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BRIEF REPORT

Breast cancer scalp metastasis as first metastatic site after scalp cooling: Two cases of occurrence after 7- and 9-year follow-up

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Abstract Chemotherapy-induced alopecia is a commonly feared chemotherapy side effect and can be prevented using scalp cooling. Scalp metastasis is a rare site of recurrence. There is a question about whether or not the risk might be increased with the use of scalp cooling. Two cases of breast cancer with scalp metastases as first metastatic site are presented. The first patient presented with a scalp metastasis as first metastatic site 9 years following breast cancer chemotherapy treatments; she used scalp cooling for the adjuvant treatment. Second case presented a scalp metastasis as first metastatic site 7 years following treatments for her first cancer; overall, she used scalp cooling in only one of her six adjuvant chemotherapy cycles. Scalp metastases as the first site of recurrence are very rare entities. Scalp cooling is unlikely to have contributed in the cases presented here.

Keywords Scalp cooling · Breast cancer · Scalp metastasis · Chemotherapy-induced alopecia

Abbreviation
CIA Chemotherapy-induced alopecia

Introduction

Chemotherapy-induced alopecia (CIA) is one of the most troublesome chemotherapy side effects for women. CIA varies according to the type of chemotherapy regimen and duration of treatment. It may be prevented by the use of scalp cooling with variable efficacy according to the type of doses of chemotherapy used [1, 2]. Scalp cooling is not universally used and one of the reasons is the concern about safety. When considering scalp cooling's mechanisms, involving reduced chemotherapy delivery and/or efficacy in the scalp, it is possible that cancer cells, if present in the scalp, are not killed by chemotherapy if scalp cooling is used. Although scalp metastasizes can occur in patients with widely diffuse metastatic disease, it is uncommon to be the first site of recurrence. The authors present two cases of scalp metastasis of confirmed breast origin as the first site of distant breast cancer metastasis.

Cases report

Case 1

A 50-year-old woman was diagnosed with an invasive lobular carcinoma in her left breast in June 2000. She had

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no breast cancer family history. Medical history shows schizophrenia and major depression, for which she was treated. She had a left modified radical mastectomy in August 2000. The pathology showed a tumor of 7.5 cm in diameter, grade I/III, estrogen receptor-positive, progesterone receptor-positive and HER2-negative. Eleven out of 12 lymph nodes were involved. Systemic treatments were 4 AC (doxorubicin and cyclophosphamide) cycles followed by tamoxifen for 5 years. Scalp cooling was used during the first two AC treatments (she developed CIA following second treatment; scalp cooling was discontinued). She developed a post-chemotherapy scalp folliculitis. She received radiation therapy to left chest wall (45 Gy) and to sus-clavicular area (40 Gy). She received adjuvant letrozole after the 5 years of tamoxifen.

Clinical follow-up was negative until January 2009, when she presented three subcutaneous nodules of less than 1 cm at the occiput. Biopsy proved a carcinoma compatible with a mammary origin; it was the first site of distant metastasis. Bone scintigraphy and CT scan showed no metastases at other sites. Since scalp metastasis developed under letrozole treatment, she received exemestane for 3 months and a regression was observed. Patient was hospitalized with a syndrome of inappropriate secretion of anti-diuretic hormones. Investigation showed bone metastases and a partially obstructive caecum lesion. She then had a right hemicolectomy and pathology showed a benign tubulovillous adenoma in the caecum and lymph nodes with mammary carcinoma. She then received capecitabine and pamidronate. She developed meningeal carcinomatosis and died in May 2010.

Case 2

A 30-year-old woman was diagnosed with an invasive ductal carcinoma in her left breast in March 1997. Tumor was 0.4 cm in diameter, grade I/III, $T_1N_0M_0$. Receptors statuses were not performed at that time. She had wide local excision and axillary dissection. She received radiation therapy to her left breast. Systemic treatment was 6 cycles of CMF (cyclophosphamide, methotrexate, 5-fluorouracil). She used scalp cooling in only one of her six CMF cycles.

She presented a local recurrence in her left breast in June 2002. She was locally treated using wide local excision. Margins were positives and treatment was completed using modified radical mastectomy. Pathology showed a 3 cm invasive ductal carcinoma, grade II/III, estrogen receptor-negative, progesterone receptor-positive, and HER2-negative. She received 6 FEC-100 (epirubicin 100 mg/m^2, 5-fluorouracil, cyclophosphamide) cycles and tamoxifen for 2 years. Scalp cooling was not used for any FEC-100 treatments.

She presented two scalp metastases in August 2004, of confirmed breast cancer origin. Biopsy showed metastases compatible with an invasive ductal carcinoma, estrogen receptor-positive, progesterone receptor-positive, and HER2-negative. She received weekly docetaxel cycles for 12 doses. She then successively received anastrozole, exemestane, and letrozole. She presented metastases in mediastinum lymph nodes in 2006. She received capecitabine. Progression was noted in 2007. She received docetaxel again. Progression was noted again and she received fulvestrant and then vinorelbine. Scalp metastasis progressed to a size of 6 × 7 cm. She received radiation therapy to scalp lesions to reduce pain and pruritus and these symptoms improved.

Discussion

Although temporary in most cases, CIA is one of the most feared and emotionally distressing consequences of breast cancer treatment [1]. Since the 1970s, scalp cooling has been used predominantly in Europe to prevent CIA. CIA occurrence depends on chemotherapy regimen, doses, duration, and previous exposition to cytotoxic agents [1]. Scalp cooling efficacy depends on the type of chemotherapy regimen [2]. Scalp cooling is carried out using series of cold caps changed at intervals to keep the scalp cold or using a machine that circulate refrigerated glycol-based fluids in the cap. Cooling is started about 15 min prior to chemotherapy treatment and continues 60–90 min after treatment completion.

Three hypotheses have been formulated to explain the decrease in the degree of CIA with the use of scalp cooling: (1) cutaneous vasoconstriction leads in local decrease in chemotherapy delivery to hair follicles; (2) decrease in hair follicle cells chemotherapy uptake; and (3) decrease in follicular cells metabolic rate [3, 4].

One of the major concerns of scalp cooling is its possible effect on chemotherapy delivery to (micro-) metastases of the scalp skin, if present. A retrospective study performed in the center showed a 1.1% incidence (6 women out of 553) of scalp metastasis in patients who used scalp cooling in the neoadjuvant or adjuvant setting versus a 1.2% incidence (1 woman out of 87) in patients who did not used scalp cooling in the neoadjuvant or the adjuvant (although the patient used it in the metastatic setting), with median follow-up of 5.8 and 5.4 years, respectively. In all cases, scalp metastasis was not the first metastatic site. Median interval between breast cancer diagnosis and first distant metastasis was 29.3 months and median interval between first distant metastasis and scalp metastasis was 3.4 months [5]. A review by Grevelman and Breed [2] reported only nine scalp metastasis among about 2,500

patients from 56 studies. However, among these studies, most did not asses scalp metastases. Two systematic follow-up studies showed reassuring results, but had short follow-up period. The first study reported no increase in scalp metastases after scalp cooling use in 98 patients (median follow-up period was 9 months) [6]. The second study found no metastases after a median follow-up of 15 months among 74 patients [7]. Results published in abstract form reported 0.39% incidence of scalp metastasis among 770 patients (93% breast cancer) who received scalp cooling and no cases in 141 patients who did not receive scalp cooling, after a median follow-up of 36 months [8]. Another abstract reported 0.5% of scalp metastases, synchronous with other metastases after palliative treatment, in 395 patients who received scalp cooling and 0.1% of scalp metastasis among 28,916 patients who did not used scalp cooling; quality of life and hair loss were also improved by scalp cooling [9]. Because of rarity of scalp metastasis occurrence following scalp cooling, no study examined scalp cooling influence on survival. However, two reported cases had a regression of their scalp metastasis under chemotherapy despite the use of scalp cooling, indicating that some cytotoxic agents circulate in the scalp during scalp cooling [10, 11].

It must be emphasized that autopsy series showed that many cancer types (lung, breast, gastric) are associated to scalp metastasis [12–16]. Some of these studies were performed before the chemotherapy era and it is then reasonable to assume that no scalp cooling was used. Based on these studies, the authors may assume that scalp is a possible metastatic site for breast cancer, whether scalp cooling has been used or not.

In most cases reported so far, scalp metastases after scalp cooling were not the first metastatic site and the scalp metastasis might then only be the result of widespread metastatic disease [2, 5, 10, 17, 18]. Two reported cases in which the scalp was the first metastatic site had hematologic malignancies, supporting the idea that scalp cooling should not be used in these cases [19, 20].

The authors report two cases of scalp metastasis as the first metastatic site of breast cancer. The first case used scalp cooling and presented a scalp metastasis 9 years after chemotherapy; many other metastases were found a few months later. With 11 out of 12 lymph nodes involved at diagnosis, she was at high risk of relapse. The authors cannot exclude that widespread metastatic disease was already present, but undetected, when scalp metastases were discovered. However, it must be emphasized that she developed CIA despite scalp cooling, strongly suggesting that chemotherapy did reach the scalp in a sufficient amount to cause CIA; it is thus unlikely that the scalp metastasis was related to scalp cooling. The second case used scalp cooling only in one out of six CMF cycles and did not use it during six FEC-100 cycles; she presented a scalp metastasis 7 years following her first breast cancer. It is unlikely that scalp cooling use in one out of 12 chemotherapy cycles induced metastatic spread to scalp about 7 years after its use.

According to previous studies and to the two presented cases, it is reasonable to conclude that breast cancer scalp metastases are rare entities that can arise whether scalp cooling was used or not. However, safe conclusions about safety, clinical outcomes and survival may arise only from a carefully designed clinical trial.

Conflict of interest All authors declare no conflict of interest with the study presented in this article. There was no financing for this study. Authors possess full control of data.

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