Case report

Cancer overturned: Endometrioma mimicking granulosa cell tumor and the importance of FOXL2 analysis

Emily R. Rosen⁎, David M. Kushner, Aparna M. Mahajan, Cara R. King

Department of Obstetrics and Gynecology, University of Wisconsin Hospital and Clinics, Madison, WI, United States

Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Vice Chair of Clinical Research, University of Wisconsin Hospital and Clinics, Madison, WI, United States

Department of Obstetrics and Gynecology, Department of Pathology and Laboratory Medicine, University of Wisconsin Hospital and Clinics, Madison, WI, United States

Department of Obstetrics and Gynecology, Division of Gynecology and Gynecologic Subspecialties, University of Wisconsin Hospital and Clinics, Madison, WI, United States

ABSTRACT

Background: Various ovarian neoplasms may show histological findings that are morphologically indistinguishable from adult granulosa cell tumor (AGCT).

Case presentation: A 36 year-old women presented with left lower extremity pain and numbness. Ultrasound revealed a 10 cm left adnexal mass treated with ovarian cystectomy. Histopathology revealed endometriotic cyst with intramural granulosa cell tumor. She underwent a laparoscopic left salpingo-oophorectomy and omental biopsy by Gynecologic Oncology. Pathologic review of residual ovarian abnormality prompted a molecular analysis. FOXL2 gene mutation was absent supporting the diagnosis of benign endometrioma.

Conclusions: A somatic missense mutation in the FOXL2 gene is a sensitive molecular marker for AGCT. Mutation analysis can help distinguish malignant from benign pathology to provide appropriate treatment and disease surveillance.

1. Introduction

In the United States, it is estimated that the lifetime risk for surgery for a suspected ovarian neoplasm is 5–10% (National Institutes of Health Consensus Development Conference Statement, 1994). Although the purpose of evaluation and surgical management of an adnexal mass is to elucidate the specific etiology to provide appropriate treatment, identifying a specific diagnosis is often challenging. Adult granulosa cell tumors (AGCT) account for 5% of malignant ovarian cancers with a propensity for late recurrence. Various ovarian masses may show benign granulosa cell proliferations which are morphologically indistinguishable from AGCT (Singh et al., 2014). It is thought that these proliferations may represent reactive stromal proliferation, similar to luteinization, and are negative for FOXL-2 mutation. As per current literature, nearly 90–97% of AGCT are reported to be FOXL-2 positive, and it is differences in methodologies to detect the mutation that are thought to be the reason for this variation. Overall, the FOXL2 402C > G mutation has been identified as a sensitive and specific marker for AGCT (Shah et al., 2009; Jamieson et al., 2010; Al-Agha et al., 2011). The importance of a correct diagnosis for AGCT is crucial to optimize patient care and address long-term medical and psychological needs.

We managed a challenging case of a premenopausal woman with an initial diagnosis of AGCT, found to be a non-neoplastic endometriotic cyst by subsequent FOXL2 molecular diagnostic testing. Clinicians should be aware of the utility of FOXL2 testing in distinguishing malignant from benign ovarian pathology, with the goal of providing appropriate treatment and surveillance.

2. Case presentation

The patient is a 35-year-old, gravida 0, who presented to an urgent care facility with a 2-week history of acute left lower back pain, left lower extremity numbness, and left lower quadrant abdominal pain in the setting of 9 months of intermittent lower back discomfort. The patient reported abnormal uterine bleeding, dysmenorrhea, and diarrhea with menses. She denied a family history of gynecologic malignancy. Laboratory evaluation was notable for a negative β-hcg. A transvaginal ultrasound (TVUS) was recommended and the patient initially declined. Due to 2-weeks of additional discomfort, a TVUS was completed and revealed an abnormal left ovary with a large septated complex mass measuring 8 × 6.6 × 10.2 cm. The mass contained homogenous low...
3.2 × 2.4 × 2.3 cm was also identified. Pelvic lymphadenopathy was also identified. Referral to a gynecologist was recommended. Due to lack of insurance, she did not present for follow-up.

The patient represented to her primary care physician 3 months later for an annual exam. Due to continued lower abdominal tenderness, she was referred to an obstetrician/gynecologist. A presumed diagnosis of endometriosis was made and she was referred to a minimally invasive gynecologic surgeon for consultation. Pelvic exam revealed a large immobile, nodular, and tender midline mass filling the posterior cul-de-sac, moderate levator obturator tenderness, cul-de-sac tenderness and nodularity, and a 2 cm tender mass palpated 7 cm from the anal verge anteriorly on rectal exam. Due to suspected Stage IV endometriosis and increase risk of bowel involvement, a pelvic magnetic resonance imaging test was performed. This demonstrated massive dilatation of bilateral fallopian tubes with no distinct ovarian masses, pelvic lymphadenopathy, or additional characteristics concerning for neoplasm (Fig. 2).

The patient was counseled regarding surgical options. She desired the least invasive option and opted to leave all potential endometriosis aside from the pelvic mass. She subsequently underwent a laparoscopic left ovarian cystectomy, right simple ovarian cyst drainage, lysis of adhesions, and Mirena IUD insertion. Findings at the time of surgery included an obliterated posterior cul-de-sac, and a 15 cm left ovarian mass adherent to the right ovary, uterus, rectosigmoid, and bladder. Due to cystectomy, the left ovarian cyst was inadvertently ruptured revealing thick, chocolate-like fluid suspicious for an endometrioma. The cyst wall was excised in its entirety, and the ovary was re-approximated using a running 3-0 unidirectional barbed suture for adequate hemostasis. The surgery was uncomplicated and the patient was discharged home on postoperative day one. Pathology returned as an endometriotic cyst measuring 8.3 × 7.1 × 5.4 cm with an intramural adult type granulosa cell tumor measuring 0.6 × 0.3 cm. Immunostaining was positive for calretinin and inhibin antibodies, supporting the granulosa cell origin (Fig. 3a-c).

Given the pathology findings, further evaluation was done postoperatively including a benign endometrial biopsy, normal inhibin A level of 28.8 pg/mL and inhibin B level of 38 pg/mL, and computed tomography scan without evidence of metastatic spread or peritoneal carcinomatosis. The pathology report was discussed with the patient, and she was referred to Gynecologic Oncology for treatment recommendations. After discussion of various treatment options including fertility-sparing surgery, Gynecologic Oncology performed an uncomplicated exploratory laparoscopy, laparoscopic left salpingooophorectomy (LSO), adhesiolysis, and omental biopsy. Pathology of the left ovary and fallopian tube were read as an endometriotic cyst with focal granulosa cell proliferation measuring 0.2 cm in greatest dimension. Microscopically, the proliferation was very similar to that seen on the first surgical specimen. Both specimens were characterized by endometriotic cysts with proliferation of nests and cords of bland cells with oval nuclei and minimal cytoplasm, which on immunohistochemistry were positive for inhibin and calretinin antibodies thus supporting granulosa cell proliferation. The omental biopsy was negative. The pathologist recommended FOXL2 mutational analysis to prove the true neoplastic nature of the proliferations due to concern that this represented non-neoplastic proliferations that mimicked AGCT.

PCR-sequencing analysis of exon 1 of the FOXL2 gene domain using laser tissue microdissection was performed on surgical specimens from both surgeries. FOXL2 gene mutation was not detected on either sample. Based on these results, the final diagnosis of a non-neoplastic proliferation rather than AGCT was made. After case discussion at the cancer center multidisciplinary tumor conference, no adjuvant therapy or surveillance was recommended.

Two months after surgery, the patient presented to her gynecologist for follow-up of her endometriosis. She noted that her bleeding and pelvic discomfort were well controlled with the Mirena IUD. She will be seen annually for well-women visits with her gynecologist.

3. Discussion

Ovarian cancer is the leading cause of death from a gynecologic malignancy, and there are approximately 22,000 new cases of ovarian cancer diagnosed in the United States annually (Siegel et al., 2017). Although AGCT comprise a small portion of ovarian cancer, these tumors are characterized by indolent growth with a propensity for late recurrence up to decades after initial diagnosis (Sekkate et al., 2013). Therefore, due to potential long-term implications of a diagnosis of AGCT, definitive diagnosis is critical. Despite specific architectural patterns and immunostaining, the histopathologic diagnosis of AGCT is often challenging. In a recent case series, granulosa cell proliferations which are morphologically indistinguishable from AGCT were identified in association with different ovarian neoplasms including mucinous tumors, mixed epithelial cystadenomas, and endometriosis (Singh et al., 2014). Up until 2009, no gene expression profile had been identified as
a specific marker for AGCT. Shal et al. found that 97% of AGCT had a mutant FOXL2 gene. The FOXL2 gene is responsible for encoding a transcription factor necessary for granulosa-cell development, and the somatic missense point mutation 402C > G in this gene is a sensitive and specific marker for AGCT (Jamieson et al., 2010; Al-Agha et al., 2011; Kommoss et al., 2013).

This case illustrates the difficulty of establishing a definitive diagnosis for AGCT. Given the malignant nature of this disease and tendency to recur late, the correct diagnosis is paramount to provide treatment and continuous surveillance for only those who need it. Incorrect diagnosis and treatment can have profound medical, financial, and emotional impact. Additionally, given the reproductive age of many patients, there are significant implications on future fertility and reproductive status.

Our report highlights the importance of performing a FOXL2 mutation analysis, particularly when the granulosa cell proliferation is in the background of benign cystic lesions such as endometriosis. It is not possible to detect the nature of these proliferations based on light microscopy alone, and molecular testing is of immense value in incidental granulosa cell proliferations. Laser capture microdissection was used to ensure a pure population of lesional cells, to eliminate the chance of a false negative result on the FOXL2 mutational analysis using a PCR assay. It is important to note that FOXL2 mutational analysis using PCR does not distinguish between germline and somatic FOXL2 mutations. Since germline mutations are associated with premature ovarian failure, additional testing and clinical correlation is recommended after a positive FOXL2 mutation results (Schrader et al., 2009). When dealing with ovarian masses where sex cord stromal tumors are in the differential diagnosis, FOXL2 immunohistochemistry (IHC) is a valuable first step in confirming the cell lineage. However, the specificity of FOXL2 mutational analysis is reported to be higher than FOXL2 IHC staining (Al-Agha et al., 2011). Since there was only a minute foci of tumor cells and FOXL2 IHC was not available at our institution, we decided to directly send for FOXL2 mutational analysis.

This is a unique case which highlights the importance of clinical, morphological, and molecular correlation for an accurate diagnosis when subtle granulosa cell proliferations are identified in the background of benign cystic ovarian lesions. Since the proliferations are morphologically indistinguishable from AGCT, it is important to perform molecular testing in these scenarios. With the correct diagnosis, the patient was able to receive the appropriate treatment for her endometriosis. Clinicians should be aware of incidental granulosa cell proliferations which are morphologically indistinguishable from AGCT and appropriately utilize FOXL2 testing to aid the diagnosis of clinically challenging cases.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Author contribution

Drs. Kushner, Mahajan, and King were the responsible surgeons or imagers, and all authors were involved in manuscript preparation.

References

Al-Agha, O.M., Huwair, H.F., Chow, C., et al., 2011. FOXL2 is a sensitive and specific marker for sex cord-stromal tumors of the ovary. Am. J. Surg. Pathol. 35, 484–494.
Jamieson, S., Butzow, R., Anderson, N., et al., 2010. The FOXL2 C134W mutation is characteristic of adult granulosa cell tumors of the ovary. Mod. Pathol. 23, 1477–1485.
Kommoss, S., Anglesio, M.S., Mackenzie, R., et al., 2013. FOXL2 molecular testing in ovarian neoplasms: diagnostic approach and procedural guidelines. Mod. Pathol. 26, 860–867.
National Institutes of Health Consensus Development Conference Statement, 1994. Ovarian cancer: screening, treatment, and follow-up. Gynecol. Oncol. 55, S4–14.
Schrader, K., Gorbatcheva, R., Sens, J., et al., 2009. The specificity of the FOXL2 c.402C > G somatic mutation: a survey of solid tumors. PLoS One(11), e7988.
Sekkate, S., Kairouani, M., Serji, B., et al., 2013. Ovarian granulosa cell tumors: a retrospective study of 27 cases and a review of the literatures. World J Surg Oncol. 11, 142.
Shah, S.P., Kobel, M., Senz, J., et al., 2009. Mutation of FOXL2 in granulosa-cell tumors of the ovary. N. Engl. J. Med. 360, 2719–2729.
Siegel, R.L., Miller, K.D., Jemal, A., 2017. Cancer statistics, 2017. CA Cancer J. Clin. 67, 7–30.
Singh, N., Gilks, C.B., Huntsman, D.G., Smith, J.H., Coutts, M., Ganesan, R., et al., 2014. Adult granulosa cell tumour-like areas occurring in ovarian epithelial neoplasms: report of a case series with investigation of FOXL2 mutation status. Histopathology 64, 626–632.