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Case Report

Breast Cancer Metastasis in the Skin with Hyperkeratotic Pigmentation Caused by Melanocyte Colonization

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Keywords
Breast cancer · Melanocyte colonization · Hyperkeratosis · IL-17 · IL-23

Abstract
Pigmented breast cancer in the skin caused by nonneoplastic melanocytes of epidermal origin is a rare condition of metastasis from breast cancer, but the pathogenesis of this phenomenon is almost unknown. In this report, we describe a case of breast cancer metastasis in the skin with prominent hyperkeratotic pigmentation caused by nonneoplastic melanocyte colonization. Immunohistochemical staining revealed that the metastatic tumor cells produced IL-23, which is reported not only to induce IL-17 but also to inhibit cell apoptosis in breast cancer cells, which affects tumor progression. In addition to IL-23, substantial numbers of IL-17-producing cells were detected at the peritumoral area, suggesting that IL-17 might induce not only melanogenesis but also keratinocyte proliferation and tumorigenesis. Our report suggests possible mechanisms of hyperkeratotic pigmentation of breast cancer metastasis in the skin.

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Introduction

Pigmented breast cancer in the skin caused by nonneoplastic melanocytes of epidermal origin is a rare condition of metastasis to breast cancer first described by Azzopardi and Eusebi [1] in 1977. Recently, Mele et al. [2] have reported another case of breast cancer with multiple pigmented macules on the skin of the affected breast and reviewed several possible mechanisms of the proliferation of normal human melanocytes at the epidermal area. However, they concluded that most of the pathogenesis is still unknown. In this report, we describe a case of recurrent breast cancer in the skin with prominent pigmented hyperkeratosis caused by the colonization of nonneoplastic melanocytes.

Case Presentation

A 48-year-old Japanese female visited our outpatient clinic with an asymptomatic black nodule on the right chest. She had undergone a right breast partial mastectomy followed by adjuvant chemoradiotherapy for the treatment of invasive ductal carcinoma 7 years before and underwent a right breast total mastectomy with dissection of the right lymph nodes in another institute 3 years before. At her initial visit, physical examination revealed 2 black, hyperkeratotic nodules with diffuse erythema, 16 × 5 mm and 16 × 7 mm in size, on the right chest (Fig. 1a). A full blood count and biochemical profile was within the normal range. There was no increase of serum CEA or CA15-5. We performed excisional biopsies from both nodules, showing dense infiltration of rounded, foamy, atypical cells throughout the dermis covered with a thickened crust (Fig. 1b). In addition, melanocyte colonization was prominent at the stromal area of the tumor sites (Fig. 1c). Immunohistochemical staining revealed that these atypical cells were positive for estrogen receptor (Fig. 2a). Although S100 and HMB45 were negative for tumor cells, there was dense infiltration of S100+, HMB45+ melanocytes at the tumor stromal area (Fig. 2b, c). From the above findings, our diagnosis was skin metastasis of breast cancer with hyperkeratotic pigmentation.

To further investigate the mechanisms of melanogenesis, metastasis, and hyperkeratosis, we employed immunohistochemical staining for IL-17, IL-23, CCL20, MMP12, and CD163. Not only the myeloid cells around the tumor cells but also the tumor cells themselves produced IL-23 (Fig. 3a) and CCL20 (Fig. 3b), leading to the dense infiltration of IL-17-producing cells around the tumor sites (Fig. 3c). Moreover, MMP12 deposition was prominent at the peritumoral area (Fig. 3d), which was abundant with CD163+ tumor-associated macrophages (TAMs) (Fig. 3e).

Discussion

Recent reports suggest the existence of several possible roles of proinflammatory cytokines in the carcinogenesis of various cancers, including breast cancer. Among them, IL-17 induces not only melanogenesis [3] but also the proliferation of keratinocytes and tumorigenesis, including that of cutaneous squamous-cell carcinomas and adenocarcinomas [4, 5]. For example, Wang et al. [3] reported that IL-17 could affect both the growth and pigment production of melanocytes in psoriasis. On the other hand, Wu et al. [3] reported that IL-17 signaling in keratinocytes drives the IL-17-dependent sustained activation of the TRAF4-ERK5 axis, leading to hyperkeratosis in cutaneous squamous-cell carcinomas [4]. Indeed, in our

present case, IL-23 and CCL20 were produced by tumor cells themselves, and a substantial number of IL-17-producing cells and CD163+ TAMs were densely distributed at the peripheral areas of the tumor mass. These findings suggest possible mechanisms for the induction of melanogenesis as well as the immunosuppressive microenvironment at the tumor site of metastatic breast cancer.

Another proinflammatory cytokine, IL-23, could also play important roles in tumor development [6]. In addition to inducing IL-17 [7], IL-23 inhibits cell apoptosis in breast cancer cell lines (MCF-7), affecting tumor progression [6]. In addition, the IL-23 and IL-23R expression levels are positively correlated with the patients' tumor size, TNM stage, and metastasis in breast cancer [6], suggesting a significant role of IL-23 in the pathogenesis of the disease. In our present case, interestingly, not only dermal myeloid cells but also tumor cells produced IL-23. Previous reports also suggest that MMP12 plays critical roles in the development of metastatic lesions, leading to a poor prognosis in various cancers, including breast cancer [8]. Hernandez et al. [9] reports that MMP12 correlates with the matrix degradation, promoting the metastasis of breast cancer. Since MMP12 is produced by TAMs under the appropriate stimulation in a proinflammatory condition [10], these findings suggested that, together with IL-17 and IL-23, MMP12 might have played a role in the development of an atypical presentation in our case. Since we present a single case, further cases are needed to gain additional insight into the pathomechanisms of pigmented breast cancer in the skin with melanocyte colonization.

Statement of Ethics

The patient gave written informed consent.

Disclosure Statement

The authors have no conflicting interests to declare.

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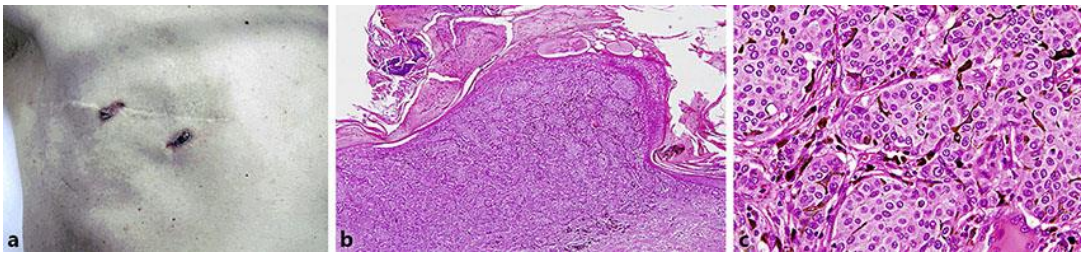

Fig. 1. **a** Two black, hyperkeratotic nodules with diffuse erythema, 16 × 5 mm and 16 × 7 mm in size, on the right chest. **b** Dense infiltration of rounded, foamy, atypical cells throughout the dermis covered with a thickened crust. H&E. ×40. **c** Melanocyte colonization is prominent at the stromal area of the tumor sites. H&E. ×400.

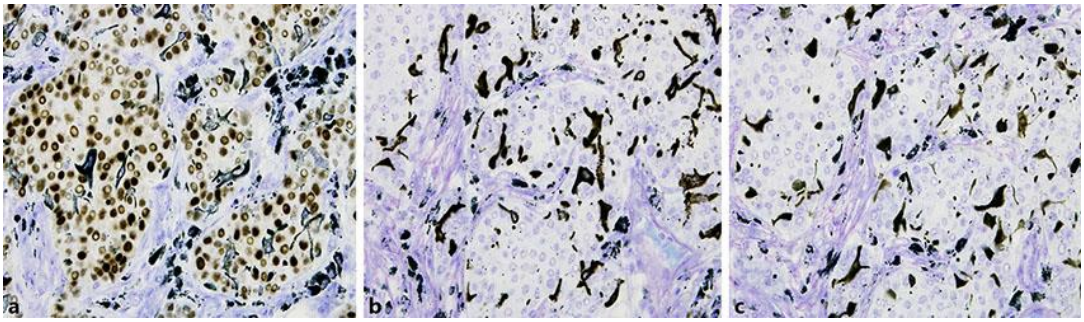

Fig. 2. Paraffin-embedded tissue samples were deparaffinized and stained with anti-estrogen receptor Ab (**a**), anti-S100 Ab (**b**), and anti-HMB45 Ab (**c**). Original magnification. ×400.

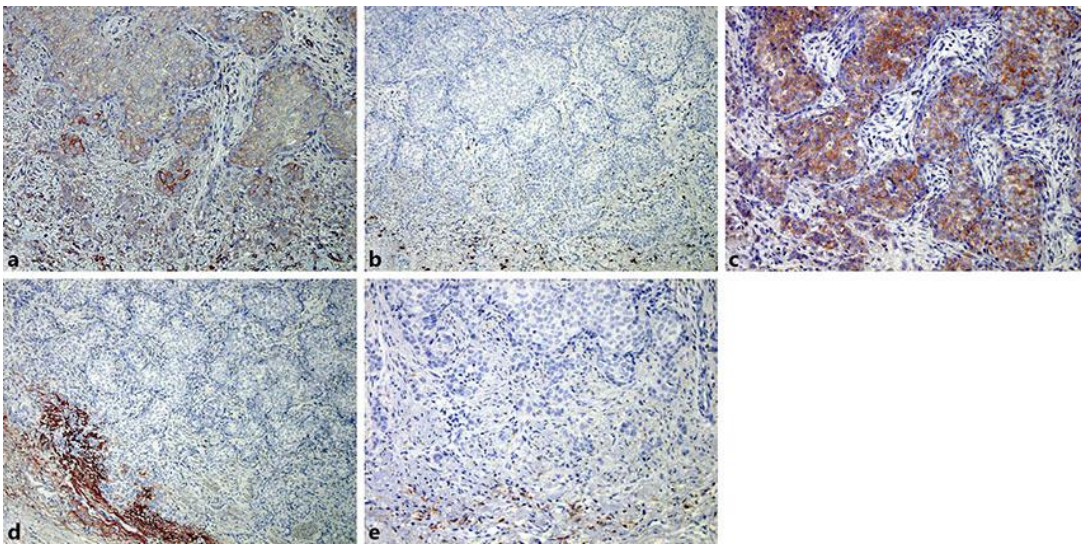

Fig. 3. Paraffin-embedded tissue samples were deparaffinized and stained with anti-IL-23 Ab (**a**), anti-CCL20 Ab (**b**), anti-IL-17 Ab (**c**), anti-CD163 (**d**), and anti-MMP12 Ab (**e**). Original magnification. ×200.