


Endometrial Carcinoma in a Patient with Type 2 Diabetes Mellitus: A Case Report

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ABSTRACT

Introduction: Endometrial cancer is often associated with obesity, type 2 diabetes mellitus (T2DM), insulin resistance, and hyperinsulinemia. **Case:** A 71-year-old woman with a history of T2DM, hypertension, and obesity (body mass index/BMI 32.08 kg/m²) presented with intermittent abdominal pain and vaginal bleeding. She had undergone a curettage procedure two weeks earlier. Ultrasound examination revealed a hyperechoic mass in the uterine corpus, and histopathological examination following staging laparotomy confirmed type 2 endometrial carcinoma (high-grade serous carcinoma) with omental metastasis. The diagnosis was stage IVB endometrial carcinoma. During hospitalization, the patient received intravenous ceftriaxone, insulin glargine, and oral antihypertensive medications (ramipril and nifedipine). She was scheduled to receive systemic chemotherapy with carboplatin and paclitaxel, the standard regimen for advanced-stage, aggressive non-endometrioid endometrial cancer. **Discussion:** Diabetes mellitus, particularly when accompanied by chronic hyperglycemia, insulin resistance, and hyperinsulinemia, is associated with an increased risk of various cancers, including endometrial cancer, as well as a poorer prognosis. Factors such as obesity, age, estrogen exposure, and insulin therapy may exacerbate this risk, while biomarkers such as IGF-2 and IGFBP-3 have the potential to be used for early detection and risk assessment of endometrial cancer. **Conclusion:** This case highlights the strong link between T2DM, obesity, and aggressive endometrial cancer, emphasizing the importance of early detection and comprehensive management in patients with metabolic risk factors.

Keywords: Case report, diabetes mellitus, endometrial cancer, hyperinsulinemia, obesity.

ABSTRAK

Pendahuluan: Kanker endometrium sering dikaitkan dengan obesitas, diabetes melitus (DM) tipe 2, resistensi *insulin*, dan hiperinsulinemia. **Kasus:** Wanita berusia 71 tahun dengan riwayat DM tipe 2, hipertensi, dan obesitas (indeks massa tubuh/IMT 32,08 kg/m²) datang dengan keluhan nyeri perut hilang timbul dan perdarahan per vaginam. Pasien telah menjalani kuretase 2 minggu sebelumnya. Pemeriksaan USG menunjukkan massa *hyperechoic* di *corpus uteri,* dan hasil histopatologi pasca-laparatomi *staging* mengonfirmasi karsinoma endometrium tipe 2 *(high-grade serous carcinoma)* dengan metastasis ke omentum. Diagnosis karsinoma endometrium stadium IVB. Selama perawatan, pasien mendapat *ceftriaxone* secara intravena, *insulin glargine*, serta *antihipertensi oral* (*ramipril* dan *nifedipine*) Tata laksana utama direncanakan berupa kemoterapi sistemik dengan kombinasi *carboplatin* dan *paclitaxel*. **Pembahasan:** Diabetes melitus, terutama dengan hiperglikemia kronis, resistensi *insulin*, dan hiperinsulinemia, dikaitkan dengan peningkatan risiko berbagai kanker termasuk kanker endometrium, serta prognosis yang lebih buruk. Faktor seperti obesitas, usia, paparan estrogen, dan terapi *insulin* dapat memperkuat risiko ini, sementara *biomarker* seperti IGF-2 dan IGFBP-3 berpotensi digunakan untuk deteksi dini dan penilaian risiko kanker endometrium. **Simpulan:** Kasus ini menyoroti hubungan erat antara DM tipe 2, obesitas, dan kanker endometrium agresif, serta pentingnya deteksi dini dan penatalaksanaan komprehensif pada pasien dengan risiko metabolik. **Ida Bagus Aditya Nugraha, Wira Gotera, Gede Vendi Cahyadi Riandika, Dian Daniella, Thomas Aquinas Ehe Teron. Penderita Karsinoma Endometrium dengan Diabetes Melitus Tipe 2.**

Kata Kunci: Laporan kasus, diabetes melitus, kanker endometrium, hiperinsulinemia, obesitas.

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INTRODUCTION

A study by Lortet-Tieulent, *et al*., indicates that endometrial cancer ranks as the sixth most common cancer among women and the 15th most common overall, with over 380,000 new cases recorded in 2018.[1] Furthermore, a meta-analysis by Saed, *et al*., reported that approximately 142,000 women are diagnosed with endometrial cancer annually worldwide, resulting in an estimated 42,000 deaths; although a specific year was not cited, these figures reflect global annual estimates.[2] Multiple studies have demonstrated that the risk of endometrial cancer is elevated in association with advanced age, early menarche, late-onset menopause, obesity, a family history of endometrial cancer (first-degree relatives), radiation exposure, infertility (specifically secondary to polycystic ovary syndrome), and long-term estrogen therapy.[1–2]

Several studies, including those by Friberg, *et al*., (2007) and Luo, *et al*., (2014), demonstrate an increasing trend in the incidence of concurrent diabetes mellitus and endometrial cancer in Western countries.[3,4] A primary risk factor underlying this association is obesity, which is closely linked to diabetes mellitus, hyperinsulinemia, and insulin resistance.[3,4] Obese women exhibit higher levels of estradiol, non-protein-bound estradiol, and estrone compared to non-obese women, thereby elevating the risk of obesity-related endometrial cancer.[5] Furthermore, hyperinsulinemia in obese women constitutes an additional risk factor for endometrial cancer, as insulin can elevate levels of sex hormones and growth factors that exert direct mitogenic effects on endometrial tissue.[3,5–6]

Friberg, *et al*., (2007) also demonstrated an association between diabetes and elevated incidence or mortality rates of endometrial cancer, a phenomenon more frequently observed in type 2 diabetes mellitus.[3] However, epidemiological studies investigating the relationship between diabetes and the risk of endometrial cancer are not entirely consistent.[3]

CASE

A 71-year-old housewife presented with a one-month history of abdominal pain. The pain was described as sharp and stabbing, generalized in the abdomen, and intermittent in nature. The patient also reported a three-month history of vaginal bleeding, for which she underwent a curettage procedure by an obstetrician-gynecologist two weeks prior to the current hospital admission. The bleeding ceased following the curettage. Nausea and vomiting were denied. The patient has a 13-year history of diabetes mellitus, for which she receives regular care at a primary healthcare center (Puskesmas) and is managed with glibenclamide. Additionally, she has a concurrent 13-year history of hypertension, with routine medical follow-ups, and is currently prescribed amlodipine and ramipril. On physical examination, the patient appeared moderately ill but was fully conscious with a Glasgow coma scale (GCS) score of 15 (E4V5M6). Vital signs were recorded as follows: blood pressure of 108/84 mmHg, pulse rate of 80 beats per minute (strong and of adequate volume), respiratory rate of 18 breaths per minute, and axillary temperature of 36.2 °C. The visual analog scale (VAS) pain score was 1/10, and oxygen saturation was 98% on room air. The remainder of the physical examination was within normal limits.

Laboratory investigations revealed a random blood glucose level of 170 mg/dL (reference range: 70–140 mg/dL) and a glycated hemoglobin (HbA1c) level of 7.7% (reference range: < 6.5%). Chest radiography demonstrated aortosclerosis with no evidence of pulmonary or bone metastases. Transthoracic echocardiography revealed concentric left ventricular hypertrophy with normal left ventricular systolic and diastolic function, alongside normal right ventricular systolic function. Abdominal ultrasonography showed a hyperechoic mass with lobulated and irregular margins located on the posterior wall of the uterine corpus, suggestive of an endometrial mass. There was no evidence of para-aortic lymphadenopathy or free fluid in the abdominopelvic cavity.

Laparotomy was performed for the purpose of surgical staging, given that type 2 endometrial carcinoma (high-grade serous carcinoma) is an aggressive variant with a propensity for early metastasis. Surgical staging is essential for guiding subsequent therapeutic decision-making. Histopathological examination of the resected omentum revealed a tumor mass with ill-defined margins, measuring 12 × 4 × 1 cm in its greatest dimensions. Microscopically, the specimen consisted of connective tissue, adipose tissue, and blood vessels, with a solid, infiltrative tumor growth pattern. The neoplastic cells demonstrated an increased nuclear-to-cytoplasmic (N/C) ratio, marked nuclear pleomorphism, and a mitotic count of 23 mitoses per 10 high-power fields (HPF). The histopathological conclusion was high-grade serous carcinoma with omental extension. Pap smear cytology demonstrated sufficient squamous epithelial and endocervical cells adequate for evaluation. There was no evidence of intraepithelial lesions or malignancy.

The patient was diagnosed with stage I, type 2 endometrial carcinoma, scheduled for surgical staging via laparotomy, alongside type 2 diabetes mellitus, stage I hypertension, and acute-on-chronic kidney disease, with suspected underlying etiologies of diabetic kidney disease and nephrosclerosis. During hospitalization, the patient received intravenous ceftriaxone at 2 g once daily for 5 days and subcutaneous insulin glargine at 6 units once daily for glycemic control, the latter of which was continued post-discharge. Hypertension was managed with oral ramipril 5 mg once daily and oral nifedipine extended-release 30 mg once daily, both of which were maintained as continuous maintenance therapy. Furthermore, the patient was administered an intravenous infusion of 0.9% sodium chloride at 2,100 mL/day to ensure adequate hydration and renal perfusion, and was placed on a 1,900 kcal/day diabetic, low-sodium diet.

Based on the tumor stage and aggressive histopathological characteristics (high-grade serous carcinoma), the patient is scheduled to undergo systemic chemotherapy utilizing a carboplatin and paclitaxel regimen, which represents the most efficacious neoadjuvant therapy for advanced endometrial carcinoma, particularly for non-endometrioid subtypes.[7] The chemotherapy is planned for six cycles alongside routine monitoring, with a specific emphasis on evaluating renal function. An individualized and multidisciplinary management approach has been adopted to ensure the safety and efficacy of the long-


term therapeutic strategy.

DISCUSSION

Diabetes is a degenerative disease characterized by impaired insulin secretion.[8] Recently, diabetes mellitus has been associated with an elevated risk of various malignancies, including cancers of the pancreas, colon, rectum, esophagus, stomach, liver, gallbladder, urinary tract, breast, and endometrium.[9,10] Diabetes mellitus and chronic hyperglycemia have been linked to increased mortality rates among cancer patients when compared to normoglycemic individuals without diabetes.[9] A meta-analysis conducted by Liao, *et al*., (2014) demonstrated that women with diabetes face a higher risk of developing endometrial cancer.[9] Furthermore, a study by Joung, *et al*., (2015) indicated an elevated risk of breast cancer among diabetic patients.[10]

The primary mechanisms underlying this association involve insulin resistance and hyperinsulinemia, which upregulate the activity of insulin-like growth factor-1 (IGF-1), thereby promoting cancer cell proliferation and metastasis.[10] Additionally, chronic hyperglycemia establishes a microenvironment conducive to tumor growth by exacerbating oxidative stress and inflammation.[10] Alterations in ovarian steroid hormones, characterized by elevated levels of estrogen and androgens coupled with reduced progesterone, further contribute to the pathogenesis of endometrial and breast cancers.[10] The confluence of these factors renders diabetic patients more susceptible to carcinogenesis and confers a poorer prognosis relative to normoglycemic individuals.[9,10] Ultimately, insulin resistance, hyperinsulinemia, hyperglycemia, and systemic inflammation are frequently implicated as catalysts in the processes of carcinogenesis, malignant proliferation, and metastasis, mediated through the upregulation of insulin-like growth factor-1 and other biological mechanisms.[9]

Liang, *et al*., (2012) investigated 58 tumor tissue samples, 31 tumor-adjacent endometrial tissue samples, and 42 normal endometrial tissue samples from patients with endometrial adenocarcinoma.[12] The results demonstrated that IGF-1 and IGF-2 mRNA levels were significantly higher in both tumor cells and tumor-adjacent cells compared to the control tissues. This suggests that IGF-1 and IGF-2 may serve as crucial mediators in the transformation of normal cells into malignant cells. Insulin-like growth factors (IGFs) play a pivotal role in estrogen-induced endometrial carcinogenesis; specifically, IGFs elicit estrogen-induced mitogenic activity and exert anti-apoptotic effects in endometrial tissue.[11] The IGF system encompasses 2 growth factors (IGF-1 and IGF-2), 2 receptors (IGF-1R and IGF-2R), and 10 IGF-binding proteins (IGFBPs), among other components.[11,12] Estrogen upregulates the expression of IGF-1 in the uterus, and IGF-1 is requisite for mediating its mitogenic effects on the endometrium. Furthermore, both IGF-1 and IGF-2 have been implicated in the pathogenesis and progression of endometrial adenocarcinoma.[12]

A study by Oh, *et al*., (2004) demonstrated that plasma IGF-2 levels were significantly higher in endometrial cancer patients than in the control group (670 ng/mL vs. 380 ng/mL, $p < 0.001$). Additionally, IGFBP-3 levels were found to be lower in patients with endometrial cancer relative to controls (1,703 ng/mL vs. 2,170 ng/mL, $p < 0.001$); similarly, IGF-1 levels were also reduced in the cancer cohort (155 ng/mL vs. 185 ng/mL, $p = 0.03$). This study indicated that women with the highest IGF-2 levels had a 9.67-fold increased risk of developing endometrial cancer compared to those with the lowest IGF-2 levels. Conversely, elevated IGFBP-3 levels were associated with a significantly decreased risk of endometrial cancer (OR = 0.23, $p = 0.003$). These findings support the role of IGF-2 in promoting endometrial cancer cell proliferation, whereas IGFBP-3 may exert a protective effect. Consequently, IGF-2 and IGFBP-3 levels hold potential as promising biomarkers for the early detection and risk assessment of endometrial cancer.[13]

Several studies have also demonstrated that the risk of endometrial cancer is elevated in association with advanced age, early menarche, late-onset menopause, obesity, a family history of endometrial cancer (first-degree relatives), radiation exposure, infertility (particularly secondary to polycystic ovary syndrome), and long-term estrogen therapy.[1,2,4] Estrogen plays a pivotal role in the process of endometrial carcinogenesis.[1] Obese women exhibit higher levels of estradiol, non-protein-bound estradiol, and estrone compared to normal-weight women. Furthermore, obese women tend to present with higher insulin levels than their normal-weight counterparts; this hyperinsulinemic state also increases the risk of endometrial cancer, as insulin can elevate the levels of sex hormones and growth factors, in addition to exerting direct mitogenic effects on endometrial tissue.[2] Anderson, *et al*., concluded that diabetes does not augment the risk of endometrial cancer in women with a body mass index (BMI) ≤ 27.4 kg/m², but it does increase the risk in women with a BMI > 27.4 kg/m². The elevated risk of endometrial cancer in obese patients is not solely attributable to concurrent diabetes. Obesity, independently, in the absence of diabetes, also significantly increases the risk of endometrial cancer.[5]

Research by Friberg, *et al*., (2007) indicates that insulin can stimulate the proliferation of endometrial stromal cells by binding to insulin receptors on these cells. Furthermore, hyperinsulinemia contributes to elevated free estrogen levels by reducing circulating sex hormone-binding globulin (SHBG) concentrations, thereby amplifying estrogen's proliferative effects on the endometrium. Estrogen that is not balanced by progesterone, particularly in postmenopausal women, can augment the risk of endometrial cancer by driving continuous endometrial cell proliferation. Hyperinsulinemia also contributes to increased circulating free IGF-1 levels by downregulating IGF-binding protein-1 (IGFBP-1) and IGF-binding protein-3 (IGFBP-3), which normally bind and regulate IGF-1 bioavailability. The resultant elevated free IGF-1 subsequently binds to IGF-1 receptors on endometrial cells, triggering cellular proliferation and potentially exacerbating the risk of endometrial carcinogenesis.[3]

Furthermore, obesity is strongly associated with reduced levels of adiponectin, an endogenous insulin sensitizer, which can ultimately precipitate type 2 diabetes mellitus and hyperinsulinemia. Decreased adiponectin levels are not only correlated


with elevated estradiol concentrations, hyperinsulinemia, and insulin resistance, but they also directly modulate cellular proliferation, apoptosis, and angiogenesis via mechanisms involving caspase enzymes in the apoptotic cascade.[3] Although the specific types of diabetes were not explicitly differentiated, the study by Friberg, *et al*., (2007) indicates that the diabetes associated with an elevated risk of endometrial cancer is most likely type 2 diabetes mellitus, given its robust correlation with obesity and insulin resistance. The putative mechanisms include hyperinsulinemia, elevated free estrogen levels, and activation of the insulin-like growth factor-1 (IGF-1) pathway.[3] Additionally, a reduction in IGF-binding protein-3 (IGFBP-3) levels contributes to a loss of regulatory control over cellular proliferation and endogenous antineoplastic mechanisms; consequently, hyperinsulinemia further fosters a pro-carcinogenic microenvironment conducive to the development and progression of endometrial cancer. These findings corroborate the hypothesis that hyperinsulinemia, insulin resistance, and the dysregulation of hormones such as adiponectin and IGFs contribute significantly to the pathogenesis of endometrial cancer, particularly in women with concurrent obesity and type 2 diabetes mellitus.[3]

The patient is a 71-year-old postmenopausal woman with a 13-year history of diabetes mellitus and obesity (BMI of 32 kg/m^2), constituting a combination of high-risk factors for endometrial cancer. Anderson, *et al*., (2001) demonstrated that diabetic women with a BMI between 27.41 and 30 kg/m^2, as well as those with a BMI > 30.7 kg/m^2, have a moderate risk of developing endometrial cancer.[5] As this patient presents with diabetes and a calculated BMI of 32.08 kg/m^2, she is stratified into the moderate-risk category for endometrial cancer. The patient was therapeutically managed with insulin glargine at a dose of 6 units per day, alongside a diabetic diet of 1,900 kilocalories (kcal) per day.

The potential carcinogenic effects of antidiabetic therapy have emerged as a critical issue in the clinical management of patients with concurrent endometrial cancer and diabetes mellitus.[14] Hyperinsulinemia, characterized by elevated circulating insulin levels, is known to activate the insulin-like growth factor-1 (IGF-1) pathway, which plays a pivotal role in stimulating cellular proliferation and inhibiting apoptosis, thereby establishing a microenvironment conducive to malignant growth.[15] Multiple studies have demonstrated that the administration of exogenous insulin, particularly via the subcutaneous route, can yield higher circulating insulin concentrations than endogenous secretion, which theoretically poses a potential risk for increased cancer incidence.[14,15] Jonasson, *et al*., (2009) reported an increased incidence of breast cancer among women utilizing insulin glargine as monotherapy compared to those using other insulin formulations, although a definitive causal relationship remains to be established.[15] Nevertheless, insulin remains a cornerstone in the management of diabetes mellitus, particularly for patients with type 1 diabetes mellitus, as well as for approximately 40% to 80% of patients with type 2 diabetes mellitus who fail to achieve optimal glycemic control with oral pharmacotherapy.[14]

Several meta-analyses and large-scale observational studies have demonstrated a significant association between insulin therapy and an elevated risk of malignancy. In a meta-analysis of 15 observational studies comprising over 562,000 participants, Janghorbani, *et al*., (2012) reported that insulin utilization is associated with an increased overall cancer risk (RR 1.39; 95% CI: 1.14–1.70), particularly for pancreatic and colorectal cancers, although the association was not statistically significant for breast or prostate cancers. These findings underscore the critical need for individualized risk assessment prior to the initiation of insulin therapy, particularly in patients presenting with risk factors for gastrointestinal malignancies or a familial history of cancer.[16] Consistent with these findings, Jonasson, *et al*., (2009) reported that women utilizing insulin glargine as monotherapy exhibited a nearly twofold increased risk of breast cancer compared to those receiving non-glargine insulins (RR 1.99; 95% CI: 1.31–3.03), although a definitive causal relationship has not been established.[15]

Nevertheless, as elucidated by Habib and Rojna (2013), insulin remains a primary therapeutic modality for patients with type 1 diabetes mellitus and is extensively utilized in patients with type 2 diabetes mellitus. Its efficacy in reducing blood glucose levels, preventing microvascular complications, and potentially mitigating the risk of cardiovascular disease renders insulin a therapy whose clinical benefits may outweigh the potential, yet still speculative, carcinogenic risks.[14]

CONCLUSION

The incidence and prevalence of gynecologic cancers are elevated in patients with type 2 diabetes mellitus. The underlying pathogenic mechanisms include elevated insulin levels, activation of the insulin-like growth factor (IGF) pathway, chronic inflammation, and the dysregulation of ovarian steroid hormones. These conditions can be further exacerbated by insulin resistance in women with type 2 diabetes mellitus.

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