Cutaneous Metastasis of Signet-ring Gastric Adenocarcinoma to the Breast with Unusual Clinicopathological Features

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Abstract. *Background: Cutaneous metastasis of gastric adenocarcinoma is rare and usually presents in men, as nodules over the abdomen. We present the case of a woman with cutaneous metastasis of gastric adenocarcinoma showing unusual clinicopathological features. Case Report: A 37-year-old woman developed florid cutaneous metastasis over the skin of the left breast two years after total gastrectomy for a signet-ring adenocarcinoma of the diffuse type. The metastasis presented as a multinodular growth developing over erythematous skin of the left hemithorax. Microscopically, the skin tumor was predominantly made up of spindle-shaped cells, mimicking a mesenchymal/fibrohistiocytic neoplasm. A comparative immunohistochemical study of the gastric primary and the skin tumor showed an almost identical profile (keratin 7/20$^+$; epithelial membrane antigen$^+$, MUC-5AC$^+$), highlighting the gastric adenocarcinoma as the origin of the skin metastasis. Conclusion: Although rare, cutaneous metastases of gastric adenocarcinomas can develop in women and may mimic inflammatory metastasis of breast adenocarcinoma. Immunohistochemistry is invaluable in establishing the correct diagnosis.*

Cutaneous metastases develop through hematogenous and lymphatic spread *via* mechanisms that are complex and not yet completely understood. Cancer cells need to detach from the primary tumor, invade and intravasate into a blood or lymphatic vessel, survive in the circulation, attach to endothelium, extravasate, invade the host tissue and proliferate at a distant site in order for metastasis to succeed. Cutaneous metastases from internal tumors develop in up to 10% of patients with visceral malignancies; they usually originate from the breast, lungs, colon, rectum, ovary, head and neck and the kidney (1-10). In 1.6-4% of cases, cutaneous metastases are the initial clinical manifestation of the neoplastic process (3, 10).

Gastric adenocarcinomas (ADC) account for the vast majority (95%) of gastric tumors. They show a male predominance and are pathologically classified as papillary, tubular, mucinous and signet-ring cell, the latter accounting for 8.7% of all gastric carcinomas (11). Cutaneous metastases arising from gastric ADC are rare, developing in fewer than 5% of patients with corresponding primaries (3-5, 7, 12). They manifest usually as nodules over the abdomen (13), and may exceptionally be the presenting sign of this malignancy. We report herein a woman with signet-ring gastric ADC who developed skin metastasis over the breast skin. This case is remarkable because of the rarity of skin metastasis of gastric ADC, the unusual localization of the lesions, their florid appearance and their misleading pathological aspect, requiring comparative immunohistochemical study of the primary and the secondary tumor in order to ascertain the diagnosis.

Case Report

A 37-year-old woman was diagnosed in April 2006 with low-differentiation signet-ring gastric ADC of the diffuse type (according to Lauren) that invaded the wall and fat of the lesser curvature of the stomach. She underwent total gastrectomy and R-N-Y anastomosis. On microscopic examination, the tumor approached the lower excision border, but the upper limit of the surgical specimen and the

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rings of the anastomosis were tumor-free. Tumor invasion was found in 4/7 and 1/3 lymph nodes of the lesser and greater curvatures of the stomach, respectively: two pyloric lymph nodes, 2/4 of those excised from the celiac artery, and a para-aortic. The patient received complementary chemotherapy cycles for two months (epirubicin 50 mg/m^2 *i.v.* on day 1, cisplatin 60 mg/m^2 *i.v.* on day 1, 5-fluorouracil 200 m^2/day *i.v.* by continuous infusion for 24 weeks). This cycle was repeated every 21 days two years later. In November 2008 the patient sought consultation for an erythematous eroded skin lesion over the left axilla. Digital mammography showed findings of fibrous mastitis (Birads class III), but no signs of malignancy; ultrasonography of the left axilla showed inflammatory lymphadenopathy. Bilateral digital mammography performed in December 2008 did not disclose pathologic findings. However, in May 2009 the patient exhibited redness around the nipple, which gradually spread peripherally, with progressive development of a papillomatous multinodular growth over the erythematous zone (Figure 1a and b). During hospitalization, the patient developed a great amount of pleural fluid at the left side, pericardial collection and ascites, confirmed by thoraco-abdominal CT and heart ultrasound. Gastroscopy did not reveal abnormalities at the level of the anastomosis.

A biopsy taken from a cutaneous nodule of the breast skin showed a diffuse dermal tumor of cells with a variable appearance. Those located in the upper and mid-dermis were mostly spindle-shaped, and formed fascicles or were interspersed individually between collagen fibres (Figure 2a and b). In the lower dermis, many neoplastic cells were round, with ample cytoplasm, occasionally with a signet-ring appearance. Tumor cells occasionally formed small nodules, and rare lymphatic emboli were also seen. The surrounding dermis contained moderate deposits of mucin. These changes were consistent with cutaneous metastasis, although the presence of spindle-shaped tumor cells in the upper dermis was reminiscent of a mesenchymal tumor, such as (dermato)fibrosarcoma.

An immunohistochemical examination was performed on deparaffinized and rehydrated 5 μm-thick sections with the Ventana ES automated AEC immunohistochemistry system (Ventana Medical Systems Inc., Tucson, AZ, USA). Both spindle-shaped and round tumor cells expressed keratin 7 and (to a lesser extent) keratin 20, epithelial membrane antigen and MUC-5AC (Figure 3), but did not express MUC-2A, CD34, CD68 or CDX2 (Table I). Sections of the gastric ADC were retrospectively examined immunohistochemically with the same antibodies. An almost identical profile with that of the cutaneous tumor was found (Figure 3 and Table I), further supporting the diagnosis of skin metastasis from the signet-ring gastric ADC.

The patient was lost to further follow-up.

Discussion

The mechanisms that predispose some internal malignancies to metastasize to the skin are poorly known. The skin may provide a favorable environment for the colonization and survival of only certain types of cancer cells. In addition, specific factors may play a crucial role in the skin-homing mechanism of metastatic cells. Recently chemokines and their receptors have been shown to be involved in tumorigenesis and metastasis. Chemokine receptor CCR10, whose ligand CCL/CTACK is constitutively expressed by epidermal keratinocytes, seems to be involved in cutaneous metastasis of melanoma. The chemokine receptor CXCR4, whose ligand stromal cell-derived factor-1a/CXCL12 is constitutively expressed by dermal fibroblasts and endothelial cells, has been shown to be important in the growth, angiogenesis and invasion of cutaneous basal carcinomas, and plays a role in the skin-homing mechanism of Sézary cells. It seems therefore that CCR10 and CXCR4 may be involved in the preferential ability of certain cancer cells to establish in the skin. Metastatic cells may survive more easily if the secondary site has similar characteristics to the primary organ. The frequency of cutaneous metastasis from carcinomas of the upper gastrointestinal tract in Western countries is lower than 1% (5).

Gastric ADC accounts for the great majority (95%) of gastric tumors. Around 9% of all gastric carcinomas are signet-ring cell ADC (11). Gastric ADC usually metastasizes to the liver, peritoneal cavity and regional lymph nodes more often than to the skin. Metastases of gastric ADC account for 5-7% of all skin metastases (12), although this frequency is much higher (20%) in Japan (15); they are more prevalent in males, reflecting the higher prevalence of the corresponding primary in men. Metastases usually appear several months or years after the diagnosis of the primary, but may also be the presenting sign of the neoplastic process or the presenting sign of the recurrence of the primary tumor (16).

Cutaneous metastases of gastric ADC usually develop on the abdominal skin (7, 8, 15), including the umbilicus (sister Mary Joseph's nodule) (17); less common sites include the breast (18, 19), eyelids, back (9), face (20), scalp, neck, upper extremities, chest, shoulders/arms (7) and perianal region (21). Such metastases usually manifest as solitary or multiple red or violaceous dermal or subcutaneous painless nodules, occasionally arranged in a zosteriform distribution (22); they may also appear as cellulitis- or erysipelas-like erythematous plaques (carcinoma erysipelatoides) (5, 7, 14), scarring alopecia (5) or cauliflower-like growths and ulcers (10). In one patient, they mimicked allergic contact dermatitis of the face (20). Cutaneous lesions are usually correctly identified as metastases by the clinician before the pathologic diagnosis if the patient has a known past history of neoplasia; however, the lesions may be misdiagnosed as

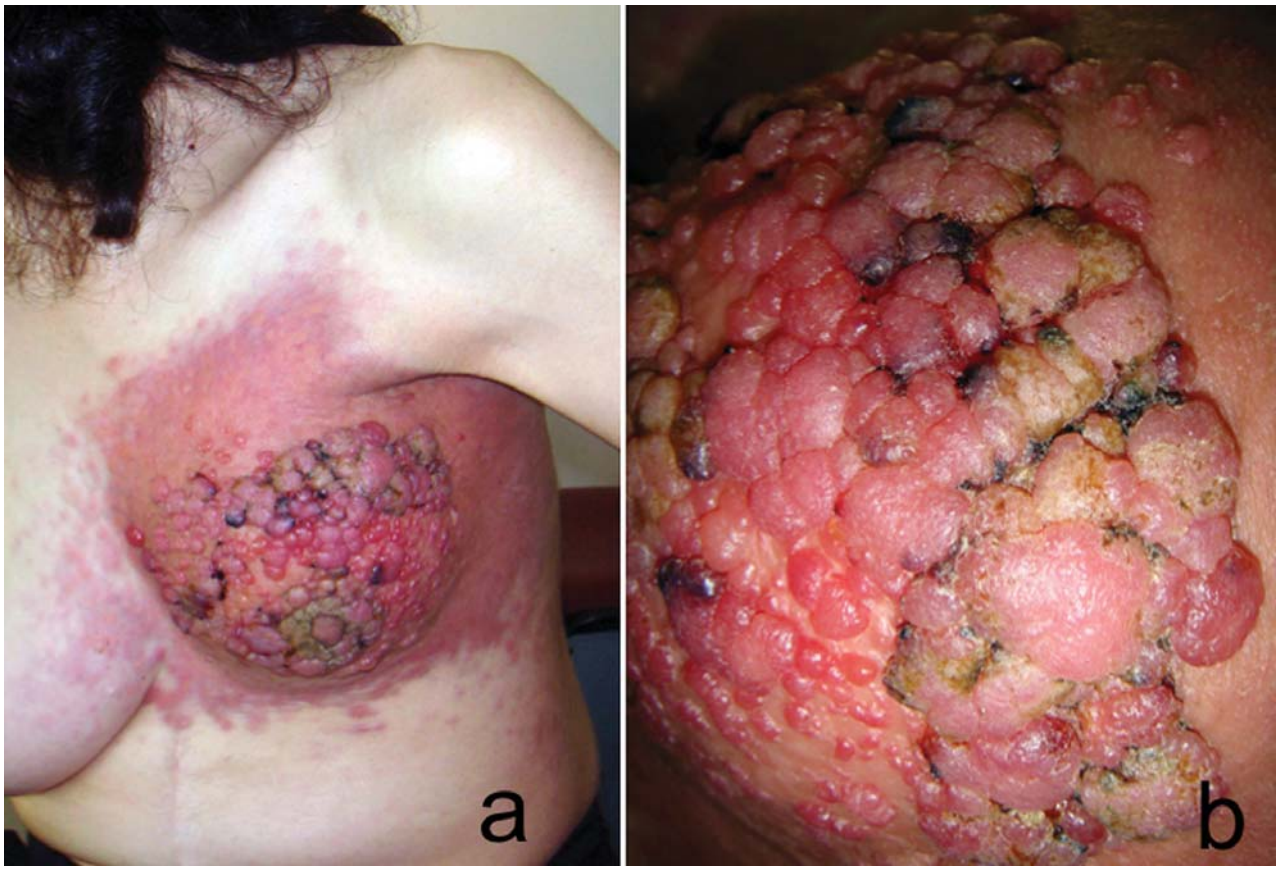

Figure 1. *a: Clinical aspect of the skin metastasis: multinodular growth over erythematous skin of the breast and the left hemithorax. b: Close-up view of the lesions.*

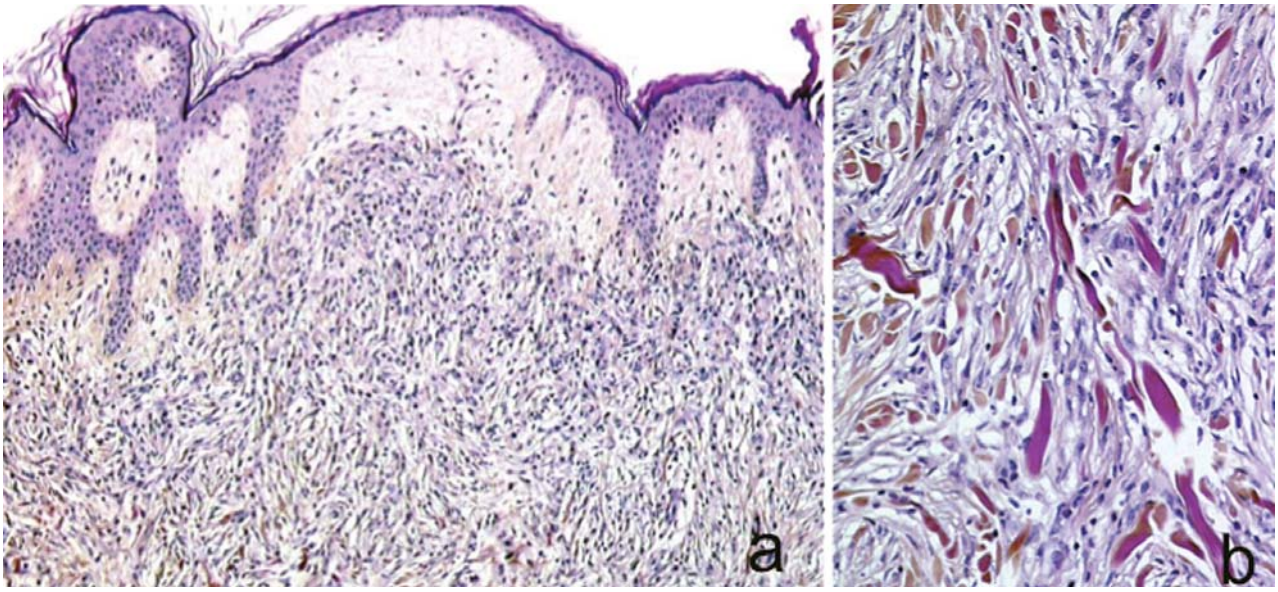

Figure 2. *Pathological aspect of the skin tumor. a: The dermis is invaded by a dense proliferation of spindle-shaped cells. b: High power view of tumor cells (hematoxylin-eosin, original magnifications: a: ×100, b: ×250).*

Table I. *Immunohistochemical phenotype of the cutaneous metastasis and the gastric primary adenocarcinoma.*

Antigen (antibody)	Gastric adenocarcinoma	Cutaneous metastasis
Epithelial membrane	+++	++ (spindle cells)
Antigen (E29)		+++ (round cells)
Keratin (AE1/AE3)	+++	+++
Keratin 7 (OV-TL)	+++	+++
Keratin 20 (Ks20.8)	+++	+
MUC-5AC (45M1)	+++	++
Ki-67 (MIB-1)	++	++
CD34 (QBend-10)	–	–
CD68 (PGM1)	nd	–
CDX2 (CDX2-88)	nd	–
MUC-2A (CCP58)	–	–

–: Negative, +: <15% positive cells, ++: 15-50% positive cells, +++: >50% positive cells. nd: Not done.

benign lesions, such as epidermal cysts, pyogenic granulomas, hemangiomas, herpes zoster or neurofibromas (15). From a pathological point of view, metastases of gastric ADC are usually anaplastic infiltrating carcinomas, with variable cellularity, a loose stroma and varying proportions of signet-ring cells (23). The mucin present in metastases from gastrointestinal carcinomas (similarly to mammary and pulmonary ones) is a non-sulfated, hyaluronidase-resistant, sialic acid-type mucosubstance. Histochemically, this mucin is positive with colloidal iron; hyaluronidase-resistant; Alcian blue-positive at pH 2.5 and negative at pH 0.4; aldehyde-fuchsin-positive at pH 1.7 and -negative at pH 1.0; PAS-positive/diastase-resistant, mucicarmin-positive (23); and metachromatic with toluidine blue at pH 3.0.

Our patient is remarkable from both a clinical and histopathological point of view. Indeed, skin metastasis of gastric ADC is rare in women, also reflecting the rarity of the

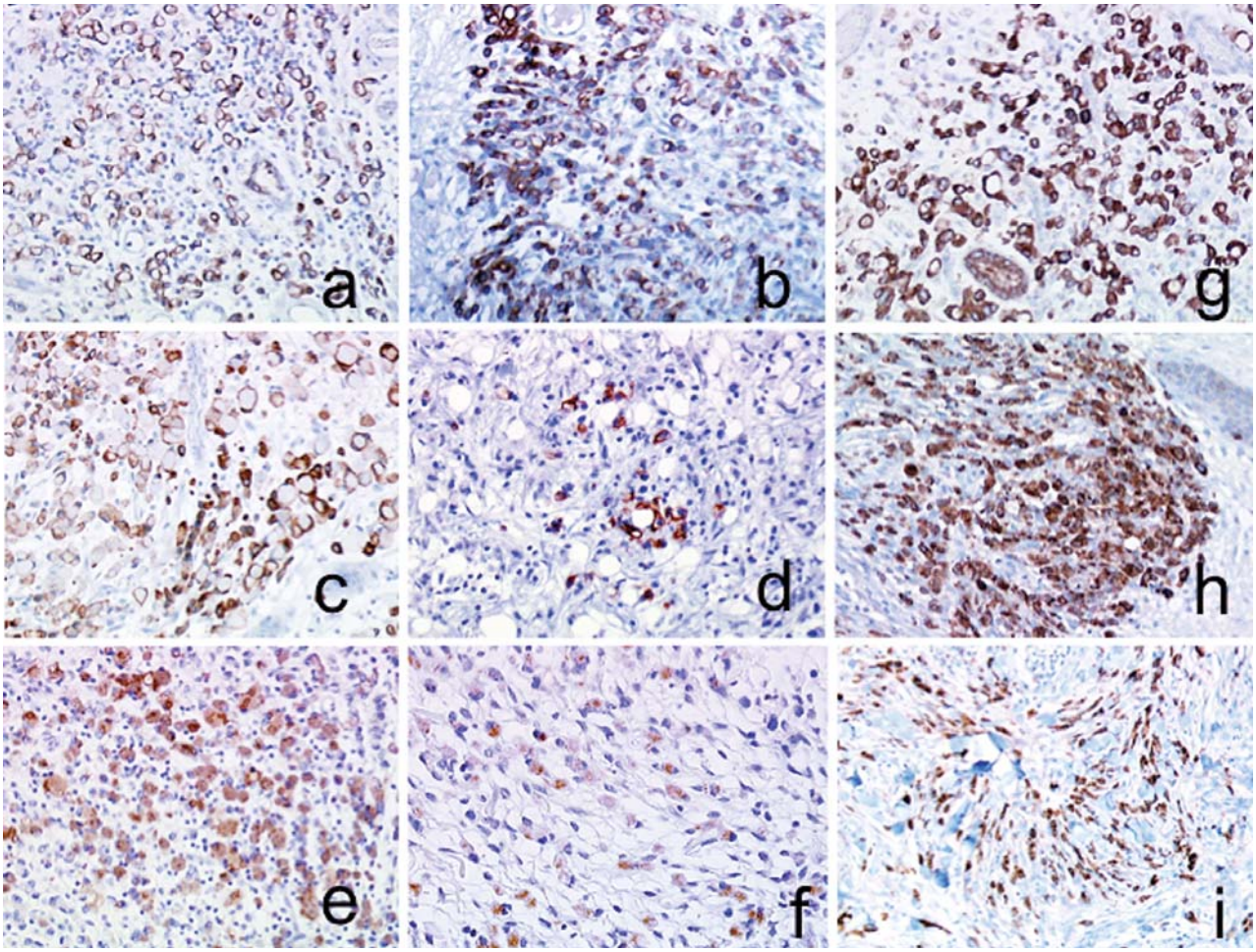

Figure 3. *Immunohistochemically, the tumor cells expressed keratin 7 (a: gastric ADC, b: skin), keratin 20 (c: gastric ADC, d: skin) and MUC-5AC (e: gastric ADC, f: skin). Epithelial membrane antigen was expressed by gastric ADC cells (g) and the skin tumor, both in signet-ring (h) and spindle cells (i) (immunoperoxidase revealed with aminoethylcarbazole, original magnifications: ×250).*

corresponding primaries. Although the anterior part of the chest is the most frequent site of cutaneous metastasis in women, the primary is such cases almost invariably in the breast; as a matter of fact, the clinical aspect of our patient was consistent with metastatic breast ADC. The clinical appearance of the metastasis was also unusual because of its florid, multinodular aspect on erythematous skin, contrasting with the more usual appearance of one or few nodules. From a pathologic point of view, the cutaneous metastasis was composed predominantly of spindle-shaped cells, therefore mimicking a mesenchymal/fibrohistiocytic tumor. This possibility was clearly excluded thanks to the immunohistochemical study, which showed that tumor cells expressed epithelial glandular markers, such as keratins 7 and 20, epithelial membrane antigen, and MUC-5AC, but not fibrohistiocytic markers (CD34, CD68). This phenotype was consistent with a gastric origin of the metastasis, given that gastric ADC expresses K7 (24-26) and MUC-5AC in 75% and 57% of cases respectively, whereas MUC-2A is not expressed in 70% of cases (27). Furthermore, for our patient, the phenotype of the metastasis proved to be very similar to that of the gastric ADC, further supporting the latter as the origin of the former.

As with other skin metastases of visceral tumors (28), the prognosis of metastatic gastric ADC is as a rule grim. Prolonged survival of several years has been recorded (29-30), but remains an exception.

In conclusion, cutaneous metastasis of signet-ring gastric ADC is rare, especially in women, and may show unusual clinicopathological features, rendering diagnosis challenging. In such cases, immunohistochemistry is a very useful adjunct in pathological diagnosis (28, 31).

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