Two cancers in one: breast carcinoma with underlying melanoma

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A 61-year-old woman presented with a diagnosis of metastatic invasive lobular carcinoma of the right breast, and after treatment it had regressed or was stable except for a scalp nodule. When biopsied, the outer edges of the scalp lesion had findings consistent with breast carcinoma; however, the bulk of the tumor's pathology was consistent with melanoma. It appeared that most of the tumor was a highly vascularized melanoma with lobular breast carcinoma noted at its edges.

Here we present the case of a 61-year-old woman diagnosed with metastatic invasive lobular estrogen receptor (ER)/progesterone receptor (PR)–positive breast carcinoma with a coinciding melanoma. The patient had numerous sites of metastases from both cancers, including bone. However, one small site on the scalp grew despite anti-estrogen treatment and chemotherapy. Upon biopsy the scalp lesion was found to contain melanoma with invasive breast carcinoma in the outer perimeter of the tumor. We discuss the clinical presentation of this unusual case and the potential predisposing factors involved in developing a synchronous invasive lobular breast carcinoma and melanoma.

CASE REPORT

A 61-year-old Caucasian woman presented with thick, indurated, and erythematous skin on her right breast accompanied by a nodule on her head. The patient reported no symptoms, except for mild tenderness of her lesions to touch. Her family history was positive for breast cancer in her maternal grandmother at age 60. Otherwise, she had no family history of early onset breast, ovarian, or endometrial cancers. She was a smoker with a 15 pack-year history.

Physical examination revealed an erythematous right breast with tethering, erythema, and skin dimpling. Matted lymphadenopathy was noted in the right axilla. There were no obvious palpable masses in the left breast. Examination of the abdomen and back revealed 1 cm erythematous plaques and nodules distributed throughout. A 5 cm protrusive, vascular mass was found on the right occipital surface of the head.

A mammogram revealed a multicentric carcinoma in the right and left breasts, with enlarged lymph nodes on the right. Histological analysis of the right breast biopsy revealed a grade II invasive lobular carcinoma infiltrating the dermis. The tumor was positive for ER and PR, but negative for HER-2 overexpression. Computed tomography imaging showed bilateral pleural effusions, with axillary, mediastinal, abdominal, and retroperitoneal lymphadenopathy. Peritoneal carcinomatosis of the greater omentum was present with a small amount of ascites. A bone scan revealed extensive bony metastases to the skull, ribs, spine, and pelvis. Due to the asymptomatic status of the patient, she began endocrine therapy with the aromatase inhibitor letrozole. Due to poor dentition, the patient was not able to start on bisphosphonate or denosumab for her bone lesions.

The large growth on the back of the patient's head continued to grow and ulcerate on letrozole therapy. Due to the worsening condition of her scalp, she was switched to chemotherapy with capecitabine. Her scalp mass continued to slowly progress while on capecitabine so she was subsequently started on paclitaxel. While on paclitaxel, her bony metastases and disease in the breasts were stable, while her scalp mass continued to grow, measuring 11.0 cm at its greatest dimension *(Figure 1a).*

Biopsy of the scalp mass showed the outer edges of the mass were consistent with breast carcinoma *(Figure 1b).* Similar to the original breast masses, the sections stained positive for ER and PR and negative for HER-2. Interestingly, however, the bulk of the tumor's pathology was consistent with melanoma, staining positively for S100 *(Figure 1c).* The *BRAF* gene was analyzed and no V600E mutation was identified in the tumor. Positron emission tomography imaging revealed intensely metabolic areas in the liver, lymph nodes, and peritoneum consistent with melanoma, as the bone metastases were not fluorodeoxyglucose avid in line with her breast cancer. No pigmented skin lesions were present on the initial exam, and no family history of melanoma was noted. Thus, she not only had metastatic breast carcinoma, but a massive metastatic melanoma on her scalp. Therapy with paclitaxel was held and the patient underwent surgical removal

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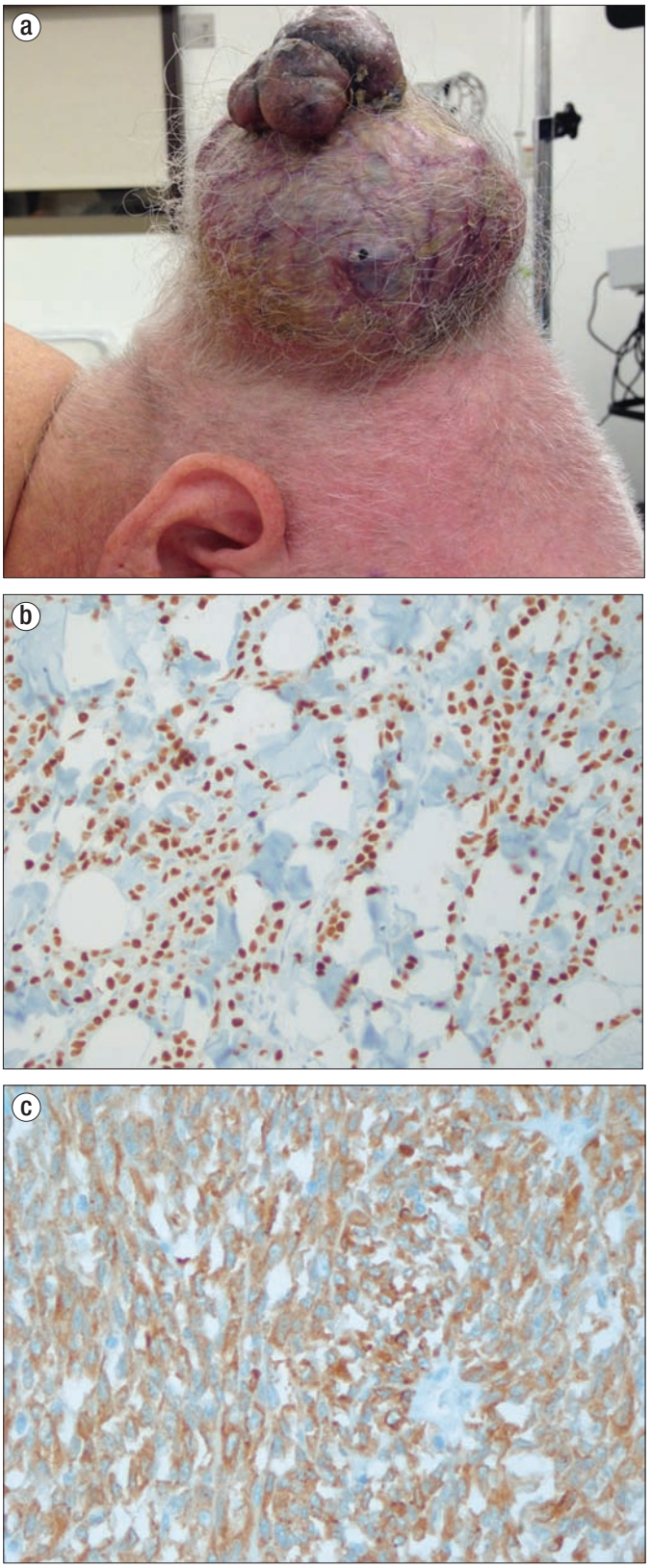

Figure 1. The patient's tumor and its histology. **(a)** Tumor on scalp that did not respond to endocrine or cytotoxic chemotherapy. **(b)** Section of tumor from the outmost part of the tumor staining positive for the estrogen receptor (100× magnification). **(c)** Section of tumor from the innermost part of the tumor staining positive for melanoma cocktail (100× magnification).the core biopsy.

of the scalp tumor. A few weeks after surgery, the patient died from non–cancer-related reasons.

DISCUSSION

Our patient presented with not one, but two cancers. While uncommon, two or more cancers can occur simultaneously, defined as multiple primary malignant neoplasms (MPMN). Studies show that up to 11.7% of cancer patients can present with MPMN (1). There are two types: metachronous, diagnosed >6 months apart, and synchronous, diagnosed <6 months apart. Our patient had synchronous cancers.

There are many cases of MPMNs; most involve patients with metachronous cancers. Women with mutations in the *BRCA2* gene appear to have a greater risk for developing cutaneous and ocular melanoma (2–5). However, there is also an increased relative risk of developing a melanoma after radiotherapy for women with breast cancer (6, 7). The prevalence of breast cancer as a secondary malignancy in melanoma patients was the third most common cause of a secondary malignancy (7). Thus, it appears there is a relationship between breast cancer and melanoma as primary and secondary cancers in MPMNs.

In relation to our patient's case, several examples of invasive lobular breast cancer occurring simultaneously with melanoma have been reported. One case study documented a patient with multiple sclerosis who presented with six metachronous primary malignancies over a 4-year period, including a double melanoma as well as a lobular invasive breast carcinoma (8). The authors investigated specific gene alterations that may predispose a patient to develop multiple malignancies and found the breast carcinoma and melanomas in their patient shared alterations in two tumor suppressor genes, *PTEN* and *P53*, as well as an insertion in codon 4 of the *HRAS* gene resulting in a frame shift mutation (8). These changes could be instrumental in causing the formation of multiple cancers. Other genetic alterations could result in synchronous primary breast cancer and melanoma seen in our patient.

An association between breast cancer and melanoma was shown in patients with strong familial cancer lineage (9, 10). In families with a high-risk genetic *CDKN2A* gene mutation for melanoma, 6 of 9 had at least one family member with multiple primary melanomas along with a high frequency of breast and pancreas cancers. Interestingly, in the families with breast cancer, there was a greater frequency of multiple melanomas (11). In another study of 82 patients with both melanoma and breast cancer, 12 patients had germline mutations in a single or various combinations of the *BRCA1*, *BRCA2*, *TP53*, or *CDKN2A* genes (12). These rare cases indicate that germline mutations may play a role in the formation of the two cancers.

In our patient, it is unclear what gene alteration may have driven her cancers, as her tumors were not sequenced. Clinicians need to keep an open mind in diagnosing tumor etiologies, especially with new molecular techniques and targeted therapies. The principle of Occam's razor states that the simplest explanation, with the fewest assumptions, is usually correct. But, in this case, the simplest explanation was not correct. The humbling discovery of a second malignancy highlights the importance of

searching for other explanations when specific treatments do not work; there may always be another explanation. Each case is different, and the diagnosis is almost never that simple.

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