

## CASE REPORT ΕΝΔΙΑΦΕΡΟΥΣΑ ΠΕΡΙΠΤΩΣΗ

### Occult breast cancer with metastasis to the scalp

Bones, lungs, liver, and brain are the main targets of breast cancer (BC) metastases. Cutaneous metastases of malignancies are uncommon, but BC is the most frequent origin of female cutaneous metastases, which can be the initially affected site. Scalp metastases are exceedingly rare (up to 7% of all skin implants), more often occurring in widespread cases; besides, occult BC have been described in less than 1% of these patients. Diagnosis of scalp metastases from BC is reported in a 75-year-old female with a chronic erythematous plaque and superficial telangiectasias on the left occipital region. Histopathological evaluation of the resected lesion was consistent with metastatic adenocarcinoma positive for estrogen receptor (100% of the cells), and progesterone receptor (60% of the cells), besides positivity for GATA3 and Ki67 in 20% of the cells.

Cutaneous metastases are more common in females with breast cancer (BC) than internal malignant neoplasms, but implants in the scalp constitute a very rare finding.<sup>1-10</sup> Skin metastases may be the first manifestation of cancer in less than 1% of cases, and implants of unknown primary site occur in one third of metastatic scalp malignancies.<sup>2</sup> Scalp is the site of 2% of all skin tumors, which either have origin in the epithelium, pilosebaceous unit, eccrine and apocrine glands, or are metastases from distant tumors.<sup>2,9</sup> Scalp invasion due to distant metastasis is derived from hematogenous or lymphatic routes.<sup>6,8,10</sup> The incidence of scalp metastases as the first site of BC recurrence (0.025%) seems not to be associated to local cooling to avoid alopecia due to adjuvant chemotherapy.<sup>3,4</sup> These implants of BC usually appear either as neoplastic alopecia, erythematous nodules and masses, ulcers, or erysipeloid, scirrhous, telangiectatic, and zoster-like patterns.<sup>2,4-8,10</sup> BCs are grouped in accordance with immunohistochemistry profile as those expressing estrogen receptor (ER) and or progesterone

receptor (PR), those expressing epidermal growth factor receptor 2 (HER2), and triple-negative (TN) without any of these markers, whereas the TN molecular type is more prone to the risk of presenting cutaneous metastases.<sup>5</sup> The cutaneous BC metastases frequently present immunohistochemistry positivity for cytokeratins (AE1/AE3 and CK-7), chromogranin, ER, PR, gross cystic disease fluid protein-15 (GCDFP-15), HER2, GATA-3, CD31, mammaglobin, e-cadherin, or podoplanin.<sup>2,3,5-7,9,10</sup> Differential diagnoses include alopecia, telangiectasia, dermatitis, cellulitis, urticaria, erysipelas, herpes zoster, and primary skin adnexal tumors.<sup>2-4,6,8-10</sup> Estimated survival of patients at diagnosis of BC cutaneous metastasis is less than one year.<sup>2</sup> The treatment includes surgery, radiotherapy, chemotherapy, electrochemotherapy, laser, brachytherapy, cryotherapy, hyperthermia, photodynamic and hormonal therapy.<sup>1,7,8,10</sup>

Scalp metastasis of BC manifested as chronic erythematous plaque with alopecia and telangiectasias on the left occipital region is described in a 75-year-old female.

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Μη εμφανής καρκίνος  
του μαστού με μετάσταση  
στο τριχωτό της κεφαλής

Περίληψη στο τέλος του άρθρου

#### Key words

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The aim of this case study is to enhance the awareness of primary care health workers about the evaluation of all cutaneous abnormalities in patients with the diagnosis of BC. The role of a careful skin evaluation during the physical examination is also emphasized. Single case reports can increase the suspicion index about very uncommon conditions, favoring the diagnosis confirmation and prompt best management choice at an early time.

## CASE PRESENTATION

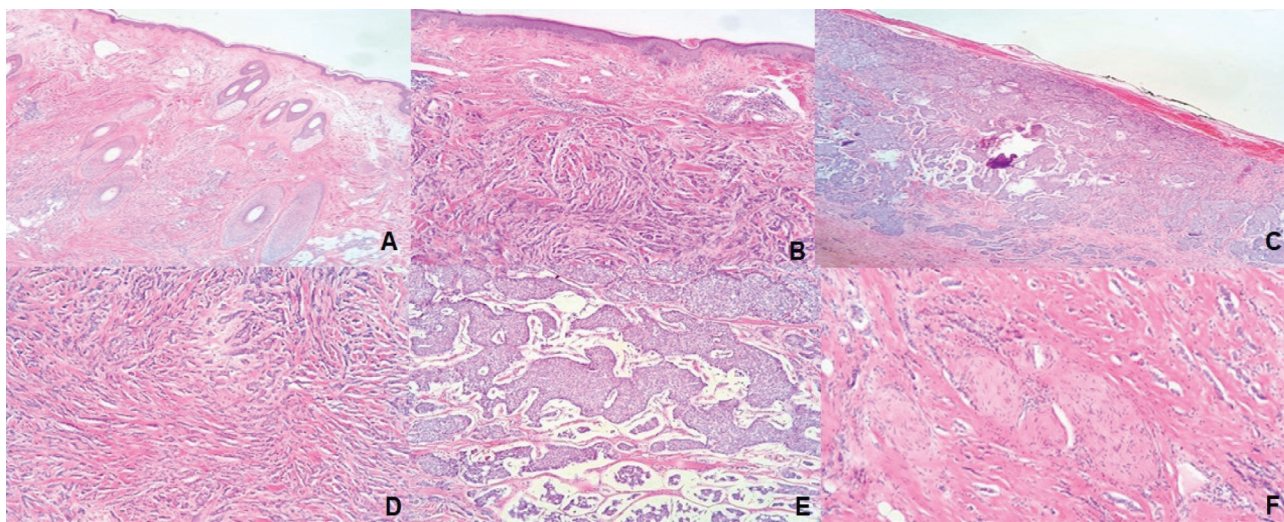
A 75-year-old female was referred by the dermatologist to the oncology section for evaluation of a chronic erythematous plaque with superficial telangiectasis sited on the left occipital scalp area (fig. 1). The pruriginous lesion measuring 4×4 cm was first noticed



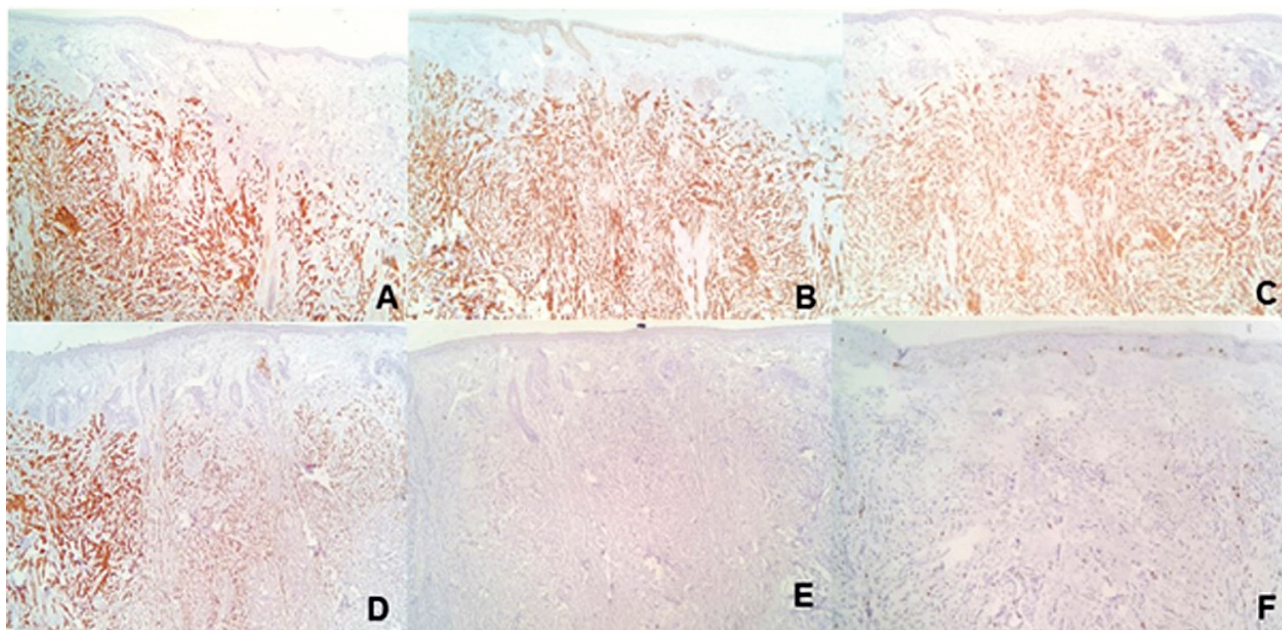
**Figure 1.** Aspect of the erythematous plaque of the scalp with alopecia foci and superficial telangiectasia.

eight years before, and previously treated in another hospital as seborrheic dermatitis and alopecia. After the initial routine evaluation, with the diagnostic hypothesis of infiltrating desmoplastic tubular carcinoma, an incisional biopsy was performed. The sample (0.4×0.3 cm) showed neoplastic proliferation in the dermis, with irregular branched and juxtaposed glands lined with columnar cells, and the nuclei at various levels of stratification, pleomorphic, atypical, with coarse chromatin and frequent mitoses. The adjacent stroma was dense with hyalinized areas, features that could correspond to an adnexal skin neoplasm or metastatic tumor. On June 1st 2021 the lesion (3.6×3.0×1.0 cm) was completely resected, and the histopathological evaluation showed a pattern of invasive adenocarcinoma (fig. 2). The immunohistochemical positivity for ER in 100% of the cells, PR in 60% of the cells, GATA3 and Ki67 in 20% of the cells (fig. 3), with the marker for HER2 negative; the profile was consistent with a metastatic BC.

Despite the absence of a history of BC, scalp metastasis originating from the breast was considered the major diagnostic hypothesis. To screen for an occult BC, initially a breast ultrasonography (USG) was performed, which showed a simple cyst in the left breast, a benign finding – category 2; and bilateral digital mammography, with rare sparse microcalcifications of benign aspects in both breasts, benign mammographic findings (BI-RADS 2). On October 8th 2021, a breast magnetic resonance imaging (MRI) showed category BI-RADS 2, with no other remarkable finding. A fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) was also performed on December 3rd 2021, and did not detect hypermetabolic alterations indicative of malignant involvement. As the possible primary focus of breast carcinoma was not found, there was a complete review of the anatomopathological and immunohistochemical data of the biopsy and excised lesion, and the cutaneous specimens were analyzed by another pathology laboratory. There was diffuse infiltration of



**Figure 2.** Histopathological study of the scalp samples stained by hematoxylin-eosin. (A) Infiltration of the dermis by neoplastic cells (4x); (B) Infiltration of the superficial dermis (10x); (C) Infiltration of the deep dermis (4x); (D) Detail of the neoplasm with a cordonal pattern (10x); (E) Detail of the neoplasm with a solid and glandular pattern (10x), and (F) Perineural infiltration (10x).



**Figure 3.** Immunohistochemistry evaluation of the scalp samples revealing CK7 (A); GATA3 (B); estrogen receptor (C); progesterone receptor (D); c-erbB-2 (E); and Ki67 (F) positive.

the dermis and hypodermis by an epithelial neoplasia, presenting cells arranged in cords, glands and solid blocks, with conspicuous hyperchromatic and irregular nuclei, and rare mitotic figures, in addition to vascular and perimetral invasion. The conclusive report was the infiltration of the dermis and hypodermis by carcinoma. The new immunohistochemical results revealed ER positive in 100% of the cells, PR positive in 60% of the cells, GATA3 positive, CK-7 positive and Ki67 positive in 5% of the cells, besides c-erbB-2 negative. As a whole, the findings were considered consistent with the primary site of the malignancy in the breast.

The patient underwent radiotherapy on the scalp from September 27th to November 3rd 2021. Still under outpatient follow-up, she remains without recurrence of cutaneous or breast lesions, and the new PET-CT with FDG on April 4th 2022 showed stability of the three small nodules previously observed at the lateral quadrant of the right breast (measuring up to 6 mm), without any detectable lesion with hypermetabolism.

## DISCUSSION

The elderly woman here described had a diagnosis of only scalp metastases of BC. This conclusion was based on the findings of histopathological studies including the positivity of immunohistochemistry markers, in accordance with the current literature. Worthy of note in this case is the lack of the primary BC site by the imaging evaluation; a phenomenon which has been rarely described in patients with skin implants of BC.<sup>2,3,6,9</sup>

A 44-year-old woman with scalp metastasis of BC had mammography, ultrasound, and tomography studies with no changes in the breast or another primary site, and the authors concluded that the implants were from an indolent BC.<sup>2</sup> Their review of literature about the scalp metastases from occult primary BCs emphasized the differential diagnosis with the sweat gland adenocarcinoma of the scalp because the female breast is considered a modified apocrine gland, and the differentiation requires a wider panel of immunohistochemical stains.<sup>2</sup> A 66-year-old female was reported with *de novo* scalp metastatic BC as the solitary site of dissemination and no identifiable breast malignancy.<sup>3</sup> The authors also highlighted the sweat gland adenocarcinoma as the main differential diagnosis, and the immunohistochemical study of BCs positive for GATA-3 and CK-7, and negative for CK-20.<sup>3</sup> A systematic review of the first discovery of primary BC occurring after the diagnosis of metastatic cutaneous lesions showed that a negative breast palpation and the unremarkable imaging evaluations do not rule out the diagnosis of BC.<sup>6</sup> The authors commented that in 20% of BC metastases the primary tumor may not be found, and the cutaneous implants can be the first clue of unsuspected primary BCs. Besides, ductal and lobular BC are positive for CK-7, ER, PR, GCDFFP-15, and mammaglobin; ductal BC is positive for e-cadherin; inflammatory BC is positive for CD31 and podoplanin; telangiectatic BC is positive for CD31, and Paget disease is positive for CK-7.<sup>6</sup> Scalp metastases were described in a 52-year-old woman with

a treated BC positive for CK-7, ER, GATA-3, GCDP-15, and mammaglobin; and these data were considered consistent with the diagnosis of cutaneous metastasis from the BC.<sup>7</sup> A 66-year-old woman was reported with erythematous alopecia, nodes, and tree-like vessels in the scalp.<sup>8</sup> Biopsy study showed epidermis of uneven thickness, slight hyperkeratosis and acanthosis; fibrosed dermis, anaplastic cells with large hyperchromic nuclei between collagen fibers, forming chains and primitive glandular structures with RE, RP, c-erbB-2, and Ki67 positive. She had a previous left BC (T2N2M0) that was treated by radical mastectomy, chemotherapy, and radiation therapy, without relapse. Considering the antecedent tumor, the scalp lesions were diagnosed as BC metastases.<sup>8</sup> A 55-year-old woman had the diagnosis of scalp metastasis of BC 10 years after the excision of the primary tumor, and the lesion palpable for 4 years had a recent increase.<sup>10</sup> The authors emphasized the developed skin lesions in patients with a history of BC and commented the positivity of CK-7, HER2, ER and PR, besides the CK-20 negative.<sup>10</sup>

Because the histopathological and immunohistochemistry patterns can be shared by both conditions, differential diagnosis between scalp metastases of BC and primary sweat gland cancer is a challenging matter if the primary breast tumor is not confirmed.<sup>9</sup> A 71-year-old female had a scalp tumor with diagnosis of BC metastasis. Biopsy study showed the dermis infiltrated by small cells with hyperchromatic nuclei grouped in nodules or cords, and ring structures, dissecting the dermis and preserving epidermis. Immunohistochemical study showed positivity for ER, CK-7, and BRST2; and PR, c-erbB-2, CK-20, TTF1, and CDX2 negative, consistent with ER-positive BC metastasis. The mammography only revealed benign calcifications and lymph nodes BI-RADS 2; ultrasonography showed hypoechogenic nodules with calcification BI-RADS 3; MRI detected heterogeneous fibrous-glandular tissue and nod-

ules with irregular margins, as well as bilateral spots with post-contrast enhancement BI-RADS 4. As the site of the primary BC was not found after the extensive search, the scalp biopsy sample was reviewed by another pathologist and the new results were ER 100% positive, PR negative, c-erbB-2 negative, Ki-67 <1% positive, and mammaglobin positive. Therefore, the previous diagnosis of BC implants ER-positive in the scalp was reiterated; the affected breast area was removed and the margins of the scalp lesion were enlarged. The histopathological study of the breast specimen showed intraductal papilloma with dystrophic calcification and fibrocystic changes with apocrine metaplasia; ER 80% positive, PR 100% positive, c-erbB-2 negative, Ki-67 <1% positive, and p63 positive. These findings were conclusive for the diagnosis of intraductal and sclerosing papilloma, whereas the study of the sample of scalp reintervention confirmed a tubule-lobular carcinoma. Thence, final diagnosis of exclusion was primary sweat gland carcinoma of the scalp.<sup>9</sup> The authors suggested that dermatologists must refer to oncological evaluation patients with suspected cutaneous implants, to establish the correct diagnosis as soon as possible.

In conclusion, even in primary care settings, the physical examination of all patients should include a careful inspection and palpation of cutaneous changes, either symptomatic or not. Solitary metastases to the scalp can rarely occur in women with occult breast cancer, and the differential diagnosis with primary sweat gland cancer is a very challenging task. Pitfalls may occur due to similar immunohistochemistry patterns of these conditions. Diagnostic pitfalls are cleared by histopathological and immunohistochemistry studies. The more often cited useful markers of BC are cytokeratins (AE1/AE3 and CK-7), ER, PR, GCDP-15, HER2, GATA-3, CD31, mammaglobin, chromogranin, and e-cadherin. The earliest diagnosis and prompt treatment often allow obtaining favorable outcomes.

## ΠΕΡΙΛΗΨΗ

### Μη εμφανής καρκίνος του μαστού με μετάσταση στο τριχωτό της κεφαλής

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Τα οστά, οι πνεύμονες, το ήπαρ και ο εγκέφαλος είναι οι κύριες εστίες των μεταστάσεων του καρκίνου του μαστού. Οι δερματικές μεταστάσεις διαφόρων κακοηθειών είναι ασυνήθεις, αλλά ο καρκίνος του μαστού είναι η πλέον συχνή προέλευση δερματικών μεταστάσεων στις γυναίκες, που μπορεί να αποτελεί και την αρχική περιοχή προσβολής. Οι μεταστάσεις στο τριχωτό της κεφαλής είναι πολύ σπάνιες (έως και 7% όλων των δερματικών μεταστάσεων)

και εμφανίζονται συχνότερα σε εκτεταμένες νεοπλασίες. Μη εμφανείς καρκίνοι του μαστού έχουν αναφερθεί σε ποσοστό <1% αυτών των ασθενών. Περιγράφεται η διάγνωση μεταστάσεων στο τριχωτό της κεφαλής από καρκίνο του μαστού σε μια γυναίκα 75 ετών, με εμφάνιση χρόνιας ερυθρηματώδους πλάκας και επιφανειακών τηλεαγγειεκτασιών στην αριστερή ινιακή περιοχή. Η ιστοπαθολογική διάγνωση της αφαιρεθείσας βλάβης ήταν συμβατή με μεταστατικό αδενοκαρκίνωμα θετικό για τον υποδοχέα οιστρογόνου (100% των κυττάρων) και τον υποδοχέα προγεστερόνης (60% των κυττάρων), εκτός από τη θετικότητα για GATA3 και Κί67 στο 20% των κυττάρων.

**Λέξεις ευρητηρίου:** Δερματική μετάσταση, Διάγνωση, Κακοήθεια του τριχωτού της κεφαλής, Καρκίνος του μαστού

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