

Case Study

The Management of a Malignant Scalp Tumour of Unknown Origin

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Key Learning Points

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The majority of scalp malignancies are primary basal cell (BCC) or squamous cell carcinomas (SCC) but in up to 10% of cases adnexal tumours are the cause. Unlike BCC's and SCC's, the histological features of adnexal tumours are often non-specific and can easily be confused with metastatic adenocarcinomas from elsewhere in the body. This case report describes a patient in whom neither incisional biopsies nor a definitive excision were sufficient to differentiate between a primary scalp adnexal tumour and a metastatic breast adenocarcinoma emphasising the difficulties facing clinicians and pathologists. A literature review was therefore conducted examining the clinical presentation, epidemiology and histological features of the various primary and secondary scalp malignancies. The case report and subsequent literature review can be used by practitioners to formulate algorithms for how to best diagnose and manage these difficult cases.

Introduction

The scalp extends from the external occipital protuberance to the supraorbital margin and anatomically consists of a stratified structure (epidermis, dermis, subcutis, epicranial aponeurosis, periosteum and skull) and closely arranged adnexa (sebaceous glands, hair follicles, eccrine and apocrine glands) that are surrounded by a dense network of blood vessels and lymphatics. It is a highly complex structure allowing for a broad range of tumours to develop across this region, with malignant tumours making up around 1-2% of all scalp tumours.¹ Scalp tumours are often diagnosed at an advanced stage due to extensive cover of the hair and inaccessibility to self-inspection.

The most common tumours found on the scalp are basal cell carcinomas and squamous cell carcinomas. Adnexal tumours originating in the hair follicles, sebaceous glands and more rarely in eccrine and apocrine sweat glands and ducts are less common and make up around 10% of scalp tumours.² The scalp's vascularity facilitates the occurrence of metastases. Over 70% of metastases of the scalp are attributable to breast cancer, followed by ovarian, lung, GI and oropharyngeal cancer in women. In men 10% originate from lung and GI, followed by ENT and renal tumours.³ Histology can help us to determine whether a scalp tumour is a primary or a secondary as primary tumours tend to originate in the skin before invading deeper whilst metastases tend to start deeper before eroding through the skin. It is important to consider the possibility of metastatic disease due to its effect on prognosis.

Surgical case

A 68-year-old lady of Caucasian origin presented

to the plastic surgeons with a scalp lesion in February 2020. The patient reported a lack of hair growth over the lesion but was otherwise asymptomatic.

The patient's past medical history included type 2 diabetes mellitus, hypertension, GORD, IBS and scoliosis resulting in reduced mobility. Her medications included amitriptyline, lisinopril, metformin, omeprazole, sotalol, temazepam and indapamide. She had an allergy to amlodipine. She was retired, lived alone and required a walking stick and mobility scooter due to her scoliosis.

Examination of the lesion showed that it measured 42 mm in maximum diameter and was bordered by two smaller satellite lesions, one to the right of 8 mm diameter and the other posterior of 7 mm diameter. The larger lesion was cream and darker than the surrounding skin with a nodular appearance and the smaller lesions were cream macules. The masses were firm and non-pulsatile and showed no central punctum. There was no hair growth over the lesions.

A biopsy was performed identifying this as an oestrogen-receptor-positive adenocarcinoma. As a result, there was a raised index of suspicion for this being a secondary tumour from either breast or gynaecological origin. A mammogram, CT and PET scan were performed but these elucidated no primary tumour sites. As a result, this was treated as a primary skin adenocarcinoma and a 1cm excision was performed with a split skin graft reconstruction and burring of the outer table.

The histology of the resected specimen showed that the skin was extensively infiltrated by poorly differentiated adenocarcinoma invading both dermis and subcutaneous fat but showing no dysplasia in the epidermis.

It was found to have features of adenocarcinoma, most likely of breast origin, although a tumour of salivary gland origin or a primary cutaneous adenocarcinoma of the sweat glands could not be excluded. The tumour was found to be positive for CK7, ER, PR, Gata3, HER2, CEA and weakly positive for GCDFP15. It was found to be negative for CK20, PAX8, TTF1, CDX2, D240, p63 and melan-A. These tumour markers also raised suspicion of a breast primary. Due to its oestrogen receptor positivity, further treatment with tamoxifen was considered.

Discussion

Cutaneous Metastases

This case posed the interesting problem of the difficulty in differentiating between cutaneous metastases and primary adnexal tumours. Cutaneous metastases from internal malignancies are seen infrequently, in around 0.7–9.0% of cancer patients, most commonly arising once the diagnosis of the primary cancer has been made.⁴ Tumour types that can metastasise to the skin include carcinomas, melanomas, haematolymphoid malignancies, germ cell tumours and some sarcomas. Cutaneous metastases are most commonly caused by breast cancer in women and by lung cancer in men, and are most often found between the fifth and seventh decade.⁵ Skin metastases can sometimes be the first clinical indication of internal, occult or even unknown primary malignancies and so their detection requires a high index of clinical suspicion.

Skin metastases most often occur on the abdomen, followed by the head and neck, and arms and legs.⁶ Tumours generally metastasise to a site close to the primary lesion but some have a propensity for specific sites such as renal cell cancer for the head and neck and breast cancer for the scalp.⁷ Some histological features that indicate a skin tumour is metastatic are the absence of epidermal involvement, necrosis, ulceration, vascular invasion and prominent inflammatory infiltrate. They often present as multiple nodules but patients can also present with rash, erythema, induration, pain, oedema, plaques and hidradenitis suppurativa lesions.⁶

Breast cancer as a cause of metastases

The scalp is a highly vascular structure facilitating the relatively common occurrence of metastases in this region, predominantly from visceral tumours.⁸ In women, 70% of scalp metastases are attributable to breast cancer³ and in this case there was a high index of suspicion of a breast primary. Skin metastases may occur in up to one quarter of breast cancer cases.⁹ Eight specific patterns are known for skin metastasis from breast: cancer en cuirasse, inflammatory metastatic carcinoma, carcinoma telangiectaticum, alopecia neoplastica, Paget's disease, breast carcinoma of the inframammary crease, metastatic mammary carcinoma of the eyelid with histiocytoid histology, nodular metastases and mucinous adenocarcinoma metastatic to the skin.¹⁰ Scalp metastases in breast cancer usually present in conjunction with other sites of disease and after detection of a primary tumour and indicate a poor prognosis with an expected survival estimated at <1 year.¹¹

Adnexal tumours

In this patient, scans showed no breast or other primary tumour which increased suspicion of this being a primary skin adnexal adenocarcinoma. Around 10% of primary scalp tumours are adnexal tumours, originating

from hair follicles, sebaceous glands, and eccrine and apocrine sweat glands and ducts.² Adnexal tumours can occur sporadically or as part of rare genetic disorders such as Hogg-Dube, Brooke-Spiegler, Cowden or Muir-Torre syndromes and many of these will present with tumours at puberty. Sporadic cases, on the other hand, manifest in the 5th or 6th decade.¹² Some examples of malignant scalp tumours include primary cutaneous adenoid cystic carcinoma and primary mucinous carcinoma of the skin (PMCS).

PMCS is a very rare neoplasm of sweat gland origin with only a handful of cases being described in the literature. It typically presents as a slow-growing, painless, soft, sometimes indurated, reddish, non-ulcerating nodule and range in size between 1 and 8 cm in diameter and most typically occurs in the head and neck. This tumour type has a high tendency for local recurrence (19.6%) and metastasis (6.1%) after surgical treatment with most metastases occurring in local lymph nodes. Despite the tendency to metastasise and recur, death due to mucinous adenocarcinoma is extremely rare.¹³

Differentiating between a skin primary and breast metastasis

It can be challenging to identify the origin of the tumour as either breast or skin due to the ability of breast tumour cells to mimic specific dermal structures. Breast metastases can show morphologic and immunohistologic features of the primary malignancy but also mimic other dermatologic patterns on histology.¹⁰ Similarly, apocrine carcinoma characteristics are very similar to those of cutaneous metastases of breast adenocarcinoma and so the main differential diagnosis of a subcutaneous adenocarcinoma of unknown aetiology is a PMCS.¹¹

Immunohistochemical staining can be useful although no specific marker in the differentiation between breast adenocarcinoma and skin adnexal tumours has been identified and so a panel of immunohistochemical stains should always be performed.¹⁴ It has been shown that p63, CK5, CK14, CK17 and mammaglobin can be used to differentiate between cutaneous metastases of breast cancer and sweat gland adenocarcinomas.¹⁵ Some additional markers such as GATA3 could also be used as this is breast cancer sensitive although not specific.¹⁶ The sensitivity, however, for such tests is low due to many breast cancers testing positive for mammaglobin and GCDFP-15, and oestrogen receptors being expressed by primary sweat gland adenocarcinomas. Additionally, many breast carcinomas are positive for CK7 and negative for CK20 but CK7 negative breast cancers also exist. The close resemblance of the two tumour types requires meticulous pathologic and radiologic analysis to differentiate between the two.¹¹ A summary of immunohistochemical stains for differentiating between the two tumour types is included below.

Management of primary mucinous carcinoma of the skin

As PMCS is very rare, optimal management guidelines have not been established. Wide local excision (WLE) with margins of at least 1 cm is currently the mainstay of treatment although Mohs micrographic surgery (MMS) is also supported by the British Association for Dermatologists because PMCS is locally aggressive, deeply infiltrating and characterised by high morbidity and frequent recurrence.¹⁷ A systematic review analysed treatment methods for this tumour type and found that of

the 159 cases, 86% were treated with traditional surgical excision and 9% by MMS. Amongst the 15 cases treated by Mohs, only 2 recurred (13%) and none of the tumours metastasized. Amongst those treated with excision, 46 cases (34%) recurred or metastasized. Due to limited evidence and a low number of cases, it is difficult to establish whether MMS is more beneficial for treatment of primary mucinous adenocarcinoma than WLE.¹⁸

The Mohs procedure involves removal of the lesion followed by a complete histological evaluation of the tumour margins. Due to complete excision and examination of tumour margins, this technique leads to higher cure rates in many skin cancers. In order to assess the suitability of MMS for such a rare tumour, it is possible to assess the suitability of this surgery in treating other tumour types. For basal cell carcinoma and squamous cell carcinoma, Mohs surgery is considered the gold standard due to its high cure rates. A comparison could also be drawn with treatment of melanoma in situ for which wide local excision (WLE) with 1 cm margins is currently the mainstay of treatment due to its recurrent nature, but with an increasing proportion of people receiving MMS in its treatment. The reasons why MMS is not used for melanoma in situ are concerns over lack of reliability in detecting atypical cells in MMS frozen sections and therefore potential recurrence of the tumour. However, studies have found an improved recurrence and survival rate with MMS when compared to WLE.¹⁹ As MMS is beneficial for BCC, SCC and melanoma in situ in preventing recurrence, mucinous adenocarcinoma could also be treated with this method with some success.

The principles of treatment are, however, different for cutaneous metastases from breast cancer, which are in many cases palliative due to the aforementioned poor prognosis of cutaneous metastatic disease. Metastatic skin cancer has been found to respond to systemic anticancer treatment, intralesional chemotherapy, surgical excision and radiation.²⁰ Surgical resection is rarely performed for cutaneous metastatic disease because the prognosis is rarely influenced by the metastatic tumour and so chemotherapy is normally the treatment of choice, other than in cases in which quality of life can be improved.²¹ This is why it is important to differentiate between a cutaneous primary and metastatic disease as surgery may not be the most beneficial course of action.

Tamoxifen is typically used in the treatment of oestrogen-receptor-positive breast cancer and can reduce the risk of recurrence of breast cancer by around 40%.²² Mucinous adenocarcinomas express oestrogen receptors in around 21% of cases.²³ Consequently, tamoxifen has been used in the past in an attempt to prevent recurrence of this tumour, although there are no current guidelines for this, and cases have reported regression of lymph node metastases and remission after tamoxifen therapy.²⁴ The necessity for tamoxifen therapy for primary mucinous adenocarcinoma is that many patients with adnexal tumours develop metastases, particularly in the lymph nodes.²⁵ Tamoxifen is also used in the treatment of metastatic breast cancer and so this treatment is suitable despite uncertainty in the origin of the tumour.

Conclusions

It can be difficult to differentiate between primary mucinous adenocarcinoma of the skin and cutaneous metastases of breast cancer although a diagnosis is important as cutaneous metastases have a poor prognosis compared to PMCS. Full body scans, histology and a thorough immunohistochemistry panel can help in identification of a tumour with p63, CK5, CK14, CK17 and mammaglobin stains being particularly helpful. Histology and immunohistochemistry are not definitive, however, for providing a diagnosis of one tumour type over the other and should be interpreted within the context of the patient. A diagnosis is important for determining the management of the patient. PMCS is most often managed by wide local excision although MMS may play an important part in future management of PMCS. Tamoxifen therapy should also be considered as a therapeutic option in oestrogen-receptor-positive tumours, even in cases where a definitive diagnosis cannot be made.

Conflicts of interest

None.

Funding

None.

Marker	Primary cutaneous adenocarcinoma	Cutaneous metastasis of breast carcinoma
Mammaglobin	Negative	Positive
Oestrogen Receptor	Usually negative	Usually positive
Progesterone Receptor	Usually negative	Usually positive
Androgen Receptor	Usually positive	Usually negative
D2-40	Positive	Negative
P63	Usually positive	Usually negative
GCDFP15	Usually positive	Negative in 50%
Calretinin	Positive or negative	Usually positive

Table 1: An immunological panel to compare cutaneous adenocarcinoma and cutaneous metastasis of breast carcinoma.⁶

Consent

The patient has consented to the publication of this case study.

References

1. Andrade, P. et al. Epidemiology of basal cell carcinomas and squamous cell carcinomas in a Department of Dermatology: a 5 year review. *An. Bras. Dermatol.* 87, 212–219 (2012).
2. Chiu, C.-S. et al. Malignant cutaneous tumors of the scalp: a study of demographic characteristics and histologic distributions of 398 Taiwanese patients. *J. Am. Acad. Dermatol.* 56, 448–452 (2007).
3. Lookingbill, D. P., Spangler, N. & Helm, K. F. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. *J. Am. Acad. Dermatol.* 29, 228–236 (1993).
4. Hussein, M. R. A. Skin metastasis: a pathologist's perspective. *Journal of Cutaneous Pathology* 37, e1–e20 (2010).
5. Mckee, P. H. Cutaneous metastases. *J Cutan Pathol* 12, 239–250 (1985).
6. Fernandez-Flores, A. Cutaneous Metastases: A Study of 78 Biopsies From 69 patients: The American Journal of Dermatopathology 1 (2010)
7. Saeed, S., Keehn, C. A. & Morgan, M. B. Cutaneous metastasis: a clinical, pathological, and immunohistochemical appraisal. *J Cutan Pathol* 31, 419–430 (2004).
8. Schulman, J. M. et al. The distribution of cutaneous metastases correlates with local immunologic milieu. *J. Am. Acad. Dermatol.* 74, 470–476 (2016).
9. Schwartz, R. A. & Rothenberg, J. Metastatic adenocarcinoma of breast within a benign melanocytic nevus in the context of cutaneous breast metastatic disease. *Journal of Cutaneous Pathology* 37, 1251–1254 (2010).
10. Muller, C. S. et al. Metastatic breast carcinoma mimicking a sebaceous gland neoplasm: a case report. *J Med Case Reports* 5, 428 (2011).
11. Alizadeh, N., Mirpour, H. & Azimi, S. Z. Scalp metastasis from occult primary breast carcinoma: A case report and review of the literature. *International Journal of Women's Dermatology* 4, 230–235 (2018).
12. Proding, C. M., Koller, J. & Laimer, M. Scalp tumors. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft* 16, 730–753 (2018).
13. Beteddini, O. S. A., Sheikh, S., Shareefi, F. & Shahab, R. Primary mucinous adenocarcinoma of the scalp: A case report and literature review. *International Journal of Surgery Case Reports* 10, 241–244 (2015).
14. Alcaraz, I., Cerroni, L., Rotten, A., Kutzner, H. & Requena, L. Cutaneous Metastases From Internal Malignancies: A Clinicopathologic and Immunohistochemical Review. *The American Journal of Dermatopathology* 34, 347–393 (2012).
15. Rollins-Raval, M., Chivukula, M., Tseng, G. C., Jukic, D. & Dabbs, D. J. An Immunohistochemical Panel to Differentiate Metastatic Breast Carcinoma to Skin From Primary Sweat Gland Carcinomas With a Review of the Literature. *Archives of Pathology & Laboratory Medicine* 135, 975–983 (2011).
16. Mentrikoski, M. J. & Wick, M. R. Immunohistochemical Distinction of Primary Sweat Gland Carcinoma and Metastatic Breast Carcinoma. *American Journal of Clinical Pathology* 143, 430–436 (2015).
17. British Association of Dermatologists. Service Guidance and Standards for Mohs Micrographic Surgery. (2017).
18. Kamalpour, L. et al. Primary Cutaneous Mucinous Carcinoma: A Systematic Review and Meta-analysis of Outcomes After Surgery. *JAMA Dermatol* 150, 380 (2014).
19. Nosrati, A. et al. Outcomes of Melanoma In Situ Treated With Mohs Micrographic Surgery Compared With Wide Local Excision. *JAMA Dermatol* 153, 436 (2017).
20. Schwartz, R. A. Cutaneous metastatic disease. *Journal of the American Academy of Dermatology* 33, 161–185 (1995).
21. Goto, H. et al. Palliative surgical treatment for cutaneous metastatic tumor is a valid option for improvement of quality of life. *J Dermatol* 43, 95–98 (2016).
22. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *The Lancet* 378, 771–784 (2011).
23. Busam, K. J. et al. Epidermal growth factor, estrogen, and progesterone receptor expression in primary sweat gland carcinomas and primary and metastatic mammary carcinomas. *Mod. Pathol.* 12, 786–793 (1999).
24. Schroder, U., Dries, V., Wittekindt, C., Klussmann, J. P. & Eckel, H. E. Successful Adjuvant Tamoxifen Therapy for Estrogen Receptor-Positive Metastasizing Sweat Gland Adenocarcinoma: Need for a Clinical Trial? *Ann Otol Rhinol Laryngol* 113, 242–244 (2004).
25. A.L, Hemalatha. Primary Mucinous Eccrine Adenocarcinoma – A Rare Malignant Cutaneous Adnexal Neoplasm at an Unconventional Site. *JCDR* (2014)