Accepted Manuscript

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PII: S0090-4295(17)30912-3
DOI: http://dx.doi.org/doi: 10.1016/j.urology.2017.08.038
Reference: URL 20644

To appear in: *Urology*

Received date: 14-7-2017
Accepted date: 28-8-2017

Please cite this article as: Alejandra Bravo-Balado, Lynda Torres Castellanos, Adriana Carrillo Rodríguez, Daniel Gómez Zapata, Juan Javier Lammoglia Hoyos, Rafael Andrade, Jaime Pérez Niño, Primary Mediastinal Pure Seminomatous Germ Cell Tumor (Germinoma) as a Rare Cause of Precocious Puberty in a 9 Year-Old Patient, *Urology* (2017), http://dx.doi.org/doi: 10.1016/j.urology.2017.08.038.

Primary mediastinal pure seminomatous germ cell tumor (germinoma) as a rare cause of precocious puberty in a 9 year-old patient

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Word count:

Abstract: 100/100

Text: 1136/1200

Figures/tables: 3/3

Reference: 15/15

Acknowledgment

No external help was received.

Conflict of interest

The authors declare no conflicts of interest regarding this case report.

Funding

No funding was obtained.

Abstract

Less than 5-7% of germ cell tumors (GCTs) are extragonadal, being the central nervous system (CNS) the most common location in children, followed by retroperitoneum and mediastinum. Only 10% of mediastinal tumors are malignant and one third of these are pure seminomas (germinomas). We report the case of a 9 year-old boy with development of secondary sexual characteristics. Beta human chorionic gonadotropin (B-hCG) was elevated and a mediastinal mass was found. Final histology showed a pure seminomatous germ cell tumor (SGCT). To our knowledge, this is the first report of a boy with precocious puberty secondary to a mediastinal germinoma.

Key words: Precocious Puberty; Human Chorionic Gonadotropin; Germinoma; Seminoma; Mediastinal.

Case report

A previously healthy 9-year-old boy was referred to our clinic for evaluation of a 5-month history of progressive precocious puberty including deepening of the voice, appearance of thick pubic hair, penile elongation and accelerated growth. A carpogram ordered by his pediatrician reported advanced bone age (13.5 years old). He was then referred to the pediatric endocrinologist who ordered an abdominal computed tomography (CT) scan, testicular ultrasonography (US), chest X-ray and spinal and head MRI, all reported as normal. Initial laboratory tests were drawn, which showed elevated B-hCG (Table 1).

Physical examination showed a fully developed laryngeal prominence (Adam's apple) (Image 1A), bilateral gynecomastia (3x1cm), Tanner G3Ph4 (Image 1B), testicular volume of 4 ml bilaterally and facial acne (Image 1C).

After the initial work-up, a chest CT scan with contrast was ordered and showed an anterior mediastinal mass measuring 29 x 26 mm, with no calcifications (Figure 2A). A chest biopsy by cervical mediastinotomy was performed. However, it failed to typify the tumor, so tumor resection by median sternotomy was performed. Final histology showed a monotonous pattern of growth of neoplastic cells with scant cytoplasm, central nuclei and prominent nucleoli (Figure 2B), with occasional multinucleated trophoblast-like cells. Immunohistochemistry studies showed intense reactivity for OCT3/4 (Figure 2C), PLAP (Figure 2D) CD117 (Figure 2E)

and focal reactivity for HCG (Figure 2F) and AE1/AE3 cytokeratins in a perinuclear pattern, without expression of CD30. These findings are highly specific of pure SGCT.

Following the histological diagnosis, a cisplatin, etoposide and bleomycin (PEB) chemotherapy regimen was initiated. To date, he has completed four cycles, with no oncologic relapse and laboratory values in normal range (BHCG 0.17 mUI/Ml (normal range <0.6), November, 2016). Also, G-banding karyotyping ruled out the diagnosis of Klinefelter syndrome, with a report of 46 XY karyotype.

Comment

Extragonadal GCTs represent less than 10% of all GCTs; main locations include the CNS, followed by retroperitoneum and mediastinum.

Germinomas occur in up to 50% of malignant mediastinal GCTs in adults, but in children, these tumors are very rare with only a few case reports in the literature. A study published by Temes et al.[1] in 2015 found that, in a population of 22 children with primary mediastinal malignancies, 55% were lymphomas, 23% were of neurogenic origin and only 18% were GCTs, out of which none were germinomas. Another study published by Moran et al.[2] using a population of 322 patients aged 1-79 years old with GCTs of the mediastinum found that 37% were germinomas, but none of those occurred in the age group of 0-9 years old.

The presenting symptoms of mediastinal SGCTs are usually related to the size of the tumor, such as cough, chest pain, hemoptysis, dyspnea and superior vena cava syndrome.[3] To our knowledge, this is the first report of a patient presenting with precocious puberty due to primary mediastinal germinoma.

Precocious puberty is defined as the development of secondary sexual characteristics before the age of 9 and 8 years old in males and females, respectively.[4] Other authors have defined it as a sexual maturation occurring in children 2.5 standard deviations of the mean earlier than in the normal population.[5]

The etiology of precocious puberty may be subdivided into GnRH-dependent and GnRH-independent causes. The former is the most common mechanism for precocious puberty, known as central precocious puberty. The etiology of this entity include congenital malformations of the CNS such as hydrocephalus, Chiari II malformations and tuberous sclerosis; acquired lesions of the CNS including tumors and cerebral palsy; and other etiologies such as endocrine disruptors and chromosomal abnormalities.[6] The gold-standard biochemical diagnosis in these patients is based on the assessment of gonadotropins, mainly luteinizing hormone (LH), after stimulation with exogenous GnRH or GnRH agonists.[6]

GnRH-independent causes include peripheral precocious puberty and is secondary to genetic or acquired disorders, among them, congenital adrenal hyperplasia, McCune-Albright syndrome and tumors that secrete human chorionic gonadotrophin (hCG).[4]

The production of B-hCG generates hyperplasia of the Leydig cells but does not stimulate the Sertoli cells, which explains why these patients have prepuberal testis.[7] Similarly, as a result of the elevation of B-hCG, testicular estradiol production is increased due to aromatization of androgens, which can cause gynecomastia.[8] Estradiol can also have an effect on lactotrophs within the anterior pituitary or an effect in the posterior pituitary via prolactin-releasing factor, resulting in increased concentration of prolactin.[9] Also, previous studies have demonstrated that serum concentrations of 17-Hydroxyprogesterone are increased due to elevated hCG, which explains why the former was also elevated in our patient.[10] On the other hand, in pre- and peripuberal boys there is an increase in growth hormone (GH) secretion with concomitant increases of baseline and GH-stimulated insulin-like growth factor I (IGF-1).[11]

GCTs are the identified cause of precocious puberty in 21% of cases in boys.[12] Characteristically, in choriocarcinomas, B-hCG is markedly elevated and serves as a specific tumor marker.[7] In contrast, the production of hCG, can be identified in

only 15% of cases of pure SGCT in any location, and occurs due to the presence of syncytiotrophoblastic cells.[13]

There are no standardized guidelines for the diagnosis and management of patients with precocious puberty, but it is accepted that an adequate clinical and family history, the age of presentation of the physical changes and the speed with which they occurred, as well as the possible exposure to steroids and the presence of CNS symptoms should be explored in order to clarify the origin of this entity and rule out central precocious puberty.[14]

In the scenario of a patient with precocious puberty and inappropriate testicular volume, the diagnosis should include baseline laboratories (i.e. testosterone, LH and FSH). If gonadotropins are suppressed, B-hCG and AFP should be ordered. If either tumor marker is elevated, the following step should include an MRI of the spine and brain. If the latter diagnostic images are negative, the clinician should order an abdominal and chest CT or MRI and a testicular US. Histological diagnosis is not necessary for the initial treatment, since the elevation of tumor markers and a diagnostic image confirming the presence of a mediastinal mass are sufficient to make the diagnosis of a GCT.[7]

Klinefelter syndrome should also be ruled out since GCTs are 50 times more common in patients with this syndrome than in patients without it, although they are usually associated with non-seminomatous GCTs (NSGCTs).[12]

In the case of a large volume mass, management with neoadjuvant chemotherapy based on platinum should be initiated, given that the resection of a large mass increases the risk of morbidity and mortality. Finally, these patients have excellent prognosis: Bokemeyer et al.[15] reported a 5-year overall survival rate of 88% for SGCTs in the mediastinum.

Conclusion

Peripheral precocious puberty is a rare manifestation of mediastinal germinomas in the male pediatric population. Although infrequent, an elevation of B-hCG should raise the suspicion of this diagnosis in order to guarantee prompt diagnosis and management.

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Figure 1. Secondary sexual characteristics. **A.** Fully developed laryngeal prominence (Adam's apple). **B.** Tanner G3Ph4 **C.** Facial acne.

Figure 2. A. Anterior mediastinal mass on CT scan (arrow). **B.** Hematoxylin and eosin (20X): monotonous pattern of growth of neoplastic cells with scant cytoplasm, central nuclei and prominent nucleoli. **C.** Intense reactivity for OCT3/4, **D.** Intense reactivity for PLAP, **E.** Intense reactivity for CD117. **F.** Focal reactivity for HCG.

Table 1. Baseline laboratory tests (July, 2016)

Laboratory test	Value	Reference range for age and sex
Follicle-stimulating hormone (mIU/mL)	0.1 (normal)	≤4.5[a]
Luteinizing hormone (mIU/mL)	0.6 (normal)	0.3-2.8[a]
Estradiol (pg/mL)	95.2 (high)	0.0-16[a]
Testosterone, Total (ng/mL)	10.37 (high)	0.07-0.2[a]
Dehydroepiandrosterone sulfate (DHEA-SO4) (ug/dL)	24.7 (normal)	2.0-60[b]
Prolactin (ng/mL)	29.02 (high)	2.64-13.13[b]
B-hCG (mIU/mL)	195.8 (high)	<0.6[b]
AFP (ng/mL)	0.98 (normal)	0.00-9.00[b]
17-Hydroxyprogesterone (ng/mL)	2.97 (high)	0.5-2.1[b]
Insulin-like growth factor I (ng/mL)	306.9 (high)	85.2-248.8[b]
Lactate dehydrogenase (U/L)	233.00 (normal)	155-290[b]

[a] Reference range from Mayo Medical Laboratories (www.mayomedilalaboratories.com/tes-info/pediatric/refvalues/reference.php)

[b] Reference range from our institution

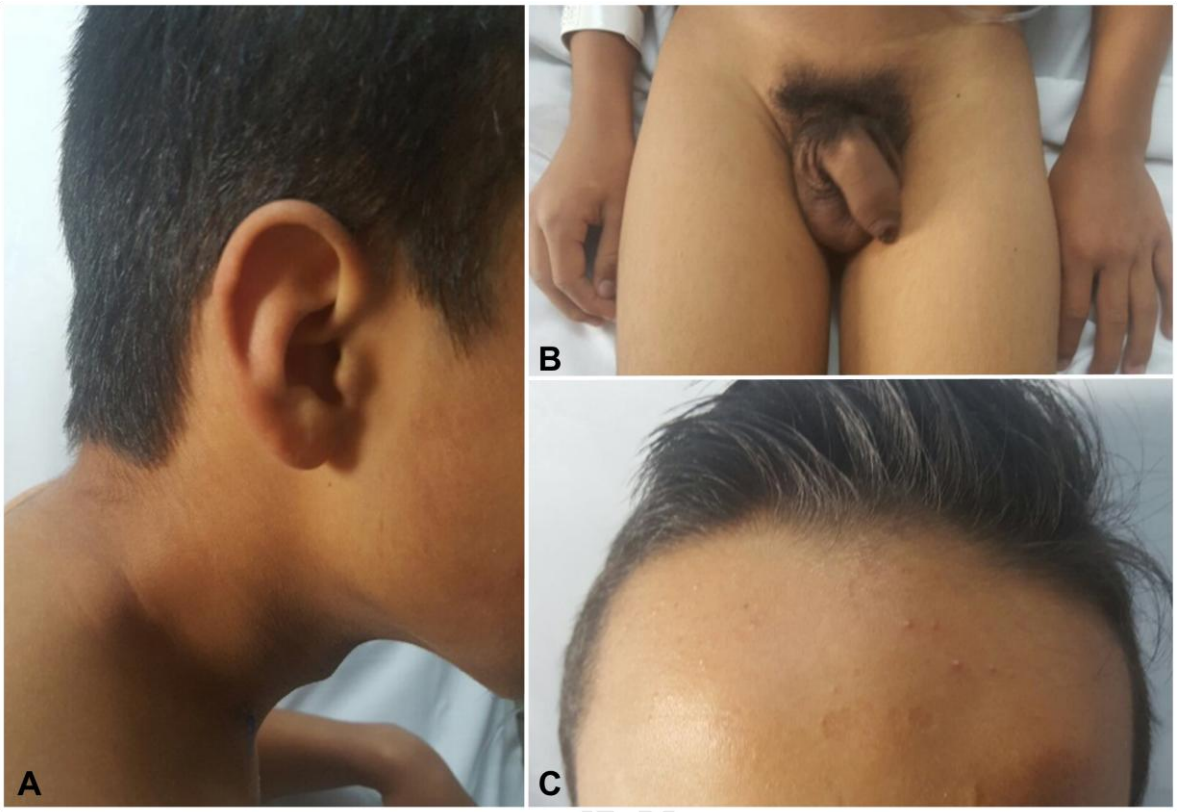

Figure 1 germinoma.tif

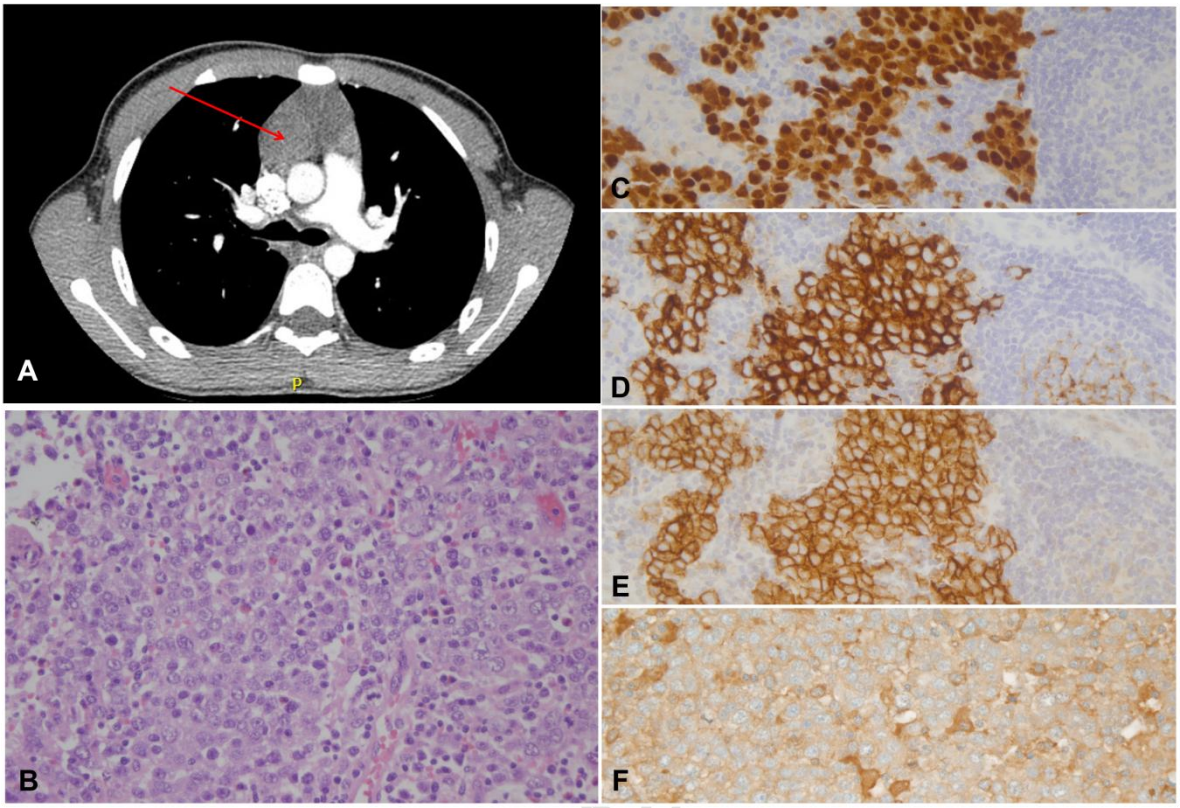

Figure 2.tif