"Double Trouble": A Case of Precocious Puberty with Concomitant Malignant Gluteal Mass

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Precocious puberty is the appearance of physical and hormonal signs of pubertal development at an earlier age than is considered normal. The causes may range from a variant of normal development to pathologic conditions such as glands that function abnormally early in life. This is a case of a seven year old female with clitoromegaly, early menarche and a gluteal mass accompanied by elevated 17-hydoxyprogesterone and decreased level of cortisol which supports the diagnosis of congenital adrenal hyperplasia. Gluteal mass cytological features are consistent with a malignant round cell tumor.

Keywords: Precocious puberty, clitoromegaly, malignant round cell tumor

Introduction

A normally timed puberty results when pulsatile secretion of gonadotropin releasing hormone (GnRH) activates the hypothalamic - pituitary - ovarian axis in females. Puberty is said to be precocious if it occurs in boys younger than nine years of age, and, in girls less than seven years of age. Peripheral precocious puberty (also known as Gonadotropin Independent Puberty) is the result of the autonomous peripheral secretion of excess sex hormones independent of the hypothalamic - pituitary - ovarian axis. Left untreated, peripheral precocious puberty can lead to central precocious puberty.

Peripheral precocious puberty can occur from many different causes. The differential diagnosis includes sex hormone secreting tumors of the adrenal gland and ovary, McCune - Albright syndrome, Van Wyk - Grumbach syndrome, adrenal gland enzyme deficiencies, and exogenous exposure to sex hormones.

Thus, early detection, prompt diagnosis and adequate treatment are of paramount importance to ensure normal physical and psychological development of affected children. One of the challenges in the diagnosis is to differentiate between central and precocious puberty as fundamental treatment options differ in each group. In the former, however, irrespective of the etiology, long acting GnRH agonistic analogues are given.

The Case

This is a case of a seven year old Filipino female, presently residing in Benguet, who was brought to the outpatient department due to left gluteal mass and clitoromegaly. Present condition started nine months prior to consult when a gluteal mass was first noted, and measured approximately 3cm x 3cm in diameter, firm, mobile, with indistinct border, and tender on deep palpation.

Five months prior to consult, patient's mother noticed gradual enlargement of the gluteal mass and patient complained of mild pain whenever she sits down. No consult was done nor medications taken. There were no associated fever, skin lesions, nor motor and sensory deficits on the lower extremities.

Due to the rapid enlargement of the gluteal mass to approximately 7cm x 7cm in its greatest

diameter, patient's mother decided to bring her to the Ob-Gyne outpatient department for consult. She reported about the patient's enlarged clitoris which started at two years of age. This began as a broadening of the distal end with subsequent gradual elongation of the length of the clitoris. At three years of age, secondary sexual characteristics also ensued starting with menarche followed by gradual enlargement of the breast, growth of pubic hair and deepening of voice. No consult was done and no medications were taken. Patient was born in a hospital by normal spontaneous delivery at thirty nine weeks age of gestation, with a birth weight of 3.3 kg, appropriate for gestational age. No newborn screening was done at the institution. Mother and child were discharged without complications a day after the delivery.

Patient is the youngest of four children. She was born to a G4P4 (4004) mother with all previous pregnancies carried to term, via normal spontaneous delivery with no complications. Mother was cognizant of pregnancy at six weeks age of gestation through a positive pregnancy test. She claims to have had regular prenatal check-ups at a Iocal health center. No illnesses such as hypertension nor any vaginal bleeding were encountered during the prenatal period. No vitamin supplements were taken throughout the pregnancy.

On the first year of life, patient was given complete vaccinations according to the expanded program on immunization (EPI) schedule. No neurodevelopmental delay was noted. She started standing at twelve months old and walking at fourteen months old. She can climb up stairs and run at twenty four months.

Symptoms of virilization started at six months old as a change in the tone of cry. At one year and eight months of age, there was a laryngeal prominence associated with a low tone speech (Figure 1). At two years of age, clitoris was noted to be externally visible from the labia majora.

Menarche was followed by thelarche at three years of age. At five years old, clitoromegaly was noted, progressively increasing in length to two cm with concomitant increase in diameter.

At six years of age, the pubic hair and external genitalia were classified as Tanner Stage IV, with the clitoris measuring approximately 3cm in length and one cm in diameter, and the distal third of the clitoris resembling a glans penis (Figure 2). There were no unusual skin pigmentations nor gross limb nor bone deformity.

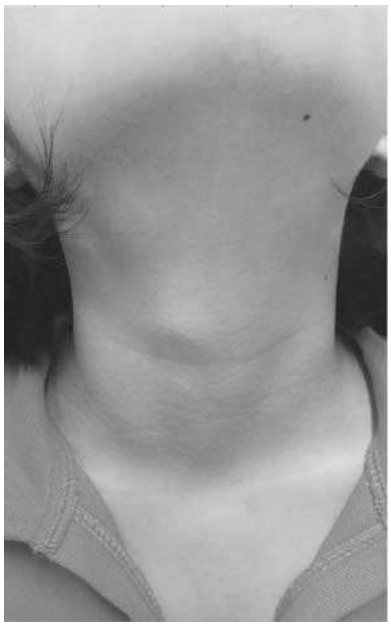

Figure 1. Laryngeal prominence associated with low tone speech.

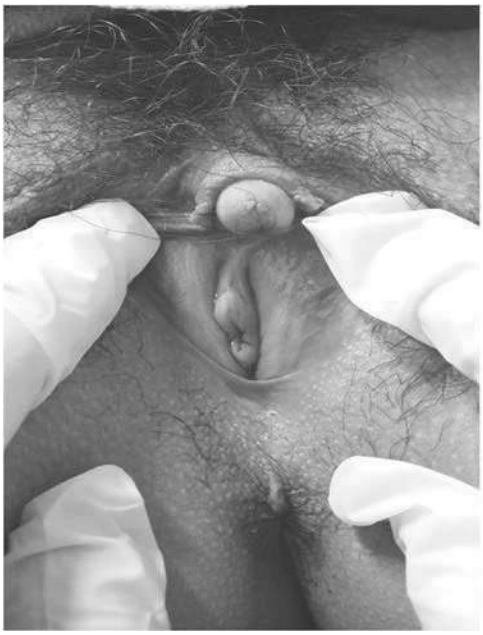

Figure 2. The clitoris measures approximately three cm in length and one cm in diameter, with the distal third of the clitoris resembling a glans penis.

On physical examination, patient was ambulatory, conscious, coherent, not in cardio - pulmonary distress, weight of 38kg which is above 3SD or obese for age; height of 131 cm with a Z score above 2SD which is normal length for age; and BMI of 22.1 with a Z score above 3SD which is obese for age.

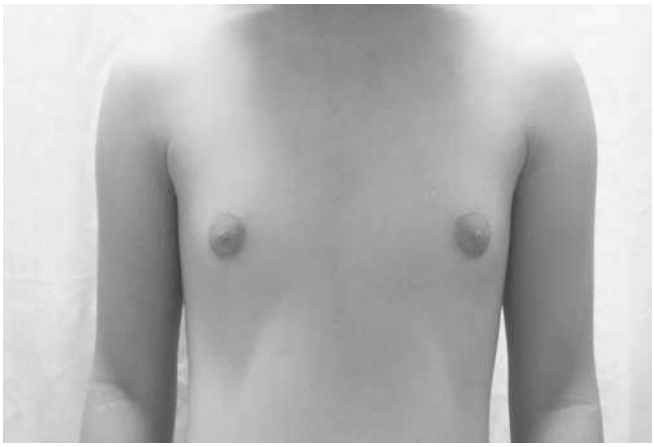

Figure 3. Breast enlargement and nipple development corresponding to tanner stage III, with noted pigmentation of areola. Further enlargement of breast and areola; no separation of their contour.

She has pink palpebral conjunctivae, anicteric sclerae, no cervical lymphadenopathy, prominent vocal cords, symmetrical chest wall expansion, clear breath sounds, adynamic precordium, with regular sinus rhythm, and no murmurs.

She has bilateral breast enlargement and nipple development with noted pigmentation of the areola corresponding to Tanner Stage II, breast bud stage with elevation of breast and papilla with enlargement of areola (Figure 3). Axillary hair is absent.

Abdomen was globular with no distended veins, normoactive bowel sounds, no tenderness and no organomegaly. The labia resembled adult form with evidence of adult pubic hair covering entire mons veneris which assimilate to tanner IV (Figure 4). On the left gluteal area, there was a palpable mass, about 7cm x 7cm in its greatest diameter, slightly movable, irregular boarder, and with mild tenderness on deep palpation (Figure 5). Extremities showed no muscle wasting, weakness nor sensory or motor deficits.

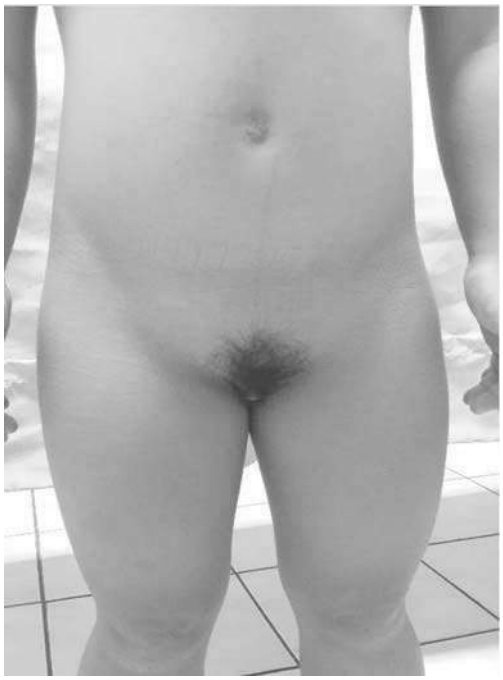

Figure 4. Pubic hair and external genitalia assimilate to tanner IV. Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs.

Figure 5. Gluteal mass was noted 9 months prior to consultation measuring about 2cm x 2cm in diameter enlarging to its present size of approximately 7cm x 7cm in its greatest diameter accompanied by symptoms of mild pain on deep palpation.

Primary impression at this time was Precocious Puberty, Central vs Peripheral, ambiguous genitalia; Gluteal Mass, etiology Undetermined.

On the first day of consult, the patient was referred to the Department of Pediatrics for further evaluation. Assessment was Precocious puberty, peripheral type secondary to congenital adrenal hyperplasia. On the other hand, gluteal mass was referred to surgery department and was advised excision biopsy. Patient was subsequently referred to Neurosurgery for evaluation to rule out involvement of spine and spinal cord. Neuroclearance was granted.

Consult with a Reproductive Endocrinology and Infertility specialist was done. Results of diagnostic exams supported the diagnosis of peripheral precocious puberty (Table 1). Karyotyping revealed 46 XX (Figure 6).

On follow up consult, section biopsy was done on the excised gluteal mass with subsequent histopathologic diagnosis consistent with a malignant round cell tumor. (Figures 7-10).

Final diagnosis is Peripheral Precocious Puberty secondary to Congenital Adrenal Hyperplasia; Gluteal mass, round cell tumor, malignant.

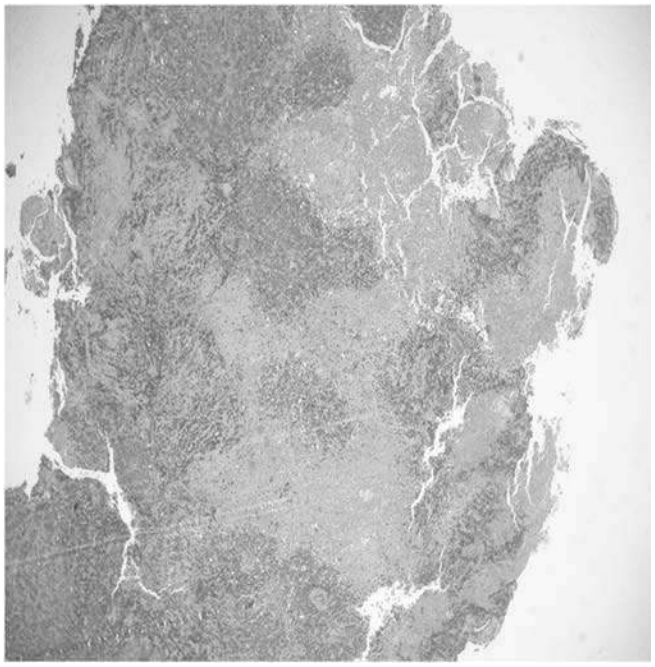

Figure 7. A section show several irregular tissue fragments with atypical cells in syncytial arrangements. These atypical cells have round to ovoid, hyperchromic to vesicular nuclei, some are bizarre with prominent eosinophilic nucleoli surrounded by a fibrotic stroma with chronic inflammatory infiltrates. Interspersed are mitotic figures, some appear to be atypical. Likewise seen are focal areas of necrosis.

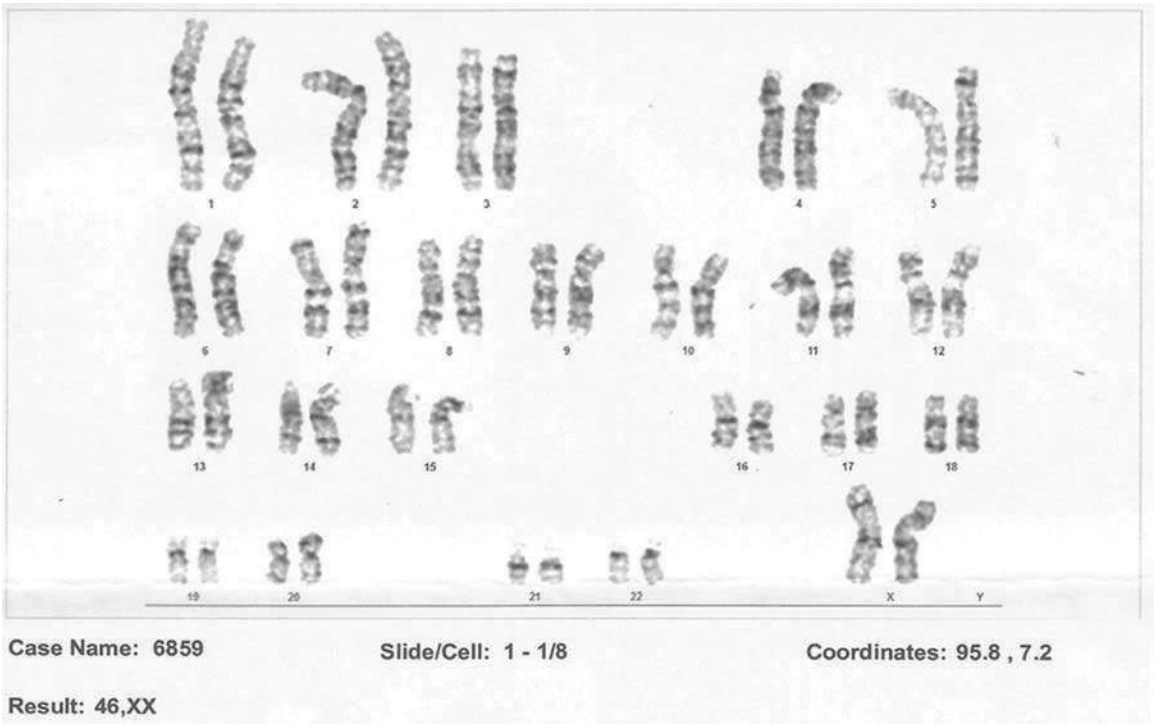

Figure 6. Karyotyping showed 46 XX.

Table 1. Laboratory results.

Test	Result		Reference interval
Cortisol (Time of extraction: 8:30 AM)	3.30 ug/dl	Decreased	Serum collected before 10:00 AM: 3.7 - 19.4 ug/dl Serum collected after 5:00 pm: 2.9 - 17.3 ug/dl
17 - Alpha-OH- Progesterone	3.07 ng/ml	Increased	0.05 - 2.0 ng/ml
ACTH	8.21 pg/ml	Normal	7.20 - 63.30
DHEA	88.90 ug/dl	Normal	24.40 - 209.70
Testosterone	9.50 ng/dl	Normal	6.00 - 82.00
Pelvic CT scan	Small complex presacral mass with punctuate calcifications (measuring 3.1 x 2.3 cm); well defined hypodense mas		
Karyotype	46 XX	Genetically female	
Pelvic ultrasound	Uterus and ovaries compatible for a reproductive age		

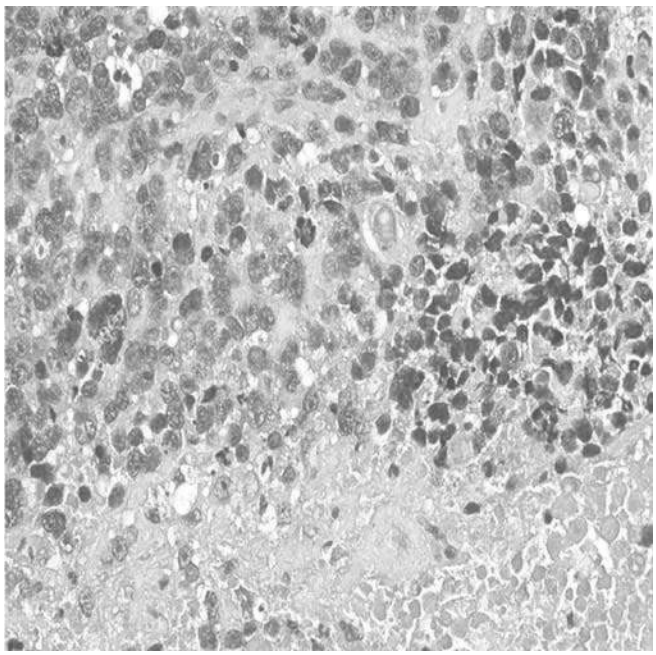

Figure 8. High power Objective showing atypical cells in syncytial arrangements.

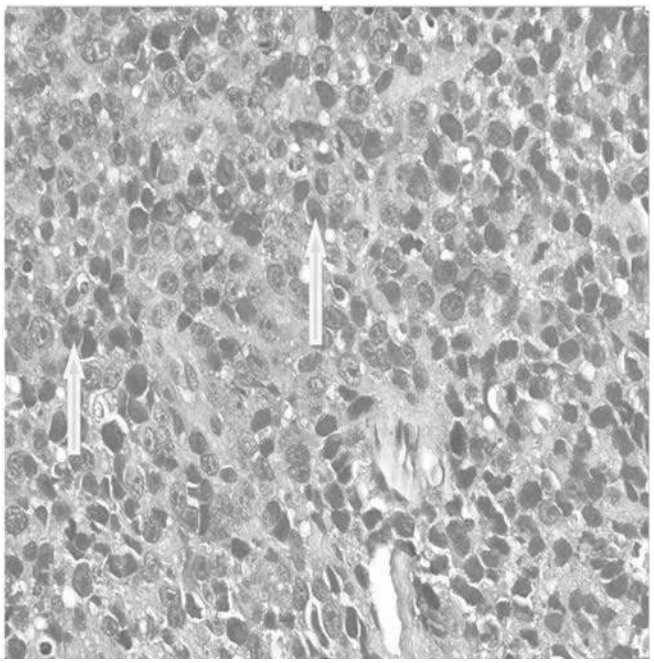

Figure 9. In low power objective: arrow points atypical cells have round to ovoid, hyperchromic to vesicular nuclei.

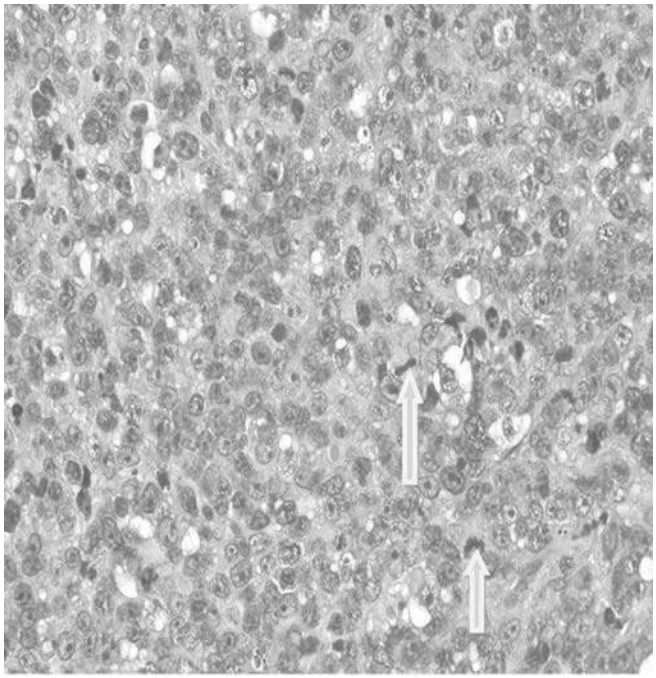

Figure 10. Interspersed mitotic figures.

Discussion

The evaluation of a child with malignancy suspected to have precocious puberty begins with a thorough history and physical examination, in order to determine the progression of pubertal development. The onset and timing of the development of secondary sexual characteristics may provide a diagnostic clue in determining the etiology of precocious puberty. In an article by Kaplowitz and associates, it was suggested that girls with breast development or pubic hair should be evaluated when these signs occur before age 7 in whites and age 6 in black girls.

Precocious puberty can be divided into 2 distinct categories. The first category is gonadotropin-dependent precocious puberty, which involves the premature activation of the hypothalamic-pituitary-gonadal (HPG) axis. The second category is gonadotropin-independent precocious puberty, in which the presence of sex steroids is independent of pituitary gonadotropin release which is seen in this patient. A definite diagnosis is established more often for pseudoprecocious puberty, which is usually related to an ovarian or adrenal disorder. This premature virilisation in a female child includes development of masculine secondary sexual characteristics. The androgens that cause heterosexual precocious puberty usually come from the adrenal gland. Causes of precocious pseudopuberty include congenital adrenal hyperplasia (CAH) as in the case of this patient. The diagnosis is made with the help of a careful history and physical examination in conjunction with the use of radiologic and other laboratory evaluations. Classic CAH is usually detected in infancy with ambiguous genitalia in girls. In addition, some clinics and hospitals include testing for increased blood concentration of 17α-hydroxyprogesterone to diagnose CAH in the routine newborn screening performed on all babies. It is just unfortunate that this was not done during birth of this patient.

Incidence of precocious puberty is estimated to be 1 per 5000-10,000 individuals. Gonadotropin-independent precocious puberty is about one fifth as common as gonadotropin-dependent precocious puberty. Classic CAH is due to 21-hydroxylase deficiency: Worldwide, the incidence is about 1 in 10,000-15,000 live births, and 25% of cases, known as simple virilizers, may be missed in infancy and may present in early childhood with signs of inappropriate somatic growth, epiphyseal maturation, pubic hair, acne, and progressive clitoromegaly in girls.[1]

It is typical to distinguish three forms of 21-hydroxylase deficiency which, in order of severity, are: the salt-losing form (most severe), the simple-virilizing form (moderate severity) and the late-onset or non-classical form (least severe).

In the case described, ambiguous genitalia was noted at 6 months old (classic virilising adrenal hyperplasia). Genital anomalies range from fusion of the labioscrotal folds and a phallic urethra to clitoromegaly, partial fusion of the labioscrotal folds, or both, due to deficiencies of 21-hydroxylase which describes simple virilizing adrenal hyperplasia.

Further laboratory evaluation is needed to confirm a diagnosis of precocious puberty based on history and physical examination. In particular, hormonal and imaging studies can help identify the etiology of precocity, whether treatment is

necessary and what mode of treatment is indicated. The first step is to confirm whether the etiology of the precocity is peripheral rather than central, and currently, a GnRH stimulation test is the gold standard for correctly diagnosing children with precocious puberty.[2,3] However, this test was not done in our index patient.

The clinical manifestations of each form of congenital adrenal hyperplasia are related to the degree of cortisol deficiency and/or the degree of aldosterone deficiency. In some cases, these manifestations reflect the accumulation of precursor adrenocortical hormones. When present in supraphysiologic concentrations, these precursors lead to excess androgen production with resultant virilization, or because of mineralocorticoid properties, cause sodium retention and hypertension. In the case described, the basal cortisol levels are particularly low; along with an increased 17-Alpha-OH- Progesterone. This finding is highly suggestive of peripheral precocious puberty.

Imaging studies and further laboratory examinations are used to elucidate the etiology of precocity once the distinction between central and peripheral precocious puberty has been made by hormonal studies. Although GnRH test has not yet been done several considerations from the case make the diagnosis of peripheral precocious puberty highly considered. First, the timing of pubertal development does not recapitulate normal puberty, as one would expect from central precocious puberty. Second, a pelvic CT - scan done on the patient revealed no CNS anomalies to exclude tumors which may cause precocity. Lastly, a pelvic ultrasound done ruled out an ovarian pathology which is the most common cause of peripheral precocious puberty.

McCune - Albright syndrome should also be considered as possible diagnosis when evaluating patients with peripheral precocious puberty. This rare disorder is caused by a G protein mutation that leads to continued stimulation of endocrine function, and is characterized by clinical triad of peripheral precocious puberty, café -au-lait skin pigmentation, and polyostotic fibrous dysplasia. In this case, the absence of the characteristic skin lesions and normal imaging studies render the triad incomplete, but at this point, one cannot completely rule out this disorder.[4]

Other than peripheral precocious puberty, the index patient also presented with a gluteal mass. Pelvic CT scan revealed small complex parasacral mass with punctuate calcifications. A section biopsy revealed a malignant round cell tumor. Malignant small round cell tumors are characterised by small, round, relatively undifferentiated cells. They generally include Ewing's sarcoma, peripheral neuroectodermal tumor, rhabdomyosarcoma, synovial sarcoma, non-Hodgkin's lymphoma, retinoblastoma, neuroblastoma, hepatoblastoma, and nephroblastoma or Wilms' tumor. Although classical histological features are generally highly suggestive of tumor type, on occasion, these tumors may be indistinguishable by light microscopy, making a definitive diagnosis difficult. Immunohistochemistry can be helpful in narrowing down the differential diagnosis. Accurate diagnosis of pediatric small-round-cell tumors has become increasingly crucial, as disparate approaches to therapy are used for distinct tumor types. Immunocytochemistry is useful in cases when tumors are undifferentiated and distinction is not possible on morphological basis alone. This would enable the institution of appropriate therapeutic protocols, including neo-adjuvant chemotherapy in advanced malignancy.[5]

However, despite recent advances in immunohistochemistry and molecular pathology, some cases of small-round-cell tumors of childhood remain diagnostically problematic. Antibodies used in immunocytochemistry studies have limitations in sensitivity and specificity. Furthermore, although chromosomal abnormalities have proven to be useful in the characterization of certain pediatric cancers, other tumors lack a consistent genetic profile. It has also become evident that many genetic abnormalities are not tumor specific. Thus, although individual molecular tests can aid in delineating the entities of small-round-cell tumors of childhood, the diagnosis should not be based solely on the result of a molecular study. Rather, standard clinical and laboratory diagnostic modalities should be combined with immunohistochemistry, cytogenetics, and molecular studies.

Management

The management of peripheral precocious puberty is directed at the underlying pathology. The plan and goal of management for congenital adrenal hyperplasia is the replacement of glucocorticoid and mineralocorticoid to prevent signs of adrenal insufficiency and to prevent the accumulation of precursor hormones that cause virilization.[6] Adequate glucocorticoid replacement should prevent excessive concentrations of ACTH from stimulating the adrenal glands to produce abnormal concentrations of adrenal androgens that result in further virilization. In the growing child with adrenal insufficiency, long-term glucocorticoid replacement must be balanced to prevent symptoms of adrenal insufficiency while still allowing the child to grow at a normal rate and prevent symptoms of glucocorticoid excess.

Because of large individual variation in cortisol secretion, it is important to monitor treatment very carefully. The means to determine an appropriate replacement dose includes measurement of plasma 17- hydroxyprogesterone and androstenedione concentrations, or of the urinary excretion of pregnanetriol (the major metabolite of 17-hydroxyprogesterone) and 17-ketosteroids (the metabolites of androgens). It is also important to follow growth (Bone Age and Height Age) in order to monitor the anabolic effects of adrenal androgens.

It is also necessary to check serum electrolytes frequently to assure normal levels of sodium, potassium and HCO_3. This is particularly important for salt-losers.

The section biopsy of gluteal mass presented with a histopathologic result of malignant round cell tumor. Ancillary diagnostic techniques of immunocytochemistry, flow cytometric immunophenotyping, and reverse- transcriptase polymerase chain reaction are extremely useful in cases when tumors are undifferentiated and distinction is not possible on morphological basis alone. These studies are extremely effective in establishing a definite diagnosis. This would enable the institution of appropriate therapeutic protocols, including neo-adjuvant chemotherapy in advanced malignancy. For this patient, immunocytochemistry was recommended to establish a definite diagnosis to enable appropriate therapeutic protocols in advanced malignancy.

Summary and Conclusion

In cases of precocious puberty, further work-ups are important to distinguish between central and peripheral precocious puberty and ideally, GnRH stimulation test is considered the gold standard for differentiating between the two types. Congenital adrenal hyperplasia is the most common cause of peripheral precocious puberty, 90% of which are due to 21 hydroxylase deficiency. The goal of therapy for adrenal hyperplasia is the replacement of glucocorticoid and mineralocorticoid to prevent signs of adrenal insufficiency and to prevent the accumulation of precursor hormones that cause virilization. It is prudent for physicians caring for this type of patients to be cognizant on the proper diagnosis, management, follow-up and early referral to a specialist because undue delay may lead to failure of treatments and complications.

As for the patient's malignant round cell tumor, accurate diagnosis and classification are very important as modern therapy is not only disease-specific but is also tailored according to patient risk. Despite advances in immunohistochemistry, cytogenetics, and molecular techniques, in some cases of small-round-cell tumors of childhood, the correct diagnosis remain elusive. Although there are no specific studies supporting higher predisposition of children who suffer from precocious puberty to certain malignancies except few studies on breast cancer, there are some literature that try to investigate further to come out with valid conclusions.

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