CLINICAL CASE SEMINAR

Localization by Venous Sampling of Occult Chorionic Gonadotropin-Secreting Tumor in a Boy with Mosaic Klinefelter's Syndrome and Precocious Puberty

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Germ cell tumors account for only 3% of pediatric malignancies (1). They are usually asymptomatic until they produce symptoms because of mass effect (2). However, germ cell tumors that secrete chorionic gonadotropin (hCG) cause precocious puberty in boys (3).

Primary mediastinal germ cell tumors are usually large at the time of detection (4). Review of the literature revealed no reports of germ cell tumors too small to be seen with modern imaging techniques. However, in 1971 Rudnick and Ode11 (5) reported a man with an occult hCG-secreting tumor that proved to be testicular at postmortem examination. Here we report a 5-yr-old boy who developed rapidly advancing precocious puberty caused by a 3-mm hCG-secreting tumor that could not be located by an exhaustive radiological evaluation. The tumor ultimately was localized to the right thymic lobe by widespread venous sampling to identify gradients of intact hCG and α-glycoprotein subunit.

Germ cell tumors are associated with Klinefelter's syndrome (6), and one germ cell tumor has been reported in a patient with mosaic Klinefelter's syndrome (25% 47XXY cells) (7). Our patient was found to have mosaic Klinefelter's syndrome with only 2-3% 47XXY cells. This is the first patient with precocious puberty caused by a germ cell tumor that could not be localized with modern imaging methods, and also the first germ cell tumor to be associated with such low level mosaicism for Klinefelter's syndrome.

Case Report

The patient was a 5.8-yr-old male referred for LHRH-independent precocious puberty of unknown etiology. The patient had had a routine physical examination at 5.2 yr of age, which was completely unremarkable. Over the next 7 months, he rapidly developed secondary sexual characteristics and accelerated growth.

Laboratory studies before referral to the National Institutes of Health (NIH) showed LHRH-independent precocious puberty. Plasma LH and FSH were both <0.3 IU/L. Plasma dehydroepiandrosterone sulfate was 100 μg/dL (2.7 μmol/L); normal is ≤41 μg/dL (≤1.1 μmol/L). Plasma testosterone was 1469 ng/dL (51.0 nmol/L); normal is <10 ng/dL (<0.3 nmol/L). Bone age was 7 yr at chronological age 5.8 yr. The patient was referred to the NIH.

A urine pregnancy screen was positive, which indicated an hCG-secreting tumor. Subsequent plasma-intact hCG levels ranged from 64–87 IU/L and plasma α-glycoprotein subunit levels ranged from 1.2–1.5 ng/mL (normal is <3 ng/mL). Plasma α-fetoprotein and carcinoembryonic antigen were normal. Plasma testosterone ranged from 1410 ng/dL (48.9 nmol/L) to 1830 ng/dL (63.4 nmol/L). Peripheral blood karyotype initially revealed 46XY in 50/50 cells examined, and subsequently showed 47XXY in 2/76 cells (46XY in 74/76 cells) and 1/50 47XXY cells (49/50 46XY cells).

Magnetic resonance imaging and computed tomography (CT) of the head were normal. hCG was undetectable in the cerebrospinal fluid (<0.24 IU/L). Testicular ultrasound showed no lesions. Magnetic resonance imaging and CT of the chest and abdomen (including ultra-fast CT after a rapid bolus of contrast) revealed only a large, water-density thymus. No abnormality was seen on mediastinal ultrasound.

Because the source of hCG could not be localized, widespread venous sampling for hCG and α-glycoprotein subunit was performed (Table 1). The patient received T3 for 1 week before venous sampling to suppress the thyrotroph cell contribution to the peripheral α-glycoprotein subunit levels. [Alpha]-glycoprotein subunit level in the right thymic vein was >2.2-fold higher than the level in all of the other locations sampled, and the intact hCG level in the same sample was >1.5-fold higher than the level in the other veins tested (Fig. 1).

Subsequent right internal mammary arteriography demonstrated a small (3–4 mm) hypervascular lesion in or near the right thymic lobe (Fig. 2). Repeat venous sampling again...
showed a \( >2.1 \)-fold gradient of \( \alpha \)-glycoprotein subunit and a \( >1.5 \)-fold gradient of intact hCG between the right thymic and peripheral veins.

At mediastinal exploration, a small tumor was visualized in the right thymic lobe. A frozen section confirmed a germ cell tumor. Thymectomy was performed and nodes were examined and biopsied. Final pathology revealed a tumor, measuring 3 mm in its largest dimension, that was predominantly immature teratoma with foci of choriocarcinoma and endodermal sinus tumor. No areas of seminoma were seen. Immunohistochemical staining was positive for hCG in the areas of choriocarcinoma and for \( \alpha \)-fetoprotein in the areas of endodermal sinus tumor. None of the five biopsied lymph nodes showed evidence of tumor.

The patient had an uncomplicated postoperative course. Plasma hCG fell below the detection limit (<0.5 IU/L) by the fourth postoperative day. The plasma testosterone level fell below the detection limit [<19 ng/dL (<0.7 nmol/L)] within 1 day after surgery.

After surgery, the patient received four courses of cisplatin, bleomycin, and etoposide. At 24 months after thymectomy, there was no clinical, laboratory, or radiological evidence of recurrence.

Discussion

This boy with low-level mosaicism for Klinefelter's syndrome developed LHRH-independent precocious puberty because of a minute, hCG-secreting thymic germ cell tumor that could not be visualized by conventional noninvasive radiological techniques. The unique features of this patient were the minute size of the tumor, its localization by venous gradients in the levels of both hCG and \( \alpha \)-glycoprotein subunit, and the low level mosaicism for Klinefelter's syndrome.

Although venous sampling has located many occult endocrine tumors, it has not previously been used to locate an

| Vein Sampled            | Intact hCG (IU/L) | \( \alpha \)-Glycoprotein subunit (ng/mL) |
|-------------------------|------------------|----------------------------------------|
| Right petrosal          | 21               | <0.7                                   |
| Left petrosal           | 23               | <0.7                                   |
| Right internal jugular (2 levels) | 10, 20       | <0.7, 0.7                              |
| Left internal jugular (2 levels) | NA, 20       | <0.7, 0.7                              |
| Common inferior thyroid  | 18               | <0.7                                   |
| **Right thymic**         | **39**           | **2.0**                                 |
| Azygos (3 levels)        | 22–26            | <0.7–0.7                                |
| Right ascending lumbar   | 24               | <0.7                                   |
| Left ascending lumbar    | 23               | <0.7                                   |
| Right hepatic            | 16               | <0.7                                   |
| Middle hepatic           | 24               | 0.9                                    |
| Left hepatic             | 9                | <0.7                                   |
| Right renal              | NA               | <0.7                                   |
| Left renal               | 22               | <0.7                                   |
| Left adrenal             | 24               | <0.7                                   |
| Right internal iliac     | 22               | 0.7                                    |
| Left internal iliac      | 23               | <0.7                                   |
| Left common iliac        | 22               | <0.7                                   |
| Right femoral            | 21               | <0.7                                   |
| Left testicular          | 24               | <0.7                                   |

\(^a\) Not currently convertible to SI units.

\(^b\) NA, Not available because of insufficient sample.

\(^c\) **Bold type** indicates single thymic sample that contained a step up in both hCG and \( \alpha \)-glycoprotein subunit levels.

**FIG. 1.** Widespread venous sampling. Catheter tip is in the common thymic vein and tip of sampling Tracker catheter (Target Therapeutics, Freemont, CA) (arrow) is in the right branch of the thymic vein. Both hCG and \( \alpha \)-glycoprotein subunit were elevated in the thymic vein samples compared with peripheral levels. A second sampling confirmed these findings.
hCG-secreting tumor (5). This reflects both the nonoccult nature of most hCG-secreting tumors and the long half-life of hCG, which decreases the concentration gradient between the tumor and the peripheral veins. In the current study we sought concordant gradients of both intact hCG and α-glycoprotein subunit as an indication of a tumor. Because the α-glycoprotein subunit is cleared 25-fold more rapidly than intact hCG (8, 9), we predicted that the α-glycoprotein subunit would exhibit a greater concentration gradient near the tumor, provided that there was sufficient tumoral secretion of the α-subunit to generate measurable peripheral levels. However, the peripheral level of α-glycoprotein subunit during thyrotroph suppression by T₃ was below the assay detection limit, and both gradients indicating a tumor were small and were restricted to a single sampling site. Nonetheless, the concordance of gradients for both intact hCG and α-glycoprotein subunit, the minute arteriographic blush at the sampling site, confirmation of the gradient during repeat venous sampling, and knowledge of the mediastinal predilection of germ cell tumors all contributed to the decision that mediastinal exploration was warranted.

Rudnick and Odell (5) reported a 22-yr-old man with gynecomastia caused by an hCG-secreting tumor who died 9 months after initial evaluation because of widespread metastases. Postmortem examination revealed a 4-mm primary lesion in the left testis, which had not been detected by physical examination, testicular venous sampling to measure intact hCG, or by surgical exploration with bisection and biopsy of the testes. Modern imaging techniques for the testes were not available at the time.

The literature contains only a single report of a germ cell tumor occurring in a patient with mosaic Klinefelter's syndrome (7). This 9.8 yr old male had LHRH-independent precocious puberty, a large mediastinal mass, and elevated
serum levels of hCG, α-fetoprotein, and testosterone (997 ng/dL, [34 nmol/L]). The peripheral karyotype revealed 25% 47XXY, 75% 46XY cells. Although the clinical presentations of these patients were similar, our patient differed by having a much smaller tumor and 10-fold fewer 47XXY cells (2-3%) in the peripheral karyotype. Although we hypothesize that our patient’s tumor arose in a 47XXY cell line, this could not be confirmed because of the small size of the tumor.

This patient exhibited three clinically important points. First, extraordinarily small hCG-secreting tumors can have dramatic systemic effects. Second, localization of such tumors can be achieved by venous sampling for hCG and the α-glycoprotein subunit. Third, karyotyping should be performed on male patients with germ cell tumors to seek evidence for Klinefelter’s syndrome because the two entities are associated.

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