A Female Pediatric Patient with Bilateral Ovarian Cysts Presenting to Gynecologic Oncology Diagnosed as Van Wyk-Grumbach Syndrome: A Case Report

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Abstract

We describe a case of a 7-year-old female who presented to the emergency department (ED) with a three-day history of vaginal bleeding, progressive abdominal pain, and dehydration. Initial computerized tomography (CT) scan of the abdomen followed by a transabdominal ultra-sound of the pelvis identified bilateral, symmetric adnexal cysts and proliferative-phase endometrium with no evidence of inflammatory or malignancy-related findings. A gynecologic oncology consult led to surgical exploration diagnosing the child with an acute surgical abdomen. Surgery was performed through a vertical infra-umbilical, mini-laparotomy (4 cm) incision. Both intra-operative and final pathology confirmed bilateral ovarian, low malignant potential (LMP), granulosa cell tumors. Post-operative bone age was over 18 months less than the patient’s age. The discrepant bone age prompted investigation into pediatric syndromes characterized by juvenile hypothyroidism, isosexual precocious puberty, and granulosa cell tumors with delayed bone age. A rare diagnosis matching all criteria was identified as Van Wyk-Grumbach Syndrome (VW-GS). This syndrome was originally reported in 1960 by Drs. Van Wyk and Grumbach. They identified the discrepancies in bone age and how simple thyroid replacement results in complete resolution of this unique syndrome. Our literature review found few reports related to VW-GS in the gynecologic oncology case studies. We hope this report will further assist in the appropriate diagnosis and management of similar cases to avoid unnecessary and invasive interventions and treatment.

Keywords: Van Wyk-Grumbach Syndrome; Precocious Puberty; Hypothyroidism; Ovarian Cyst; Pediatric Syndrome

Introduction

In 1960, Drs. Van Wyk and Grumbach first published and “coined” this collection of related diagnoses, Van Wyck - Grumbach Syndrome (VW-GS) [1-3]. The initial report described a young female with precocious puberty, galactorrhea, ovarian cysts, and delayed bone age resulting from hypothyroidism. Since their initial description, the majority of literature appears in pediatric specialty journals [3-7]. Most gynecologic specialists would recommend surgical exploration to evaluate pediatric adnexal masses, while our pediatric colleagues likely would recommend medical management [8-10]. VW-GS appears to be most commonly caused by a non-congenital form of autoimmune hypothyroidism [11]. Due to the disruption in the negative feedback loop that thyroid hormone exerts on the hypothalamus and pituitary, there is an increase in TRH and TSH as observed in this patient.

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Case Presentation

A 7-year-old Hispanic female was brought to the ED complaining of lower abdominal pain and vaginal bleeding for several days. Her mother reported no fever or oral hydration (PK1) but worsening nausea without vomiting over the last 36 hours. Bowel function was unknown. Physical exam found the patient in obvious distress, lying in the fetal position and crying due to abdominal pain. Bowel sounds were absent. The abdomen was distended with guarding and rebound tenderness. The patient’s acute abdomen necessitated surgical evaluation. Prior to gynecologic oncology consultation, computerized tomography (CT) and abdominal ultrasound (AUS) identified bilateral 4 x 5 cm, simple ovarian cysts with thin-walled capsules. Other findings include a proliferative phase endometrium, absent ascites, normal appendix, and no obvious metastatic or inflammatory findings. Pre-operative laboratory tests found elevated tumor markers associated with ovarian granulosa cell tumors, i.e., elevated levels inhibin A and B, estradiol, and Mullerian inhibitory substance (MIS) and an elevated thyroid-stimulating hormone ((TSH), 1970 mIU/mL(normal 0.6-7.4 mIU/mL)), suggestive of severe hypothyroidism.

Following induction of general anesthesia, visual examination demonstrated Tanner stage 1 breast buds and absent axillary hair. The patient’s external genitalia were edematous without terminal hair or vaginal discharge. An obvious linea nigra was identified, resulting in an evaluation of serum progesterone, which was elevated as expected. Surgery was performed through a 4 cm infra-umbilical incision. No evidence of an acute inflammatory process was identified. Due to suspected ovarian cysts, oncology consultation, computerized tomography (CT) and abdominal ultrasound (AUS) identified bilateral 4 x 5 cm, simple ovarian cysts with thin-walled capsules. Other findings include a proliferative phase endometrium, absent ascites, normal appendix, and no obvious metastatic or inflammatory findings. Pre-operative laboratory tests found elevated tumor markers associated with ovarian granulosa cell tumors, i.e., elevated levels inhibin A and B, estradiol, and Mullerian inhibitory substance (MIS) and an elevated thyroid-stimulating hormone ((TSH), 1970 mIU/mL(normal 0.6-7.4 mIU/mL)), suggestive of severe hypothyroidism.

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GnRH-agonist (Depot Lupron TM 7.5 mg IM) was administered (PK2) to block the production of sex hormones. Since levothyroxine was not started following hospital discharge, thyroid replacement was started at 25 micrograms daily and titrated every 4-6 weeks until normalized. To evaluate the patient’s hypophysial-pituitary axis, CT was performed, and the results identified an enlarged pituitary gland. The pituitary gland was described as both homogenous and symmetric, consistent with pituitary gland hyperplasia. Further investigation identified the patient had a bone age of 18-month less than her age (7 years). The patient’s bone-age findings were contradictory to her elevated estradiol levels (326 pg/ml, normal <16pg/ml), which characteristically causes premature closure of the bony epiphyses and advanced bone-age.

With the list of findings highlighted by isosexual precocious puberty, the bilateral, symmetric benign-appearing ovarian tumors, severity of the hypothyroidism, and a bone-age opposite of what was expected, our interest in pediatric syndromes ensued. Using a common search engine and the following characteristics - isosexual precocious puberty, bilateral ovarian tumors, hypothyroidism, and delayed bone age, a perfect match identified VW-GS. This syndrome appears to be a unique manifestation of severe, chronic hypothyroidism [15-19]. After reviewing the literature, especially the reports describing delayed bone age and how the syndrome resolves completely with thyroid replacement, the family was counseled on the importance of daily dosing of levothyroxine and follow-up. Soon after starting levothyroxine, the patient’s vaginal bleeding stopped, tumor markers decreased, and ovarian cysts resolved. Additionally, she had a rapid increase in height by 2-3 inches in 3-4 months. No further GnRH-agonist therapy was administered after the initial injection of levothyroxine. We cannot exclude the effects of a single goserelin (GnRH Agonist) injection, though the steady decline of all tumor markers and symmetric, consistent with pituitary gland hyperplasia. A somatic mutation in the FOXL2 gene was found in 97-98% of all tumors [20]. This specific mutation is now considered a pathognomonic variant for AGTs. The more aggressive juvenile granulosa cell tumors lack the FOXL2 mutation. In our patient, both cystic ovarian tumors tested negative for the FOXL2 mutation. Although one would expect an advanced bone age due to elevated levels of estradiol in granulosa cell tumors, there is a striking difference in VW-G syndrome, a decreased bone age. The decreased bone age can be attributed to severe hypothyroidism, which delays the fusion of epiphysis [21]. Upon administering thyroid hormone replacement, the delayed bone age is rapidly corrected.

Van Wyk Grumbach syndrome is described as isosexual precocious pseudopuberty, multicystic enlarged ovaries, hypothyroidism, and delayed bone age. In addition, it is not uncommon to see enlarged pituitary glands [1, 22, 23]. This pituitary hyperplasia is secondary to hyperstimulation by TRH due to the loss of negative feedback from thyroid hormone [24]. Homogeneous pituitary hyperplasia has been reported in chronic, severe forms of hypothyroidism due to the demand to produce greater quantities of thyroid-stimulating hormone (TSH), as seen in our case [25]. When physiological equilibrium is restored by exogenous thyroid hormone, there is a regression of pituitary hyperplasia. With thyroid hormone playing a prominent role throughout the majority of the body, it is imperative to recognize and treat hypothyroidism in children in a timely manner. Typical symptoms include constipation, weight gain, lack of energy, slow thinking, but in severe cases, hypothyroidism may cause restricted bone growth and delayed puberty [26]. The latter features are commonly associated with VW-G Syndrome. It should be of note that in this case, the 7-year-old 2nd grader was academically exceptional in math skills and had limited signs or symptoms despite her chronic, severe hypothyroidism. It is of interest to consider how this syndrome protects bone development from epiphyseal closure [27-30] and possibly, the brain from learning disabilities despite severe hypothyroidism during developmental years.

Although hypothyroidism is common in children, especially girls, which are four times more susceptible to hypothyroidism compared to boys, there are very few causes of VW-G syndrome [31]. Further, the molecular aspects or plausible genetic mutation of VW-G Syndrome have not yet been elucidated. Therefore, it is imperative we are aware of this syndrome to ensure early diagnosis and avoid unnecessary invasive procedures. This report contributes to the gynecologic oncology knowledge base by informing and educating our subspecialty about this rarely reported pediatric syndrome. Gynecologic oncologists with knowledge of Van Wyck Grumbach Syndrome should consider thyroid evaluation and bone-age determination to avoid misdiagnosis, unnecessary surgery or other therapies, and possible complications of these interventions [25].

Discussion

On initial observation, the bilateral tumors in our patient resembled granulosa cell tumors. Adult-type granulosa cell tumors (AGTs) are considered a low-malignant potential neoplasm. A somatic mutation in the FOXL2 gene was found in 97-98% of all tumors [20]. This specific mutation is now considered a pathognomonic variant for AGTs. The more aggressive juvenile granulosa cell tumors lack the FOXL2 mutation. In our patient, both cystic ovarian tumors tested negative for the FOXL2 mutation. Although one would expect an advanced bone age due to elevated levels of estradiol in granulosa cell tumors, there is a striking difference...
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