CASE REPORT

UDC: 618.11-006-033.2::616.411
DOI: https://doi.org/10.2298/VSP200930043L

The first case report of a solitary metastasis of the transitional cell carcinoma of the ovary to the spleen

Prvi slučaj izolovane metastaze primarnog karcinoma prelaznih ćelija jajnika u slezinu

Ranko Lazović*†, Batrić Vukčević*†, Petar Milić‡, Jelena Lazović§

Clinical Center of Montenegro, *Center for Digestive Surgery, §Department of Neurology, Podgorica, Montenegro; †University of Montenegro, Faculty of Medicine, Podgorica, Montenegro; ‡General Hospital Kotor, General Surgery Department, Kotor, Montenegro

Abstract

Background. Primary transitional cell carcinoma (TCC) of the ovary is characterized by the presence of papillary projections of malignant transitional epithelial cells or their aggregates in the fibrous stroma. This type of tumor represents nearly 1% of all ovarian surface epithelium carcinomas. We presented the first report of a solitary splenic metastasis of primary ovarian TCC. **Case report.** A 60-year-old female patient was admitted because of an asymptomatic splenic tumor in December 2018. Two years prior, she underwent a total abdominal hysterectomy, bilateral adnexectomy, and infracolic omentectomy for the primary TCC of the ovary. Control abdominal ultrasonography, computed tomography, and magnetic resonance imaging performed two years after primary surgery showed a splenic tumor. An open splenectomy was performed, with the intraoperative finding of a hilar splenic tumor and the absence of other pathological lesions in the abdomen. Frozen section analysis showed a TCC metastasis, which was subsequently confirmed by definitive histopathological examination. During the one-year follow-up, there was no relapse of the disease. **Conclusion.** This is the first report of a solitary splenic metastasis of primary ovarian TCC based on the literature review. This case may serve as an example of the diagnostic and therapeutical role of splenectomy in isolated splenic metastases of ovarian cancer.

Key words:
carcinoma, transitional cell; diagnosis; histological techniques; neoplasm metastasis; ovarian neoplasms; spleen.

Apstrakt

Uvod. Primarni karcinom prelaznih ćelija (KPĆ) jajnika karakteriše prisustvo papilarnih projekcija malignih ćelija prelaznog epitela ili njihovih agregata u fibroznoj stromi. Ovaj tip tumora obuhvata oko 1% svih karcinoma površinskog epitela jajnika. Prikazali smo prvi slučaj solitarne metastaze primarnog ovarijalnog KPĆ u slezinu. **Prikaz bolesnika.** Bolesnica stara 60 godina primljena je u decembru 2018. godine, zbog asimptomatskog tumora slezine. Dve godine ranije joj je zbog primarnog KPĆ jajnika urađena totalna abdominalna histerektomija, bilateralna adneksektomija i infrakolična omentektomija. Kontrolna ultrasonografija abdomena, kompjuterizovana tomografija i magnetna rezonanca, sprovedene dve godine nakon operacije, pokazale su tumor slezine. Urađena je otvorena splenektomija, a intraoperativni nalaz je pokazao tumor hilusa slezine, bez drugih patoloških lezija u abdomenu. Patohistološka analiza je pokazala metastazu KPĆ, što je potvrđeno naknadnom definitivnom patohistološkom analizom. U toku jednogodišnjeg praćenja nije bilo relapsa bolesti. **Zaključak.** Prema literaturnim podacima ovo je prvi prikazani slučaj solitarne metastaze primarnog KPĆ jajnika u slezinu, koji može predstavljati primer dijagnostičke i terapijske uloge splenektomije kod izolovanih metastaza karcinoma jajnika u slezinu.

Ključne reči:
karcinom prelaznih ćelija; dijagnoza; histološke tehnike; neoplazme, metastaze; jajnik, neoplazme; slezina.

Correspondence to: Batrić Vukčević, University of Montenegro, Faculty of Medicine, Kruševac bb, 81 000 Podgorica, Montenegro.
E-mail: batricvukcevic@gmail.com

Introduction

Ovarian transitional cell tumors may present as transitional cell carcinoma (TCC), as well as benign, borderline, or malignant Brenner tumors, in total accounting for nearly 2% of all ovarian tumors [1]. It is considered that Brenner tumors arise from the surface epithelium and stroma through the process of transitional cell metaplasia [2] and that around 1% of all Brenner tumors are malignant [3]. Primary TCC of the female genital tract is described in the ovary, vagina, uterine cervix, endometrium, and Fallopian tubes [4]. Primary ovarian TCC was first described by Austin and Norris in 1987 [5]. It represents 1% of all ovarian surface epithelium carcinomas [6]. The lack of urothelial markers suggests a Mullerian origin of TCC, therefore distinguishing it from urothelial cancer [7]. TCC is characterized by the lack of the Brenner component [8, 9] and the lack of stromal calcification [10]. On the other hand, TCC shows malignant transitional type cells in papillary proliferations or aggregates in the fibrous stroma [6]. Silva et al. [11] showed that focal or diffuse ovarian TCC components presented in 88 of 934 ovarian cancer cases. Primary ovarian TCC has a better prognosis compared with other ovarian carcinomas due to a higher degree of chemosensitivity [6, 7, 10].

We present the first case of a solitary splenic metastasis of primary ovarian TCC based on the histopathological examination and the medical history of the patient.

Case report

In December 2018, a 60-year-old female patient was admitted for elective splenectomy to treat an asymptomatic splenic tumor. In 2016, she underwent a total abdominal hysterectomy, as well as bilateral adnexectomy and infracolic omentectomy for a massive pelvic tumor. The initial imaging finding [abdominal computed tomography (CT) scan interpretation] did not show any evidence of other intraabdominal pathological lesions, confirmed by the operative report from primary surgery (which was not performed in our institution). Multiple biopsies from the visceral peritoneum (mesentery) as well as the parietal peritoneum (central, anterolateral, and pelvic peritoneum) were taken. Histopathology of the pelvic tumor showed a primary ovarian TCC with infiltrative growth and partial necrosis. It also showed papillary projections of pleomorphic epithelial cells expressing multiple mitoses and acidophilic cytoplasm. Immunohistochemistry stain showed CK7 positivity and CK20 negativity. The tumor stage was determined as pT1c, histologic grade 2–3, and nuclear grade 3. The peritoneal biopsies were all negative. Afterward, she underwent six cycles of chemotherapy (paclitaxel and carboplatin). Other medical history was unremarkable.

On admission, the patient did not report any symptoms, and the physical finding was normal (besides the scar from the previous laparotomy). A preoperative abdominal ultrasonography exam (performed during the oncological follow-up) showed a splenic mass consisting of multiple focal lesions (48 × 32 mm; vertical and transverse diameter, respectively). An abdominal CT scan showed an interpolar splenic mass (42 × 42 × 36 mm; vertical, laterolateral, and anteroposterior diameter, respectively) (Figure 1). Magnetic resonance imaging (MRI) showed a 10.0 × 5.5 cm sized spleen (vertical and laterolateral diameter, respectively) with a tumor located on the superior aspect of the splenic hilum, posteriorly from the stomach (Figure 2). The tumor size was 44 × 24 × 36 mm (vertical, laterolateral, and anteroposterior diameter, respectively). The lesion showed diffusion restriction and was hypovascular in comparison with the splenic parenchyma. The other imaging findings in the abdomen, as well as chest X-ray and head CT, were normal. The laboratory results showed that CA 125 was elevated (50.6 U/mL). Other results (complete blood count, biochemical parameters, and other tumor markers) were normal.

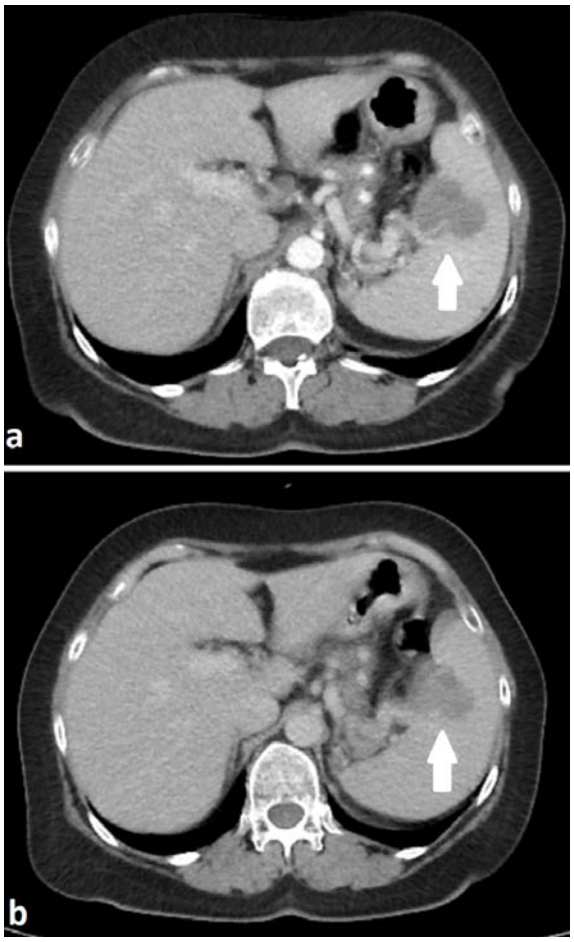

Fig. 1 – Contrast-enhanced axial computed tomography scans of the upper abdomen with the arrow indicating the splenic tumor: a – arterial phase; b – delayed phase.

After the patient was presented with the risk of potential complications of laparoscopic splenectomy being performed after the previous laparotomy, she was suggested for open splenectomy. A left subcostal laparotomy was performed, with the intraoperative finding of a splenic hilar tumor in close contact with the tail of the pancreas and the posterior gastric wall. Further exploration did not reveal any locoregional relapse of TCC, peritoneal dissemination, or metastatic disease in other organs. An open splenectomy was per-

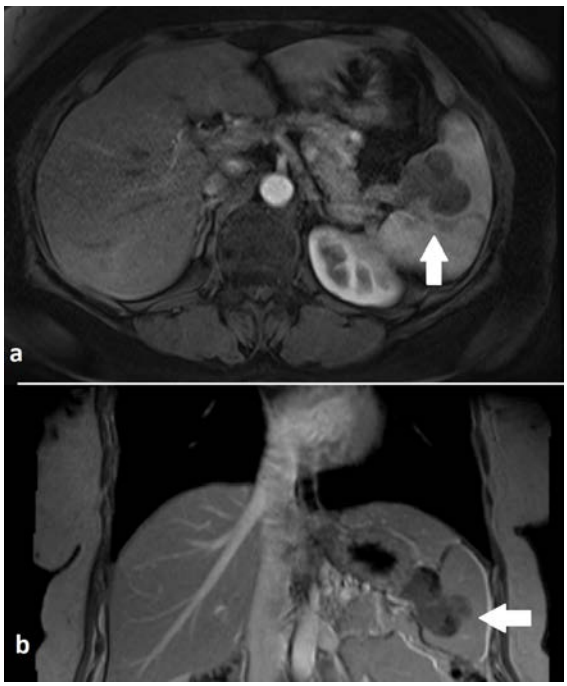

Fig. 2 – Contrast-enhanced T-1 weighted magnetic resonance imaging of the abdomen with the arrow indicating the splenic tumor: a – axial slice, arterial phase; b – coronal slice, delayed phase.

formed, and the splenic bed was drained with two surgical drains. The tumor exhibited yellowish and greenish color with a lobular structure (Figure 3). Frozen section analysis was suggestive of TCC metastasis. Histopathology showed malignant transitional type cells organized into papillary structures (Figure 4), multiple pathologic mitoses, CK7 positivity and CK20 negativity. This histopathological finding was seen in the hilar lymph nodes of the spleen as well. The final conclusion was that the splenic tumor represented a metastasis of the primary ovarian TCC.

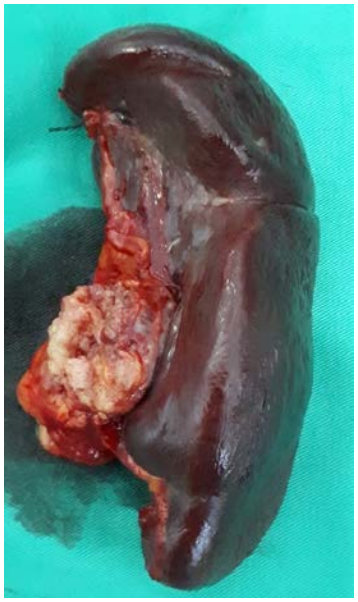

Fig. 3 – Gross examination finding of the removed spleen.

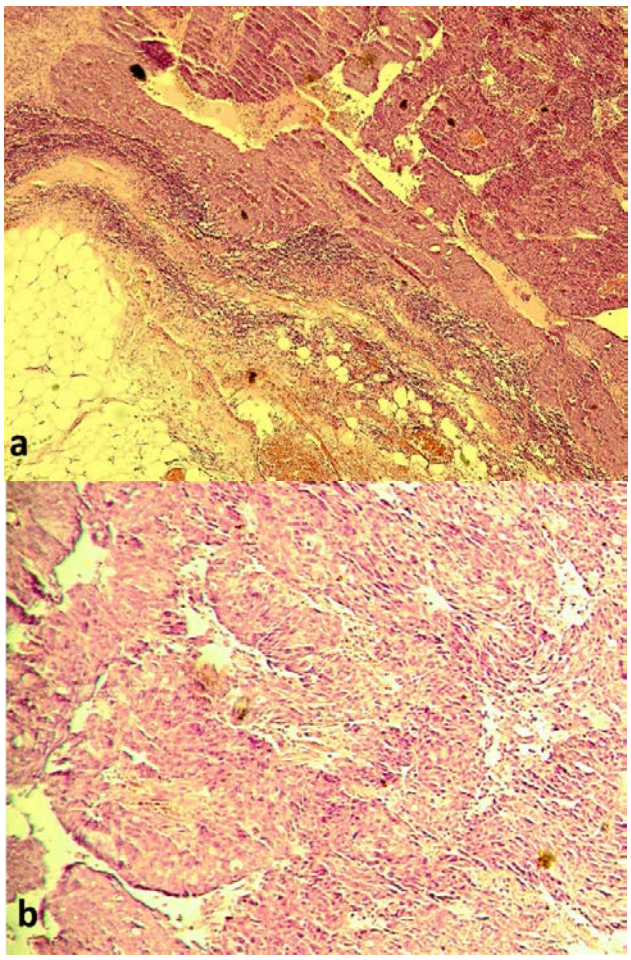

Fig. 4 – Histopathology finding (haematoxylin-eosin staining): a – ×50; b – ×100.

The recovery was uneventful, and the patient was discharged on the seventh postoperative day. Postsplenectomy antimicrobial prophylaxis was performed, including pneumococcal, meningococcal, and *Haemophilus influenzae* type b vaccinations. Postoperative oncological treatment consisted of six cycles of paclitaxel and carboplatin. A one-year follow-up (chest and abdominal CT, abdominal MRI, and CA 125 levels) did not show any recurrence of the disease.

Discussion

This report is based on a late manifestation of primary ovarian TCC in a solitary metastatic behavior to the spleen. The metastatic pathway of ovarian TCC resembles the metastases from urothelial carcinoma due to the loss of E-cadherin [10]. In a study on 302 patients [with 5.3% (16 patients) suffering from primary TCC], Kommoss et al. [7] showed that primary ovarian TCC exhibits micronodular extraovarian growth more commonly than other ovarian cancers (usually characterized by direct macronodular spreading). Owing to this, primary TCC often has a lesser preoperative extraovarian component, as well as a smaller extent of postoperative residual tissue leading to a superior 5-year

survival (57.14%) compared with non-TCC ovarian carcinomas (30.68%). In 2008, Keepanasseril et al. [12] presented a patient with right-sided cervical lymphadenopathy (levels II and III) as a solitary metastasis of right-sided primary TCC of the ovary, without metastases to the abdomen and thorax.

Metastatic tumors of the spleen are usually accompanied by malignant peritoneal dissemination [13], while solitary splenic metastases usually arise from gastrointestinal cancers [14]. A literature review by Izuishi et al. [15] in 2010 showed that 27% of all solitary splenic metastases arise from ovarian cancer. Bearing in mind that there are several papers published before the year 2000 [16], Table 1 contains short descriptions of solitary ovarian cancer metastases to the spleen published in the relevant literature as of the year 2000 (also, there are several papers published before the year 2000) [17–25]. Based on the literature review, we can conclude that this is the first reported case of a solitary splenic metastasis of primary ovarian TCC. It is considered that solitary splenic metastases are rare due to the sharp angle of splenic artery origin from the celiac trunk, the contractile washout of blood from the splenic sinusoids to the splenic vein, the scarcity of afferent lymph nodes, as well as to the inhibitory effect of the histological milieu of spleen on the growth of malignant tissue [13, 26]. Unlike the metastases to the liver parenchyma, splenic metastases are not considered stage IV malignant disease. Splenectomy is described as a part of the first-step cytoreductive surgery for ovarian cancer, as well as secondary cytoreduction – independently from the presence of splenic metastases [16]. Farias-Eisner et al. [14] hypothesized that the spleen could present as "a pharmacological and immunological sanctuary" for ovarian cancer cells.

Primary ovarian TCC is treated with optimal surgical resection and cisplatin-based chemotherapy [10, 27]. Ichigo et al. [10] showed that surgical resection with postoperative cisplatin results in superior survival. A 5-year follow-up of 88 patients showed a survival rate of 37% in the group of patients treated with surgery (as the only treatment method) and 41% in the group that underwent surgery combined with chemotherapy. They concluded that the TCC component contributed to a better prognosis, which depends on the clinical stage of the disease [10].

The patients in Table 1 had a disease-free interval from 11 months to 5 years after splenectomy. The case presented herein exhibits splenectomy as a diagnostic step (to determine the presence of metastatic disease), as well as a curative approach (with a one-year disease-free interval after surgery). This may serve as an inspiration to report solitary ovarian TCC metastases to the spleen in order to recognize the true incidence of this metastatic pattern, as well as the therapeutic benefit from splenectomy.

The importance of differentiation between primary ovarian TCC and metastatic urothelial cancer lies in the fact that the presence of malignant urothelial cells leads the diagnostic approach in the direction of searching for a primary urinary tract cancer. Badin et al. [1] presented an 83-year-old female patient who had an ovarian tumor surgery, with the histopathological finding inconclusive between primary ovarian TCC and metastatic urothelial cancer. Six years prior, she underwent transurethral resection of a bladder urothelial cancer, with subsequent intravesical administration of interferon-alpha and Bacillus-Calmette-Guerin vaccine. This anamnestic information – together with immunohistochemical positivity of the tumor to CK7 and CK20 – leads to the conclusion that this was a metastatic urothelial carcinoma. Lee et al. [28] presented two female patients with metastatic urothelial carcinomas to the ovary (from the renal pelvis and the bladder). Their literature review showed that urothelial carcinoma metastases to the ovarium are rare and that the most frequent metastases from the urinary tract to the ovarium were from clear cell renal adenocarcinoma. Ichigo et al. [10] stated that the most significant parameters in differentiating between primary ovarian TCC and urothelial cancer are positivity to CK7, CK20, uroplakin III, and Wilms tumor protein. Moreover, primary ovarian TCC exhibits broad papillae with mucin collections, while metastatic urothelial cancer forms pseudo-papillae after necrosis of the tumor cells [28].

Urothelial carcinoma[4] and malignant Brenner tumors express CK7 and CK20 positivity, while Mullerian serous tumors express only CK7 positivity [1, 9]. Ovarian TCC is unreactive with CK20 [7, 27] and uroplakin III [6, 12], while 30% of ovarian TCC are reactive with thrombomodulin. On the other hand, ovarian TCC expresses positivity for Wilms tumor protein 1 [1], vimentin, and CA 125 [2]. In benign and borderline Brenner tumors, p63 is expressed. On the other hand, its expression is absent in malignant Brenner tumors and primary ovarian TCC [10]. Cuatrecasas et al. [2] showed an increase in p16 and p53 expression as well as more frequent p53 mutations in primary ovarian TCC compared with malignant Brenner tumors. This characterizes primary ovarian TCC as a high-grade tumor. Coffman et al. [29] combined human and murine models to show the tropism of high-grade ovarian cancer cells for the ovary, therefore supporting the role of hematogenous spread of ovarian cancer [30]. Furthermore, the authors comment on the possible role of oophorectomy in preventing peritoneal metastases and ascites. Owing to this, it is interesting to consider that primary surgery reduced the risk of peritoneal metastases in our patient. On the other hand, given the fact that the circulating tumor cells (paramount in hematogenous metastatic route [31]) are present in nearly 50% of all the International Federation of Gynecology and Obstetrics stage I-II ovarian cancers [30], this supports the theory of hematogenous spread to the spleen in the patient presented herein. Despite the fact that the relevant literature does not contain data on the ovarian TCC metastasis growth rate, it is known that the survival rate for TCC patients is similar to the survival rate for advanced high-grade serous carcinoma [32].

Table 1

Solitary metastases of ovarian cancer to the spleen reported in the relevant literature from the year 2000 to present

Authors and year	Age of patient (years)	Histologic type of cancer	Grade	Stage (FIGO)	Chemotherapy after first surgery	Time after first surgery	Elevated CA 125	Relapse*
Yano et al., 2002 [17]	38	serous adenocarcinoma	-**	IIIC	-	3 years	-	-
Koh et al., 2004 [18]	29	mucinous (borderline)	-	-	-	1 year	yes	yes (2 years)
Tserkezoglou et al., 2005 [19]	53	serous cystadenocarcinoma	-	IIIB	cisplatin	27 months	yes	no (20 months)
Otrock et al., 2006 [20]	59	serous adenocarcinoma	high	IIA	carboplatin+paclitaxel	6 years	yes	no (11 months)
Izuishi et al., 2010 [15]	52	serous adenocarcinoma	-	IIC	5-FU; adriamycin; cisplatin; cyclophosphamide	20 years	no	no (5 years)
Karni et al., 2014 [21]	56	endometrioid-type	3	IA	carboplatin i paclitaxel	6 years	yes	-
Lee et al., 2014 [22]	66	serous adenocarcinoma /squamous cell carcinoma	-	-	-	48 months	yes	-
Resta et al., 2014 [23]	67	adenocarcinoma	-	-	-	10 years	yes	no (1 year)
Lv et al., 2014 [24]	53	clear cell adenocarcinoma	-	-	cisplatin+docetaxel	simultaneously	yes	-
Sorbi et al., 2015 [25]	66	tuboovarian serous carcinoma	2	IIIA	carboplatin+paclitaxel; trabectedin+doxorubicin	5 years	no	no (16 months)

*** – relapse of cancer after splenectomy (the follow-up period is given in brackets); ** – no available information.**
FIGO – International Federation of Gynecology and Obstetrics.

Conclusion

This is the first case report of solitary ovarian TCC metastasis to the spleen. Additionally, this case report can serve as an example of therapeutic splenectomy in solitary TCC splenic metastasis. The follow-up of this patient, as well as reporting other similar cases in the future, will demonstrate the effect of this metastatic pattern and splenectomy on the 5-year survival rate and the disease-free interval in primary ovarian TCC.

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. *Badin J, Abello A, Gupta M, Das AK*. Urothelial Carcinoma of the Bladder With a Rare Solitary Metastasis to the Ovary. Urology 2020; 135: 24–7.
2. *Cuatrecasas M, Catasus L, Palacios J, Prat J*. Transitional cell tumors of the ovary: a comparative clinicopathologic, immunohistochemical, and molecular genetic analysis of Brenner tumors and transitional cell carcinomas. Am J Surg Pathol 2009; 33(4): 556–67.
3. *Weinberger V, Minář L, Felsinger M, Ovesná P, Bednaříková M, Čihalová M*, et al. Brenner tumor of the ovary – ultrasound features and clinical management of a rare ovarian tumor mimicking ovarian cancer. Ginekol Pol 2018; 89(7): 357–63.
4. *Giordano G, D'Adda T, Gnetti L, Merisio C, Raboni S*. Transitional cell carcinoma of the endometrium associated with benign ovarian brenner tumor: a case report with immunohistochemistry molecular analysis and a review of the literature. Int J Gynecol Pathol 2007; 26(3): 298–304.
5. *Austin RM, Norris HJ*. Malignant Brenner tumor and transitional cell carcinoma of the ovary: a comparison. Int J Gynecol Pathol 1987; 6(1): 29–39.
6. *Chandanwale SS, Kamble T, Mishra N, Kumar H, Jadhav R*. A pure primary transitional cell carcinoma of the ovary: A rare case report with literature review. Int J Appl Basic Med Res 2016; 6(2): 140–2.
7. *Kommoss F, Kommoss S, Schmidt D, Trunk MJ, Pfisterer J, du Bois A*, et al. Survival benefit for patients with advanced-stage transitional cell carcinomas vs. other subtypes of ovarian carcinoma after chemotherapy with platinum and paclitaxel. Gynecol Oncol 2005; 97(1): 195–9.
8. *Eichhorn JH, Young RH*. Transitional cell carcinoma of the ovary: a morphologic study of 100 cases with emphasis on differential diagnosis. Am J Surg Pathol 2004; 28(4): 453–63.
9. *Logani S, Oliva E, Amin MB, Folpe AL, Cohen C, Young RH*. Immunoprofile of ovarian tumors with putative transitional cell (urothelial) differentiation using novel urothelial markers: histogenetic and diagnostic implications. Am J Surg Pathol 2003; 27(11): 1434–41.
10. *Ichigo S, Takagi H, Matsunami K, Murase T, Ikeda T, Imai A*. Transitional cell carcinoma of the ovary (Review). Oncol Lett 2012; 3(1): 3-6. (English)
11. *Silva EG, Robey-Cafferty SS, Smith TL, Gershenson DM*. Ovarian carcinomas with transitional cell carcinoma pattern. Am J Clin Pathol 1990; 93(4):457-65.
12. *Keepanasseril A, Suri V, Gupta N, Ghoshal S*. Transitional cell carcinoma of the ovary: unusual presentation as metastatic cervical lymph node. J Obstet Gynaecol Res 2008; 34(4 Pt 2): 696–8.
13. *Ghani AA, Hashmi ZA, Chase DM, Patel SB, Jones DF*. Intraparenchymal metastases to the spleen from ovarian cancer: a case report. J Med Case Rep 2010; 4: 30.
14. *Farias-Eisner R, Braly P, Berek JS*. Solitary recurrent metastasis of epithelial ovarian cancer in the spleen. Gynecol Oncol 1993; 48(3): 338–41.
15. *Izuishi K, Sano T, Usuki H, Okano K, Masaki T, Kushida Y*, et al. Isolated splenic metastasis of ovarian cancer 20 years after operation: a case report and literature review. Tumori 2010; 96(5): 784–6.
16. *Gemignani ML, Chi DS, Gurin CC, Curtin JP, Barakat RR*. Splenectomy in recurrent epithelial ovarian cancer. Gynecol Oncol 1999; 72(3): 407–10.
17. *Yano H, Iwazawa T, Kinuta M, Nakano Y, Tono T, Matsui S*, et al. Solitary splenic metastasis from ovarian cancer successfully treated by hand-assisted laparoscopic splenectomy: report of a case. Surg Today 2002; 32(8): 750–2.
18. *Koh YS, Kim JC, Cho CK*. Splenectomy for solitary splenic metastasis of ovarian cancer. BMC Cancer 2004; 4(1): 96.
19. *Tserkezoglou A, Kontou S, Hatjieleftheriou G, Nikolaidou ME, Plataniotis G, Apostolikas N*, et al. Solitary parenchymal splenic recurrence of ovarian adenocarcinoma: a case report and review of the literature. Anticancer Res 2005; 25(2B): 1471–6.
20. *Otrock ZK, Seoud MA, Khalifeh MJ, Makarem JA, Shamseddine AI*. Laparoscopic splenectomy for isolated parenchymal splenic metastasis of ovarian cancer. Int J Gynecol Cancer 2006; 16(5): 1933–5.
21. *Karni D, Kopelman D, Abu Hatoum O*. Solitary splenic metastasis of ovarian carcinoma: a case report. J Med Case Rep 2014; 8: 154.
22. *Lee DH, Yoon JK, Lee SJ, Jo KS, Yoon SH, An YS*. Isolated splenic metastasis of ovarian cancer detected with 18F-FDG PET/CT. Clin Nucl Med 2014; 39(4): 349–51.
23. *Resta G, Vedana L, Marino S, Scagliarini L, Bandi M, Anania G*. Isolated splenic metastasis of ovaric cancer. Case report and literature review. G Chir 2014; 35(7–8): 181–4.
24. *Lv M, Li Y, Luo C, Liu P, Yang J*. Splenic metastasis of ovarian clear cell adenocarcinoma: A case report and review of the literature. Exp Ther Med 2014; 7(4): 982–6.
25. *Sorbi F, Prosperi P, Villanucci A, Berti V, Sisti G, Fambrini M*. Laparoscopic Splenectomy as Quaternary Cytoreduction for Isolated Parenchymal Splenic Recurrence of Epitelial Tubo-Ovarian Cancer: Report of a Case and Literature Review. Gynecol Obstet Invest 2015; 80(4): 265–71.
26. *Max LD, Stastny JF, Frable WJ*. Solitary splenic metastasis of an adenocarcinoma of the ovaries. Gynecol Obstet Invest 1996; 42(3): 214–6.
27. *Tazi EM, Lalya I, Tazi MF, Ahellal Y, M'rabti H, Errihani H*. Transitional cell carcinoma of the ovary: a rare case and review of literature. World J Surg Oncol 2010; 8: 98. (English)
28. *Lee M, Jung YW, Kim SW, Kim SH, Kim YT*. Metastasis to the ovaries from transitional cell carcinoma of the bladder and renal pelvis: a report of two cases. J Gynecol Oncol 2010; 21(1): 59–61.
29. *Coffman LG, Burgos-Ojeda D, Wu R, Cho K, Bai S, Buckanovich RJ*. New models of hematogenous ovarian cancer metastasis demonstrate preferential spread to the ovary and a requirement for the ovary for abdominal dissemination. Transl Res 2016; 175: 92–102. e2.

30. *Yousefi M, Dehghani S, Nosrati R, Ghanei M, Salmaninejad A, Rajaie S, et al.* Current insights into the metastasis of epithelial ovarian cancer - hopes and hurdles. Cell Oncol 2020; 43(4): 515–38.
31. *Giannopoulou L, Kasimir-Bauer S, Lianidou ES*. Liquid biopsy in ovarian cancer: recent advances on circulating tumor cells and circulating tumor DNA. Clin Chem Lab Med 2018; 56(2): 186–97.
32. *Ramalingam P*. Morphologic, Immunophenotypic, and Molecular Features of Epithelial Ovarian Cancer. Oncology (Williston Park) 2016; 30(2): 166–76.

Received on September 30, 2020
Revised on April 3, 2020
Accepted on April 22, 2021
Online First April 2021