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Case Report

Pure Choriocarcinoma of the Ovary in Silver-Russell Syndrome

Tomoko Haruma[a]*, Chikako Ogawa[a], Takeshi Nishida[a], Tomoyuki Kusumoto[a], Keiichiro Nakamura[a], Noriko Seki[a], Takaaki Katayama[b], and Yuji Hiramatsu[a]

[a]Department of Obstetrics and Gynecology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700–8558, Japan, [b]Department of Obstetrics and Gynecology, Himeji St Mary's Hospital, Himeji, Hyogo 670–0801, Japan

Pure ovarian choriocarcinoma is an extremely rare malignancy that can be gestational or non-gestational in origin. Silver-Russell syndrome (SRS) is a rare congenital developmental disorder characterized by pre- and postnatal growth failure, relative macrocephaly, a triangular face, hemihypotrophy, and fifth-finger clinodactyly. We report a rare case of pure ovarian choriocarcinoma occurring in a 19–year-old woman with SRS. Following surgery, multiple chemotherapy courses were effective and she was free of disease at the 10-month follow-up.

Key words: choriocarcinoma, ovary, Silver-Russell syndrome

Pure ovarian choriocarcinoma is an extremely rare malignancy that can be gestational or non-gestational in origin. The gestational type may arise from the gestational tissue of an ectopic ovarian pregnancy or present as a metastasis from a uterine or tubal choriocarcinoma. The non-gestational type is a rare germ-cell tumor with trophoblastic differentiation [1]. The estimated incidence of gestational ovarian choriocarcinoma is 1 in 369 million pregnancies [2]. Non-gestational ovarian choriocarcinoma corresponds to less than 0.6% of all ovarian neoplasms; the pure type is extremely uncommon [3].

Silver-Russell syndrome (SRS) is a rare congenital developmental disorder characterized by pre- and postnatal growth failure, relative macrocephaly, a triangular face, hemihypotrophy, and fifth-finger clinodactyly. Most people affected by SRS show normal intelligence [4]. Although some SRS cases are complicated by various kinds of gonadal dysgenesis, a case of normal pregnancy and delivery has been reported [5]. SRS occurs sporadically; often, no genetic cause can be clearly identified. In recent years, more than 38% of patients have been shown to have hypomethylation in the imprinting control region 1 of 11p15 and around 10% of patients carry a maternal uniparental disomy of chromosome 7 [6–7]. Interestingly, maternally imprinted *PEG10* and *SGCE*, separated by ~2.15 Mb from the syncytin (*HERV-W*) gene at 7q21.3, are implicated in both SRS and choriocarcinoma [8], and may be associated with each other. We herein report a unique case of a purely ovarian choriocarcinoma occurring in a 19–year-old woman with SRS.

Case Report

A 19–year-old woman with SRS was referred to us after suffering lower abdominal pain for several days

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*Corresponding author. Phone:+81–86–235–7320; Fax:+81–86–225–9570
E-mail:m_tochan@yahoo.co.jp (T. Haruma)

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and menstrual delay for 2 months although her previous menstrual cycles had been regular. She had engaged in sexual intercourse, so pregnancy was a possibility. Her height was 126.4 cm but her body weight was only 24.5 kg because of growth failure from SRS. Physical examination revealed abdominal tenderness and anemia (Hb 8.2 g/dL). Ultrasound showed a 10-cm solid mass at the pelvis and fluid in the Douglas pouch. Her serum level of β-human chorionic gonadotropin (β-hCG) was 373,170 mIU/mL. Emergency surgery was performed for abdominal bleeding due to suspected ectopic pregnancy. Intraoperatively, a dark-red, soft, friable 10-cm mass was found in place of the left ovary and was bleeding; hence, a left salpingo-oophorectomy was performed (Fig. 1A). The right ovary and uterus were normal in appearance. Microscopically, the tumor was confirmed to be a pure choriocarcinoma (Fig. 1B, C). Two weeks post-surgery, her serum β-hCG level was 58,855 mIU/mL. Computed tomography (CT) revealed 2 lung metastases (the larger of which was 5 mm) and multiple disseminated peritoneal metastases (Fig. 2A, B). Magnetic resonance imaging (MRI) showed a 58-mm mass in her left pelvis (Fig. 2C, D). The patient scored 8 on the International Federation of Gynecology and Obstetrics (FIGO) scoring system, placing her in the high-risk gestational trophoblastic neoplasia group (≥ 7), at FIGO stage III. Therefore, the patient was treated with EMA/CO chemotherapy, including etoposide (100 mg/m^2 on days 1–2), methotrexate (300 mg/m^2 on day 1), actinomycin-D (0.5 mg/kg on day 1–2), cyclophosphamide (600 mg/m^2 on day 8), and vincristine (1,000 mg/m^2 on day 8) at 14-day intervals. After one cycle of chemotherapy, she suffered from strong side effects—Grade 4 neutropenia and Grade 3 hepatic dysfunction—so we reduced the chemotherapy doses to 70% and extended the interval. She tolerated a total of 6 cycles of chemotherapy with Grade 1–2 neutropenia, nausea and hepatic dysfunction. Her serum β-hCG level decreased to within the normal range after 5 cycles of chemotherapy, and then through the 6th cycle of EMA/CO chemotherapy (Fig. 3). After 6 cycles of chemotherapy, CT and MRI showed that most of the lung metastases and peritoneal disseminations had disappeared, but small lesions in her left pelvis remained. Positron emission tomography (PET)-CT showed fluorodeoxyglucose uptake by that lesion (SUVmax = 3.20) (Fig. 4). Four

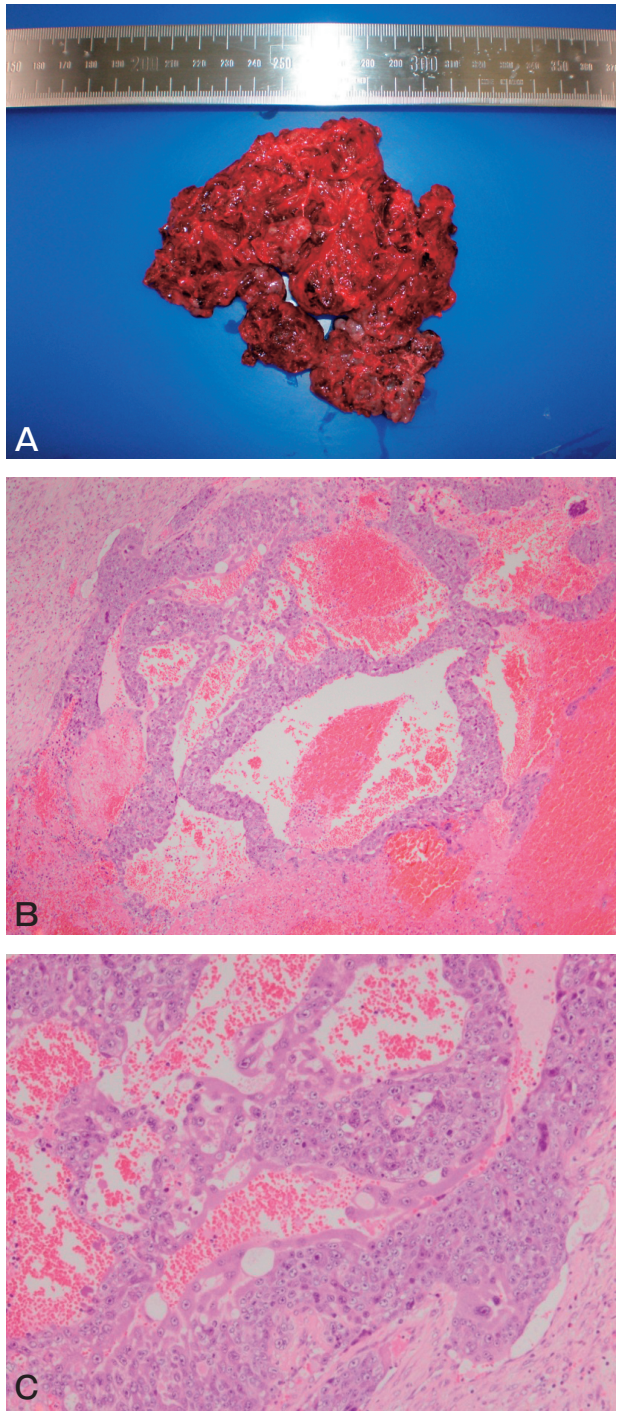

Fig. 1 The left ovary had been replaced by a dark-red, soft, friable 10-cm mass (**A**). Microscopically, the proliferation of cytotrophoblast and syncytiotrophoblast with widespread necrosis was detected. The tumor was confirmed to be a pure choriocarcinoma (Hematoxylin and eosin stain) (**B**, **C**).

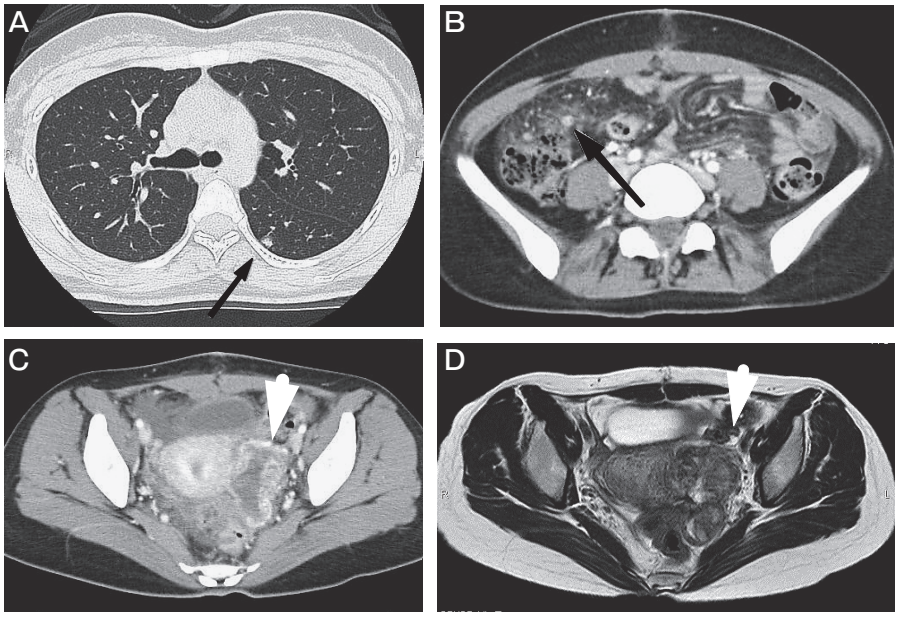

Fig. 2 Computed tomography (CT) showed lung metastasis of 5 mm (**A**) and peritoneal dissemination (**B**). CT and magnetic resonance imaging (MRI) showed a mass of 58 mm in her left pelvis (**C** and **D**).

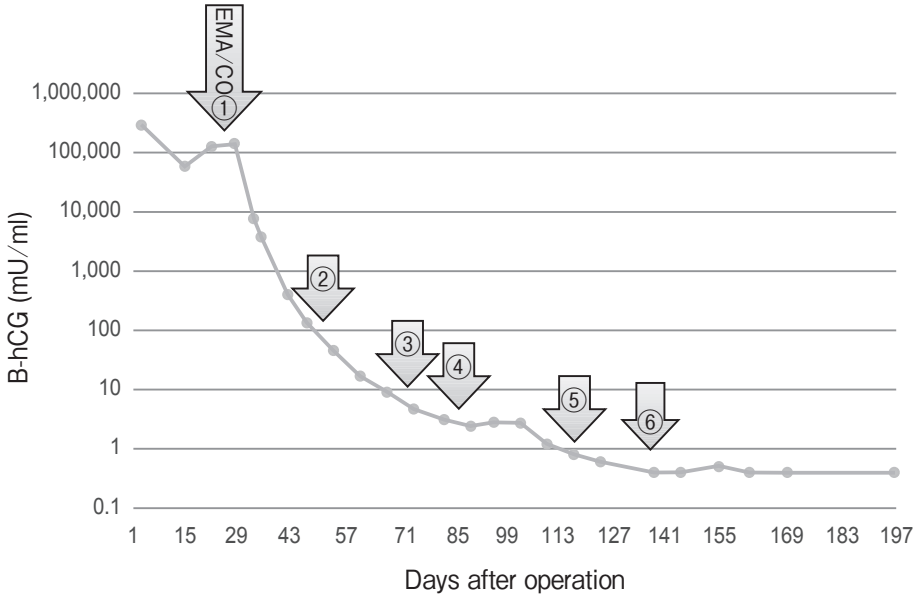

Fig. 3 The serum β-hCG level steadily decreased after chemotherapy started. It was within the normal range after 5 cycles of chemotherapy.

weeks after the final chemotherapy, we observed her abdominal cavity under laparoscopy and found a small, dark brown tumor at the stump of left ligament of the ovary (Fig. 5). We resected it as much as possible; specimens showed no viable residual tumor. The patient remains without evidence of disease after 10 months of follow-up.

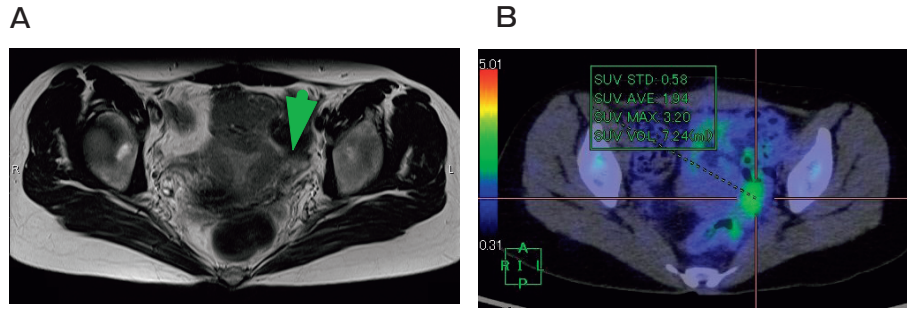

Fig. 4 After 6 courses of chemotherapy, the tumor of the left pelvis had become smaller but still remained (**A**); positron emission tomography (PET)-CT revealed the uptake of fluorodeoxyglucose (SUVmax = 3.20) (**B**).

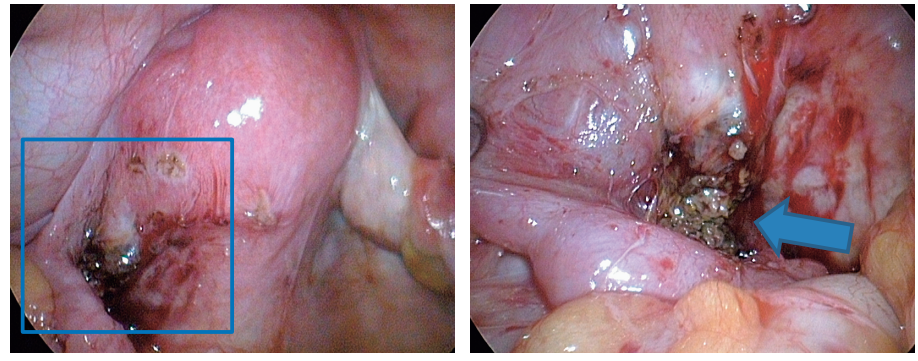

Fig. 5 A small, dark brown tumor at the stump of the left ligament of the ovary was observed during laparoscopy.

Discussion

SRS was first described by Silver and co-workers in 1953, and then independently by Russell in 1954 [9, 10]. It is a rare, genetically heterogeneous disorder occurring in approximately 1 in 50,000–100,000 births, in which patients demonstrate intrauterine and postnatal growth retardation, relative macrocephaly, triangular faces, asymmetry and feeding difficulties [4]. In general the features of the syndrome are most pronounced in young children and become less obvious as the patient becomes older [11]. The condition occurs sporadically and, in many cases, no genetic cause can be clearly identified. Recent studies have shown that epimutation (hypomethylation) of the paternally derived differentially methylated region (DMR) upstream of H19 (H19-DMR) on chromosome 11p15.5, and maternal uniparental disomy for chromosome 7 (upd(7)mat) account for ~45% and 5–10% of SRS patients, respectively [4–8]. Interestingly, maternally imprinted *PEG10* and *SGCE*, separated by ~2.15 Mb from the syncytin (*HERV-W*) gene at 7q21.3, are implicated in both SRS and choriocarcinoma [8, 12–16]. *PEG10*, which is normally a paternally expressed gene, is predominantly expressed in the placenta and testis and to a lesser extent in the brain and lung [17], and codes for a protein homologous to mouse MyEF-3 (myelin expression factor 3), which is presumed to be necessary for producing myelin-binding protein (MBP) and has been shown to participate in myelinating neurons [18]. *SGCE*, the epsilon member of the sarcoglycan family, is a component of the transmembrane dystrophin-glycoprotein (DGC) complex. It mediates communication between the muscle cytoskeleton and extracellular matrix by stabilizing membranes [19]. As these neighboring genes are maternally imprinted in SRS and choriocarcinoma, there is some possibility that they link to placental and fetal development. This is the first case of pure ovarian choriocarcinoma described in a patient with SRS. In this case, maternally imprinted *PEG10* and *SGCE* may have played a role in the histogenesis.

Pure ovarian choriocarcinoma is an extremely rare malignancy which can be gestational or non-gestational in origin. Differentiating between a gestational and non-gestational origin is important because non-gestational choriocarcinoma of the ovary is generally believed to have a poor prognosis. However, in the reproductive-aged group, distinguishing between the two is often unclear, because of both their rarity and the lack of distinctive ultrastructural or immunohistochemical differences [3, 20, 21]. Molecular genetic analysis can reliably identify the genetic origin of pure ovarian choriocarcinomas [22–25], but is an expensive technique with limited availability, so we could not utilize it in this case. We strongly suspected a gestational rather than non-gestational origin because the patient had intercourse 2 months before the surgery and noted interrupted menses; hence, there was the possibility of an ectopic ovarian pregnancy. Furthermore, the tumor's microscopic appearance showed a pure choriocarcinoma without another germ cell tumor component.

As the definitive treatment modality for pure ovarian choriocarcinoma has not been established owing to its low incidence, it is generally treated by the same protocols used for ovarian germ-cell tumor and gestational trophoblastic disease; in recent years, many cases have been treated by cytoreductive surgery followed by post-operative chemotherapy [1, 21]. Our patient was treated with EMA/CO therapy after tumor resection, as her multiple metastases and large lesion remnants required more aggressive combination chemotherapy. The patient responded well to the chemotherapy with a satisfactory decrease in serum β-hCG level. EMA/CO therapy is very effective for choriocarcinoma [26]. Another patient of ours who presented with choriocarcinoma after a term delivery has survived for more than 25 years in complete remission; she initially had lung and brain metastases with motor aphasia and hemiplegia, and was treated by an EMA/CO regimen [27].

Although the present patient's serum β-hCG level was normalized, pelvic lesion remnants were detected by MRI. Observation and laparoscopy-guided biopsy were very useful in deciding to end the treatment. We saw no evidence of recurrence or metastasis at the 10-month follow-up. Close observation of serum β-hCG levels and imaging examinations is necessary because pure ovarian choriocarcinoma is aggressive with a high risk of metastasis.

In conclusion, we report the first known case of a purely ovarian choriocarcinoma occurring in a patient with SRS. Maternally imprinted *PEG10* and *SGCE* have been reported to be implicated in both SRS and choriocarcinoma. This case may have occurred because of this common genetic cause.

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