Understanding the behavior of a low-grade serous carcinoma

Lee Saw Joo, Engku Husna Engku Ismail, Mohd Pazudin Ismail, Nik Mohd Zaki Nik Mahmood, Wan Fadhлина Wan Adnan, Hoo Pek Sung

ABSTRACT

Low-grade serous carcinoma (LGSC) of ovary represents 10% of all serous carcinoma of ovary and up to 7% of total ovarian malignancy. Low-grade serous carcinoma being less common, hence have not been well studied. Here, we report a case of LGSC in a 22-year-old young woman in which her clinical presentation and her intraoperative findings were not in-line with her final histopathological diagnosis. Management of this patient has been challenging not only because of her young age, but also because LGSCs were found to be relatively chemoresistant as compared to its high-grade counterpart, however to date, there are no other more effective therapies with robust evidence. Nevertheless, reports on treatment with primary cytoreductive surgery followed by adjuvant hormonal therapy has shown promising results.

Keywords: Epithelial ovarian cancer, LGSC treatment option, Ovarian low-grade serous carcinoma, Type 1 and Type 2 epithelial ovarian carcinoma

INTRODUCTION

Serous adenocarcinoma of the ovary is the most common and lethal type of Epithelial Ovarian Carcinoma, comprising up to 68% [1]. Traditionally, ovarian serous carcinoma had been graded as—well, moderately and poorly differentiated, also known as Silverberg's Grade [2]; based on the architecture (glandulary, papillary, or solid sheets), degree of nuclear atypia, and mitotic index. Recently, a two-tier system in which tumors are simply subdivided into low grade and high grade was introduced by Malpica et al. in 2004 [3]. Many studies done by various centers all over the world have shown that the two-tier system is easy to apply, reproducible, and based on underlying molecular biologic differences between low-grade serous carcinoma (LGSC) and high-grade serous carcinoma (HGSC) [3–5]. In these studies, apart from the differences at the molecular level and pathogenesis, LGSC and HGSC have clear differences in terms of epidemiology, clinical presentation, and treatment response as well as patients survival outcome.

Here, we report a case of LGSC of ovary which only represents 10% of all serous carcinoma of ovary [6]. Upon
presentation, the huge tumor volume shows clinically and radiologically along with intraoperative findings of widely disseminated and infiltrative disease, one would think the patient would be having a carcinoma or sarcoma of high-grade type. The histopathological report comeback was beyond our clinical suspicion. Even though the advanced stage of presentation of her cancer can be attributed by the nature of a slow growing low-grade tumor, but the aggressive infiltrative disease found intraoperatively has made it worthwhile for our discussion. Furthermore, in view of her young age and the fact that LGSC is relatively chemoresistant, it was a challenge in treating her malignancy while trying to find a small possibility of preserving her fertility.

**CASE REPORT**

We have a 22-year-old Malay woman, a chemical engineering student, with no previous medical illness. She presented with progressively growing abdominal mass over two years duration. It was told to be initially confined to suprapubic region and gradually grew till occupying her whole abdomen. It had later caused her to have abdominal discomfort and urinary symptoms. She then began to have loss of appetite and weight about one month prior to presentation. Further questioning revealed history of on and off fever for the past three years, however denied abnormal per-vaginal discharge or high risk behavior. Infective disease workouts done previously were unremarkable. Her menstrual and childhood history were unremarkable.

Patient was an obese woman with body mass index (BMI) 35 kg/m² (Class II) with a normal vital signs, not septic. Cardiovascular, lung, breasts examinations were unremarkable. Her abdomen was grossly distended with a mass arising from pelvic region, extending toward xiphisternum mass was firm, tender, irregular, and fixed. Per rectal examination revealed extra-luminal mass felt anteriorly occupying whole Pouch of Douglas, fixed, and tender on pressure.

Trans-abdominal scan showed a huge right abdominopelvic mass, multiloculated measuring 20×15 cm, with mixed solid and cystic echogenicity with another smaller left sided mass of similar echogenicity. Uterus was not identified. Tumor markers showed only elevated CA 125 of 376 IU. Otherwise, other markers were within normal range. On computed tomography (CT) scan imaging (Figure 1), there was a huge heterogeneously enhanced solid mass with cystic component in arising from the right side of pelvis measuring 13.3 cm×16.4 cm×11.9 cm extending extending toward the liver. In the pelvis, another smaller heterogenous enhancing solid cystic mass presents. The uterus was embedded within these mass and obliterated. These lesions have poor plane with each other and no clear plane with the uterus, bladder, and anterior abdominal wall. No radiological evidence of ascites is found. There were multiple sub-centimeter para-aortic/paracaval lymphadenopathy. Mild right hydrourater, due to tumoral compression. Overall impression was in keeping with bilateral aggressive ovarian mass with local infiltration and nodal metastasis. No distant metastasis.

She was subjected to an exploratory laparotomy and debulking surgery. Intraoperatively, there was a huge omental cake upon entering the abdomen measuring 15×15 cm extending downward and adhered to the urinary bladder and uterus. The huge right ovarian tumor was solid-cystic sized 30×15 cm extending to right lobe of liver, with 800 cc of tumor necrotic pus content drained. Left side of pelvis was frozen pelvis with the left ovarian tumor densely infiltrated into the rectosigmoid colon posterior-laterally, and an enlarged uterus (equivalent of 16–18 weeks size gravid uterus) was seen infiltrating onto the urinary bladder anteriorly. There was also tumor seedling over the bowels which was excised. Only right salpingo-oophorectomy and omentectomy were done at that setting as a complete debulking surgery was not possible without causing morbidity to the bowels and urinary bladder. Liver and other solid organ were noted to be normal intraoperatively. Based on radiological and intraoperative findings, a clinical diagnosis of high grade bilateral ovarian tumor surgically International Federation of Gynecology and Obstetrics (FIGO) stage 3C with the differential diagnosis of possible carcinosarcoma had been made postoperatively.

Histopathological report of right ovarian tumor and omental cake was suggestive of primary LGSC of ovary which showed malignant epithelial tumor forming hierarchical branching pattern characterized by irregular papillae and also micropapillae formations (Figure 2). The individual malignant cells exhibit mild to moderate nuclear pleomorphism, vesicular nuclei, prominent nucleoli and were also seen invading into the stroma. Mitoses was 7 in 10 high power field. Psammoma bodies are frequently seen. The surrounding stroma appears

[Figure 1: CT-scan imaging illustrating complex abdominopelvic tumor mass of this patient.]
Further studies into BRCA 1 and 2 gene mutations had established that these genes are responsible for the development of ovarian cancer. In 1994, the scientists of National Institutes of Health, United States in patients with breast cancer. They identified the presence of BRCA gene mutations in a significant number of patients with breast cancer, which has led to a better understanding of the pathogenesis of ovarian cancer.

Postmenopausal age women and infertile women treated with gonadotropin. The theory of “incessant ovulation” being the mechanism of ovarian malignant transformation. This theory partly explained the higher incidence of ovarian malignancy in the postmenopausal age women and infertile women treated with gonadotropin.

Welch [8, 9] introduced the “gonadotropin theory,” postulating overstimulation of ovarian gonadotropin receptors by the gonadotropins (follicular stimulating hormone and luteinizing hormone) causing ovarian malignant transformation. This theory partly explained the higher incidence of ovarian malignancy in the postmenopausal age women and infertile women treated with gonadotropin.

Major evolution came after the discovery of BRCA gene mutation in 1995 by the scientists of National Institutes of Health, United States in patients with breast cancer. Further studies into BRCA 1 and 2 gene mutations had demonstrated the carrier of these gene mutations were not only at higher risk of getting breast cancer, they too have increased risks of having HGSC of ovaries, fallopian tubes, and peritoneal carcinomas [10–12]. However, BRCA gene mutations were not able to explain the occurrence of smaller percentage of patients with LGSC of ovaries which have been suggested to have a closer relationship with its borderline counterpart (Borderline Serous Ovarian Tumour) [13].

Type 1 and Type 2 ovarian tumorigenesis pathway was first proposed by Shih I and Kurman RJ in 2004 following extensive morphological and molecular genetic analysis [14, 15]. Based on this proposed model, all epithelial ovarian tumors were categorized into two main groups based on the two main pathways of tumorigenesis. Type 1 tumors are of the low grade neoplasm which arise in a stepwise manner from adenomas to borderline tumors to low-grade carcinomas. While Type 2 tumors are of high grade neoplasms which developed de novo without precursor lesion identified.

Generally, patients with Type 1 tumors (low grade serous, mucinous, endometrioid, malignant Brenner tumour, and clear cell carcinomas) usually demonstrate BRAF and KRAS molecular genetic mutations, take on a slow clinical course, and have better prognosis. On the other hand, patients with Type 2 tumors (high grade serous, endometrioid, clear cell, undifferentiated, and carcinosarcomas) were shown to have frequent p53 genetic mutation, progress rapidly with poor outcome [15].

Narrowing down to LGSC, patients typically present at the earlier age (mean age of 55.5 years) as compared to patients with HGSC with the mean age of 62.6 years at presentation [16]. Our patient in particular is only 22 years of age. Despite having a slow growing clinical courses, patients with LGSC tend to present at advanced stage with prevalence reported as high as over 80% (Stage III/IV) [3, 17], just as like our patient. Nevertheless, overall survival rates of patients with LGSC were found to be significantly higher as compared to patients with HGSC; with 5 years and 10 years survival rate of 75 and 70% respectively in the LGSC group as compared to 40 and 26% respectively in the HGSC group [16]. Interestingly, one study pointed out that age at diagnosis of 35 and below, and presence of residual disease after primary treatment were predictors of poor survival and adverse outcome [18].

In regard to treatments for patients with LGSC, most centers advocate optimal debulking surgery followed by combined platinum/taxane-based adjuvant chemotherapy. This is despite the fact that LGSC was found to be relatively chemoresistant as compared to HGSC [19] (Table 1). Similar response was observed as well in cases of neoadjuvant chemotherapy and chemotherapy given in recurrent diseases [19]. It was postulated that the relative chemoresistant of the low-grade cancer was attributed by the longer cell cycle [20]. One retrospective study published recently by Amanda N. Fader et al., patients with advanced stage LGSC treated with neoadjuvant chemotherapy.
with primary cytoreductive surgery followed by adjuvant hormonal therapy were compared to those treated with primary cytoreductive surgery followed by conventional adjuvant chemotherapy. The overall survival and two years progression-free in both group were almost comparable [21]. However, robust evidence with larger patient samples is required to support it as a standard management for LGSC.

In near future, treatment advancement may go toward targeted therapy on the specific somatic mutations (BRAF and KRAS mutations) which are commonly found in these tumors.

CONCLUSION

Management of LGSC remained to be a challenging one especially when patient presents at advanced stage. Survival prognosis of the patient is poor, it should be optimal debulking, and it cannot be achieved after primary surgery as LGSC tend to be resistant to chemotherapy. Optimal debulking on the contrary offers better survival outcome, however at the expense of patient’s fertility and surgical morbidity.

REFERENCES


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Author Contributions
Lee Saw Joo – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Engku Husna Engku Ismail – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Mohd Pazudin Ismail – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Nik Mohd Zaki Nik Mahmood – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Hoo Pek Sung – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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All relevant data are within the paper and its Supporting Information files.

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