CK7 negative (×100). CDX2: Caudal-type homeobox 2; CK7: Cytokeratin 7.***

Samples from the paraffin-embedded tissue were analyzed for somatic mutations of Kirsten rat sarcoma viral oncogene homolog (*KRAS*) and neuroblastoma *RAS* viral oncogene homolog (*NRAS*) genes, being known that mutations of those genes have been found in a variety of human malignancies. A targeted resequencing assay was used for mutation detection in exons 2, 3 and 4 of the *KRAS* and *NRAS* genes. This analysis identified the mutation c.38G>A (p.G13D) in exon 3 of the *KRAS* oncogene. This mutation predicts poor response to epidermal growth factor receptor monoclonal antibody therapy in patients with metastatic colorectal cancer, although preclinical studies and retrospective clinical data suggest that patients may benefit from Cetuximab [32–35].

At two months after surgery, the patient has had a positron emission tomography (PET) scan that did not show any 2-[$^{18}$F]fluoro-2-deoxy-D-glucose ($^{18}$F-FDG) hypercaptant lesions (suggestive of a malignant tumor).

The oncological treatment started with FOLFIRI regimen [two courses of Folinic acid (Leucovorin calcium), 5-Fluorouracil (5-FU) and Irinotecan].

Three months postoperatively, the tumor markers were in normal levels [CA125 17.01 IU/mL, cancer antigen 19-9 (CA19-9) 12.36 IU/mL, carcinoembryonic antigen (CEA) 1.19 ng/mL].

After the two courses of FOLFIRI regimen, the combination of Paclitaxel, Cisplatin and Capecitabine was administered for one cycle, followed by monotherapy FOLFOX regimen [21-day cycles for six months – Folinic acid (Leucovorin calcium), 5-FU, Oxaliplatin]. This chemotherapy is frequently used in the treatment of advanced-stage or metastatic colorectal cancer.

One year after surgery, the clinical examination and paraclinical investigations were in normal range.

## Discussions

Krukenberg tumors are metastatic ADKs with mucin-filled signet-ring cells associated with a striking proliferation of the ovarian stroma although many variations on this pattern can occur, signet-ring cells, although sometimes scant, are still definitional but a cellular stroma is not as requiring its presence would exclude otherwise typical tumors from the Krukenberg category [36]. These tumors usually originate in the stomach in the vast majority of cases [7, 8, 36]. In some cases, at the time of the oophorectomy, the gastric cancer may be small and asymptomatic, thus remaining undetected for several years [9, 36]. Much less frequently, the primary tumor is in the large intestine, breast, gallbladder, uterine cervix, appendix, or urinary bladder [9–11]. Patients with Krukenberg tumors usually are between 40 and 50 years of age, younger than patients with metastatic carcinoma [7, 36]. In our case, the patient was 47-year-old, and the metastatic Krukenberg tumor originated from a less frequent organ – the large intestine. Also, in this case the mucin-filled signet ring cells were rather rare, which it was a particular element that made harder the HP diagnosis before the immunohistochemistry analysis was performed.

Sometimes, metastatic tumors can present as unilateral ovarian tumors, although in the majority of cases, the metastatic disease affect both ovaries in a simultaneous way [37]. In our case, the metastasis was located only in one ovary, the other one being affected by a different type of tumor. Due to overlapping morphological features, the differentiation between primary ovarian ADK and a metastasis from a colorectal ADK is often difficult, but it is vital [14, 37], in order to prevent inappropriate management and suboptimal treatment [23]. In a similar way, a differential diagnosis between primary colorectal ADK and ovarian secondary determinations into the colorectum is important, although is an uncommon situation [13, 15, 37]. Even rarer sites of metastasis of genital cancers, like splenic metastasis, have been reported so all possibilities must be taken into consideration when evaluating such complex oncological cases [38]. Several clinicopathological aspects are useful in cases with heterogeneous presentation, like those of ovarian invasion by a metastatic ADK of the large intestine and *vice versa* [12, 13, 37]. The different pattern of CK7 and CK20 immunostaining is extremely helpful in resolving these dilemmas [12–16]. A study conducted by Chou *et al.* in 2003 that investigated the utility of $\beta$-catenin immunostaining concluded that $\beta$-catenin is, so far, the best marker for differentiating these two groups of tumors [39]. However, markers that are more specific need to be further explored and validated with substantial studies to resolve these diagnostic dilemmas.

The last aspect reviewed in our discussion is the one related to synchronous tumors. The prevalence of patients with synchronous or metachronous multiple primary tumors will increase in the upcoming years, based on an association of factors (demographics, diagnosis, treatment, etc.) [22]. In studies with data gathered more than a decade ago, the incidence of multiple primary neoplasms varies between 2.4% and 17%, this large range resulting from the different definitions that were used [22, 23]. It is important to notice that with extended follow-up periods and with more advanced treatment options for different malignancies and increased survival, the incidence of multiple primaries will grow considerably [22–28]. Due to the advances in genetic testing, patients with multiple primaries are more and more commonly identified with different underlying cancer predispositions, thus better therapeutic plans and protocols will be developed [22, 28, 29]. In the area regarding the treatment of patients with multiple primary malignant tumors, more research is necessary to establish the best management for these rare conditions [22, 26].

## Conclusions

Early-stage ovarian tumors are frequently paucisymptomatic and pose diagnostic challenges. Although synchronous multiple primary cancers in a young patient is a rare condition, this situation should be taken into account in the differential diagnosis when clinical and HP diagnostic difficulties are encountered. The IHC analysis and the examination of somatic mutation of the *KRAS* and *NRAS* genes were the cornerstones in diagnostic and therapeutic management of this rare, complex case.

**Conflict of interests**

The authors declare that they have no conflict of interests.

**Authors' contribution**

George-Alexandru Roşu and Adrian Neacşu have equal contribution.

## References


[1] Quirk JT, Natarajan N. Ovarian cancer incidence in the United States, 1992–1999. Gynecol Oncol, 2005, 97(2):519–523.

[2] Schorge JO. Chapter 35: Epithelial ovarian cancer. In: Hoffman BL, Schorge JO, Bradshaw KD, Halvorson LM, Schaffer JI, Corton MM (eds). Williams Gynecology. 3rd edition, McGraw–Hill Education, USA, 2016, 735–754.

[3] Morgan RJ, Armstrong DK, Alvarez RD, Chen LM, Copeland L, Crispens MA, Gershenson DM, Gray HJ, Hakam A, Havrilesky LJ, Johnston C, Lele S, Martin L, Matulonis UA, O'Malley DM, Penson RT, Plaxe SC, Powell MA, Remmenga SW, Sabbatini P, Santoso JT, Spillmann M, Teng N, Werner TL. Ovarian cancer, including Fallopian tube cancer and primary peritoneal cancer, version 3.2014. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®), 2014, available at: https://www2.tri-kobe.org/nccn/guideline/archive/gynecological2014/english/ovarian.pdf.

[4] Trimbos JB, Parmar M, Vergote I, Guthrie D, Bolis G, Colombo N, Vermorken JB, Torri V, Mangioni C, Pecorelli S, Lissoni A, Swart AM; International Collaborative Ovarian Neoplasm 1; European Organisation for Research and Treatment of Cancer Collaborators-Adjuvant ChemoTherapy un Ovarian Neoplasm. International Collaborative Ovarian Neoplasm trial 1 and Adjuvant ChemoTherapy in Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. J Natl Cancer Inst, 2003, 95(2):105–112.

[5] Chan JK, Tian C, Fleming GF, Monk BJ, Herzog TJ, Kapp DS, Bell J. The potential benefit of 6 *vs.* 3 cycles of chemotherapy in subsets of women with early-stage high-risk epithelial ovarian cancer: an exploratory analysis of a Gynecologic Oncology Group study. Gynecol Oncol, 2010, 116(3):301–306.

[6] Earle CC, Schrag D, Neville BA, Yabroff KR, Topor M, Fahey A, Trimble EL, Bodurka DC, Bristow RE, Carney M, Warren JL. Effect of surgeon specialty on processes of care and outcomes for ovarian cancer patients. J Natl Cancer Inst, 2006, 98(3):172–180.

[7] Al-Agha OM, Nicastri AD. An in-depth look at Krukenberg tumor: an overview. Arch Pathol Lab Med, 2006, 130(11): 1725–1730.

[8] Hale RW. Krukenberg tumor of the ovaries. A review of 81 records. Obstet Gynecol, 1968, 32(2):221–225.

[9] Holtz F, Hart WR. Krukenberg tumors of the ovary: a clinico-pathological analysis of 27 cases. Cancer, 1982, 50(11): 2438–2447.

[10] Yakushiji M, Tazaki T, Nishimura H, Kato T. Krukenberg tumors of the ovary: a clinicopathological analysis of 112 cases. Nihon Sanka Fujinka Gakkai Zasshi (Acta Obstet Gynaecol Jpn), 1987, 39(3):479–485.

[11] Lindner V, Gasser B, Debbiche A, Tomb L, Vetter JM, Walter P. [Ovarian metastasis of colorectal adenocarcinomas. A clinico-pathological study of 41 cases]. Ann Pathol, 1999, 19(6): 492–498.

[12] Park SY, Kim HS, Hong EK, Kim WH. Expression of cytokeratins 7 and 20 in primary carcinomas of the stomach and colorectum and their value in the differential diagnosis of metastatic carcinomas to the ovary. Hum Pathol, 2002, 33(11):1078–1085.

[13] Wauters CC, Smedts F, Gerrits LG, Bosman FT, Ramaekers FC. Keratins 7 and 20 as diagnostic markers of carcinomas metastatic to the ovary. Hum Pathol, 1995, 26(8):852–855.

[14] Ronnett BM, Kurman RJ, Shmookler BM, Sugarbaker PH, Young RH. The morphologic spectrum of ovarian metastases of appendiceal adenocarcinomas: a clinicopathologic and immunohistochemical analysis of tumors often misinterpreted as primary ovarian tumors or metastatic tumors from other gastrointestinal sites. Am J Surg Pathol, 1997, 21(10):1144–1155.

[15] Loy TS, Calaluce RD, Keeney GL. Cytokeratin immunostaining in differentiating primary ovarian carcinoma from metastatic colonic adenocarcinoma. Mod Pathol, 1996, 9(11):1040–1044.

[16] Berezowski K, Stastny JF, Kornstein MJ. Cytokeratins 7 and 20 and carcinoembryonic antigen in ovarian and colonic carcinoma. Mod Pathol, 1996, 9(4):426–429.

[17] Herghelegiu CG, Neacşu A, Oprescu ND, Cărbunaru AE, Brăila AD, Curea FG, Marcu ML, Ioan RG, Bohîlţea RE. Difficulties of clinical and histopathological diagnosis in advanced vulvar clear cell carcinoma. Rom J Morphol Embryol, 2018, 59(4):1233–1237.

[18] Anghel RM, Trifanescu OG, Mitrica RI, Curea FG, Botnariuc I, Herghelegiu CG, Orlov CM, Ilie SM. Good prognosis went badly: fulminant evolution of a 29-year-old patient with verrucous carcinoma of the cervix. J Adolesc Young Adult Oncol, 2017, 6(3):499–502.

[19] Călin FD, Gheorghiu D, Ionescu CA, Neacşu A, Navolan DB, Dimitriu MCT, Ionescu A, Constantin VD, Terzea DC, Marcean C, Pădure L, Pacu I. Endometrial stromal sarcoma in a 27-year-old woman. Case report and literature review. Rom J Morphol Embryol, 2018, 59(3):933–938.

[20] Malati T. Tumour markers: an overview. Indian J Clin Biochem, 2007, 22(2):17–31.

[21] Braila AD, Ionescu CA, Calin A, Musetescu AE, Lungulescu C, Braila M, Navolan D, Neacsu A. Hormonal biochemical markers in ectopic pregnancy monitoring. Rev Chim (Bucharest), 2018, 69(6):1558–1561.

[22] Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, Cerny T, Omlin A. Multiple primary tumours: challenges and approaches, a review. ESMO Open, 2017, 2(2):e000172.

[23] Ogawa H, Hata T, Uemura M, Nishimura J, Hayashi T, Takemasa I, Mizushima T, Doki Y, Mori M, Yamamoto H. Two cases of synchronous metastasis of colon cancer to the ovary. Gen Med (Los Angel), 2013, 1(4):123.

[24] Ionescu CA, Vlădăreanu S, Pleş L, Dimitriu MCT, Furău GO, Vlădescu TC, Călin AM, Oprescu ND. Synchronous bilateral primary ovarian carcinoma – case presentation. Rom J Morphol Embryol, 2017, 58(1):219–223.

[25] Ionescu CA, Matei A, Navolan D, Dimitriu M, Bohâltea R, Neacsu A, Ilinca C, Ples L. Correlation of ultrasound features and the risk of ovarian malignancy algorithm score for different histopathological subtypes of benign adnexal masses. Medicine (Baltimore), 2018, 97(31):e11762.

[26] Soerjomataram I, Coebergh JW. Epidemiology of multiple primary cancers. In: Verma M (ed). Cancer epidemiology. Vol. 471, Book Series "Methods in Molecular Biology", Humana Press, 2009, 85–105.

[27] Pacu I, Ionescu C, Vladareanu S, Banacu M, Neacsu A, Calin A. Predictive value of the AMH level and serum estradiol for ovarian hyperstimulation syndrome in the assisted human reproduction. Rev Chim (Bucharest), 2017, 68(5):1118–1121.

[28] Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med, 2003, 348(10):919–932.

[29] Win AK, Lindor NM, Winship I, Tucker KM, Buchanan DD, Young JP, Rosty C, Leggett B, Giles GG, Goldblatt J, Macrae FA, Parry S, Kalady MF, Baron JA, Ahnen DJ, Marchand LL, Gallinger S, Haile RW, Newcomb PA, Hopper JL, Jenkins MA. Risks of colorectal and other cancers after endometrial cancer for women with Lynch syndrome. J Natl Cancer Inst, 2013, 105(4):274–279.

[30] Ionescu CA, Navolan D, Calin A, Matei A, Bohiltea R, Dimitriu M, Ilinca C, Ples L. Hormonal contraception in postpartum patients with gestational diabetes mellitus. Rev Chim (Bucharest), 2018, 69(2):478–483.

[31] Neacşu A, Marcu ML, Stănică CD, Brăila AD, Pacu I, Ioan RG, Grigorescu CC, Ionescu CA. Clinical and morphological correlations in early diagnosis of endometrial cancer. Rom J Morphol Embryol, 2018, 59(2):527–531.

[32] De Roock W, Jonker DJ, Di Nicolantonio F, Sartore-Bianchi A, Tu D, Siena S, Lamba S, Arena S, Frattini M, Piessevaux H, Van Cutsem E, O'Callaghan CJ, Khambata-Ford S, Zalcberg JR, Simes J, Karapetis CS, Bardelli A, Tejpar S. Association of *KRAS p.G13D* mutation with outcome in patients with chemo-therapy-refractory metastatic colorectal cancer treated with cetuximab. JAMA, 2010, 304(16):1812–1820.

[33] Tejpar S, Celik I, Schlichting M, Sartorius U, Bokemeyer C, Van Cutsem E. Association of *KRAS G13D* tumor mutations with outcome in patients with metastatic colorectal cancer

treated with first-line chemotherapy with or without cetuximab. J Clin Oncol, 2012, 30(29):3570–3577.

[34] Segelov E, Thavaneswaran S, Waring PM, Desai J, Robledo KP, Gebski VJ, Elez E, Nott LM, Karapetis CS, Lunke S, Chantrill LA, Pavlakis N, Khasraw M, Underhill C, Ciardiello F, Jefford M, Wasan H, Haydon A, Price TJ, van Hazel G, Wilson K, Simes J, Shapiro JD. Response to cetuximab with or without irinotecan in patients with refractory metastatic colorectal cancer harboring the *KRAS G13D* mutation: Australasian Gastro-Intestinal Trials Group ICECREAM Study. J Clin Oncol, 2016, 34(19):2258–2264.

[35] Lièvre A, Bachet JB, Le Corre D, Boige V, Landi B, Emile JF, Côté JF, Tomasic G, Penna C, Ducreux M, Rougier P, Penault-Llorca F, Laurent-Puig P. *KRAS* mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res, 2006, 66(8):3992–3995.

[36] Prat J. Ovarian carcinomas, including secondary tumors: diagnostically challenging areas. Mod Pathol, 2005, 18(Suppl 2): S99–S111.

[37] Rekhi B, George S, Madur B, Chinoy RF, Dikshit R, Maheshwari A. Clinicopathological features and the value of differential cytokeratin 7 and 20 expression in resolving diagnostic dilemmas of ovarian involvement by colorectal adenocarcinoma and *vice-versa*. Diagn Pathol, 2008, 3:39.

[38] Marcu ML, Neacşu A, Stoica C, Bacalbaşa N, Contolenco A, Radu E. Clinical and pathological features of splenic metastasis from cervical squamous cell carcinoma. Rom J Morphol Embryol, 2017, 58(4):1157–1164.

[39] Chou YY, Jeng YM, Kao HL, Chen T, Mao TL, Lin MC. Differentiation of ovarian mucinous carcinoma and metastatic colorectal adenocarcinoma by immunostaining with beta-catenin. Histopathology, 2003, 43(2):151–156.

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