



Lobular Carcinoma Metastasis to Endometrial Polyp 19 Years after Primary Diagnosis: A Report of an Exceptional Case

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Abstract

Metastasis of extragenital neoplasms to an endometrial polyp is rare and pathologists and gynecologists should be aware of this possibility in women with a history of breast carcinoma treated with tamoxifen.

Keywords: Endometrial polyp; Metastasis; Lobular; Breast carcinoma; Tamoxifen

Introduction

Endometrial polyps are rare sites for metastatic breast carcinoma. Such cases have mostly been reported in tamoxifen and most recently in toremifene and aromatase inhibitors (anastrozole) related polyps. Tamoxifen, a non-steroidal anti-estrogen agent, is a widely used adjuvant treatment of breast carcinoma with partial estrogenic agonist effect. This activity may result in a spectrum of proliferative endometrial abnormalities including endometrial polyps as well other polypoid lesions, like mixed müllerian tumors, endometrial stromal sarcomas and uterine sarcomas. Metastases in the female genital tract from extragenital sites are uncommon. When they occur, they frequently involve the ovary, whereas breast is the second most frequent primary source after the gastrointestinal tract. Among breast malignancies, lobular carcinoma is the most common type metastasizing to the female genital tract. Furthermore, malignancy within an endometrial polyp is an unusual event. Metastatic involvement of endometrial polyps is extremely rare, primary malignant transformation being more frequent. Metastatic tumors involving endometrial polyps have been reported and predominantly originate in the breast. The reported time interval is up to six years after diagnosis of the primary disease. We report a case of breast carcinoma metastasis in an endometrial polyp, as first presentation of disease recurrence, 19 years after primary diagnosis.

Case Report

An 82-year-old woman complaining of abnormal uterine bleeding and under the diagnosis of 'poorly differentiated carcinoma of the endometrium' in D&C curetting (endometrial sampling), underwent total abdominal hysterectomy with bilateral oophorectomy, in our gynecology clinic. The hysterectomy specimen consisted of the uterus measuring 7.5 cm × 4 cm × 3 cm. On dissection an endometrial polyp was found, protruding in the endometrial cavity, measuring 2 cm in maximum diameter (Figure 1). Histological examination showed an endometrial polyp containing glands, partly cystically dilated, set in a fibrovascular stroma (Figure 2). The stroma in areas was highly cellular (Figure 3A and 3B) and on high power examination was infiltrated by a small cell population of cells with increased N/C ratio, atypical nuclei and increased mitotic activity (Figure 4). The cells were arranged in compact clusters in between unremarkable endometrial glands. There were no areas of necrosis or ulceration, nor endometrial dysplasia, or EIN. Two additional separate, relatively circumscribed, minute foci of neoplastic infiltration were found, one in the superficial myometrium, of 1 mm and one near the serosa, of 4 mm (Figure 5 and 6), where the cells were arranged in trabeculae (Figure 7). The morphologic features posed a differential diagnosis between a lobular carcinoma metastatic from the breast, an endometrial stromal sarcoma, infiltration from lymphoma/leukaemia cells and an adenosarcoma. Reticulin stains revealed a carcinomatous pattern and mucin stains revealed glycogen and rare intracytoplasmic luminae with mucin vacuoles (Figure 8). Immunohistochemical staining showed strong diffuse positivity of the 'stromal' cells for Ker AE1/AE3 (Figure 9), Ker7 (Figure 10A and 10B), CD10 and focally for EMA. The cells were

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Figure 1: Gross appearance of endometrial polyp protruding in the endometrial cavity (uterus cut in half).

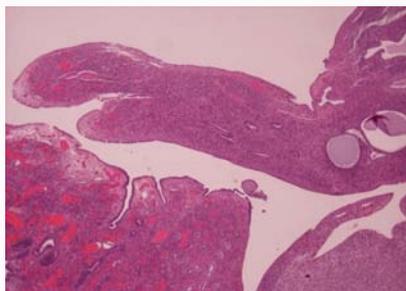


Figure 2: Histological appearance of an endometrial polyp with partly cystically dilated glands set in a fibrovascular stroma.

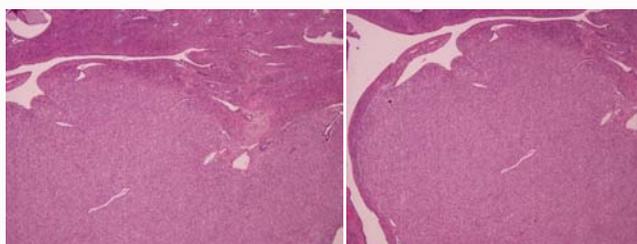


Figure 3: Histologic appearance of a highly cellular area in the stroma of the endometrial polyp, in contrast with normal appearance in the upper field (H&E, low magnification).

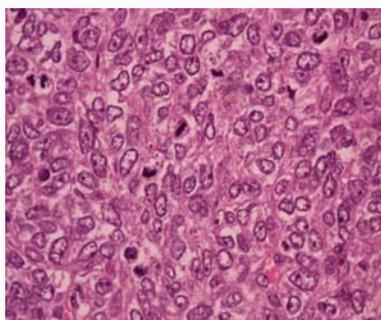


Figure 4: Higher magnification of the cellular area of the endometrial polyp shows infiltration by a highly pleomorphic small cell population with high N/C ratio, abnormal nuclei and increased mitotic activity (H&E, high magnification).

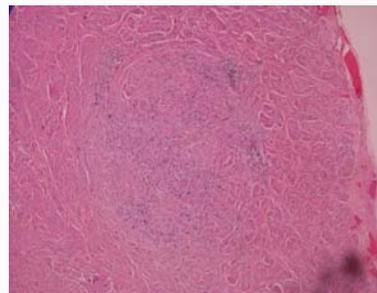


Figure 5: Focus of neoplastic infiltration of the myometrium (low magnification).

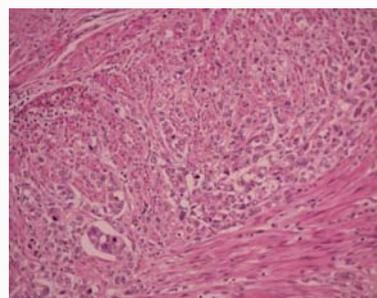


Figure 6: Another focus of microscopic infiltration of the myometrium.

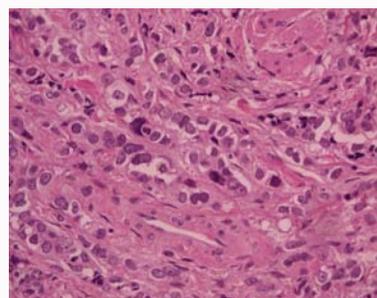


Figure 7: Microscopic appearance of neoplastic cells arranged in trabeculae (Indian file growth pattern) in metastatic focus of the myometrium, reminiscent of lobular carcinoma (H&E X20).

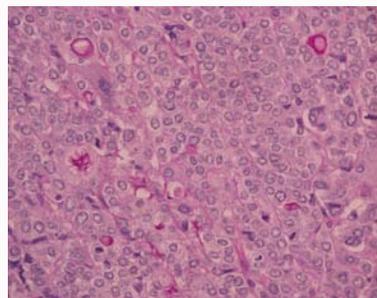


Figure 8: PAS stain reveals intracytoplasmic luminae in the metastatic area of the myometrium, consistent with lobular carcinoma.

negative for mammoglobin, GCDFFP-15, h-caldesmon (Figure 11), ER, PR, e-cadherin and WT1. The proliferation rate was high (MIB-1 expression in approximately 30% to 40% of the neoplastic cells) (Figure 12). The findings were compatible with metastatic breast carcinoma, of lobular type. We searched the patient's past history. The patient

had undergone a left modified radical mastectomy and axillary lymph node dissection, 19 years ago. Pathological examination of the breast tumor had revealed a 1.5 cm × 1.2 cm × 1 cm, invasive carcinoma of the lower outer quadrant of her left breast, of lobular type, grade II, with no metastatic deposits in all the 20 co-excised axillary lymph nodes. The woman was put on tamoxifen for at least 5 years. Our final diagnosis was of a poorly differentiated carcinoma, most probably

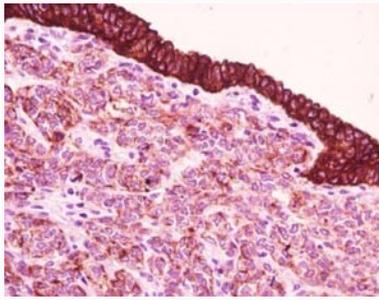


Figure 9: Positive expression of the neoplastic cells in the immunostain for KerAE1/AE3.

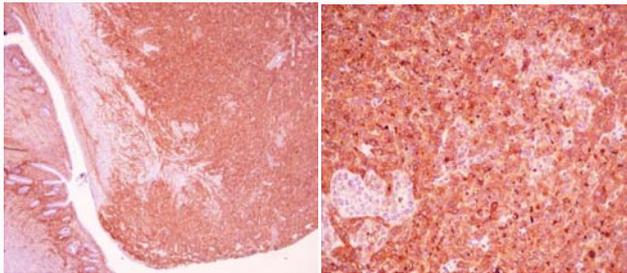


Figure 10: Positive expression of the neoplastic cells in the immunostain for Ker7.

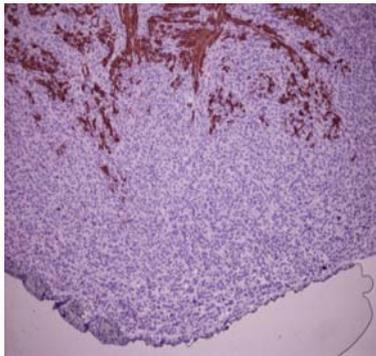


Figure 11: Negative immunoeexpression of the neoplastic cells for h-caldesmon.

of breast origin, of lobular type. We suggested examination of the contralateral breast as well, which was unremarkable.

Discussion

Metastases to the female genital tract from extragenital cancers are uncommon. When they occur, they frequently involve the ovary, where breast is the second primary most frequent source after the gastrointestinal tract [1]. Other primary sites include lung, kidney, urinary bladder, pancreas and gallbladder, as well as cutaneous melanomas, carcinoid tumors, sarcomas and medullary thyroid carcinoma [1]. Among breast tumors, lobular carcinoma is the most common type metastasizing to the female genital tract. Metastases to the uterus are rare, accounting for less than 10%. When it involves the uterus, myometrium involvement is more frequent than metastases to the endometrium [2]. Metastasis to an endometrial polyp is even rarer. Fifteen cases of metastatic breast carcinoma to endometrial polyp had been described till 2011 [3]. Most of the cases were metastases from lobular carcinoma, but also a ductal carcinoma involving a polyp and metastatic apocrine carcinoma of

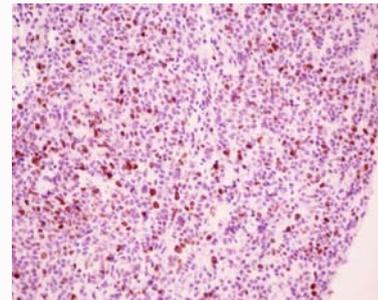


Figure 12: High proliferative rate of the neoplastic cells in MIB-1 immunostain.

the breast to a polyp have been reported [4,5]. Most of the patients were postmenopausal and usually presented with vaginal bleeding, as in our case. In the literature an association with tamoxifen has been noted in several cases of lobular carcinoma metastatic to an endometrial polyp and more recently with toremifene [6] and anastrozole (aromatase inhibitor) [7]. The particular propensity of lobular carcinoma to involve endometrial polyps is in keeping with the observation that this type of breast carcinoma is most likely to metastasize to the female genital tract. Nevertheless, similar findings have been described, not related to tamoxifen [8]. Endometrial polyps are characteristic complications of tamoxifen therapy [9]. Glandular metaplastic changes and periglandular stromal condensation have been described as characteristic, but not pathognomonic of tamoxifen-associated endometrial polyps. In our case the features were of an ordinary endometrial polyp with cystically dilated endometrial glands. The stroma was diffusely infiltrated by small, histiocytoid cells, resembling plump endometrial stromal cells. The increased cellularity and the high power examination, coupling with the positive immunohistochemical staining for the wide range anti-cytokeratin AE1/AE3, confirmed the epithelial nature of the neoplastic cells. The absence of necrosis or endometrial pathology of the glandular or superficial epithelium was compatible with a secondary carcinoma. Positive CD10 expression has been mentioned in breast carcinoma [10]. Although, breast markers were negative, the morphology, especially in the co-existent tumor foci of the myometrium, the presence of intracytoplasmic luminae and the history of breast cancer, confirmed the diagnosis of metastatic lobular carcinoma.

Other polypoid uterine lesions that may occur in association with tamoxifen include mixed Mullerian tumors. Adenofibromas, adenosarcomas and carcinosarcomas have all been described [11]. Endometrial stromal sarcomas and uterine leiomyosarcomas may also present as polypoid lesions protruding into the endometrial cavity. Nevertheless, it is unclear whether a true association exists between tamoxifen therapy and the development of these lesions or whether their occurrence is coincidental.

Breast carcinoma is the most common malignancy in women. Infiltrating ductal carcinoma is the most common histologic subtype of breast carcinoma and accounts for approximately 90% of all invasive cancers. Lobular carcinoma accounts for only 10% to 14% of all breast cancers. With early diagnosis and treatment, many women can become long-term breast cancer survivors; however, 20% to 30% of patients with early breast cancer will develop metastatic disease following therapy. The common metastatic sites for breast cancer are bone, lung and liver. Invasive lobular carcinoma (ILC) exhibits unusual clinicopathological and metastatic patterns and has been

found to frequently metastasize in gastrointestinal tract, genital tract, peritoneum and retroperitoneum [12-15]. Metastases to the genital tract can constitute the first manifestation of a clinically occult breast carcinoma [16]. Unusual sites of dissemination, like the urinary bladder and bile duct have also been described [17]. Various studies have attributed this behavior to the small size and shape of ILC cells, with E-cadherin over expression favoring dyscohesiveness between the cells to migrate to areas of microanatomy more conducive to stop these cells [18,19]. Thus, metastatic spread can happen early in the disease course with barely detectable primary tumors. Alternatively, the microenvironment of the ovary or peritoneum may provide growth and survival factors that favor ILC cells over IDC cells, explaining the difference in the metastatic pattern between the two subtypes [20].

Late development of metastatic disease in unique anatomical locations is a known characteristic of invasive lobular carcinoma (ILC). The longer time interval from diagnosis of the primary tumor to metastases has been reported in a case of gastric metastasis from breast carcinoma occurring 30 years after surgery of the primary tumor [21].

In the literature, most of the cases of breast cancer metastasis occurred in breast cancer while on tamoxifen treatment or during follow up. There are only a few cases where genital tract involvement, as initial presentation, was reported [16].

Risk of recurrence is influenced by stage at initial presentation and the underlying biology of the tumor. Models of metastatic spread describe a complex interaction of seed and soil factors involving tumor intravasation, circulation, extravasation, proliferation and angiogenesis [22] and the microenvironment of the target tissue [23]. Characteristics of the primary tumor are usually preserved in metastases [24]. Among patients with breast cancer lung and bone metastasis gene signatures have been reported [25]. Furthermore, different patterns of metastasis have been described according to the major intrinsic biologic subtypes [26] which may be defined by gene expression profiles [27] or immunohistochemical biomarkers [28]. There are distinct differences in the timing of relapse, with virtually all relapses occurring within the first 5 years among basal-like, triple negative non-basal, and HER2 groups, whereas luminal subtypes, including luminal/HER2, experience continued relapses between 5 and 15 years [29]. Luminal B tumors attain a distinct relapse rate equivalent to that of basal tumors at 15 years. It has been shown that ER-negative tumors are associated with early relapse, and ER-positive tumors are associated with a persistent late risk beyond 5 years [30,31].

Occurrence of metastases, years after the primary tumor, is probably related to the ER and HER-2 status. Over-expression of HER2 receptor in breast cancer has been associated with fast growth and poorer prognosis. ILC is typically a HER-2 negative tumor, which is consistent with its biological behavior and patient surveillance. Furthermore, given the fact that lobular carcinomas are hormone positive tumors, it may be assumed that long disease free interval is mainly the result of a positive effect of endocrine therapy, including oophorectomy and tamoxifen.

A large series of 12,506 breast cancer patients entered in 15 International Breast Cancer Study Group (IBCSG) trials, demonstrated the prognosis for lobular carcinoma to be better than for ductal carcinoma in the early years. However, the relapse rate progressively increased and surpassed ductal carcinoma at six

years. This is postulated to be because of the ER-positive lobular carcinoma tends to relapse late. The median survival of individuals with metastatic breast cancer is 18-24 months [32].

In the retrospective analysis by Sanuki-Fujimoto [33] prognosis of patients with unusual metastases was similar to that of patients with metastasis only at usual sites.

Attempts to investigate the risk of late recurrence have been made using multi-parameter assays, like 12-gene Endo Predict, Breast Cancer Index (BCI) or 50 gene PAM50 ROR [34,35]. These molecular assays can separate patients with low risk of developing recurrence at 5-10 years or 10-15 years [36]. Among these molecular assays, PAM50 ROR was the strongest molecular prognostic factor for late recurrence and possibly predicted who could benefit most from extended hormone treatment [37]. These multiparameter assays are nevertheless limited by availability and cost. Clinicopathological parameters remain the key to clinical decision making in routine practice. Factors that predict late recurrence are luminal tumors, especially with concomitant PR-positive status, high ER-titer, small tumor size, negative lymph node, low grade and HER2-negative disease.

Late metastatic recurrence is due to tumor dormancy. Multiple mechanisms have been proposed to explain how cancer cells survive and remain in dormancy, and they become reactivated and exit dormancy, including angiogenic switch, immunosurveillance, and interaction with extracellular matrix and stromal cells [38,39]. In particular, it has been shown that these dormant breast tumor cells reside preferentially in bone marrow, and eventually become the source of metastatic recurrence [40]. Clinically, the presence of disseminated tumor cells (DTCs) in bone marrow is a predictor for late metastatic recurrence [41]. However, the exact factor that triggers metastatic reactivation in bone has not been identified yet.

In our case, the time interval between tumor diagnosis and tumor recurrence as metastasis to endometrial polyp is exceptionally long and has not been described before as long as it concerns metastasis in an endometrial polyp.

The cause of the 'incidental' finding of the secondary breast carcinoma, was uterine bleeding, which could be attributed to the endometrial polyp in our case. There was no other evidence of cancer recurrence. In the case series by Yazigi et al. [42] out of 27 cases, more than 60% had no evidence of disease on examination and the metastasis would have been missed if complete evaluation had not been performed. Taking into consideration the case series, as in our case, we see it is easy to mistake the common presentation of abnormal vaginal bleeding as primary disease rather than metastatic involvement of the genital tract.

Metastases from a primary breast carcinoma may mimic primary tumors of the gastrointestinal or gynecological tract. It is imperative to differentiate the metastasis from primary carcinoma of genital tract, as the management is dramatically different. The histological diagnosis of the secondary deposit is crucial for the correct diagnosis. Microscopically, metastases from ILC consist of small cells which usually show a single-file growth pattern. They may resemble plump stromal cells, histiocytes, whereas their misinterpretation for luteinized stromal cells has also been reported. The presence of intracytoplasmic lumina with eosinophilic secretion or a signet ring appearance, should pose the suspicion of lobular carcinoma cells. The most important biomarkers for ILC are GCDFP-15, loss of

E-cadherin, positivity for ER and PR. The histological recognition of lobular carcinoma at the metastatic sites may be difficult, especially if hormone-negative. Studies have found that ILC are more likely to be ER+/PR+, than ductal carcinomas. HER-2 protein over expression or gene amplification have been reported in <1% to 6.2% of all ILC cases. Few ILC (1.5%) exhibit a triple negative phenotype [43].

ER positive lobular carcinoma tends to relapse late. It has been shown that ER positivity is a risk factor for the late metastatic recurrence of breast carcinomas [44,45]. Most than half ER+ tumor recurrences occur 5 years or longer after surgery of the primary tumor. This long-term recurrence risk remains despite the use of the adjuvant tamoxifen and chemotherapy. In particular ER expression and lymph node involvement are strong predictors of breast carcinoma late-onset (>3 years) recurrences, especially in skeletal sites.

Non-skeletal metastases in ER+ tumors develop mostly around 5 years postoperatively, which is about 2 to 3 years later than ER- tumors. In contrast, skeletal metastases in ER+ tumors are frequent around 8 to 10 years postoperatively, while in ER- tumors skeletal metastases are rare after 5 years. Triple negative tumors exhibit similar or lower risk of bone recurrence during 0 to 5 years of follow up, while exhibiting significantly higher risk of visceral recurrence in the same period [46]. After 5 years, the risk of both bone and visceral recurrences in the triple-negative group is significantly lower than for the other forms of breast cancer. These emphasize the importance of follow-up protocol optimization according to the time period and the biological characteristics of the tumor. For instance, more frequent surveillance is suggested in skeletal system (by bone scan) in patients with ER+ breast carcinoma with positive lymph node involvement, especially after 3 postoperative years.

Our patient was positive for ER and PR in the primary tumor and negative in the metastatic foci. Documented discordance between primary and metastatic breast cancer is reported for both hormone receptors and HER-2/neu, with the rates of discordance ranging between 6% and 48% [47]. The lack of standardized pre-analytic and analytic variables may have accounted for some of these discrepancies, as well as the interpretation of hormone receptor positivity, tumor sampling and intrinsic tumor heterogeneity. Heterogeneous tumor clones with different hormone receptor and HER-2/neu biomarkers can occur as the result of host environmental changes or treatment consequences [48]. In particular, tumors from patients who previously received adjuvant hormone or HER-2/neu-targeted treatment may develop receptor down regulation or resistance. The chance of discordance between the primary and metastatic tumors for both hormone receptors approximates 20% to 30%.

Features that are typically used for distinction include the tumor cell morphology [49] and a detailed immunohistochemical analysis. Metastatic breast cancers are usually positive for CK7, CEA, ER, PR and GCDFP-15. CK7 and CEA positivity is non-specific. Positivity for ER PR GCDFP-15 and mammaglobin are indicative of breast origin.

Pathologists and especially clinicians should be aware of the possibility of involvement of endometrial polyps (tamoxifen-associated or not) by metastatic breast carcinoma in a woman with a history of breast cancer. Abnormal vaginal bleeding in a patient with known history of breast carcinoma can be the first sign of metastasis, even in the absence of dissemination elsewhere and should be included in the differential diagnosis of endometrial carcinomas. After the initial diagnosis, an event can take place for a long time.

A high level of suspicion is needed for metastatic breast cancer, especially in patients with history of ILC, even if the patient is disease-free for several years, as it frequently metastasizes to unusual sites and presents with a wide spectrum of symptoms. A good medical history is always imperative for the correct diagnosis. Differential diagnosis with plump endometrial stromal cells, neoplasia of the haemopoietic system and adenosarcomas should be made.

A better understanding of patterns of metastatic spread may influence adjuvant therapy and surveillance decisions and determine which investigations and therapies are appropriate once distant disease has been diagnosed.

ER-positive patients might need more frequent follow-up because of the risk of recurrence is retained as long as they survive.

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