High-Grade Serous Carcinoma of Ovary With Choriocarcinomatous Differentiation: A Case Report and Review of Literature

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Abstract

Non-gestational choriocarcinoma (NGC) of the ovary is a rare, highly malignant neoplasm usually of germ cell origin. Rarely, NGC has been observed in association with ovarian epithelial neoplasms. So far 11 cases of NGC with choriocarcinomatous differentiation have been described in the relevant literature. Here we describe a case of NGC differentiation in a high-grade serous carcinoma of the ovary. A 53-year-old nulliparous, postmenopausal woman presented with abdominal pain and vaginal bleeding. Abdominal imaging revealed a complex pelvic mass and carcinomatosis. The patient underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy and peritoneal tumor debulking. Microscopic examination of the bilateral ovarian mass tissue revealed a high-grade serous carcinoma with a distinct component of choriocarcinomatous differentiation. The presence of choriocarcinomatous differentiation in epithelial malignancy is associated with a very poor prognosis. Our patient succumbed to disease within 2 months of diagnosis.

Keywords: Ovary; Non-gestational choriocarcinoma; High-grade serous carcinoma

Introduction

Choriocarcinoma, a tumor of most primitive trophoblast, is the most common gestational trophoblastic neoplasm seen in women of reproductive age. Non-gestational choriocarcinoma (NGC) in the ovary is either germ cell in origin or observed in association with epithelial neoplasms. NGC of germ cell origin is typically seen in children and young adults, with a

prognosis less favorable than for gestational choriocarcinoma (GC) [1]. Choriocarcinomatous differentiation in epithelial neoplasms has a poor prognosis [2]. This rare differentiation has been reported in various organs, including the breast, esophagus, stomach, colon, and the female genital tract. The first two cases of ovarian epithelial neoplasms that differentiated into choriocarcinoma were described by Oliva et al in 1993 [3]. Nine more cases were reported subsequently. Here, we report a case of high-grade serous carcinoma of the ovary with choriocarcinomatous differentiation in the context of relevant information in the literature.

Case Report

A 53-year-old, nulliparous, post-menopausal Asian woman presented with abdominal pain, distension, and heavy vaginal bleeding. She was diagnosed with stage III C ovarian carcinoma at an outside clinic. Ultrasound examination revealed a complex pelvic mass measuring approximately $13.5 \times 12.3 \times 9.8$ cm. The largest cystic portion of the mass was posterior midline with irregular internal borders and papillary projections and measured $5.9 \times 5.4 \times 4.6$ cm. Computed tomography (CT) scan demonstrated bilateral ovarian masses, ascites and carcinomatosis consistent with ovarian cancer (Figs. 1, 2). Her carbohydrate antigen-125 (CA-125) levels were 25 U/mL. She underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy with peritoneal tumor debulking for the widespread intra-abdominal disease.

Pathology

Gross examination showed a tan-white, friable $9.4 \times 6.2 \times 4.7$ cm left tubo-ovarian mass with papillary excrescences. The right ovary ($8.2 \times 3.8 \times 3.0$ cm) was solid and cystic and showed a friable papillary tumor involving approximately 55% of the ovary. Histopathological examination of the bilateral ovaries revealed a high-grade malignant neoplasm comprising two morphologically distinct tumors (Fig. 3). The epithelial component showed mixed papillary, glandular, and cribriform architecture with mitotically active, high-grade nuclei (Fig. 4). Adjacent to the tumor was a histologically distinct high-
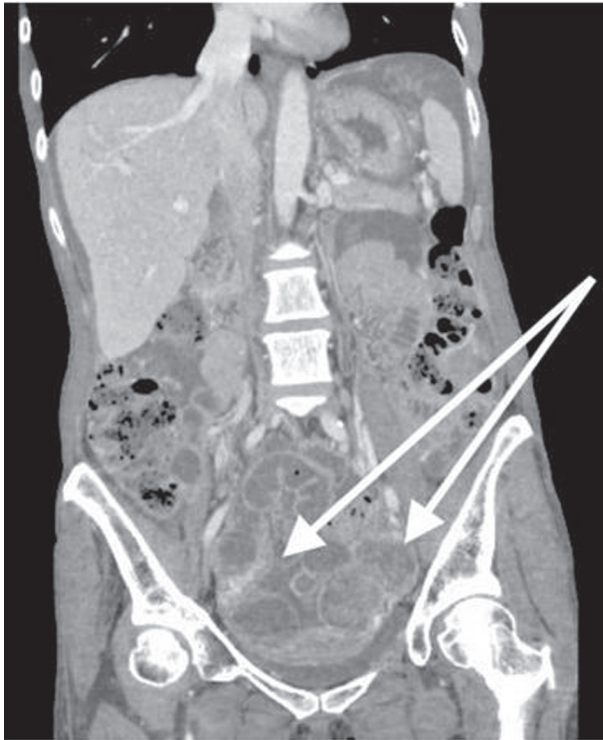
Figure 1. CT of abdomen and pelvis shows bilateral ovarian masses, and short arrow shows left ovarian mass. CT: computed tomography.

grade tumor growing in clusters and sheets and was found surrounding blood lakes. The tumor cells were polygonal, with centrally placed hyperchromatic, vesicular nuclei, prominent nucleoli, clear cytoplasm, and had a distinct cytoplasmic membrane (Figs. 5, 6). Admixed with these tumor cells was a second population of mononucleate pleomorphic cells with abundant eosinophilic cytoplasm. Rare multinucleated hyperchromatic syncytiotrophoblast-like, basophilic cells were identified. Extensive immunohistochemical studies were performed to verify trophoblastic differentiation while ruling out
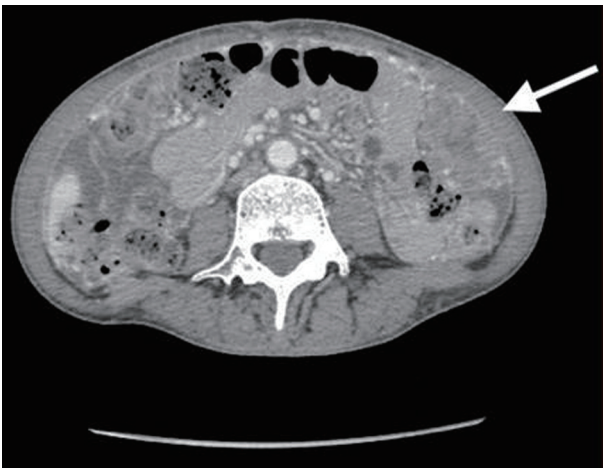
Figure 2. CT of abdomen and pelvis shows large bulky nodular mass in the omental carcinomatosis. CT: computed tomography.
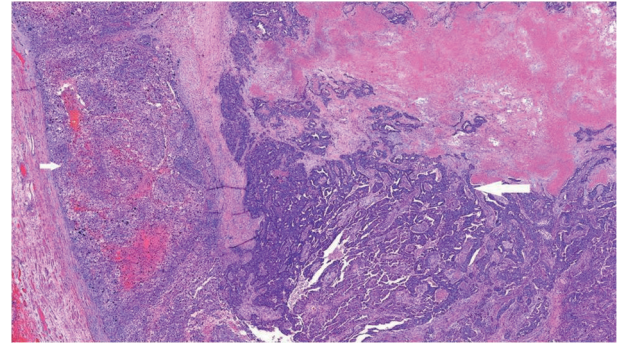

Figure 3. High-grade serous carcinoma with papillary and glandular architecture (long arrow) with adjacent choriocarcinomatous differentiation (short arrow), × 4.
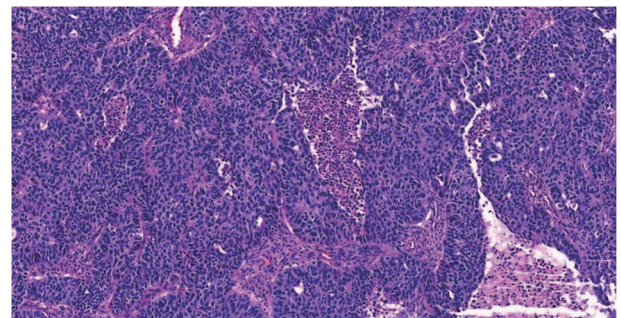
Figure 4. High-grade serous carcinoma with papillary and glandular architecture, × 20.

other ovarian neoplasms including clear cell carcinoma, and germ cell tumors (described below in the immunohistochemistry (IHC) section). Our case did not show the luteinization of ovarian stroma, which was attributed to steroidal hormones observed in a few case reports [3, 4].

Although serous and trophoblastic components were well-demarcated, the transition zone showed merging of the two components (Fig. 7). Intra-abdominal (bladder, ureters, rectosigmoid, transverse colon) carcinomatosis and lymph node metastasis were mainly comprised of choriocarcinomatous component.
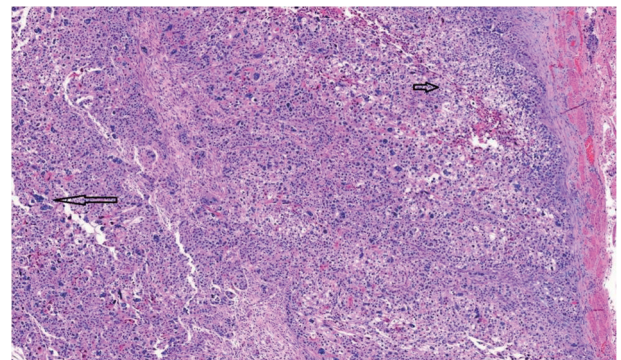
Figure 5. Choriocarcinomatous differentiation comprising an admixture of mononucleate cytotrophoblastic cells (short arrow) and multinucleate syncytiotrophoblast-like cells (long arrow), × 10.
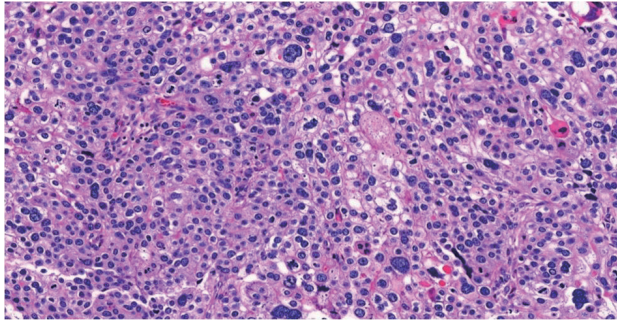
Figure 6. Choriocarcinomatous differentiation, × 20.

IHC

The epithelial tumor showed diffuse and strong expression for p53 (Fig. 8) (DU-7, Leica; RTU), WT1 (wt49, Leica; RTU), and PAX8 (MRQ-SO Mab, Cell Marque; RTU) consistent with serous phenotype. GATA3 (LSO-823 Mab, Cell Marque, RTU), a highly sensitive marker for trophoblasts, was strongly and diffusely positive in the choriocarcinomatous component. This component was also strongly positive for P53, CK-OS-CAR, placental alkaline phosphatase (PLAP) (NB-10, Roche; RTU), and negative for WT1, PAX8, ER (SP1, Roche; RTU), napsin A (IP64, Leica; RTY), alpha-fetoprotein (AFP) (Polyclonal, Roche; RTU), CD30 (JCM182, Leica; RTU), and programmed cell death ligand-1 (PD-L1) (NAT105, Cell marque). Trophoblasts showed patchy zonal staining for p63, supporting the presence of a dimorphic population of trophoblasts. Human chorionic gonadotrophin (hCG) immunostaining was negative. Summary of IHC study with review is enumerated in Table 1 [5-11].

Follow-up

The patient presented with weakness, cachexia, and worsening ascites 6 weeks after surgery. Imaging revealed enhancement of liver capsule, liver distortion, diffuse bowel serosal enhancement, and circumferential thickening of the bowel wall with mesenteric enhancement, which was concerning for metastatic carcinoma. Her follow-up labs, including hCG
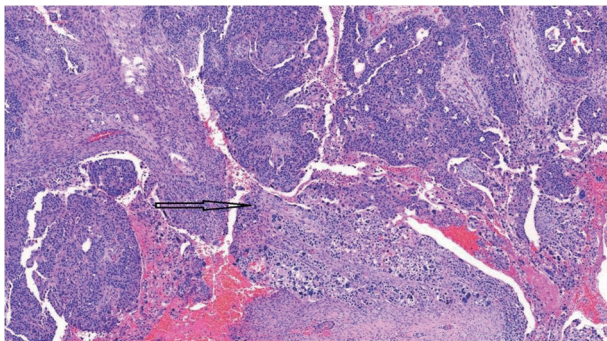
Figure 7. Transition zone (arrow) showing intermingling of epithelial and choriocarcinomatous components, × 10.
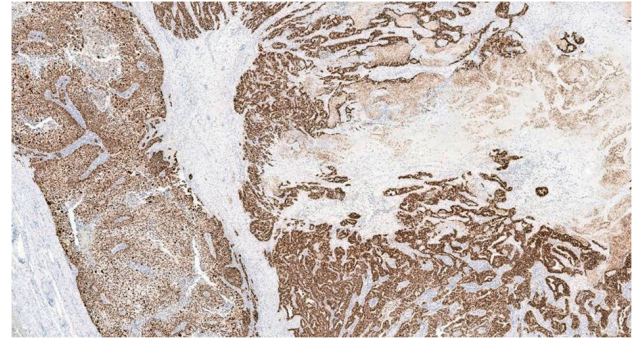
Figure 8. P53 IHC in both choriocarcinoma and serous carcinoma shows diffuse and strong nuclear positivity, × 4. IHC: immunohistochemistry.

(2.00 mIU/mL), carcinoembryonic antigen (CEA) (0.6 ng/mL) and AFP (4.0 ng/mL), were within reference ranges. She received the first cycle of chemotherapy comprised of paclitaxel and carboplatin. However, she succumbed to death within 2 months of surgical and medical management.

Discussion

Choriocarcinoma is a malignant gestational trophoblastic neoplasm comprised of an admixture of intermediate trophoblasts, cytotrophoblasts, and multinucleated syncytiotrophoblasts. It can be classified into: 1) GC or 2) NGC. The non-gestational tumor can be further sub-divided into germ cell origin or as a component of a somatic high-grade neoplasm. GC primarily arises in the uterus after full-term pregnancy or after a hydatidiform mole. Although rare, it can also occur at various ectopic sites (e.g. fallopian tubes [12], ovary [13], and greater omentum [14]). Non-gestational ovarian choriocarcinoma is mostly of germ cell origin. It is commonly found in children and young adults. Unlike GC, it spreads via both lymphatic and hematogenous pathways and also shows intra-abdominal spread. It has an intermediate prognosis between GC and NGC associated with somatic malignancies [15].

Choriocarcinomatous differentiation in somatic malignancy has been reported in various organ systems and has a worse prognosis than GC and NGC of germ cell origin. In the gastrointestinal (GI) tract, this differentiation is commonly found in the stomach and rectosigmoid carcinomas in elderly men [16]. This differentiation was noted in metastatic deposits of colonic adenocarcinomas. Other GI sites include the esophagus, sigmoid colon, and rectum [17-19]. The prognosis is poor with early metastasis and death within a year of diagnosis [19]. Lung adenocarcinoma and mammary carcinomas can also show this differentiation [20-23]. The occurrence of NGC with somatic malignancy in the urinary tract is a well-established phenomenon, with several cases reported in urinary bladder [24], kidney, and renal pelvis [25]. It is classified into three main morphologic subtypes: 1) Presence of only scattered syncytiotrophoblasts within urothelial carcinoma; 2) Presence of focal areas of complete trophoblastic differentiation; and alternatively, 3) Tumors manifesting only immunohistochemical

Table 1. Summary of IHC Findings in All Cases

Authors	IHC expression in choriocarcinomatous component	IHC expression in epithelial component
Oliva et al [3]	Case 1: β-hCG positive in multinucleated cells; case 2: β-hCG in SCT cells	N/A
Ozaki et al [5]	N/A	N/A
Jimenez-Heffernan et al [4]	β-hCG in SCT	N/A
Hirabayashi et al [6]	α-hCG and β-hCG positive in SCT	CEA, CA-125, CA19-9 positive in endometrioid adenocarcinoma; Chr focal positive, Syn positive in small cell carcinoma; CA-125 positive in clear cell carcinoma
Oladipo et al [7]	β-hCG positive; PLAP focal positive; MNF-116 (CK) positive	N/A
Hafezi-Bakhtiari et al [8]	α inhibin positive; HPL positive in SCT; β-hCG positive in both CYT and SCT	EMA positive; AE1/AE3 positive; P53 positive; WT1 negative
Hu et al [9]	HCG positive in SCT; CYT focal positive; HPL positive in CYT	CK7 positive; CD117 negative; CD30 negative; PLAP negative; AFP negative; glypican 3 negative
Shanmugasundaram et al [10]	β-hCG negative	
Koyanagi et al [11]	β-hCG positive; AFP negative	CK7 negative; CK20 positive; CDX2 positive; ER negative; CD30 negative; PLAP negative; β-hCG negative
Xing et al [2]	β-hCG positive; PD-L1 positive	β-hCG negative; PD-L1 negative
Present case	GATA-3, PLAP, CK positive; focal p63 positive; WT1, PAX-8, ER, napsin A, AFP and CD30 negative; β-hCG: negative	P53, WT1 and PAX-8 positive in serous component

SCT: syncytiotrophoblast; CYT: cytotrophoblast; HPL: human placental lactogen; PLAP: placental alkaline phosphatase; AFP: alpha-fetoprotein; CEA: carcinoembryonic antigen; Chr: chromogranin; Syn: synaptophysin; EMA: epithelial membrane antigen; PDL-1: programmed death ligand-1; IHC: immunohistochemistry; β-hCG: beta-human chorionic gonadotrophin; N/A: not applicable.

evidence with no morphological identification of trophoblasts. Outcomes are worse in urothelial neoplasms containing syncytiotrophoblasts, necessitating the reporting of this morphological variant [26]. In the female reproductive tract, these tumors have been found in ovaries and the uterine corpus [27, 28], and, rarely, in cervical carcinoma. In the uterus, it is commonly seen in association with endometrioid endometrial adenocarcinoma and is predominantly found in postmenopausal women (median = 62.3 years). In the cervix, it is reported in association with squamous cell carcinoma, endocervical adenocarcinoma, and clear cell carcinoma [29-31]. NGC associated with somatic malignancy (NGC-SM) has a worse prognosis, with distant metastases and a short survival period [28, 32, 33]. The most common sites of metastasis are lung and liver.

A thorough search of the relevant literature in English was conducted to identify previously reported cases of ovarian epithelial tumors differentiating towards choriocarcinoma, with a total of 11 cases identified. We report the 12th case of ovarian neoplasm with choriocarcinomatous differentiation. NGC-SM is an extremely rare, possibly under-recognized, or under-reported entity. Clinicopathological features, histomorphology of co-existing epithelial tumors, and prognosis for reported cases are summarized in Table 2 [2-11]. NGC-SM is common in postmenopausal women but can be found in relatively younger [3, 11] and premenopausal women [2], with an age range of 29 - 65 years (mean: 51.7 years, median:

53 years). The common presenting symptoms include abdominal pain, distension, and vaginal bleeding. On imaging, tumors are typically solid and cystic, with size varying from 5 to 30 cm. Grossly, a separate nodule with hemorrhage and necrosis can be found adjacent to the epithelial tumor [3, 4, 6, 11]. The most common laboratory finding includes elevated serum levels of beta-hCG (β-hCG) [2-4, 6, 7, 9, 11, 27], CA-125, and normal levels of AFP, which is a yolk sac tumor marker. A normal β-hCG was reported by Shanmugasundaram et al [10], a finding similar to our case. Pre-procedure β-hCG was not performed in our patient due to low suspicion for choriocarcinomatous differentiation. Post-surgery, β-hCG was found to be within the reference range. CA-125 was elevated in six cases, including our case [3, 4, 7, 9, 10]. Variation in levels of neuron-specific enolase (NSE) has also been reported [6]. Xing et al performed PD-L1 on five somatic neoplasms with choriocarcinomatous differentiation. PD-L1 was positive in all tumors, with 90% of tumor cells positive in four tumors, and 50% positive in one tumor. In their study, PD-L1 was positive only in the choriocarcinomatous component, while the somatic component was completely negative [2].

Choriocarcinomatous differentiation has been found in a wide range of benign and malignant ovarian neoplasms, including benign mucinous cystadenoma (n = 2), mucinous carcinoma (n = 2), endometrioid carcinoma admixed with other types (n = 2), undifferentiated carcinoma (n = 1), high-grade

Table 2. Summary of Clinico-Pathologic Features

Author	Year	Cases	Age	Size (cm)	TZ	Histological type of associated ovarian cancer	Metastatic sites	Prognosis (follow-up)
Oliva et al [3]	1993	2	59	25	N	Case 1: undifferentiated	Lung, brain	Death in 15 months
			33	30	Y	Case 2: mucinous cystadenoma	Liver, peritoneum	Death in 7 months
Ozaki et al [5]	2001	1	54	12.4		Mucinous cystadenoma	Myometrium, liver, lung	Death in 6 days
Jimenez-Heffernan et al [4]	2002	1	63	17	Y	Mucinous cystadenocarcinoma	None	No recurrence after 7 months of FU
Hirabayashi et al [6]	2006	1	50	12.8	Y	Endometrioid and small cell, focal clear cell component	Peritoneum, liver, lung	Death in 10 months
Oladipo et al [7]	2007	1	60	16		High-grade mixed (Adeno and squamous) Carcinoma	Lung, brain	Died of brain mets, over a year
Hafezi-Bakhtiari et al [8]	2010	1	65	5		High-grade papillary serous carcinoma	Lung	Lung mets after 9 months of FU
Hu et al [9]	2010	1	48	R = 6 cm, L = 5 cm	N	Clear cell carcinoma	Lung, liver, abdominopelvic	Death after 11 months
Shanmugasundaram et al [10]	2015	1	64	R = 4 cm, L = 4 cm		High-grade papillary serous carcinoma	Peritoneum	Stable after 1-year FU
Koyanagi et al [11]	2016	1	29	20	N	Adenocarcinoma (mucinous carcinoma)	Lung	NA
Xing et al [2]	2019	1	44	11.5		Mixed clear cell and endometrioid carcinoma	Lung	Alive with multiple lung mets after 8 months
Present case	2019	1	53	9.4		High-grade serous carcinoma	Liver	Death in 2 months

R: right; L: left; mets: metastases; FU: follow-up; TZ: transition zone; Y: yes; N: no.

adenocarcinoma (n = 1), clear cell carcinoma (n = 1), and high-grade serous carcinoma, including our case (n = 3). A history of endometriosis was noted in two cases of endometrioid and clear cell carcinoma, respectively [2, 6]. Prognosis in these patients was typically poor. Seven out of 12 patients died of disease within 6 days to 15 months after diagnosis. Two patients had lung metastasis and brain metastasis respectively, while one patient had widespread peritoneal involvement (Table 2) [2-11]. One out of 12 patients showed a positive response to chemotherapy with no evidence of recurrence 7 months after following up [4]. It is important to note that choriocarcinomatous differentiation was not limited to high-grade epithelial neoplasms of the ovary but was also found in benign mucinous cystadenoma [3, 5] and low-grade endometrioid adenocarcinoma. One of the benign mucinous cystadenomas showed an abrupt transition to poorly differentiated carcinoma that differentiated into choriocarcinoma. Identification of this rare pattern of differentiation is crucial as it follows an aggressive clinical course, irrespective of the background ovarian disease.

The most accepted hypothesis for the presence of the choriocarcinomatous component is the theory of dedifferentiation or retro-differentiation. This idea has been supported by the identification of a transition zone between the tumor components [3, 4, 6]. Merging of two morphological components was also observed in our case, suggesting the possibility of retro-differentiation of the extra-embryonic component towards a more primitive tumor. Diffuse positive staining for p53 in both components also favors the same clonal origin for the two elements. Xing et al performed next-generation sequencing (NGS) on gynecological tumors with choriocarcinomatous differentiation and drew the inference that all tumor components shared somatic mutations and identical alleles upon single-nucleotide polymorphism (SNP) analysis, thus favoring the implication that all components have the same precursor origin [2].

It is imperative to differentiate between GC versus NGC, as this distinction has prognostic implications. This can be accomplished by short tandem repeat (STR) analysis using a set of highly polymorphic markers to determine the parental origin of tumors. GC usually can demonstrate either paternally derived DNA or both paternal and maternal contributions to the tumor, while NGC shows an identical homozygous allelic pattern in all tumor components, with no evidence of any paternal alleles [7]. The genetic origin of choriocarcinoma can also be established by fluorescent microsatellite genotyping of DNA.

As these tumors are typically chemotherapy resistant, the outcome is fatal. Routine PD-L1 testing may help in determining the role of checkpoint inhibitors as a therapeutic option [2].

Conclusions

Choriocarcinomatous differentiation in somatic high-grade

malignancy can be found in various organ systems. Its recognition is important as it is associated with a worse prognosis. Choriocarcinomatous differentiation in the ovary is not limited to high-grade epithelial tumors but can also be observed in benign neoplasms of the ovary, well-differentiated endometrioid tumors, and other epithelial subtypes. Determination of the genetic origin of a tumor can differentiate NGC from GC. Knowledge of this differentiation and its identification is essential for prognostic information. There is a definite need for the development of standard management protocols, including routine PD-L1 testing.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

All authors have made substantial contribution to this case report. QS was involved in review of literature, creating tables and figures and made significant contribution to drafting result and discussion. RS contributed to drafting Introduction. SL helped in revising the paper in keeping with the intellectual contents including final approval of the draft before publication.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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