Case report

Treatment of recurrent granulosa cell tumor with metformin and letrozole, a case report

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1. Case report

A 37 year old G0 female was initially diagnosed with granulosa cell tumor (GCT) after left ovarian cystectomy for symptomatic pelvic mass in 2005. She declined further surgery or treatment due to fertility desires. In June 2007 she was diagnosed with recurrent left ovarian mass and underwent exploratory laparotomy, left salpingo-oophorectomy, left pelvic mass resection, omentectomy and left pelvic and periaortic lymph node dissection. Pathology confirmed recurrent disease in the cul de sac, omentum, pelvic side wall, and rectosigmoid implants. She was recommended to undergo definitive therapy at that time with completion hysterectomy and RSO, but the patient refused again desiring fertility. She ultimately conceived and had a normal term spontaneous delivery.

In 2010, an inhibin B level was found to be 870 and a CT suggested recurrent disease in the left pelvis. She was advised to proceed with hysterectomy and chemotherapy but wanted to conceive a second child. In 2011, she ultimately agreed to a second tumor debulking, which included exploratory laparotomy, radical resection of pelvic tumor, resection of bladder peritoneal tumor and anterior wall tumors, argon beam ablation over spleen and bowels, and appendectomy. The uninvolved uterus and right ovary and tube were left in situ per patient request, but an endometrial curettage was performed during surgery. Pathology confirmed recurrent GCT, with endometrium being weakly proliferative without evidence of neoplasia. The patient attempted 3 IVF treatments, which were unsuccessful.

In December 2013, given increasing symptoms, rising inhibin B, and CT evidence of growing disease burden, the patient underwent exploratory laparotomy, total abdominal hysterectomy, right salpingo-oophorectomy, en bloc resection of spleen and omentum, bowel and peritoneal implant resections, and extensive lysis of adhesions. Just before surgery, inhibin was 661 and at post-operative visit 2 months later, inhibin was 439. Post-operatively, given the patient's refusal to undergo cytotoxic chemotherapy, she was started on letrozole 2.5 mg daily and metformin 500 mg. She was counseled that neither metformin nor letrozole had proven efficacy against GCTs, but she wanted to try all non-cytotoxic chemotherapeutic options that might delay progression of disease. She was offered letrozole given case reports of aromatase inhibitors having efficacy against progression of GCTs, and metformin given evidence in other cancer types of improved cancer outcomes.

The patient has been on letrozole and metformin with dose adjustments for the last four years. Since definitive surgery and initiation of treatment with letrozole and metformin, disease had been stable with inhibin in the 200 s. In 2017 she had a gradual increase in inhibin from 200 s to 300 s and admitted to non-compliance with therapy. She was restarted, adherence was emphasized, and metformin was increased to 500 mg BID. CT scans have since shown stable disease and Inhibin B levels over time are shown in Fig. 1.

2. Discussion

Our patient presented with a granulosa cell tumor (GCT), a hormonally active sex cord stromal tumor. GCTs account for 2–5% of all ovarian tumors, with an incidence of 0.99/100,000 in the US (Schumer
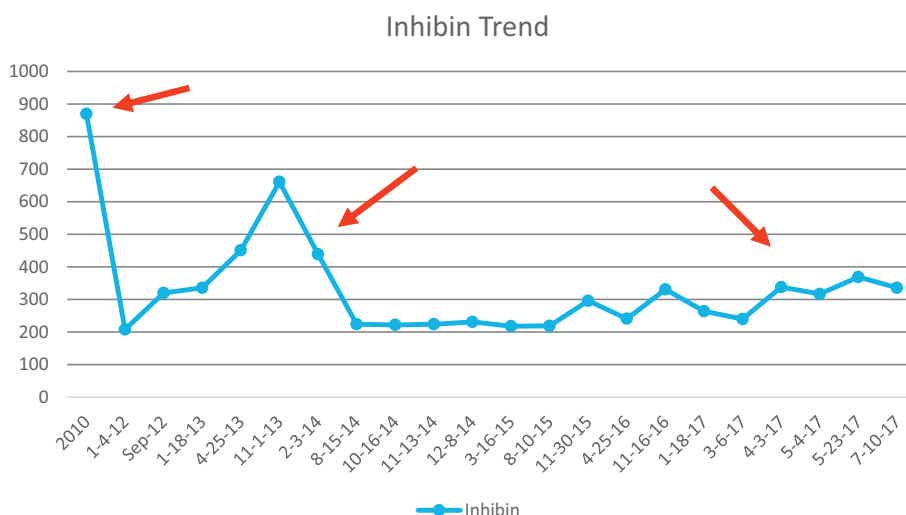

Fig. 1. First Arrow: Inhibin 870 during IVF, prior to 2nd Tumor Debulking surgery.
Second Arrow: Inhibin falls from 661 to 439 after TAH completion surgery.
Third Arrow: Inhibin bumps after discontinuing Metformin and Letrozole.

and Cannistra, 2003). GCTs typically present in premenopausal women with menorrhagia and infertility. They are far more common in peri- and post-menopausal women, where they typically present with post-menopausal or abnormal uterine bleeding, given the increased amount of estradiol secreted by the tumor (Schumer and Cannistra, 2003).

Inhibin B serves as the tumor marker for GCTs; it is normally secreted by granulosa cells and is secreted at increased levels with GCTs. Estradiol and CA-125 are less reliable tumor markers as they have not been shown to be as effectively correlated with disease status as inhibin (Bryk et al., 2016; Schumer and Cannistra, 2003). As can be seen in Fig. 1, our patient's disease burden as confirmed by surgical exploration correlated with elevated inhibin.

GCTs are typically treated surgically in the early stage, and unilateral salpingo-oophorectomy is an option for those wishing to preserve fertility. These tumors typically present bilaterally in only 2–8% of cases, so completion surgery with contralateral oophorectomy and hysterectomy are reserved for those who have completed childbearing. In recurrent disease, surgery is again the mainstay of management. Seagle's 2017 observational retrospective cohort analysis demonstrates that incomplete staging with unilateral salpingo-oophorectomy (versus performing hysterectomy and bilateral salpingo-oophorectomy) conferred greater risk of death (HR 1.67 (95% CI)), regardless age, co-morbidity, or stage (Seagle et al., 2017). Other studies have demonstrated that staging, whether complete (with removal of all gynecologic organs) versus incomplete (leaving uterus and/or contralateral ovary and fallopian tube) may be protective against recurrence, and that fertility sparing surgery does not confer decreased survival (Bryk et al., 2016; Mangili et al., 2013; Park et al., 2012).

With GCT recurrences or higher stages, there had been earlier reported success of chemotherapy with platinum, vinblastine and bleomycin (PVB), or bleomycin, etoposide, and platinum (BEP) (Schumer and Cannistra, 2003) (Park et al., 2012). Others have opted to utilize platinum + paclitaxel regimens for better potential side effect profiles, though with little data to support (Schumer and Cannistra, 2003). The Multicenter Italian Trials in Ovarian Cancer-9 (MITO-9), a prospective multi-site study focusing on rare ovarian tumors and their clinical manifestations and treatment modalities, demonstrated increased recurrence free survival for primary GCTs treated with adjuvant chemotherapy, however without overall survival benefit (Mangili et al., 2013). Another study highlighted that while only tumor rupture at initial surgery was associated in the multivariate model with recurrence of stage IC GCT tumors, adjuvant chemotherapy and complete surgical

staging were protective against recurrence in secondary univariate analyses (Bryk et al., 2016).

However, the role of adjuvant chemotherapy both at initial diagnosis and recurrence has been called into question. A newer analysis of stage IC GCT in the MITO-9 study treated with or without adjuvant chemotherapy at initial diagnosis demonstrated no benefit of disease free survival (Mangili et al., 2016). Meisel demonstrated in a larger group of 118 GCTs that adjuvant chemotherapy at initial diagnosis actually significantly decreased the time to recurrence compared to those treated with surgery alone (Meisel et al., 2015). Further, Seagle demonstrated no difference in 5-year survival rates between those who did and did not receive adjuvant chemotherapy, with the caveats that type of chemotherapy and amount of residual disease after surgery were unknown (Seagle et al., 2017).

In addition to questionable efficacy, chemotherapy has side effects that many patients are eager to avoid. Such was the case with our patient, who first was counseled for debulking surgery and then agreed to maintenance therapy with hormonally targeted letrozole and metformin but not cytotoxic chemotherapy agents.

There are case reports demonstrating that aromatase inhibitors either reduce or stabilize GCT disease. Korach reported on four cases, wherein all patients received debulking and cytotoxic chemotherapy prior to switching to anastrozole. After the switch to anastrozole, all four patients were either stable or improved in their disease burden (Korach et al., 2009). Freeman reported two cases of recurrent ovarian GCT treated with anastrozole. In both cases, after debulking and initiation of anastrozole, inhibin levels normalized (Freeman and Modesitt, 2006). While our patient's inhibin levels never fully normalized she returned to levels in the 200 s–300 s and has remained thus for 4 years.

Metformin may be an important adjunct to aromatase inhibitors. Metformin works to reduce gluconeogenesis, lowers the Warberg Effect of tumor cells making ATP by glycolysis rather than oxidative phosphorylation, and may increase p53 mediated apoptosis of cancer cells (Chae et al., 2016). It decreases insulin and insulin-like growth factor, as well as VEGF and pro-inflammatory cytokines (Gadducci et al., 2016). Observational studies have shown lower rates of ovarian, endometrial and breast cancers in diabetics who take metformin over those who do not. Metformin is also associated with reductions in all-cause mortality for those already with cancer diagnoses. There are 3 ongoing actively recruiting trials of metformin treating endometrial cancer, either alone or in concert with traditional cytotoxic

chemotherapy. There are over 50 ongoing clinical trials of metformin in treatment of cancers of all types (Gadducci et al., 2016).

3. Conclusion

GCTs are indolent neoplasms that are primarily treated surgically. Given their incidence in otherwise young, healthy women, less toxic therapies such as aromatase-inhibitors and metformin may pose a more palatable and effective alternative to adjuvant chemotherapy. Further, traditional cytotoxic adjuvant chemotherapy, especially in patients with stage IC disease, may be less effective in treating this disease than previously thought.

There are no conflicts of interest to report for neither Dr. Barbara Goff nor Dr. Shannon Rush.

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