Metastasis to the Cervix Uteri 15 Years After Treatment of Lobular Carcinoma of the Breast

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Seminars in Oncology

At times we encounter clinical problems for which there are no directly applicable evidence-based solutions, but we are compelled by circumstances to act. When doing so we rely on related evidence, general principles of best medical practice, and our experience. Each "Current Clinical Practice" feature article in *Seminars in Oncology* describes such a challenging presentation and offers treatment approaches from selected specialists. We invite readers' comments and questions, which, with your approval, will be published in subsequent issues of the Journal. It is hoped that sharing our views and experiences will better inform our management decisions when we next encounter similar challenging patients. Please send your comments on the articles, your challenging cases, and your treatment successes to me at dr.gjmorris@gmail.com. I look forward to a lively discussion.

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Invasive lobular carcinoma (ILC) represents the second most common histologic subtype of invasive breast cancer, accounting for approximately 10% of all invasive breast cancers,[1–6] whereas invasive ductal carcinoma (IDC), by contrast, constitutes 70%–80% of invasive breast cancers.[6] There are both histologic and biological differences between ILC and IDC. For example, the typical histopathology of ILC consists of small monomorphic neoplastic cells with bland round nuclei invading normal tissue stroma in strands or chains in a single file pattern.[7] ILCs are typically well differentiated, more commonly positive for surface expression of the estrogen receptor (ER) and progesterone receptor (PR), and negative for *HER2/neu* amplification.[8–10] Occasionally, ILC cases can show large and pleomorphic nuclei, and are thus classified as pleomorphic ILC; rarely, they can be Her2-positive.[11]

ILC and IDC have distinct metastatic patterns. Locally, lobular carcinomas are more commonly multicentric and bilateral when compared to other invasive tumors of the breast. They have a tendency not to form distinct masses, making it more difficult to detect on routine screening modalities such as a mammogram. Due to these characteristics, breast-conserving therapies can be problematic.[12] Distantly, ILC tends to diffusely infiltrate organs and surfaces in the peritoneum and retroperitoneum, including the uterine myometrium, endometrium, and cervix, as well as ovaries, ureters, and stomach (in which it produces a characteristic "linitis plastica"-type appearance).[2,6] In one series, six of 14 ILC patients were found to have uterine metastases at autopsy. Carcinomatous meningitis is also preferentially associated with lobular carcinoma.[6] Breast cancer is furthermore the most common nongenital malignancy to metastasize to the uterus,[13] presumably owing to the behavior of the lobular subtype. The reason for these differences in the metastatic patterns between ILC and IDC has never been fully understood but it is thought that the loss of a functional E-cadherin transmembrane adhesion molecules plays an important role in the unusual metastatic pattern of ILC,[14] and ascribes a poorly cohesive nature.[15]

A case is presented here as follows.

CASE SUMMARY

A 53-year-old menopausal Indian female presented to an outpatient clinic with a 2-month history of postcoital bleeding. She was examined by a gynecologist who detected a growth on the uterine cervix upon vaginal examination. A biopsy was taken, which was initially reported as "poorly

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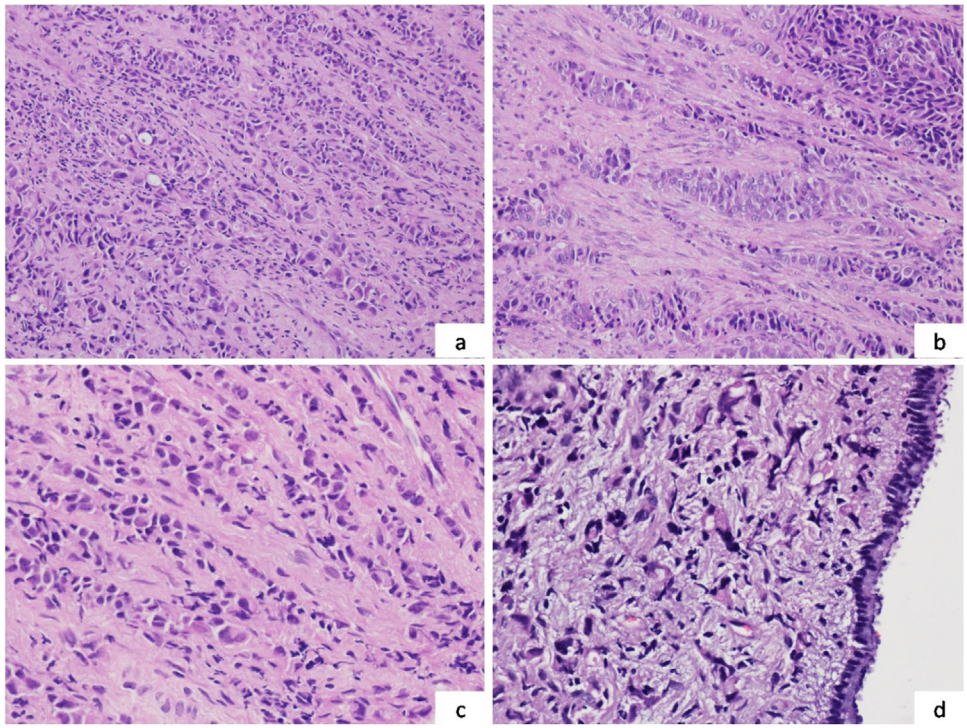

Figure 1. A panel of microphotographs. (a & b) Small tumor cells present in nests and in prominent "Indian file" pattern (hematoxylin and eosin [H&E] 20x); (c) Indian file pattern of tumor cells present in desmoplastic stroma (H&E 40x); (d) tumor cells infiltrating the endocervical stroma with intact benign endocervical glands (H&E 40x).

differentiated squamous cell carcinoma" and she was staged clinically as having International Federation of Gynecology and Obstetrics (FIGO) stage IIB cervical carcinoma. She had a history of premenopausal breast cancer diagnosed at age 38, when she had presented at an outside hospital with a mass in her right breast, from which fine-needle aspiration cytology revealed ILC. She subsequently underwent breast-conservation surgery with axillary lymph node dissection, which yielded final stage T2N1M0. Postoperatively, she received chemotherapy (methotrexate + cyclophosphamide + 5-fluorouracil [5-FU]) and radiation therapy (50 Gy in 25 fractions over 5 weeks). The tumor was reportedly positive for expression of ER and PR, and she was thus given tamoxifen for 5 years. She was clinically disease-free, and underwent regular follow-up until the present.

At this time, 15 years later, she was subsequently referred to a tertiary care facility for the treatment of presumed cervical cancer. Biopsy slides from the outside hospital were re-reviewed onsite and showed small-sized tumor cells present in solid sheets and nests and in a prominent single-file pattern (Figure 1) in desmoplastic stroma. The tumor cells were seen infiltrating the endocervical stroma with intact benign endocervical glands (Figure 1d). On high-power examination, the individual tumor cells had intracytoplasmic vacuoles or lumina with characteristic magenta bodies. Immunohistochemistry (IHC) was done, which showed tumor cells were negative for p63, p16, and Her-2 neu. ER staining showed focal mild positivity (30% expression) and PR staining showed focal strong nuclear positivity (70% expression) (Figure 2). A diagnosis of lobular carcinoma metastatic to uterine cervix was made considering her history, the characteristic histo-morphology, and the IHC pattern. Fluoro-deoxy-glucose positron emission tomography (FDG-PET) scan showed FDG-avid lesions (standardized uptake value [SUVmax] 14.9) in the cervix uteri, a satellite nodule in the corpus of the uterus and metastasis in the pelvic (SUVmax 11.7), and para-aortic lymph nodes (SUVmax 5.2) without any FDG-avid lesions in the bilateral breasts or axillae (Figure 3).The differential diagnosis in this case included primary cervical adenocarcinoma or primary endometrial adenocarcinoma with lymph node metastasis. However, considering her history and the characteristic histological findings, she was deemed as most likely having metastatic lobular carcinoma, and was treated with combination chemotherapy.

We posed the following clinical questions: (1) Is this a new primary cancer? How would this best be distinguished? And if so, are they related in a syndrome, versus explainable by other risk factors? (2) If metastatic from the patient's