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BREAST METASTASIS OF A COMPLETELY REGRESSED CUTANEOUS MELANOMA – CASE REPORT AND REVIEW OF LITERATURE

Boșoteanu Luana-Andreea[1,2], Așchie Mariana[3,4,5], Hangan Tony[6,7], Ursică Oana-Andreea[4], Boșoteanu Mădălina[3,4]

[1] Department of Dermatology, "Elias" University Emergency Hospital, Bucharest, Romania
[2] Institute of Doctoral Studies, Doctoral School of Medicine, "Ovidius" University of Constanța, Romania
[3] Department of Pathology, Faculty of Medicine, "Ovidius" University of Constanța, Romania
[4] Clinical Service of Pathology, "Saint Andrew" Emergency County Hospital, Constanța, Romania
[5] Department VIII – Medical Sciences, Romanian Academy of Science, Bucharest, Romania
[6] Department of Dermatology, Faculty of Medicine, "Ovidius" University of Constanța, Romania
[7] Dermatology Department, "Saint Andrew" Emergency County Hospital, Constanța, Romania

Luana-Andreea Boșoteanu

email: luana.bosoteanu@gmail.com

ABSTRACT

Spontaneous regression of cutaneous melanoma represents a more frequent circumstance in tumors with intense MelanA immunoprofile. Melanoma-derived breast metastases are uncommon and have been predominantly reported in premenopause, as an indicator for widespread disease. We report the case of a 60-year-old female patient, who presented to the surgical department after auto-palpation of a left mammary mass. Digital mammography indicated malignant characteristics, also objectified in the ipsilateral axillary lymph nodes. The microscopical examination and immunohistochemical profile revealed left nodal and upper-outer mammary quadrant metastases of a BRAF-positive achromic melanoma. The clinical and dermoscopic evaluation confirmed the complete regression of the malignant melanocytic lesion, localised at the level of the right inframammary fold. The upper-outer breast quadrant designates the main site of primary tumors (66%), as well as metastases of other malignancies (50%), due to its well-represented vascularisation and glandular tissue. Dermoscopic characteristics of regressed melanoma comprise scar-like depigmentation and polymorphous vessels (irregular linear and globular). The particularities of this case include the age > 40 years old, survival under therapy with Vemurafenib superior to that cited in the literature (24 months to this date), the involvement of the contralateral lymph nodes in relation to the skin lesion and the inverse diagnostic approach – from pathologist to dermatologist. Completely regressed achromic melanoma, identified through diagnostic techniques performed on clinically apparent loco-regional and distant metastases, represents a rare dermato-oncological entity, with controversial implications regarding the prognosis and survival, that requires future histopathological and dermoscopic homogenization.

Keywords: Dermoscopy, Breast metastasis, Achromic melanoma

Introduction:

Spontaneous regression of cutaneous melanoma represents a more frequent circumstance in tumors with intense MelanA immunoprofile (1), but it is – however – a scarce phenomenon, described in only 0.22-0.27% of all melanoma cases (2). To our best knowledge, approximately 50 cases of completely regressed melanomas have been reported in the English-language literature up to this date (3).

Smith and Stehling have noted certain criteria, that have later been updated, for diagnosing regressed melanomas, that include: history and/or clinical evidence of a pigmented lesion located in an area drained by tumor-involved lymph nodes; absence of any other primary lesions identifiable by history or physical examination that could represent the origin of primary melanoma; presence of atypical pigmented or depigmented change in the skin at the site of the untreated presumed primary lesion, with all or a majority of the typical histologic features associated with regression found on biopsy (attenuated epidermis, dermal melanophages, lymphocytic or chronic inflammatory infiltrate,

reactive vascular proliferation, and fibrosis); and histologic absence of melanoma cells in excised lesions (4,5).

Melanoma-derived breast metastases are uncommon and have been predominantly reported in premenopause, as an indicator for widespread disease (6). In almost 50% of cases, the upper-outer breast quadrant is the main site of the metastasis generated by an occult, overlooked or untreated melanoma (7).

The purpose of this case report is to highlight the diagnostic pitfalls that arise in the process of differentiating between a primary and secondary mammary tumor, especially with the understanding that certain occult medical contexts render the histopathological segregation difficult. Moreover, this article aims to present a brief review of literature, indispensable to positioning the originality of the described case in association with the current specialty literature context.

Case report:

We report the case of a 60-year-old overweight (BMI=27.5 kg/m2) female patient, previously diagnosed with essential arterial hypertension, who presented to the surgical department after auto-palpation of a left mammary mass, with a 1-year evolution. The clinical exam revealed erythema, oedema, and warm teguments at the aforementioned level, as well as an ipsilateral lymph node block with high consistency and mobility over the underlying tissular structures, measuring approximately 5cm. Bilateral digital mammography indicated the presence of a 54/40mm mass developed in the left mammary gland, accompanied by left axillary adenopathies with a maximal diameter of 12/20mm. The mammographic aspect implied the necessity of a breast MRI that outlined left axillary lymph nodes of 58/42mm. The malignant characteristics visualised through imagistic techniques channelled the management towards a fine needle aspiration biopsy (FNAB) of the left breast lump.

The histopathological examination of the 5 whitish, elastic tissular samples described an intensely pleomorphic population of medium-large cells arranged in a discohesive manner; the microscopical elements were compatible with an invasive mammary carcinoma (NST) with poor differentiation (G3) and pleomorphic type (Figure 1). A 9-point Nottingham score was obtained as follows: tumor tubule formation – 3 points, nuclear pleomorphism – 3 points and mitotic activity – 3 points, in conjunction with lympho-vascular involvement.

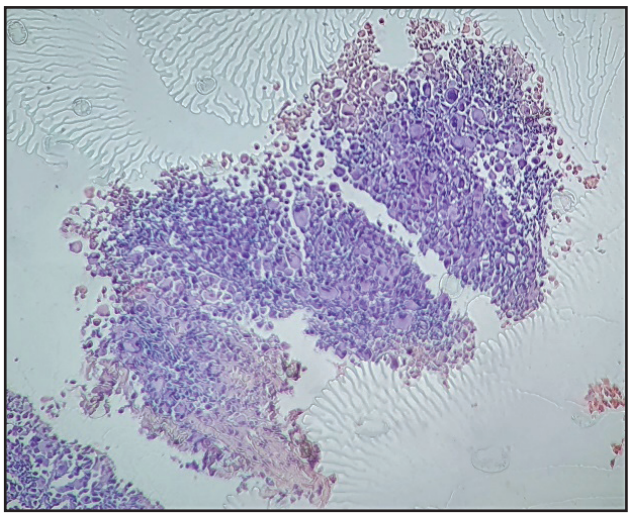


Figure 1. The left breast mass tissular samples (HE x 100): intensely pleomorphic population of medium-large cells arranged in a discohesive manner, compatible with an invasive mammary carcinoma (NST) with poor differentiation (G3)

The immunohistochemical testing comprised negative reactions to Estrogen Receptor (SP1 Clone, Master Diagnostica), Progesteron Receptor (SP42 Clone, Cell Marque), C-erb2/HER2/NEU (SP3 Clone, Master Diagnostica), AE1-AE3 (AE1-AE3 Clone, Master Diagnostica), Cytokeratine CK5/6 (CK5/6.007 Clone, BIOCARE), while Ki-67 (SP6 Clone, Master Diagnostica) indicated a positive nuclear reaction in 80% of the tumor cells (Figure 2). Additionally, Cadherin E (BS38 Clone, Master Diagnostica), GCDFP15 – Mammaglobin (D6 (GCDFP-15) and 31A5 (Mammaglobin), BIOCARE) revealed negative immunostaining (Figure 3). Therefore, the exposed immunoprofile, conjoined with the histopathological elements, established the diagnosis of triple-negative non-basal-like high-grade (G3) invasive mammary carcinoma.

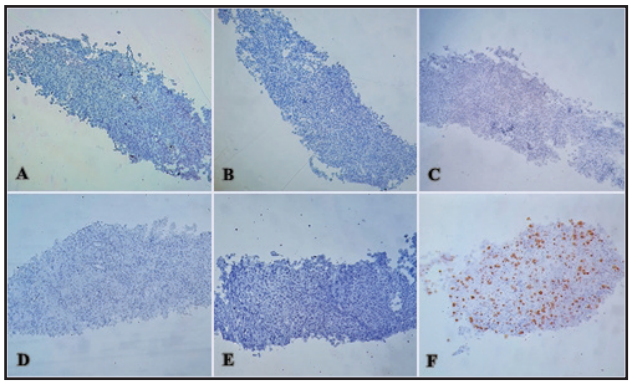


Figure 2. The microscopical analysis of the specimen obtained through FNAB from the initial left mammary mass: A. ER staining – negative; B. PR staining – negative; C. HER2 staining – negative; D. AE1-AE3 staining – negative; E. CK5/6 staining – negative; F. Ki-67 – positive nuclear reaction in 80% of the tumor cells

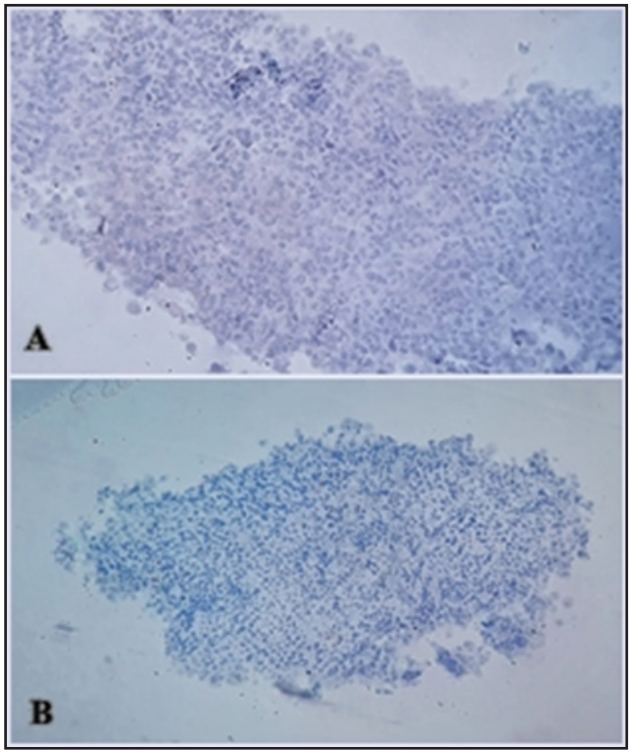


Figure 3. The microscopical analysis of the specimen obtained through FNAB from the initial left mammary mass: A. Mammaglobin staining – negative; B. E-Cadherin staining – negative

This type of neoplasm requires extensive assessment to exclude an entity with different histogenesis, thus MelanA and S100 were performed and developed positive reactions in the cellular population, shifting the pathological suspicion towards a melanoma.

As a result, the patient was referred to the dermatologist, who designed the consequent management plan. The dermatological approach included total body dermoscopy, using the FotoFinder Medicam1000s video-dermoscope – that allows a variable range of magnification between 20 – 140x and the stockage of images for later comparison. In conjunction, the clinical exam and the thorough monitoring of the cutaneous and mucosal sites using a hand-held dermoscope (DermLite) were completed. The dermoscopic evaluation was performed with polarised light, along with non-polarised light, in contact mode, through the immersion medium created by the use of 70% ethanol, to minimize the reflection, increase the image resolution and continuously disinfect the examined areas (8).

The corroborated dermatological findings included the skin phototype 2 (according to the Fitzpatrick scale (9), proof of solar elastosis in the cephalic extremity and the presence of a dermoscopically suspicious plaque located at the level of the right inframammary fold. It presented scar-like depigmentation and polymorphous vessels, comprising irregular linear and globular patterns. When mentioning it to the patient, she remembered having noticed a pigmented macule 4 years prior to the evaluation that evolved by modifying its contour, reducing its size and, eventually, disappearing. Therefore, the suspicion of a completely regressed melanoma of the anterior thorax was sustained by patient's history, clinical and dermoscopic aspects.

The CT thoraco-abdominal scan identified a unique pulmonary nodule of 11/10mm located in the right inferior lobe. The cerebral tomography displayed no abnormality.

Afterwards, considering the latest uncovered information, the patient underwent a left axillary lymph node dissection and left breast upper-outer quadrantectomy. The macroscopic features of the matted lymph nodes included 6 whitish nodules with a maximal diameter of 2 cm and medium consistency, while the mammary fragment corresponded to the upper-outer quadrant, measuring 16/15/6 cm and presenting multiple nodules. On the section surface, they appeared white-yellowish and accompanied by necrosis areas of variable consistency.

The specimens were stained with haematoxylin and eosin and evaluated microscopically. The histopathological report described epithelioid-polygonal pattern of

large cells with evident cyto-nuclear atypia, significant mitotic activity and neoplastic emboli located in the lympho-vascular spaces visualised at the evaluation of lymph nodes' samples. Secondly, the left upper-outer quadrantectomy specimen objectified a 5.5-cm nodule with altered histological configuration due to the presence of a malignant population composed of medium-large polyhedric and bizarre-looking cells, with abundant eosinophilic cytoplasm, atypical mitoses, high proliferation rate and areas of extensive discohesivity (Figure 4.A). Importantly, no melanin pigment was detected. The angio-lymphatic and perineural invasions, as well as hypocellular fibrosis were also described. The histopathological aspect indicated lymph node and mammary melanoma metastases.

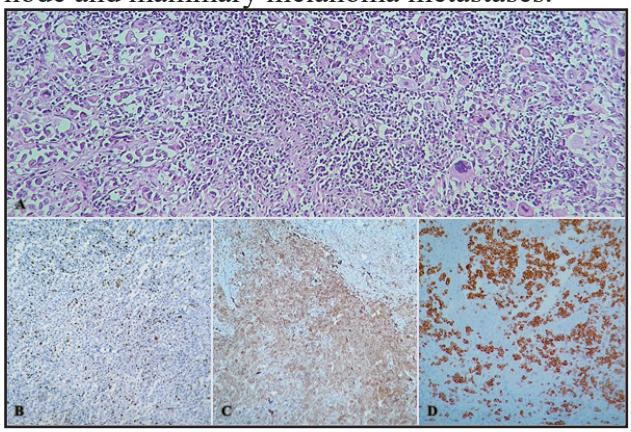


Figure 4. The melanoma metastasis in the left upper-outer quadrantectomy sample – histological and immunohistochemical aspect: A. Malignant population composed of medium-large polyhedric and bizarre-looking cells, with abundant eosinophilic cytoplasm and atypia; B. Ki-67 staining – positive in 50% of the tumoral population; C. S100 staining – positive; D. Melan A staining – positive

Furthermore, immunohistochemical profiling was mandatory for the guidance of the oncological approach. Ki-67 (SP6 Clone, Master Diagnostica) triggered nuclear positivity in 50% of the cellular population (Figure 4.B). A negative reaction was encountered when applying AE1-AE3 (AE1-AE3 Clone, Master Diagnostica), while the neoplastic cells depicted a positive phenotype regarding S100 (4C4.9 Clone, Master Diagnostica) and Melan A/MART-1 (EP43 Clone, Master Diagnostica) (Figure 4.C-D). The entire immunohistochemical panel was concordant with the diagnosis of left nodal and upper-outer mammary quadrant metastases of an achromic regressed melanoma of the right inframammary fold.

Considering the available therapeutic resources, BRAF testing was de riguer and revealed a BRAF V600mut status. Subsequently, the patient was administered Vemurafenib that was well tolerated; currently, regular follow-up visits and CT screenings are up-to-date.

Discussion:

The BRAF mutation is the most frequent genotype encountered in melanoma, most commonly associated with primary melanomas developed on the trunk and also having a proven implication in approximately 70% of benign nevi (10).

Differential diagnosis problems in case of a mammary tumor that initially encapsules the histological pattern of a triple-negative invasive breast carcinoma

It must be thoroughly investigated so that the other possible diagnoses are optimally excluded or – as in our case – confirmed. Takada et al. stated that one of the main nosological entities that should be differentiated is the ductal carcinoma in situ (DCIS), which encompasses a high rate of misdiagnosis (40.7%) using preoperative biopsy (11). Nevertheless, the method used for tissue sampling notably influences the results, such as the use of a 14-Gauge core needle biopsy (CNB) instead of an 11-Gauge CNB; despite the more intense discomfort caused to the patient, a thicker needle is requisite for a precise diagnosis (11). From an immunohistochemical perspective, Ozkan-Gurdal et al. illustrated that independent predictors for microinvasion were represented by negative reactions to ER and/or PR in cases where the influence of tumor dimensions and nuclear grade were precluded (12).

The immunoprofile of invasive mammary carcinoma (NST) may incorporate S100 positive reactions in 10-45% of cases (13), while the majority (95%) of melanomas depict positivity when this stain is applied (14) This reagent's name derives from its capacity to be soluble in 100% saturated ammonium sulfate, when conjoined at neutral pH (14). An immunohistochemical study conducted by Matsushima et al. revealed

the connection between S100 positivity in breast carcinomas and their more favorable prognosis, such as low nuclear grade, as well as ER positive immunophenotype (15).

SOX10, a marker originally attributed to neural crest derivation, is also an indicator of mammary myoepithelial cells, revealing a positive reaction in 66-74% of triple-negative breast carcinomas; as highlighted by our report, the main downfall of its use is represented by the diagnostic challenge imposed by metastatic melanoma (16). Aside from a mammary metastasis of melanoma, other mimickers of primary breast carcinoma may include secondary determinations deriving from lung adenocarcinomas (morphologically similar to low- and high-grade breast carcinomas), from prostatic adenocarcinomas (due to the resemblant structure – glandular, cribriform and papillary) and from pancreatic adenocarcinomas (especially originating from two main histopathological subtypes – signet-ring cell and gland-forming adenocarcinomas) (16). In the process of differentiating between a SOX10-and S100-positive high-grade breast carcinoma and melanoma, at least one pan-cytokeratin reagent must be included (e.g., AE1/AE3, CK903 or Cam5.2) (16). The rationale of this approach is to highlight a positive immunoreaction in case of a mammary neoplasia, in comparison with the negative cytokeratin stain in melanoma.

Primary breast melanoma vs melanoma-derived breast metastasis

The upper-outer breast quadrant designates the main site of primary tumors (66%) (17), as well as metastases of other malignancies (50%) (7), due to its well-represented vascularisation and glandular tissue. The specific character of the mammary gland as a receiving site of secondary tumors generated by leukaemia, lung cancer or melanoma (18) implies a challenge in differentiating their origin, considering the fact that these entities neither behave distinctively from an imagistic point of view, nor present pathognomonic facets at the histopathological investigation. In addition, the prognosis and therapeutic resources vary depending on the histogenesis of the entity presenting in the mammary parenchyma; considering metastatic melanomas, the median survival rates reach approximately 10-11 months (19). In our case, the patient has already survived for 24 months until the present moment, a period calculated starting with the first presentation in our clinic. This point may be explained by the implicit immunophenotype, by a potentially slow-growing primary tumor or by the biological behaviour specifically attributed to regressive melanomas, even though no significant correlation between these factors and prognosis have been disclosed in the literature (20).

From an imagistic point of view, the aspect of a metastatic mass is more frequently discrete, round and without spiculation, resembling certain primary mammary malignant lesions, such as papillary, medullary or mucinous carcinomas (21). However, the distinction between a primary melanoma of the breast and a melanoma metastasis of the mammary parenchyma is done by the site and presentation of the mass, with a large papillary or polypoid lesion emerging from a unique pedicle in favour of the former (22) Moreover, a primary melanoma of the breast should present – at the microscopical evaluation – clustered melanocytes at the epithelial-stromal interface, juxtaposed to the tumoral lesion; this junctional component is considered by some study authors as the most compelling marker for primary melanomas arising in uncommon sites (23). Furthermore, on a histological note, minimal or absent epithelial hyperplasia, as well as no evidence of in-situ carcinoma, are described in the tissues adjacent to the metastatic melanoma (21).

Dermoscopy features as an adjuvant of diagnosing spontaneously regressed melanomas

Dermoscopic characteristics of regressed melanoma comprise scar-like depigmentation in all cases, in the context of pink background, linear-irregular (86%) and globular (43%) vessels (24). Depending on the pigmentation status and duration of evolution prior to regression, the dermoscopic evaluation may also exhibit melanin residues (86%) in the form of macules (43%) or embodying a peppering pattern (43%) (24).

The particularities of this case include the age > 40 years old (6), survival under therapy with Vemurafenib superior to that cited in the literature (24 months to this date), the involvement of the

contralateral lymph nodes in relation to the skin lesion and the inverse diagnostic approach – from pathologist to dermatologist.

Conclusions:

Completely regressed achromic melanoma, identified through diagnostic techniques performed on clinically apparent loco-regional and distant metastases, represents a rare dermato-oncological entity, with controversial implications regarding the prognosis and survival, that requires future histopathological and dermoscopic homogenization.

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Conflict of interest:

The authors declare that they have no conflict of interest regarding the elaboration and publication of this article.

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