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Hereditary endometrial cancer: a case report

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Summary

Introduction: Endometrial cancer (EC) is one of the commonest malignancies of the female reproductive tract. In recent years, the heredity and familial clustering of EC has been described by researchers, but few cases are reported from China. *Cases Report:* A 50-years-old Chinese women presented with irregular vagina bleeding for more than 20 days.The clinical impression was EC and she was treated by surgery and chemotherapy. Four years later, her mother and two sisters were also diagnosed with EC in the same hospital. The authors therefore summarized the case profiles of this family to learn more about familial hereditary EC. *Conclusion:* The authors present four cases of hereditary EC from one family pedigree. For individuals who have a family history of EC, it is necessary to promote molecular genetic test and gynecological screening for early detection and prevention.

Key words: Endometrial cancer (EC); Heredity and familial clustering; Genetic testing.

Introduction

Endometrial cancer (EC) is one of the commonest malignancies of the female reproductive tract with an increasing high incidence. Some of the risk factors for EC have been identified by epidemiologic studies, such as postmenopausal status, obesity, and exogenous estrogen use [1]. However, it has been suggested that a family history of EC was an independent risk factor for EC alone [2], women carrying a germline mutation have a higher possibility to develop EC, therefore the heredity and familial clustering of EC remain an issue to be further discussed. The total number of EC patients admitted in the present hospital was 4,120 during the last decade (from January 2006 to December 2016), while only one case observed was characterised by family clustering, as three of the patient's relatives were also diagnosed EC afterwards. It is highly likely that the clinical case of hereditary EC is under-reported to some extent due to the difficulty in tracing and follow-up. Here the authors report four cases of EC from one family who was admitted consecutively in the present hospital from May 2011 to July 2015.

Case Report

The propositus was a 50-year-old Chinese women (150 cm, 46 kg, BMI 20.4), gravida 6, para 2, complaining of irregular vagina bleeding for more than 20 days. Before the onset she had regular menses. On pelvic examination, no abnormal sign was detected in vulva and vagina, the cervix was smooth and hypertrophic, the uterus was tender, motile, normal in size, and in the posterior position. No thickness and nodules were palpated in the adnexal area. A pelvic sonogram showed that the uterus had a size of 3.9×5.1×4.4 cm, the endometrium strip measured 0.3 cm, and a 2.7×2.3×2.5-cm mass was detected in the right adnexus. The endometrial diagnostic curettage revealed complex hyperplasia with atypical hyperplasia and muti-focus carcinogenesis. The clinical diagnosis of this case was "EC". Total hysterectomy and bilateral salpingo-oophorectomy (TAHBSO), combined with pelvic lymphadenectomy, omentectomy, and appendectomy were performed. As seen in the surgery, the uterus was normal in size and unremarkable except for an erosion of 1×1 cm in the left cornua uteri. The right ovary was normal in size, but the texture was rotten and fragile. The left ovary appeared normal anatomically. Postoperative pathological findings demonstrated simple and complex hyperplasia, accompanied by atypical hyperplasia and multi-focus carcinogenesis in the uterus without myometrial invasion. Endometrioid adenocarcinoma was found in the right ovary. The patient was given six courses of taxol + carboplatin (TP) chemo- therapy after surgery, and was regularly followed up after discharge, she was unremarkable thereafter and presently alive.

Four years later, three relatives of the propositus (mother and two sisters) were diagnosed with EC and admitted to the present hospital within the same year. The family pedigree is shown in Figure 1. The clinical characteristics of all four cases in this family are summarized in Table 1.

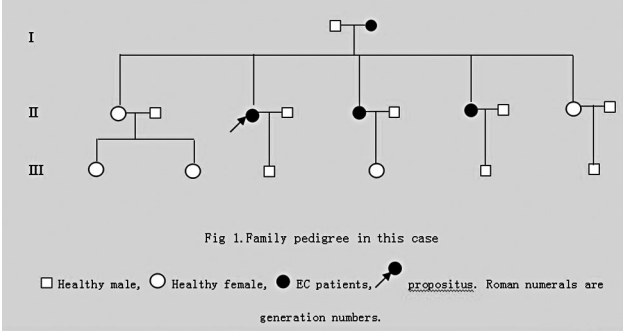

Figure 1. — Family pedigree in this case

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Table 1. — *Clinical characteristics of EC patients of this family.*

	Propositus	**Her mother**	**Her sister A**	**Her sister B**
Age (years)	50	75	46	44
History of pregnancy	2	5	1	2
Age of first sex (years)	20	19	20	25
Menarche age (years)	14	13	13	15
BMI (kg/m^2)	21.4	19.02	21.9	20.44
Menstrual history	Normal	Normal	Normal	Normal
Chief complaint	Irregular vagina bleeding.	Postmenopausal vagina bleeding.	Physical examination	Irregular vagina bleeding.
Preoperative diagnostic curettage	Endometrial atypical hyperplasia accompanied by muti-focus carcinogenesis.	Endometrial mixed adenocarcinoma (serous adenocarcinoma and carcinosarcoma).	Endometrial atypical hyperplasia accompanied by muti-focus carcinogenesis, well-differentiated endometrial carcinoma	Endometrial serous papillary adenocarcinoma with clear cell carcinoma differentiation.
Uterus in surgery	Normal size, 1×1c m erosion was found in the left cornua uteri.	Atrophic uterus with rotten and fragile endometrium, intrumural invasion >1/2.	Enlarged uterus similar to 40+ days of getation, 1×1 cm cauliflower-like neoplasm was found in the left cornua uteri.	Normal size, the endometrium appeared normal anatomically.
Adnexus in surgery	The right ovary was normal in size, rotten, and fragile. The right fallopian tube and left and adnexus was anatomically normal.	Atrophic bilateral adnexus, appeared normal anatomically.	Unremarkable from the appearance.	Unremarkable from the appearance.
Surgical procedures	TAHBSO + pelvic lymphadenectomy + omentectomy + appendectomy.	TAHBSO + pelvic lymphadenectomy.	Laparoscopic hysterectomy + bilateral salpingo-oophorectomy.	Laparoscopic extrafascial hysterectomy + bilateral salpingo-oophorectomy + pelvic lymphadenectomy + omentectomy + para-aortic lymph node biopsy.
Pathological findings	Simple, complex hyperplasia with atypical hyperplasia and multi-focus carcinogenesis was found in the endometrium without myometrial invasion. Endometriod adenocarcinoma was detected in the right ovary. No pelvic lymph node metastases.	Poorly-differentiated endometrial adenocarcinoma with squamatization. Cancer embolus was found in adjacent vascular, with myometrial invasion >1/2. No implication of cervical invasion and pelvic lymph node metastases.	Complex and atypical endometrial hyperplasia with multi-focus carcinogenesis,well- differentiated endometriod adenocarcinoma, myometrial invasion <1/2. No implication of cervical invasion and pelvic lymph node metastases.	Papillary serous endometrial cancer was found in the uterus; myometrial invasion <1/2. No implication of cervical and pelvic invasion.
Chemotherapy	TP	TP	TP	TP
Courses	6	6	6	6
Survival time until present (months)	63	14	13	14

Four EC cases were found in this family; all of them had regular menses, and they all denied history of hypertension, diabetes mellitus, other cancer, and estrogen intake. As summarized in Table 1, the onset age of the four cases in this pedigree was 44-75 years, with a mean age of 52.5 years. The onset of three cases (sisters) were premenopausal, and one case (mother) was postmenopausal.The chief complain of two cases was irregular vagina bleeding, one was postmenopausal vagina bleeding, and the other was detected in physical examination. Preoperative diagnostic curettage of two cases revealed simple hyperplasia with atypical hyperplasia, and multi-focus carcinogenesis. One case showed mixed endometrial adenocarcinoma, and the other demonstrated

endometrial serous papillary adenocarcinoma with clear cell carcinoma differentiation. All four cases had undergone surgery followed by TP chemotherapy and were regularly followed up after discharge. They are all presently alive with no recurrence.

Discussion

EC is one of the commonest gynecological malignant neoplasms, accounting for about 7% of all female malignancies. Obesity, delayed menopause, long-term anovulation, and estrogen replacement therapy are regarded as high risk factors of EC. Obesity, hypertension, and diabetes are considered as typical triad related to EC. Among all the EC patients, 3% are associated with hereditary nonpolyposis colorectal cancer (HNPCC)[3]. The familial heredity and clustering of EC has been increasingly recognized in recent years.

Familial endometrial adenocarcinoma has been defined by Kuliev *et al.* [4], that report to at least three EC affected patients in two successive generations of one pedigree, and at least one case diagnosed before the age of 50 years. In this present family pedigree the authors studied, four first-degree relatives were affected (mother and sister), and three cases had an onset age before 50 years, therefore consistent with the site-specific endometrial adenocarcinoma syndrome described by Kuliev *et al.*. None of the cases had a history of diabetes mellitus, hypertension and obesity (BMI < 22). Currently the familial endometrial adenocarcinoma has been considered as an autosomal dominant inherited disease, induced by mutations of the DNA mismatch repair (MMR) genes [5]. Similar to tumor-suppressor gene, the inactivation of MMR follows the "double hit" phenomenon, i.e. the hereditary defects caused by germline mutation in one of several MMR (MLH 1, MSH 2, MSH 6, and PMS 2) are directly involved in carcinogenesis. Roupret *et al.* revealed that 80-90% of hereditary EC patients were associated with germline mutation in MLH1 and MSH2. Parc *et al.* assessed 62 women affected with EC for microsatellite instability (MSI), and found a higher incidence of mutation in hMLH1 compared with hMSH2 [6].

It has been reported that the mean age of hereditary EC at diagnosis was 45 years, the onset age of about 80% EC patients was 50 years, women with a family history of EC had a higher incidence of EC, but better prognosis compared with sporadic EC patients [7]. In the present family, three sisters were diagnosed EC before 50 years. Since hereditary ECs are characterized by early onset age and high incidence, it has been suggested by Kwon *et al.* that women with a family history of EC should be screened by transvaginal ultrasonography and endometrial biopsy, from 30 yeas of age. Whether to adopt preventive surgery for high-risk women above 40 years of age still remains a debate [8].

In this study, the authors present four cases of hereditary EC from one family pedigree, which were discovered in a total of 4,120 EC cases admitted in the present hospital during the last decade. Although China has the largest population of the world, few cases of familial EC have been reported. It is very likely that the incidence of hereditary EC in China has been underestimated, partly because the molecular genetic detection is not fully-utilized, and the patient follow-up system has not been well established. For individuals who have a genetic predisposition of EC, it is necessary to promote genetic diagnosis and gynecological screening for early detection and prevention.

References

[1] Purdie D.M., Green A.C.: "Epidemiology of endometrial cancer". *Best Pract. Res. Clin. Obstet. Gynaecol.*, 2001, *15*, 341.

[2] Gruber S.B., Thompson W.D.: "A population-based study of endometrial cancer and familial risk in younger women". *Cancer Epidemiol. Biomarkers Prev.*, 1996, *5*, 411.

[3] Liu H., Zhao Y.: "Research Progress of Hereditary Endometrial Carcinoma. Maternal and Child Health Care of China. 2015; 30: 972-4.

[4] Kuliev A, Verlinsky Y. The role of preimplantation genetic diagnosis in women of advanced reproductive age". *Curr. Opin. Obstet. Gynecol.*, 2003, *15*, 233.

[5] Rouprêt M., Yates D.R., Comperat E., Cussenot O.:" Upper urinary tract urothelial cell carcinomas and other urological malignancies involved in the hereditary nonpolyposis colorectal cancer (Lynch syndrome) tumor spectrum". *Eur. Urol.*, 2008, *54*, 1226.

[6] Parc Y.R., Halling K.C., Burgart L.J., McDonnell S.K., Schaid D.J., Thibodeau S.N., *et al.*: "Microsatellite instability and hMLH1/hMSH2 expression in young endometrial carcinoma patients: associations with family history and histopathology". *Int. J. Cancer*, 2000, *86*, 60.

[7] Lynch H.T., Smyrk T.C., Watson P., Lanspa S.J., Lynch J.F., Lynch P.M., et al.: "Genetics, natural history, tumor spectrum, and pathology of hereditary nonpolyposis colorectal cancer: an updated review". *Gastroenterology*, 1993, *104*, 1535.

[8] Kwon J.S., Sun C.C., Peterson S.K., White K.G., Daniels M.S., Boyd-Rogers S.G., *et al.*: "Cost-effectiveness analysis of prevention strategies for gynecologic cancers in Lynch syndrome". *Cancer*, 2008, *113*, 326.

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