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''Vanishing Cancer Phenomenon'' in Endometrial Cancers: A Report of Three Cases and Review of the Literature

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ABSTRACT

"Vanishing carcinoma" phenomenon has previously reported and accepted on prostate cancer cases as a distinct clinico-pathological entity in uro-pathology. However, although it may be seen in cervical and endometrial carcinoma, it has not been evaluated by extensively in gynecology literature. This review has evaluated the ''vanishing endometrial carcinoma'' phenomenon through observing three similar cases and available literature reports. With this respect, causes and occurrence rates of the ''vanishing endometrial carcinoma'' has been discussed. Also, clinical indications including stage and prognosis of the disease have been evaluated, and suggestions have been made on how to determine if it is a really vanishing case. In conclusion, recognition of the concept, the vanishing endometrial carcinoma, might be a useful for gynecologic pathologist and gynecologic oncologist in order to prevent mismanagement and medico-legal ligitation.

Keywords: Endometrial Carcinoma, No Residual Tumor, Vanishing Cancer Phenomenon, Vanishing Carcinoma

ÖZET

Endometriyal Kanserlerde "Vanishing Cancer Phenomenon": Üç Klinik Vaka ve Literatür Değerlendirmesi

"Vanishing karsinom" fenomeni üro-patolojide bildirilen prostat kanseri vakalarında, farklı bir klinik ve patolojik durum olarak daha önce bildirilmiş ve kabul edilmiştir. Diğer yandan, bu durum servikal ve endometrial karsinoma vakalarında görülebilmesine rağmen, jinekoloji literatüründe yoğun olarak ortaya konmamıştır. Bu makale "vanishing endometrial karsinom'' fenomenini üç benzer vaka ve mevcut literatür bilgileri ışığında ele almıştır. Bu doğrultuda, ''vanishing endometrial karsinom'' fenomeninin sebepleri ve görülme sıklığı tartışılmış, prognoz ve aşamaları içeren klinik göstergeler değerlendirilmiş ve vakanın gerçekten böyle bir fenomen olduğunun nasıl belirlenebileceği ile ilgili öneriler ortaya konmuştur. Sonuçta, vanishing endometrial karsinom konseptinin tanımlanması jinekolojik patolojist ve jinekolojik onkolojistler için olayı yanlış değerlendirme ve yönetme ve mediko-legal süreçlerden korunma anlamında faydalı olabilir.

Anahtar Kelimeler: Endometriyal karsinoma, Rezidü tümör yokluğu, Vanishing kanser Fenomeni, Vanishing karsinom

INTRODUCTION

Endometrial carcinoma (EC) is the most commonly seen gynecologic malignancy in women, affecting particularly the postmenopausal stage.[1] Hence, the disease shows early warning signs especially bleeding, leading the patient to seek medical care.

There are several diagnostic procedures for EC, including endometrial biopsy taken either with dilatation and curettage (D&C) or by the use of a pipelle aspiration technique, as well as the hysteroscopy.[2,3] D&C is the most commonly used method worldwide even though the other techniques have also been routinely practiced. They may not only reveal the initial diagnosis but also offer additional knowledge on contribution to the treatment such as tumor's type and grade, and possible cervical involvement. Even though D&C is apparently the most reliable diagnostic procedure, determination of certain tumor characteristics is not always accurate.[4] This may cause to under or overestimation of the disease, directly affecting the treatment planning.

Literature reports have indicated that a ratio of 8% to 25% of the endometrial cancer cases is failed to be detected by endometrial biopsy. Furthermore, there is an inconsistency regarding the ultimate diagnosis for tumor type and grade with a range from 8% to 55%.[5-8] Due to the relative insufficiency in detection, pathological examination of the hysterectomy specimen is considered as a gold standard. Yet, studies have occasionally reported that the hysterectomy specimen comprises no residual carcinoma in previously EC diagnosed patients with endometrial biopsy, even without any chemotherapy and radiotherapy.[4,9-13] Even though not clarified so far, this is usually explained by the curative biopsy theory, specimen misinterpretation and immunological factors. A similar situation, "vanishing cancer phenomenon'', has previously been reported and accepted on prostate cancer cases as an entity in urological pathology.[14,15]

In our study, a number of 54 cases of the patients who underwent surgery in Baskent University Hospital due to endometrial cancer, within a period of March 2007 and December 2007, were evaluated retrospectively, and three cases were considered as "vanishing endometrial carcinoma'' (vanishing EC). Hereby, our findings will be compared with the available literature reports. With this respect, causes and ratio of the "vanishing EC'' will be reviewed, clinical indications such as stage and prognosis of the disease will be evaluated, and suggestions will be made on how to determine if it is a really vanishing case.

CASE 1

A 50 year old woman presented with abnormal vaginal bleeding. Ultrasonographic examinations revealed a 1-1.5 cm mass recalling a polyp within the endometrial cavity. In fact, it was later proven to be a polyp by hysteroscopic examination, and later, polypectomy was performed. Histological examination displayed polyps comprising endometrioid adenocarcinoma. The patient underwent a surgery 4 days after the polypectomy, including peritoneal washing, total abdominal hysterectomy with bilateral salpingo-oophorectomy, omental biopsy, and bilateral pelvic and paraaortic lymphatic dissection. In histological examination of the hysterectomy specimen, no residual tumor was observed. Malignancy was also not seen in peritoneal washing and lymph nodes. The previous slides were reviewed to exclude possible misdiagnosis, clarifying the presence of the EC while the hysterectomy specimen again showed no residual tumor. The patient is still alive, living with no apparent evidence of disease and neither receiving any adjuvant therapy for 8 months after hysterectomy.

CASE 2

A 47 year old woman presented with abnormal vaginal bleeding. Endometrial biopsy was done by the use of the pipelle aspiration technique, displaying hyperplasia with complex atypia and well differentiated endometrioid adenocarcinoma. The patient underwent a surgery 5 days after endometrial biopsy, including peritoneal washing, total abdominal hysterectomy with bilateral salpingo-oophorectomy, omental biopsy, and bilateral pelvic and paraaortic lymph dissection. The histological examination of the hysterectomy specimen showed no residual tumor, neither malignancy in peritoneal washing and lymph nodes. Like wise, the previous slides were reviewed to exclude possible misdiagnosis, thus conformed the presence of the EC while the hysterectomy specimen showed no residual tumor, as well. The patient is still alive, living with no

Table 1. Occurrence rate of the vanishing EC cases by the literature reports

	Occurrence rate	%
Stovall TG et al.[3]	1/ 40	2.5
Vorgias G et al.[4]	7/263	2.7
Mittal K et al.[10]	1/11	9
Marchesoni D et al.[11]	1 (case report)	-
Stovall et al.[12]	3/619	0.5
Eifel et al.[13]	38/193	19.7
Christopherson WM et al.[16]	3/46	6.5
Abeler VM et al.[17]	1/97	1
Carcangiu ML et al.[18]	2/88	2.3
Carcangiu ML et al.[19]	1/13	7.7
Kelly MG et al.[20]	10/51	19.6
Aquino-Parsons C et al.[21]	8/320	2.5
Sesti F et al.[22]	1 (case report) (sarcoma)	-
Marabini A et al.[23]	1 (case report) (sarcoma)	-

apparent evidence of disease and neither receiving any adjuvant therapy for 7 months after hysterectomy.

CASE 3

A 45 year old woman presented with irregular menses. Ultrasanography indicated a suspicious polyp, the polyp was proven by the hysteroscopy, and it was taken out by the hysteroscopy. Histopathological examination of the polyp revealed endometrial well-moderately differentiated adenocarcinoma. The patient underwent a surgery 7 days after endometrial biopsy, including peritoneal washing, total abdominal hysterectomy with bilateral salpingo-oophorectomy, omental biopsy, appendectomy, and bilateral pelvic and paraaortic lymph dissection. No malignancy was seen in intraoperative frozen examination. Histological examination of the hysterectomy specimen revealed no residual tumor, and malignancy was also not seen in peritoneal washing and lymph nodes. The previous slides were reviewed to exclude possible misdiagnosis, indicating the presence of the EC, and the hysterectomy specimen showed no residual tumor. The patient is still alive, living with no apparent evidence of disease and neither receiving any adjuvant therapy for 4 months after hysterectomy.

On determining whether the three cases were in fact ''vanishing cases'', no extra verification was done rather than re-evaluating the pre and postoperative slides of the patients.

DISCUSSION

Recently, vanishing cancer cases have increasingly been documented particularly in prostate cancers, and yet widely accepted as a phenomenon by urological pathology. Like wise, a similar case has also been described in the endometrium for the first time by Dube et al, 2007, who suggested a ''vanishing cancer phenomenon'' in the endometrium.[9] With the aid of our findings of the three cases as we also have a tendency of calling them ''vanishing cancer phenomenon'', and with the available related literature reports, we will discuss the phenomenon in the light of the literature.

Frequency of the Vanishing EC

Vanishing cancer cases have been documented as case reports. The case has also been reported in more broad studies[3,4,7,9-13,16-23], (Table 1). Occurrence ra-

te of this phenomenon has been shown to vary between 0% and 19.7%. In particular, Stoval et al.[3] reported 3 similar cases out of 619 patients, representing 0.5% of the total number which is the ever largest one mentioned in the literature. Eifel et al.[13] indicated this level to be 38 out 193 cases, equal to 19.7% which has also been the highest rate so far seen in the literature. The level determined in our clinic was 5.5%. The rate variation might be because of the tumor type, stage and grade, and the sampling techniques. It is also very interesting to mention that no residual tumor is seen in the hysterectomy specimen even though it is determined in polypectomy specimen.

Most of the vanishing cancers in prostate have been graded as well or moderate.[14,15] No adequate data are present on EC yet since the related reports have mostly indicated no tumor grade. A report graded it in one case to be moderate and in two cases to be poor.[9] In our study, one case was graded to be well while the second case was differentiated well-moderate. No clear decision was done on the third one.

International Federation of Gynecology and Obstetrics (FIGO) accepted surgical staging of EC in 1988. Stage I is defined as tumor limited to the corpus of uterus (Stage Ia as tumor limited to endometrium, Ib as invasion of less than half of the myometrium, and Ic as invasion of more than half of the myometrium). Cervical glandular or stromal invasion of tumor is present in stage 2 whereas in stage 3 and 4 the disease can be determined in extrauterine structures, organs or lymph nodes. Vanishing cancer cases are normally seen in early stage of the ECs. We need to consider this to be the FIGO stage 1a. In the vanishing cancer cases we observed, no cancer tissue was determined in any other localization such as peritoneal washing fluid and lymph nodes. The related literature reports have not mentioned such metastases either.

Vanishing cancer cases can be observed in all the subtypes of the EC. Of all, endometrioid subtype shows well prognosis while serous and clear cell types progress poorly. We have seen the endometrioid subtype only in our three vanishing cancer cases even though several other reports have determined the serous and clear cell subtype.[17,20]

Taking more endometrial tissue during the endometrial biopsy may lower the chances of thereby finding residual tumor. Hence, no residual tumor has been found after the biopsies by D&C and pipelle techniques, indicating the presence of the vanishing cancer.[4,9,12] Since most available literature reports do not mention the biopsy type performed, it is impossible at this stage to commend on the differences among the biopsy types. However, it is very obvious to say that the rate in hysteroscopic biopsies would be higher than that in blind ones including pipelle techniques. Upon revealing vanishing cancer cases in our study, we have done pipelle technique in one case and polypectomy under hysteroscopic evaluation in the other two cases.

If the cancer is to be in the polypectomy specimen, the presence of no residua tumor seems to increase. In a report[4], a number of 7 vanishing cancer cases out of 263 have been documented, all confining to the polyps previously extirpated. Another research has examined 11 cases of carcinoma within polyps, and 9 being endometrioid type. The subsequent hysterectomy revealed that 4 of the cases were myoinvasive adenocarcinoma, 1 complex atypical hyperplasia (CAH) with adenocarcinoma in situ (AIS), and 3 CAH of nonpolyp endometrium, and there was also one benign endometrium case. The cancer was indeed not observed in nearly two-thirds of the cases (5 out of 9) even though endometrial pathology on hysterectomy was seen in 90% and 10% (one case) was benign.[10] Two of our vanishing cancer cases were observed after the polypectomy.

Etiology of Vanishing EC

Various hypotheses have been suggested on the causes of the vanishing cancer phenomenon. It may sometimes be elucidated by the extirpation of the tumor by the sampling equipment. It is also called curative biopsy theory where the entire tumor is removed by the sampling instrument. The early stage of the tumor increases the percentage of such removal. Another explanation on the vanishing cancer phenomenon is that the postulated immunophysiological developments via biopsy within the tumor may end with the termination of the carcinomatous foci. Literature suggests also that both hypotheses might work together.[24] Overall, the EC seen in polypoid nature can be more susceptible to inclusive removal by biopsy.[9]

Like wise, studies have also hypothesized that a sudden deterioration in vascular nourishment can lead to hypoxia, thus causing to necrosis. In such case, the hysterectomy specimens need to be evaluated in terms of vascular thrombi and prominent necrotic areas. Cytoxic immune responses have well been considered in explaining regression of the tumors including testicular ones[25], melanomas[26], and colonic carcinoma.[27] Dube et al. 2007 have mentioned the cytoxic immune responses to be probable cause in the three cases.[9] Finally, the immune recognition of tumor cells could lead to antibody production against antigen targets in the tumor, or the tumor cells could be killed by natural killer cells. Hence, no residual tumor in EC has been shown to observe naturally in the patients who receive either neoadjuvant hormone therapy including high level of progesterone or preoperative radiotherapy. None of our patients received any kind of neoadjuvant treatment. Yet, we performed hysterectomy at most one week later after endometrial biopsy. At the same time, the fact that we have seen two of the vanishing cancer cases after the polypecomy has led us to suggest that they could indeed be explained by the curative biopsy theory. However, it needs to be searched further to exclude other potential theories on revealing the vanishing cancer cases.

Diagnosis of Vanishing EC

The recognition of vanishing EC cases possesses both clinical and medicolegal importance for certain reasons. Not observing EC in a hysterectomy specimen could lead clinicians to assume wrongly that they are just because of the errors that have done by the laboratory during the process of the material. Hence, determining whether the case is a vanishing cancer is important in deciding if any additional treatment is needed. Moreover, adjuvant postsurgical treatment is carefully considered in some vanishing EC cases. They are classified into the FIGO stage 1a, and the prognosis of endometrioid type is good. It might also appropriate to use additional adjunctive medical treatment in the vanishing EC of clear and serous histological types since patients with stage 1a clear cell or serous adenocarcinoma of the endometrium might deserve postsurgical adjuvant treatment including chemotherapy.[20] Revealing the vanishing case appropriately will surely protect the clinician from thinking wrong during the evaluation of the disease. In other words, confirming the fact that it is indeed a vanishing cancer will help the clinician reassure the patient that his or her case has been handled properly. Determination of vanishing EC has such useful implications to medicolegal practices.

Due to such conditions mentioned above, the case needs to be clarified whether it is in fact a vanishing EC or not. Diagnose of vanishing EC can be done on account of three histological and historic criteria. The malignancy seen must be confirmed by analyzing the biopsy and curettage specimen. On doing exact diagnose, the possibility of any identity mismatch and discrepancy between the macroscopic evaluation and microscopic slides and any probable laboratory contamination such as ''pickups'' and ''floaters'', should be undermined. To avoid such mismactch and discrepancy, all the procedures that have previously done should be re-examined. The previous findings of endometrial intraepithelial carcinoma and endometrial hyperplasia should also have the clinician think that smaller malignant components might be native to the biopsy.[9]

Examining the hysterectomy's endometrium only that has completely embedded may not be enough on determining the malignancy, the entire cervix should also be submitted for histological evaluation, and serial sections of the entire cervix need to be taken.[9]

The high-dosage progestin and preoperative radiotherapy can eradicate EC sufficiently.[28] On the vanishing EC cancer cases, whether the patient have received any neoadjuvant hormonal or radiotherapy needs to be questioned.

If there still appears to be any discrepancy in recognition of any vanishing EC case, the DNA profiling for proper identification can be done in order to confirm it, especially in the cases where tissue contamination or any mix-up is suspected, and a potential medicolegal issue is ongoing. On using DNA in the recognition of vanishing cancer cases, several methods have been described on tissue identification such as fluorescent in situ hybridization technology[29] and immunohistochemistry.[30] Hence, the recent and most used technique in such cases is PCR amplification of DNA. In fact, a report[9] has proven the presence of a vanishing EC cancer in three cases by using this technique.

Management of Vanishing EC

The vanishing EC cases needs to be classified to be FIGO stage 1a. Studies have indicated that prognosis of vanishing EC of endometroid type is very good while that of others including clear and serous histological types is poor.[19,20] In the post-operative follow up of the patients, requirement of any adjuvant therapy depends on the type of vanishing EC. If it is indeed endometroid type, there is a clear consensus among the clinicians on the fact that hysterectomy is sufficient and no adjuvant therapy is required. We have decided to observe all three cases after hysterectomy since they are endometrioid type.

In cases of the clear and serous histological types of EC stage 1a FIGO, different ideas have been raised as to whether any adjuvant therapy should be applied. Some studies have suggested no need of any adjuvant therapy since the recurrence rate of the disease is very low; even so, it tends to recur locally.[31,32] Hence, some of the studies have informed that recurrences have been observed in the patients who have received adjuvant therapy.[33] Adversely, some researchers have pointed out that adjuvant therapy might be required in the cases of the clear and serous histological types because of the fact that prognosis in these types are poor in general.[34]

A recent report on EC with uterine papillary serous carcinoma (UPSC) type has stressed that stage 1a patients with vanishing EC can be followed up without any adjuvant therapy; however, adjuvant therapy such as concomitant vaginal brachytherapy should be applied to stage 1a patients with residual endometrial cancer.[20]

The requirement of adjuvant therapy in the case of stage 1a patients with clear and serous histological types of vanishing EC will become clear as more data continue to appear on the literature. Thus, more detail researches on that particularly those of the molecular biology aspects need to be conducted.

In conclusion, vanishing cancer phenomenon in EC is a fact however it has not studied as it deserve and future studies with larger sample size are needed to determine it's frequency, clinical importance and management. Also, recognition of this concept might be a useful for gynecologic pathologist and gynecologic oncologist in order to prevent mismanagement and medico-legal ligitation.

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