CASE REPORT

Intraepidermal sebaceous carcinoma with superficial dermal invasion of the nipple

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ABSTRACT

Sebaceous carcinoma (SC) is a rare malignant neoplasm usually presenting as an ocular lesion or, less commonly, an extraocular cutaneous lesion mostly on the head and neck, whereas it seldom found on other sites. We present a case of a 56-year-old woman with SC on her left nipple. To our knowledge, this is the second reported SC arising in the nipple, but may be the first case of SC of the nipple displaying predominance in intraepidermal proliferation with superficial dermal invasion—a very seldom described growth pattern of extracutaneous SC in literature. An early invasive stage of the rare intraepidermal variant is suggested, with the location of the originating tumor cells being different from that of the usual intraepidermal cases. Free/ectopic sebaceous gland is one of the possible origins.

Introduction

Sebaceous carcinoma (SC) is a rare, potentially aggressive malignancy demonstrating exclusive sebocytic differentiation with unknown etiology. It accounts for less than 1% of all cutaneous malignancies, and is traditionally subcategorized into two groups based on the site of origin: ocular (periocular) and extraocular. In spite of the widespread anatomic distribution of sebaceous glands, extraocular SC is less common than its ocular counterpart (comprising about 25% of all reported cases of SCs) and most commonly presents in the 6th and 7th decades of life on the head and neck where sebaceous glands are most plentiful. Other reported primary sites of extraocular SC include the external genitalia, parotid and submandibular glands, buccal mucosa, external auditory canal, trunk, extremities, breast, laryngeal or pharyngeal cavities, and lung.1−5 SC arising in the nipple has been only once reported.6

Histopathologically, extraocular SC typically shows a variably organoid but asymmetric “intradermal” proliferation of infiltrative lobules/nests of atypical oval/polyhedral cells with variable degrees of sebaceous differentiation typified by vacuolated or multivesicular/foamy cytoplasm with occasionally scalloped nuclear contour. The particular vacuolization must be distinguished from the usual simple cytoplasmic clarity.7 A variety of histological features can exist in SC, e.g., multinodularity, comedo-type necrosis, pagetoid spread into the overlying epithelium/epidermis, and carcinoma in situ; the latter two features have been occasionally depicted in the literature, but are more commonly found in the ocular type than in the extracutaneous type.4,8,9 Extraocular SCs with only/mainly intraepidermal growth (intraepidermal SCs) are extremely rare.10−12

Rarely, SC occurs in Muir-Torre syndrome (MTS), with at least an associated visceral malignancy (usually a gastrointestinal carcinoma, occurs less in other organs) that may precede or follow the SC. Therefore, SC sometimes is a diagnostic sign of MTS.13

Case report

A 56-year-old woman visited a surgical clinician with a firm, mildly eroded, gradually enlarging light yellow nodule measuring about 0.5 cm located eccentrically on her left nipple, which had been noticed a few weeks earlier (Figure 1). She had no other cutaneous tumor, breast tumor, regional lymphadenopathy, or any clinical evidence of other internal malignancy.

Histopathologically, the lesion in the partially excised nipple (cut into 3 sections) showed mainly intraepidermal proliferation in a broad zone of the basal part of the epidermis, with many large and occasionally connecting blunt bulbous downward extensions (only slightly more than 1 mm in depth) composed of atypical/hyperchromatic oval germinative cells, frequently owning clear to fine multivesicular cytoplasm with various degrees of sebaceous...
differentiation, and occasionally with small foci exhibiting some features of holocrine secretion/abortive sebaceous ducts (Figure 2A, B, C and D). The mature neoplastic sebocytes, differentiating/transitional cells, and immature germinative cells were haphazardly arranged with a variable ratio; the average ratio was about 1:2:2. The tumor cells possessed atypical round to irregular vesicular nuclei with obvious nucleoli and occasional scalloped nuclear membrane, and exhibited sporadic necrosis and frequent mitoses [counting from 1 to 6 in most high-power fields (HPFs), about 20/10 HPFs on average]. Focally there were some small nests of atypical sebocytes invading the upper dermis (Figure 2C and E) but no prominent haphazard intradermal growth of invasive tumor lobules. No aggregations of uniform basaloid cells with peripheral palisading and retraction artifact from stroma were seen. Few individual and small clusters of tumor cells showed a pagetoid feature in the epidermis, while the epidermis lacked atypical keratinocytes. No lymphatic–capillary permeation was found. Many tumor cells showed immunoreactivity for cytokeratin (CK) 7 (OV-TL 12/30; Dako) and epithelial membrane antigen (EMA) (E29; Dako), with more intensity in those fairly or frankly differentiated tumor cells (Figure 3A); some tumor cells were positive for CD15 (Carb-3; Dako); and none were positive for carcinoembryonic antigen (CEA). A minority of tumor cells were positive for androgen receptor (AR441; Dako). The subsequent available IHC analysis for expression of DNA mismatch repair gene products (proteins) related to MTS revealed expression of Mutl protein homolog 1 (MLH-1) (ES05; Dako North America) and MutS protein homolog 2 (MSH-2) [G219;1129; Roche-Ventana, Rocklin, CA, USA; performed with BenchMark XT (Ventana, Tucson, Ariz, USA)], with diffuse strong MLH-1 staining (Figure 3D) and partial reduction in MSH-2 staining.

**Discussion**

Clinically, extraocular SC often appears as a pink to red-yellow nodule, but can exhibit diverse clinical presentations and is commonly confused with other lesions, especially basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). The tumor may appear on top of pre-existing dermatoses, like nevus sebaceous, actinic keratos, and Bowen’s disease. However, the following facts may render the differential diagnosis difficult: (1) sebaceous differentiation may be rarely found in the less/poorly differentiated cases; (2) sebaceous differentiation can be focally encountered in other types of cutaneous tumors, like SCC, BCC, and trichoblastoma; (3) there are some cases/variants of SC (e.g., the basaloid) with other feature(s) similar to that of the other cutaneous tumors, e.g., superficial epithelioma with sebaceous differentiation, sebaceous adenoma, sebaceoma, and BCC with sebaceous differentiation; (4) similar foamy cytoplasm can be seen in the rare signet-ring cell variant of melanoma.

The key points for making a differential diagnosis have been well described in the textbooks and literature. We will focus on those encountered in diagnosing the case displaying, as ours, predominance in intraepidermal proliferation with blunt bulbous downward extensions and superficial dermal invasion. The frequent classical multivesicular cytoplasm/sebaceous differentiation, occasional holocrine secretion, the absence of dysplastic keratinocytes in the overlying epidermis, the absence of pagetoid growth of tumor cells in the whole thickness of epidermis, and frequent staining with CK7 and androgen receptor in the tumor cells of our case are helpful in making a diagnosis of SC rather than SCC and invasive carcinoma arising in Bowen’s disease with sebaceous differentiation. Sebaceoma is well circumscribed: it has bland basaloid cells with some bland mature sebocytes, it stains in a similar way to sebaceous adenoma and hyperplasia, and it has statistically significant lower expression levels of p53 compared to SC (11% versus 50%, respectively) and Ki-67 (10% versus 30%, respectively). The prominent blunt bulbous downward growth pattern, apparent nuclear atypia of neoplastic sebocytes and germinative/immature cells, disordered arrangement of kinds of tumor cells without peripheral palisading, high p53 level, and frequent mitoses in our case all render the diagnosis of malignancy and help to distinguish it from superficial epithelioma with sebaceous differentiation and BCC with sebaceous differentiation. Paget’s disease and some melanomas tend to have marked intraepithelial spread and pseudo-papillary myxoid cytoplasm. However, they express clinical features, histologic findings, and immunophenotypes much different from those of SC. The IHC stain for adipophilin, another sensitive and fairly specific marker said to be useful especially in diagnosing poorly

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Figure 1 Clinical photograph of the left nipple nodule in a 56-year-old woman (note the eccentric location).

Figure 2A, B, C and D. The mature neoplastic sebocytes, differentiating/transitional cells, and immature germinative cells were haphazardly arranged with a variable ratio; the average ratio was about 1:2:2. The tumor cells possessed atypical round to irregular vesicular nuclei with obvious nucleoli and occasional scalloped nuclear membrane, and exhibited sporadic necrosis and frequent mitoses [counting from 1 to 6 in most high-power fields (HPFs), about 20/10 HPFs on average]. Focally there were some small nests of atypical sebocytes invading the upper dermis (Figure 2C and E) but no prominent haphazard intradermal growth of invasive tumor lobules. No aggregations of uniform basaloid cells with peripheral palisading and retraction artifact from stroma were seen. Few individual and small clusters of tumor cells showed a pagetoid feature in the epidermis, while the epidermis lacked atypical keratinocytes. No lymphatic–capillary permeation was found. Many tumor cells showed immunoreactivity for cytokeratin (CK) 7 (OV-TL 12/30; Dako) and epithelial membrane antigen (EMA) (E29; Dako), with more intensity in those fairly or frankly differentiated tumor cells (Figure 3A); some tumor cells were positive for CD15 (Carb-3; Dako); a minority of tumor cells were positive for androgen receptor (AR441; Dako). The subsequent available IHC analysis for expression of DNA mismatch repair gene products (proteins) related to MTS revealed expression of Mutl protein homolog 1 (MLH-1) (ES05; Dako North America) and MutS protein homolog 2 (MSH-2) [G219;1129; Roche-Ventana, Rocklin, CA, USA; performed with BenchMark XT (Ventana, Tucson, Ariz, USA)], with diffuse strong MLH-1 staining (Figure 3D) and partial reduction in MSH-2 staining.

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differentiated SC\textsuperscript{18} is not yet available in our laboratory and seems not indispensable to our case, which reveals apparent sebaceous differentiation. Finally, another important differential diagnosis cutaneous spreading from an underlying sebaceous carcinoma of the breast parenchyma/duct can be ruled out due to lack of tumor in the underlying breast tissue and the excised lactiferous ducts in our case.

Except for a few anatomic sites, the sebaceous glands are hair follicle-associated intradermal structures, therefore, extraocular SC (thought to arise from the sebaceous gland) will generally present as a dermal tumor, as expected. It also seems reasonable that cases of extraocular differentiated sebocytes in the right lower field [H&E; original magnification, 400×]. (D) High-power view of extending aggregations/nests in one section in Figure 2A revealing hyperchromatic oval cells with frequent sebaceous differentiation. There is presence of three foci with some features of holocrine secretion/abortive sebaceous ducts (red circles), with absence of dysplastic keratinocytes in the overlying epidermis and absence of pagetoid growth of tumor cells in the whole thickness of the epidermis (H&E; original magnification, 200×). (E) Small nests of atypical sebocytes in the dermal papillae and the presence of a small portion of sebaceous ducts near some intraepidermal atypical sebocytes are shown in the lower left corner (red circle) (H&E; original magnification, 500×).


Figure 2 (A) Low-power view of two of three sections of the specimen showing tumor growth involving broad horizontal dimension of the epidermis with only slightly more than 1 mm in depth of tumor growth [hematoxylin and eosin (H&E); original magnification, 30×]. (B) Low-power view of the third section of the tumor showing the predominant intraepidermal proliferation with large blunt downward extensions containing mainly hyperchromatic immature cells in the left field and more differentiated pale cells in the right field [H&E; original magnification, 50×]. (C) High-power view of the red square in Figure 2B showing aggregations of atypical germinative cells with mildly pleomorphic vesicular nuclei, distinct nucleoli, frequent mitoses, and mild sebaceous differentiation, but no peripheral palisading or retraction artifact from stroma. Also note the small isolated clusters of atypical differentiated sebocytes in the right lower field [H&E; original magnification, 400×]. On review of the description and figures of the reported extraocular intraepidermal SCs/SC in situ, we note that the intraepidermal growth, as predominant as in our case, basically shows expanding aggregations of tumor cells in the lower part of the epidermis. In our case, besides the few small infiltrative tumor nests, those deep blunt extensions from the epidermis (only slightly more than 1 mm in depth) might be considered, by some authors, to be invasive. Nevertheless, this tumor can be regarded as only superficially invasive, and we intend to use a special diagnostic term “intraepidermal SC with superficial dermal invasion” to reflect its actual growth features, progression manner, and distinctive clinicopathological character, which are different from those of usual invasive SCs. Cibull et al did not mention the intraepidermal proliferation in their case, but based on their image of it, we considered the possibility of an initial intraepidermal growth in such an exophytically enlarged nipple tumor.\textsuperscript{6}

Owing to the scarcity of intraepidermal SC/SC in situ and rare association with usual extraocular SC, some authors think that the intraepidermal SC/SC in situ may not be the precursor of the latter. In clinical practice, however, one should always consider the
Clinical and histological features of visceral malignancies.\textsuperscript{17,19} Many reported cases without MTS, does not indicate increased risk reduction rather than complete loss of MSH-2 staining, as seen in underlying MTS is unlikely in our patient. The partial retention of MLH-1 and MSH-2, which are lost in case as ours is not yet proposed due to the small number of cases. Removal of any lymph nodes that are affected is recommended. Apart from considering the origination from pluripotent cells in the basal layer of epidermis, as suggested by some authors,\textsuperscript{15} we presume another possible derivation from certain sebaceous-committed germinative cells situated in or shortly below the basal layer of the epidermis—i.e., cells in the superficially-located free/non-hair follicle-associated or ectopic sebaceous glands such as those seen on the lip/buccal mucosa, labia minor, prepuce, and the nipple—area complex; the latter contains free glands either in the Montgomery’s tubercles or widely covering the surface.

Treatment involving entire excision of the lesion of SC with removal of any lymph nodes that are affected is recommended. However, the standard treatment for such a superficial invasive case as ours is not yet proposed due to the small number of cases. The retained expression of MLH-1 and MSH-2, which are lost in most internal malignancy-associated sebaceous neoplasms in MTS, suggests that underlying MTS is unlikely in our patient. The partial reduction rather than complete loss of MSH-2 staining, as seen in many reported cases without MTS, does not indicate increased risk of visceral malignancies.\textsuperscript{17,19}

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References