Case Report

Van Wyk and Grumbach Syndrome: An Unusual Case and Review of the Literature

Kaci L. Durbin MD [1], Teresa Diaz-Montes MD, MPH [2], Meredith B. Loveless MD [1,*]

[1] University of Louisville School of Medicine, Louisville, Kentucky, USA
[2] Johns Hopkins University, Baltimore, MD

A B S T R A C T

Background: The syndrome consisting of primary hypothyroidism, precocious puberty, and massive ovarian cysts was termed Van Wyk and Grumbach syndrome in 1960. Little is known about the effect of the cysts on ovarian tumor markers.
Case: A 12-year-old Caucasian female presented with headaches and fatigue. Imaging to evaluate her headaches revealed a pituitary macroadenoma. Soon after her macroadenoma was discovered, she presented to the emergency room with abdominal pain. Imaging at that time revealed massive bilateral ovarian masses with the left measuring 17 × 13 × 8.5 cm and the right measuring 18 × 11 × 10 cm. Ovarian tumor markers were drawn at this time, most of which were highly elevated. Subsequent evaluation revealed extreme hypothyroidism.
Given these findings of a pituitary macroadenoma, bilateral ovarian masses, and severe hypothyroidism, the patient was diagnosed with Van Wyk and Grumbach syndrome. We followed the cyst conservatively and the ovaries and tumor markers returned to normal after adequate thyroid replacement.
Comments: This case supports conservative treatment as the first-line approach to massive ovarian cysts caused by hypothyroidism. In addition this case shows that tumor markers can be abnormal in the absence of a malignancy in this setting. Before proceeding with surgical evaluation, exclusion of hypothyroidism to exclude this rare but treatable syndrome should be undertaken. The most important diagnostic clue that the cyst may be caused by an endocrine source is the finding of bilateral ovarian cysts rather than one ovary affected as seen in most ovarian malignancies in this age group.
Key Words: Ovarian cyst, Hypothyroidism, Van Wyk and Grumbach syndrome, Tumor markers

Introduction

The syndrome consisting of primary hypothyroidism, precocious puberty, and massive ovarian cysts has been described since 1905, but the term Van Wyk and Grumbach syndrome was coined in 1960.

Clinically this syndrome is often a diagnostic challenge, because long-standing primary hypothyroidism traditionally leads to both pubertal and growth delay. In these rare cases, hypothyroidism leads to growth delay with, paradoxically, precocious puberty.

Review of the literature provides many examples of large and multicystic ovarian masses resulting in various presentations of precocious puberty in the setting of hypothyroidism.[1–10] Additionally, abnormalities in pituitary function, including pituitary hyperplasia or pituitary adenomas, may result in abnormal levels of prolactin and FSH.[1–9] The precocious puberty is unique in that it is classically associated with decreased bone age. It often presents as early thelarche and vaginal bleeding without adrenarche.

Most reported cases of Van Wyk and Grumbach syndrome report the findings in prepubertal girls; however, it can be manifested during various stages of sexual development.[1–3,10] Ovarian cysts can become massive; and prior cases have revealed abnormal tumor markers that normalized after thyroid replacement.[1–5]

For these reasons many experts advocate conservative management of the ovarian masses to avoid unnecessary surgical intervention. We report a unique case featuring remarkably abnormal tumor markers in this setting. This case also provides further support for conservative management in patients with Van Wyk and Grumbach syndrome.

Case

An 11-year-old female presented to her physician with a chief complaints of headaches. She was referred to neurology by her primary care physician. An MRI of the brain revealed a solid enhancing sellar mass compressing the optic chiasm, 20 × 19 × 14 mm, with a differential diagnosis including macroadenoma or craniopharyngioma . A referral was made to pediatric endocrinology for further work up of this lesion.

Two weeks after her brain lesion was discovered, she presented to the emergency room with severe abdominal pain. Computed tomography (CT) imaging at that time revealed bilateral ovarian masses. At this point, she was referred to pediatric gynecology.

Gynecologic history was significant for one menses about 6 months prior to evaluation. She had experienced intermittent pelvic pain which had been attributed to her recent onset of menses. She also complained of fatigue for

* *Address correspondence to:* Meredith B. Loveless, MD, 550 South Jackson Street, 3rd Floor, Louisville, KY 40202
E-mail address: meredith.loveless@louisville.edu (M.B. Loveless).

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Table 1
Laboratory results at presentation and 6 weeks post-treatment

Laboratory Test	Patient's Value	Patient's Value 6 Weeks post Treatment	Normal Values
TSH	1889.9	5.63	0.5– 4.5 mIU/mL
Free T4	0.3	0.9	0.7–1.8 ng/dL
Prolactin (ng/mL)	77	ND	3.0–23.2 ng/mL
Cortisol (mcg/dL)	16.1	ND	Reference: 7–9 AM: 6.0–26.0 UG/DL 4–6 PM: 4.0–18.0 UG/DL
Cortisol 30 min post ACTH stim (mcg/dL)	26.7	ND	n/a
Cortisol 60 min post ACTH stim (mcg/dL)	30.1	ND	n/a
FSH (mIU/mL)	19.1	8	Pre-pubertal Child: 0.0–2.8 Adult Female: 3.7–28.6 (depending on cycle phase)
LH (mIU/mL)	<0.2	ND	122–220 U/L
Estradiol (pg/mL)	568	34	Ovulating Females: Follicular Phase: None Detected - 266 pg/ml Midcycle - 118–355 pg/ml Luteal Phase 26–165 pg/ml
CA-125 (U/mL)	91	16	0–35 U/mL
LDH (U/L)	589	WNL*	122–220 U/L
AFP (ng/mL)	12	WNL*	0–10 ng/mL
Inhibin (pg/mL)	1057	<10	Reference ranges for Inhibin A: Females Premenopausal: Less than 98 pg/mL
hCG (mIU/mL)	<2	ND	<2 mIU/mL

Abbreviation: ND, not done
* Done at different lab than initial set

the past year, feelings of depression with crying spells, and weight gain for the past three years. She denied any history of constipation or cold intolerance. Physical examination revealed Tanner stage III breasts and stage III pubic hair with an absence of axillary hair. She had a distended abdomen with a palpable mass to the level of the umbilicus. She was unable to tolerate a pelvic examination.

Pelvic ultrasound confirmed findings of the CT scan, revealing a left ovary measuring 17 × 13 × 8.5 cm; the right measured 18 × 11 × 10 cm (Figs 1 and 2). Each ovary contained multiple large cysts versus a large septated cyst. The uterus appeared postpubertal with an endometrial stripe of 12 mm. Due to the size and the complex nature of the masses, ovarian tumor markers were drawn. As seen in Table 1, estradiol, cancer antigen 125 (CA-125), lactate dehydrogenase (LDH), inhibin-A, and alpha-fetoprotein (AFP) were markedly elevated. Human chorionic gonadotropin (hcG) and testosterone were within the normal reference range.

At this point laboratory results from her endocrinology evaluation revealed extremely abnormal thyroid function with a thyroid stimulating hormone (TSH) level of 1889.9 ng/dL and a free T4 of 0.3 ng/dl. In addition, prolactin and follicle-stimulating hormone (FSH) were found to be elevated. Cortisol, adrenocorticotropic hormone (ACTH) stimulation testing, and 24-hour urine free cortisol were all within normal limits. The patient was started on levothyroxine 50 mcg and increased to 75 mcg one week later. At this time a decision to closely monitor the massive ovarian cysts was made. Several times she experienced severe pain that would rapidly resolve. The possibility of ruptured cyst was considered after ovarian torsion was excluded. The cysts were followed by serial ultrasonography and showed decreasing size at each evaluation.

Six weeks later, her thyroid function and all elevated tumor markers normalized (Table 1). Three months later, the final pelvic ultrasound showed that the massive ovarian cysts had essentially resolved with ovaries measuring 2.9 × 3.6 × 4.6 cm on the right with a 1.3 cm cyst and 4.7 × 3.5 × 6.3 cm on the left with a 0.6 cm cyst.

Repeat MRI showed a minimally prominent pituitary and sella turcica with a normal optic chiasm.

Clinically, the patient's fatigue, abdominal pain, and headaches resolved. She did not have any additional menstrual cycles throughout the next seven months of follow up.

Discussion

Primary hypothyroidism has classically been associated with delayed growth and delayed puberty in children. Rarely, however, primary hypothyroidism can be associated with precocious puberty. First reported in 1905, Kendle describes an "astonishing case" of a 9-year-old girl with menarche at age 5, fully developed breasts, and the clinical symptoms of "female cretinism."[11] After treatment with thyroid extract, her growth resumed, her menstruation stopped, and her symptoms of cretinism resolved.

This syndrome was more fully described by Van Wyk and Grumbach in 1960 and is now known as Van Wyk and Grumbach syndrome.[12] Since that time, multiple reports have added to our understanding of this syndrome. The constellation of symptoms including hypothyroidism, precocious puberty, and delayed bone age is well recognized.[1–12] The majority of these case reports also describe bilateral ovarian masses.[1–10] Additionally, the association with pituitary tumors is well recognized.[1,4–7,12] Most important, this constellation of signs and symptoms regresses with treatment of the underlying hypothyroidism.

Many theories exist to explain this seemingly paradoxical precocious puberty in association with primary hypothyroidism. Van Wyk and Grumbach believed that hormonal

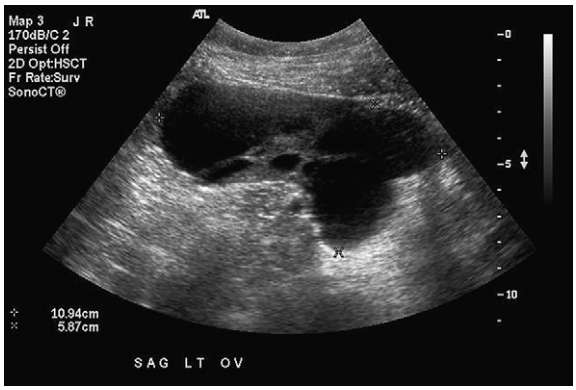

Fig. 1. Left ovary sagittal view with muliple cysts versus single multi-septated mass.

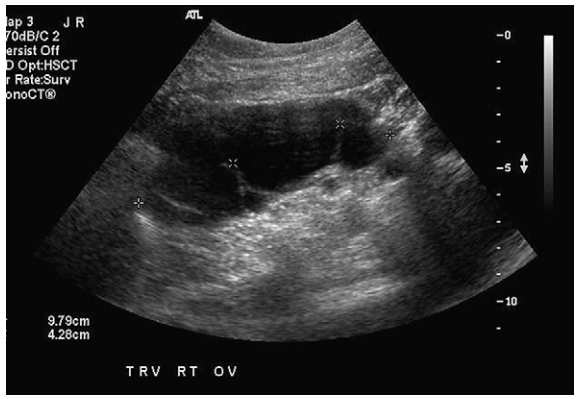

Fig. 2. Transverse view of right ovary with multiple thin-walled septations.

overlap in the negative feedback mechanism associated with hypothyroidism caused elevated gonadotropins.[12] However, this does not explain the cases in the literature where FSH levels were found to be normal.[1,2,6,7] Given the inconsistent findings regarding FSH, a more accepted theory is the fact that TSH can act on the FSH receptor. TSH and FSH, along with luteinizing hormone (LH) and hcG, share a common beta subunit. It is theorized that in large amounts, TSH is capable of activating the FSH receptor secondary to this common subunit. Gordon et al[8] demonstrated that the elevated estrogen levels seen in this disorder do come directly from the ovaries. Comparison of the patient's serum estradiol with estradiol directly aspirated from her ovary was performed. Her serum level measured 99pg/mL while ovarian estradiol measured 32,100 pg/mL.[8]

Pituitary hyperplasia or pituitary adenoma, as was seen in our case, has been blamed on long standing thyrotrope hyperplasia in response to the decreased thyroid hormone. Hyperprolactinemia, another common finding that was also present in our patient, has two etiologies. Some postulate that the thyrotrope hyperplasia in the pituitary compresses the pituitary stalk, thereby disrupting hypothalamic inhibition of prolactin. TRH is also known to stimulate prolactin. When thyroid hormone is low, TRH increases lead to increased levels of prolactin.

Similar to other reported cases in the literature, our patient exhibited bilateral ovarian masses. Review of the literature reveals that the majority of these patients do have bilateral rather than unilateral masses.[1–8,10,13–15] Of 27 cases reviewed, 20 patients were found to have bilateral masses while seven were found to have an isolated unilateral ovarian mass. Interestingly, in three of those patients with unilateral masses, the opposite ovary was found to be larger than expected.[4,13]

It is important to recognize, however, that although bilateral ovarian masses are a hallmark of this syndrome, Van Wyk and Grumbach is a possibility in those individuals with an isolated unilateral mass. Browne et al described a 10-year-old girl with a 11.3 × 9.2 × 19.6 cm complex unilateral mass with solid components. This patient was ultimately diagnosed with Van Wyk and Grumbach.[10] Unilateral multilocular as well as unilateral simple cysts have also been described. Unfortunately, whether or not the cysts were unilateral or bilateral did not seem to correlate with the level of thyroid hormone or presence or absence of tumor markers.

Our case fit the description of Van Wyk and Grumbach syndrome, yet it is unique in multiple ways. Although the patient exhibited hypothyroidism and associated bilateral ovarian masses, the precocious pubertal changes were not obvious, and bone age was normal. Presumably, the patient's hypothyroidism did not develop until pubertal changes had already begun. Therefore, she did not exhibit classic precocious puberty. She had experienced adrenarche already and had Tanner Stage III pubic hair. Breasts had developed to Tanner Stage III as well. Although she had experienced one menstrual cycle at age 11, it was thought that this was her manifestation of precocious puberty secondary to her pathologically elevated estrogen levels, given that menses ceased once she was treated.

It is important to recognize that this syndrome can occur at various ages and that it is not always a disease of prepubertal children. Findings of Browne et al[10] and Kubota et al[3] support these findings, reporting a 17-year-old girl with hypothyroidism, oligomenorrhea, and bilateral enlarged ovarian masses as well as a 21-year-old female with hypothyroidism, abdominal pain, distention and ovarian masses.[3,10] Both of these patient's symptoms resolved after their hypothyroidism was treated.

It can be inferred that the basic pathological mechanism remains the same in both prepubertal and postpubertal females. The clinical presentation can vary depending on where the patient is in her development. Imaging, however, reveals the same pathology. Ultrasound findings of bilateral or unilateral ovarian multicystic masses are seen in both prepubertal and postpubertal females with uncontrolled hypothyroidism.[10] It is important to evaluate for hypothyroidism in the evaluation of ovarian masses, especially when the masses are bilateral.

Unique to this case was a description of the significant abnormality tumor markers can have in Van Wyk and Grumbach syndrome. The marker CA-125 had been found to be elevated previously.[1–5] This is not surprising, because CA-125 is nonspecific and has been found to be elevated in multiple other benign conditions such as endometriosis, fibroids, and tubo-ovarian abscesses. In contrast, certain

Table 2
Literature review of Laboratory Abnormalities Seen in Van Wyk and Grumbach syndrome cases

	FSH (mU/mL)	Prolactin (ng/mL)	Serum Estradiol (pg/mL)	CA-125 (U/mL)	LDH (U/L)	AFP (ng/mL)	Inhibin	Hcg (mlU/mL)
Singh[9]	5.0 ↑	NM	NM	15	NM	1.66	NM	negative
Hunold[1]	4.6	124.2 ↑	639 ↑	91.4 ↑	354 ↑	NM	NM	NM
Browne[10]								
Kubota[3]	9.7 ↑	NM	164 ↑	73 ↑	405 ↑	NM	NM	NM
Sanjeevaiah[4] Case 1	5.75 ↑	77.6 ↑	NM	80 ↑	NM	30↑	NM	1.08
Sanjeevaiah[4] Case 2	5.75 ↑	49 ↑	55.97 ↑	NM	NM	15.39 ↑	NM	NM
Panico[2]	18.2	50.6 ↑	201.99 ↑	64.9 ↑	521 ↑	2.3	NM	NM
Mohsin[5]	5.52	250.5 ↑	70.72 ↑	83.3 ↑	NM	NM	NM	NM
Campaner[7]	6.4	160 ↑	463 ↑	NM	NM	2.1	NM	<0.1

Abbreviation: NM, Not measured

other tumor markers are not commonly elevated in benign conditions. Both LDH and AFP, historically associated with dysgerminomas and other germ cell tumors respectively, were elevated in this and a few other reported cases (Table 2). Inhibin, a classic granulosa cell tumor marker, was also found to be markedly elevated in our patient and has not been previously described in the literature (Table 2). It is unknown whether this could be a marker for this particular syndrome. No prior cases were found that had measured an inhibin level. All of the tumor markers, including inhibin, returned to normal values after treatment of her hypothyroidism and resolution of her ovarian masses.

As we know from prior case reports in the literature, it is possible for a young woman to have a unilateral ovarian mass with solid components and still be diagnosed with Van Wyk and Grumbach syndrome.[10] Therefore, even in a girl with a unilateral solid mass, signs of excess estrogen such as precocious puberty, and an elevated inhibin level, Van Wyk and Grumbach syndrome is still in the differential. Given the concern for malignancy, however, many of these girls with both unilateral and bilateral masses have been taken to surgery. Pathologic specimens of ovarian masses found in the clinical setting of hypothyroidism show that these masses are benign despite elevations in tumor markers. Sanjeevaiah et al describe a case in which CA-125 and AFP were elevated and the patient's left ovary was removed. Final pathology revealed numerous cystic follicles with occasional corpura albincantia and luteal cysts and the absence of neoplastic tissue.[4] A right ovarian biopsy showed stromal hyperplasia with numerous primordial follicles without neoplasia. Panico et al obtained a wedge resection of a right ovary in a patient with elevations of both CA-125 and LDH in the setting of primary hypothyroidism and precocious puberty, revealing a benign cyst with myxedematous infiltration of the ovarian stroma.[2]

This finding provides important information in the evaluation of ovarian cysts. Large ovarian masses, as large as 18 cm as in our case, in association with one or more tumor markers would generally imply malignancy. However, before proceeding with surgical evaluation, exclusion of hypothyroidism to rule in or out this rare but treatable syndrome should be undertaken.

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