Original Paper

Low Grade Ovarian Serous Carcinoma- A Clinical-Morphologic Study

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ABSTRACT: Low grade ovarian serous carcinomas (LGSC) are rare tumors, representing only a small part of all ovarian carcinomas. The study included six LGSC cases for which we followed the clinical-epidemiological and morphological parameters depending on the tumoral stages. The tumors corresponded to stage I in four cases, in one case to stage II and in another case to stage III. The majority of the analyzed histopathological parameters were present in all tumoral stages. The accuracy of the diagnostic and the correct staging of the LGSC affected patients is very important, because the grade and stage of the serous ovarian tumors impose the therapy and the prognosis.

KEYWORDS: *Low grade serous carcinoma, histopathology, tumor staging*

Introduction

The ovarian cancer remains the most lethal neoplasm in the gynecological oncological pathology.

Over time, epithelial ovarian tumors with different histology and grades have been grouped and studied as entities of the same disease. In the last decade, the amplitude of the heterogeneity of the ovarian cancer has been frequently underlined.

Recent data highlight that both the histological type and the tumor grade have a prognosis importance for these patients, the ovarian serous carcinoma being finally grouped in high grade serous carcinoma and low grade serous carcinoma [1].

This binary classification system represented a major progress because it led to separate clinical studies for the patients with these tumoral subtypes.

LGSCs (low grade ovarian serous carcinoma) are rare tumors, representing only a small part of all ovarian carcinomas, respectively 10% of all serous carcinomas [2].

In the last decade it was accepted that LGSC represents an entity with pathological and clinical distinctive characteristics, even if the number of the studies is quite limited [3-6].

The literature data indicate the fact that women with this type of tumor are younger, present a relative chemoresistance and a longer survival compared to women with high grade tumors [7].

Gershenson DM et al. [8] have reported for LGSCs that women with age under 35 years and with a persistent disease at the end of the treatment have the most unfavorable prognosis [9].

In the present we followed a series of clinical-epidemiological and morphological parameters in relation with the tumoral stage of LGSCs.

Material and methods

This study has been realized retrospectively over a number of six LGSC cases diagnosed over an interval of three years (2014-2016), which came from the Gynecology and Surgery Clinics of the Emergency County Clinical Hospital Craiova.

The surgical excised specimens were fixed in 10% neutral buffered formalin, processed by the usual paraffin embedding technique and Hematoxylin and Eosin (HE) staining in the Pathology Department of the same hospital (BioOptica automatic histoprocessor and stainer).

We followed the evaluation of clinical-epidemiological and morphological parameters according to the tumoral stage.

The classification of the tumors has been done according to World Health Organization (WHO) recommendations [1].

Image acquisition has been performed by Nikon Eclipse E600 microscope with a photo-camera and Lucia 5 software.

The study was approved by the local ethical committee (no.38/27.03.2018), and written informed consent was obtained from all the patients.

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Results

The performed study indicated that the age of the patients group was between 28-62 (mean of 55.3 years).

The analyzed LGSC cases were unilateral located, with sizes between 12-21cm (mean of 16cm), the exophytic component being present only in one case.

The classification of the tumors in the pTNM system indicated the stage I in four cases (three cases IA-T1AN0M0, one case IC-T1CN0M0), stage II in one case (T2A1N0M0) and stage III in another case (T2A1N1M0) (Table 1).

Among the analyzed histophological parameters, most were observed in all tumor stages.

Table 1. Clinico-morphological parameters according to the tumoral stage

Parameters		Stage I	Stage II	Stage III
Clinical	Mean Age	46	58	62
Macroscopy	Mean dimensions (cm)	12	15	21
	Laterality	unilateral	unilateral	unilateral
	Exophytic component	-	-	1
Microscopy	Growth pattern	micropapillary, mixed/4/1	micropapillary	micropapillary
	Mitosis	4/10 HPF	6/10 HPF	9/10 HPF
	Tumoral invasion/pattern	2/insular 2/microinvasive	1/insular	1/insular
	Stroma	fibrous/3	fibrous/1	fibrous/1
	Desmoplasia	1	1	1
	Necrosis	-	-	-
	Lympho-vascular invasion	-	-	-
	Psammoma bodies	4	1	1
	Noninvasive component	2	1	1
	Peritoneal implants /pattern	1/micropapillary	1/micropapillary	1/micropapillary
	Uterine body invasion /pattern	-	1	1 micropapillary
	Lymph node metastasis /pattern	-	-	1/micropapillary

The LGSC growth pattern was uniform in all tumoral stages, respectively they present a micropapillary pattern, and only in one stage I case was associated with a cribriform component.

The micropapillae with small sizes were frequently surrounded by a clear optical space.

The architectural complexity was marked in 2 tumors, the micropapillae being anastomosed one with the other, forming thin, elongated and ramified structures.

In one case the micropapillary growth pattern was associated with a cribiform aspect, characterized by the presence of tumoral islands surrounded by optically empty microcystic spaces (Fig.1).

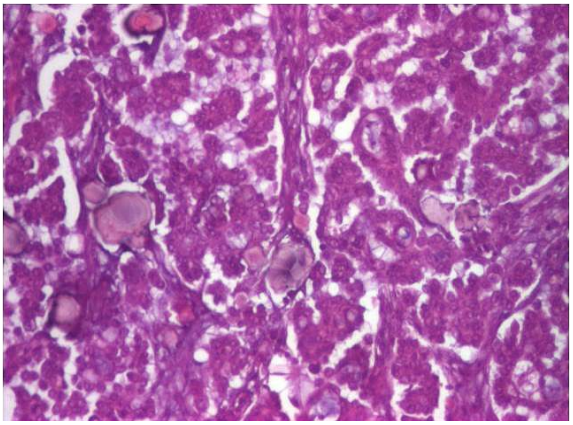

Fig.1. LGSC with micropapillary pattern and psammoma bodies, HE staining, x40

The neoplasic cells had a reduced or moderate eosinophilic cytoplasm, uniform small, round or oval nuclei, with uniformly distributed chromatin.

Often, we observed small nucleoli, but the mitosis were rare, between 4-9 mitosis/10 high power field (HPF) (mean 3.1 mitosis/10 HPF).

In all cases the tumoral stroma was fibrous, generally reduced, in three cases with desmoplastic aspect.

The psammoma bodies were constantly present and numerous in two cases.

The tumoral invasion had micropapillary aspects in three cases and microinvasion aspect in two cases (Fig.2).

We didn't identify tumoral necrosis or lympho-vascular invasion.

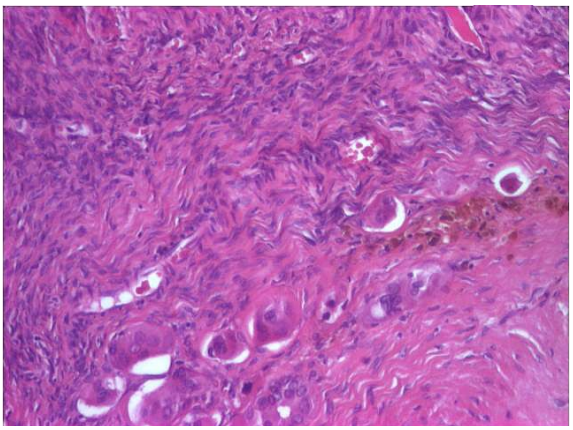

Fig.2. LGSC with micropapillary invasion pattern, HE staining, x40

The association with a noninvasive component of serous borderline tumor type has been identified in all six cases with typical conventional aspect.

The analysis of the peritoneal implants indicated the presence of the tumoral extension at this level in three cases, one in every tumoral stage, with micropapillary aspect and the presence of numerous psammoma bodies.

The mitotic activity of the peritoneal component was reduced, respectively 1 mitosis/10 HPF.

The tumoral extension at the level of pelvic structures was identified in only one case classified in stage II, in which the primitive tumor with micropapillary pattern has associated a peritoneal extension in uterine serosa and the external myometrial invasion.

Similar to the primitive tumor, we observed a micropapillary pattern and numerous psammoma bodies (Fig.3).

The mitotic activity of the invasive component was also reduced to 1 mitosis/ 10 HPF.

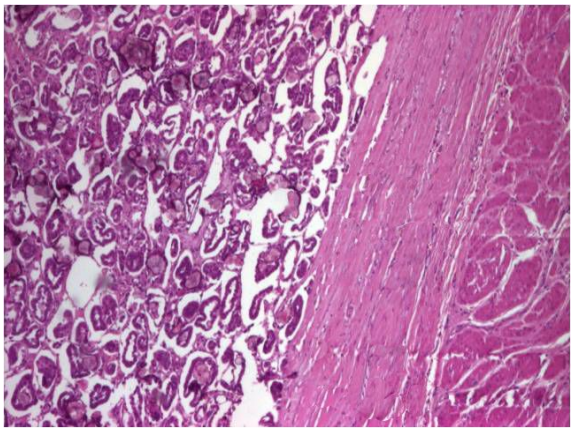

Fig.3. LGSC invasive in myometrium, HE staining, x40

The investigation of the lymph nodes indicated their implication in only one stage III case with retroperitoneal location.

The primitive tumor and the metastasis had a similarly micropapillary growth pattern (Fig.4).

The mitotic activity of the invasive component was also reduced, under 1 mitosis/ 10 HPF.

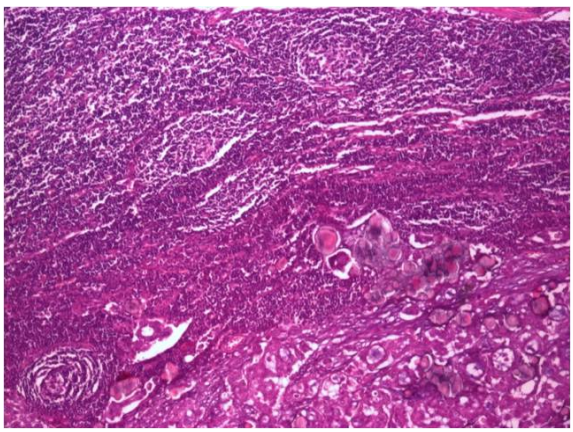

Fig.4. LGSC-lymph node metastasis, HE staining, x40

Discussions

The study included six LGSC cases highlighted some particularities.

The average age at the diagnostic moment for these patients was of 55.3 years, the youngest patient being in tumoral stage I.

Similar studies in literature report the LGSC patients' age between 45-57 years [2,8,10,11], the majority being in the stage I of disease [10].

For the six investigated cases we noticed that all tumors were unilateral, with the mean dimension of the maximum diameter being 16cm, and in only one case there was an exophytic component.

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For the tumors classified in the stage I we noticed a micropapillary or mixed growth pattern, with a medium number of 4 mitosis/10 HPF, the presence of desmoplasia in only one case, the constant presence of psammoma bodies, the association with a typical borderline component, positive washing liquid and peritoneal implant with micropapillar pattern.

The corresponding stage II tumor presented a micropapillary growth pattern, a mitotic index of 6 mitosis/10 HPF, association of desmoplasia, a typical borderline component, a positive peritoneal washing liquid and a peritoneal and myometrial invasion with micropapillary pattern and the presence of numerous psammomatous bodies.

For the stage III tumour we also observed a micropapillary growth pattern, mitotic activity of 9 mitosis/10 HPF, the presence of desmoplasia, psammoma bodies, a typical borderline component, a positive peritoneal washing liquid, with peritoneal invasion and retroperitoneal lymph nodes metastasis with micropapillary pattern and the presence of psammoma bodies.

Similar studies on larger groups of patients indicate similar aspects to our observations, respectively an uniform aspect of the neoplasic proliferation with a predominance of the micropapillary pattern as well in the primitive tumor and in the invasive component. In a recent study of 33 cases, Okoye et al. find the micropapillary pattern in 93% of the analyzed cases [12].

The papillary growth pattern is frequently identified in serous carcinoma, the micropapillary aspect being associated to the low grade forms, while the macropapillary aspect is characteristic to the high grade tumors [13,14].

The nuclear atypia and the mitotic activity was reduced for the analyzed cases, in the primitive tumors, the mean mitotic activity being 5.3 mitosis/10 HPF, in contrast to the invasive component which presented 1 mitosis or less than 1 mitosis/10 HPF.

The literature data report a mild to moderate nuclear atypia (stage I or II) for LGSC and a mitotic index under 12 mitosis/10 HPF [6] or even under 5 mitosis/10 HPF [15].

Some authors reported a reduced pleomorphism and absent mitotic activity or reduced to 1 mitosis/10 HPF for the lymph node invasive component [5].

The tumoral stroma was fibrous in three cases, the desmoplasic reaction with various grades of inflammatory infiltration of lymphocytic type disposed around the tumoral islands being evident. Similar studies reported the presence of fibrosis and desmoplasia in 37% and respectively 44% of the cases [12].

The tumoral invasion varied from micropapillary aspects in three cases to unicellular invasion in two cases. The classical histological model is the micropapillary with optically empty spaces, but alternative models can appear, the micropapillary, solid, glandular with or without microcalcification of psammoma bodies patterns [16].

The psammoma bodies can be observed in the serous carcinoma regardless of the histological grade, but they are more frequent in LGSCs [13,14].

Similarly to our study, other authors have reported the constant presence of psammomatous bodies in LGSC [5].

For the analyzed cases, the psammoma bodies were identified as well in the primitive tumor as in the invasive component, regardless of the affected structure (peritoneum, uterus, lymph nodes) without any link to the tumoral stage. The presence of psammoma bodies had different significances in various studies, while in some the prognostic has been better [17,18] in other they didn't have a prognosis significance [19].

LGSC can develop de novo or after a serous tumor with low malignity potential, so that the association with a noninvasive component of serous borderline tumor type represents a quite common aspect [1].

For the investigated cases we observed the synchronous association of the neoplasia in all six cases, all the borderline tumors associated with LGSCs having a conventional aspect. In some reports over a larger number of cases, the low grade serous carcinoma was associated with borderline serous tumors in approximatively three quarters of the cases [10,12,20].

Conclusions

LGSC is an entity with distinct morphological characteristics on whose identification depend the precision of the diagnosis.

The mostly of the analyzed histopathological parameters were common to all tumoral stages.

The accuracy of the diagnosis and the correct staging is very important because the grade of the serous ovarian carcinoma impose the therapy and the prognostic of those patients.

References

1. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO Classification of Tumours of Female Reproductive Organs. 4th Edition, Volume 6, IARC Press, Lyon, France, 2014, 11-15.
2. Seidman JD, Horkayne-Szakaly I, Cosin JA, Ryu HS, Haiba M, Boice CR, Yemelyanova AV. Testing of two binary grading systems for FIGO stage III serous carcinoma of the ovary and peritoneum. Gynecol Oncol, 2006, 103(2):703-708.
3. Singer G, Stöhr R, Cope L, Dehari R, Hartmann A, Cao DF, Wang TL, Kurman RJ, Shih IeM. Patterns of p53 mutations separate ovarian serous borderline tumors and low- and high-grade carcinomas and provide support for a new model of ovarian carcinogenesis: a mutational analysis with immunohistochemical correlation. Am J Surg Pathol, 2005, 29(2):218-224.
4. Okoye E, Euscher ED, Malpica A. Ovarian Low-grade Serous Carcinoma: A Clinicopathologic Study of 33 Cases With Primary Surgery Performed at a Single Institution. Am J Surg Pathol, 2016, 40(5):627-635.
5. Djordjevic B, Malpica A. Ovarian serous tumors of low malignant potential with nodal low-grade serous carcinoma. Am J Surg Pathol, 2012, 36(7):955-963.
6. Ahn G, Folkins AK, McKenney JK, Longacre TA. Low-grade Serous Carcinoma of the Ovary: Clinicopathologic Analysis of 52 Invasive Cases and Identification of a Possible Noninvasive Intermediate Lesion. Am J Surg Pathol, 2016, 40(9):1165-1176.
7. Gershenson DM. Low-grade serous carcinoma of the ovary or peritoneum. Ann Oncol, 2016, 27 Suppl 1:i45-i49
8. Gershenson DM, Sun CC, Lu KH, Coleman RL, Sood AK, Malpica A, Deavers MT, Silva EG, Bodurka DC. Clinical behavior of stage II-IV low-grade serous carcinoma of the ovary. Obstet Gynecol, 2006, 108(2):361-368.
9. 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.
10. Malpica A, Deavers MT, Lu K, Bodurka DC, Atkinson EN, Gershenson DM, Silva EG. Grading ovarian serous carcinoma using a two-tier system. Am J Surg Pathol, 2004, 28(4):496-504.
11. Fader AN, Java J, Ueda S, Bristow RE, Armstrong DK, Bookman MA, Gershenson DM, Survival in Women With Grade 1 Serous Ovarian Carcinoma. Obstet Gynecol, 2013, 122(2 Pt 1): 225-232.
12. Okoye E, Euscher ED, Malpica A. Ovarian Low-grade Serous Carcinoma: A Clinicopathologic Study of 33 Cases With Primary Surgery Performed at a Single Institution. Am J Surg Pathol, 2016, 40(5):627-635.
13. Vang R, Shih IeM, Kurman RJ. Ovarian low-grade and high-grade serous carcinoma: pathogenesis, clinicopathologic and molecular biologic features, and diagnostic problems. Adv Anat Pathol, 2009, 16(5):267-282.
14. Rosen DG, Zhang Z, Shan W, Liu J. Morphological and molecular basis of ovarian serous carcinoma. J Biomed Res, 2010, 24(4):257-263.
15. Ayhan A, Kurman RJ, Yemelyanova A, Vang R, Logani S, Seidman JD, Shih IeM. Defining the cut point between low-grade and high-grade ovarian serous carcinomas: a clinicopathologic and molecular genetic analysis. Am J Surg Pathol, 2009, 33(8):1220-1224.
16. Kühn W, Kaufmann M, Feichter GE, Schmid H, Hanke J, Rummel HH. Psammoma body content and DNA-flow cytometric results as prognostic factors in advanced ovarian carcinoma. Eur J Gynaecol Oncol, 1988, 9(3):234-241.
17. Motohara T, Tashiro H, Miyahara Y, Sakaguchi I, Ohtake H, Katabuchi H. Long-term oncological outcomes of ovarian serous carcinomas with psammoma bodies: a novel insight into the molecular pathogenesis of ovarian epithelial carcinoma. Cancer Sci, 2010, 101(6):1550-1556.
18. Sorbe B, Frankendal B. Prognostic importance of psammoma bodies in adenocarcinomas of the ovaries. Gynecol Oncol, 1982, 14(1):6-14.
19. Silva EG, Deavers MT, Malpica A. Patterns of low-grade serous carcinoma with emphasis on the nonepithelial-lined spaces pattern of invasion and the disorganized orphan papillae. Int J Gynecol Pathol 2010, 29(6):507-512.
20. Malpica A, Deavers MT. Ovarian low-grade serous carcinoma involving the cervix mimicking a cervical primary. Int J Gynecol Pathol, 2011, 30(6):613-619.

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