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CLINICAL CASE

# Beta-hCG-producing thymic teratoma: an uncommon cause of peripheral precocious puberty

## Teratoma tímico productor de β-HCG: una causa infrecuente de pubertad precoz periférica

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### Abstract

**Introduction**: Among the causes of peripheral precocious puberty in men are the beta- human chorionic gonadotropin (β-HCG)-secreting tumors, such as hepatoblastomas, dysgerminomas, choriocarcinomas, and immature teratomas. In pediatrics, the mediastinal teratomas are rare, representing the 7-10% of extragonadal teratomas. **Objective**: To describe the case of a patient with peripheral precocious puberty due to a β-HCG -secreting thymic teratoma. **Clinical case**: A seven-years-old schoolboy presents a three-months history of voice changes, gynecomastia, pubic hair appearance, and increased genital volume. In the exams, bone age of nine years, total testosterone 9.33ng/ml (< 0.4ng/ml), dehydroepiandrosterone sulfate (DHEAS), 17-hydroxyprogesterone (17-OHP), and normal adrenocorticotropic hormone (ACTH) test stand out; luteinizing hormone (LH) and follicle stimulating hormone (FSH) with low basal levels, β-HCG 39.5mU/ml (< 2.5 mUI/ml), alpha fetoprotein (α-FP) 11,2ng/ml (0.6-2.0 ng/ml). Imaging study to determine the origin of β-HCG secretion shows normal testicular ultrasound and thoracic, abdominal, and pelvic computerized axial tomography (CAT); brain and sellar resonance without significant findings. The positron emission tomography/computed scan (PET SCAN) shows a tumor image in the anterosuperior mediastinum. The tumor is resected, and the biopsy shows an immature cystic teratoma in the thymus. Post-operatory evolution was satisfactory, with normalization of hormonal levels. **Conclusion**: The appearance of a teratoma in a pediatric patient is rare, even more if it is immature, with thymic location and β-HCG-secretor. It is important to consider it within the differential diagnosis facing precocious puberty, as a better way to handle appropriately.

**Keywords:**
Teratoma;
precocious puberty;
beta-human chorionic gonadotropin

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## Introduction

Teratoma is a germ cell tumor that develops as a result of embryonic differentiation[1]. It contains tissues from the three germinal layers: ectoderm, mesoderm, and endoderm1. Teratomas composed of mature cellular elements show a higher degree of differentiation, are classified as benign and do not produce tumor markers[1,4]. Elevated levels of these are indicative of the discovery of an immature or potentially malignant component[1,4]. A small portion of germ cell tumors can produce β-HCG[2]. 5-10% of germ cell tumors are extragonadal, including those of mediastinal location[9]. Immature mediastinal teratomas (TM) account for 1% of all these[4,7]. Clinical manifestations will depend on the location and effect of the markers secreted by the tumour[1]. Most patients with TM have no symptoms. In case of manifestations, they are generally respiratory. The small proportion of patients with a teratoma producing β-HCG has unique clinical features, such as the development of precocious puberty and other endocrine dysfunctions depending on their location[2]. The development of precocious puberty is explained by the fact that the molecules of β-HCG and LH have identical alpha subunits (α) and similar beta subunits (β), thus the β-HCG stimulates the production of testosterone by the cells of Leydig[10,11,12]. Within the TM we can find those located in thymus[8]. To date, there are no reports of cases of early puberty caused by teratoma producing β-HCG in Chilean pediatric patients.

The objective of this study is to describe a clinical case of a male school-child patient who underwent peripheral precocious puberty due to thymic teratoma secreting β-HCG.

## Clinical case

A 7-year-old schoolboy, he consulted an endocrinology polyclinic for a 3-month evolution characterized by pubertal development that included voice changes, facial acne, pubic hair appearance and increased genital volume. Previously healthy. Pregnancy and childbirth without pathology. Physical examination: Eutrophic, size 131.5 cm, 0.68 standard deviation (SD), on target size (172 cm, -0.68 DE), (Figure 1), normotensive, thick voice, presence of gynecomastia, axillary hair, Tanner pubic hair 4, thickened penis with glans formation and increased length, 3 ml testes, normal segmental in the rest of the examination; compatible with diagnosis of peripheral precocious puberty. Some of the most important results from the requested examinations were: bone age 9 years according to Greulich and Pyle atlas (2 x 18.2 months), total testosterone 9.33 ng/ml (< 0.4 ng/ml), androstenedione 1.2 ng/ml (0.1-0.9 ng/ml), DHEAS 47.3 ug/dl (80-560 ug/dl), estradiol 68.4 pg/ml (< 10 pg/ml prepubescent man), FSH < 0.1 mUI/ml (0.26-3.0 mUI/ml), LH < 0.1 mUI/ml (0.02-0.3 mUI/ml), 17-OH-P 0.62 ng/ml (0.3-2.2 ng/ml), ACTH test for 17-OH-P basal 1.3 ng/ml - 60 min 2.1 ng/ml (normal) and β-HCG 39.5 mUI/ml (< 2.5 mUI/ml), α-FP 11.2 ng/dl (0.6-2.0 ng/ml). In joint evaluations with the pediatric hemato-oncologist, imaging was requested to look for the origin of β-HCG tumor secretion: testicular ultrasound, normal thoracic, abdominal and pelvic CT scans, brain and selar resonance reports small pineal cyst that is considered as a finding (Figure 2); in parallel, periodic clinical and hormonal controls were performed, including measurement of β-HCG in cerebrospinal fluid (CSF), (Table 1). Due to a negative tumor localization study, a positron emission tomography scan (PET/CT F18-FDG) was ordered, revealing soft tissue in an upper-anterior mediastinum, which may suggest a germinal tumor (Figure 3). At 8 years and 4 months of age, an exploratory thoracotomy was performed and the thymus was dissected. Between the lobes of this gland, a more consistent mass of 2 cm in diameter, spherical, was found and removed, including the left lobe. Contemporary biopsy reported cystic teratoma of the thymus (Figure 4). A decrease of β-HCG was observed in the postoperative period to < 1.5 mUI/ml (< 2.5 mUI/ml), (Table 1). In endocrinological evaluations after surgery, regression of pubertal development was observed: disappearance of gynecomastia, partial regression of Tanner 3 pubic hair, no progression of penile development and normalization of hormonal values (Table 1).

## Discussion

Germ cell tumors are a heterogeneous group of neoplasms, with a diverse clinical and biological behavior[1]. During the embryonic development in the third gestation week, the primordial germ cells dorsally migrate from their origin towards the wall of the yolk sac, following a route through the posterior mesentery towards the gonadal anlage1. In this process, it can be ectopically nest along the midline, in the central nervous system, mediastinum, sacrococcygeal zone, retroperitoneum, and gonads. They can then proliferate and experience a neoplastic transformation. If this occurs without differentiation, a dysgerminoma1 will occur. On the other hand, in the case of differentiation, if it is an embryonic type, it can lead to embryonic carcinoma or teratoma; if it is extra-embryonic, choriocarcinoma or endodermal breast tumor will form[1]. Germ cell tumors represent 3% of all malignant tumors in children under 15 years of age[2].

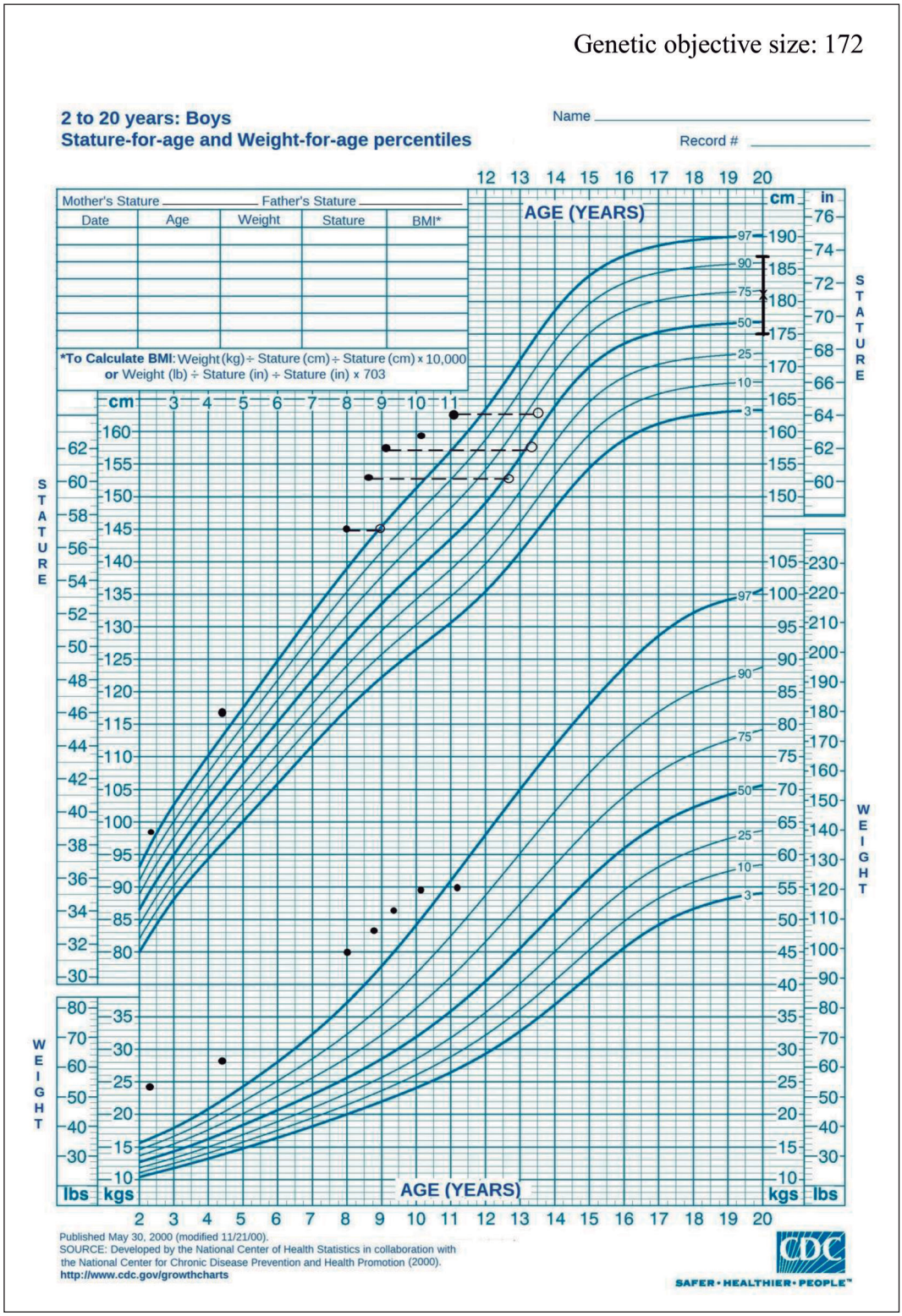


**Figure 1.** Growth curve.

Teratoma contains tissues derived from the three germinal layers: ectoderm, mesoderm, and endoderm[1]. It is found in different stages of maturity, with solid and cystic areas. Histologically, they can be classified according to the World Health Organization (WHO) as: mature, immature, mixed, monodermal and with somatic malignant phenomena[3]. Teratomas composed of differentiated or mature cellular elements are clas-

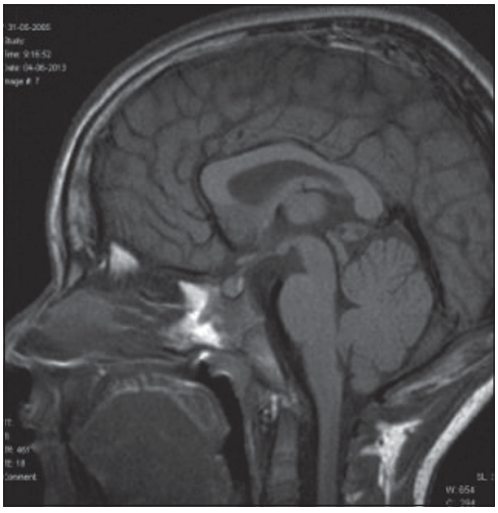

**Figure 2.** Brain magnetic resonance imaging (MRI). Brain and sellar resonance reports a small pineal cyst that is considered a finding.

sified as benign and do not produce tumor markers such as alpha-fetoprotein (α-FP) or β-HCG1[4]. Elevated levels of these markers indicate the discovery of an immature or potentially malignant component1,[4]. A small proportion of teratomas can produce β-HCG[2]. TM contains undifferentiated tissue that may resemble embryonic structures, such as areas containing immature neuroectoderm and mesenchymal tissue[3,4]. Germ cell tumors are commonly found in gonads, but 5-10% are extragonadal, in locations such as the pineal gland, retroperitoneum, mediastinum, and sacral area; being the mediastinum, the most common extragonadal location in adults, however in children the sacrococcygeal corresponds to 40%-80% of cases[4,5,6]. Of mediastinal tumors, 6-18% are caused by germ cell tumors and 86% of these are benign9. Immature MTs

**Table 1. Laboratory tests**

| | Age | β-hCG (mUI/ml) | α-FP (ng/dl) | Testosterone (ng/dl) | Estradiol (pg/ml) |
|---|---|---|---|---|---|
| Pre-surgery Blood study | 7y 10m | 39.5 | 11.2 | 9.33 | 68.4 |
| | 7y 11m | 44.16 | 6.5 | - | - |
| | 7y 11m | 44.2 | 9.42 | 7.95 | - |
| | 8y 0m | 25.92 | 12.9 | 5.33 | - |
| Pre-surgery CSF study | 8y 0m | < 1.2 | 0.02 | | |
| Post-surgery Blood study | 8y 7m | < 1.2 | 0.99 | 0.059 | 10 |
| | 9y 1m | < 1.2 | 0.82 | < 0.025 | - |
| | 9y 9m | - | 0.8 | < 0.13 | < 10 |
| | 10y 2m | < 1.2 | - | 0.11 | - |

β-hCG: beta-subunit of human chorionic gonadotropin, α-FP: alpha fetoprotein, CSF: cerebrospinal fluid, y: years, m: months. Reference value: β-hCG < 2,5 mUI/ml; α-FP 0,6-2,0 ng/ml; Testosterone <0,4 ng/ml; Estradiol prepuberal male < 10 pg/ml.

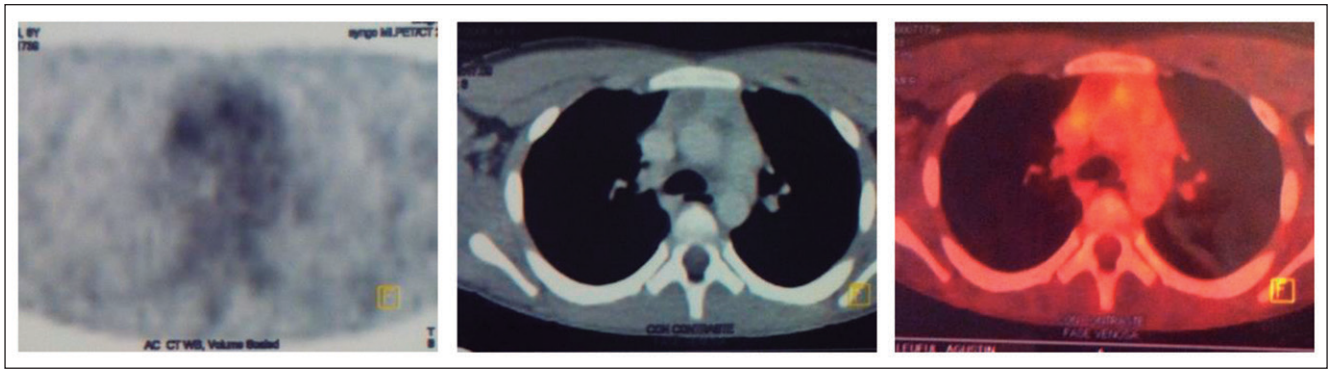

**Figure 3.** Positron emission tomography/computed scan (PET SCAN) reveals tissue of soft parts in antero-superior mediastinum, which can correspond to a germinal tumor.

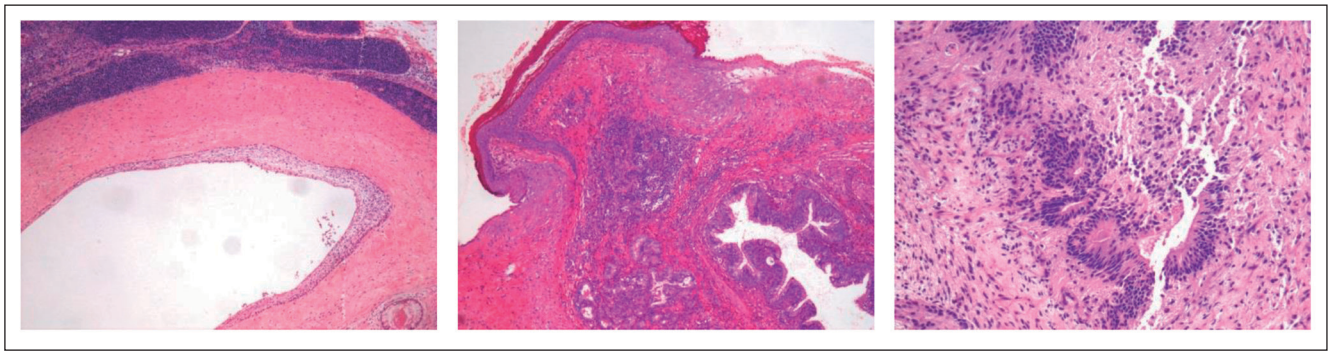

**Figure 4.** Thymic tissue with cystic formation coated by epidermoid ephitelium in keratinized parts, ciliated pseudostratified columnar ephitelium, glandular tissue and neuroectodermal tissue, with neuroepithelial cells driving rosette formation. The lesion contains approximately a 20% immature neuroectodermal tissue, therefore, teratoma under study is in G2 of González Crussi grading system (10-50% of immature tissue)[13]. Courtesy of Dr. Lilia Antonio. Anatomic Pathology Unit, Dr. Hernán Henríquez Aravena Hospital, Temuco.

are very rare and constitute 1% of all these,[7]. TM may originate from primitive germ cells lost in the mediastinum during caudal migration in early embryogenesis or from native pluripotent mediastinal cells[6]. Most of these teratomas are located in the anterior mediastinum, only 3-8% are located in posterior mediastinum[6,7]. Studies show that in patients under 15 years of age, immature TMs often behave in a similar way to mature teratomas, following a benign course, as opposed to those over 15 years of age[4,7]. Clinical manifestations will depend on the location and effect of markers secreted by the tumour1. Most patients with TM are asymptomatic, usually not diagnosed until they have an imaging study that shows them[6]. The patient signs are usually respiratory, such as respiratory distress, coughing, wheezing, chest pain6. The mass may cause deformation of the chest wall or signs of spinal cord compression[6].

The small proportion of patients with a teratoma that produces β-HCG is related to a delay in diagnosis in 60% of cases and presents unique clinical characteristics, such as the development of early puberty, as our patient, and other endocrine dysfunctions depending on their location which includes growth alterations, diabetes insipidus and hypopituitarism[2]. The development of precocious puberty is due to the fact that the molecules of β-HCG and LH have identical subunits α and similar subunits β, thus the β-HCG stimulates the production of testosterone by the cells of Leydig[10,11,12]. Precocious puberty occurs independently of gonadotrophin levels and occurs more frequently in males[2]. It is less frequent in females because both FSH and LH activity is necessary for follicular maturation[2,14]. About ten cases of pediatric patients with immature teratoma have been reported, of which five[10,11,12,14] evolved with early puberty because the tumor was secreting β-HCG. Regarding the latter cases, they all refer to immature teratomas located in the central nervous system; one in pellucidum septum[11], three in the pineal gland[10,12], and one described as a suprasellar mass[14]; in two of the cases the teratoma was associated with choriocarcinoma[10]. Four of the patients were male, the age range was between 6 and 7 years, all of the patients had early puberty, one of them also had headache[12], and another had diabetes insipidus and increased intracranial pressure[14]. In all cases, an elevation of β-HCG in plasma and cerebrospinal fluid was observed, and the tumor was observed in cerebral magnetic resonance imaging. All had surgical resection and chemotherapy, while three received radiotherapy[10,11,12]. One of the patients died[10], his tumor was an immature pineal teratoma associated with choriocarcinoma. The rest of the cases showed a favorable evolution. The case reported in this article differs from those previously mentioned in the location of the teratoma, which was thymic, did not require treatment with radiotherapy or chemotherapy, since the current evidence indicates that it is not necessary to indicate it in pure teratoma without elements of other tumor tissue. Surgical resection was performed with a satisfactory clinical response.

Among the TM we can find those located in the thymus, which are described as of epithelial origin, classified as mature or immature[8].

Teratoma treatment typically consists of complete surgical resection without the need for chemotherapy[6]. The prognosis of patients with immature teratomas is determined by factors such as the age of the patient, anatomical site of the tumor, number of immature elements of the teratoma, and integrity of surgical resection[4].

This particular case involved a patient who presented a thymic teratoma containing approximately 20% immature neuroectodermal tissue, and who secreted β-HCG, triggering peripheral precocious puberty.

When the tumor was resected, the manifestations of puberty involuted.

## Conclusion

Male early puberty should alert about possible tumoral causes, especially if the clinical course is rapid and progressive, performing a diagnostic evaluation intended to discard these aetiologies. If there is pubertal development with tests in the pre-pubertal range it is an indicator of independent cause of gonadotrophin secretion, and within these, in addition to congenital adrenal hyperplasia, there are tumoral pathologies and therefore the study should be directed to discard an etiology of this type, and if so, look for its origin, as this determines treatment and prognosis.

The presentation of a teratoma, in pediatric patients, is infrequent, even more so, if it is immature, if its location is mediastinal, specifically thymic and is a secretor of β-HCG generating a picture of peripheral precocious puberty, being not always easy to find tumoral source of secretion of β-HCG, as in our patient. Therefore, despite its low prevalence, it is important to consider this pathology within the spectrum of differential diagnoses compared to a similar clinical situation, so that timely management can be carried out, in this case, a tumor resection that meant its definitive resolution.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

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Authors state that no economic support has been associated with the present study.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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