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REVIEW ARTICLE

Primary squamous cell carcinoma of the ovary. Review of the literature

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Summary

Purpose: *Primary squamous cell carcinoma (SCC) of the ovary is rare. Most cases arise from a cystic teratoma or less frequently from Brenner tumor or endometriosis. We reviewed 36 cases of primary ovarian SCC reported in the literature including a case diagnosed and treated in our institution.*

Methods: *Data was collected by using the key-words "primary squamous cell carcinoma" and "ovary" on Google Scholar and PubMed in April 2018. All reviewed cases were analyzed according to diagnosis, surgical approach, adjuvant therapy and outcome.*

Results: *To date 23 articles presenting 36 cases of primary ovarian SCC are reported. Nine patients had stage I, 8 stage II, 11 stage III and 5 stage IV disease, whereas 3 patients had in situ carcinoma. All patients underwent surgery (mainly hysterectomy with bilateral salpingo-oophorectomy). Adjuvant therapy was reported in 24 patients, 15 of which received chemotherapy, 6 radiotherapy and 3 a combination of both. Chemotherapy regimens were similar to the ones used in ovarian carcinoma (more often platinum plus paclitaxel). Follow-up period was in general short and survival varied between 9 days and 14 years, depending on the stage at diagnosis.*

Conclusions: *Primary ovarian SCC is a rare entity with poor prognosis, compared to serous carcinoma. Treatment is usually extrapolated from classical ovarian carcinoma algorithms, including surgical management combined with adjuvant chemotherapy with or without radiotherapy. Further investigations are needed to define optimal treatment, such as chemotherapy regimens and the role of radiation therapy and lymph node dissection.*

Key words: *squamous cell carcinoma, ovary, ovarian cancer, HPV, dermoid cyst, endometriosis, cervical intraepithelial neoplasia.*

Introduction

Squamous cell carcinoma (SCC) of the ovary is a rare entity accounting for less than 1% of primary ovarian malignant tumors [1].

In most cases it arises from malignant transformation of mature cystic teratoma [2] and less frequently is associated with endometriosis [3] or

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Brenner's tumor [4]. Finally, the pure or *de novo* ovarian SCC is not associated with any of the above mentioned preexisting ovarian lesions.

In 1964 Black and Benitez published the first article describing a pure primary SCC of the ovary [5]. Since then 35 additional cases have been reported in the literature [6-27]. The majority of the articles describing pure primary ovarian SCC are case reports that may incorporate a literature review section.

This paper reviewed the clinical and pathological features of primary ovarian SCC described in the literature including one case diagnosed and treated in our institution [27]. Additionally, histogenesis, diagnosis, current treatment options and prognosis are discussed.

Methods

Data was collected by researching the following keywords: "primary squamous cell carcinoma" and "ovary" on Google Scholar and PubMed in April 2018.

For each patient we collected demographic data and detailed histological report. In addition, staging, surgical treatment, radiotherapy, systemic treatment and clinical outcome were analyzed.

This is a qualitative analysis for which no statistical methods were used. Survival analysis was not performed due to the limited sample size and the short follow-up period.

Results

In our review 22 articles were included from 1964 to 2018. Most articles were single case reports, while one of them described 2 cases [21]. Two articles reported case series, the first one described 10 cases including 7 associated with a dermoid cyst and 3 pure ovarian SCC [12], while the second one reported 37 cases including 19 associated with a dermoid cyst, 7 associated with endometriosis and 11 pure ovarian SCC [17].

Some case reports were not fully analyzed, with important data missing such as the tumor size, details concerning surgical management, adjuvant therapy and survival.

Clinicopathological findings and treatment features of 36 primary ovarian SCC cases are presented in Tables 1 and 2.

Patients' age ranged from 27 to 90 years (mean 52.9). Tumor size ranged from 1.5 to 26 cm in the greatest axis (mean 10.3). Regarding laterality, 8 patients had right, 8 left and 7 bilateral ovarian involvement.

The most frequent symptom was abdominal pain. Other symptoms were related to tumor growth (palpable abdominal mass, abdominal distension, vaginal bleeding), metastasis or local extension (cough, rectal bleeding) or were nonspecific (weight loss, fever, constipation). Only 3 patients were asymptomatic. Our patient experienced palpable mass and abdominal distension.

High grade Cervical Intraepithelial Neoplasia (CIN III) was found in 10 cases [5-7,9,11,14,15,17]. One patient had previous history of CIN III and high grade vaginal intraepithelial neoplasia (VIN III) [16]. The time interval from diagnosis of CIN III to ovarian SCC ranged from 18 to 156 months (median 87). Ovarian and cervical lesions were synchronous in 3 cases [7,9,14]. Past history of cervical conization for CIN III 23 years ago was also noted in our patient.

Two patients had past history of malignancy. The first one had malignant thymoma treated with surgical excision and radiotherapy 10 years prior to ovarian SCC diagnosis [7] and the second one had breast carcinoma 6 months before ovarian tumor was diagnosed while being under tamoxifen [14].

On gross examination of all 36 cases, 9 tumors were cystic [6,11,14,15,17,21,22] either unilocular or multilocular, 13 were partly cystic [5,9,10,13,16,17,19,21,24] and 9 were solid [8,17,18,20,23,25,26]. In several cases necrosis was identified macroscopically [16,17,25]. In one patient the ovary was normal on gross examination [7].

On microscopic examination several different morphological patterns were present including papillary or polypoid, cystic with central occasionally comedo-like necrosis of solid masses, diffusely infiltrative with associated desmoplastic response and verruciform [17].

Regarding histological grade, 7 tumors were well, 9 were moderately well and 12 were poorly differentiated with 2 cases having an associated spindle cell (sarcomatoid) component [17,19].

In few cases morphological diagnosis was supported by appropriate immunohistochemical findings [24] or by electron microscopy [6].

In our case the carcinoma was poorly differentiated, displaying a diffusely infiltrative pattern with extensive necrosis (Figure 1). Cells were polygonal with large, central, pleomorphic nuclei and eosinophilic cytoplasm. No keratin pearl formation was seen. Few intercellular bridges were recognized. Extensive sampling did not reveal glandular formations or other preexisting lesions (dermoid cyst, Brenner tumor or endometriosis). The immunohistochemical panel included Vimentin, CK7, CK20, CK5, GATA-3, TTF-1, p16, p53, p63, WT-1, estrogen and progesterone receptors. Markers of squamous differentiation (CK5 and p63) and unexpectedly CK7 (Figure 2) were diffusely and intensely positive. In the literature one more case displayed positive CK7 staining [18].

Regarding staging 3 patients had noninvasive SCC, 9 had stage I, 8 stage II, 10 stage III and 5 stage IV disease.

All patients underwent surgery: 26 had hysterectomy and bilateral salpingo-oophorectomy (HBSO) [5,7,9-12,14-21,23-26], 1 had left salpingo-oophorectomy [12,17], 1 had right salpingo-oophorectomy [22], 1 had right salpingo-oophorectomy and left oophorectomy [17], 1 had right oophorectomy [6], 1 had oophorectomy without mentioning laterality [8] and 2 had ovarian and omental biopsies [17]. The following surgical intervention was also performed: tumor debulking [10,13,17,19,23,25], bowel resection [20,23,26], ileectomy [10,25], appendectomy [18,21], omentectomy [19,20,25,26], nephrectomy [18], pelvic lymph node dissection [11,18,19,21,26] and paraaortic lymph node dissection [18,19,21].

Adjuvant therapy was reported in 24 patients. Fifteen patients received systemic therapy, 6 radiotherapy and 3 a combination of both. In 7 cases administration of chemotherapy was mentioned with no further details, while in some others there was no information regarding adjuvant therapy. Pa-

Table 1. Clinicopathological features of pure primary squamous cell carcinoma reported in the literature

Case	*Author*	*Year*	*Age*	*FIGO stage*	*Grade*	*Cervical lesion*	*Size (cm)*	*Gross features*	*Laterality*
1	Black and Benitez	1964	35	I with CIS	1	CIN III	8.2	Partly cystic	NR
2	Shingleton et al.	1974	54	I with CIS	1	CIN III	8	Cystic	Right
3	Genandry et al.	1979	41	CIS	1	CIN III	NR	Normal	Bilateral
4	Macko and Johnson	1983	90	I	2	Absent	24	Solid	NR
5	Chen	1988	49	I	1	CIN III	1.5	Partly cystic	Left
6	Ben-Baruch et al.	1988	65	III	2	Absent	8	Partly cystic	Left
7	Yetman and Druzinski	1989	33	I with CIS	2	CIN III	6	Cystic	Left
8	Kashimura et al.	1989	50	I	NR	Absent	13	NR	Right
9	Kashimura et al.	1989	61	II	NR	Absent	7	NR	Right
10	Kashimura et al.	1989	42	III	NR	Absent	NR	NR	Left
11	Radhi and Awad	1990	64	IV	2	Absent	15/13	Partly cystic	Bilateral
12	Mc Grady et al.	1993	53	CIS	1	CIN III	8.5/2.5	Cystic	Bilateral
13	Sworn et al.	1995	39	CIS	3	CIN III	10	Cystic	Right
14	Mai et al.	1996	40	I with CIS	2	CIN III/ VIN III	15/3.5	Partly cystic, necrotic	Bilateral
15	Pins et al.	1996	64	IB	2	Absent	26/19	Partly cystic	Bilateral
16	Pins et al.	1996	73	IIA	3	CIN III	10.5	Cystic, necrotic	NR
17	Pins et al.	1996	61	IIB	3	Absent	8.5	Cystic, necrotic	NR
18	Pins et al.	1996	55	IIB	3	Absent	7	Solid, necrotic	NR
19	Pins et al.	1996	38	IIC	3	Absent	14	Partly cystic	NR
20	Pins et al.	1996	55	IIIB	3	Absent	8	Partly cystic	NR
21	Pins et al.	1996	52	IIIC	3	Absent	10	Solid	NR
22	Pins et al.	1996	46	IIIC	3	CIN III	NR	Partly cystic	Bilateral
23	Pins et al.	1996	27	IIIC	3	CIN III	12	Partly cystic	NR
24	Pins et al.	1996	70	IIIC	3	Absent	15	Cystic, necrotic	NR
25	Pins et al.	1996	73	IV	3	Absent	6	Solid, necrotic	NR
26	Balat et al.	2001	40	IB	NR	Absent	5/4	Solid	Bilateral
27	Chien et al.	2005	63	IV	3	Absent	15	Partly cystic	Right
28	Amjad and Pal.	2008	31	IIIC	1	Absent	13	Solid	Right
29	Park et al.	2010	76	IIC	1	Absent	6	Partly cystic	Left
30	Park et al.	2010	48	IV	2	Absent	9.2	Cystic	NR
31	Nakamura et al.	2014	71	IIB	NR	Absent	8.5	Cystic	Right
32	Park and Bae	2014	46	IV	2	Absent	NR	Solid	Left
33	Sharma et al.	2015	66	IIIC	2	Absent	14	Partly cystic	Left
34	Shrivastava et al.	2017	30	IIIC	NR	Absent	7	Solid, necrotic	Right
35	Mimura et al.	2017	50	IIB	NR	Absent	9	Solid	Left
36	Koufopoulos et al.	2018	55	IIIC	3	CIN III	8.6	Partly cystic, necrotic	Right

CIN: cervical intraepithelial neoplasia, VIN: vaginal intraepithelial neoplasia, NR: not reported

Table 2. Treatment and outcome features of pure primary squamous cell carcinoma reported in the literature

Case	*Author*	*Year*	*Surgical Treatment*	*Adjuvant therapy*	*Follow-up*
1	Black and Benitez	1964	HBSO	No additional therapy	NR
2	Shingleton et al.	1974	RO	RT	DOD 6mo
3	Genandry et al	1979	HBSO	No additional therapy	NR
4	Macko and Johnson	1983	UO	No additional therapy	ANED 30mo
5	Chen	1988	HBSO	RT	ANED 12mo
6	Ben-Baruch et al.	1988	HBSO,ileectomy,TD	Cyc/Adriamycin/Cis	DOD 6mo
7	Yetman and Druzinski	1989	HBSO, O, PLND, PALND, Appendectomy	No additional therapy	ANED 16mo
8	Kashimura et al.	1989	HBSO	RT	ANED 14years
9	Kashimura et al.	1989	HBSO	Cyc 4000 mg, RT	DOD 9mo
10	Kashimura et al.	1989	LSO	RT	DOD 8mo
11	Radhi and Awad	1990	TD	No additional therapy.	DOD 9days
12	Mc Grady et al.	1993	HBSO		ANED
13	Sworn et al.	1995	HBSO		ANED 60mo
14	Mai et al.	1996	HBSO		NR
15	Pins et al.	1996	RSO, LO	NR	AWD60 mo
16	Pins et al.	1996	HBSO	RT	DOD 49mo
17	Pins et al.	1996	HBSO	RT, Chemo	ANED 60mo
18	Pins et al.	1996	HBSO, TD	Chemo	ANED 30mo
19	Pins et al.	1996	HBSO	Chemo	DOD 8mo
20	Pins et al.	1996	HBSO	Chemo	DOD 2mo
21	Pins et al.	1996	Ovarian, omental biopsy	NR	NR
22	Pins et al.	1996	Ovarian, omental biopsy	NR	NR
23	Pins et al.	1996	HBSO	Chemo	DOD 1mo
24	Pins et al.	1996	HBSO	Chemo	DOD 5mo
25	Pins et al.	1996	LSO	RT	DOD 1mo
26	Balat et al.	2001	HBSO, PLND, I-O, Right Nephrectomy, Appendectomy	Chemo	DOD 24mo
27	Chien et al.	2005	HBSO, PLND, T-O, TD	Pac/Cis x 6	DOD 7mo
28	Amjad and Pal	2008	HBSO, TO, BR	Cis/Etoposide	AWD 1mo
29	Park et al.	2010	HBSO, PLND, PALND, T-O, Appendectomy	Pac/Platinum x5	ANED 90mo
30	Park et al.	2010	HBSO, PLND, PALND, T-O, Appendectomy	Pac/Platinum x3	AWD 9mo
31	Nakamura et al.	2014	RSO, LO	1st line: Pac/Car x2 2nd line: Irinotecan x6	ANED 18mo
32	Park and Bae	2014	HBSO, TD, BR	1st line: Pac/Car x6 2nd line: Top/Cis x3 3rd line: I/E x3	DOD 12mo
33	Sharma et al.	2015	HBSO, I-O. Removal of right parietal wall mass.	Cis + RT	DOD 2mo
34	Shrivastava et al.	2017	HBSO, TD, I-O, ileectomy.	Pac/Cis x7	DOD 12mo
35	Mimura et al.	2017	HBSO, PLND, PALND, O, BR	Pac/Car	ANED 7mo
36	Koufopoulos et al.	2018	HBSO	1st line: Pac/Cis x1 Pac/Car x5 2nd line: Gemcitabine x1	DOD 9mo

HBSO: hysterectomy and bilateral salpingo-oophorectomy, RSO: right salpingo-oophorectomy, LSO: left salpingo-oophorectomy, LO: left oophorectomy, UO: unilateral oophorectomy, BR: bowel resection, TD: tumor debulking, PLND: pelvic lymph node dissection, PALND: para-aortic lymph node dissection, I-O: infracolic omentectomy, T-O: total omentectomy, Pac: paclitaxel, Car: carboplatin, Cis: cisplatin, Cyc: cyclophosphamide, Top: topotecan, I/E: ifosfamide/etoposide, RT: radiotherapy, ANED: alive no evidence of disease, AWD: alive with disease, DOD: died of disease

tients with *in situ* and early invasive lesions didn't receive chemotherapy. In 3 cases with stage I disease radiotherapy was administered after surgical management [6,9,12]. Adjuvant radiotherapy was also administered in 3 patients with stage II, 2 patients with stage III and 1 patient with stage IV disease.

In cases where systemic therapy was specified, the most common therapeutic regimen used was combination of Platinum (either Cisplatin or Carboplatin) with Paclitaxel. Other cases involved the administration of Cyclophosphamide alone [12] or combined with Adriamycin and Cisplatin [10], Cisplatin with Etoposide [20] and Cisplatin alone [24]. One patient received second (Topotecan and Cisplatin) and subsequently third line (Etoposide and Ifosfamide) chemotherapy with poor results [23]. Excellent response to Irinotecan was observed in a patient showing disease progression while on first line regimen [22].

With a follow-up period ranging from 9 days to 90 months, 11 patients were alive with no evidence of disease, 3 were alive with metastatic disease and 17 died of disease. In the remaining 5 cases survival information was not provided. Overall survival varied between 9 days and 14 years, with a median value of 9 months. There was a clear association of survival with stage, with survival up to 12 months in stage III-IV disease. Survival time per stage was poorer compared to the classical ovarian carcinoma.

In our case, due to acute renal failure, there was a change in the administered adjuvant therapy from Paclitaxel and Cisplatin to Paclitaxel and Carboplatin. One month after the completion of the sixth cycle of the chemotherapy regimen there was evidence of progressive disease (enlarged right para-aortic lymph nodes, liver and peritoneal metastases) on computed tomography and positron emission tomography scan. As a result, second-line monotherapy with Gemcitabine was given. The patient was eventually admitted to the hospital due to acute lower abdominal pain and succumbed to disease, 9 months after initial diagnosis.

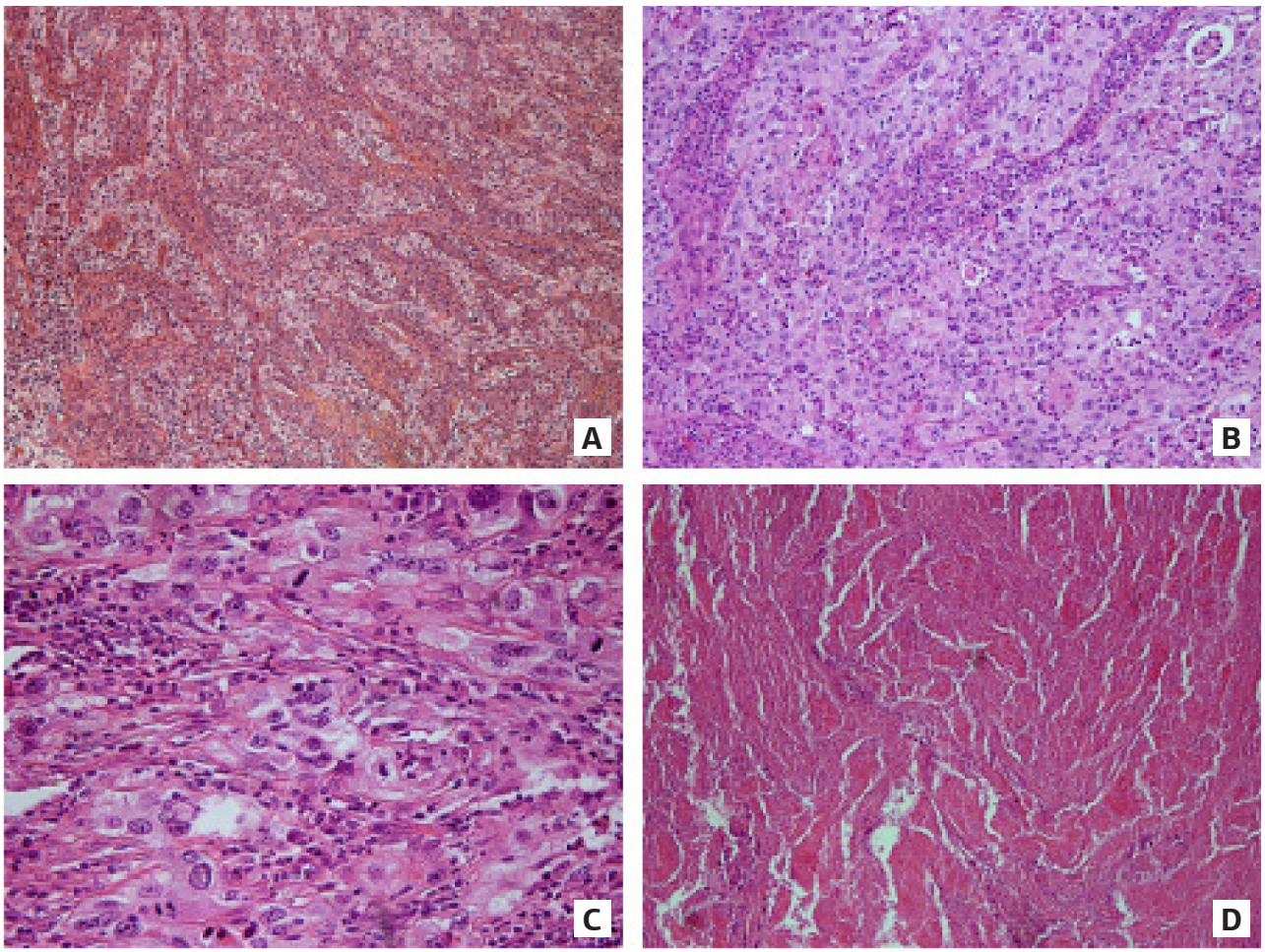

Figure 1. A: The ovary was extensively infiltrated by a malignant tumor composed of polygonal squamoid cells (HE x10 obj). **B:** Keratin pearls or individual cell keratinization were not observed (HE x20 obj). **C:** Tumor cells were pleomorphic, mitotic figures were numerous (HE x40 obj). **D:** Extensive necrosis was also present (HE x10 obj).

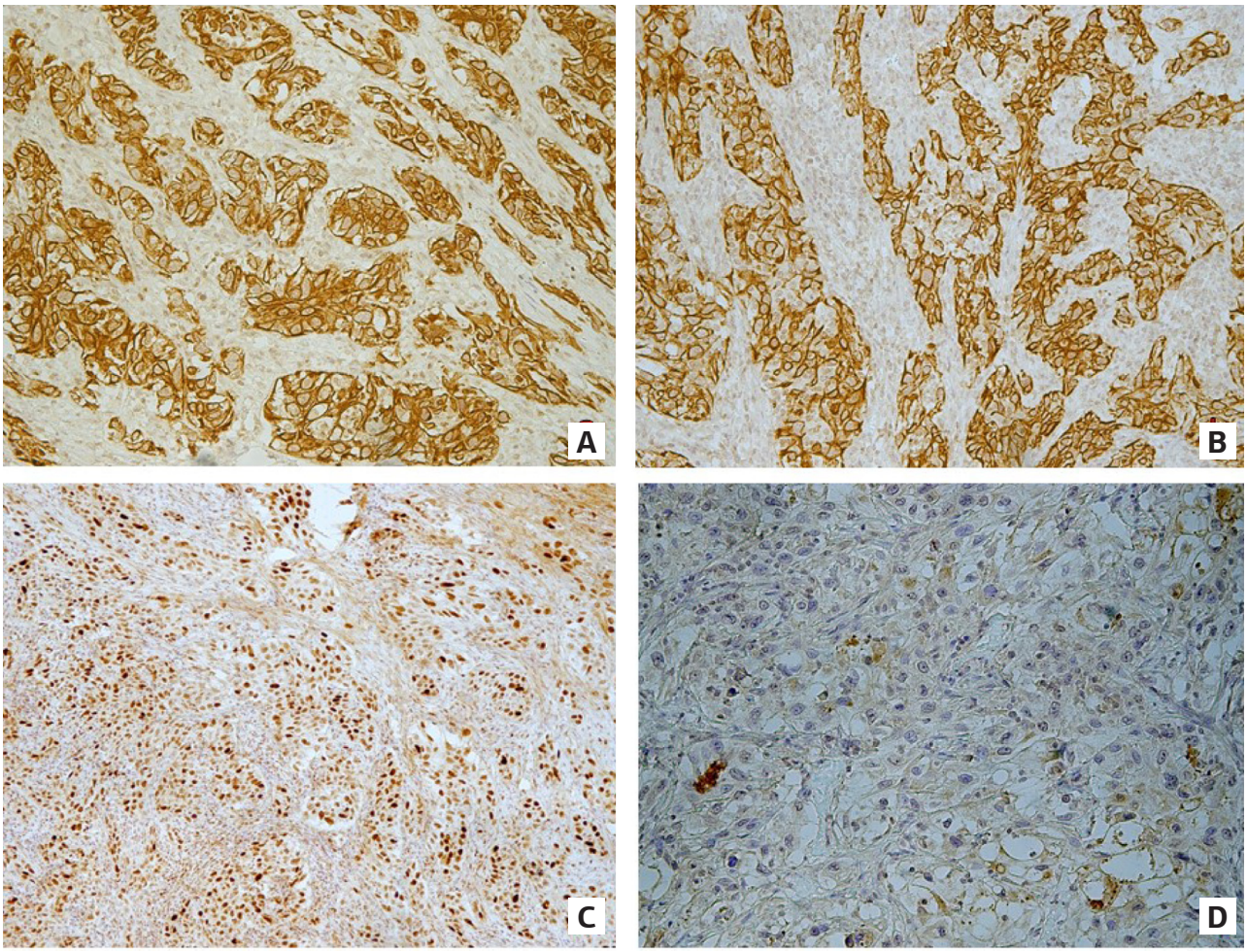

Figure 2. A: In our case tumor cells were positive for cytokeratin 7 (x 20 obj), **B:** cytokeratin 5 (x 20 obj) and **C:** P63 (x 10 obj). **D:** Staining for cytokeratin 20 was negative (x 20 obj).

Discussion

Ovarian carcinomas are the second most common malignant neoplasms of the female genital tract [1]. The histological types of primary ovarian carcinomas include high-grade serous (68–71%), clear cell (12–13%), endometrioid (9–11%), mixed (6%), low-grade serous (3–4%), mucinous (3%), transitional (1%) and SCC (<1%) [1,28].

In most cases primary SCC of the ovary arises from dermoid cysts [2]. The incidence of malignant transformation of dermoid cysts is 1-2% [29]. Less frequently, SCC are associated with Brenner's tumor [4] or endometriosis [3]. Pure or *de novo* primary SCC of ovary is extremely rare [17]. Because of lack of data and a deterministic association with a preexisting ovarian lesion, its histogenesis remains largely unclear [17].

Coelomic epithelium is capable of squamous differentiation and the rare epidermoid cysts of the ovary arise by metaplasia. Some authors suggest that primary ovarian SCC may represent its malignant counterpart [13,30].

The widely accepted explanation is the "field effect" of an oncogenic stimulus causing synchronous or metachronous neoplasia in histologically or embryologically similar tissues [7,10,14,15,17,21]. This theory would explain the presence of cervical intraepithelial lesions in about one third of the cases in the literature.

High risk human papilloma virus (HPV) infection has been suggested by several authors as the common oncogenic agent (stimulus) associated with ovarian SCC development [2,3,7,11,13-16,21].

HPV infection has been linked to the development of SCC of the uterine cervix [31], as well as carcinomas of the vagina [32], vulva [33], penis [34], anus [35], and oropharynx [36]. HPV has also been rarely detected by polymerase chain reaction and *in situ* hybridization (ISH) in breast carcinoma [37].

In one reported case HPV was detected in neoplastic lesions of the cervix (CIN III), vulva (VIN III) and in the left ovary (both *in situ* and invasive SCC) by ISH [16].

Other explanations mentioned in the literature regarding SCC histogenesis include contiguous spread of cervical intraepithelial lesion along the mucosal surface of the female genital tract [38] or undetected microinvasive, angioinvasive cervical SCC metastatic to the ovary [17].

Secondary ovarian involvement from other neoplasms is common. The incidence of secondary malignancies to the ovary ranges from 5 to 30%. The most common secondary neoplasms are of breast, intestinal and gastric origin [39]. Metastatic ovarian involvement by SCC is rare. In previous series its incidence ranged from 2.5 to 3.3% [40,41].

Primary ovarian SCC diagnosis may be challenging for pathologists. The differential diagnosis includes primary ovarian lesions with squamous differentiation such as SCC associated with mature cystic teratoma, endometriosis, endometrioid carcinoma with squamous differentiation, ovarian carcinosarcoma (malignant mixed mesodermal tumor) as well as metastasis from another organ or anatomical location.

Mature cystic teratoma elements (sebaceous material, hair, teeth, bone and adipose tissue) or endometriotic cysts will be easily identified by careful gross examination. Adequate tumor sampling is necessary.

In poorly differentiated carcinomas or when another primary focus is suspected immunohistochemistry will usually be needed.

Distinction of primary from secondary SCC may prove more complex. Morphology, as well as immunohistochemistry, is almost identical in SCC regardless of anatomic locations. Therefore, in order to rule out metastatic involvement, clinical examination and imaging of the upper gastrointestinal tract, thoracic cavity, head and neck, bladder and skin have to be performed.

The treatment of most patients (>75%) consists of hysterectomy and bilateral salpingo-oophorectomy (HBSO) with or without omentectomy. Retrospective data indicate that there might be a survival benefit from lymphadenectomy (mean survival of 59.2 months with lymphadenectomy versus 40.4 months without) [2].

However, the role and the type of adjuvant treatment is not well established, mainly due to the lack of prospective data and the small number of cases worldwide. In most centers, management is extrapolated from ovarian carcinoma treatment algorithms, despite the SCC histology. Close follow-up is suggested only for early stage IA disease, whereas stage IB, II-IV disease should be treated with adjuvant chemotherapy with or without radiotherapy. Few patients with stage II disease and excessively long survival period received adjuvant chemotherapy [16,29]. Limited experience indicates that platinum-based regimens combined with paclitaxel or with gemcitabine, may offer remarkable results especially for paclitaxel [42]. Efficiency of further treatment options, such as EGFR or VEGF inhibitors, can only be extrapolated from studies of SCC in other anatomical locations (cervical and head & neck), with case reports indicating that there might be a survival benefit [43].

Regarding radiotherapy and given that SCC is a radiosensitive tumor, whole-pelvis radiation and concurrent chemotherapy following aggressive cytoreduction have been shown to be of benefit for ovarian SCC arising from teratomas in some case series [44], with contrasting results in others [2].

In a multivariate analysis, only stage and optimal debulking were independent prognostic factors for survival and not the postoperative treatment [45]. In the two largest retrospective case series, there was no significant survival difference across stages II, III and IV and survival was poor, supporting the notion that once spread beyond the ovary has occurred, the prognosis is uniformly poor.

Despite occasional responses in patients with recurrent or metastatic disease, the outcome is poor in this setting regardless of the therapy.

Stage at the time of diagnosis is best correlated to prognosis, with stage I patients having a 5-year survival of 76%, but this drops drastically for advanced disease with 5-year survival of 34%, 21%, and 0% in stages II, III, and IV, respectively [43]. The prognosis of cases associated with endometriosis is relatively worse with a higher mortality rate of up to 80% within 6 months after diagnosis [46]. Generally, compared to other ovarian carcinomas, primary ovarian SCC prognosis is poorer [47].

Due to its rarity it is impossible to include primary ovarian SCC in randomized control trials. Therefore, optimal management of this entity is not well known [25]. Inclusion into basket trials and international collaborative trials may solve the rarity issue.

Conclusions

Primary SCC of the ovary is a rare tumor and few cases are reported in the literature. It remains controversial whether it should be managed like serous carcinoma of the ovary or SCC in general. Optimal debulking surgery is crucial in all stages and adjuvant chemotherapy seems to play an important role for stage II-IV disease. The role of adjuvant radiotherapy is not well established, whereas it is proposed by some authors given the

radiosensitivity of SCC. The response to chemotherapy in advanced disease has been variable in the limited number of cases. Its prognosis is best correlated with stage, histological grade and optimal debulking. Prognosis of SCC of the ovary seems poorer compared to classical serous histotype. Further studies specifically designed for this histotype involving international collaboration and long term follow-up are needed in order to define optimal treatment and prognosis.

Conflict of interests

The authors declare no conflict of interests.

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