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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Insulin resistance as a risk factor for endometrial cancer – a case report of fertility-sparing treatment of early-stage endometrial cancer

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SUMMARY

Introduction Endometrial cancer is the most common gynecologic malignancy, and up to a quarter of cases are diagnosed in patients under the age of 45. Important risk factors that create a hyperestrogenic environment are obesity, polycystic ovary syndrome, insulin resistance, and type 2 diabetes mellitus. The standard treatment is classic hysterectomy with bilateral salpingo-oophorectomy; however, this treatment leads to loss of fertility, which poses an issue for younger patients who have not completed childbearing. Therefore, in certain cases, hormonal therapy could be used for early-stage endometrial adenocarcinoma to preserve fertility.

Case outline A 32-year-old female patient with insulin resistance presented with an ultrasonographic finding of an endometrial polyp, and after hysteroscopy and thorough evaluation, a well-differentiated adenocarcinoma of the endometrium (G1), FIGO stage IA, was verified. A conservative treatment was carried out with a levonorgestrel intrauterine device and a gonadotropin-releasing hormone (GnRH) analog for six months. After six months of therapy, there were no signs of malignant cells, and she conceived naturally. Eventually, the patient delivered a healthy baby.

Conclusion Insulin resistance is a potentially modifiable risk factor and thus important in cases of fertility preservation treatment. Management could reduce cancer risk and improve reproductive outcomes. Further studies are needed to better understand the impact of insulin resistance treatment on the success of fertility- sparing management and the rate of recurrence.

Keywords: endometrial cancer; oncofertility; fertility-sparing treatment of endometrial cancer; insulin resistance

INTRODUCTION

Endometrial cancer (EC) has an incidence of 4.3% and is the most common malignancy of the genital tract among Caucasians [1]. Available data suggest that up to a quarter of cases are diagnosed in patients under the age of 45 who have not yet completed childbearing [2]. In these cases, the diagnosis is often made incidentally after hysteroscopy or curettage of the uterine cavity, typically performed as part of an infertility evaluation, due to ultrasound findings of an endometrial polyp or irregular bleeding. Although most histopathological types of EC are considered hormone-sensitive, lifestyle and environmental factors have a significant impact on the development of cancer [3]. Known risk factors for EC include age, race, early menarche, late menopause, nulliparity, and conditions that create a hyperestrogenic environment, such as obesity, polycystic ovary syndrome, insulin resistance (IR), type 2 diabetes mellitus, and metabolic syndrome [4]. Metabolic disorders characterized by hyperinsulinemia can impact carcinogenesis through various molecular mechanisms [3]. IR is a fundamental component of metabolic syndrome, and many studies have linked IR to cancer [5]. Genetic predisposition, such as Lynch syndrome and BRCA mutations, is also a significant nonmodifiable risk factor [6, 7].

The importance of discussing treatment options for EC among premenopausal women is significant. The standard treatment is hysterectomy with bilateral salpingo-oophorectomy [8]. However, this treatment results in the loss of reproductive function, which poses an issue for younger patients who have not completed childbearing and wish to become pregnant. Thus, in certain cases, hormonal therapy could be used as a treatment option for early-stage adenocarcinoma of the endometrium to preserve fertility [9]. This treatment option is also important in terms of quality of life because five-year survival rate of stage I EC is 85% [10].

According to the guidelines of the leading European societies for gynecologic oncology [the European Society of Gynecological Oncology (ESGO)], radiotherapy and oncology [the European Society for Radiotherapy and Oncology (ESTRO)], and pathology [the European Society of Pathology (ESP)], a conservative treatment approach could be taken for patients under 45 years old with well-differentiated early-stage endometrial adenocarcinoma [9]. Hormonal therapy may include oral progestins, GnRH analogs, and an intrauterine device with levonorgestrel. In case of complete

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response, pregnancy is recommended. After successful pregnancy and completing childbearing, definitive surgery (standard hysterectomy) is advised, as the recurrence rate can be as high as 25% [11].

Since EC is strongly associated with modifiable risk factors such as insulin resistance, timely recognition and adequate treatment are important. It could be substantial for EC prevention, the success of fertility- sparing treatment, and lowering recurrence risk. Therefore, the aim of this case is to emphasize the significance of modifiable risk factors in a cancer patient.

CASE REPORT

A 32-year-old female patient, G0P0, presented with an ultrasonographic finding of an endometrial polyp during a regular checkup, with regular menstrual cycles and no irregular intermenstrual bleeding. Apart from insulin resistance calculated by the homeostatic model assessment index, there was no other comorbidity. The patient was taking only metformin. Body mass index was normal (20 kg/m^2). Family history was unremarkable. As a gold standard for endometrial polyp evaluation, hysteroscopy was performed. Well-differentiated adenocarcinoma of the endometrium (G1) was verified after hysteroscopy, polypectomy, and uterine curettage. The next step was to determine the clinical stage according to the International Federation of Gynecology and Obstetrics (FIGO) classification [12]. An MRI of the abdomen and pelvis was performed to rule out myometrial invasion, adnexal involvement, and concomitant ovarian tumor. According to pelvic MRI, the endometrial lining was nonhomogeneous, with a hypovascular 3-mm lesion within the endometrium without myometrial invasion; the endometrial–myometrial junction was intact.

To initiate conservative treatment, assessment by two expert pathologists is required to confirm the diagnosis, which was also done, confirming the diagnosis of endometrioid adenocarcinoma (G1) of the endometrium. Standard evaluation for patients preparing for fertility- sparing treatment includes a chest radiograph, hormonal and thyroid status assessment, Pap smear for cervical cancer screening, and breast ultrasound. After complete evaluation, an early stage of well-differentiated adenocarcinoma (FIGO stage IA) was diagnosed. Considering the type and stage of EC, young age, nulliparity, and a strong desire to preserve fertility, the clinical board approved conservative treatment that involved insertion of a levonorgestrel intrauterine device along with a GnRH analog for six months. The ultrasound examination after three months of therapy was unremarkable, and no side effects were reported. Menstrual bleeding ceased after three months of therapy. Intrauterine device removal and a follow-up hysteroscopy with curettage of the uterine cavity were performed after six months. Histopathological examination showed no atypia or malignant cells. After two negative biopsies six months apart and three months after the last hysteroscopy, the patient conceived spontaneously. She had an uncomplicated pregnancy and delivered a healthy male child weighing 4500 g via elective cesarean section. Postpartum hysteroscopy and curettage revealed no signs of malignancy.

Ethics: According to the journal's position on issues involving ethical publication, written consent for publication of this article has been obtained from the patient.

DISCUSSION

The case of a young patient with insulin resistance as a risk factor for endometrial cancer, who was successfully treated conservatively with hormone therapy, is presented.

There are two types of endometrial cancer that differ in their pathogenesis, aggressiveness, and prognosis. The far more common type is type I, which is found in almost 90% of cases [8]. It is considered an estrogen-dependent, well-differentiated cancer and is associated with insulin resistance, obesity, and type 2 diabetes mellitus [8, 10]. Type I occurs more frequently before menopause and during early menopause and has a favorable prognosis [8]. In contrast, type II is estrogen-independent, less differentiated, occurs in older patients, and carries a higher risk of rapid progression and an unfavorable outcome [3, 13].

The case presented is a type I, well-differentiated carcinoma that occurred in a young patient with no symptoms. The incidence of this malignancy is increasing in women younger than 50 years old [14]. This trend could be linked to today's sedentary lifestyle and the higher incidence of risk factors among the younger population, such as obesity, insulin resistance, and type 2 diabetes mellitus [15].

The only risk factor noted in this patient was insulin resistance. The influence of insulin resistance on the development of malignancy can be explained by metabolic dysregulation involving inflammatory cytokines, growth factors, various enzymes, and free fatty acids [16]. Elevated insulin levels, chronic inflammation, and hyperactivation of growth pathways are associated with the development and progression of cancer [17]. An important metabolic pathway activated by insulin and insulin-like growth factor 1 (IGF-1) is the PI3K/AKT/mTOR pathway, leading to cell proliferation, invasion, and metastasis [16]. This pathway is also crucial for understanding the effect of treatment with metformin, which is the drug of choice [18]. Metformin leads to the suppression of the mTOR signaling pathway, reducing the concentration of insulin and IGF-1, thus suppressing protein translation and cell proliferation [19]. Although previous studies' results are controversial regarding the reduction of cancer incidence in patients with diabetes treated with metformin, it is still important to recognize risk factors [16, 20]. Timely recognition of risk factors such as insulin resistance, diabetes, and obesity and their treatment as part of conservative treatment for early-stage endometrial cancer is valuable because it reduces the effect of insulin and IGF-1 on the endometrium [21]. Insulin is thought to influence estrogen receptor expression, thus affecting endometrial proliferation and potential

carcinogenesis [22]. This influence may contribute to a better endometrial response to the local action of the levonorgestrel intrauterine device.

A levonorgestrel-releasing intrauterine device, alone or in combination with oral progestins or GnRH analogs, is a recommended option for conservative treatment of endometrial adenocarcinoma [9]. The latest guideline from ESGO advises a levonorgestrel intrauterine device and/or oral progestins as first-line treatment [9]. GnRH analogs are an alternative therapy with protective effects on ovarian reserve, contributing to improved pregnancy rates, and many studies reported satisfactory results with GnRH analogs [9]. Standard protocol in our institution for conservative treatment of early-stage endometrial cancer consisted of a levonorgestrel intrauterine device with GnRH analogs for six months and was introduced over a decade ago [23].

Although no statistical significance was observed in studies examining the effect of insulin resistance on mortality after hysterectomy in endometrial cancer, the effect of insulin resistance on the outcome of conservative treatment could be more significant because the uterus remains, and the endometrium could still undergo malignant transformation [20]. This is supported by the results of the study by Li et al. [21], who showed that the time to relapse in patients with endometrial cancer treated conservatively is significantly shorter in those with insulin resistance compared to those without. Also, considering the normal values of the body mass index in our patient, the influence of obesity and peripheral conversion of estrogen on the endometrium and tumor formation is ruled out.

Furthermore, recognizing risk factors is important because they affect fertility, fertilization, and could complicate pregnancy, and the aim of conservative treatment of endometrial cancer is to achieve a successful pregnancy [9]. Insulin resistance is linked to recurrent miscarriages, gestational diabetes, and gestational hypertension [19, 24, 25]. This impacts the fetus, leading to macrosomia and the need for operative delivery, which carries its own risks [25]. The best way to prevent these complications is to establish proper glycemic control before conception [19]. Despite our patient's normal oral glucose tolerance test during pregnancy, the newborn weighed 4500 g, exceeding the 90th percentile for that gestational age [26].

Nevertheless, in terms of the generally high survival rate for early-stage endometrial cancer, the aforementioned risk factors are associated with lifelong cardiovascular morbidity and mortality [10]. This should be noted especially in cases of definitive radical treatment where the protective estrogen effect is lost.

Insulin resistance is recognized as a significant and potentially modifiable risk factor for endometrial cancer. Its role could be particularly important in cases of fertility preservation treatment. Early identification and management of metabolic abnormalities could reduce cancer risk and improve reproductive outcomes. A multidisciplinary approach, including an endocrinologist, is essential to optimize cancer treatment and reproductive potential. Further studies are needed to better understand the impact of insulin resistance treatment on the success of fertility-sparing management and the rate of recurrence.

Conflict of interest: None declared.

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Инсулинска резистенција као фактор ризика за карцином ендометријума – приказ случаја конзервативног лечења раног стадијума карцинома ендометријума

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САЖЕТАК

Увод Карцином ендометријума најчешћи је гинеколошки малигнитет и скоро четвртина случајева се дијагностикује код болесница млађих од 45 година. Важни фактори ризика који стварају хиперестрогену средину су гојазност, синдром полицистичних јајника, инсулинска резистенција и дијабетес мелитус типа 2. Стандардни вид лечења је класична хистеректомија са билатералном аднексектомијом, али овај третман доводи до губитка фертилитета, што представља проблем за млађе болеснице које још нису остариле репродуктивну функцију. У одређеним случајевима могуће је спровести хормонску терапију као вид конзервативног лечења у циљу очувања фертилитета.

Приказ болесника Болесници старој 32 године, са инсулинском резистенцијом као фактором ризика, урађена је хистероскопска полипектомија због ултразвучног налаза ендометријалног полипа. Након хистопатолошке верификације и евалуације дијагностикован је добро диференован аденокарцином ендометријума, стадијум IA. Спроведен је конзервативни третман применом интраутериног улошка са левоноргестрелом и *GnRH* аналога током шест месеци. С обзиром на то да је после шестомесечне терапије урађена контролна хистероскопија и да хистопатолошки налаз није указао на присуство малигнитета, саветована је трудноћа. Болесница је спонтано затруднела, успешно је изнела терминску трудноћу и родила здраво мушко дете.

Закључак Инсулинска резистенција је фактор ризика на који можемо да утичемо и тако смањимо ризик од настанка малигнитета, али и побољшамо репродуктивни исход. Њена улога је посебно важна у конзервативном лечењу карцинома ендометријума и зато су потребна додатна истраживања како би се боље разумео утицај лечења инсулинске резистенције на успех конзервативног лечења, али и на појаву рецидива.

Кључне речи: карцином ендометријума; онкофертилитет; поштедно лечење карцинома ендометријума; инсулинска резистенција