Peripheral precocious puberty in a girl with an intracranial hCG-producing tumor: case report and literature review

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Abstract. Human chorionic gonadotropin (hCG)-producing tumors cause peripheral precocious puberty (PP) in boys, but generally not in girls. Homology between LH and hCG activates the LH receptor in testicular Leydig cells, increases testosterone production, and causes virilization. However, since FSH action is required for follicle development, hCG action alone does not increase estradiol (E2) production and does not cause feminization. Only a few cases of peripheral PP with hCG tumors in girls have been reported. We describe the case of a 7-year-old Japanese girl with peripheral PP associated with an hCG-producing tumor. She had prolonged vomiting, loss of appetite, and Tanner stage III breast development. Although no apparent increase in growth rate, bone age was advanced at 9.8 years. Serum E2 was slightly elevated and LH and FSH were below the measurement sensitivity, and abdominal ultrasonography and computed tomography images showed no abnormal findings in the uterus or ovaries. Subsequently, she developed visual field disturbance and loss of consciousness, and brain magnetic resonance imaging revealed an intracranial tumor. Based on pathological findings and abnormally high serum hCG-β level (48,800 IU/L), intracranial choriocarcinoma was diagnosed. 2.5 months after the start of chemotherapy, the hCG-β level became almost negative and the breast development disappeared synchronously. Tissue immunostaining of the tumor showed strong positivity for aromatase and hCG, indicating that the choriocarcinoma cells themselves may have produced estrogen via aromatase. This unique case highlights the possibility that hCG-producing tumors can cause peripheral PP in girls as well as boys.

Key words: Peripheral precocious puberty, Human chorionic gonadotropin-producing tumor, Choriocarcinoma, Aromatase

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Case Report

A 7.5-year-old girl with a history of surgery for congenital duodenal stenosis was admitted to our pediatric surgery department because of vomiting and loss of appetite for the past 6 months. Physical examination on admission revealed breast enlargement (Fig. 1A), and the patient was consulted by a pediatric endocrinologist. She weighed 19.6 kg, and her height was 117 cm (–1.0 SD), with a 4.2 cm/year increase in height (Fig. 1B). Her breast development was Tanner stage III, and there were no signs of pubic hair, genital bleeding or clitoromegaly. Bone age was accelerated at 9.8 years, while serum LH, FSH, and estradiol (E2) levels were all below the measurement sensitivity. Abdominal ultrasonography and computed tomography (CT) images showed no ovarian cysts or tumors, uterine size at prepubertal level, and no endometrial structures in the uterus. Based on these findings, we tentatively diagnosed her with peripheral PP with functional ovarian cyst regression and planned to monitor her pubertal progress.

The cause of her vomiting and loss of appetite could not be identified. One month later, she developed visual field disturbance and loss of consciousness, and brain magnetic resonance imaging (MRI) revealed a large suprasellar mass (Fig. 1C). Head CT demonstrated a 3rd ventricular tumor with intra-tumoral hematoma. The hCG-β levels were markedly increased in serum (48,800 IU/L) and cerebrospinal fluid (28,200 IU/L), α-fetoprotein levels were within the normal range, and

Fig. 1  A. Breast development
The photo on the left shows Tanner stage III upon admission, and the photo on the right shows Tanner stage I upon completion of chemotherapy.
B. Growth Curve
There is no growth acceleration associated with precocious puberty.
C. Magnetic resonance images in the sagittal view
A tumor is found extending from the upper part of the intracranial saddle to the third ventricle. The tumor size is 4 cm × 5 cm and irregular. There are findings suggestive of bleeding around the mass. The hypothalamus and the vicinity of the brain pons are compressed. The hyperintense signal of the posterior pituitary lobe is absent in T1 weighted images.
serum levels of LH, FSH, and E2 were <0.2 mIU/mL, <1.0 mIU/mL, and E2 30 pg/mL, respectively. Based on the biopsy findings and a marked increase in hCG levels, she was diagnosed with choriocarcinoma. She was immediately treated with chemotherapy and whole brain and spinal radiation. A decrease in hCG-β level to 17 UI/L was observed in the post-neoadjuvant chemotherapy period. 2.5 months after the start of chemotherapy, endocrinological evaluation showed regression of puberty, including the disappearance of breast development (Fig. 1A) and below measured sensitivity of serum E2 levels (Fig. 2). The results of the insulin, TRH, and LHRH loading tests performed after the completion of chemotherapy are shown in Fig. 2. She presented with panhypopituitarism due to hypothalamic dysfunction and no recovery of gonadotropins.

Pathological Findings

Histologically, the tumor specimen showed multinucleated syncytiotrophoblast-like cells. Immunohistochemical findings were positive for hCG and cytokeratin. Based on these findings, a diagnosis of choriocarcinoma was made. Additional aromatase staining was performed, which was strongly positive. A control specimen (9-year-old girl, serum hCG-β 2,491 IU/L, no signs of precocious puberty) was stained for aromatase as well, but only a small portion of the specimen stained lightly (Fig. 3).

Discussion

The present case was a girl with peripheral PP associated with an hCG-producing intracranial tumor. After treatment for choriocarcinoma, the serum hCG-β level became less sensitive, and breast development subsequently disappeared. This clinical course suggests that the tumor may have caused the peripheral PP.

Most patients with peripheral PP due to hCG-producing tumors are boys, but it has been reported in a few girls [3-7] (Table 1). Four of the five patients had intracranial hCG-producing tumors, and the tumor in the remaining patient was of ovarian origin. Serum hCG or hCG-β concentrations varied and did not correlate with serum E2 levels or genital bleeding. Serum androgens were slightly elevated in three patients [3, 4], and there was no apparent increase in the other cases. Breast development was present in all cases but disappeared within a few months after tumor shrinkage. Two patients with genital bleeding had serum E2 levels over 100 pg/mL.

Half of the reports of peripheral PP in girls associated with hCG-producing tumors are from Asia. Central nervous system (CNS) germ cell tumors (GCTs) in Western
countries account for 3–4% of primary brain tumors in children; however, in Japanese and Asian cases it has been reported to be approximately 15% of pediatric CNS tumors [10-13]. It is important to note that tumors containing choriocarcinoma components can be present in the background even in girls with peripheral PP, especially if the patient is Asian.

The mechanism of PP in girls with hCG-producing tumors has not been elucidated. Kitanaka et al. [3] suggested that tumors secreting hCG can produce estrogen because the tumor-derived hCG has a very weak FSH effect; therefore, E2 is produced when hCG levels are markedly high. Meanwhile, O’Marcaigh et al. [4] reported that tumor-derived aromatase causes the production of E2 from androgens, inducing PP. High hCG levels do not necessarily cause peripheral PP in girls [14, 15], suggesting that tumor-derived aromatase production may be involved in PP development. The results of our immunohistological study support the production of aromatase from the tumor. Furthermore, in vitro studies have reported testosterone-free estradiol production in choriocarcinoma cells [16]. In fact, gynecomastia has been reported in males with hCG-producing tumors [17-20], presumably because tumors themselves produce estrogen.

In summary, we report a case of peripheral PP in a girl associated with an hCG-producing tumor. hCG-producing tumor-derived aromatase may cause peripheral PP even in girls.

### Fig. 3
Immunohistological study of the tumor
The tumor cells strongly stained for hCG (left panel) and aromatase (right panel).

### Table 1
Summary of patients with peripheral precocious puberty in girl due to the hCG-producing tumor

| Age (years) | Bone Age (years) | B (Tanner stage) | P (Tanner stage) | M | L | LH (mIU/mL) | FSH (mIU/mL) | E2 (pg/mL) | T (ng/dL) | A (ng/mL) | DHEA-S (μg/dL) | hCG-β (IU/L) | Time to treatment | Tumor site and pathological diagnosis | Reference |
|-------------|------------------|------------------|------------------|---|---|---------------|--------------|-------------|-----------|----------|-------------|---------------|----------------|-------------------------------------|------------|
| 6.3         | 7.6              | II               | I                | No |   | <2.0         | <1.0         | 31–47      | 17.5      | 2.1       | 19           | 1,800.5       | 2 months      | Suprasellar immature teratoma         | 3          |
| 8           | ND               | II               | I                | No |   | <0.2         | <0.5         | 62.1       | <10       | 0.96      | 47.9         | 187           | ND            | Suprasellar germ cell tumor           | 4          |
| 5           | 5                | II               | I                | No |   | 306.2        | 8.9          | not detected | 40        | ND        | ND           | 47            | 747.4         | 8 months                  | Suprasellar pinealoma            | 5          |
| 6           | ND               | III              | ND               | Yes |   | <0.7         | <1.0         | 104        | ND        | ND        | ND           | ND            | 7 months      | Ovarian dysgerminoma                  | 6          |
| 5.8         | 5                | III              | III              | Yes |   | 0.37         | 0.45         | 213.4      | 120       | ND        | 69.8         | 924.5         | 2 weeks       | Suprasellar mixed germinoma or embryonic carcinoma | 7          |
| 7.5         | 9.8              | III              | I                | No |   | <0.2         | <1.0         | 30         | 4.36      | ND        | ND           | 48,800        | 8 months      | Suprasellar choriocarcinoma           | Present case |

Abbreviations: B, breast development; P, pubic hair; M, menstruation; E2, estradiol; T, testosterone; A, androstenedione; DHEA-S, dehydroepiandrosterone-sulfate; ND, No data

* Time from breast development to diagnosis for tumor
* The LH and FSH kit (RIA method) shows elevated LH/FSH levels due to cross-reactivity between LH/FSH and hCG.
* The data shows the serum hCG level.
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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

Authorship

K.N. and N.S. conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. M.O. provided immunostaining of pathology specimens and reviewed and revised the manuscript. H.N., S.S. and Y.O. collected data and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Compliance with Ethics Guidelines

Written consent to present the manuscript was obtained from the mother. A single case report does not require our ethics approval.

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