Good prognosis for primary ovarian pure nongestational choriocarcinoma using the EMA/CO regime

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Summary

Nongestational choriocarcinoma of the ovary is a rare germ cell tumor with a worse prognosis than gestational choriocarcinoma. In this report we present a case of nongestational chroriocarcinoma where the EMA/CO regime was applied. The clinical features, management, and outcome are discussed.

Key words: Primary ovarian pure nongestational choriocarcinoma; EMA/CO regime.

Introduction

Nongestational choriocarcinoma of the ovary is a rare germ cell tumor and the pure type is less frequent than mixed type among other germ cell tumors [1]. Pure the nongestational choriocarcinoma is extremely rare and accounts for less than one percent of primitive germ cell tumors of the ovary and aggressive tumors [2].

Although the surgical approaches are well identified, there is no concensus on the medical treatment of nongestational ovarian choriocarcinoma.

In this report we present a patient with nongestational choriocarcinoma treated with optimal debulking surgery and chemotherapy with the EMA/CO regimen (etoposide, methrotrexate, actinomycin-D, cyclophosphamide, vincristine) which resulted in the cure of the patient.

Case Report

A 21-year-old woman was referred to our hospital because of abdominal pain. She had a history of a vaginal delivery six months earlier as her only confirmed pregnancy. Pelvic examination revealed bilateral adnexal masses. Pelvic ultrasound (US) scan showed evidence of large complex masses measuring 13 x 11 cm in the right adnexal region and 14 x 12 cm in the left adnexal region, containing both solid and cystic components. A computed tomography (CT) scan showed large bilateral masses which were mostly solid and displaced the uterus. Physical examination documented normal findings. Laboratory findings showed high levels of βhCG (1869 mIU/ml) and CA-125 (86 IU/ml).

Explorative laparatomy including bilateral cyctectomy and appendectomy was performed. As the intraoperative frozen section evaluation reported benign findings, the operation was ended. However, the final pathology report with paraffin blocks showed a diagnosis of choriocarcinoma. The patient consulted with the Oncology Department and decided to be treated with the EMA/CO regimen. Three courses of the EMA/CO regimen were performed with 21-day intervals. Before the first courses βhCG was ≥ 100,000 mIU/ml and the prognostic score of FIGO was seven. After the third course βhCG level was 99.2 mIU/ml. Thus one more EMA/CO regimen was performed. After the fourth cure, βhCG level was 3.09 mIU/ml. However, the 7 x 5 cm semisolid cystic lesion which was documented by pelvic CT, showed optimal debulking surgery was needed. The second laparotomy demonstrated a 6 x 6 multilocular cystic mass in the right ovary, and a normal left ovary. Peritoneal washing material was collected for cytological examination. Total hysterectomy, bilateral salpingo-oophorectomy, total omentectomy and pelvic lymph node dissection were performed. Pathological examination revealed no tumor invasion in the lymph nodes of the omentum.

After the second operation, the patient was treated with an extra six courses of the EMA/CO regimen. After the sixth cure, βhCG was below 1 mIU/ml. In the first six months after therapy the patient was followed monthly with hCG levels and US. At the end of the six months, controls were performed at 3-month intervals. The patient was well and free of disease at the end of 12 months with normal laboratory and imaging findings and no recurrence was documented. She continues to undergo check-ups every six months.

Results

Pathology report: On gross examination a hemorrhagic circumscribed mass was observed. Microscopically, mononuclear cells, hemorrhagia and necrosis were found. Nuclear pleomorphism, hyperchromasia and nucleoli were predominant (Figure 1). Immunohistochemically, βhCG was observed in the syncytiotrophoblasts (Figure 2).

Genetic analysis: We performed genetic analyses from the patient's blood and tumoral tissue to distiguish nongestational choriocarcinoma from gestational choriocarcinoma. DNA was isolated from paraffin blocks and peripheral blood sampling was carried out using the Invisorb Spin Tissue Mini Kit (Invitek, Germany) according to the manufacturer's instructions. For QF-PCR aneuploidy screening, the ChromoQuant TM version 2 kit was used in DNA samples. Samples were analyzed using a 1-

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Fig. 1

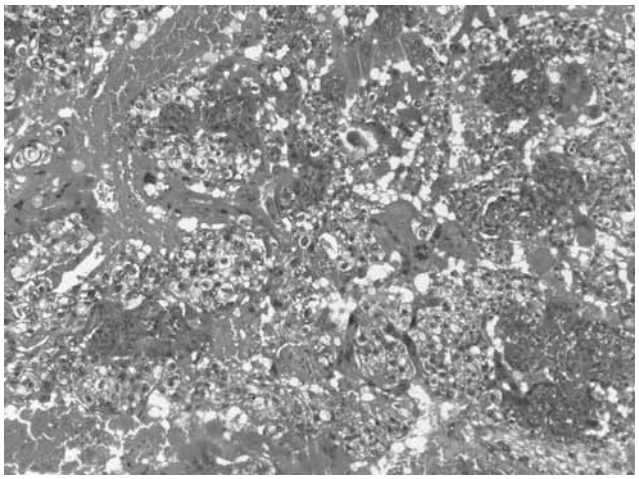

Fig. 2

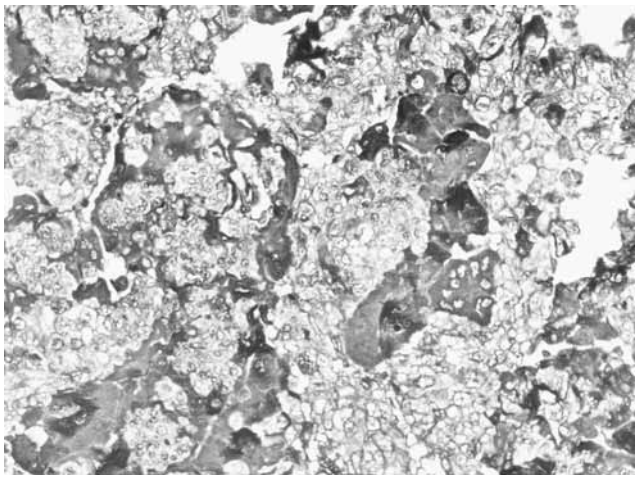

Fig. 3

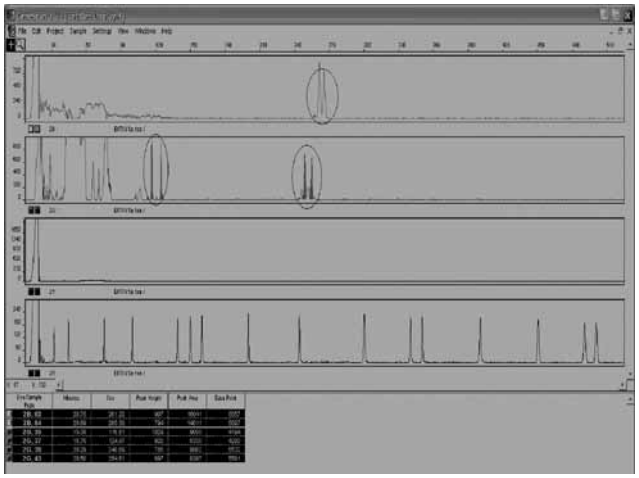

Fig. 4

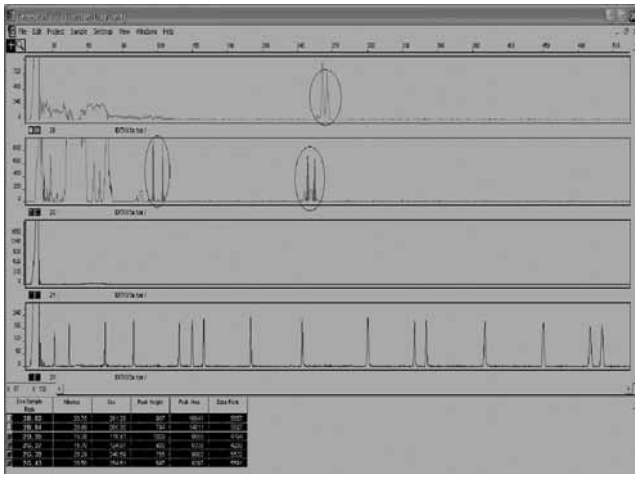

Figure 1. — A mixture of cytotrophoblastic and syncytoiotrophoblastic cells can be seen (H&E x 100).
Figure 2. — Immunohistochemically βhCG positive cells were observed (streptavidin biotin HRP, x 100).
Figure 3. — QF-PCR analysis of extra XY markers from the patient's blood.
Figure 4. — QF-PCR analysis of extra XY markers from tumor paraffin blocks.

tube multiplex QF-PCR in which four STR markers were included. The four markers for chromosomes were SR, DXYS218, DXS6803, and DXS6809 [3] (Table 1). As a result, the same STR regions in both tumor tissue and patient blood were established (Figures 3/4). This result supported the diagnosis of primary ovarian pure nongestational choriocarcinoma.

Table 1. — *List of SRY markers analyzed with the ChromoQuant version 2 kit [3].*

Marker	Label Het.	Choromosomal location of known alleles	bp
SRY	6-FAM	Yp11.2	Y:463
DXYS218	PET 0.63	Xp22.32 Yp11.3	(PAR1)266,270,274,278,282, 286,290,294
DXS6803	VIC 0.68	Xq12-Xq21.33	106,110,114,118,120,124,128
DXS6809	VIC 0.75	Xq	238,242-6,250,252-4-8,260-2-6-8,270-4

Discussion

Nongestatiaonal pure ovarian choriocarcinoma is an extremely rare and very malignant tumor with only 30 cases described to date [4]. Ovarian choriocarcinomas typically occur in children and young adults [2] presenting with pain and an adnexal mass [2]. Since nongestational choriocarcinoma appears like its gestational counterpart, serum βhCG levels are useful in both diagnosing and monitoring the response to therapy for nongestational choriocarcinoma. It should be noted that normal levels of βhCG do not eliminate the presence of metastases or recurrences [1]. In our case after the first operation and EMA/CO therapy the βhCG level was normal but we established a metastatic pelvic mass and performed a second operation.

Choriocarcinoma of the ovary may originate from an ovarian pregnancy or by metastasis from another part of the genital tract (mainly the uterus) or as a germ cell tumor differentiating in the direction of trophoblastic structures commonly with other neoplastic germ cell ele-

ments [1]. Gestational choriocarcinoma includes the first two groups mentioned. The latter origin encompasses nongestational choriocarcinomas. In our patient the pathologist did not determine any ovarian or uterine gestational substance during examination of the surgical material. To distinguish nongestational choriocarcinoma from gestational choriocarcinoma we performed genetic analyses from the patient's blood and tumor tissue in paraffin blocks. We observed XX chromosomes and the same alleles in both examinations. This result supported the diagnosis of primary ovarian pure nongestational choriocarcinoma. Thus we planned a chemotherapy regime for nongestational choriocarcinoma.

Nongestational choriocarcinoma of the ovary is a highly malignant germ cell neoplasm which has fulminant progression [5]. Although gestational choriocarcinoma tends to spread primarily via the blood stream, nongestational choriocarcinoma shows lymphatic and intraabdominal spread as well as hematogenous spread and ovarian choriocarcinomas of germ cell origin may be less responsive to chemotherapy than gestational choriocarcinomas [1]. Goswami *et al*. reviewed 30 cases of nongestational choriocarcinoma in the English literature and their report demonstrated that there was no concensus on the optimal chemotherapy following surgery [4]. Due to its rarity, long-term results with chemotherapy have not been specifically described. Therefore both the MAC (methotrexate, actinomycin, cyclophosphamide) and BEP (bleomycin, etoposide, cisplatin) regimens have been used in patients with nongestational choriocarcinoma. For our patient we used the EMA/CO regimen after surgery. At present our patient's general health is good with no recurrence.

In conclusion, in nongestational choriocarcinoma of the ovary we recommend surgery followed by the EMA/CO regimen as soon as possible to prevent fulminant progression.

References

[1] Talerman A.: "Germ cell tumors of the ovary". In: Kurman RJ (ed.), Blaustein's Pathology of the Female Genital Tract. New York, Springer, 2002, 967.

[2] Scully R.E., Young R.H., Clement P.B.: "Germ cell tumors. General features and primitive forms". In: Rosai J., Sabin L.H. (eds.), Atlas of Tumor Pathology. Tumors of the Ovary, Maldevaloped Gonads, Fallopian Tube, and Broad Ligament. Washington, Armed forces Institute of Pathology, 1998, 239.

[3] Onay H., Ugurlu T., Aykut A., Pehlivan S., Inal M., Tinar S. *et al*.: "Rapid prenatal diagnosis of common aneuploidies in amniotic fluid using quantitative fluorescent polymerase chain reaction". *Gynecol. Obstet. Invest*., 2008, *66*, 104.

[4] Goswami D., Sharma K., Zuthsi V., Tepme A., Niagam S.: "Nongestational pure ovarian choriocarcinoma with contralateral teratoma". *Gynecol. Oncol*., 2001, *80,* 262.

[5] Balat O., Kutlar I., Ozkur A., Bakır K., Aksoy F., Ugur M.G.: "Primary pure ovarian choriocarcinoma mimicking ectopic pregnancy: A report of fulminant progression". *Tumori*, 2004, *90,* 136.

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