Virchows Arch (1996) 429:185–188

CASE REPORT

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Choriocarcinoma in situ at a first trimester

Report of two cases indicating an origin of trophoblast of a stem villus

Received: 13 February 1996 / Accepted: 24 April 1996

Abstract Two cases of choriocarcinoma in situ arising in a first trimester placenta are reported in a 28-year-old gravida 2, para 1, Japanese woman and a 38-year-old gravida 2, para 0. Both had a dilation and curettage (D and C) for vaginal bleeding and the absence of intrauterine fetus. No macroscopic abnormalities were noted in either case. However, histologically, localized nodules of neoplastic trophoblastic proliferation measuring 5 mm in the first case, and 6 mm in the second appeared to arise directly from normal stem villi and project into the intervillous space. Both tumours were composed of biphasic cytotrophoblast and syncytiotrophoblast. Fetal elements were not observed in either case. Radiographic studies showed no metastatic lesions in either patient. Urinary human chorionic gonadotropin levels were within normal range in both patients. The first patient had a normal full-term spontaneous vaginal delivery 22 months after the D and C and was free from disease without therapy at 32 months. The second patient was free from disease without therapy with a limited follow-up. These tumours provide evidence for an origin of choriocarcinoma from trophoblast of a stem villus. This report illustrates the need to perform thorough microscopic examination of the products of conception especially in the absence of a fetus or fetal parts.

Key words Choriocarcinoma · Placenta · In situ · Flow cytometry · Immunohistochemistry

Introduction

Forty to fifty percent of choriocarcinomas stem from antecedent hydatidiform moles and 25%–30% from previous abortions or ectopic pregnancies. Around 20% follow normal pregnancies and deliveries [1, 22]. Choriocarcinoma in a seemingly normal placenta is rarely documented with only a few cases in the English language literature [1–8, 10, 11, 13–21]. The term "choriocarcinoma in situ", which is used to designate neoplastic trophoblastic proliferation localized to the placenta and implies the absence of metastases, is a very rare condition and has been reported in only eight cases in the English language literature [6–8, 10, 13, 17, 20]. In this report, two cases of choriocarcinoma in situ arising in first trimester gestational placentas are described. The early development of choriocarcinoma is also discussed.

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Case reports

Case 1

A 28-year-old gravida 2, para 1, Japanese woman presented with vaginal bleeding after an 11-week history of amenorrhoea in September, 1992. She had had a full-term spontaneous vaginal delivery in November 1990. Physical examination and ultrasound examination showed no evidence of a fetus in an enlarged uterus. Pregnancy tests were positive. Serum and urine levels of β-subunit human chorionic gonadotropin (β HCG) were not evaluated at the time of admission. She had no history of miscarriage in the 20 months between the pregnancies. A dilatation and curettage (D and C) was performed. Urine HCG level was within normal range (5.7 IU/l) on the 23rd post-operative day. Chest radiographs did not show any significant abnormalities. The patient had a normal full-term spontaneous vaginal delivery 22 months after the D and C and was free from disease without therapy at 32 months. This case has been reported in more detail elsewhere [10].

Case 2

A 38-year-old gravida 2, para 0, Japanese woman presented with vaginal bleeding after a 9-week history of amenorrhea in September, 1995. She had two voluntary abortions at the ages of 29 and 31, respectively. Pregnancy tests were positive and urine levels of HCG was within normal range (4000 IU/l) at the time of admission. Physical examination and ultrasound examination showed no evidence of a fetus in an enlarged uterus. Following a clinical diagnosis of incomplete abortion, a D and C was performed. Urine HCG level was within normal range (80 IU/l) on the 15th post-operative day. Chest radiographs did not show significant abnormalities. The patient was free from disease without therapy at 4 months.

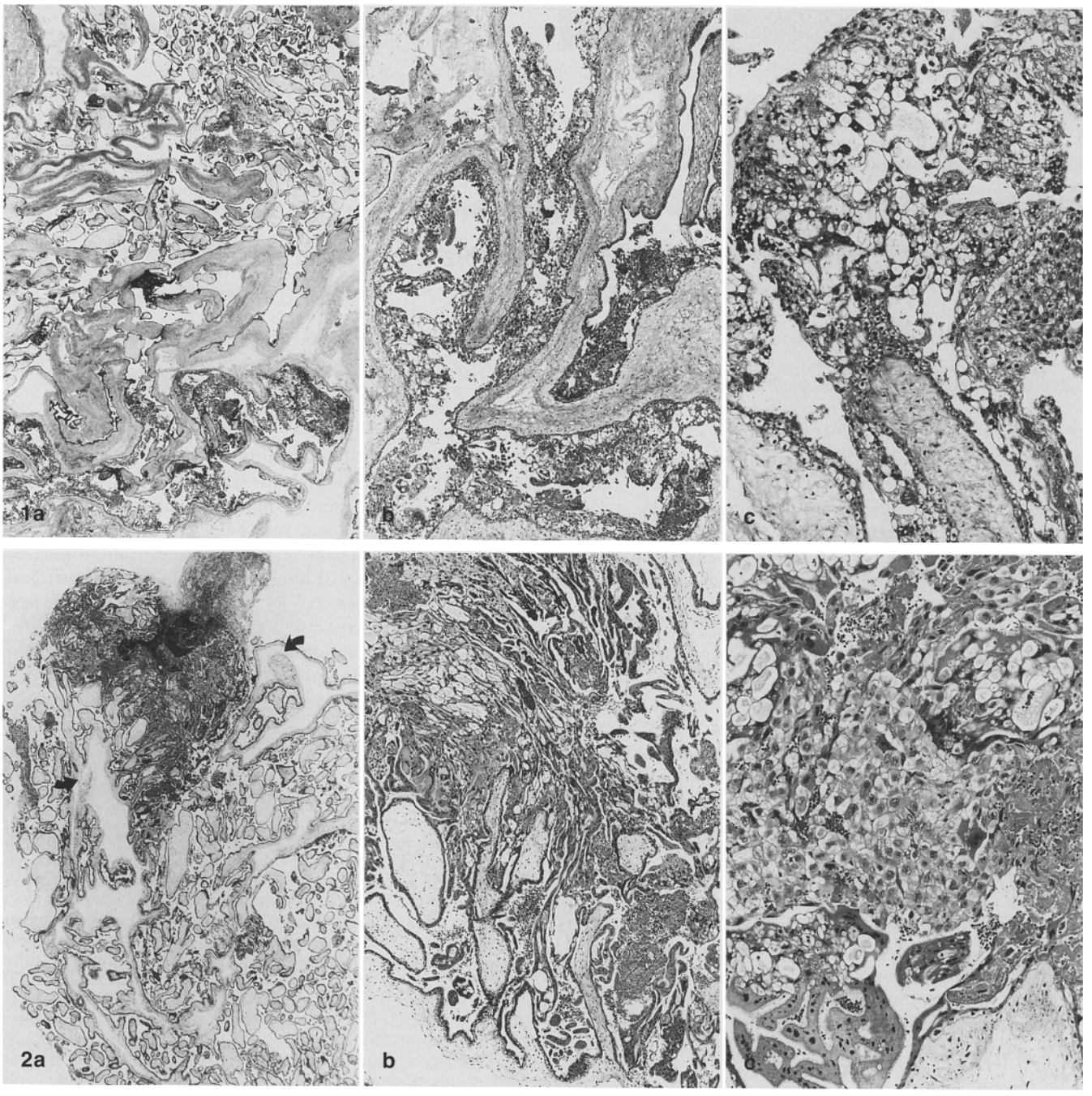

Fig. 1a–c Case 1. **a** Neoplastic trophoblastic proliferation appears to arise from a stem villus (*bottom*) and uninvolved villi do not show hydropic change or trophoblastic hyperplasia (*top*). **b** Tumour cells are in direct continuity with a normally appearing stem villus. There is no stromal or vascular invasion. **c** The tumour is composed of cytotrophoblasts and syncytiotrophoblasts with lacunae formation

Fig. 2a–c Case 2. **a** The neoplastic trophoblastic nodule (*top*) appears to be closely associated with a stem villus (*arrows*) and uninvolved villi do not show hydropic change or trophoblastic hyperplasia. **b** Note a prominent neoplastic proliferation of trophoblast. **c** Solid nest composed of cytotrophoblasts and syncytiotrophoblasts is accompanied by haemorrhagic necrosis (*right*)

Pathological findings

The curettage specimens of 3 ml and 5 ml in case 1 and case 2, respectively, contained non-hydropic villi and decidual tissues. There appeared to be no macroscopic abnormalities in each case. Histologically, 5 mm and 6 mm nodules, of neoplastic trophoblastic proliferation, appeared to arise directly from normal stem villi and project into the intervillous space (Figs. 1a, 2a). Both tumours were composed of biphasic malignant cytotrophoblast and syncytiotrophoblast. Some tumour cells were in direct continuity with normally appearing villi (Figs. 1, 2). Nuclear atypia of cytotrophoblastic cells was mild to moderate and mitotic figures were scattered. Haemor-

rhagic necrosis was observed in the lesions (Fig. 2c). Serial sections showed no tumour invasion in villous stroma or vascular spaces. Uninvolved villi did not show hydropic change or trophoblastic hyperplasia. Fetal elements were not observed in either case.

The immunohistochemical profiles in case 1 and case 2 were identical. The malignant cyto- and syncytiotrophoblast showed diffuse reactivity for monoclonal anti-cytokeratin, PKK1 (44, 46, 52 and 45 kDa, Labsystems, Helsinki, Finland, diluted 1:200). Most of the syncytiotrophoblastic cells and some cytotrophoblastic cells were positive for polyclonal anti-β HCG (Dakopatts, Glostrup, Denmark, diluted 1:200), polyclonal anti-human placental lactogen (HPL; Dakopatts, diluted 1:400) and polyclonal anti-placental alkaline phosphatase (PLAP; Dakopatts, diluted 1:300). β HCG and PLAP reactivities in the tumour component were stronger than those in the surrounding normal villi; HPL reactivity was almost the same as in the normal villi.

Flow cytometric analysis using formalin-fixed, paraffin embedded tissue blocks showed that both neoplasms had diploid DNA content with S-phase fraction of 10.8% and 14.6%, respectively. The half peak coefficients of variation were 7.4% and 3.2%, respectively.

Discussion

Placental choriocarcinomas are classified into the following clinicopathological groups; choriocarcinoma in situ and choriocarcinoma with metastases in a patient or a fetus. The majority of patients with choriocarcinoma following a seemingly normal pregnancy are diagnosed after or around a term delivery. However, the current lesions were characterized by their early gestational stages, very small lesions confined in or closely associated with stem villi, the presence of non-molar villi, scattered mitotic figures, moderate atypia of cytotrophoblasts and the absence of a fetus or fetal parts. The small volume of the curettage specimens might be due to the previous passage of some tissue per vagina. These tumours were clinically and pathologically unsuspected. Our initial diagnoses were "products of conception, first trimester" and "products of conception with focal trophoblastic hyperplasia, first trimester", respectively. It is assumed that a pathologist hesitated to make a diagnosis of choriocarcinoma because of the presence of normally appearing villi, of the early gestational stage and of the curettage specimen. No β HCG evaluation was performed before the D and C in case 1. The patient in case 2 had low levels of β HCG before and after curettage. It is not certain whether the level of β HCG will be elevated in the presence of such a small choriocarcinoma. We assume that almost all choriocarcinomas in situ at an early gestational stage have been expelled as a spontaneous abortion, or curettaged. Most of them will not have been recognized by clinician or pathologist. The immunoreactivity of these neoplasms was almost the same as that of previously reported gestational choriocarcinomas [9].

Both tumours were diploid by flow cytometry with S-phase fraction of 10.8% and 14.6%, respectively. To our knowledge, there have been only two flow cytometric studies of placental choriocarcinoma. Our previous study [9] showed that all gestational choriocarcinomas were exclusively diploid with an average S-phase fraction of 15.6%. Hemming et al. [12] recorded the presence of diploidy in all four cases of choriocarcinoma. However, a possibility of near-diploid aneuploidy cannot be ruled out completely. Studies of additional cases are necessary to determine whether ploidy, cell cycle analyses and genetic studies are helpful in predicting behaviour in placental choriocarcinomas [10].

The origin of choriocarcinoma in situ has been assumed to be in normal villous trophoblast, in focal placenta accreta or in normal intravascular trophoblast at or near the implantation site. But these assumptions are based entirely on interpretation of clinical events and remain to be proved [3, 10]. The present tumours, which were found at the earliest gestational stages among reported cases, suggest that choriocarcinoma may arise from trophoblast at any stage of pregnancy and in association with a stem villus. The absence of villi in late lesions has been attributed to the extensive degeneration or necrosis associated with choriocarcinoma [2, 19]. In the present two cases fetal vessels were observed, but no fetal element was found. We assume that the lesion might be due to chromosomal abnormality although chromosomal analysis was not performed.

The majority of patients with choriocarcinoma following a term pregnancy are diagnosed late when they present with a bizarre clinical picture elicited by the presence of widespread metastases. Labour and delivery might be factors in the dissemination of choriocarcinoma localized to the placenta. Almost all reported placental choriocarcinomas have been extremely small or have macroscopic appearance of infarction [2, 3, 5–8, 13, 15, 17, 19–21]. Among the seven reported choriocarcinomas in situ, four were associated with a fetus or living infant [7, 13, 17, 20] and in the remaining three not fetus was found [6, 8]. The uncommon occurrence of early choriocarcinoma in the placenta of a pregnancy which resulted in a viable newborn may provide justification for detailed gross examination of term placentas with sampling of any nodules or suspicious areas.

As in the current cases, all the reported cases of choriocarcinoma in situ had a good prognosis [6–8, 13, 17, 20]. All patients with placental choriocarcinomas require immediate clinical evaluation, including monitoring of serum HCG and radiographic studies, for metastatic disease. Even an early or small choriocarcinoma associated with villi and a fetus is capable of metastastosis. The infants also require follow-up study. In the presence of metastases, the patient can receive timely chemotherapy conducive to a favorable outcome.

In conclusion, the present tumours provide evidence for an origin of choriocarcinoma from trophoblast of a stem villus. This report illustrates the need to perform thorough microscopic examination of the products of

conception especially in the absence of a fetus or fetal parts.

Acknowledgements The authors thank Masaki Sugimoto, Tae Makino, Toshiko Yoshida and Ukihiro Takeuchi for their technical assistance, and Michiko Takaki for preparation of the photographs.

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