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Triple-negative breast cancer possibly transforming into malignant melanoma due to targeted therapy? A case report and review of literature

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Summary
Background Triple-negative breast cancer (TNBC) is characterized by lacking expression of estrogen receptor and progesterone receptor as well as absence of human epidermal growth factor receptor 2 overexpression and is an aggressive clinical phenotype.

Patients and methods We report the case of a 33-year-old woman who has been treated using a targeted approach for TNBC and developed a malignant melanoma metastasis without any primary.

Results and conclusion Using targeted therapies, tumors can be treated much more effectively, but up to now, we do not know much about potential adverse reactions. Due to the targeted therapy, tumors may be pressurized for transformation. We call for further investigations to rule out the potential risks of targeted therapy in TNBC. This is the first report of a potential transforming of one tumor entity to another by a targeted therapy.

Keywords Breast cancer · Triple-negative disease · Targeted therapy · Malignant melanoma

Umwandlung eines triple-negativen Mammakarzinoms in ein Melanom aufgrund zielgerichteter Therapie? Fallbericht und Literaturübersicht

Zusammenfassung
Grundlagen Triple negative Mammakarzinome sind aggressive Tumore, welche Hormonrezeptor (ER, PgR) negativ sind und keine Überexpression des Onkogens HER2 aufweisen.

Patienten und Methodik Wir berichten über eine 33-jährige Patientin, welche mit zielgerichteter Therapie gegen das Mammakarzinom behandelt wurde und eine Melanommetastase ohne auffindbares Primum entwickelte.

Ergebnisse und Schlussfolgerungen Mit Hilfe zielgerichteter Therapie können Tumoren effektiver behandelt werden. Tatsächlich aber wissen wir bis dato wenig über mögliche, Nebenwirkungen. Es ist z. B. möglich, dass sich der Tumor unter der zielgerichteten Therapie „Auswege" in Form der Aktivierung alternativer Signaltransduktionswege sucht. Weiterführende Untersuchungen werden nötig sein. Dies ist der erste Bericht einer möglichen Umwandlung einer Tumorentität in eine andere unter einer zielgerichteten Tumortherapie.

Schlüsselwörter Mammakarzinom · Triple-negatives Mammakarzinom · Melanom · Zielgerichtete Therapie

Introduction

Triple-negative breast cancer (TNBC) is characterized by lacking expression of estrogen receptor (ER) and progesterone receptor (PgR) as well as absence of HER2 (human epidermal growth factor receptor 2) overexpression [1, 2]. It accounts for approximately 15 % of all breast cancers [2], is an aggressive clinical phenotype, shows higher rates of recurrence, and is known for its poor outcome [3]. TNBC

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is known to show a multitude of specific alterations at the molecular level, including a high rate of p53 alterations, a high mitotic index, the loss of BRCA1 function, or activating tyrosine kinases (TKs; e.g., fibroblast growth factor 2) [1]. Because of its expression profile, therapeutic strategies are difficult to develop. Up to now, systematic treatments are limited to cytotoxic chemotherapy [2]. Although chemotherapy is currently the mainstay, results are disappointing, and evidence-based therapeutic studies for this entity are missing. Identification of qualitative and quantitative differences of molecular events and pathways in cancer cells has led to potential and novel targets for cancer therapy [4]. Targeted agents are specifically designed to regulate or inhibit critical signal transduction pathways in malignant cells, and ideally result in apoptosis of tumor cells [4]. The points of vantage are molecules responsible for proliferation, angiogenesis, or apoptosis. So far, no report has discussed a potential transformation from TNBC to another tumorous entity, possibly induced by a potent targeted therapy.

Case report

A 33-year-old woman had been diagnosed for cancer of the right breast in October 2007. Histopathology revealed a triple-negative, multifocal, ductal breast cancer [pT3 (ø 6 cm), N2a (5/10), Mx, G3, ER neg., PgR neg., HER2: neg.]. The patient did undergo mastectomy and axillary dissection, and the breast was reconstructed using a TRAM flap in October 2007; adjuvant therapy had been denied by the patient. Nine months later, she presented with a local recurrence in an infraclavicular lymph node at the right site, which has been excised. The afresh rejection of adjuvant therapy led to another local relapse in the skin 3 months later in July 2008. Four months later, the patient reported extensive back pain. Magnetic resonance imaging evaluation showed bone metastases in the thoracic and lumbar spine. The patient denied any systemic therapy or radiation therapy. In February 2009, progressive disease was diagnosed; massive destruction of the body of the thoracic vertebra XI and the lumbar vertebra III as well as lung metastases were detected. The patient agreed now to undergo systemic therapy. Skin metastases were excised for further evaluations. A proteome analysis by immunohistochemical proofs had been performed, which verified the triple-negative carcinoma. Additionally, extensive expressions of thymidine phosphorylase, COX-2, and vascular endothelial growth factor-A (VEGF-A) were seen with a moderate proliferation of Ki-67 (10 %). The patient initially refused any type of conventional chemotherapy until presence of metastatic disease. She asked for a therapeutic option that is likely to offer a maximum in quality of life and may avoid alopecia. According to those results and due to the patient's request in February 2009, we started with an individualized combination chemotherapy using capecitabine (3,000 mg/day), which uses tumor-derived thymidine phosphorylase to release 5-fluorouracil (5-FU) in and immediately around the tumor cells (metronomic chemotherapy); celecoxib (400 mg/day), due to the strong COX-2 expression; and bevacizumab (15 mg/kg bodyweight), due to the strong VEGF-A expression, each for 3 weeks for a total of 8 months. Due to this therapy, we could see partial response for 10 months. In December 2009, progressive disease was diagnosed. Therapy was changed to paclitaxel, carboplatin, and bevacizumab as well as celecoxib for six cycles. The administration of celecoxib and bevacizumab was prolonged, providing further inhibition of angiogenesis. The subcutaneous metastasis diminished gradually, and evaluation showed again a partial response. A novel immunohistochemical analysis revealed a high Ki-67 proliferation index (40 %) and increased HER2 (1+) and epidermal growth factor receptor (EGFR) (2+) expression. To further alter the tumor growth, therapy was changed to lapatinib 2 × 250 mg/day (as both HER2 and EGFR will be affected by this agent), bevacizumab 10 mg/kg, capecitabine 500 mg twice daily, and celecoxib 200 mg twice daily. The patient tolerated therapy very well. A large metastasis (7 cm in diameter) on the right chest wall disappeared under treatment almost completely. However, after the sixth cycle, the patient developed massive neurological failure, in particular with loss of ambulatory ability. Computed tomography evaluation showed brain metastases located in the spinal canal, leading to a stenosis of at least 50 %. Laminectomy was done. Histology showed a multitude of S100-positive cells (Fig. 1) and revealed a malignant melanoma metastasis. Our patient was screened accurately, but no primary malignant melanoma could be detected. After excision of the melanoma metastases of the spinal cord, the region was radiated with 20 Gy. Due to expression of c-kit, therapy was changed to imatinib. However, before the therapy could be started, the patient died 40 months after initial diagnosis and 3 months after the occurrence of the malignant melanoma metastasis.

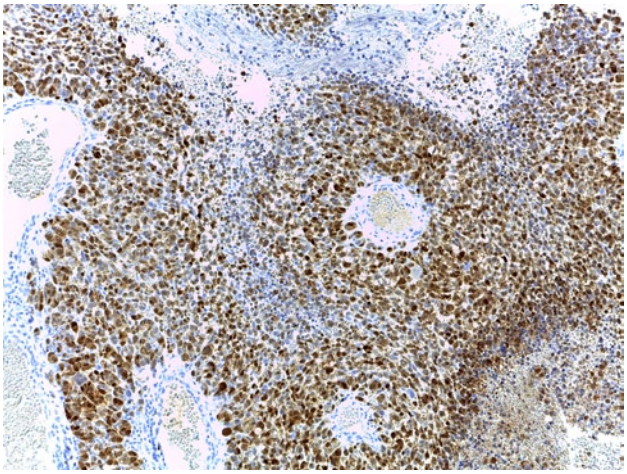

Fig. 1 Histology showed a multitude of S100-positive cells

Discussion

We report the case of a 33-year-old woman suffering from a TNBC, who has been treated with targeted therapeutic agents and developed a melanoma metastasis without any detectable primary melanoma.

TNBC is known to be linked with younger age, high aggressiveness, high mitotic index, and poor life expectancy compared with other breast cancer types [2, 3]. In our patient, we used targeted therapy after informed consent was given, as the therapeutic regimen was highly individual. Therefore, we developed a schemata based on the molecular changes we found in the proteomic analysis (oncobiogram® product of the Sanoxsys GmbH, Munich, Germany). Immunohistochemical analysis revealed—except for the absence of ER, PgR, and HER2 (over)expression—a high Ki-67 proliferation index (40 %) and high EGFR (2+) and VEGF (3+) expression.

EGFR is a transmembrane growth factor receptor TK [4], the overexpression of which is characteristic for TNBC and which is frequently expressed in epithelial tumors [4]. EGFR is crucial for cell proliferation and malignant growth [4], and its overexpression can be linked with aggressive clinical behavior. As angiogenesis has an essential role in cancer incidence as well as invasion and metastasis [4], agents that block VEGF-A are important targets in tumor therapy. An increase of VEGF-A has been detected in 34 % of TNBC patients [5]. Keratin 18 (K18) test has been negative, and its expression has been found to be low in highly metastatic cell lines [6]. It has been proven that high K18 expression in tumor cells is associated with reduced aggressiveness and metastatic spread of breast cancer [6]. In our case, the patient was treated according to a targeted approach and received paclitaxel, carboplatin, capecitabine, and bevacizumab, for combating the tumor's characteristics. Using targeted therapies, tumors can be treated much more effectively, but up to now, we do not know much about potential adverse reactions. Paclitaxel belongs to the group of taxanes, is a mitotic inhibitor, and is one of the most widely used first-line therapeutic agents in metastatic breast cancer [7]. In 2002, Loesch et al. [8] reported approximately a 62 % ORR achieved by weekly paclitaxel plus carboplatin, an alkylating agent that is able to interact with DNA, in advanced breast cancer. In 2010, Chang et al. [9] discovered the combination of taxanes and carboplatin as one of the most effective first-line therapies for TNBC patients. Bevacizumab is a humanized, monoclonal antibody directed against VEGF, and therefore targeting tumor vessel growth [4]. In 2008, bevacizumab was approved by the United States Food and Drug Administration for metastatic HER2-negative breast tumor, in combination with paclitaxel, and significant benefit could be observed [10]. Capecitabine is an oral prodrug of 5-FU and a highly tumor-specific chemotherapeutic agent inhibiting DNA synthesis, as it is activated by the enzyme thymidine phosphorylase, which is more expressed in high concentrations in neoplastic than healthy tissue [11] and is especially used in HER2-negative tumors.

Malignant melanoma is a neoplasm of melanocytes, which originates from the neuro-ectodermal crest and can migrate to the epidermis, uvea, leptomeninges, and ectodermal mucosa. In the majority of cases, melanoma develops de novo. Ultraviolet radiation, family (or previous personal) history of melanoma, and dysplastic or congenital nevi present risk factors. In our patient, no history of familial or personal melanoma, dysplastic or congenital nevus, or extensive sun exposure could be detected. It has been demonstrated that patients who had breast cancer are more likely to develop second malignancies [12]. It has to be stated that there exists the possibility that our patient developed a second "de novo" malignancy. However, no primary was found, and our patient had no risk factors for melanoma. Further histological evaluation was discussed extensively. Immunohistochemical analysis of the melanoma metastasis revealed absence of ER, PgR, CA 15-3, and the prolactin-producing protein GCDFP-15; S100, HMB-45, and melan-A were found in high concentration. Comparison of the TNBC with melanoma metastasis revealed an expression of K18 in the breast cancer histology only. In contrast to the TNBC, the melanoma metastasis showed strong expression of vimentin and c-kit. Ki-67 was found in 10 % of the TNBC and in 80 % of melanoma metastasis. The expression of EGFR was found in the TNBC, but not in melanoma metastasis. Those results led histopathologists to the diagnosis of a melanoma metastasis. However, whether the melanoma metastasis was due to transformation of the primary breast cancer remains unclear. In general, due to dual blockade of EGFR/HER2 and subsequent activation of c-kit, a transformation might be possible by activating the alternative signal transduction pathway. Regardless, a de novo development of the melanoma might be possible too. Further specific investigations were limited by the death of the patient. In 2008, Kirova et al. [13] noted that patients who are treated for breast cancer are at a higher risk to develop second malignancies compared with the overall population, but found no increased risk for developing malignant melanoma [13]. In contrast, some studies demonstrated that women who had breast cancer are likely to develop melanoma [12, 14]. Further on, there are reports of the occurrence of melanoma and breast cancer within the same patient [15], although synchronous presence is rare.

The development of novel drugs that intervene in the microenvironment and metabolism of tumor cells gave us the opportunity to provide an individualized therapy for patients. In our patient, an experimental therapeutic regime was chosen, as the patient rejected consistently any conventional chemotherapy, even in the adjuvant setting. To implement an individualized treatment, we initially identified possible targets and administered the corresponding agents. The administration of those drugs was based on the premise that blocking specific targets would prevent a multidrug resistance, well known by the use of conventional chemotherapy. Rather, we assumed

that disease progression under targeted therapies might be also interpreted as the capability of the tumor developing alternative molecular pathways. Moreover, nowadays several studies observed benefits after a treatment regime beyond progression by adding additional therapeutic agents rather than discontinuation of the initial drug [16]. In our patient, disease was relatively stable for approximately 40 months after that approach. However, sudden appearance of melanoma metastasis led to relatively unexpected and rapid death.

This case raises the question whether TNBCs, treated with targeted therapy, may transform to other entities. Due to the targeted therapy, tumors may be pressurized for transformation. We call for further investigations to rule out the potential risks of targeted therapy in TNBC.

Conflict of interest

The authors declare no conflict of interest.

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