Case report
Granulosa cell tumor resection with subsequent onset of rheumatoid arthritis

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ARTICLE INFO

Keywords
Granulosa cell tumor
Rheumatoid arthritis
Hypoestrogenism

ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disorder with an estrogen correlation. The disease can worsen or present with menopause. Granulosa cell tumors (GCT) are estrogen-secreting ovarian sex-cord stromal tumors with median incidence in the early postmenopausal years. We report a 38-year-old female who presented with a 20 cm pelvic mass and elevated inhibin and underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy for a Stage I GCT. She developed progressive post-operative joint pain and weakness before an eventual diagnosis of seropositive RA. With tumor resection and surgical menopause, the patient experienced an abrupt decline in estrogen levels precipitating the onset of RA symptoms. Prior research identified that hormone fluctuation at menopause correlates with onset of RA. While unfortunately direct estrogen measurements were not obtained perioperatively, this case does support circumstantial evidence correlating RA with menopause and a decline in estrogen, irrespective of age.

1. Introduction

Rheumatoid arthritis (RA) is a disease that affects women three times more frequently than men, though the pathophysiology driving this sex-difference has yet to be fully elucidated (Mollard et al., 2018). Diagnostic criteria includes a multifocal synovitis with elevated rheumatoid factor, elevated acute phase response such as erythrocyte sedimentation rate or C-reactive protein, and symptom duration of 6 weeks (Aletaha et al., 2010). Studies have shown that women are at increased risk for the development of RA after menopause suggesting a link between fluctuating sex hormones levels and RA (Goemaere et al., 1990). Other studies have demonstrated that women with RA prior to menopause have worsened functional status in the post-menopausal period (Mollard et al., 2018).

Granulosa cell tumors (GCT) represent about five percent of all ovarian tumors and are the most common sex-cord stromal tumors. GCTs are divided histologically into adult and juvenile subtypes. Adult GCTs can occur in all ages but have a peak median age presentation between age 50–54 (Jamieson and Fuller, 2012). GCTs are generally treated with surgical resection and, in more advanced disease, platinum-based adjuvant chemotherapy. It is theorized that GCTs arise from normally proliferating granulosa cells in the ovarian stroma, which often produce estrogen and inhibin like that of normal granulosa cells. Some GCTs also produce estradiol via unregulated aromatase activity (Jamieson and Fuller, 2012). Due to this hyperestrogenism, post-menopausal women often present with vaginal bleeding due to endometrial hyperplasia and are at increased risk for endometrial adenocarcinoma (Jamieson and Fuller, 2012).

The case discussed herein details a premenopausal woman with no prior history of RA symptoms who developed the condition following surgical management of her GCT. To the best of our knowledge, there are no cases in the literature describing this development of rheumatoid arthritis following GCT removal, but this may help substantiate the association between estrogen levels and progression of RA.

2. Case

The patient is a 38-year-old female who presented to a gynecologic oncology office for a pelvic mass. Pelvic and abdominal CT scans demonstrated a complex pelvic mass with echogenic material, measuring 12 × 15 × 20 cm that was presumed to arise from one of her ovaries. Her Inhibin B was elevated at 26592.1 pg/mL (<286.0 pg/mL).
(Sehested et al., 2000). Other tumor markers such as CEA, CA-125, and LDH were unremarkable. Due to high clinical suspicion for a granulosa cell tumor, she underwent an exploratory laparotomy, total abdominal hysterectomy with bilateral salpingo-oophorectomy for diagnosis and treatment of her pelvic mass. An intraoperative frozen section confirmed a malignancy, and the patient had completed childbearing and strongly desired completion rather than fertility-sparing surgery given her prior surgical history. Final pathology demonstrated a Stage IA ovarian adult type granulosa cell tumor. Her immediate post-operative course was uncomplicated, and she was discharged home. She presented two weeks later for post-operative follow-up and was doing well from a surgical perspective. However, she complained of new onset arthralgias and menopausal symptoms such as hot flashes, mental fog, and decreased libido. She reported joint pain, hand swelling, and aches primarily in the waking hours that lasted up to 3 h. Her joint pain was located in multiple sites, but primarily upper extremities and jaw. She specifically reported experiencing multiple episodes of sensation of her jaw locking. She had no relevant personal or family history of rheumatologic symptoms prior to surgery. She was referred to rheumatology for further evaluation of her new joint symptoms. She subsequently was seropositive for cyclic citrullinated peptide antibody greater than 250 units (0–20.0 units (ABIM) and rheumatoid factor of 196.2 IU/ ml (0–24 IU/mL (ABIM)). With her constellation of multifocal joint symptoms and abnormal laboratory values, the patient met the diagnostic criteria for RA and was started on a regimen of prednisone and sulfasalazine with improvement of symptoms. She initially reported menopausal symptoms including decreased libido and hot flashes, which improved with venlafaxine. Hormone replacement therapy was deferred after discussion of risks and benefits.

3. Discussion

This patient was diagnosed with a granulosa cell tumor which is a histology in the minority of all ovarian malignancies (Young, 2005). Often, GCTs produce high levels of estrogen that cause symptoms related to hyperestrogenism. Given the timing proximity, one must suspect the patient’s surgical menopause and acute drop in estrogen precipitated the onset of her RA. Menopause occurs at an average age of 51.4 years old and reflects ovarian follicular depletion with resulting -hypoestrogenemia. Studies indicate a link between the onset of menopause and worsening symptoms and functional decline in women with RA. In one US-wide observational cohort study, health assessment questionnaires (HAQ) were measured on 8189 women with RA. Of the 8189 women, 2005 women were pre-menopausal, 611 went through menopause during the course of the study, and 5573 were post-menopausal. When comparing HAQ’s of pre- and post-menopausal women, pre-menopausal women had less functional decline. That functional decline also worsened in post-menopausal women with RA.

Women also experience more severe functional decline and increased disability compared with men who have RA (Mollard et al., 2018). Additional observational studies have shown that the average woman with RA, first develops symptoms around the time of menopause (Goemaere et al., 1990). Mechanisms for this phenomenon have been proposed from mice studies that reveal estrogen may have intrinsic immune-regulatory properties that decrease with the onset of menopause (Engdahl et al., 2018). Given that this patient was placed in surgical menopause by the removal of bilateral ovaries, in addition to her likely preexisting elevated estrogen production from the GCT, the case supports that declining estrogen levels are tied more closely than other factors, such as age, to the onset of RA.

Hormone replacement therapy is supported in the literature to reduce symptoms of RA. However, medical risks and benefits of HRT must be assessed, and treatment individualized. A placebo controlled double-blind study consisting of 62 patients analyzed the effects of hormone replacement therapy (HRT) on disease progression and symptoms (Ray-Coquard et al., 2018). The HRT group consisted of 40 women and the remaining 22 women were in the in the placebo group. Using the Nottingham Health Care Profile, significant improvement in well-being was found in the HRT group compared to the placebo group. A reduced articular index was found in the HRT group, as well (MacDonald et al., 1994). Guidelines for HRT in granulosa cell tumors are unclear. Per ESMO guidelines, it is generally not recommended (Ray-Coquard et al., 2018). NCCN suggests that unilateral salpingo-oophorectomy could be considered for Stage IA granulosa cell tumors (NCCN, 2020). Generally this is considered for fertility-sparing therapy but also preserve hormonal function for the patients. Other reviews on hormone replacement therapy in gynecologic cancer do not specifically comment on granulosa cell tumors (Ibeanu et al., 2011; Sinno et al., 2020). This patient strongly desired complete surgery if an intraoperative malignancy was identified given anxiety and that she is a poor surgical candidate. After discussion of options, the patient has opted to control her menopausal symptoms with other pharmacotherapy at this time.

While the association between physiologic menopause and RA has been discussed in the literature, this is the first example of an association between surgical menopause and RA. Although previous literature has noted this association to exist, it is hard to separate age from the equation as RA and menopause are both medical conditions that affect women in their later years. The authors acknowledge that a weakness of this case is that direct estrogen measurements were not obtained perioperatively; however, a bilateral oophorectomy in and of itself results in diminished estrogen levels and granulosa cell tumors are known to be associated with elevated estrogen so one could construe that this patient’s hormone levels were higher than average preoperatively. This case report supports the already established literature’s association between declining estrogen levels and onset of RA irrespective of age.

Consent

Informed consent to publish this report was granted from the patient.

CRediT authorship contribution statement

Morgann Madill: Investigation, Writing - original draft. Amy Gee: Investigation, Writing - original draft. Shannon M. Grabosch: Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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