

Endometrial cancer detected unusually after an ankle fracture secondary to severe anemia in an obese woman with heavy menstrual bleeding: A case report

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Abstract. Endometrial cancer (EC) is a growing public health concern in developed countries. The incidence of EC is increasing, particularly in younger women (aged <50 years). Ankle fractures are relatively common orthopedic injuries, with the most common mechanisms being falls or trauma. A 36-year-old woman presented to the emergency department with right ankle pain secondary to a fall caused by dizziness and headache after menstruation. Initial radiography revealed a right ankle fracture without dislocation. Initial laboratory results revealed a hemoglobin level of 4.9 g/dl. She had a recent history of menorrhagia that lasted for two years. The body mass index was 36.2 kg/m². During the evaluation, she was referred to the authors' gynecology unit after a computed tomography scan revealed a significant endometrial mass that was suspected to be EC. Magnetic resonance imaging revealed a 6.7-cm-sized endometrial mass with restricted diffusion, myometrial invasion of <1/2, and bilateral polycystic ovaries. The patient underwent open reduction and internal fixation involving screw fixation of a right ankle fracture. The post-operative follow-up showed successful healing and functional recovery. A total of 4 weeks later, robot-assisted total hysterectomy, bilateral salpingectomy and sentinel lymph node sampling were performed. Final histopathology revealed stage 1B, grade 2 endometrioid adenocarcinoma with lymphovascular space invasion. The patient received 50.4 Gy radiation to the whole pelvis. At 26 months of postoperative follow-up, the patient remained disease-free. The present case report describes a rare presentation of EC in an obese woman with

heavy menstrual bleeding after ankle fracture secondary to severe anemia. The present case highlights the importance of assessing gynecological conditions through a detailed review of gynecological history with caution when an obese female patient presents with abnormal uterine bleeding, even during a non-gynecologic assessment.

Introduction

Endometrial cancer (EC) is the most common and frequently diagnosed gynecological malignancy in high- and middle-income countries. Most patients with EC are diagnosed after menopause; only 5% of EC cases occur before 40 years of age (1). In Korea, the incidence of EC has rapidly increased in recent years. In 2021, the age-standardized incidence rate was 8.8 cases per 100,000 women, and the number of newly diagnosed EC cases and deaths attributed to EC were 3,749 and 429, respectively (2). This may be partly explained by the rising prevalence of obesity, a well-established risk factor for EC. The 2023 Obesity Fact Sheet of Korea reported that the overall prevalence of obesity in 2021 was 38.4% (49.2% in men and 27.8% in women). This increase is particularly pronounced in young adults (3). Although early-onset EC (EOEC; age at diagnosis <50 years) is relatively uncommon, its incidence has been increasing in recent decades, possibly linked to the rising obesity epidemic in younger women (4). In Korea, the incidence of EC between 1999 and 2017 increased most rapidly in young women aged ≤30 years and 30-39 years (annual percentage change, 8.7 and 7.4%, respectively) (5).

Iron deficiency anemia associated with heavy menstrual bleeding (HMB) is prevalent among women of reproductive age. Obese women are at risk of abnormal uterine bleeding (AUB), and ~75-90% of patients with EC present with AUB. Patients often present with atypical symptoms (6). The present case is an example of an atypical presentation of EC in a woman who presented with ankle fracture secondary to severe anemia. Although AUB can have serious medical consequences, most women do not seek treatment for these symptoms. Ankle fractures are relatively common orthopedic injuries, with falls or

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trauma being the most common mechanism (7). A total of 50% of the EC cases occur in individuals with risk factors, such as obesity and unopposed estrogen stimulation (8). In addition, a meta-analysis has suggested an increased risk of EC among patients with hypertension (9). Knowledge of the risk factors for EC helps gynecologists to evaluate possible gynecological malignancies. This case underscores the significance of recognizing rare clinical presentations, such as ankle fracture secondary to severe anemia in an obese woman with HMB, necessitating further gynecologic evaluations. This report presents a case of EC detected incidentally after an ankle fracture secondary to severe anemia in a woman with HMB.

Case report

A 36-year-old, virgin woman, presented to the emergency department of another institution with right ankle pain due to a fall caused by dizziness and headache after menstruation. The initial evaluation revealed swelling of the right ankle. Initial radiography revealed a right ankle fracture without dislocation. The patient was hypertensive, with a heart rate of 102 beats/min. Initial laboratory results showed a severely low hemoglobin level (4.9 g/dl, reference range, 12.0-16.0 g/dl) and hematocrit (16.6%, reference range 36.0-46.0%). She was treated with packed red blood cells and iron infusion. Her weight and height were 95.0 kg and 162 cm, respectively, and her body mass index (BMI) was 36.2 kg/m². She had a recent history of menorrhagia and irregular cycles that lasted for two years. She had never presented to a doctor because of her symptoms. The patient was transferred to the Pusan National University Hospital (Busan, Korea) and evaluated by an orthopedic surgery team (Fig. 1). The decision was made to proceed with the surgical intervention. During the evaluation, she was referred to the gynecology oncology unit for further workup after a computed tomography (CT) scan revealed a significant endometrial mass suspected to be EC. Magnetic resonance imaging (MRI) of the pelvis revealed a 6.7-cm-sized endometrial mass with restricted diffusion, myometrial invasion of <1/2, and bilateral polycystic ovaries. She had been receiving antihypertensive drugs for two years but had recently stopped taking them because she experienced hypotension caused by the drug. Her family history included hypertension in her father and elder brother. Endometrial pipelle sampling revealed FIGO grade 2 endometrioid adenocarcinoma. Positron emission tomography-CT showed no evidence of metastases.

Laboratory findings including fasting blood sugar, HbA1c, C-reactive protein and CA125 levels, were unremarkable. First, the patient underwent open reduction and internal fixation involving screw fixation for a right ankle syndesmosis injury, distal fibular fracture, and ankle posterior malleolar fracture. The postoperative follow-up showed successful healing and functional recovery (Fig. 1). A total of 4 weeks later, robot-assisted total hysterectomy, bilateral salpingectomy and sentinel lymph node sampling were performed. Final pathology revealed stage 1B, grade 2 endometrioid adenocarcinoma with substantial lymphovascular space invasion (LVSI) (Fig. 2). Regional lymph node involvement was not identified. The peritoneal fluid cytology was negative for malignant cells. Immunohistochemistry staining revealed



Figure 1. Radiological findings. (A and B) Preoperative AP and lateral X-ray view of the patient's right ankle showing a distal fibular fracture and a posterior malleolar fracture. (C and D) Postoperative AP and lateral X-ray view of the right ankle fracture treated with a plate and screws showing good bony healing. AP, anteroposterior.

p53 (-), MLH1 (+), PMS2 (+), MSH-2 (+) and MSH-6 (+). The patient received 50.4 Gy external beam radiotherapy (EBRT) to the whole pelvis. Chest and abdominopelvic imaging (CT or MRI) were checked every 6 months. The 26-month postoperative follow-up showed that the patient was disease-free. The present study was reviewed and approved by the Institutional Review Board of Pusan National University Hospital (approval no. 2404-017-138; Busan, Korea). Written informed consent was obtained from the patient for publication of data of her medical case and associated images.

Discussion

Obesity and obesity-related diseases present a major global health challenge associated with several major chronic illnesses, including diabetes mellitus, cardiovascular disease and several common cancers (10). A total of ~4-8% of all cancers are attributed to obesity (11). The rising incidence of EC is largely attributable to rising rates of obesity in developed countries. The underlying mechanisms of obesity-associated cancer are complex and incompletely understood. Endoplasmic reticulum stress, macrophage infiltration and polarization, hypoxia-induced inflammatory signaling, direct immune system activation, and free fatty acid-Toll-like receptor signaling have been suggested as the causative factors (12).

Up to 1/3 of women of reproductive age experience HMB. Iron deficiency anemia associated with HMB is a common problem that remains underdiagnosed and undertreated, and the consequences of anemia are beyond the scope of gynecology. Common symptoms include fatigue, weakness, irritability, poor concentration, shortness of breath, headache, hair loss,

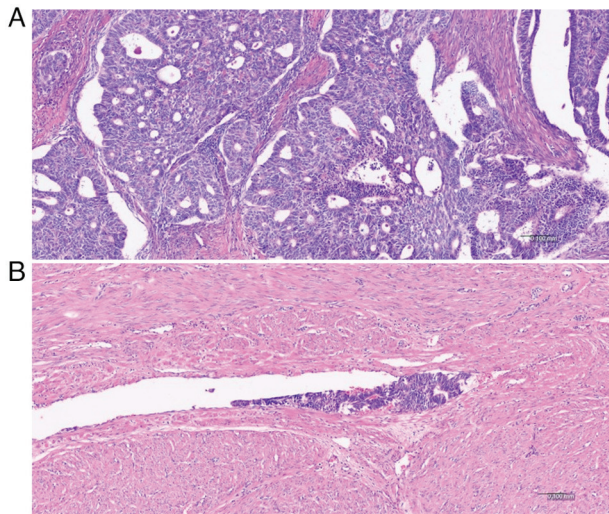


Figure 2. Microscopic findings. (A) The tumor exhibited endometrioid differentiation with focally solid non-squamous growth pattern (H&E stain, x100 magnification). (B) Lymphovascular invasion was present (H&E stain, x100 magnification).

brittle nails, cold intolerance and restless legs syndrome. EC is mainly diagnosed at an early stage confined to the uterus, and women must seek medical attention for early symptoms, such as AUB. HMB is frequently underreported, and a relevant number of women are unaware of the condition because 46% have never consulted a doctor for HMB symptoms (13). HMB is a clinical entity with different underlying structural and non-structural causes. Some causes of HMB are endometrial precursors to cancer (14). EC presents primarily with gynecological symptoms, but the patient of the present case report visited the hospital due to orthopedic problems despite having troublesome gynecologic complaints such as HMB, dizziness and headache after menstruation, necessitating treatment. Numerous women of reproductive age may not perceive AUB as a significant health concern and frequently normalize its symptoms. The presence of menorrhagia and anemia in high-risk populations requires further investigation to ensure that pathology is not missed. A comprehensive history should be received and additional investigations ordered. Increasing BMI levels are directly correlated with a proportional increase in EC risk, underscoring the potential significance of weight management interventions in EC prevention strategies. Preventative approaches such as intrauterine device with progestogen (for example Mirena) may help reduce disease burden in those identified at higher risk. In addition, interventions directed at weight reduction are an important component of the survivorship care of overweight patients with cancer. Lifestyle interventions that include diet, exercise and behavior therapy are the primary elements of weight reducing strategies (11). She was found to be severely anemic, with a hemoglobin level of 4.9 g/dl. She may have been reluctant to visit the gynecological clinic because she had no coital history and did not know what gynecological conditions could cause her risk factors.

Several risk factors for EC have been established, including excess body weight (BMI >30 kg/m²), polycystic ovarian syndrome (PCOS), nulliparity, early menarche, late

menopause, low physical activity, diabetes mellitus and the use of unopposed hormone replacement therapy (9). These conditions are considered to contribute to unopposed estrogen exposure. As in this case, EC should be suspected in a patient with severe anemia and HMB, particularly if she has risk factors for EC such as obesity, hypertension and irregular cycles due to PCOS.

The global burden of obesity is well represented in World Health Organization data. In 2016, ~13% of the global adult population was obese, with a higher prevalence among women (15%) than among men (11%) (15). Regarding the Korean population in 2021, data suggest a 38.45% obesity prevalence in adults (49.2% in men and 27.8% in women) (3). An excess BMI is a risk factor for several major types of cancer, including breast (postmenopausal), endometrial, colorectal and kidney (11). Korean data show that women with metabolic syndrome, especially premenopausal women with abdominal obesity, are at high risk of developing EC (5).

The role of obesity in the etiology and carcinogenesis of EC has been reviewed (12). Increasing BMI is directly correlated with a proportional increase in the risk of EC. Obesity causes chronic inflammation through a multifactorial process, and this chronic inflammatory state contributes to the development of various obesity-associated comorbidities such as EC.

PCOS is the most common endocrine disorder in women of reproductive-age. This disorder is associated with chronic anovulation and unopposed estrogen exposure, which can lead to EC. Additionally, higher insulin levels in women with PCOS can increase the risk of developing EC. The risk of EC is 2-6-fold higher in women with PCOS (16). The association between PCOS and EC is complex and multi-faceted. However, the association between PCOS and EC remains inconclusive. It has been previously reported that women with obesity are at risk of AUB and PCOS caused by insulin resistance and elevated unopposed estrogens, increasing the risk of EC (17). Others have reported that the risk may be due to age or endometrial thickness rather than a direct effect of PCOS on the development of the disease (16). Routine screening for EC in PCOS is not indicated, despite the recommendation that women with PCOS are at risk of EC and should be monitored closely. The risk factors for EC include obesity, long-term use of unopposed estrogen, family history of EC, prolonged amenorrhea and AUB. In this case, bilateral polycystic ovaries were observed on MRI, but the patient was unaware of this because she had never visited the hospital before.

The prevalence of hypertension, another component of metabolic syndrome, is also increasing, and emerging evidence suggests that it may be associated with the development of certain cancers, mainly through inflammatory, hormonal and metabolic pathways (18). However, the role of hypertension as an independent risk factor for EC remains unclear. Obesity and diabetes are important risk factors of hypertension and EC. Therefore, it is unclear whether these factors confounded the association between hypertension and EC because certain studies did not adjust for BMI or diabetes (9). A recent study reported that hypertension was associated with a 14% increased risk of EC, independent of known risk factors, such as BMI, diabetes and reproductive factors (19). A previous systematic review and meta-analysis suggested that women with hypertension might have a 61% increase in

the relative risk of developing EC (9). The inconsistencies in the risk among studies may be explained by the fact that the meta-analysis included effect estimates from studies that did not adjust for all known risk factors for EC, particularly BMI. In the present case, the patient was known to have hypertension under treatment, with no other comorbidities. Her family history included hypertension in her father and elder brother. In this case, obesity (BMI, 36.2 kg/m²) contributed most significantly to the EC, with some contribution from PCOS and hypertension.

EC has disproportionately increased in adults aged ≤50 years and has become a major public health problem (20). The faster increase in EOEC was possibly linked to the rising obesity epidemic in younger women and also coincides with the observations of broader increases in cancer among younger adults (21,22). Fertility-sparing treatment for carefully selected patients with low-stage EC is a possible therapeutic option for premenopausal women desiring to preserve fertility. There is insufficient experience to support the recommendation of fertility-sparing therapy for higher-grade tumors (grade 2-3) (23). In the present case, the disease was stage 1B, grade 2 endometrioid adenocarcinoma with lymphovascular space invasion. No fertility-sparing management was performed. Instead, total hysterectomy, bilateral salpingectomy and sentinel lymph node sampling were performed, and postoperative radiation was administered.

EC can present in an atypical fashion with non-gynecologic symptoms, such as angina and pancytopenia (6), singular bone metastasis (24), or solitary adrenal metastases (25). Therefore, receiving careful history is needed not only for gynecological symptoms but also for non-gynecologic symptoms. EC is an important differential condition in obese patients with AUB. In addition, endometrial sampling should be considered in individuals <45 years of age with AUB if there are other risk factors for EC, as well as in any patient with a BMI >30 or persistent AUB (6).

Lifetime incidence of EC among the risk factors as in the present case, class 2 obesity (BMI ≥35 and <40 kg/m²), premenopausal PCOS and premenopausal AUB is 9, 4 and 0.3%, respectively. In this premenopausal period, the low incidence of EC entails frequent diagnostic delays. EC should be considered in premenopausal women with AUB, particularly those with obesity, PCOS, a strong family history or other risk factors (26). EC is overwhelmingly a disease of postmenopausal women, with >90% occurring in women >50 years old; however, increasing rates of obesity may lead to a rise in the proportion of premenopausal cases. Early screening for EC in obese women with AUB or other risk factors could detect the disease in the pre-invasive or early stage (before developing myometrial invasion), which would improve cure rates, reduce the morbidity associated with aggressive treatment and offer fertility-sparing management options for younger women (27).

There has been marked discussion over the adjuvant treatment of this high-intermediate risk group of patients which includes those with stage IA and IB disease with substantial LVSI (such as the present case), stage IB G3 and stage II G1 disease with substantial LVSI and stage II G2-G3 (dMMR or NSMP) disease: i) Adjuvant EBRT is recommended in NCCN and ESMO guidelines; ii) Adding (concomitant and/or sequential) chemotherapy to EBRT could be considered, especially

for G3 and/or substantial LVSI. The high incidence of short- and long-term side-effects associated with the addition of chemotherapy to EBRT, whilst conferring minimal benefit, needed to be discussed with these patients; iii) Despite evidence of a benefit from adjuvant treatment, its omission is an option, when close follow-up can be ensured, following shared decision making with the patient (28).

Surveillance can be adjusted according to the risk factors of the patient. No consensus on what surveillance tests should be carried out. In the high-risk groups, physical and gynecological examinations are recommended every 3 months for the first 3 years, and then every 6 months until 5 years. Imaging should be guided by patient symptoms, risk assessment and clinical concern for recurrent disease. As CT scans detect only 15% of recurrences, routine use is not advocated. Nevertheless, it could be considered in the high-risk group (for example, every 6 months the first 3 years and then on an individual basis) (28).

Obesity is associated with low quality of life and physical function. In terms of long-term management, lifestyle interventions may improve fatigue, physical functioning and result in weight loss and psycho-educational program could improve mood disorders and sexuality complaints. Long-term management requires careful attention to metabolic variables, including weight control. Regular exercise, healthy diet and weight management should be promoted with all EC survivors (28).

In summary, the patient was in the high-risk group for EC. She had several risk factors for EC, such as obesity, high blood pressure and PCOS, indicating that these risk factors caused EC. However, she had never visited a gynecological clinic prior to the diagnosis of EC. She was relatively young, therefore, she did not consider this possibility. This case highlights the importance of assessing gynecological conditions through a detailed review of the patient's gynecological history, with caution when an obese female patient presents with AUB, even during a non-gynecologic assessment.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HJY, YJS, DSS and KHK made substantial contributions to the conception and design of the study, acquisition of data, and analysis and interpretation of data. TSG and KBK contributed to data interpretation and confirm the authenticity of all the raw data. HJY, YJS, DSS and KHK contributed to data acquisition, conception, and reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was reviewed and approved by the Institutional Review Board of Pusan National University Hospital (approval no. 2404-017-138; Busan, Korea).

Patient consent for publication

Written informed consent was obtained from the patient for publication of data of her medical case and all associated images.

Competing interests

The authors declare that they have no competing interests.

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