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Clinical report

Two cases of Klinefelter syndrome with precocious puberty due to mediastinal germ cell tumor

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Background: Klinefelter syndrome may present as precocious puberty, which can be either central precocious puberty or peripheral precocious puberty, caused by an extragonadal germ cell tumor.
Objective: Report two cases of Klinefelter syndrome that presented with precocious puberty due to a β-hCG producing mediastinal tumor.
Method: Review of the clinical history, physical examination, and laboratory investigations.
Results: Pseudo-precocity developed some years before diagnosis of -hCG producing tumor. The patients did not have typical physical features of this syndrome. The testes were small and had loose consistency.
Conclusion: Klinefelter syndrome must be excluded in all boys presenting with precocious puberty due to a β-hCG producing tumor. Conversely, patients with Klinefelter syndrome should be regularly checked for β-hCG and α-fetoprotein levels. In those cases, the patients can be diagnosed and treated early. With the early treatment, they will be able to attain normal adult height and have fewer complications from the tumor.

Keywords: Klinefelter syndrome, mediastinal germ cell tumor, precocious puberty

The prevalence of Klinefelter syndrome is 1:660 in men and the most common karyotype is 47, XXY. The majority of patients have hypergonadotropic hypogonadism due to seminiferous tubule degeneration causing small and loose testicular consistency, sparse body hair, gynecomastia, and other signs of androgen deficiency. However, Klinefelter syndrome may present with precocious puberty, which can be either central [1-4] or peripheral precocious puberty caused by an extragonadal Germ cell tumor [1-2, 5-8]. The incidence of Germ cell tumors, particularly at the mediastinum, is 50 times more than in the normal population and 8% of males with primary mediastinal germ cell tumors (PMGCT) have underlying Klinefelter syndrome [8]. The presentation of precocious puberty due to β-hCG producing tumor at the mediastinum takes some years before the onset of respiratory symptom or mass detection [9]. The tumor is in a silent area and slow growing by nature. The combination of chemotherapy to decrease tumor size and surgical resection are the usual treatment modalities [8, 10-11]. However, there have been reports demonstrating that only radical surgical resection can cure the disease [6, 12].

We report two cases who first presented at prepubertal and peripubertal age and had a history of precocious puberty for a few years before being diagnosed as having a β-hCG producing tumor at the mediastinum. Their karyotype showed 47, XXY and they did not have any typical signs of Klinefelter syndrome except for small and loose testicular consistency.

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Case 1

A 14-year-old boy presented with an abnormal chest X-ray. He had only mild chest discomfort and had no other symptoms. He had a deep voice, facial and pubic hair since the age of 10. His mother brought him to the hospital and examination reported genital stage V, pubic hair stage V and 3-4 mL of testicular volume of both testes. The baseline level of LH was <0.3 IU/L (0.4-7.0), FSH of 0.03 IU/L (2.6-11.0) and Testosterone of 38 nmol/L (12.1-33.6). The random

17-hydroxyprogesterone level was 180 ng/dL (24.0-175.0). He was diagnosed as having central precocious puberty and 3.75 mg of GnRH analog injectious were started every month for two years. Magnetic resonance imaging showed a small size of the pituitary gland. During the treatment course, the genital staging was progressing and the testicular volume had been up to 6 mL. His school performance was of an average level. The father's height was 167 cm and mother's height 162 cm and they had been through puberty at the normal age. Physical examination at our hospital revealed a height of 162 cm (P50), a body weight of 49.5 kg (P50-75), an upper and lower segment ratio of 0.8:1 and an arm span of 151 cm. Chest examination was normal. No gynecomastia or hepatosplenomegaly was found. Pubertal examination revealed genital stage V, pubic hair stage V and 4 mL with a loose consistency of both testes. The chest X-ray showed an anterior mediastinal mass without pulmonary infiltration as shown in **Figure1A**. The computed tomography of the chest demonstrated a large anterior mediastinal mass, 8.1×6.8×7.6 cm in size, deviating to the right and compressing the Superior vena cava (SVC) and ascending aorta (**Figure 1C**). The bone age was 17 years using the Greulich and Pyle method. The hormonal evaluations revealed a peak of LH 84.7 IU/L (2.9-65.4), FSH 27.5 IU/L (5.8-24.7) and Testosterone 16.4 nmol/L (12.1-33.6) [13]. The level of β-hCG and alpha-fetoprotein were 63 mU/mL (0-5) and 45,769 IU/mL (0-10), respectively. Biopsy of the mass showed a yolk sac tumor. The karyotype revealed 47, XXY. Chemotherapy including Bleomycin, Etoposide and Cisplatin, it was started for four cycles before undertaking dubulking of the mass. Levels of β-hCG and alpha-fetoprotein came into the normal range after treatment. The clinical presentations and investigations can be seen in **Table 1**.

Case 2

An eight year and 10 month old boy presented with hemoptysis of one-week duration. He had no dyspnea, fever or lost of weight. No history of tuberculosis contact was known. When he was seven years old, his mother had noticed that his genitalia had become bigger than usual for his age and pubic hair was developed. Unfortunately, she did not consult a physician for this problem. The developmental milestone was normal for his age. The physical examination revealed a height of 154 cm (>P97), an upper and lower segment ratio of 1.03:1. He had no pallor or jaundice. Decreased breath sounds and tractile fremitus with vocal resonance at left upper lung were noted. He had no hepatosplenomegaly. The Tanner assessment of the genitalia was stage IV, pubic hair stage IV and 2 mL of testicular volume of both testes with a loose consistency. The chest X-ray showed an anterior mediastinal mass without pulmonary infiltration as shown in **Figure 1B**).

Table 1. The clinical presentations and investigations of two patients with Klinefelter syndrome

	Case 1	**Case 2**
Age at diagnosis of precocious puberty (year)	10.8	7.0
Testicular volume at diagnosis (mL)	3-4 (normal consistency)	N/A
Age at presentation (year)	14.0	8.8
Bone age (year)	17.0	15.0
Presenting symptoms	mild chest discomfort	hemoptysis
Testicular volume (mL)	3-4 (loose)	2 (loose)
Tanner stage of genitalia/ pubic hair	V/IV	IV /IV
GnRH stimulation test		
Peak LH (IU/L, 2.9-65.4)	84.7	22.8
Peak FSH (IU/L, 5.8-24.7)	27.5	10.3
Testosterone (nmol/L, normal 12.1-33.6)	16.4	6.3
β-hCG (mU/mL, normal 0-5)	63	265.3
Alpha-fetoprotein (IU/mL, normal 0-10)	45769	5423
Pathology	yolk sac tumor	mixed germinoma (mature, teratoma, yolk sac)

Computed tomography demonstrated an anterior mediastinal mass, 9.0×6.0×7.2 cm in size with central necrosis that invaded LUL bronchus, great vessels, and thymus (**Figure 1D**). The bone age was 15 years using the Greulich and Pyle method. The GnRH stimulation test revealed a peak LH of 22.8 IU/L, FSH 10.3 IU/L and a Testosterone of 6.3 nmol/L. The level of β-hCG and alpha-fetoprotein were 265.3 mU/mL and 5,423 IU/mL, respectively. A core needle biopsy of the mass showed mixed germinoma including immature teratoma, yolk sac, and seminomatous components. The karyotype revealed 47, XXY. Chemotherapy included Bleomycin, Etoposide, and prednisolone. It was started for four cycles before undertaking dubulking of the mass. The levels of β-hCG and alpha-fetoprotein became normal after surgery. The clinical presentations and investigations can be seen in **Table 1**.

Discussion

Although, hypergonadotropic hypogonadism is the most common presentation of Klinefelter syndrome [13], precocious puberty can also occur in some individuals. It can be either central or peripheral puberty. The latter is most commonly due to -hCG producing tumors of an extragonadal site most commonly at the mediastinum. The incidence of germ cell tumor is increased to about 50 times in patients with Klinefelter syndrome. Eight percent of boys with primary mediastinal germ cell tumors (PMGC) have underlying Klinefelter syndrome without any typical features of this syndrome [8]. Case 1 had been treated with GnRH analog after being missed diagnosed with central precocious puberty. The investigation was not complete and the treatment response was ineffective in controlling pubertal progression. The bone age advancement progressed to 17 year, which is almost the final height in a male. In case 2, there was not enough data about his puberty when he was seven years old. The testicular volume at that time was expected to be at least 4 mL but less than the genital staging, which was a typical finding in -hCG producing tumors in a boy. This condition was similar to that of testotoxicosis [14] and primary hypothyroidism [15].

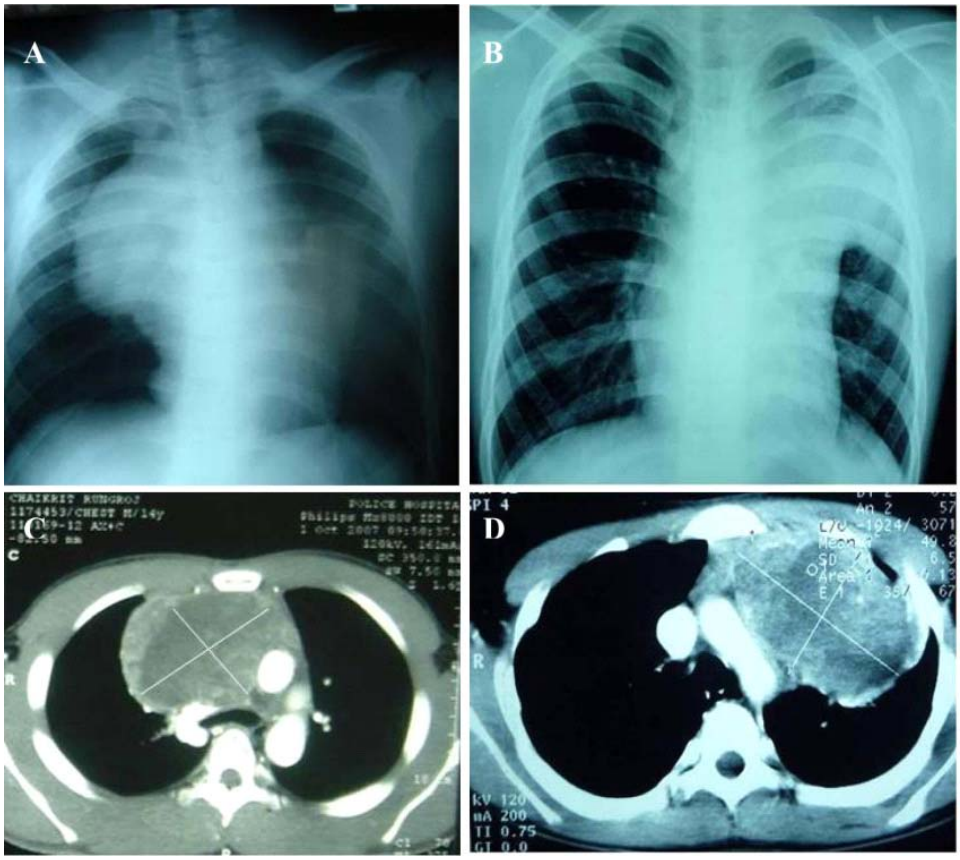

Figure 1 The chest X-ray and computerized tomography of the patient (case 1: **A** and **C**, case 2: **B** and **D**).

Testotoxicosis is a male-limited pseudoprecocious puberty caused by an activating mutation of LH receptor. At the first presentation in our hospital, the testicular volume was small and the consistency was loose in both cases. Furthermore, hypergonadotropic hypogonadiam was confirmed by the GnRH stimulation test with markedly increased FSH and LH levels and decreased testosterone level. The mechanism is postulated that advancement of bone age initiated the function of the hypothalamic-pituitary-gonadal axis but the seminiferous tubules start degenerating at the time due to Klinefelter syndrome per se. V lkl *et al*. reviewed and summarized the clinical data of 54 boys who were diagnosed as Klinefelter syndrome and mediastinal germ cell tumor. The data showed that most of the patients who were younger than 10 years presented with pseudo-precocity with variation in size of testes (2-13 mL). Respiratory symptoms including dyspnea, chest pain, or hemoptysis were more common in the older patients and small or atrophic testes with gynecomastia were usually present [5]. It takes a few years from the onset of precocious puberty to produce respiratory symptoms or mass effects. This may be because the tumor is located in the mediastinum, which is in a silent site, and the nature of tumor itself tends to be slow growing [9].

The therapy objective is to manage the mass and to attain final adult height. Our patients first received four cycles of chemotherapy including bleomycin, etoposide, and cisplatine to decrease tumor size, and then underwent total surgical resection. The tumor markers were within the normal limits after treatment and no sign of metastasis was seen. The recent height of case 1 was 162 cm, which is already the final height and lower than the target height (164-178 cm). The same result holds for case 2, the recent height is 152 cm and the target height is 163.5-170.5 cm. The final height of the two cases is lower than their genetic potential and what it should be in Klinefelter syndrome [16]. In conclusion, boys with precocious puberty due to β-hCG producing tumors, especially of the mediastinum, must have the karyotype checked. Early diagnosis will improve the prognosis and the final adult height. Conversely, patients with Klinefelter syndrome should be screened for tumor markers regularly or when clinically indicated.

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The authors have no conflict of interest to declare.

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