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Combined Central Precocious Puberty and Primary Gonadal Failure after Treatment of Childhood Malignancy in Two Boys: A Diagnostic and Therapeutic Conundrum

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Abstract

Central precocious puberty and primary gonadal failure are known sequelae of childhood cancer or its treatment. Here we report two boys with coexistent central precocious puberty and primary gonadal failure after treatment for childhood malignancies.

It is estimated that more than 70% of children diagnosed with a pediatric malignancy will survive,¹ but this improvement in prognosis has been accompanied by serious late endocrine complications.² Pubertal disorders after cancer therapy are common and include precocious puberty, as well as hypogonadism. However, the simultaneous coexistence of central precocious puberty (CPP) and primary gonadal failure (PGF) in the same patient is atypical and unexpected. Here we describe two boys with CPP and PGF after treatment for childhood cancer.

Case 1

An African American male was diagnosed with a hypothalamic pilocytic astrocytoma at 5 years of age. He was treated with chemotherapy alone, which included thioguanine, procarbazine, lomustine, and vincristine. He came to the endocrine clinic at 8.5 years of age with a 1-year history of pubic hair and adult body odor. His height was at the 75th percentile. On examination he was noted to have Tanner IV pubic hair and 2 cc testes. Bone age was read as 10 years (+2.5 SD). Initial laboratory workup was consistent with premature adrenarche except for a pubertal testosterone level of 48 ng/dL (nl<10 ng/dL). The patient was seen again at age 10 years 3 months after being lost to follow-up. His physical examination result was unchanged, and growth velocity was 7.4 cm/year. His bone age was read as 16 years, giving him a predicted adult height of 152 ± 5 cm (−3.28 SDS). Laboratory studies showed a testosterone of 251 ng/dL and an elevated follicle-stimulating hormone (FSH) of 24 mIU/mL (nl; 1–12 mIU/mL). Tumor markers were normal. Insulin-like growth factor–1 was low for pubertal stage. The patient underwent a leuprolide stimulation test,

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which revealed evidence of PGF with peak FSH and luteinizing hormone of 59.2 and 73.2 mIU/mL, respectively. Growth hormone (GH) stimulation testing revealed a peak GH level of 3.47 ng/mL (nl > 5 ng/mL). The patient was started on GH therapy. At the last clinic visit his height was 146.3 cm (0.52 SDS) and growth velocity was 4.6 cm/y.

Case 2

A Hispanic male was diagnosed with acute lymphoblastic leukemia at 3 years of age. He received multiple cycles of chemotherapy which consisted of prednisone, vincristine, daunomycin, l-asparaginase, methotrexate, mercaptopurine, cyclophosphamide, thioguanine, and Ara-C. Two years later testicular relapse developed, which was treated with testicular radiation (2100 cGy). The patient's condition relapsed at 6 years of age and received reinduction chemotherapy with methotrexate, Ara-C, mercaptopurine, VM-26, VP-16, prednisone, and vincristine. This was followed by total body irradiation (TBI) of 1440 cGy and unmatched cord blood transplantation.

The patient presented to the endocrine clinic at age 7 years 4 months for evaluation of early puberty. On examination he had 4 cc testes and Tanner 1 pubic hair. Laboratory study results showed an elevated testosterone of 273 ng/dL (nl <10 ng/dL), as well as an elevated FSH of 20.3 mIU/mL (nl; 1-12 mIU/mL). Tumor markers were normal. The patient was started on a gonadotropin-releasing hormone analog (GnRHa) for CPP. He received 3 doses of Depo-Lupron after which therapy was discontinued because of insurance reasons. He was lost to follow-up but presented again at 9 years with 2-cc testes and Tanner II pubic hair. His bone age was 11 years, giving him a predicted adult height of 168 ± 5 cm (-1.13 SDS). His growth velocity was 3.8 cm/y. Laboratory study results were significant for a pubertal testosterone, as well as markedly elevated gonadotropins consistent with PGF. At the last visit his height was 140.5 cm (-0.11 SDS), growth velocity was 3 cm/y, and bone age was 13 years. Laboratory study results in both patients are summarized in the Table, and growth data are provided in the Figure.

Discussion

Endocrine sequelae of childhood cancer are often associated with the location of the malignancy as well as the treatment modality used (surgery, radiation, or chemotherapy).³ However, these factors do not always predict outcome. Our patients had two different cancers and received different therapies yet had very similar presentations, illustrating the unpredictability of endocrine late effects. Patient 1 received only chemotherapy, which has been shown to be damaging to both male and female gonads.⁴ In boys, alkylating agents such as procarbazine act as inhibitors of DNA synthesis, leading to severe germinal aplasia and oligo/azospermia.⁵ Although it has been suggested that prepubertal children with inactive gametogenesis should have a lower incidence of injury, most young boys treated with chemotherapeutic agents still show classic features of gonadal failure.^{6,7} Patient 2 was exposed to chemotherapy, testicular, and TBI. Although testicular radiation causes severe germ cell depletion and less severe Leydig cell damage,⁸ the fact that he presented with early puberty illustrates that complete loss of gonadal function after radiation evolves over time. The diagnosis of PGF in both cases was made on the basis of elevated baseline and

stimulated gonadotropins, as well as disproportionately small testicular volumes and a decline in testosterone levels during follow-up.

CPP may be the presenting symptom of a central nervous system tumor or can develop as a complication of cancer therapy. Low-dose cranial irradiation (< 3000 cGy) is associated with precocious and rapidly progressing puberty, whereas a high dose often results in hypogonadotropic hypogonadism.^{9,10} In this report, the hypothalamic tumor in patient 1 could have resulted in loss of inhibition of GnRH release, whereas the TBI received by patient 2 represented a risk factor for CPP.

Our cases are unusual in several respects. Both patients had evidence of CPP (defined as the onset of central puberty in boys before age 9) despite a small testicular volume and elevated gonadotropins, indicating concurrent primary hypogonadism. In case 1, the CPP masked the presence of underlying GH deficiency and resulted in an inordinately rapid rate of skeletal maturation (6 years in 2 years). Although initially attributed to premature adrenarche (which is why a luteinizing hormone level was not obtained at baseline), the combination of a pubertal testosterone, dehydroepiandrosterone sulfate, and pubic hair in a Tanner IV range, and bone age advancement of > 2 SD are strongly suggestive of CPP. In case 2, the midpubertal testosterone and pubertal gonadotropins at baseline were indicative of CPP, despite testes that were barely above a prepubertal size. The slow growth velocity in case 2 suggests that this patient may also have had growth hormone deficiency, although this diagnosis was not formally pursued. Although many cases of either CPP or PGF have been recognized in childhood cancer survivors, to our knowledge the simultaneous combination of both has not been reported. Because of the seemingly contradictory clinical features, these cases also highlight unique diagnostic and treatment challenges. Although GnRHa are effective for treatment of CPP, their role in preservation of height potential in patients with simultaneous PGF has never been systematically investigated and is unclear. Similarly, whether aromatase inhibitors might have a role in patients such as ours is unknown. In summary, these 2 cases underscore the potential for unusual and atypical combinations of endocrinopathy in survivors of childhood cancer and emphasize the need for careful and continual surveillance in this patient population.

Glossary

CPP	Central precocious puberty
FSH	Follicle-stimulating hormone
GH	Growth hormone
GnRHa	Gonadotropin-releasing hormone analog
PGF	Primary gonadal failure
TBI	Total body irradiation

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Figure.
Summary of growth data for **A**, case 1 and **B**, case 2. *Circles* represent height and weight measurements, *triangles* represent bone age assessments, and the *horizontal line* represents target height.

Table

Summary of laboratory workup

Variable (prepubertal range)	Patient 1		Patient 2	
	Initial visit	F/U visit	Initial visit	F/U visit
Age in years	8.08	10.25	7.33	9
Testosterone (< 10 ng/dL)	48	251	122*	273
LH (1-12 mIU/mL)	ND	6.12/73.2 [†]	7.5	172
FSH (1-12 mIU/mL)	ND	24/59.2 [†]	20.3	151*
IGF-1 (ng/mL) [‡]	ND	86 (139-395)	141 (113-261)	74
Inhibin B (< 162 pg/mL)	ND	<10	<10	254
HCG (< 0.8 mIU/mL)	0.4	ND	0.5	ND
AFP (0-25 ng/mL)	1.4	ND	2.4	ND
17 OHP (3-115 ng/dL)	26	ND	101	ND
DHEAS (13-83 mcg/dL)	164	ND	19	ND
Androstenedione (< 0.9 ng/mL)	0.4	ND	0.6	ND

F/U, Follow-up; *ND*, not done; *LH*: luteinizing hormone; *HCG*, Human chorionic gonadotropin; *AFP*, alpha feto-protein; *17 OHP*, 17-hydroxyprogesterone, *DHEAS*, dehydroepiandrosterone sulfate.

Leuprolide stimulation involves administering leuprolide at 20 mcg/kg SQ. LH and FSH are sampled at baseline, 30, 60, 120, and 180 minutes. Testosterone is drawn at baseline and 24 hours after testing.

* Testosterone level 6 months later.

[†] Peak values during leuprolide stimulation testing.

[‡] Normal ranges were adjusted for pubertal stage.