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Clinico-pathological aspects of vanishing endometrial cancer

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Abstract

Aims: To assess the prevalence, pre-operative findings, and clinical outcomes of endometrial cancer (EMC) patients who had vanishing cancer.

Methods: Patients who had pre-operative tissue diagnosis of EMC, and had surgical treatment including hysterectomy in the institution between 1995 and 2015 were identified. The patients who had no residual carcinoma in all pathologic specimens including the uterus were included. Pre-and post-operative clinico-pathological data were collected. Clinical outcomes including recurrence and survival of the patients were studied.

Results: Among 422 patients who had tissue diagnosis of endometrial cancer, twenty patients had no residual cancer in the hysterectomy specimens. Three patients who had pre-operative radiation therapy or had evidence of endometrial cancer outside the uterus were excluded, so 17 patients (3.8%) were diagnosed as having vanishing cancer. One of the 17 patients, who had pre-operative endometrioid endometrial cancer, had adjuvant chemotherapy for synchronous serous carcinoma of fallopian tube. From a follow-up period of 62.7 months (range, 6.8-184.4 months), no recurrences were found. Only 2 patients were dead of other diseases.

Conclusion: Patients with vanishing endometrial cancer had excellent prognosis. Adjuvant treatment may not be needed. However, periodic surveillance was still recommended because data were derived from only small number of patients.

Introduction

The majority of endometrial cancer (EMC) patients present with abnormal uterine bleeding. Primary investigations include physical including pelvic examination followed by ultrasonography. Tissue diagnosis is generally made by endometrial sampling biopsy or uterine curettage. When the diagnosis of EMC is made, the patients usually undergo total hysterectomy, bilateral salpingo-oophorectomy. Pelvic and para-aortic lymph node sampling are also performed in the presence of risk factors for extra-uterine spread [1]. Adjuvant therapy will be tailored according to the presence of clinico-pathological risk factors.

In clinical practice, it is not uncommon that the pathologic results from the hysterectomy specimens would be different from that of the endometrial tissue biopsy/ curettage [2,3]. Examples are the changes of tumor grading, histologic types, or finding of other histopathologic components [4,5]. An even less common phenomenon was the absence of the tumor in hysterectomy specimen of the patients diagnosed pre-operatively as EMC, so called 'vanishing carcinoma' [6].

An absence or resolution of cancer after a pre-operative radiation therapy or chemothreapy prior to surgery is not surprising. This finding will be regarded as a 'complete response' to the induction therapy. However, the disappearance of cancer after an initial diagnosis without any definite treatment, particularly without any evidence of disease elsewhere, would be unexpected.

The gynecologic oncologist/radiation oncologist dealing with a change in histopathology or grade usually consults the pathologist (s) who made the primary and the final reports. The consultation is to confirm the final diagnosis for an appropriate further management. This is especially important when no residual cancer is found after a pre-operative tissue sampling biopsy or curettage. If the EMC is still evidenced at other locations, a decision of further clinical management may not be a problem. However, a clinician may be uncertain regarding the need of adjuvant treatment when there was no extra-uterine disease particularly in those with aggressive cancer revealed from an initial diagnosis. From a pathological point of view, this event requires a thorough review of the primary section along with an additional sectioning of the hysterectomy specimens.

Some authors proposed criteria for a diagnosis of vanishing cancer: there was no residual tumor in the hysterectomy specimen, no prior treatment for cancer, and the diagnosis of EMC must be confirmed from a pathological review of pre-operative tissue [6]. There had been few case reports of vanishing cancer in prostate [7-9], thyroid [10], and endometrium [6,11-13]. Few underlying reasons had been proposed. Particular to the reports of vanishing EMC, different points of view were presented and some data were lacking.

This study aimed to assess the prevalence of vanishing EMC during the 20-year period in our institution which is a tertiary hospital for cancer care. The clinico-pathologic features of the patients including

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pre-operative findings, adjuvant treatment, and clinical outcomes were also studied.

Materials and methods

An approval by the Ethical Committees of the institution was obtained. The list of EMC patients who had treatment in the institution between 1995 and 2015 were identified in the database of Departments Obstetrics and Gynecology and Anatomical Pathology of the institution. Inclusion criteria were patients who: had pre-operative biopsy/curettage of endometrial tissue in the institution or elsewhere with a record of pathologic review or available slides for a re-review, had surgical treatment including hysterectomy, and had no evidence of residual carcinoma in the hysterectomy specimen. The patients who had any pre-operative treatment aside from tissue diagnostic biopsy or curettage and those who had evidences of cancer outside the hysterectomy specimens were excluded.

As a standard practice in the Department of Anatomical Pathology, data from the pathological request form were checked for the patient's identification including the patient's name, hospital number, types and number of the submitted specimens prior to the registration and pathological processing. Information of clinical data, operative findings, and prior pathologic reports were required in the request form. These data were re-checked by the pathologist and the technician before the gross examination and the sectioning process for histologic study.

For uterine cancer, grossly visible cancer in the hysterectomy specimen was sampling by a pathologist for a minimum of 3-5 sections for histopathologic examination. Any gross lesions in the myometrium, adnexa, and other organs were sectioned as appropriate, or else samplings of representative areas were taken. Sections at 2 to 3 mm intervals were taken for the embedding. Additional sampling was carried out when there were any problems in diagnosis, such as, inconsistent diagnoses of the pre-operative sampling tissue and hysterectomy specimens, mixed carcinomas, inadequate issue for a diagnosis, or no residual cancer in the uterus as well as other specimens.

Clinical and pathologic data collected were: age of the patient, sampling method, amount of tissue retrieved, histopatholgy and grade of EMC in both settings, interval between dates of pre-operative tissue sampling and surgery, details of surgical procedure, adjuvant therapy, disease status, and date of recurrence, death, or last follow-up.

Data were analyzed using SPSS 22.0 statistical software (IBM Corporation, Armonk, NY, USA). Descriptive statistics were used to analyze demographic data, and were summarized as numbers with percentage, mean with standard deviation or median with range.

Results

Among 422 EMC patients who had EMC diagnosis from pre-operative EMC tissues and underwent surgery in the institution during the study period, 20 had no residual tumor in the hysterectomy specimens. Three patients were excluded for having had radiation therapy prior to surgery (2 patients) or had pelvic and para-aortic lymph node metastasis found from surgical specimens (1 patient). Hence, 17 patients met inclusion criteria of vanishing cancer (3.8%) and were included in the study. Their clinic-pathological data are presented in Table 1.

Mean age of the 17 patients was 53.7 ± 12.3 years. All presented with abnormal uterine bleeding. Majority (15 patients, 88.2%) had diagnosis of EMC from curettage tissue. The other two had either endometrial sampling by pipelle aspirator or direct biopsy under hysteroscopic examination. Other pre-operative clinical data, particularly image findings of the endometrial lesions, were not available.

The mean maximal dimension of pre-operative specimens submitted for pathologic evaluation was 1.98 ± 1.01 cm in aggregation. Histopathology was either endometrioid with or without squamous differentiation (14 patients) or adenocarcinoma, not otherwise

Table 1. Clinico-pathological characteristics of vanishing endometrial cancer

No.	Age	Pre-operative data of endometrial tissue				Operation	Final pathologic report of endometrium
		Retrieved by	Tumor size (cm)	Histopathology	Grade		
1	48	Curettage	Not available	EM squamous	3	TAH BSO PND APP	Atrophic endometrium
2	55	Curettage	4*4*1.5	ACA, not otherwise specified	1	TAH BSO PND PAND OMT	Adenofibroma with focal atypia
3	51	Curettage	Not available	Endometrioid	1	TAH BSO PND OMT	Proliferative endometrium
4	57	Curettage	Not available	EM squamous	3	TAH BSO PND PAND	Atrophic endometrium
5	49	Curettage	Not available	EM squamous	2	TAH BSO PND PAND	Atypical complex hyperplasia
6	49	Curettage	Not available	EM squamous	1	TAH BSO PND APP	Atypical complex hyperplasia
7	40	Curettage	2.6 *2.5 * 0.5	EM	2	TAH BSO PND PAND OMT APP	Atypical complete hyperplasia
8	64	Polypectomy with curettage	Not available	Adenosquamous	3	TAH BSO	Shaggy irregular endometrial surface
9	70	Curettage	3.0 * 2.8 * 6.0	EM	2	TAH BSO PND	Simple hyperplasia, polyps with atypia
10	52	Curettage	1.2*1.0*0.8	EM	1	TAH BSO PND PAND OMT APP	Proliferative endometrium
11	50	Curettage	2.5*2.0*0.6	EM	1	TAH BSO	Proliferative endometrium
12	86	Curettage	3.0*2.0*1.0	ACA, not otherwise specified	3	TAH BSO PND OMT	Polyps with simple hyperplasia
13	45	Curettage	Not available	EM	1	TAH BSO	Atypical complete hyperplasia
14	53	Aspiration biopsy	1.7*1.5*1.2	EM	1	TAH BSO	Atypical endometrial gland
15	39	Curettage	Not available	EM	2	TLH BSO PND PAND	Proliferative endometrium
16	38	Curettage	2.5*2.3*1.1	EM	2	TAH BSO PND PAND OMT APP	Mixed serous & clear cell carcinoma of fallopian tube
17	67	Hysteroscopic Bx	1*0.8*0.3	EM	2	TLH BSO PND PAND OMT	Atypical cells at stalk of the polyp

Abbreviations: ACA, adenocarcinoma; APP, appendectomy; BSO, bilateral salpingo-oophorectomy; EM, endometrioid; EM squamous, endometrioid with squamous differentiation; OMT, omentectomy; PND, pelvic node dissection; PAND, para-aortic node dissection; TAH, total abdominal hysterectomy

specified (2 patients), or adenosquamous carcinoma (1 patient). One of them had pathologic report of adenocarcinoma arising on polyps. Overall, only four had grade 3 whereas the others had grade 1-2 tumors.

Total hysterectomy with bilateral salpingo-oophorectomy (BSO) was performed either via laparotomy (15 patients) or laparoscopy (2 patients). Pelvic with or without para-aortic lymph node dissection were additionally performed in 11 patients. One patient who had hysterectomy specimen submitted for frozen section examination had negative finding. The remaining had routine pathologic assessment with permanent section.

Regarding the pathological process and findings, the median number of pathologic sections of endometrium was 6 sections (range, 3-15 sections). Among these 17 patients with no residual EMC, 6 (37.5%) were found to have endometrial hyperplasia: complex hyperplasia with atypia (4 patients) and simple hyperplasia either with or without atypia (2 patients). Endometrial polyps were found in four patients (25.0%). Three polyps (without cancer) were still evidenced in the hysterectomy specimens and one with only shaggy endometrial surfaces. The other incidental finding was a co-existing mixed serous and clear cell fallopian tube carcinoma. She had grade II endometrioid carcinoma found from endometrial biopsy specimen. Other pathologic specimens in the remaining patients were unremarkable.

Except the one patient with co-existing tubal carcinoma who received 6 cycles of adjuvant chemotherapy, the remaining did not have any further treatment. After a median follow-up of 62.7 months (range, 6.8-184.4 months), two patients were dead of medical illnesses. The other 15 patients were doing well without any evidence of disease at the time of this report.

Discussion

Vanishing cancer was first described in 1995 by Goldstein et al. who reported an absence of carcinoma in prostatectomy specimen after a preoperative diagnosis of prostate cancer [7]. For EMC, Dube et al., in 2007, reported 3 patients of vanishing cancer and proposed criteria for the diagnosis. Their 3 criteria were: 1) the biopsy/curettage specimen should be reviewed to confirm the diagnosis of EMC, 2) there were no residual tumor presented in hysterectomy specimen, and 3) no prior radiation, chemotherapy or hormonal therapy had been given [6].

Our study applied all 3 criteria of Dube et al. and added the criteria of absence of cancer at any other tissues removed from surgery. This was to fulfill the definition of vanishing cancer. We identified 20 patients who had no residual tumor in hysterectomy specimen. After excluding the 3 patients who had pre-operative radiation therapy or had lymph node metastasis, 17 patients met criteria of vanishing EMC. Despite of more rigid criteria, our 3.8% prevalence was still higher than two previous reports which found 1.6% and 2.4% of vanishing cancer in 1567 and 320 EMC patients respectively [12,13].

One may question about the adequacy of sections especially if no/ minimal/ microscopic cancer was remained. Few previous reports provided some related information [11,13]. Bharani et al. [13] described serial 2-3 mm interval of pathologic sectioning of uterine specimen; however, the number of tissue sections embedded was not given. Another study by Ahmed et al, who also processed 2-3 mm interval of their pathologic sectioning, reported total retrieved number of 4-54 sections [11]. The pathologist in our institution also had a standard practice 2-3 mm interval of pathological sectioning. The median number of endometrial tissue was 6 sections (range, 3-15 sections). This should be considered as sufficient to detect any microscopic cancer.

Previous reports proposed few possible causes of vanishing cancer. First was a technical problem of specimen handling and identification errors. One previous report by Dube et al. performed DNA analysis of preoperative biopsy/curettage specimen to confirm the patient identification [6]. Our study did not perform any DNA analysis in our patients because it was costly and not practical for routine service. Besides, we were ascertained with the standard process of specimen registration and processing in our institution that this type of errors should be prevented.

Some surgeon may request intra-operative assessment of the hysterectomy specimen [12]. Öz et al. submitted 74% of their specimens for frozen section. However, this process may deem unnecessary because all samples they submitted for intraoperative assessment were pathological confirmed as negative for malignancy. The only one hysterectomy specimen, which was submitted for frozen section in our series, also had negative finding.

The second possibility was a removal of all tumors by the diagnostic procedures, endometrial biopsy or especially curettage. This was possible especially when there was only small volume of lesion. We collected data from 69 patients from 4 previous studies of vanishing cancer of EMC including 17 patients in our study (Table 2) [6,11-13]. Majority (75 out of 86 patients or 87%) had pre-operative curettage procedure. We attempted to collect clinical data especially image findings. However, they were not available in the data repository. Nevertheless, the mean maximal dimension of approximately 2 cm of pre-operative tissue in our study rather supported this proposal that all of the small volume tumors had been removed. No previous reports had described data of their pre-operative pathologic specimens. In other cancers, some authors proposed that an inflammatory process i.e. cytotoxic immune response may eradicate all tiny or microscopic residual cancer [14,15].

Another possibility aside from the small size of lesions responsible for vanishing cancer was the pathologic feature of polypoid lesion. Ahmed et al. found 10 patients with vanishing cancer had evidence that EMC arising on the polyps [11]. Our study also found all 4 cases of the tumors arising on the polyps had vanishing cancer in the hysterectomy

Table 2. Clinico-pathological findings from other studies and our report of vanishing cancer

Author, year	Dube, 2007[6]	Ahmed, 2015[11]	Öz, 2017[12]	Bharani, 2018[13]	Our study	Total (%)
N	3	23	38	5	17	86 (100)
Prevalence (%)	NA	NA	2.0	1.6	3.8	-
Histopathology, n (%)						
Endometrioid	2	15	38	4	14	73 (84.9)
Serous or clear cell	1	8	-	1	3	13 (15.1)
Grade, n (%)						
1	-	12	33	2	7	54 (62.8)
2-3	3	11	5	3	10	32 (37.2)
Tissue retrieved by, n (%)						
Biopsy	-	6	3	-	2	11 (12.8)
Curettage	3	17	35	5	15	75 (87.0)
Adjuvant treatment	-	2*	-	-	1***	3 (3.5)
Follow up (month)	-	14-104	3-156	11-26	-	-
Recurrence	-	-	1**	-	-	1 (1.2)

*Adjuvant chemotherapy for serous histopathology of endometrial carcinoma from preoperative tissue sampling

**Recurrent serous carcinoma at omentum in a patient with pre-operative endometrioid carcinoma of endometrium

***Adjuvant treatment for synchronous fallopian tubal cancer

specimens (3 still had evidence of polyps with only atypia or simple endometrial hyperplasia).

The third possibility was a discordance of the pathologic diagnoses from biopsy/ curettage and the hysterectomy specimens. Few previous studies reported that the pre-operative diagnosis of endometrial hyperplasia can be either upgraded to EMC [3,16] or cancer of grade I to grade II or III [17-20]. On the other hand, the EMC can also be downgraded to hyperplasia or even normal findings [17-21]. These possibilities were unlikely in our study because our practice was to review all pre-operative tissue diagnosis of cancer by the same or different pathologist especially in all patients referred from other hospitals.

The last possibility as had been described in Dube et al. was that all tumors were eliminated by previous treatment[6]. Our study excluded these patients because they could be clearly interpreted as a complete response to pre-operative treatment, and should not be regarded as vanishing cancer.

The EMC patients who had vanishing cancer had excellent prognosis because of good prognostic features especially the small size of tumor (that no residual cancer was evidenced after pre-operative diagnostic procedure). Other favorable features were endometrioid histopathology and low grade cancer found in the majority of patients (Table 2). Out of 86 patients (including our study), only 3 had adjuvant therapy (2 in the report of Ahmed et al. [11] for having serous cancer and 1 in our study for co-existing serous tubal cancer). Only one patient from previous report experienced recurrence [11]. However, this could be questioned because her preoperative diagnosis was grade 2 endometrioid cancer whereas the recurrent cancer at omentum was serous carcinoma [11]. The other patients from all available reports were alive without evidence of disease after a follow-up duration of 3 months to 204 months (Table 2).

In conclusion, vanishing EMC was not common. The prevalence was lower than 5% in most series. Few possible underlying reasons for the phenomenon had been proposed. Although no evidence-based data to support a definite conclusion of their clinical outcomes, collective data from available literatures with a long term follow-up supported a good prognosis of the condition. These data should be useful in counseling the patients and a consideration for surveillance rather than an aggressive additional treatment even in high grade cancer identified in pre-operative endometrial tissue.

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Conflict of Interest

The authors declare that they have no competing interests.

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