Section: Gynaecological Oncology

Case Series

LOW GRADE SEROUS CARCINOMA OF OVARY: A CASE SERIES

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ABSTRACT

Background: Serous ovarian cancer of low grade histology (LGSOC) is a rare ovarian cancer which differs from High grade serous carcinoma (HGSC) in epidemiology, pathogenesis, presentation and prognosis. Due to its rare incidence, LGSOC has been understudied, prompting this retrospective review. The aim is to contribute to the limited pool of data on this histologic subtype by describing the clinico-radiological features, management strategies, and survival outcomes of cases treated at a single cancer care centre.

Materials and Methods: This was a retrospective observation study of histologically proven low grade serous ovarian cancers which had undergone surgery during the five-year study period. Hospital records were reviewed to find the demographics, clinical features, tumor characteristics, pathological findings, surgical data, FIGO stage, adjuvant treatment, and survival data of the patients.

Results: Only seven cases of LGSOC underwent surgery during the period of study. The mean age of presentation was 51.7 years. 5 cases presented in early stage (FIGO stage IA, IB) and only 2 in advanced stage (FIGO stage IIIB, IVB). Early stage cases underwent primary debulking surgery while 2 advanced cases received chemotherapy (NACT) followed by debulking surgery. 30 months was the median follow-up duration. To date, all patients were alive and only one had recurrence at 25 months post primary treatment. The mean progression free survival (PFS) of the patients was 31.85 months.

Conclusion: Optimal debulking surgery aimed at eradicating residual disease appears to be a contributing factor to improve outcome in cases of LGSOC. Given the limited response of these tumors to chemotherapy, it is imperative to explore targeted treatment approaches alongside surgery.

Keywords: Low grade serous ovarian cancer (LGSOC), High grade serous cancer (HGSC), Progression free survival (PFS), Debulking surgery.

INTRODUCTION

Ovarian cancer encompasses a range of histologic subtypes, determined by the origin of the cells. Low-grade serous ovarian cancer is a rare histological type and constitutes about 2% of all epithelial ovarian carcinomas.[1] Earlier, LGSOC were considered to be a part of high grade serous carcinoma (HGSC) but now it is considered as a distinct subtype of serous epithelial ovarian cancer. Low grade serous cancers differ from HGSC in pathogenesis, epidemiology, presentation and prognosis.[2]

Low-grade serous carcinoma typically exhibits a slow-progressing clinical course and occurs at a younger age as compared to high grade serous carcinomas. LGSOC can develop spontaneously or as a result of a prior diagnosis of a serous borderline

tumor1. The clinical manifestation of LGSOC closely resembles that of HGSOC, featuring symptoms such as abdominal pain, distension, and bowel or bladder dysfunction. Radiologically LGSOCs typically manifest as multilocular cysts containing solid components or papillary projections, frequently accompanied by extensive calcification.[3]

Pathologically, in LGSOC there is mild to moderate nuclear atypia (up to 12 mitoses per 10 high power fields), low proliferative activity and these tumors lack nuclear pleomorphism which is commonly present in HGSOC.[4] Low-grade serous ovarian carcinoma (LGSOC) often harbours activating mutations in genes linked to the mitogen-activated protein kinase (MAPK) pathway. It is defined by the presence of KRAS and BRAF mutations, while the lack of p53 serves as a distinguishing characteristic from high-grade serous carcinoma.[5] ER and PR expression is relatively higher in LGSOC, thus endocrine therapy can be considered as an adjunctive treatment option.[6] Patients with LGSOC who demonstrate positive estrogen receptor (ER) and progesterone receptor (PR) statuses typically have a more favourable prognosis than those with negative receptor statuses.

Surgery is the treatment of choice in cases of LGSOC and optimal cytoreductive surgery should be done even in advanced stage disease. If the tumor is unresectable or the ECOG performance status of the patient is poor, neoadjuvant chemotherapy followed by interval debulking surgery may be considered after histological confirmation of disease. However, low-grade serous cancers are generally regarded as relatively resistant to chemotherapy compared to high-grade serous cancers.[7]

As low-grade serous carcinoma has received limited research attention owing to its infrequent occurrence, this retrospective review aimed to contribute to the scarce data available on this uncommon histologic subtype by delineating the clinic-radiological features, management strategies, and survival outcomes of seven cases of LGSC at a state level cancer care hospital.

MATERIAL AND METHODS

The study was a retrospective observation case study which was done after approval from institute ethical committee. A review of hospital records were made to find the data of low grade serous ovarian cancer patients treated from 2019-2023. The demographics, clinical features, tumor characteristics, pathological findings, surgical data, stage of the disease, adjuvant treatment, and survival data were collected from the hospital records. Overall survival (OS) and progression-free survival (PFS) of patients were also measured. Overall survival was calculated from the time of primary treatment (surgery or neoadjuvant chemotherapy) or date of tissue diagnosis to the last contact date or death from any cause. Progression-free survival was determined from the time of initial treatment or date of tissue diagnosis until the occurrence of disease progression or recurrence, or until the last contact date or death attributable to ovarian cancer. Kaplan Meier survival curve was drawn. Descriptive data were collected and analysed.

RESULTS

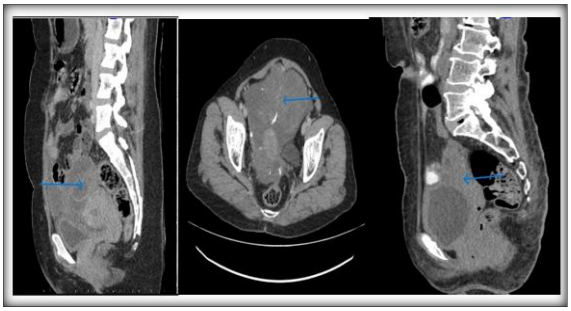

Figure 1: CECT image of the cases. (A): Sagittal view showing heterogeneous solid-cystic adnexal mass. (B): Heterogeneously enhancing hypodense bilateral adnexal lesion containing both solid and cystic components with areas of calcification and mild ascites. (C): Sagittal section showing solid & cystic adnexal mass with ascites

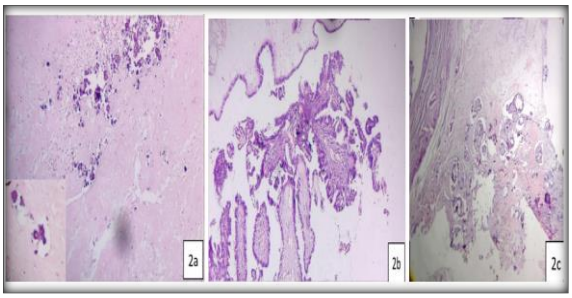

Figure 2 (a): Microphotograph showing concentric calcium containing lamellated bodies (Psammoma bodies). Inset showing the same. (H&E; 40X)
2(b): Microphotograph showing papillary configuration with fibrovascular core. (H&E; 10X)
2(c): Microphotograph showing tumor deposit with areas of myxoid degeneration. (H&E; 40X)

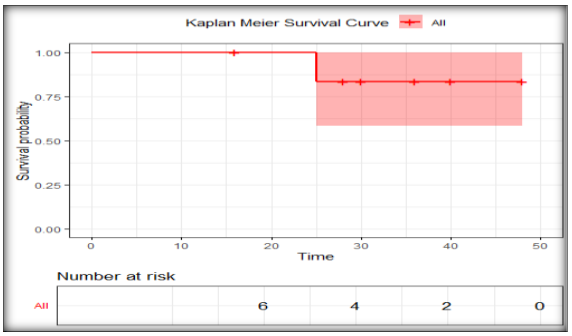

Figure 3: Showing Kaplan Meier survival curve. The curve is horizontal line at 1 (100% progression-free) until the first recurrence (25 months). Then, it drops to 6/7 (around 85.7%) at 25 months, indicating one patient experienced recurrence. It remains persistent up to 48 months

A total of 7 cases of histologically proven LGSOC patients who had undergone surgery were identified and analysed.

Clinical characteristics

The patients' age ranged from 38-70years with mean age being 51.7 years (standard deviation of 13.9). 57.1% patients were menopausal female. The predominant presenting symptom was abdominal pain, present in 5 out of 7 cases (71.4%). (Table1)

All patients had raised CA-125 (mean 2797.9 U/ml; range 59.8 U/ml to 8,632 U/ml) and 5 patients also had raised levels of HE4 (range 298 to 1407). One patient was a follow up case of carcinoma rectum operated and received adjuvant chemotherapy 6 years back. She has raised CA-125 as well as her CEA was also raised (8.4ng/ml). (Table 2). Post-treatment CA-125 ranged from 15-42.3U/ml. [Table 3]

Imaging features

All 7 patients had undergone CECT of abdomen and pelvis during evaluation. In 4 out of 7 patients (57.1%) the tumor was bilateral. The tumor diameter ranged from 4.1 cm to 16.8 cm with mean diameter being 11.8 cm (SD 4.5cm). In majority of the cases the masses were solid-cystic. Ascites was present in 4 cases and lymphadenopathy in 3 cases out of 7. [Table 2]

Management and follow-up

FIGO 2014 staging was used to stage the cancer. Out of 7 cases 5 presented in early stage (IA, IB) and only 2 (28.5%) were advanced stage disease (IIIB, IVB). The two advanced cases underwent three cycles of neoadjuvant chemotherapy using carboplatin and paclitaxel, followed by debulking surgery. 5 (71.4%) patients underwent complete staging and optimal cytoreduction was achieved in all cases. None of the patients with lymph node dissections were found to have positive nodal disease. The two advanced stage patients also received adjuvant chemotherapy with carboplatin and paclitaxel followed by maintenance therapy with bevacizumab. All patients showed no signs of disease at the completion of primary treatment. The mean CA-125 level at first follow-up after surgery was 28.7 U/ml (range 15-42.3U/ml). [Table 3]

To date, all 7 patients are alive with 6 patients (85.7%) having no evidence of disease. The median duration of follow-up of the cases was 30 months (mean 32.14 months; range 16-48months). One patient, who presented as FIGO stage IVB carcinoma had recurrence at 25months. Her disease continued to progress despite on maintenance therapy of bevacizumab, the recurrence was locoregional, limited to the pelvis and she was planned for secondary cytoreductive surgery. The mean progression free survival (PFS) of the patients was 31.85 months. [Table 3] Kaplan Meier survival curve was calculated based on progression free survival. However, the survival data had limitations of small sample size (7) which can lead to a less reliable estimate and also single recurrence limits the curve's informativeness. [Figure 3]

Table 1: Demographic and clinical characteristics of the seven cases of LGSOC

Case	Age (years)	Menopausal status	Parity	Presenting complaint (duration in months)	Tumor marker (Pretreatment)
1	38	Premenopausal	P3L3A2	Pain abdomen (6months)	CA-125- 306
2	59	Menopausal	P4L3	Pain abdomen, vomiting and distension(5months)	CA-125- 4312 HE4-597
3	45	Menopausal	P5L5	Abdominal distension, loss of appetite(8months)	CA-125- 8,632 HE4-1407
4	36	Premenopausal	P2L2	Pain abdomen, decreased appetite (6months)	CA-125- 59.8 CEA- 8.4
5	68	Menopausal	P4L4A1	Abdominal distension, weight loss (6months)	CA-125- 819 HE4-298
6	46	Perimemopausal	P5L5	Pain abdomen (3months)	CA-125- 1232 HE4-533
7	70	Menopausal	P1L1	Pain abdomen (2months)	CA-125- 4225 HE4-449

Table 2: Radiological features of the cases

Cases	CECT		
	Laterality	Size (cm)	Additional features
1	Bilateral	5.8*4.1® 5.4*6.5(L)	Solid, no ascites, no LN
2	Bilateral	13*10(L) 8.7*8.3®	Solid -cystic, mild ascites, LN (paraaortic), peritoneal nodules, bowel serosal & mesentric deposits
3	Unilateral	10.5*9.8 (L)	Solid, moderate ascites, LNs (pelvic & paraaortic), liver deposit
4	Bilateral	20*11 (L) 8.5*9®	Solid -cystic, no ascites, no LN
5	Bilateral	13*12.2® 7.4*8.6 (L)	Solid -cystic, mild ascites, LN (Paraaortic)
6	Unilateral	14.8*13 (L)	Solid, mild ascites, no LN
7	Unilateral	16.8*15 (R)	Solid -cystic, no ascites, no LN

L- Left, R- Right, LN- Lymphnode

Table 3: Management and follow-up of cases

Case	NACT	Surgery	FIGO stage
1	×	Complete staging	IB
2	3cycles (C+P)	Debulking suegery	IIIB
3	3 cycles (C+P)	Debulking suegery	IVB
4	×	Complete staging	IB

5	×	Complete staging	IB
6	×	Complete staging	IA
7	×	Complete staging	IA

Complete staging-peritoneal washing, hysterectomy, bilateral salpinoophrectomy, total omentectomy, pelvic and paraaortic lymphadenectomy and peritoneal biopsy.
Debulking surgery- hysterectomy, bilateral salpinoophrectomy, total omentectomy, pelvic and paraaortic lymphadenectomy
C+P- Carboplatin & Paclitaxel

DISCUSSION

Low grade serous ovarian cancers are unusual distinct neoplasm that belong to the category of serous epithelial ovarian cancers. Patients diagnosed with LGSOC typically present at a younger age compared to those with HGSC. Age at diagnosis did not independently predict progression or death in LGSOC. Patients of LGSOC have a median age of presentation ranging from 41.7 to 55.5 years 8. In the current cohort also the mean age of the patients of LGSOC was 51.7 years.

The clinical signs and symptoms observed in patients with low-grade serous ovarian carcinoma closely resemble those commonly caused by other ovarian malignancies. In the current study, most common symptom reported was abdominal pain (71.4%), followed by abdominal distension (42.8%). According to the literature, approximately 90% of patients diagnosed with LGSOC typically present at advance stage of the disease (FIGO stage II to IV).[9,10] However, the majority of patients (71.4%) in the current case series were found to have early-stage disease. This unexpected finding could be due to the small number of cases analyzed in the current study.

In the present study, serum levels of CA-125 were elevated in all cases at initial presentation, and the mean value of CA-125 was 2797.9 U/ml. However, following surgery, the CA-125 level reduced significantly and the post-treatment mean CA-125 was 28.7 U/ml. A study investigating the prognostic significance of pre- and post-treatment CA-125 in grade 1 serous ovarian carcinoma found that pretreatment CA-125 levels were significantly lower in LGSOC compared to those with high-grade disease. The study concluded that post-treatment CA-125 levels are predictive of disease outcome.[11] Another multicenter study supported this finding, indicating that elevated CA-125 levels (≥35 U/mL) after completion of primary treatment serve as an independent prognostic marker and is associated with poor progression-free survival (PFS) in LGSOC.[12]

Imaging can offer valuable insights to aid in the preoperative differentiation of LGSOC from other ovarian tumors. LGSOC typically presents as mixed lesions characterized by variable papillary projections and solid components, often in distinct proportions compared to HGSC, calcifications are frequently seen in these lesions, however necrosis is a rare finding 2. As contrast-enhanced CT remains the preferred imaging modality for evaluating metastatic ovarian disease, offering high diagnostic accuracy, up to 89%, in detecting lymphadenopathies and peritoneal metastases, it was performed in all cases at initial evaluation in the current study.[13] In the present case series, in 57.1% cases the lesion was appeared heterogenous with solid-cystic component on imaging.

On histopathological examination the LGSOC exhibits cuboidal or low columnar cells with mild to moderate atypia and lack of nuclear pleomorphism. Mixed architectural patterns like micropapillary, elongated papillae, medium-sized papillae, macro-papillae, cell clusters, and single cells are commonly seen in these tumors. Absence of necrosis and presence of psammoma bodies are typical findings 13. IHC examination of the histopathological slides of LGSOC typically show diffuse positivity for CK7, PAX8, ER, and WT1, while p16 expression tends to be patchy. Unlike HGSCs, LGSOCs demonstrate a wild-type p53 expression pattern.[14]

The primary treatment strategy for low-grade serous ovarian carcinomas (LGSOCs), similar to other types of epithelial ovarian carcinomas is surgical debulking. The surgical approach is favoured as LGSOC demonstrates relatively high chemo-resistance.[15] Literature suggests that the disease burden upon completion of primary treatment is a crucial factor in determining the disease outcome 16. A subgroup analysis of GOG-182 study also demonstrated that women with LGSOC who had underwent suboptimal cytoreduction (residual disease >1 cm) have worse outcome 17. In our case series, all patients achieved disease-free status following surgery, contributing to their improved progression-free survival (PFS) outcomes. In the current study, all patients (100%) were alive after a mean follow-up period of 32.14 months. The literature shows that the most of the women with LGSOC have a favourable prognosis, with a 5-year overall survival of about 62-85%.[4,10,18] Although low-grade serous carcinoma demonstrates better survival outcomes, in over 70% of LGSOC, the disease ultimately recurs and patient dies of the disease.[5]

Presently, chemotherapy comprising a combination of platinum and taxane, with or without bevacizumab, is administered to most of the histological types of advanced epithelial ovarian cancer including advance stage low grade serous ovarian cancers. In the current study also the two advanced stage diseases received platinum and taxane combination chemotherapy along with bevacizumab, despite one patient presented with

recurrence. Research indicates that LGSOC demonstrates considerable resistance to platinum-taxane-based chemotherapy, leading to decreased efficacy of chemotherapy in treating the disease.[4] As LGSOC exhibits ER, PR receptors as well as genetic mutations (KRAS/ BRAF), targeted therapies may be offered to these tumors.

CONCLUSION

Despite the limitation of a small patient cohort in our series, a notably promising median progression-free survival of 30 months for the entire group was observed. Optimal debulking surgery aimed at eradicating residual disease appears to be a contributing factor to improved outcome in cases of low grade serous ovarian cancers. Given the limited response of these tumors to chemotherapy, it is imperative to explore novel targeted treatment approaches alongside surgery.

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