Tamoxifen Induced Ovarian Hyperstimulation Syndrome

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Ovarian Hyperstimulation Syndrome in a Patient Treated with Tamoxifen for Breast Cancer

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Rare report of tamoxifen-induced OHSS in an older female with breast cancer. OHSS usually resolves with temporary tamoxifen discontinuation. Recurrence of symptoms when resuming tamoxifen is better treated with salpingo-ophorectomy to enable anastrazole adjuvant treatment.

Case Report Summary

A 50 year old woman with breast cancer was diagnosed with ovarian hyperstimulation syndrome (OHSS) while taking tamoxifen. Tamoxifen-induced OHSS is rare. Furthermore, OHSS is very rare in the older female. The patient experienced progressively worsening suprapubic pain and a single episode of inter-menstrual bleeding, likely to represent initial manifestations of OHSS. Symptoms spontaneously resolved with discontinuation of tamoxifen, but resumption of tamoxifen caused a recurrence of symptoms, with the patient developing severe lower abdominal pain and distension. Surgical bilateral salpingo-oophrectomy was performed enable the commencement of the aromatase inhibitor anastrozole as an alternative adjuvant therapy for breast cancer.

Abstract

Objective: To report the management of a rare case of ovarian hyperstimulation syndrome (OHSS) induced by tamoxifen therapy for breast cancer in a 50 year old lady.

Design: Case Report.

Setting: Gynaecology outpatient department of a university hospital.

Patient(s): A 50 year old pre-menopausal patient with a history of breast cancer was prescribed adjuvant treatment with tamoxifen.

Intervention(s): Temporary discontinuation of tamoxifen therapy resolved symptoms, but resumption of tamoxifen caused a recurrence of symptoms. Surgical bilateral salpingo-oophrectomy was therefore performed.

Main outcome measure(s): Resolution of symptoms of OHSS.

Result(s): Bilateral salpingo-oophrectomy rendered the patient post- menopausal and enabled the commencement of the aromatase inhibitor anastrozole as alternative adjuvant therapy for breast cancer.

Conclusion(s): Tamoxifen-induced OHSS is rare. Furthermore, OHSS is very rare in the older female. OHSS usually resolves with temporary discontinuation of tamoxifen, however, the recurrence of symptoms when resuming tamoxifen is better treated with bilateral salpingo-ophorectomy to enable adjuvant treatment with anastrazole.

Key words: OHSS; ovarian hyperstimulation syndrome; tamoxifen, Breast cancer.

Introduction

Tamoxifen is a selective oestrogen receptor modulator (SERM) that acts as an oestrogen antagonist in breast tissue. As such, tamoxifen is widely used as an adjuvant treatment for oestrogen receptor positive breast malignancies and metastatic disease in both pre- and post- menopausal women (1) and (2). The evidence shows tamoxifen therapy to result in a 25% reduction in breast cancer recurrence rates and 17% reduction in mortality compared to no adjuvant treatment (1). Although tamoxifen primarily has anti-oestrogenic properties, the drug has been shown to have an oestrogenic effect on the female genital tract, via its positive stimulation of the hypothalamic-pituitary axis, resulting in supraphysiological levels of oestradiol (E_2) (3), (4), (5), (6), (7), (8) and (9). Tamoxifen is thus a useful drug for induction of ovulation in the treatment of anovulatory infertility, being of similar efficacy to clomiphene citrate (10) and (11). However, the oestrogenic properties of the drug mean that it is associated with hyperplasia, polyps and malignant changes of the endometrium (2) and (12) fibroids (9) and cystic enlargement of the ovaries (13), (14), (15), (16), (17), (18), (19) and (20). Tamoxifen has several side effects including ovarian hyperstimulation syndrome (OHSS). However, OHSS is a very rare side effect of tamoxifen treatment, especially in an older woman. There has been a case report of a 28 year old female with a unilateral controlled ovarian hyperstimulation as a result of tamoxifen treatment (21). In this report, we describe a 50 year old woman with OHSS as a result of tamoxifen therapy, necessitating bilateral oophrectomy in order to resume appropriate adjuvant therapy.

Case Report

A pre-menopausal 50 year old woman was referred for a gynaecological opinion with a diagnosis of moderate OHSS. 10 months earlier she underwent a wide local excision of a left sided invasive lobular breast malignancy 12mm in diameter, accompanied by sentinel node biopsy. Radiotherapy was administered and adjuvant therapy with tamoxifen citrate 20 mg/ day was prescribed and continued for three months. During this period, the patient noted progressively worsening suprapubic pain and a single episode of inter-menstrual bleeding. The patient had no gynaecological history that could account for her symptoms. These symptoms are likely to be the first manifestation of OHSS and improved when the tamoxifen therapy was temporarily discontinued by the breast surgeon. However, when it was recommenced two months later, severe lower abdominal pain and abdominal swelling started.

Transvaginal and transabdominal ultrasound scans in addition to pelvic MRI scan with contrast revealed a normal uterus with bilateral adnexal masses caused by enlargement of the ovaries. The right adnexa disclosed a 72 x 28 x 67 mm cystic mass with some evidence of vascularity. The mass was believed to be comprised of two ovarian cysts with possible haemorrhagic components. The left adnexa disclosed a smaller 45 x 37 x 47 mm ovarian cyst. A moderate amount of free fluid, which was not identified as blood by ultrasound, was also visualised in the pelvis. This was later confirmed to be ascitic fluid at laparoscopy. The patient had no other symptoms such as nausea or vomiting. All parameters of the full blood count and liver function tests were within normal ranges. Serum levels of carcinoembryonic antigen Ca-125 were mildly elevated at 62 Ul/ml. Although unlikely given the Ca-125 levels, ovarian malignancy could not be excluded.

Besides confirming the nature of the ovarian masses, an alternative form of adjuvant therapy for breast cancer was needed to complete the patient's treatment plan. As the patient was pre-menopausal, an aromatase inhibitor was not appropriate. Rendering the patient menopausal medically through the administration of long acting GnRH agonists, or bilateral oophrectomy were the two options considered. The decision was taken to perform laparoscopic bilateral salpingo-oophrectomy to enable a histopathological examination as well as eliminating the source of oestrogen. When the patient was admitted for surgery the ovarian masses had decreased in size and a histological diagnosis confirmed no evidence of neoplasia. Following surgery, the aromatase inhibitor, anastrozole was commenced with no further complications.

Discussion

Tamoxifen is known to stimulate the ovary in pre-menopausal females (3), (4), (5), (6), (7), (8) and (9) therefore can potentially result in hyperstimulation which has been reported in the literature, but mainly as functional ovarian cysts (13), (14), (15), (16), (17), (18), (19) and (20). The serum oestradiol levels in such cases have been demonstrated to be two to three times higher in tamoxifen treated women compared to a control group (13) and (16). Furthermore, transvaginal ultrasonography has demonstrated cystic enlargement of the ovaries in up to 80.0% of tamoxifen-treated pre-menopausal patients compared to just 8.3% in a matched control group who did not receive tamoxifen (13). OHSS, however is rare with tamoxifen. A review of the literature revealed no previously reported cases of tamoxifen associated OHSS even in more vulnerable women such as polycystic ovary syndrome patients (22). One case report does exist in which ovarian enlargement resembling unilateral OHSS is described (21). However, ultrasonographic evidence of ascites was not recorded, serum Ca-125 levels were within the normal range and plasma E_2 were only modestly elevated suggesting a tamoxifen induced ovarian cyst rather than OHSS (23) and (24).

We have highlighted several clinical features in this case report to verify that we encountered OHSS and not simply a tamoxifen associated functional ovarian cyst. The ultrasonographic evidence of ascites, confirmed at laparoscopy, supports a diagnosis of OHSS. In OHSS, the increased capillary permeability leads to ascites and can cause intravascular dehydration and accumulation of fluid in the third-space (25). Ascites, however, is not a common feature of simple cystic enlargement of the ovaries. Additionally, elevated concentrations of Ca-125 have been associated with OHSS (26) as reported in hyperstimulated cycles resulting in levels in excess of 70 Ul/ml (27). However, in tamoxifen-associated ovarian cyst formation, Ca-125 concentrations have been shown to remain below the physiological limit of 35 Ul/ml (14), (17) and (28). In this case report the Ca-125 level was moderately raised at 62 Ul/ml which also supports an OHSS diagnosis.

The timing of onset and resolution of the patient's symptoms also suggests OHSS over hormonally induced ovarian cysts. This case report describes progressively worsening suprapubic pain and inter-menstrual bleeding within three months of commencing tamoxifen. When tamoxifen treatment was withdrawn and later resumed, evidence of ovarian masses and ascites were identified by ultrasound

within two months. Ovarian cysts tend to have a slower onset, with studies suggesting mean time to diagnosis of 28 months (16–41 months) (17). Furthermore, the symptoms subsided spontaneously within 2-4 weeks of discontinuing tamoxifen, as expected with OHSS. This is not usual for hormonally induced ovarian cysts which can take up to three months to resolve (17).

According to the classification proposed by Rizk and Aboulghar (1999), the patient we describe had a moderate OHSS, due to a presentation of discomfort, pain, perceived abdominal distension, ultrasonic evidence of ascites and enlarged ovaries. This classification states that for moderate OHSS haematological and biological profiles should be normal, as identified in this patient (29).

OHSS is not only uncommon with tamoxifen therapy, (10) (11) and (22) but is also a rare side effect to ovarian hyperstimulation for ovulation induction in assisted conception treatment amongst older women (30) (31) and (32). Furthermore, it is well known that chorionic gonadotrophins or lutenising hormone (LH) surge are important in triggering OHSS in those receiving either exogenous gonadotrophins or stimulated by clomiphene citrate (23). However, as we had no means of measuring the lady's LH levels at the onset of her symptoms it will be impossible to know if the OHSS in this case resulted from LH surge or not. The likelihood is that it did.

The pathophysiology of OHSS is generally speaking uncertain (33) and is more mysterious in this case. Nonetheless, the mechanism by which tamoxifen leads to ovarian cyst formation which has been widely discussed (14), (15), (34) and (35) is likely to be the underlying mechanism in this case too. Jolles et al. (1990) have proposed that tamoxifen being a SERM may have a similar mode of action to clomephine on the hypothalamus leading to increased endogenous gonadotrophin release from the pituitary gland causing either cystic enlargement of the ovary or proper OHSS. There are literature reports of clomephine citrate-induced OHSS (25) and (32).

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