

Case Report

Histiocytoid invasive lobular carcinoma detected on a cervical smear: a case report of breast carcinoma metastasizing to the uterus

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Abstract: Among cases of breast carcinoma metastatic to the uterus, the percentage of these cases that are invasive lobular carcinoma (ILC) is higher than what may be expected when one considers the relative infrequency of ILC at the primary site. However, fewer than 10 cases of metastatic ILC of the breast detected in the cervical smear have been reported in the literature. Although several variants of ILC exist aside from classic ILC, previously reported ILC cases detected by cervical smear are probably not ILC variants because there was no description as variants of ILC in such cases. Herein, we present a case of a 52-year-old woman having a histiocytoid variant of ILC metastatic to the uterus that was detected on a conventional cervical smear. It is important to keep in mind that ILC can metastasize to the uterus, because its morphology is easily confused with a high-grade squamous intraepithelial lesion. Being aware of the possibility of metastatic ILC, non-high-grade nuclei of tumor cells with poorly differentiated appearance, namely loose cohesiveness, would lead to a more confident diagnosis.

Keywords: Histiocytoid variant, invasive lobular carcinoma, breast, cervical smear

Introduction

Fewer than 10 cases of metastatic invasive lobular carcinoma (ILC) of the breast diagnosed in the cervical smear have been reported in the literature [1-6]. Metastases of extragenital tumors to the uterus are relatively rare but well recognized, with tumors of the gastrointestinal tract and breast being the most common [7-9]. In breast carcinoma metastatic to the uterus, the incidence of ILC in these cases is higher than one might expect, considering the incidence of ILC at the primary site [10].

Aside from classic ILC, several variants exist and are recognized in one of two ways: either by their architectural pattern, including alveolar, trabecular and solid variants, or by their cytological features, including signet-ring cell, apocrine, histiocytoid and pleomorphic variants [11]. In the diagnosis of any such ILC variant, these particular characteristics must account for more than 50% of the tumor [12].

Herein, we present a case of a histiocytoid variant of ILC metastasizing to the uterus and

detected by conventional cervical smear. Previously reported ILC cases detected by cervical smear were probably not variants of ILC because there was no description as variants of ILC in such cases.

Clinical summary

A 52-year-old woman was referred to our hospital owing to an abnormal shadow on the left breast on mammography. Contrast-enhanced fat-suppressed T1-weighted magnetic resonance imaging of the patient's breast showed a large enhanced area (**Figure 1A, 1B**). Following a biopsy, the patient was diagnosed with ILC. Neoadjuvant chemotherapy was administered and a unilateral mastectomy was carried out on the left breast. Although surgical margins were negative, metastases were found in the lymph nodes. Postoperatively, the patient underwent anti-estrogen therapy. Two years after the mastectomy, the patient visited our hospital for a regular gynecologic check-up that included cervical cytology; such check-ups are common in Japan. At that time, metastasis of ILC was

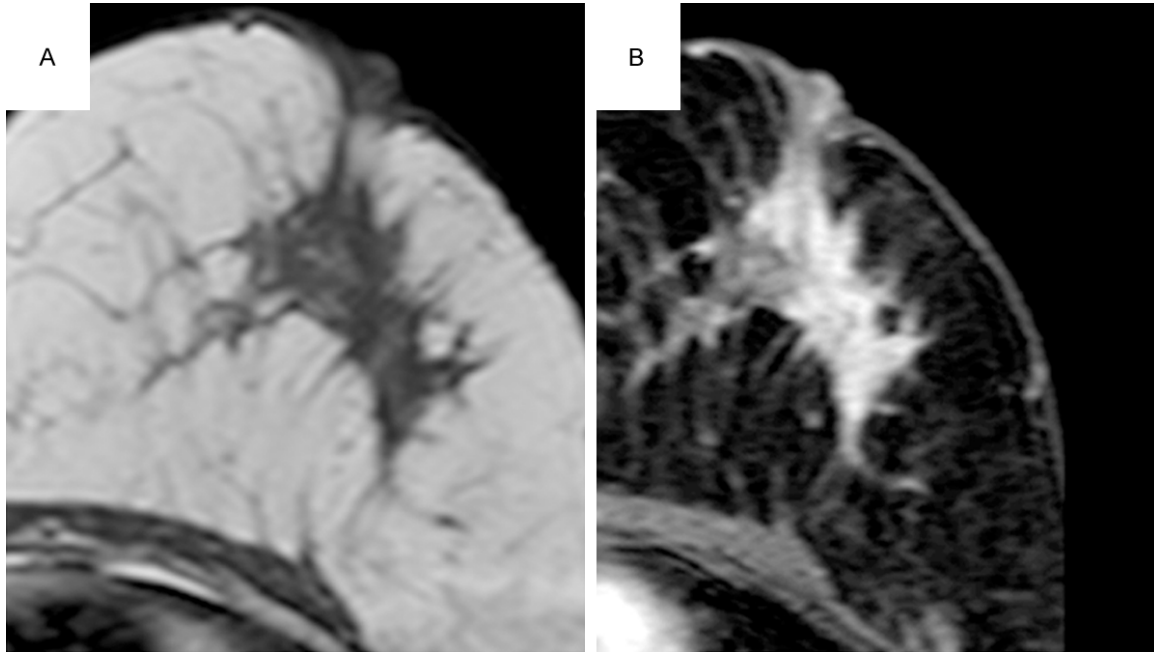


Figure 1. Radiological findings. A. T1-weighted image; B. Contrast-enhanced fat-suppressed T1-weighted image. On contrast-enhanced fat-suppressed T1-weighted magnetic resonance imaging, there is a large enhanced area compared to a non-enhanced T1-weighted image.

detected on a conventional cervical smear, which was not detected on radiological examination including PET-CT. Furthermore, brain metastasis occurred, and her condition had deteriorated. We tried to give her best supportive care putting an emphasis on her wishes.

Pathological findings

Biopsy revealed a relatively monotonous appearance of histiocytoid atypical cells that were discohesive (**Figure 2A**). Intracytoplasmic lumina were not apparent in atypical cells. Immunohistochemically, the atypical cells were positive for 34 β E12 (**Figure 2B**) and negative for E-cadherin (**Figure 2C**). Thus, the diagnosis of ILC, specifically the histiocytoid variant, was made.

In the mastectomy specimen, areas corresponding to the ILC were not clearly visible. Microscopically, there were dispersed atypical cells of ILC. Fibrosis was prominent on the background, which was consistent with the disappearance of ILC cells and reflected highly effective neoadjuvant therapy. However, metastases to axillary lymph nodes were found in 5 out of 10 dissected nodes.

Conventional cervical smear revealed a large amount of histiocytoid atypical cells with enlarged nuclei and moderate hyperchromasia. They had non-high-grade nuclei, but were discohesive simulating poorly differentiated carcinoma (**Figure 2D**). Intracytoplasmic lumina were not apparent in atypical cells. Considering similarity of atypical cells to the ILC cells observed in biopsy and mastectomy specimens, a diagnosis of ILC metastatic to the uterus was confirmed.

Discussion

The main differential diagnosis of metastatic ILC in a cervical smear is high-grade squamous intraepithelial lesion (HSIL) [2]. Differentiating between classic ILC and carcinoma in situ (CIS) requires careful examination, because both have a high nuclear-to-cytoplasmic ratio and rounded nuclei with little nuclear irregularity. However, nuclear hyperchromasia is prominent in CIS, while a non-hyperchromatic nucleus is a feature of classic ILC. Meanwhile, the histiocytoid variant of ILC should be distinguished from moderate dysplasia by its relatively lower nuclear-to-cytoplasmic ratio, and its nuclear irregularity is not as conspicuous as it is in severe dysplasia. With respect to other differ-

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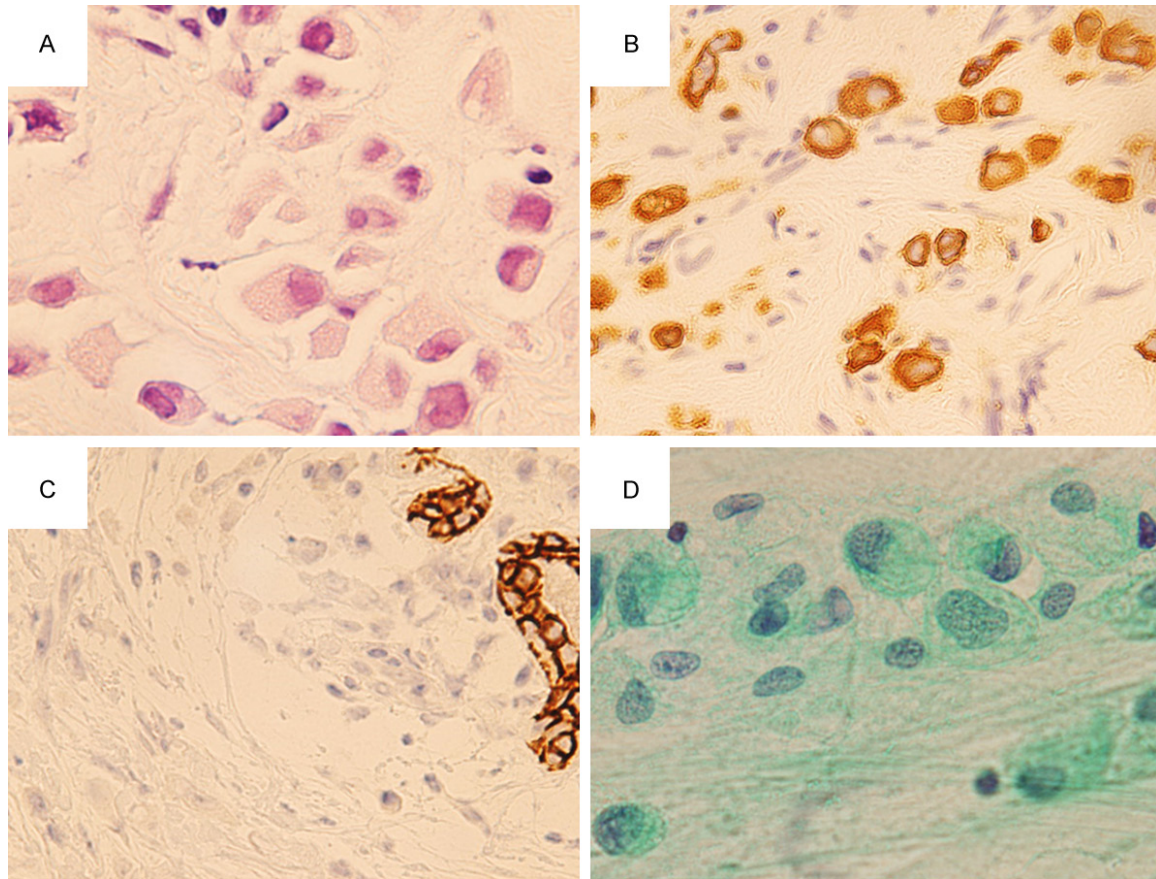


Figure 2. Pathological findings. A. Biopsy revealed a relatively monotonous appearance of histiocytoid atypical cells that were discohesive. B. Immunohistochemically, the atypical cells were positive for 34βE12. C. Immunohistochemically, the atypical cells were negative for E-cadherin. E-cadherin-positive normal epithelia were visible on the right side of the field. D. Conventional cervical smear revealed a large amount of histiocytoid atypical cells, whose nuclei were enlarged and showed moderate hyperchromasia. The histiocytoid atypical cells are discohesive.

ential diagnoses of ILC, cervical and endometrial adenocarcinomas may also be considered, but they are more cohesive if they have non-high-grade nuclear atypia as was found in this case. If cellular discohesiveness of cervical and endometrial adenocarcinomas is prominent to such a degree as was observed in this case, poorly differentiated adenocarcinomas are considered; however, in such cases, tumor cells have more pleomorphic nuclei than those seen in this case. Thus in ILC, squamous lesions are a more common differential diagnosis than adenocarcinomas despite the fact that ILC is of glandular origin.

In confidently distinguishing ILC from HSIL, it is important to find intracytoplasmic lumina in ILC. Typically, mucin is present inside intracytoplasmic lumina. There are two types of intracytoplasmic lumina: one having non-stained

material in the vacuole, and the other one having concretion at the center of the vacuole [13]. As the former one is sometimes hard to distinguish from a degenerative vacuole, the latter is a more important finding than the former. One should try to find the latter-type intracytoplasmic lumina by close examination, although it might be difficult to find it, especially in variants of ILC, experienced from this case.

In cervical smear screening, when in a malignancy is suspected, it is important to review the patient's clinical information to see if there is a previous history of malignancy. In cervical cytology, as is true in cytology of other regions, a diathetic background supports the diagnosis of malignancy. However, in the case of metastasizing carcinoma to the uterus, a lack of tumor diathesis is noted in 80% of samples containing malignant cells [14]. This is true in many

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cases of metastasizing ILC, including our own, but two cases have been reported showing a diathetic background on cervical smear [3, 5]. Thus, this might not provide enough reliable evidence to determine whether malignant cells appearing on a smear are from a primary uterine tumor or have their origins in another part of the body.

Regarding prognosis among classic ILC and its variants, patients with variant ILC are at an increased risk of metastasis, and have lower rates of disease-free survival and overall survivals compared to patients with classic ILC [15]. Thus, in this case of histiocytoid variant of ILC, metastases to parts of the body including but not limited to the uterus should be carefully monitored.

In conclusion, we reported an extremely rare case of an ILC variant metastasizing to the uterus and being detected on conventional cervical smear. Despite its rarity, it is important to keep in mind that ILC can metastasize to the uterus, because its morphology is easily confused with HSIL. Being aware of the possibility of metastatic ILC, non-high-grade nuclei of tumor cells with poorly differentiated appearance, namely loose cohesiveness, would lead to a more confident diagnosis.

Disclosure of conflict of interest

None.

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