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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 extraocular 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 intradermal 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 extraocular 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

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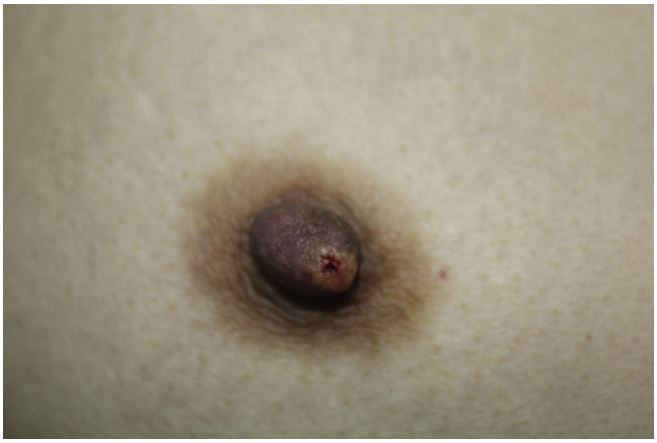

Figure 1 Clinical photograph of the left nipple nodule in a 56-year-old woman (note the eccentric location).

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); a minority of tumor cells were positive for humen epithelial antigen (Ber-EP4, Dako) and CK5/6 (D5/16 B4; Dako); and none were positive for carcinoembryonic antigen (CEA) (II-7; Dako) or gross cystic disease fluid protein 15 (GCDFP-15) (23A3; Dako). CK5/6 also more intensely stained the basal–suprabasal layers of epidermis and highlighted the residual normal basal cells in the lower periphery of the intraepidermal tumor growth (Figure 3B). The proliferative fraction as detected by Ki-67 staining (MIB-1; Dako) was greater than 20% in some HPFs. There was a high percentage of tumor cell staining for p53 (DO-7; Dako), about 50% on average (Figure 3C). In addition, many tumor cells were positive for androgen receptor (AR441; Dako). The immunohistochemical (IHC) study was performed with Dako Autostainer Link48 and the provided ready-to-use antibodies; the antibodies for CK7, EMA, Ber-EP4, CK5/6, CEA, Ki-67, and p53 were produced by Dako Denmark A/S (Glostrup, Denmark); the others were produced by Dako North America (Carpinteria, CA, USA). Based on the particular pathological findings, we made a diagnosis of SC that was predominant in intraepidermal proliferation with superficial dermal invasion.

The lesion was completely removed. Our patient did not undergo lymph node dissection. She had no recurrence of tumor or metastasis during the 23 months of follow-up, and she did not show clinical evidence of MTS either. 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 keratosis, and Bowen's disease.[4,14,15] SC arising in the nipple is much rarer than other types of nipple tumors, such as Paget's disease and nipple duct adenoma, which may appear similar in clinical images.

On pathological examination, IHC stains are often less necessary for distinguishing SC from most cutaneous tumors. Identification of the characteristic histologic feature—the multivesicular appearance of tumor cells—is beneficial to differentiating SC from the more common tumors of other lineages with simple cytoplasmic clarity, such as BCC, pagetoid variant of Bowen's disease, SCC, poroma/porocarcinoma, trichilemmal tumor, and Paget's disease.[7] 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.[15] (CK7 has been reported in pagetoid Bowen's disease but not in the other types of SCC.[16]) 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).[17] 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 pale to sometimes vacuolated 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