



Case Report

Enterouterine Fistula as Initial Presentation of Advanced Endometrial Cancer: Description of a Rare Case and Review of the Literature

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Abstract

Endometrial cancer is the most common gynecological malignancy, and it usually presents with abnormal uterine bleeding as initial symptom. Cases of advanced endometrial cancer with uncommon symptoms at presentation are reported in the literature but, to our knowledge, no case of an enterouterine fistula as the initial presentation of the disease has been previously described.

We report the case of a 54-year-old woman, with a 2-month history of permanent vaginal discharge of partly non-digested stool masses due to an enterouterine fistula that was the initial presentation of an advanced endometrial cancer. Interestingly, in this case, not all the preoperative exams (CT, colonoscopy and hysteroscopy) identified the fistulous openings, and the enterouterine fistula was confirmed only at the time of surgery.

Keywords

Endometrial cancer; Enterouterine fistula; Vaginal discharge; Advanced cancer; Uterine cancer

Introduction

Endometrial cancer is the most common gynecological malignancy and, globally, it represents the sixth most common cancer in women [1].

Endometrial cancer can be categorized broadly into two types that differ in epidemiology, genetics, prognosis and treatment [2]. Type I (endometrioid adenocarcinoma) is the most common histologic type of endometrial cancer, accounting for 80-90% of cases; it is usually oestrogen dependent, with a generally good prognosis [3]. Most cases of type I cancer are low grade and confined to the uterus when diagnosed [2]. Type II endometrial cancer (clear cell, papillary, serous, undifferentiated) is not oestrogen-related, usually presents at a later stage (with a significant risk of extrauterine disease), behaves more aggressively and carries a poorer prognosis [3].

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Abnormal uterine bleeding (including irregular menses, intermenstrual bleeding and postmenopausal bleeding) is the most common initial symptom for both type I and type II endometrial cancer, and leads to diagnosis in approximately 90% of cases [4]. Patients who have an advanced disease may have symptoms similar to those seen with advanced ovarian cancer, such as abdominal or pelvic pain, abdominal distention, bloating, early satiety, and change in bowel or bladder function [2].

Cases of advanced endometrial cancers with uncommon clinical manifestations at presentation (such as primary bone metastasis) are reported in the literature [3,5]. However, to our knowledge, no case of an enterouterine fistula as the initial presentation of endometrial cancer has been previously described.

Case Presentation

We report the case of a 54 years old woman diagnosed with an enterouterine fistula as the initial presentation of an advanced endometrial cancer.

The woman presented to our Institution in February 2011 with a 2-month history of continuous, but mild, dull aching abdominal pain and permanent vaginal discharge of partly non-digested stool masses. She referred no other symptoms and was apparently healthy; however, she referred cardiac arrhythmia and an episode of acute myocardial infarction in 2009. Moreover, she underwent neurosurgery for a cerebral aneurysm in 1996. No other comorbidities were referred. In particular, the woman went through menopause at 50 years old, and no abnormal uterine bleeding was referred. The patient had performed regular pap tests every 3 years (the last one in the 2009), with negative results.

The gynecological examination revealed normal cervix and vagina, but a huge, non-tender pelvic mass apparently involving both the uterus and the adnexa was found. This mass reached the transverse umbilical line and was slightly mobile. Moreover, no parametrial infiltration was found at the pelvic side-wall through inspection and palpation. After positioning the vaginal speculum, the stool discharge was observed to come from the cervical os, and no enterovaginal fistula was detected. The transvaginal and transabdominal ultrasound scans revealed a huge pelvic mass of about 16 cm, with dishomogeneous ultrasound appearance, apparently involving both the uterus and the adnexa. In particular, the uterus was enlarged, and the limits of the fundus were not clearly definable. A thickened, dishomogeneous, endometrium (48 mm) was detected; the endometrium-miometrial junction was not clearly definable, and apparently interrupted in the fundal zone.

Subsequently, a thoracic and abdominal computed tomography (CT) scan with contrast was performed, revealing the presence of a huge, solid and partially dishomogeneous mass of 16 × 15 × 15 cm, involving the uterus and the adnexa, with multiple little air bubbles in the context. The endometrium appeared thickened and dishomogeneous, but the boundaries of the endometrial layer were not clearly definable. The pelvic mass was close to both the ileum and the sigmoid colon, apparently without a cleavage. A moderate small bowel distension was detected, but the CT scan did not identify any enterouterine fistula. No other pathologic findings emerged on CT: in particular, no lesion was found in the liver, lungs and retroperitoneum.

In this patient, the magnetic resonance (MR) was contraindicated because of the presence of incompatible surgical clips used for previous surgical treatment of a cerebral aneurysm.

Subsequently, a colonoscopy was performed and an *ab estrinseco* compression of the descending colon, near the left colonic flexure, was observed. No mucosal abnormalities or other pathological findings were found; in particular, no fistulous openings were detected.

A diagnostic hysteroscopy was then performed. The visualization of the endometrial cavity was suboptimal because of the stool discharge. However, a huge exophytic mass, dishomogeneous and cerebroid in appearance and partially necrotized, was observed and cautiously biopsied. No fistulous opening was detected by hysteroscopy. The histological examination of such a biopsy revealed a poorly differentiated adenocarcinoma of the endometrium. Thus, considering both the diagnosis of advanced endometrial cancer (without distant metastasis on CT) and the suspect of enterouterine fistula, we opted for surgery.

A laparotomy with usual xipho-pubic midline incision was performed and a huge mass of about 15-20 cm involving the uterus, the adnexa and multiple intestinal loops was observed. Small bowel loops were found to be densely adherent to the fundus of the uterus, and multiple fistulous openings involving the ileum, ascending and transverse colon were seen on the uterine fundus. The endometrial mass, partially necrotized, reached the serosal surface of the uterus on the fundus, near the fistulous openings, and the adjacent intestinal loops appeared macroscopically involved by the neoplasia. An “*en bloc*” radical hysterectomy with bilateral adnexectomy and colorectal resection was performed. More specifically, a right hemicolectomy with partial resection of the transverse colon and resection of the ileum was necessary. Even part of the sigma, involved in the enterouterine fistula, was resected, as well as bulky peri-intestinal lymph nodes. A functional end-to-end ileocolonic anastomosis was performed with a circular stapler (Proximate, CDH29; Ethicon Endo-Surgery, Cincinnati, Ohio) and, because of the resection of part of the sigma, a temporary descending colostomy was necessary.

The “*en bloc*” removed specimen including the uterus, the adnexa and the adjacent intestinal loops involved in the enterouterine fistulas is shown in [Figure 1](#).

The histopathological examination of the surgical specimen ([Figure 2](#)) showed a mixed carcinoma of the endometrium (according to 2014 WHO classification) [6], composed of clear cell and serous adenocarcinoma (about 10% of all neoplastic tissue) and of high - grade endometrioid adenocarcinoma with squamous differentiation ([Figure 2A, 2B](#)). The tumor infiltrated the entire uterine wall, including the serosa and showed diffuse lymphovascular space invasion, with neoplastic emboli mainly composed of the squamous component of the tumor. Both the small and large intestinal wall were massively infiltrated by neoplastic cells ([Figure 2F](#)), with ulceration of the mucosa. Metastases were microscopically detected in 2 out of 3 peri-intestinal bulky lymph nodes. Final pathological staging was pT4 Nx M1 (LYM) according to the pTNM criteria [7]. 2.5-micron sections were cut from formalin-fixed paraffin embedded tissue of representative tumor sections, and immunohistochemical analysis was performed in an automated system (Benchmark-XT, Ventana, Tucson, AZ, US). Neoplastic cells showed immunoreactivity for Cytocheratin7 (with a less intense staining in the squamous areas - [Figure 2C](#)), Estrogen receptors ([Figure 2D](#)) and Progesterone receptors; whereas, they were completely negative for Cytocheratin 20, CDX2, TTF1, p63

and p40. Only a few isolated adenocarcinomatous cells of the serous component were found positive for p53 ([Figure 2E](#)) and p16 (<5%). This nearly complete absence of p53 by immunohistochemistry was interpreted as indicative of Tp53 mutations, as nonsense or frameshift mutations in p53 can result in a protein that is undetectable by immunohistochemistry [8].

After the surgical procedure, the patient underwent chemotherapy with 9 cycles of carboplatin. At the subsequent follow up visits with CT scans, a complete remission of the disease was observed.

In September 2013, the patient underwent another surgical procedure to restore the intestinal integrity; after a further resection of stenotic sigma, an end-to-end colorectal anastomosis was performed with a circular stapler (Proximate, CDH29; Ethicon Endo-Surgery, Cincinnati, Ohio).

The subsequent follow up visits with CT scans (the last one performed on June 2016) were negative, and a complete remission of the disease was achieved. Furthermore, a normal intestinal function and canalization was reported.

A written consent was obtained from the patient to describe the clinical case and to publish pertinent images.

Discussion

A fistula is an abnormal connection or passageway between organs or vessels that normally do not connect [9]. An intestinal fistula is a relatively common complication of patients with chronic inflammatory diseases of the bowel, such as diverticulitis and Crohn’s disease; in particular, an estimated 5% to 15% of Crohn patients and up to 20% of patients with diverticulitis, will experience this disease-related complication during their lifetime [9,10]. In patients with chronic inflammatory diseases of the bowel, enteroenteric, enterocolonic, enterovaginal and perianal fistulas are the most commonly observed, while other types of fistulas, such as enterocutaneous or enterourinary are relatively uncommon [10]. In particular, enterouterine fistulas are extremely rare because of the thickness of the myometrium [11].

To our knowledge, only a few cases of enterouterine fistula have been previously reported, but in no case did the enterouterine fistula represent the first clinical sign of endometrial malignancy. Noecker was the first to report a colo-uterine fistula in 1929 [12] and after



Figure 1: Surgical specimen including the uterus, the adnexa and the adjacent intestinal loops involved in the enterouterine fistulas.

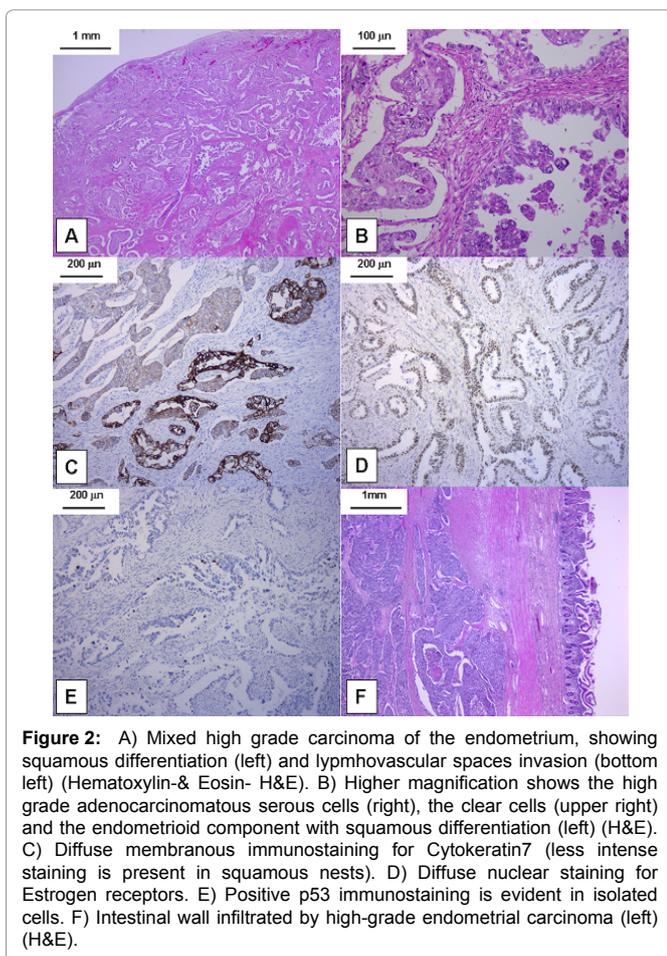


Figure 2: A) Mixed high grade carcinoma of the endometrium, showing squamous differentiation (left) and lymphovascular spaces invasion (bottom left) (Hematoxylin- & Eosin- H&E). B) Higher magnification shows the high grade adenocarcinomatous serous cells (right), the clear cells (upper right) and the endometrioid component with squamous differentiation (left) (H&E). C) Diffuse membranous immunostaining for Cytokeratin7 (less intense staining is present in squamous nests). D) Diffuse nuclear staining for Estrogen receptors. E) Positive p53 immunostaining is evident in isolated cells. F) Intestinal wall infiltrated by high-grade endometrial carcinoma (left) (H&E).

him, other authors reported a few cases of enterouterine fistulas in patients with diverticulitis or Crohn's disease [13-23]. Furthermore, enterouterine fistulas have been described as rare complications of curettage procedures by some authors [24,25].

The largest review of enterouterine fistulas was published in 1956 by Martin and colleagues [26] which described 80 cases; among them, 42 cases followed obstetric injury, 17 resulted from bowel inflammatory processes, 12 following curettage, and 9 related to advanced carcinoma (however, none of these cases described the enterouterine fistula as the first symptom of cancer).

In 2006, Eichbaum et al. [27] reported the most recent case of an enterouterine fistula related to advanced endometrial cancer. However, in the reported case, the initial symptom of the cancer was, as usual, an abnormal uterine bleeding, while the vaginal discharge due to the enterouterine fistula appeared 3 months after the radiotherapy.

To our knowledge, we reported the first case of an advanced endometrial cancer with an enterouterine fistula (and consequent stool vaginal discharge) as the first clinical sign. Interestingly, the preoperative examinations (abdominal CT, colonoscopy and hysteroscopy) were not able to detect the fistulous openings, while MR was contraindicated for our patient.

Sometimes, imaging techniques such as CT or MR have been used to diagnose an enterouterine fistula [9,28] as well as hysteroscopy [9]. However, our case demonstrates that such techniques are not

always able to determine a correct diagnosis. Therefore, the diagnosis of an enterouterine fistula is sometimes difficult. This condition can be suspected on clinical findings, and explorative laparotomy is always necessary, both for diagnosis confirmation and treatment. Moreover, in the present case, we opted for surgery also because of the histopathological diagnosis of high grade endometrial cancer. As recommended by the current guidelines [2,28], even in case of advanced disease, the maximum surgical effort has to be provided in order to remove all the visible disease. Indeed, optimal surgical cytoreduction (variably defined as less than or equal to 1 cm or 2 cm) has been found to improve progression-free and overall survival rates in patients with advanced stage or recurrent endometrial cancer [2,29,30].

Conclusion

An enterouterine fistula is exceptionally rare, but should be taken into account on clinical examination. The diagnosis of such a condition can be a difficult challenge, due to the inaccuracy of standard imaging techniques such as CT. Sometimes the enterouterine fistula and the subsequent stool vaginal discharge can represent the outset of a locally advanced uterine cancer.

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