

Choriocarcinoma Arising in a Serous Carcinoma of Ovary: An Example of Histopathology Driving Treatment

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Abstract

Background: Choriocarcinoma within an ovarian carcinoma is exceptionally rare. Nevertheless, recognition of this mixed tumour is important for administration of appropriate chemotherapy.

Case: A 65-year-old woman underwent resection of an ovarian mass after presenting with a pelvic mass and breast tenderness. On pathologic examination the mass showed a choriocarcinoma in association with a serous carcinoma. This pathologic diagnosis led to a specific chemotherapy regimen with cisplatin, etoposide, and bleomycin, suitable for both types of malignancy.

Conclusion: Both gynaecologists and pathologists should be aware that the histopathologic classification of ovarian epithelial carcinoma and its variants, such as this one, may have an increasing role in the management of this disease.

Résumé

Contexte : La présence d'un chorio-carcinome au sein d'un carcinome ovarien est exceptionnellement rare. Néanmoins, le fait de reconnaître cette tumeur mixte s'avère important pour ce qui est de l'administration de la chimiothérapie appropriée.

Cas : Une femme de 65 ans a subi la résection d'une masse ovarienne après avoir présenté une masse pelvienne et une sensibilité mammaire. Au moment de l'examen pathologique, la masse présentait un chorio-carcinome en association avec un carcinome séreux. Ce diagnostic pathologique a mené à un schéma chimiothérapeutique particulier (cisplatine, étoposide et bléomycine) convenant au deux types de malignité.

Conclusion : Les gynécologues et les pathologistes devraient garder à l'esprit que la classification histopathologique du carcinome épithélial ovarien et de ses variantes (comme celle qui est susmentionnée) peut en venir à jouer un rôle accru dans la prise en charge de cette maladie.

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INTRODUCTION

Ovarian carcinoma comprises more than 90% of all ovarian malignancies, and because symptoms are commonly only vague and non-specific, most cases present at an advanced stage with extensive extra-ovarian involvement.¹ The standard treatment of women with advanced stage disease has been hysterectomy and bilateral salpingo-oophorectomy; debulking or cytoreductive surgery; and staging biopsies, including omentectomy, peritoneal biopsies, and pelvic and para-aortic lymph node dissection, followed by platinum-based combination chemotherapy.^{2,3} More recently, use of initial (neoadjuvant) chemotherapy has increased.⁴

The histologic type of ovarian carcinoma, based upon the predominant pattern of differentiation, has not been a major determinant of chemotherapy in women with advanced ovarian carcinoma. There is increasing interest, however, in the accurate histologic typing of ovarian carcinoma because different pathogenetic pathways underlie these various types, and knowledge of these pathways may be used to determine optimal chemotherapy and guide treatment decisions.^{5,6} For example, it has been suggested that mucinous ovarian carcinoma should be subject to specific therapeutic strategies different from those used in the much more common serous carcinoma.^{6,7}

In the very unusual case described here, postoperative chemotherapy was individualized, based upon the histopathologic classification of the ovarian carcinoma, because an otherwise typical high-grade papillary serous carcinoma of ovary demonstrated an adjacent choriocarcinomatous component. Subsequently, the patient received chemotherapy for both

Figure 1. Hematoxylin and eosin stain. Junction between serous adenocarcinoma (right) and choriocarcinoma component (left)

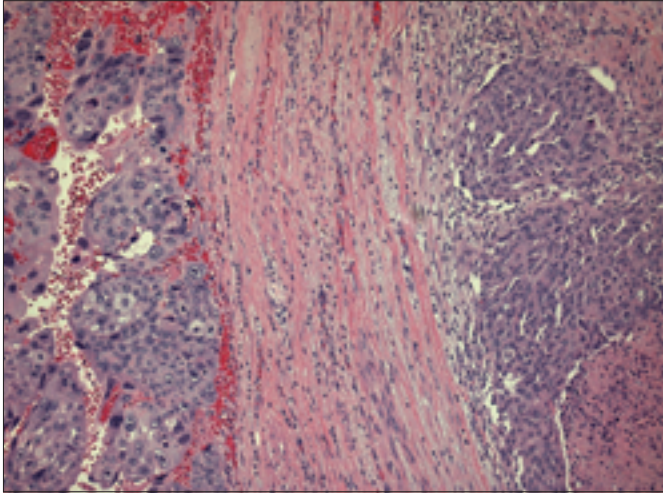


Figure 2a. Hematoxylin and eosin stain. High power view of the serous adenocarcinoma component. Note the well formed, solid epithelial papillae with slit-like spaces.

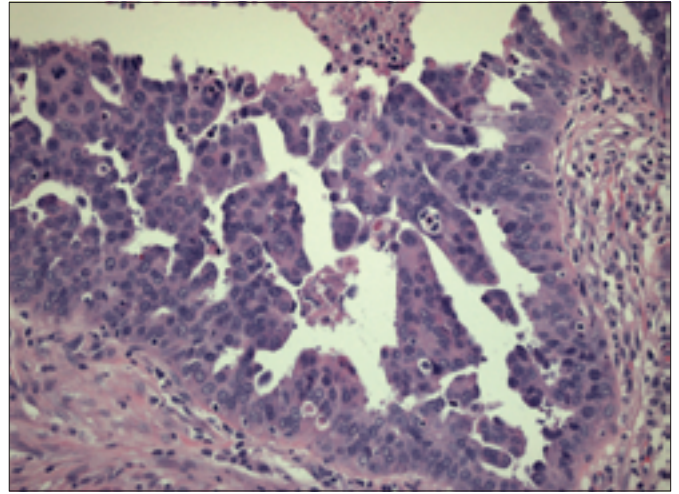
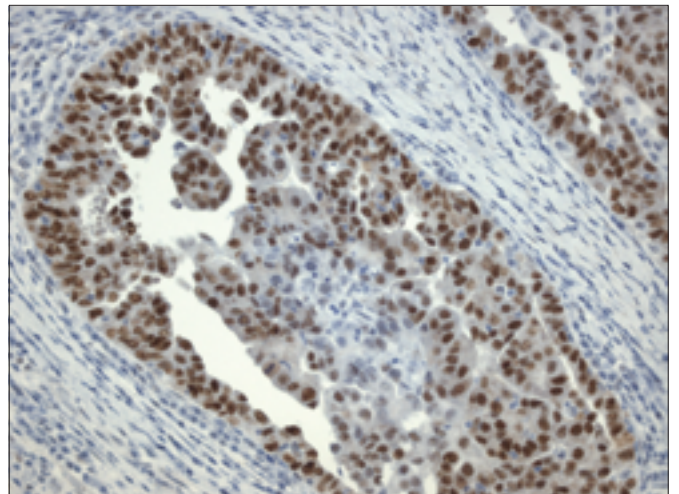


Figure 2b. Immunohistochemical stain for p53 of the serous carcinoma component. Note the strong nuclear staining in virtually all carcinoma cells.



serous carcinoma and choriocarcinoma. The probable origin of this mixed neoplasm is discussed.

THE CASE

A 65-year-old woman (gravida 4, para 4) with postmenopausal status for 12 years presented with symptoms of rectal pressure. The patient had a prior vaginal hysterectomy. A niece had a history of ovarian cancer. After initially being treated for a bladder infection, the patient returned one month later with the additional complaint of breast tenderness. Imaging studies (barium enema and CT scan) revealed a pelvic mass filling the pouch of Douglas, right hydronephrosis, and multiple lung nodules highly suspicious for metastases. Serum β -hCG was elevated to 332 966 IU/L (normal < 5 IU/L) and serum LDH was 342 IU/L (normal range 190–360 IU/L). Levels of serum AFP, CEA, and CA-125 were within the normal range. With a preoperative suspicion of an ovarian germ cell tumour, a laparotomy was performed. A mass attached to the rectosigmoid, the anterior pelvic peritoneum, and the bladder dome was resected with both ovaries.

Omentectomy, pelvic washings, and lymph node sampling were also performed.

Macroscopically, the right ovary consisted of an irregular, opened mass that weighed 212 g. The transected ovarian surface was variegated, with hemorrhagic, sponge-like, and solid areas. The left ovary consisted of a thin-walled cystic lesion with a maximum diameter of 5 cm. Microscopic examination of the right ovary showed extensive areas of necrosis and two distinct neoplastic components that abutted but were separate from each other (Figure 1). One component consisted of solid sheets and islands of cohesive highly pleomorphic neoplastic cells with occasional formation of acini, slit-like spaces, and papillae (Figure 2a). Immunohistochemical studies of this component showed

ABBREVIATIONS

AFP	alpha-fetoprotein
CEA	carcinoembryonic antigen
p53	p53 gene protein
WT-1	Wilm's tumour suppressor gene protein

Figure 3a. Hematoxylin and eosin stain. High power view of the choriocarcinoma component. Note the biphasic population of cytotrophoblastic and syncytiotrophoblastic cells.

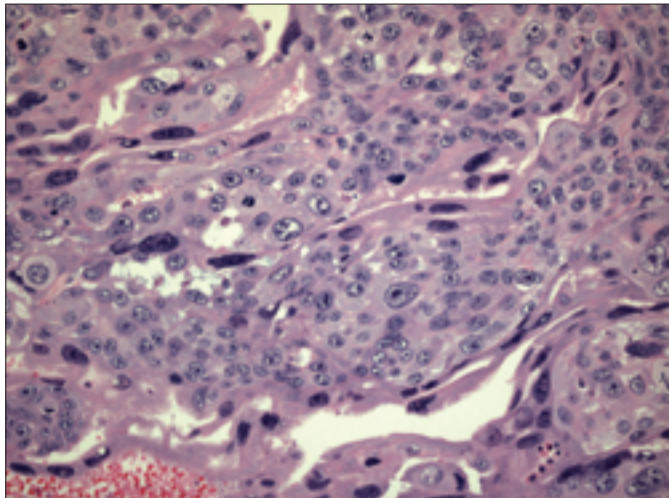
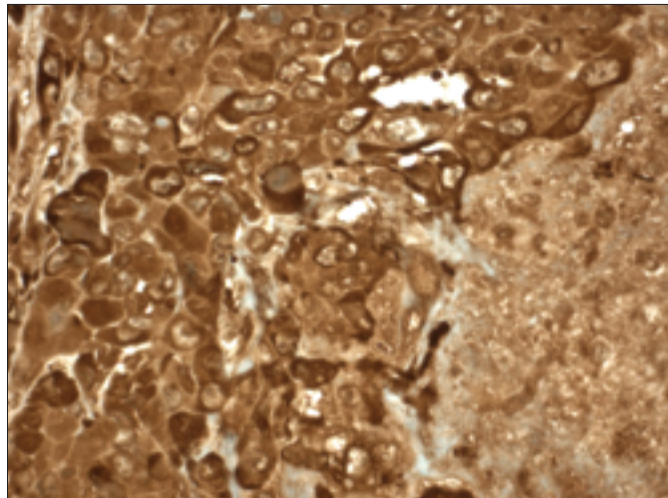


Figure 3b. Immunohistochemical stain for β -hCG of the choriocarcinoma component. Note the strong cytoplasmic staining on both types of trophoblastic cells.



epithelial membrane antigen, keratin (AE1/AE3), and p53 positivity, although the WT-1 was negative (Figure 2b). Thus, this component was diagnostic of the usual type of high-grade papillary serous carcinoma. The second component demonstrated solid aggregates of neoplastic cells with a biphasic morphology consisting of cytotrophoblastic-like mononuclear cells with overlying draping syncytiotrophoblastic giant cells (Figure 3a). Necrosis and hemorrhage were prominent in this second component. Immunohistochemical studies of this component showed both alpha-inhibin and human placental lactogen positivity in the syncytiotrophoblastic cells, and β -hCG positivity in both the cytotrophoblastic and syncytiotrophoblastic cells (Figure 3b). This second component was diagnostic of choriocarcinoma. No other neoplastic elements, specifically other germ cell tumour types, were identified. Intravascular invasion by the choriocarcinomatous component was present. A diagnosis of choriocarcinoma arising in a serous carcinoma was made. The contralateral ovary, and biopsies of the rectosigmoid, bladder dome, and left pelvic side wall all showed metastatic disease consisting of serous carcinoma, choriocarcinoma, or both. Peritoneal and lymph node biopsies were negative.

Post-surgical chemotherapy consisting of combination cisplatin-etoposide-bleomycin therapy was given for four cycles, which is the regimen for malignant germ cell tumours and refractory or advanced gestational trophoblastic disease. This was followed by additional cisplatin cycles for the ovarian epithelial carcinoma. After four cycles of chemotherapy, serum β -hCG levels declined

to normal. At nine months post operation, serum AFP, hCG, and CA-125 had returned to normal, but metastatic lung disease was present. The patient has elected to have no further treatment

DISCUSSION

Choriocarcinomas in the ovary occur as gestational and non-gestational types. It is important to distinguish between these types because prognosis and chemotherapeutic response may differ.^{8,9} The distinction, however, can be challenging because there are no morphologic differences between the two types. Consequently, the differential diagnosis relies upon other features, specifically clinical presentation and the finding of other germ cell elements, if present. Although gestational choriocarcinomas may arise decades after an antecedent pregnancy, it is unlikely that this was the case in the postmenopausal woman we describe. Rather, the absence of any other malignant germ cell component in this case and the presence of an adjacent serous carcinoma indicate that this was a non-gestational choriocarcinoma arising in a serous carcinoma.

Choriocarcinoma arising within an ovarian carcinoma is a very rare and only recently documented occurrence.^{10,11} A summary of the clinical findings and course of ovarian epithelial tumours exhibiting mixed chorio- and serous carcinomas is provided in the Table. An elevated serum β -hCG, present in this case, is characteristic of this rare tumour. The present case is similar to another report of an undifferentiated carcinoma of the ovary that exhibited fully

Clinical findings and course of choriocarcinoma associated with epithelial tumours of the ovary

Case No.	Patient age	Size, cm	Coexisting tumour(s)	hCG level	Metastasis and invasion	Surgery	Chemotherapy	Outcome
1 ¹⁰	59	25	Poorly differentiated carcinoma	Urine: 2.291.300IU/24h postoperation	Brain, lung	TAH BSO	Carboplatin MTX, PCM	DOD, 15 months
2 ¹⁰	33	30	Mucinous cystadenoma	Serum:524 IU/L preoperation	Liver, peritoneum	RSO	CDDP VP-16 ACT-D, CPM, DXR, BLM	DOD, 7 months
3 ¹¹	63	17	Mucinous cystadeno carcinoma	Serum:145.672 IU/L preoperation	none	Pelvic debulking TAH, omentectomy	CDDP, VP-16	NED, 7 months
4 ¹⁵	54	12.4	Mucinous cystadenoma	Serum:1.600 IU/L postoperation	Myometrium, liver, lung	TAH	None	Death, 6th day after surgery
5 ¹²	50	13	Clear cell, small cell, endometrioid adenocarcinoma	Serum: 704.1 IU/L preoperation	Peritoneum, liver, lung	TAH BSO LND	CDDP PTX CBDCA EMA/EP	DOD, 10 months
6 ⁹	60	16	Poorly differentiated carcinoma	Serum: 11 945 IU/L 4 weeks postoperation	Lung, brain	RSO, debulking	POMB ACE	DOD, over a year

TAH: total abdominal hysterectomy; DOD: dead of disease; BSO: bilateral salpingo-oophorectomy; MTX: methotrexate; CPM: cyclophosphamide; RSO: right salpingo-oophorectomy; CDDP: cisplatin; ACT-D: actinomycin-D; VP-16: etoposide; DXR: doxorubicin; BLM: bleomycin; PTX: paclitaxel; EMA/EP: etoposide-cisplatin and etoposide-methotrexate- dactinomycin; POMB/ACE: cisplatin, vincristine, methotrexate, bleomycin / actinomycin D, cyclophosphamide, and etoposide; NED: no evidence of disease; LND: lymph node dissection.

developed choriocarcinomatous histologic differentiation and β -hCG production,¹⁰ with the exception that the surface epithelial component of this case was better differentiated and showed histologic evidence of papillary serous carcinoma. Definitive evidence of a maternal origin of the choriocarcinoma arising in an ovarian serous carcinoma has been provided in one report using DNA identity analysis.⁹

A diagnosis of choriocarcinoma arising in a serous carcinoma of the ovary needs to be distinguished from the more common occurrence of carcinoma with syncytiotrophoblastic giant cells. Similar to adenocarcinomas of several other organs (breast, lung, stomach, prostate, and bowel), ovarian surface epithelial carcinomas can occasionally contain scattered trophoblastic cells that secrete hCG.^{2,10} In contrast, choriocarcinomas, such as in this case, exhibit the typical biphasic cell populations of cytotrophoblasts and adjacent draping syncytiotrophoblasts.

Two hypotheses have been postulated to explain the association of ovarian carcinoma and choriocarcinoma. A true collision tumour arising between two separate neoplasms, a carcinoma and a choriocarcinoma, is a highly unlikely possibility in this postmenopausal woman. Instead, divergent differentiation of the serous carcinoma seems plausible.^{9,10,12} Such differentiation has been labelled as a “neometaplastic” process, or as “retrodifferentiation” or “dedifferentiation.”

Such an origin is favoured because a transition zone can be identified in some cases,^{9,11} and cases of coexistent adenocarcinoma and choriocarcinoma have been described in sites where primary germ cell tumours are rare.

The diagnosis of choriocarcinoma arising in an ovarian surface epithelial carcinoma has important management implications. Different chemotherapeutic regimens have been used in cases of mixed choriocarcinoma and carcinoma, but established chemotherapeutic regimens have not been described.^{8,9,13} Use of chemotherapeutic regimens that target both components have been advocated and used.¹⁴ Non-gestational choriocarcinoma have responded to chemotherapy initially used for gestational choriocarcinoma.¹³ Refractory cases may respond to alternative chemotherapeutic regimens such as platinum-based chemotherapy.⁸ In our case, regimens of chemotherapy including agents effective against both malignant germ cell and ovarian carcinoma were administered.

Mixed carcinoma and choriocarcinoma tumours are biologically aggressive regardless of treatment, and case reports with at least one year of follow-up¹¹ have shown death within two years (Table). Presumptive hematogenous spread to the lung, as in our patient, is characteristic of choriocarcinoma, and would be an unusual finding in patients with pure epithelial carcinoma.^{9,10}

CONCLUSION

Non-gestational choriocarcinoma may arise from ovarian carcinoma. The accurate histopathologic diagnosis of these rare mixed malignancies is important, because the prognosis for these malignancies is poor, and chemotherapy specific to each histologic component may be chosen. The case described is an example of the increasing interest in using the histopathologic type of ovarian carcinoma to direct specific chemotherapy.

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The woman whose story is told in this case report has provided signed permission for its publication.

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