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Armand Asarian, Olubunmi Esan, Philip Xiao, Segun Adeoye

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Case Report: We present a case report of a patient with a history of modified left radical mastectomy and chemo-therapy for breast cancer twenty years earlier, who presented for surgical evaluation of multiple painful skin lesions. Initial punch biopsy of skin lesions reported negative for malignancy. Surgical biopsy provided tissue which demonstrated a rare histopathological morphology for cutaneous metastatic breast adenocarcinoma.

Conclusion: This report makes the case for considering surgical biopsy when conventional biopsy reports negative for malignancy, especially in the setting of remote or recent cancer history. It also advises prolonged relapse surveillance, well beyond the current protocol, as well as development of prognostic markers for identifying patients at risk of long disease latency after primary treatment.

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CASE REPORT

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INTRODUCTION

Cutaneous metastasis complicating solid organ malignancy is a common clinical entity, and the primary is often metastatic breast cancer. Skin metastasis (local and distant) from breast cancer occurs in about 25% of breast cancer patients [1, 2]. There is an array of histopathological morphologies of metastatic cutaneous cancer reflective of a wide range of potential primaries. The diversity is further compounded by the myriad of typologies of the primary malignancy. A complete description of metastatic cutaneous lesions involves the identification of the primary cancer as well as the categorization of the histological subtype. An initial negative report from a conventional skin biopsy does not definitively exclude the possibility of cutaneous metastasis, especially in the setting of a positive personal history of malignancy. The explanations for false negative result include: inadequate sampling, inappropriate handling, sub-optimal processing and erroneous reporting. Arguably, one of the most striking variables in metastatic disease is the length of clinical latency. Though most metastatic diseases are identified within a relatively short-period (within 3 years) of the primary cancer diagnosis, many are discovered more remotely (many years to decades).

CASE REPORT

A 79-year-old female presented to the surgical outpatient clinic for evaluation of five distinctly painful skin lesions. The lesions appeared nine months earlier and had progressively increased in size. Initial punch biopsy done at the dermatology clinic did not show any evidence of malignancy. The patient's history was significant for recent development of cough, and dyspnea on exertion, associated with malaise and 20 lbs weight loss over a one-year period. Significant negatives included, the absence of: fever, chest pain, gastrointestinal or neurological symptoms. Her medical history included hypertension, dyslipidemia, diabetes mellitus (II), coronary artery disease and myocardial infarction status post-percutaneous coronary intervention. Family history was unremarkable. She had a modified left radical mastectomy, and post-surgical chemotherapy as well as tamoxifen therapy for left breast cancer twenty years ago. She reported adherence with annual clinical breast examination and mammographic surveillance schedules. The last mammogram of her right breast lesion was reported as consistent with fibroadenoma with a BiRADs 2 rating, and demonstrated clinical and radiological stability. The radiologist recommended against further evaluation. An intravenous contrast-aided chest tomography done earlier to evaluate respiratory symptoms revealed multiple pulmonary lesions suspicious for metastatic disease. On physical examination, she was found to have five raised skin lesions: 2 cm lesions in the right upper back and subclavicular area, 1 cm lesions over the left shoulder and left chest wall; and 0.5 cm lesion in the right supraclavicular area. The lesions were firm, fixed and well circumscribed. Clinical breast examination revealed a nodular lesion in the outer quadrant of the right breast without associated skin changes or nipple discharge. This lesion had been shown to be benign and stable by mammogram evaluation. A scar noted on the left side of the chest was consistent with her modified radical mastectomy history.

The records on TNM classification of the primary breast tumor, initial investigations and initial and subsequent treatments of the breast malignancy were not available as the hospital only kept records for up to seven years after the medical encounter. More so, at that time electronic medical record (EMR) system was non-existent. Differential diagnoses included: cutaneous metastasis of breast carcinoma, cutaneous lymphoma or sarcoidosis, cutaneous manifestation of mycobacteria or fungi infection, allergic, hyperimmune or systemic inflammatory disease. The multiplicity of lesions made primary apocrine tumor very unlikely.

The patient underwent a successful excisional biopsy of all the skin lesions. Microscopic examination revealed sheets of poorly differentiated malignant cells under the skin surface (Figure 1). Higher magnification revealed that the tumor was composed of sheets, nests and cords or individual cells with pleomorphic nuclei and

prominent nucleoli in a background of desmoplastic stroma (Figure 2). Immunohistochemical stain results showed that the tumor cells were positive for AE1/AE3, CK7 and mammaglobin (Figure 3), focally positive for GCDFP-15, and negative for CK20, napsin A, thyroid transcription factor-1 (TTF1), p63, CA19.9 and CDX2. Negative staining for napsin A and TTF1 make lung primary less likely. Negative staining for CK20, CDX2 and positive staining for CK7 essentially exclude a colorectal primary. Combined with the morphological features, the immunoprofile supported the diagnosis of metastatic adenocarcinoma with breast origin (Table 1). Further study revealed that the tumor cells were positive for estrogen and progesterone receptors, and negative for HER-2/Neu (Figure 4). The patient was discharged home postoperatively for outpatient management of metastatic disease and is currently receiving treatment for metastatic disease.

DISCUSSION

The incidence of cutaneous metastasis from solid organ malignancy has been reported to range from 0.7–10% [1]. Though cutaneous metastasis occurs in only a minority of patients diagnosed with breast cancer, it

Figure 1: (A, B) Microscopic examination reveal there are clusters of sheets of tumor cells infiltrating under the skin surface (H&E stain, x200).

Table 1: Summary of immunoprofile of biopsied sample

Antibody	Clone	Results	
		Description	Results
AE1/AE3	AE1, AE3	Pancreatin cocktail, low or high molecular weight	+ve
CK7	SP52	Carcinoma subset (non-gastrointestinal); 54kD Keratin	+ve
CK20	SP33	Carcinoma subset (most-gastrointestinal, others); 46kD Keratin	-ve
CEA polyclonal	Polyclonal	Carcinoembryonic antigen, adenocarcinoma	+ve
p63	BCA4A4	Nuclear transcription factor, basal and myoepithelial	-ve
GCDFP-15	EP1582Y	Gross cystic fluid disease protein, breast tumor, others	+ve (focal)
Mammaglobin	31A5	Breast terminal duct and lobular epithelium	+ve
ER	SP-1	Estrogen receptor	+ve
PR	1E2	Progesterone receptor	+ve
CDX2	EPR27G4Y	Carcinoma subset; intestinal-type tumors	-ve
TTF-1	8G7G3/1	Thyroid transcription factor-1; Thyroid and lung tumors	-ve
Napsin A	Polyclonal	Type II pneumocytes, Pulmonary adenocarcinoma	-ve
CA19.9	121SLE	Gastrointestinal, ovarian and lung tumors	+ve (focal)

occurs at a greater rate than with any other solid organ malignancy. In women, the incidence of cutaneous metastasis from breast cancer is second only to malignant melanoma. 23% of patients diagnosed with breast cancer have cutaneous manifestation, often in the form of skin nodules [3]. The relatively high incidence of breast cancer in the general population extrapolates to potentially high metastatic events in dermatology practices. This is even more of a truism in patients with a recent or remote diagnosis of breast cancer [2]. The presentation of metastatic cutaneous disease from metastatic breast cancer has been reported as nodular (80%), telangiectatic (11%), en cuirasse (3%), alopecia neoplastica (2%), or zosteriform type (0.8%) [1].

Accurate assessment of the lesions as metastatic can be difficult because the lesions are often ambiguous, and indistinguishable from the more common benign process, such as cellulitis and lymphedema [4]. As exemplified in our case, there may be long latency between the diagnosis and treatment of the primary malignancy and the identification of cutaneous metastasis [5]. Rarely, the metastatic cutaneous lesions may be the only sinister sign indicative of an underlying primary malignancy or its recurrence [6]. Unfortunately, it often portends a poor prognosis [4]. Though death usually occurs within six months of diagnosis of the metastatic cutaneous disease, long-term survival (in years) with appropriate and timely treatment has been reported. In this case, though tissue biopsy was not pursued for chest tomography-identified metastatic pulmonary disease, and absent overt evidence of another primary cancer, and an immunoprofile supportive of a breast origin, we found no reason to question our impression of a breast primary.

The case we present is unique in two ways. Firstly, it emphasizes the potential fallibility of conventional dermatological biopsies (often punch biopsies), with the inherent risks of false reassurance and delayed

Figure 2: Higher magnification revealed that tumor is composed of sheets, cords or individual cells with pleomorphic nuclei and prominent nucleoli in a background of desmoplastic stroma (H&E stain, x200).

Figure 3: Immunohistochemical stain results showing that tumor cells are positive for mammaglobin (Immunoperoxidase, x200).

interventions. The causes of false negative punch biopsy are enumerated above. We cannot with certainty pinpoint the reason for the false negative report in this case, though we lean towards inadequate tissue sampling. The experience leads us to suggest lowering the threshold for recommending surgical biopsies when initial punch biopsies report negative for malignant disease in patients with recent or remote history of cancer. Furthermore, a recent history of constitutional symptoms (weight loss, as reported by our patient) should be sinister for

Figure 4: Immunohistochemical stain results showed that tumor cells are positive for estrogen receptor (Immunoperoxidase, x200).

the non-benign nature of such cutaneous lesions. The patient's chest computed tomography scan findings were suggestive of metastatic lung disease. It should have necessitated complete elucidation of the nature of skin lesions by excisional biopsy. Secondly, and perhaps more importantly, the presentation of cutaneous metastasis may be remote in temporality from the initial diagnosis of the primary neoplasm. Latent metastases resulting in late-onset relapses occur frequently in breast and bone cancer [3]. The majority (two-thirds) occurring within three years of the diagnosis of breast cancer, but cases presenting decades later have been reported [7–9]. In our case, there was a 20-year latency.

The disseminated cells presenting as secondaries often progress and evolve independently of the primary tumor, they may develop mutations over time, making them more genetically and immunologically different from the primary breast cancer. This observation informs the need for comprehensive genetic testing and cellular targeting when selecting adjuvant chemotherapy, radiotherapy or immunotherapy for latent metastatic disease [9]. Furthermore, it makes the case for extending the duration of surveillance for relapses well beyond the current protocol. For example, the use of anastrozole (arimidex) and other adjuvant hormonal therapies are promoted for up to five years after definitive treatment of the breast cancer, a recommendation partially informed by the fact that most latent relapses occurs within five years of the primary treatment. Perhaps, the development of prognostic markers associated with primary tumors with inherent risk for prolonged latency of metastatic disease, a novel and appealing venture, will help identify patient requiring more prolonged surveillance program and longer adjuvant hormonal/antiestrogen therapy [10].

CONCLUSION

The possibility of cutaneous metastasis should be entertained in the dermatopathological considerations of skin lesions in patients with current, recent or past history of breast cancer. The implications of a false negative punch biopsy and ramifications with regards

to prognosis should justify a confirmatory excisional biopsy in the setting of recent or remote history of cancer. Beyond circumventing the problem of a falsely negative, falsely reassuring punch biopsy, surgical (excisional) biopsy provides a more representative sample for the complete elucidation of the morphology of metastatic cutaneous disease; thus informing the staging process, and directing management and prognostic considerations.

Author Contributions

Armand Asarian – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Olubunmi Esan – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Philip Xiao – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Segun Adeoye – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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