Case Report

An aggressive rare entity - Pure (*de novo*) primary squamous cell carcinoma of ovary: Review of literature and a case report

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ABSTRACT

Ovarian cancers are commonly diagnosed gynecological malignancies worldwide. It ranks among the top ten diagnosed cancers and top five deadliest cancers in most countries. However, in spite of this squamous cell carcinoma (SCC) of the ovary is extremely rare. Here, we present a review of the literature along with a case of a 66-year-old postmenopausal female who presented with swelling, pain abdomen with constipation, and weight loss. She was diagnosed with pure (*de novo*) primary SCC of left ovary. No pre/co-existing ovarian lesion was identified. Despite external radiation and adjuvant chemotherapy, the patient died in 2 months.

Key words: *De novo*, ovary, pure primary, squamous cell carcinoma

INTRODUCTION

Ovarian squamous cell carcinoma (SCC) is a rare clinicopathological entity, accounting for <1% of all malignant tumors of the ovary.[1] Pure primary SCC have been classified by the World Health Organization criteria as surface epithelial-stromal tumors.[2] This entity is of importance as it not only mimics other gynecological malignancies creating a diagnostic dilemma but also presents an interesting insight into the histopathological variation that may be seen in epithelial malignancies of the ovary. Primary SCC ovary usually originates from malignant transformation of a benign cystic teratoma, Brenner tumor, or endometriosis. The *de novo* development of a primary SCC, in an otherwise healthy ovary without preexisting ovarian lesions is extremely rare.[3] Only 34 cases have been published till date in the world literature [Table 1]. Paucity of knowledge of this malignancy along with the lack of understanding about its genesis and treatment prompted us to present this case. The present case study describes a patient with pure (*de novo*) primary ovarian SCC, with emphasis on the role of epithelial mesenchymal transition (EMT) in the genesis of this tumor.

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CASE REPORT

A postmenopausal 66-year-old female presented with swelling and pain in the lower abdomen associated with constipation since 3 months. She had a history of weight loss with a decrease in appetite. There was no family history of breast, ovarian, colon cancer, or any other malignancy.

On general physical examination, she was anemic. Per abdominal examination revealed a firm to hard, mildly tender mass measuring 20 cm × 18 cm in size with restricted side to side mobility occupying the hypogastrium, and extending to right and left iliac fossa up to the umbilicus. There was no evidence of ascites or any organomegaly. Per speculum examination showed a healthy cervix and

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Table 1: Cases of pure (*de novo*) primary squamous cell carcinoma ovary reported in the literature

Case	Year	First author (references)	Age (years)	Site	FIGO stage/ grade	Treatment	Outcome/ follow-up (months)
1	1964	Black[19]	35	Left	I/1	TAH, BSO	NA
2	1974	Shingleton[20]	54	Right	I/1	RO, RT	Died, 6
3	1983	Macko[21]	90	B/L	I/2	UO	Alive, 30
4	1988	Chen[22]	49	Left	I/1	TAH, BSO, RT	Alive, 1
5	1988	Ben-Baruch[23]	65	Left	III/2	TAH, BSO, CT	Died, 6
6	1989	Yetman[24]	33	Left	I/2	TAH, BSO	Alive, 15.6
7	1989	Kashimura[25]	61		II/NR	TAH, BSO, RT, CT	Died, 9
8			42	Left	III/NR	LSO, RT	Died, 8
9			50		I/NR	TAH, BSO, RT	Alive, 14.4
10	1990	Radhi[26]	64	B/L	IV/2	TD	Died, 9 days
11	1993	McGrady[27]	53	Right	II/1	TAH, BSO	NA
12	1996	Pins[7]	73	NA	IIA/3	TAH, BSO, RT	Died, 49
13			61		IIB/3	TAH, BSO, RT, CT	Alive, 60
14			55		IIB/3	TAH, BSO, TD, CT	Alive, 30
15			38		IIC/3	TAH, BSO, CT	Died,8
16			64		B/2	RSO, LO	Alive, 60
17			55		IIIB/3	TAH, BSO, CT	Died, 2
18			52		IIIC/3	Ovarian, omental biopsy	NR
19			46		IIIC/3	Ovarian, omental biopsy	NR
20			27		IIIC/3	TAH, BSO, CT	Died, 1
21			70		IIIC/3	TAH, BSO, CT	Died, 5
22			73		IV/3	LSO, RT	Died,1
23	1996	Mai[28]	40	B/L	I/2	TAH, BSO	NR
24	1996	Khanfar[29]	14	Right	IV/3	SO, CT	Died, 6
25	2001	Balat[30]	40	B/L	IB/NR	TAH, BSO, PLND, AP, right nephrectomy, CT	Died, 24
26	2005	Chien[31]	63	NR	IV/3	TAH, BSO, PLND, TO, TD	Died, 7
27	2005	Todo[32]	56	Right	IIIC/3	TAH, BSO, PLND, sigmoidectomy, CT	Died,12
28	2008	Amjad[1]	31	Right	IIIC/1	TAH, BSO, TO, bowel resection, CT	Alive,3
29	2010	Park[3]	76	NA	IIC/1	TAH, BSO, PLND, PALND, TO, AP, CT	Alive, 42
30			48	NA	IV/2	TAH, BSO, PLND, PALND, TO, AP, CT	Alive, 6
31	2013	Shakuntala[33]	50	Left	IIC/2	TAH, BSO, PLND, RT, CT	Died, 6
32	2014	Nandedkar[4]	28	Left	IIB/3	TAH, LSO, CT	Died, 2
33	2014	P. Vidyadhara Rani[34]	45	B/L	NR/2	BO	NR
34	2015	Park[35]	46	Left	IVB/2	TAH, BSO, TD, bowel resection	Died, 12
35	2015	The present case	66	Left	IIIC/2	TAH, BSO, infracolic omentectomy, right parietal wall mass removal	Died, 2

FIGO: International Federation of Gynecology and Obstetrics, TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo-oophorectomy, RO: Right oophorectomy, RT: Radiation therapy, CT: Chemotherapy, UO: Unilateral oophorectomy, BO: Bilateral oophorectomy, PLND: Pelvic lymph node dissection, LSO: Left salpingo-oophorectomy, TD: Tumor debulking, RSO: Right salpingo-oophorectomy, LO: Left oophorectomy, TO: Total omentectomy, PALND: Para-aortic lymph node dissection, AP: Appendectomy, NR: Not recorded, NA: Not available

vagina. Bimanual pelvic examination revealed a mass of 18–20 weeks size with irregular margins, the uterus was not felt separately, a hard nodule of 4 cm × 2 cm was also felt in the pouch of douglas. On per rectal examination, the rectal mucosa was free. All other systemic examinations were within normal limits.

All the hematological investigations were unremarkable. Urine and blood cultures were negative. Kidney, liver function tests, and X-ray chest were normal. Serum antibodies to human immunodeficiency virus, hepatitis B surface antigen, syphillis were negative. Fractional curettage revealed atrophic endometrium with a normal cervix. Pap smear was performed which was negative for dysplasia or malignancy. Abdominal ultrasonography showed a left ovarian mass. An abdominal and pelvic contrast enhancement computed tomography scan demonstrated a complex cystic mass with solid component of variable densities occupying the lower abdomen arising from left ovary [Figure 1]. There was a right parietal wall mass involving the right abdominal wall which was continuous with the left ovarian mass. Ca-125 level was 49 U/ml.

On explorative laparotomy, a left ovarian mass of 12 cm × 10 cm in size was seen with implants on its surface, the capsule was ruptured, omentum, and bowel were adherent to it. Another 5 cm × 5 cm mass was seen in the right parietal wall with cecum and omentum adherent over it. A 4 cm × 2 cm mass was also felt in the pouch of douglas. Multiple small nodules were seen in the peritoneum, and the mesentry of the sigmoid colon. The right ovary had few deposits on its surface. The uterus was atrophic. No palpable para-aortic or pelvic nodes were identified. The tumor was clinically staged as International Federation of Gynecology and Obstetrics stage IIIC. A total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, and the removal of right parietal wall mass were performed. Postoperative period was uneventful.

Gross examination of the specimen received showed a solid cystic mass measuring 14 cm × 9 cm × 8 cm with the breech in the capsule at one place. On cut section, the tumor was partly solid partly cystic with clear fluid and no teratomatous components [Figure 2]. The right parietal wall mass measured 5 cm × 5 cm × 4 cm and on cut section was solid gray white. Histopathological examination of both the left ovarian mass and right parietal wall mass showed a moderately differentiated SCC. The uterus, cervix, right ovary, bilateral tubes, bilateral parametrii and omentum were unremarkable. Two lymph nodes recovered from omentum were free of tumor. On immunohistochemitry (IHC), tumor cells were positive for high molecular weight keratin, epithelial membrane antigen (EMA), p63 [Figure 3]. A final diagnosis of pure (*de novo*) primary SCC of the left ovary was made. In addition to these markers, EMT markers like E-cadherin, vimentin, and cytokeratin were also put, to predict if there was any role of EMT in this tumor biology. In our case, there was a loss of E-cadherin and cytokeratin expression by some tumor cells and patchy uptake of vimentin by many tumor cells [Figure 4]. Thus, suggesting that EMT is a component of this tumor.

Despite external radiotherapy and adjuvant chemotherapy with cisplatin, over a period of next 2 months, her condition deteriorated, and she died of respiratory complications.

DISCUSSION

Primary or metastatic SCC rarely arises from the ovary.[4] Till date about 34 cases have been published worldwide [Table 1]. The present case is 35th in the world literature and 4th in India and the Asian subcontinent. Its diagnosis is also quite elusive primarily because of the low incidence, low index of suspicion, incidental, and deceptive array of symptoms that are characteristic of more common other pathological entities.[1] Thus, its exact incidence, epidemiology, and geographic distribution is still unknown.

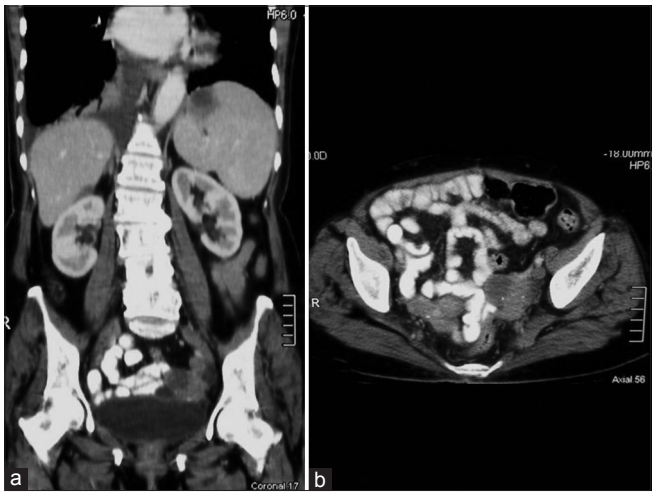

Figure 1: Contrast enhancement computed tomography abdomen (coronal and axial section) revealing a cystic, solid mass arising from left ovary (a and b)

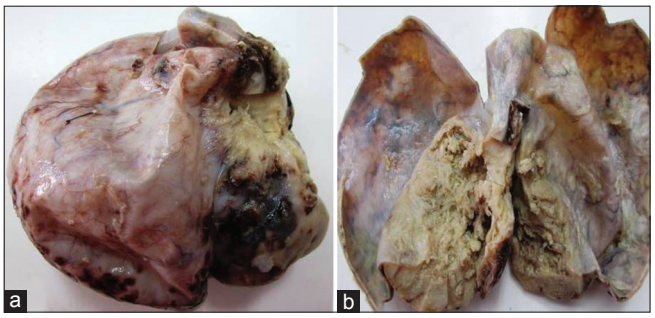

Figure 2: (a) Gross specimen of left ovarian mass with the breech in the capsule. (b) Cut section revealing solid and cystic components of the tumor

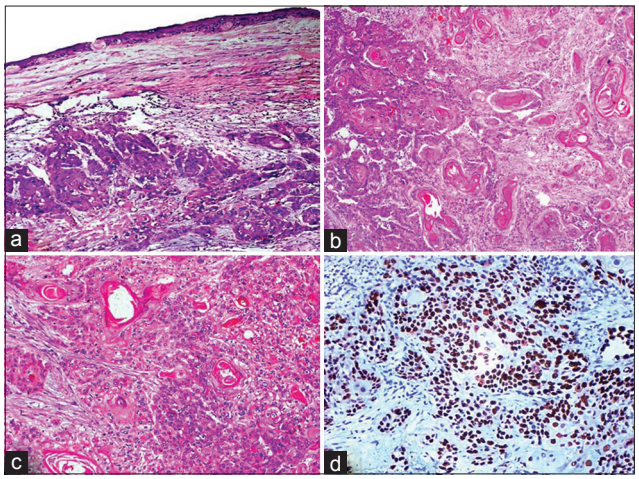

Figure 3: (a) Histopathology of the left ovary showing benign squamous epithelium and underlying malignant tumor cells (H and E, ×20). (b) Photomicrograph showing tumor cells infiltrating the stroma with keratin pearl formation (H and E, ×10). (c) Histopathology of right parietal wall metastatic mass showing tumor cells with keratinization (H and E, ×10). (d) p63 positivity by tumor cells (immunohistochemitry, ×20)

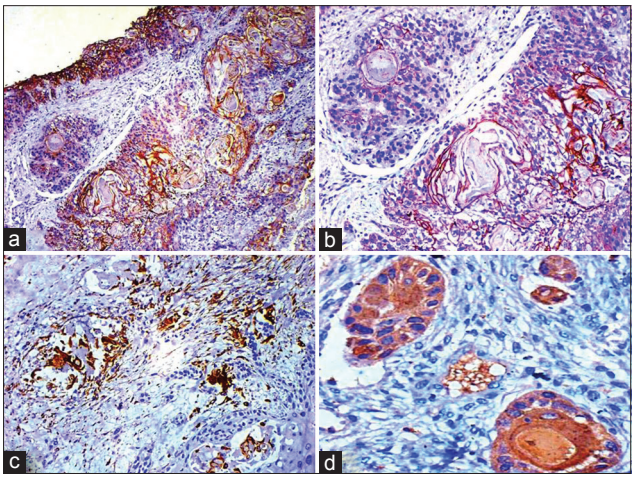

Figure 4: (a) Photomicrograph is showing loss of E-cadherin expression by the epithelial tumor cells (immunohistochemitry, ×10). (b) E-cadherin expression loss (immunohistochemitry, ×20). (c) Epithelial tumor cells are showing vimentin expression (immunohistochemitry, ×20). (d) Expression of cytokeratin lost by few epithelial tumor cells (immunohistochemitry, ×40)

In the present case, the patient's age, tumor size, signs, and symptoms overlapped amongst few entities creating a diagnostic dilemma. It was difficult to diagnose whether the SCC was arising *de novo* or was a malignant transformation of a mature cystic teratoma. The other rare differential diagnosis were also taken into consideration that is, the metastases from extra-ovarian squamous lesions especially cervix, or as part of a metaplastic process in an endometrioid adenocarcinoma or Brenner tumor.[5,6] However, in the present case the preoperative Pap smears and fractional curettage examination revealed no dysplasia or malignancy of the cervix and any other foci of SCC in the body was also ruled out.

Histopathologically, numerous sections were taken to locate the different elements of teratoma or any evidence of glandular or transitional differentiation microscopically. No evidence of teratoma, Brenner's tumor, or endometrioid carcinoma could be identified. However, after extensive sampling, a benign squamous epithelium could be identified. Yet, no transformation of this benign squamous epithelium to malignant squamous epithelium could be seen in any place. Whether this benign squamous epithelium was one of the elements of teratoma was difficult to comment upon since other germ cell components were not seen. Thus, we designated this case as pure (*de novo*) primary SCC of the ovary. The benign squamous epithelium seen might be the metaplastic coelomic epithelium. Some authors have also suggested that SCC of the ovary might have arisen as a result of seeding from occult pre or fully malignant squamous lesions in other locations.[7] On extensive search in our case, the primary was detected in the left ovary, and similar search failed to find any suspicious focus such as severe dysplasia or *in situ* change or any foci of malignancies.

The level of Ca-125 and radiological workup was of limited significance in our case which was similar to the reports by other authors.[7,8] Histopathology remains the gold standard in the diagnosis of SCC. These tumors are usually high grade and show a variety of patterns including papillary or polypoid, cystic, insular, diffusely infiltrative, verruciform or sarcomatoid. They are known to express "pseudogland" formation and are often poorly differentiated, requiring ancillary IHC or electron microscopic studies to confirm the diagnosis.[2,9] Though in the present case IHC was performed, the morphological picture was classical and unambiguous. Immunohistochemically, the tumor was positive for high molecular weight keratin, EMA, p63.

Recently, the role of EMT in tumor progression and metastasis is being debated by many researchers.[10,11] Ovarian cancers have this unique ability to co-express epithelial and mesenchymal determinants. Cells undergoing EMT lose their epithelial morphology, reorganize their cytoskeleton and acquire a motile phenotype through the up and down regulation of several molecules including tight and adherent junctions proteins (E-cadherin), and mesenchymal markers (vimentin) leading to reduced cell adhesiveness, increased cell motility, and invasiveness.[12] However, these changes do not fully occur in ovarian carcinoma and are even reversed in tumor cells present in malignant peritoneal and pleural effusions.[11] Carcinoma cells in primary tumor lose cell-cell adhesion mediated by E-cadherin repression and break through the basement membrane with increased invasive properties and enter the bloodstream through intravasation. Later, when these circulating tumor cells exit the bloodstream to form micrometastases, they undergo reverse differentiation to mesenchymal epithelial transition (MET) for clonal outgrowth at the metastatic sites.[12] Thus, EMT and MET form an integral part of the tumor biology which is not yet fully understood.[13]

The occurrence of an altered E-cadherin expression has been correlated with low histological differentiation, increased the risk of local invasion and metastatic disease as well as poor prognosis.[14] Whereas high expression of vimentin is seen as an indicator of an advanced disease with a poorer prognosis.[15]] In our case, immunohistochemically, E-cadherin and cytokeratin expression was lost in some tumor cells whereas vimentin expression increased in many tumor cells. Thus, suggesting that EMT plays a vital role in the genesis of this tumor.

EMT has also been found to be involved in acquiring drug resistance. The gain of EMT markers was associated with the resistance of ovarian carcinoma epithelial cell lines to paclitaxel.[16] Thus, EMT not only enables cells, the migratory phenotype but also acts on multiple immunosuppression, drug resistance, evasion of apoptosis, thus showing an altered response of the host to the tumor.

The optimal management approach and standard effective treatment for *de novo* ovarian SCC have not been well established. The literature shows that the patients with *de novo* ovarian SCC have a very poor survival outcome, despite a combination of surgery, radiotherapy, and chemotherapy.[3] Surgical cytoreduction and use of adjuvant therapy (cisplatin and alkylating drugs) for these cases is similar to the other epithelial ovarian tumor, though there role and effectiveness is more doubtful and challenging in this malignancy as compared to other ovarian malignancies.[17] Some authors have also mentioned the use of radiotherapy as SCC is a radiosensitive tumor. However, it still remains unclear whether these patients would be benefited from it.[6] The present case also expired within 2 months, even after optimal cytoreduction, adjuvant chemotherapy, and external radiation. In ovarian cancers, EMT is induced by transforming growth factor-beta, epidermal growth factor, hepatocyte growth

factor, and endothelin-1. Alterations in these cellular pathways candidate them as a useful target for ovarian cancer treatment which can be used as future therapy in this tumor also.[18]

EMT property of this tumor has never been reported so far in the previous cases of pure (*de novo*) primary ovarian SCC, hence our case is an important contribution to the updated knowledge of this malignancy.

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Conflicts of interest
There are no conflicts of interest.

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