Massive ovarian edema masquerading as an androgen-secreting tumor

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Objective: To highlight the management of massive ovarian edema in young reproductive-age women.
Design: A case report of a healthy female with clitoromegaly and elevated androgen levels secondary to massive ovarian edema.
Setting: Reproductive Endocrinology and Infertility Department of an academic hospital.
Patient: A healthy 20-year-old woman who presented for routine gynecological care and was found to have a 2-cm clitoromegaly and elevated androgen levels.
Interventions: The patient underwent a diagnostic laparoscopy and right oophorectomy.
Main Outcome Measures: Measurement of androgen levels.
Results: Final pathology showed massive edema of the ovary with no evidence of malignancy or androgen-secreting tumor cells. In addition, resolution of the elevated androgen levels was observed.
Conclusions: Massive ovarian edema due to asymptomatic subacute torsion should be included in the differential diagnosis of reproductive-age patients who present with ovarian mass and hyperandrogenemia within the tumor range. Although not performed in our case, conservative management that involves detorsion, ovarian biopsy, and oophoropexy to prevent a recurrence should be the treatment of choice. (Fertil Steril Rep® 2021;2:468–71. ©2021 by American Society for Reproductive Medicine.)
Key Words: Massive ovarian edema, adnexal mass, isolated virilization, hyperandrogenemia, isolated clitoromegaly

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INTRODUCTION

Massive ovarian edema (MOE) is a rare gynecological condition and often an incidental finding on histological examination of an adnexal mass. The incidence and prevalence of this phenomenon in reproductive-age women are not stated in the current literature. The presenting features, in addition to hyperandrogenemia with or without hirsutism and/or virilization, include menstrual irregularities, precocious puberty or a triad of ascites, pleural effusion, and benign ovarian tumor as in Meigs syndrome (1). Massive ovarian edema can be easily mistaken for neoplasm, given its radiographic features of cystic mass with solid components. The majority of enlarged edematous ovaries are unilateral (85%), and most involve the right ovary (2). Roth (3) reported the first case in 1971 and theorized that ovarian edema resulted from incomplete torsion of mesovarium, not complete enough to cause ovarian tissue necrosis but enough to lead to increased capillary flow and interference with lymphatic drainage. Therefore, any risk factors for ovarian torsion could cause MOE. There is no clinical or laboratory study that can confirm this diagnosis as it solely depends on histologic examination. It is therefore not surprising that the management, in many cases, is inadvertent oophorectomy. In this case report, we describe a patient who presented with signs of virilization and an enlarged adnexal mass later confirmed to be a torsed ovary. Additionally, we present a brief review of the cases reported to date and discuss what is known so far regarding management. Informed signed consent was obtained from the patient to publish the case potentially.

CASE REPORT

Our patient was a healthy 20-year-old nulligravida, with unremarkable past medical and family history, who presented to the clinic for her annual

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gynecological evaluation. She reported having regular menstrual cycles generally occurring every 28 days with 5 days of normal flow. She did note occasional irregular cycles with bleeding lasting >7 days. She denied a history of abnormal hair growth, acne, and galactorrhea. She was sexually active without any contraception and denied a history of dyspareunia. She was not in distress and did not report any pain. She was neither obese (body mass index of 18.6 kg/m^3) nor hirsute and had no acne. Examination of her cardiovascular system was unremarkable. Her pulse and blood pressure were within normal limits. Abdominal examination was also normal with no physical signs of ascites. However, her pelvic examination showed clitoromegaly (2 cm). The patient was unaware of this finding and could not elaborate on how long it may have been present. Additionally, bimanual examination revealed mild right adnexal tenderness and the presence of an approximately 6 cm right adnexal mass. Given the associated clitoromegaly and laboratory studies that revealed increased serum androgens, the patient was referred to the Reproductive Endocrinology and Infertility department. Transvaginal ultrasound evaluation demonstrated a right solid ovarian mass with a 6-cm mid-diameter with irregular cystic areas. Both ovaries had regular-color Doppler flow, and no ascites was noted. The left ovary had features of polycystic ovarian syndrome (PCOS) (an antral follicle count of >20 was reported). Repeat serum androgen and tumor marker levels are as shown in Table 1. Magnetic resonance imaging (MRI) with a contrast of the abdomen and pelvis confirmed an enlarged right ovary (measuring 6.8 × 5.0 × 5.0 cm), with its follicles displaced to the periphery by cystic mass with enhancing. The official statement reported a right ovarian mass suspicious of cystadenoma and a left ovary with a polycystic appearance. The presence of normal serum DHEAS levels ruled out any adrenal etiology as a cause of the patient's biochemical hyperandrogenemia. Discussion at a multi-disciplinary meeting with a gynecologic oncologist concluded that an androgen-secreting tumor was the most likely diagnosis. A decision was made to proceed with diagnostic laparoscopy, peritoneal washing, and right-sided oophorectomy.

Following extensive counseling, the patient underwent a diagnostic laparoscopy on December 11, 2019, which showed the right ovary twisted twice around its pedicle. The ovary had a smooth capsule and measured about 6 to 7 cm in diameter, appearing whitish, firm, and edematous. There was no ascites, and a sample of peritoneal washing fluid was sent for cytological evaluation, which later returned negative for malignant cells. An extensive survey of the abdomen and pelvis revealed otherwise normal pelvic and abdominal organs. A right oophorectomy was performed. Given the possibility of an androgen-producing tumor within the mass, the ovary was bagged, brought to the umbilical incision, and morcellated, taking care not to breach the retrieval bag. A frozen section of the mass was performed and reported to be negative for malignancy. The procedure was uncomplicated, and the patient was discharged the same day. Final pathology showed massive edema of the ovary with no evidence of malignancy. The peripheral areas of the ovary showed normal ovarian parenchyma with edematous changes in the deeper zones. Discrete clusters of luteinized ovarian stromal cells were scattered throughout the ovarian parenchyma. The pathologist examined additional sections, and the reviewed slides presented no evidence of a microscopic androgen-secreting tumor. At the 6-week postoperative follow-up, laboratory test repetition showed a significant decline in androgen levels. Physical examination showed persistent clitoromegaly but no further enlargement of the clitoris and no other androgenic features. The patient was diagnosed with unexplained infertility and underwent fertility evaluation approximately a year after her diagnosis of MOE. She was diagnosed with C-phenotype PCOS, considering her left ovary and clinical and biochemical hyperandrogenism.

DISCUSSION

The presented case adds to the few cases reported in the literature of clinical hyperandrogenism secondary to luteinization of stromal cells of the ovary. The case of the youngest reported patient was from 2004: a 6-month-old girl who presented with precocious puberty with Tanner stage 2 breast and pubic hair development.

The patient had no evidence of clitoromegaly (4). Unlike our case, this patient had bilaterally enlarged ovaries with cystic and solid components on ultrasound evaluation. She underwent diagnostic laparoscopy, which was converted to a laparotomy, and showed bilateral torsion of the ovaries. As a result, a left oophorectomy with right oophoropexy was performed. The final pathology report described MOE with no evidence of stromal luteinization (or neoplasia), explaining the mildly elevated testosterone level and lack of virilization in this case. The infant's abnormal laboratory findings resolved with no further physical signs of hyperandrogenism.

The mechanism by which stromal luteinization occurs is widely debated. One hypothesis is that this happens due to asymptomatic partial but gradual torsion of the ovary, which over time may or may not lead to stromal luteinization, causing virilization (1). The ovarian stroma contains theca cells and is the site of excess testosterone and androstenedione production. It is hypothesized that mechanical stimulus or stretching of the stromal theca cells by the edematous fluid is the cause of hyperandrogenism due to subacute torsion of the ovary (5). Preoperative diagnosis of this phenomenon is often difficult given that there are no distinct phenotypic or laboratory characteristics that delineate MOE from other benign or malignant neoplasms. Presentations are variable, ranging from an asymptomatic presentation to the most common complaints, such as abdominal/pelvic pain, menstrual irregularity, with or without features of hyperandrogenism.

It has been demonstrated that ovarian edema due to torsion with no phenotypic manifestation can be treated conservatively following ovarian detorsion, ovarian drilling, or wedge resection with oophoropexy. However, these options would be appropriate after intraoperative histological exclusion of premalignant or malignant tumor by frozen section. This has to be balanced with the risk of surgical spillage should the mass result malignant. Therefore, it is not surprising that very few reports exist in the literature of conservative management, particularly in young symptomatic patients.

TABLE 1

Figures summarizing patients' laboratory findings with the dates that the studies were obtained.

Variables	Initial laboratory values (10/30/19)	Repeat laboratory values (11/11/19)	Repeat laboratory values following the procedure (01/15/20)	Laboratory reference ranges
Total testosterone (ng/dL)	439.0	405.0	60.0	1.0–75.0
Free testosterone (ng/dL)	3.35	2.54	0.33	0.04–0.53
Bioavailable testosterone (ng/dL)	103.3	84.8	9.8	1.2–14.0
Androstenedione (ng/dL)	—	428.0	—	41.0–262.0
DHEAS (μg/dL)	—	261.0	—	51.0–321.0
CA-125 (units/mL)	—	3.9	—	0.5–35.0
AFP (ng/mL)	—	2.2	—	0–18.0
CEA (ng/mL)	—	1.9	—	<5.1
Estradiol (pg/mL)	—	68.0	—	
SHBG (nmol/L)	104.6	127.9	144.2	18.0–135.5
17-OHP (ng/dL)	—	354.0	—	—
LH (mIU/mL)	—	41.84	—	—

Note: AFP = alpha-fetoprotein, CA-125 = cancer antigen 125, CEA = carcinoembryonic antigen, DHEAS = dehydroepiandrosterone, LH = luteinizing hormone, 17-OHP = 17-hydroxyprogesterone, SHBG = sex hormone-binding globulin.

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Perhaps the most extensive review on this topic was conducted by Praveen et al. (2), who performed a literature review of MOE cases and identified 177 patients who had undergone treatments between 1969 and 2011. In this review, almost all patients presented with abdominal pain. Virilization was noted in 20.9%, and all had an adnexal mass. Of these patients, 42.9% had ovarian torsion intraoperatively, and 81.9% underwent a salpingo-oophorectomy (SOP) with or without ovarian suspension, while 11.3% were managed conservatively with ultrasound/MRI surveillance following negative wedge biopsy and frozen section.

A review of the most recent 10 articles about this subject published since 2011 shows that the most common presenting symptom in cases of MOE is right lower quadrant pain (6–11). Of these 10 cases, 80% underwent either oophorectomy or unilateral SOP, similarly to 81.9% reported by Praveen et al. (2), suggesting that definitive surgery remains the most common approach for MOE. One of the 10 reported cases was managed conservatively, as the incidental diagnosis of MOE was made intraoperatively during an appendectomy attempt (12). In this case, the patient underwent a diagnostic laparoscopy, but the procedure was aborted due to dense adhesions. The patient was treated conservatively with antibiotics and subsequent resolution of the ovarian edema and inflammatory changes. Gobara et al. (13) reported a case of a 24-year-old woman with a 12-week gestation who presented with lower abdominal pain. The patient was found to have a left adnexal mass that was initially $6.8 \times 3.6 \times 6.7$ cm then subsequently increased to $9.9 \times 6.1 \times 6.0$ cm. The MRI study characterized the mass as solid with displaced follicles with evidence of ovarian torsion. The patient had normal levels of the tumor markers (carcinoembryonic antigen [CEA] and cancer antigen 125[C-125]), and as a result, a presumable diagnosis of MOE was made due to ovarian torsion. Due to the continued pain and increase in mass, the patient underwent an exploratory laparotomy, detorsion of the ovarian pedicle, partial resection of the left ovary, and oophoropexy. The patient continued to have a successful pregnancy. Although our patient was not pregnant, the case was similar to ours regarding the size of the mass and MRI description. This further supports the notion that when the mass is well characterized with negative tumor markers, conservative management is appropriate. This case is particularly unique in that the symptoms presented during pregnancy and necessitated immediate operative intervention. This is likely because the patient had persistent pain due to ovarian torsion, which may have delayed or prevented the development of hyperandrogenism. As a result, one could postulate that if a patient reports recurrent severe pelvic pain, a diagnostic laparoscopy should be considered to fix the more enlarged ovary to help decrease or prevent the risk of torsion.

We propose that when an ovarian mass is associated with hyperandrogenism in young reproductive-age women, MOE should be considered, especially when associated with torsion of the ovarian pedicle. A strong diagnostic indicator is a pelvic ultrasound and MRI study demonstrating multiple follicles pressed toward the peripheral cortical area of the ovary by edematous fluid (2). When ovarian enlargement is found intraoperatively in a patient with negative preoperative evaluation, it would be prudent first to untwist the ovary, ensure restoration of blood flow, and then perform oophoropexy to prevent a recurrence, as seen in the case reported by Gobara et al. (13). This should be followed by expectant management by trending appropriate laboratory values. The exact time frame for normalization of the androgen levels or the resolution of edema is unknown in these women as many sources do not specify this detail. In one source, androgen levels were shown to normalize as early as 4 weeks postoperatively (14). In our case, testosterone level remained low to normal in range at the 6th-week visit, as highlighted in Table 1.

Concomitant oophoropexy is strongly encouraged to decrease the risk of recurrence, as the rate of relapse is higher without this procedure though incidence is unknown.

In conclusion, MOE in association with torsion is an uncommon phenomenon but should be part of the

differential diagnosis of abdominopelvic pain with an enlarged adnexal mass in a young, reproductive-age woman with clinical and/or biochemical hyperandrogenism but no signs of malignancy. Cases exist in the literature that suggest that conservative management could resolve ovarian edema and patients' symptoms. Our goal is to increase awareness of this phenomenon and ensure providers consider MOE in the differential diagnosis of reproductive-age women to decrease the performance of inadvertent oophorectomy. This can be done by obtaining the necessary tumor markers, using MRI as an imaging modality as it is able to characterize adnexal masses better, and trending the biomarkers following conservative measures. The interval for when to obtain surveillance tests would be provider-dependent as there is no reported standard. Though our case underwent oophorectomy with the diagnosis made after histopathologic examination, an awareness of the benign nature of MOE would have helped and could have spared fertility in many young reproductive-age women.

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