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Suppressed gonadotropins as a warning sign of an extragonadal tumor in an adolescent with Klinefelter syndrome

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ABSTRACT

Patients with Klinefelter syndrome have an increased risk of certain neoplasms, particularly germ cell tumors, especially those located outside the gonads.

We report a case of a mediastinal germ cell tumor in an adolescent patient. The diagnosis was reached based on unusual gonadotropin values.

Keywords: *Klinefelter syndrome; germ cell and embryonic neoplasms; mediastinal neoplasms.*

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INTRODUCTION

Klinefelter syndrome (KS) is the most common sex chromosome disorder in humans, occurring in 1 out of every 600 males. Characteristically, they present with hypergonadotropic hypogonadism.[1]

Patients with KS have increased morbidity and mortality resulting from the impact on the endocrine-reproductive, cardiovascular, neurocognitive, and metabolic systems.[1] The risk of neoplasms is increased in patients with KS.[2-4] Germ cell tumors (GCTs) originate in gamete precursor cells. Between 5% and 10% of GCTs are extragonadal, usually located in the midline, central nervous system, mediastinum, or abdomen.[5]

The increased incidence of GCT in SK is based on case reports. One review reports fewer than 150 cases of extragonadal GCT, with a peak incidence in late puberty and a predominantly mediastinal distribution. The hormonal profile of these patients is not described.[6]

We report a patient with SK whose unusual gonadotropin levels alerted us to the presence of GCT.

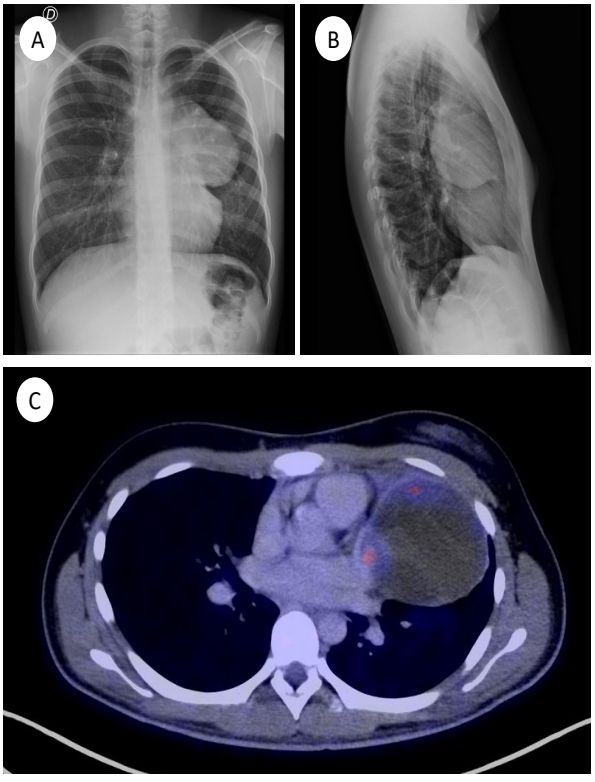
CLINICAL CASE

A 15-year-old male consulted the Pediatric Endocrinology Service for the recurrence of gynecomastia.

He had consulted another institution a year earlier for bilateral gynecomastia. Firm, small testicles (5 ml) were found. Additional tests were performed: karyotype 47XXY, follicle-stimulating hormone (FSH) 19.9 mU/ml (reference value [RV] 1-8), luteinizing hormone (LH) 13.5 mU/ml (RV 0.6-12), testosterone 3.99 ng/ml (RV 2.4-8.4), anti-Müllerian hormone (AMH) 0.85 ng/ml (RV 4-25), and estradiol 51 pg/ml (RV <20). He was diagnosed with KS.

At the 15-year-and-3-month visit, his weight was 62 kg (Z score 0.43) and his height was 176.3 cm (Z score 1.31). Physical examination

Figure 1. Frontal chest X-ray



A. Front chest X-ray.
B. Lateral chest X-ray.
Mass occupying the anterior mediastinum (arrow).
CPositron emission tomography (PET-CT). Tumor in the anterosuperior mediastinum (arrow).

revealed a trophic and painful left breast, Tanner stage 4 pubic hair, and bilateral testicular volume of 5 ml. New studies showed FSH and LH <0.1 mU/ml, testosterone 4.9 ng/ml, and estradiol 110 pg/ml.

Given the finding of suppressed gonadotropins, human chorionic gonadotropin (βHCG) beta subunit was determined and reported as 50 340 mU/mL (VR <5).

A chest X-ray (*Figures 1A* and *1B*), brain MRI (normal), and positron emission tomography (PET-CT) scan (*Figure 1C*) were performed. Once the diagnosis of GCT was confirmed, he received four cycles of preoperative chemotherapy and two postoperative cycles (etoposide, carboplatin, and ifosfamide).

The pathology revealed a germ cell tumor (teratoma) with necrosis (*Figure 2*).

After treatment, βHCG levels became negative and gonadotropins increased to the range of hypergonadotropic hypogonadism (*Figure 3*).

There were no complications during the 5-year follow-up.

DISCUSSION

We report on a teenager with KS and suspected GCT due to the detection of inappropriately suppressed gonadotropins.

Multiple reports in the literature have suggested an association between KS and cancer. An association with breast cancer, mediastinal tumors, lymphomas, and leukemias has been described. This predisposition is attributed to chromosomal alterations, the characteristic hormonal environment, comorbidities in KS, or a combination of these factors. Few cohort studies have confirmed the increased risk of certain tumors.

A report from a Danish cohort of 696 patients with KS identifies 39 oncological events over more than 40 years. It finds no significant differences in relative risk (RR) across all tumors but reports an RR of 66 for the development of mediastinal tumors.[3]

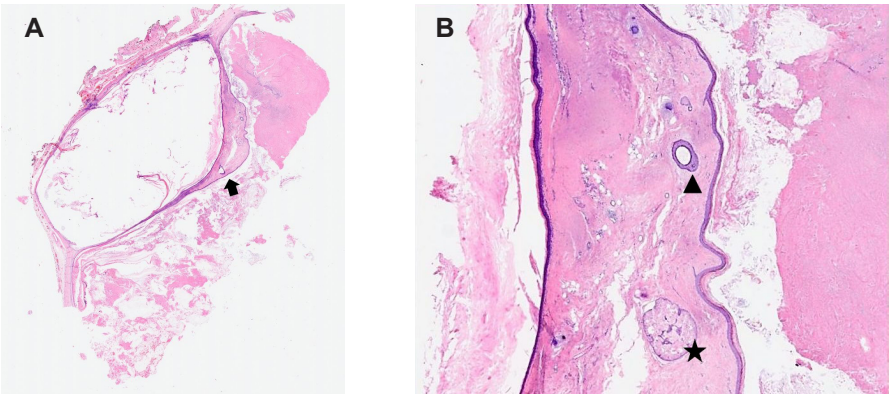
Another British cohort report of 4806 patients with KS analyzes cancer mortality. It describes a slight increase in overall mortality expressed as a standardized mortality rate. This increase is noticeable when considering mortality from breast cancer and non-Hodgkin lymphoma. No deaths attributed to mediastinal tumors are reported.[4]

GCTs are neoplasms originating in primordial germ cells that can be located in the gonads or extragonadally. They can be classified as seminomas/dysgerminomas if they contain a single cell type, or as non-seminomas/non-dysgerminomas if histopathological analysis reveals derivatives of different embryological components.

Non-seminomatous tumors include mature or immature teratomas, choriocarcinomas, yolk sac tumors, embryonal carcinomas, and mixed germ cell tumors.[7]

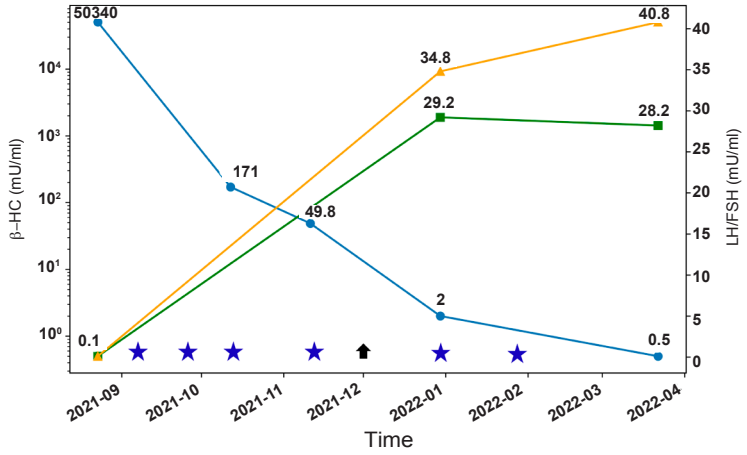
Extragonadal GCTs account for less than 5% of GCTs. They are mostly located in the anterior mediastinum, with incidence peaking in late

Figure 2. Pathological anatomy of a resected specimen from the upper mediastinum



Tumor lesion with extensive hyaline necrosis (arrow), fibrosis, accumulations of multinucleated giant cells of the foreign body type (star), viable sectors consisting of cystic structures lined by keratinized squamous epithelium with horny material in the lumen (triangle), and glandular structures without atypia compatible with germ cell tumor are observed.

Figure 3. Determinations of human chorionic gonadotropin beta subunit, follicle-stimulating hormone, and luteinizing hormone during evolution



Correlation with chemotherapy infusion (star) and surgery (arrow).
βHCG: beta subunit of human chorionic gonadotropin (blue); FSH: follicle-stimulating hormone (orange); LH: luteinizing hormone (green).

adolescence and being more common in males. Non-seminomatous variants predominate among extragonadal GCTs.

A publication reviewing reports published between 1972 and 2020 compiles data from 141 patients with SK and extragonadal GCT. The mean age at diagnosis is 17.3 years, and 58% are between 10 and 19 years old. Eighty-five percent of cases present with non-seminomatous variants; teratomas predominate in children under 14 years of age, and teratomas, germinomas, and mixed germ cell tumors predominate in those over 15 years of age.[6]

Furthermore, a study by *the National Children's Oncology Group* analyzed the karyotypes of 433 patients under 19 years of age with GCT and found KS in 13 patients (3%), a higher incidence than the estimated rate in the general population (0.16%). In addition, it highlights that, in the subgroup of patients with thoracic GCT, one-third have SK.[8]

Given the increased RR and karyotype findings in several series of patients with extragonadal GCT, some authors suggest the need for genetic testing in male patients with these tumors. Conversely, clinicians who follow up patients with KS should screen for mediastinal tumors in adolescents with symptoms, but active screening with chest X-rays in adolescents with KS is controversial.[1,9]

Patients with KS present hypergonadotropic hypogonadism with increased levels of both gonadotropins at puberty. The notable increase in FSH results from progressive dysfunction of the seminiferous tubules and Sertoli cells, accompanied by a drop in inhibin B levels.

Likewise, testosterone levels in lower quartiles with progressive decline represent Leydig cell dysfunction. In response to this, LH values are elevated. Since feedback is the main mechanism regulating LH synthesis and release, testosterone administration decreases LH levels in patients with KS.

βHCG levels tend to increase in patients with GCT when they have a trophoblastic component, and their determination contributes to screening, differential diagnosis, and monitoring.[10] The initial drop in βHCG levels in our patient may correlate with the extensive degree of necrosis evident in the resected specimen.

Since βHCG binds the LH receptor, prepubertal males with βHCG-producing GCT may present features compatible with gonadotropin-independent precocious puberty. This condition has even been described in prepubertal KS carriers.[11]

Our patient had elevated LH at diagnosis with testosterone levels appropriate for the pubertal stage. One year later, LH values below the detection limit, along with increased serum testosterone, prompted βHCG testing, which raised suspicion of GCT.

FSH levels also decreased at the time of GCT diagnosis. This cannot be attributed to

the increase in testosterone induced by βHCG, considering that FSH values do not decrease in KS patients treated with testosterone.

The main negative regulator of FSH secretion is inhibin B secreted by Sertoli cells. Inhibin B decreases after the onset of puberty in KS patients, reflecting dysfunction of the testicular tubular component.[12]

Although inhibin measurements are not used in practice as tumor markers in cases of GCT, its expression has been described in gonadal and extragonadal tumors.[13] It is possible that this is one of the explanations for the suppressed FSH levels in our patient. We did not determine inhibin B levels or perform immunohistochemistry techniques on the resected specimen.

One of the concerns that prompted the second consultation was the recurrence of painful bilateral gynecomastia. This correlates with a doubling of estradiol levels compared to the initial determination, likely due to peripheral aromatization of testosterone, whose synthesis was stimulated by βHCG. Elevated estrogen levels could exert negative feedback by suppressing FSH secretion at the pituitary level or by suppressing kisspeptin secretion from hypothalamic neurons.[14]

Finally, we present a patient with KS who developed extragonadal (mediastinal) GCT, whose diagnosis was reached upon observation of suppressed gonadotropin levels. Gonadotropin monitoring is not suggested in clinical practice guidelines, but values that do not correspond to hypergonadotropic hypogonadism should raise an alarm. ■

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