Vanishing endometrial carcinoma in hysterectomy specimens: probable implications for fertility sparing management

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Background/aim: The vanishing cancer phenomenon was first reported in radical prostatectomy specimens in the absence of neo-adjuvant treatment. Reported cases are mostly well-differentiated and low-volume tumors. A similar entity was described for hysterectomy specimens of patients with biopsy proven endometrial cancer (EC). In this study, we discuss the probable reasons for vanishing EC and long-term follow-up results of EC patients without residual tumors in hysterectomy specimens.

Materials and methods: This study was carried at two institutions in Ankara, Turkey, in a retrospective design. The computerized databases of both institutions were searched for endometrioid type EC patients whose final pathological specimens failed to show any residual tumor.

Results: We evaluated 38 endometrial biopsy confirmed EC patients with no residual tumor detected in the hysterectomy specimens among a total of 224 women (17%) with the disease confined to the endometrium. During the follow-up period, no recurrences were noted among the patients.

Conclusion: It can be suggested that premenopausal women with FIGO grade 1 endometrioid type EC with MRI proven "absent myometrial invasion" would have a significant probability of having no residual tumor after endometrial biopsy without any further medical treatment.

Key words: Endometrial cancer, fertility sparing, vanishing cancer, residual tumor, endometrioid type

1. Introduction

The vanishing cancer phenomenon was first described by Goldstein in 1995 (1), who described two cases in which no residual carcinoma was present in radical prostatectomy specimens. Both cases involved low-grade and early stage disease with low-volume tumors in the biopsy specimens. The authors proposed that the possible reasons for vanishing cancer in biopsy proven specimens as early detection of prostate cancer in asymptomatic men (2,3) and a larger number of low-stage cancers being treated by prostatectomy. In early stage and low volume tumors (<0.01 cc), determining the residual microscopic tumor in the radical prostatectomy specimen is challenging for the pathologist. After 1995, more researchers reported increasing numbers of vanishing cancers in radical prostatectomy specimens with a prevalence of 0.07%–0.67% (1–5).

In many cases, the diagnosis of EC is made upon endometrial biopsy and then confirmed on the hysterectomy specimen. No residual carcinoma is found in the paraffin sections of the hysterectomy specimens in some of the patients with preoperative diagnosis of EC, in the absence of any neo-adjuvant treatment (chemotherapy, hormonal therapy, or radiation therapy) (6–8). The real incidence of this entity has not been clearly identified because previous studies included a limited number of patients with heterogeneous diagnoses. In this study, we will discuss the probable reasons for vanishing EC, the long-term follow-up results of EC patients without residual tumor in hysterectomy specimens, and the probable implications of this entity for fertility sparing management of EC.

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2. Materials and methods

This study was carried out at two major referral hospitals for gynecological oncology surgery in Ankara, Turkey. After approval was obtained from the Institutional Review Board, the surgical pathology records of Zekai Tahir Burak Women's Health Education and Training Hospital between May 2008 and January 2015 and the Etlik Zübeyde Hanım Women's Health Education and Training Hospital between January 1993 and May 2013 were searched for EC patients whose final pathological specimens failed to show any residual tumor. Women with a preoperative diagnosis of nonendometrioid histologic subtypes (i.e. serous, mucinous, clear cell, carcinosarcoma, etc.) were excluded from the study; patients receiving medical therapy (progestagen, or neo-adjuvant chemotherapy prior to surgery) were excluded as well. The pathology reports of preoperative endometrial samplings and postoperative hysterectomy specimens were retrieved using the computerized database of the pathology departments of both institutions. We included only those patients whose preoperative EC diagnosis was made in one of the above-mentioned institutions. All patients had total abdominal hysterectomy + bilateral salpingo-oophorectomy (TAH-BSO) with peritoneal washings. Retroperitoneal lymph node dissection was performed according to the frozen section result (if present) or if recurrence risk was high for the individual patient. The preoperative endometrial biopsy specimens and postoperative hysterectomy specimens of the patients were retrieved and re-evaluated by the same experienced gyneco-pathologist.

The endometria in the hysterectomy specimens were examined entirely via serial sections to prevent possible skip outs of microscopic residual tumors. Representative sections from the cervix, bilateral tubes, and ovaries were submitted as a routine procedure. The pathological sections were stained with hematoxylin and eosin (H&E) as a standard procedure. Patient names, date of birth, operation dates, and medical record numbers of the patients were cross-checked with patient identifiers on the specimen container and the pathology request forms.

Follow-up visits were scheduled according to the institutional guidelines: every 3 months for the first 2 years, every 6 months for the following 3 years, and annually after the first 5 years with routine vaginal and pelvic examination, transvaginal and abdominal ultrasonography, serum CA-125 levels, and vaginal cuff cytology.

Clinical, pathological, and demographic characteristics as well as menopausal status, type of diagnostic procedure, follow-up periods, status at last follow-up, and recurrence rates of the patients were presented in a descriptive manner.

3. Results

A total of 1888 patients diagnosed with EC were operated on in both institutions during the aforementioned time periods with the diagnosis of EC. Three hundred twenty-one patients (17%) had nonendometrioid type tumors, whereas 1567 women (83%) had endometrioid type EC, 224 (14.3%) of which were confined to the endometrium (Stage IA according to the 1988 International Federation of Gynecology and Obstetrics (FIGO) classification for EC staging) or had no residual tumor in the hysterectomy specimens. The remaining 1343 patients had either tumors with myometrial invasion in the hysterectomy specimens or a more advanced disease. Among the 224 patients with Stage IA disease, 4 patients had FIGO grade 3, 22 patients had FIGO grade 2, and the remaining 198 patients had FIGO grade 1 disease. Thirty-eight (17%) of the 224 patients with stage 1A disease (FIGO 1988 staging) showed no residual tumor in the paraffin sections of the hysterectomy specimens. Among those 38 patients, 33 patients (14.7%) had FIGO grade 1 endometrioid type adenocancer and 13 of them were premenopausal, while 5 patients (2.3%) had FIGO grade 2 tumors, only one of whom was premenopausal, according to their preoperative endometrial sampling specimens.

The prevalence of vanishing EC was 2.4% (N= 38/1567) among all the women with endometrioid type EC. The study design is summarized in Figure 1.

The mean age of the vanishing EC patients was 54 ± 9.6 years (ranging 32–83). The preoperative mean serum CA-125 levels were 13.1 ± 7 IU/mL (ranging 3–30 IU/mL). Fourteen women (36.8%) were premenopausal, while the remaining 24 patients (63.2%) were postmenopausal. More than half of the patients (20 out of 38 patients) were obese and mean body mass index (BMI) of the patients was 32.8 ± 4.1 kg/m^2 and obesity was the most common identifiable risk factor among patients. The main compliant was postmenopausal bleeding, in 20 of 24 postmenopausal patients, while abnormal uterine bleeding was the main complaint for premenopausal patients. Other complaints are summarized in Figure 1. Thirteen out of the 14 premenopausal women had FIGO grade 1 disease.

Three patients (7.9%) were diagnosed via office hysteroscopic biopsy procedure whereas 35 patients were diagnosed by dilatation and curettage (D&C) or pipelle endometrial biopsy procedure. All the preoperative diagnoses were endometrioid type, as mentioned above.

An intraoperative frozen section procedure was applied for 28 patients to evaluate tumor diameter, myometrial invasion, and tumor grade, if feasible. Since the frozen section studies for 28 patients showed no evidence of malignancy, TAH ± BSO with peritoneal cytology procedure was carried out with inspection of
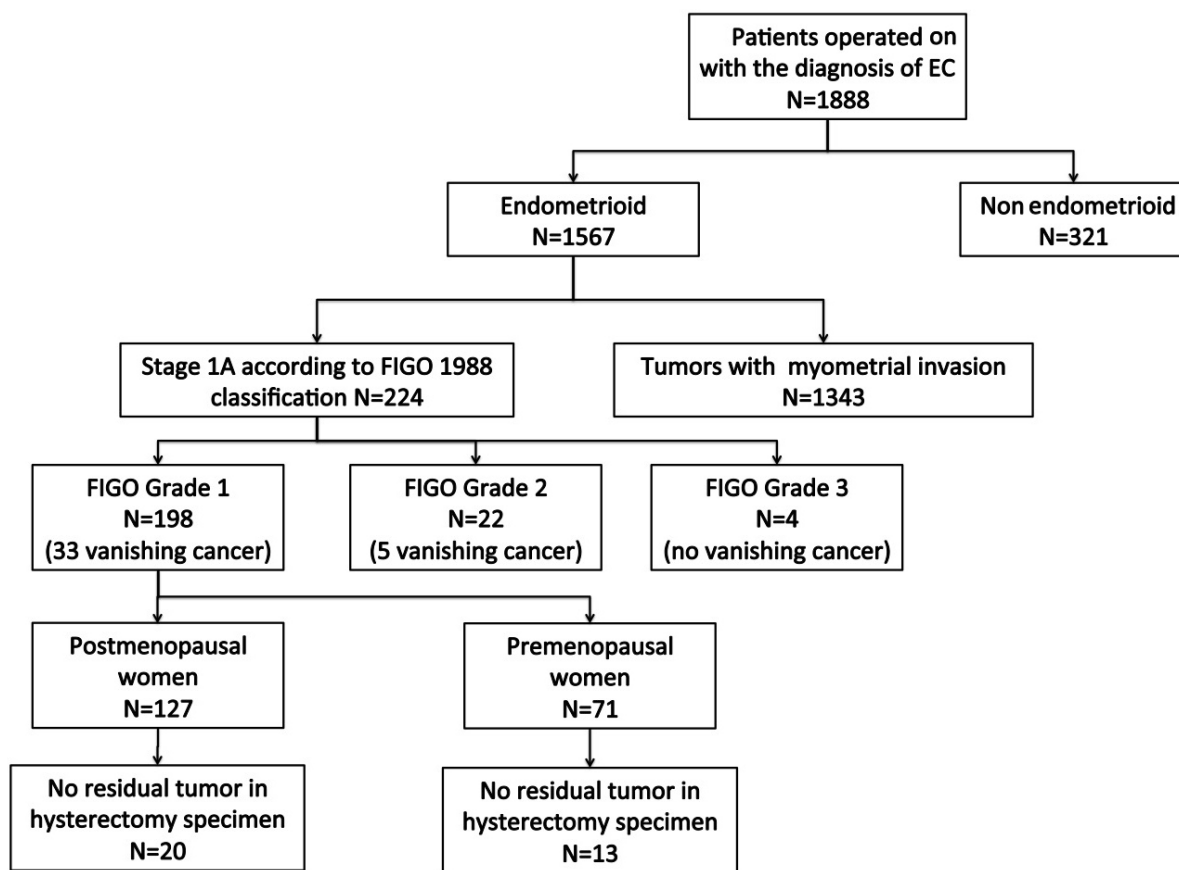
Figure 1. Flowchart of the study design.

the peritoneal surfaces. The diagnostic accuracy of the frozen section examination for these patients was 100%. The remaining 10 patients underwent a comprehensive surgical staging procedure without frozen section study. For women undergoing surgical staging, dissected mean pelvic and para-aortic lymph node counts were 39 ± 16 (ranging 22–73) and 18 ± 13 (ranging 4–49), respectively. No lymphatic involvement and no malignant peritoneal cytology were noted for these patients. Clinical, pathological, and demographic characteristics of the patients are summarized in the Table.

Re-evaluation of all available slides and sections from the paraffin blocks of 38 cases confirmed the absence of any residual tumor. Final diagnoses of the endometrial sections were complex endometrial hyperplasia with atypia in 14 (36.8%) patients, simple endometrial hyperplasia with atypia in 3 (7.9%) patients, simple endometrial hyperplasia without atypia in 3 (7.9%) patients, secretory endometrium in 10 (26.3%) patients, proliferative endometrium in 5 (13.1%) patients, and atrophic endometrium in 3 (7.9%) patients. An example for a vanishing tumor is shown in Figures 2 and 3; the D&C specimen shows morphological characteristics of grade 1 endometrioid adenocancer, but

the hysterectomy specimen of the same patient is indicative for secretory endometrium.

The median follow-up time was 35 months (ranging 3–156 months). Median interval between the initial diagnosis and surgery was not more than 12 weeks. None of the patients received any kind of adjuvant therapy (i.e. chemotherapy, hormonal therapy, or radiation therapy) and there were no recurrences in the follow-up period of the vanishing EC patients.

4. Discussion

The vanishing carcinoma phenomenon was first described for endometrial carcinoma in 2007 (8). The authors presented three cases of vanishing EC (8). All of the patients presented with postmenopausal bleeding. In two cases, the endometrial biopsy showed high-grade adenocarcinoma (subtype not specified) with abundant mitotic activity (as high as 40 mitotic figures per high power field) and the other case had grade 2 adenocarcinoma. These findings do not support the view that vanishing cancers are most likely to be well-differentiated tumors and the authors could not make a valid explanation for this situation (8).

Table. Clinical, pathological and demographic characteristics of the patients.

	Number, mean ± SD
Age (years)	54 ± 9.6
Menopausal status	
Premenopausal	14 (36.8%)
Postmenopausal	24 (63.2%)
Body mass index (BMI) (kg/m^2)	32.8 ± 4.1
Main compliant	
Postmenopausal patients:	
Postmenopausal bleeding	20 (52.6%)
Increase in endometrial thickness	4 (10.5%)
Premenopausal patients:	
Abnormal uterine bleeding	9 (23.6%)
Ovarian cyst related symptoms	2 (5.2%)
Pelvic pain	1 (2.6%)
Other	2 (5.2%)
Possible identifiable risk factors for EC	
Obesity (BMI > 30 kg/m^2)	20 (52.6%)
Oligo-anovulation, PCOS	7 (18.4%)
Infertility, early menarche, late menopause, etc.	3 (7.9%)
Hereditary (Lynch, Cowden, BRCA, etc.)	None
Not identifiable	8 (21%)
Preoperative serum CA-125 levels (U/mL)	13.1 ± 7
Initial diagnostic procedure	
Office hysteroscopic biopsy	3 (7.9%)
Dilatation and curettage	35 (92.1%)
Initial tumor grade	
Grade 1	33 (87%)
Grade 2	5 (13%)
Frozen section study	
Yes	28 (73.6%)
No	10 (26.3%)
Lymph node dissection	
Yes	28 (73.6%)
No	10 (26.3%)
Number of dissected pelvic lymph nodes	39 ± 16
Number of dissected para-aortic lymph nodes	18 ± 13
Final pathology results (%)	
Complex endometrial hyperplasia with atypia	14 (36.8%)
Simple endometrial hyperplasia with atypia	3 (7.9%)
Secretory endometrium	10 (26.3%)
Proliferative endometrium	5 (13.1%)
Atrophic endometrium	3 (7.9%)

(The sum of percentages may not equal to 100% because of rounding off.)
EC: endometrial cancer; PCOS: polycystic ovarian syndrome

The authors defined three criteria to describe a vanishing EC: first the diagnosis should be confirmed by a review of the endometrial biopsy specimen. Second, no residual tumor should be demonstrated in the microscopic examination of the endometrium in the hysterectomy specimen. Third, patients should not receive any type of hormonal therapy, neo-adjuvant therapy, or radiation therapy prior to the surgery (8). All of the 38 cases in our study fulfill the above-
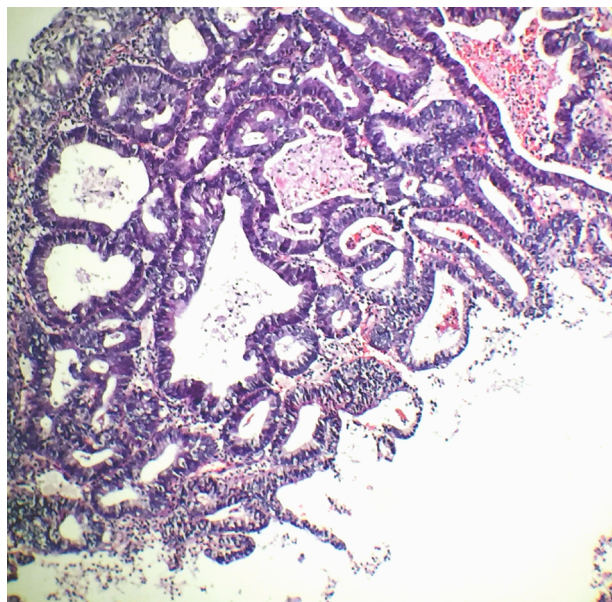
Figure 2. FIGO grade 1 endometrioid type endometrium cancer pattern is shown in the D&C specimen of the patient. H&E staining, ×20 magnification.
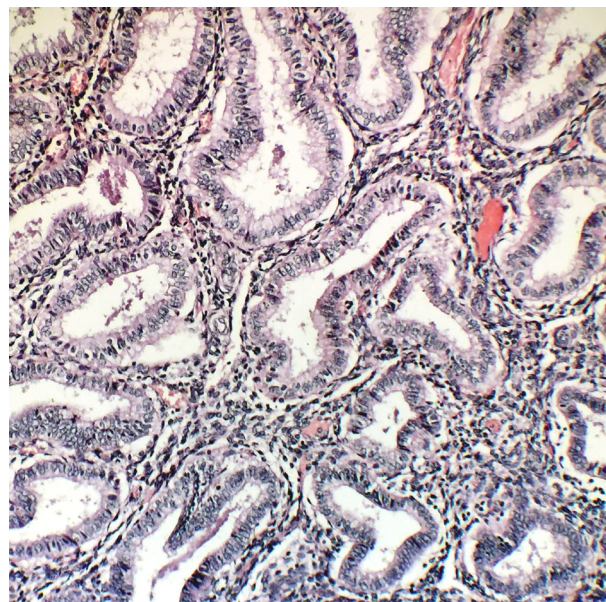

Figure 3. Microphotograph of the hysterectomy specimen of the same patient shows subnuclear vacuoles in the gland cells demonstrative for secretory phase of the endometrium. H&E staining, ×20 magnification.

mentioned criteria and, to our knowledge, the present study represents the largest patient series described in the English literature associated with vanishing EC.

In our series, we had 38 vanishing EC of endometrioid type among 224 patients (17%) with Stage 1A disease according to the FIGO 1988 classification. One hundred ninety-eight of the 224 patients had FIGO grade 1 disease, 71 of them were premenopausal, and there were 13 (18.3%) vanishing EC cases among this population. In 1998, Aquino-Parsons et al. reported 8 cases of vanishing EC in the hysterectomy specimens of 94 EC cases (8.5%) of the endometrioid subtype (9). We think that the prevalence of this phenomenon might have increased in the past decade and will be detected more frequently in the future in a similar fashion described for prostate cancer.

There are several possible ways to explain the vanishing EC phenomenon. The first possibility is switched specimens. DNA fingerprint analysis should be done for both the endometrial biopsy and the hysterectomy specimens to rule out this possibility (4,8). We did not perform DNA fingerprint matching on the samples but crosschecked the barcodes on the pathology request forms with the ones on the specimen containers to provide accurate specimen identification. In this fashion, the risk of specimens being switched was minimalized but not totally eliminated. The second possibility is the complete clearance of the tumor using the endometrial biopsy procedure. This condition may be acceptable for small or microscopic tumors. Small tumors accompanying endometrial polyps are more likely

to be removed completely by hysteroscopic resection or a D&C procedure. The pathologist may have failed to demonstrate the residual tumor in spite of serial sections of the endometrium due to very small volume of the residual tumor. In our study, all available slides relating to endometrial biopsy and hysterectomy specimens were re-evaluated, and additional sections from the hysterectomy specimens were obtained from paraffin embedded blocks by an experienced gyneco-pathologist to minimize the possibility of an unsampled tumor within the tissue blocks. Overdiagnosis of EC in endometrial biopsy specimens may be responsible for the vanishing cancer phenomenon, since the differential diagnosis between well-differentiated EC and atypical endometrial hyperplasia may be challenging for an inexperienced pathologist. It is known that there is substantial interobserver variation regarding the distinction between well-differentiated adenocancer and complex endometrial hyperplasia with atypia. To minimize the diagnostic dilemma of grade 1 EC, both preoperative endometrial biopsy specimens and hysterectomy specimens were examined by the same experienced gyneco-pathologist. The third possibility is the regression of the tumor with hormonal therapy, chemotherapy, or radiation therapy. This was stated as an exclusion criterion for our study population.

In fertility sparing management of EC, patient selection is the key point. There is a consensus among the clinicians that only women with anticipated stage

1A with no myometrial invasion and FIGO grade 1 EC should be offered fertility sparing treatment if desired (10). Such patients have a very low risk of advanced disease or recurrence. However, there are some challenges concerning predicting the correct grade and stage of the disease without performing a hysterectomy. Establishing the grade of the tumor is very important, and this can be done either by office endometrial biopsy (pipelle), dilatation and curettage (D&C), or office hysteroscopy. D&C is the recommended way to detect the grade of the disease, and this method has a 91.3% correlation with the final histopathologic result of the hysterectomy specimen showing FIGO grade 1 disease (7). When our finding is extrapolated to premenopausal women with FIGO grade 1 endometrioid type EC who desire to preserve their fertility, they have an 18.3% theoretical chance of having no residual tumor after the initial diagnostic procedure. In this clinical scenario, the diagnostic accuracy of magnetic resonance imaging (MRI) in detecting women with no myometrial invasion deserves critical importance. According to a metaanalysis by Frei et al., the probability of having myometrial invasion after a negative MRI scan is less than 1% for grade 1 EC patients (11).

The main aspect of fertility sparing management of EC is use of oral progestins for at least 6 months (10). In this case, it can be suggested that women with FIGO grade 1 endometrioid type EC with MRI proven absent myometrial invasion and who desire to preserve their fertility would have an 18.3% theoretical probability of having no residual tumor after endometrial biopsy without any further medical treatment. This patient population can be detected after a negative hysteroscopic endometrial biopsy procedure and immediately offered either spontaneous conception or ART to conceive without any time delay. This 18.3% chance of having no residual tumor after the initial diagnostic procedure should not be underestimated and must be taken into account in the management of women with EC who desire to preserve their fertility. If appropriate candidates are chosen for fertility sparing management, approximately one of every five women will have no residual disease after the initial diagnostic procedure.

Hysterectomy specimens with no residual cancer after EC diagnosis made by endometrial biopsy may be a problem from the medico-legal perspective. Frozen section study at the time of the hysterectomy had a perfect concordance with the final pathology results in our study. Twenty-eight of 38 patients had frozen section study at the time of hysterectomy and all frozen pathology results showed no residual tumor in the endometrial sections. Therefore, these patients underwent only the TAH ± BSO procedure. For the remaining 10 patients, we did not perform a frozen section study during surgery and they were surgically staged according to the FIGO recommendations for endometrial cancer staging. The women who underwent surgical staging without a frozen section study belonged to earlier years of the study period when frozen section study was not routinely performed during EC surgery.

None of the patients developed clinical evidence of disease recurrence within the follow-up period. Especially for endometrioid subtypes, a frozen section study guides the surgeon in avoiding unnecessary radical surgical procedures. Our findings suggest that the vanishing cancer phenomenon for endometrioid-type tumors can be managed with a simple hysterectomy and no adjuvant therapy is needed. However, these findings are not applicable for nonendometrioid subtypes, since serous or clear cell variants of endometrial cancer generally require adjuvant systemic chemotherapy even for tumors confined to the endometrium (9) due to higher recurrence rates (12,13).

The retrospective study design and absence of DNA analysis in order to rule out the risk of switched specimens are the main limitations of the present study. However, our study population seems to be the largest series for vanishing EC in the literature.

We conclude that women with FIGO grade 1 endometrioid type EC with MRI proven absent myometrial invasion would have an 18.3% theoretical probability of having no residual tumor after endometrial biopsy without any further medical treatment. This 18.3% chance of having no residual tumor after the initial diagnostic procedure should be taken into account in the management of women with EC who desire to preserve their fertility.

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