

Sebaceous carcinoma in situ as a concept and diagnostic entity

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ABSTRACT Although carcinoma in situ has been accepted as a well-established concept and diagnostic category, for reasons unknown sebaceous carcinoma in situ has not been recognized yet in general pathology or dermatopathology. Such lesions have always been misinterpreted as either benign neoplasm or sebaceous carcinoma. In the present essay, we provide a convincing account supporting sebaceous carcinoma in situ as a valid concept and diagnostic entity via critical literature review and histopathological assessment and illustration. Recognizing sebaceous carcinoma in situ as a valid concept and diagnostic entity will certainly help to avoid misinterpretation and subsequently under or over treatment of such lesions.

Commentary

Conceptually and practically all epithelial neoplasms can and should be classified as one of the following three categories, namely, benign lesion, carcinoma in situ and invasive carcinoma. When the term carcinoma used unmodified, such as squamous cell carcinoma, sebaceous carcinoma, adenocarcinoma, generally means invasive carcinoma. Non-invasive carcinoma is synonymous to carcinoma in situ. The concept of carcinoma in situ was first introduced by Broders in 1932 [1] and has been accepted as a well-established term and diagnostic category in many organ systems such as breast and skin (e.g., ductal carcinoma in situ of the breast and squamous cell carcinoma in situ of the skin). However, for unknown reasons, sebaceous carcinoma in situ (SCIS) has not yet to be recognized by many as a concept and diagnostic entity. From the first classification of neoplasms with sebaceous differentiation proposed by Warren and Warvi in 1943 [2], to the one by Rulon and Helwig in 1974 [3], Lever in 1949 and 1989

[4, 5], Elder et al in 1997 and 2005 [6, 7], Prioleau and Santa Cruz in 1984 [8], Troy and Ackerman in 1984 [9] and Steffen and Ackerman 1994 [10], Mehregan and Hashimoto in 1991 and 1995 [11,12] and Burgdorf in 1990 [13], McKee in 1996 and 2012 [14,15], Barnhill in 1998 [16], Maize in 1998 [17], Farmer and Hood in 2000 [18], and Weedon in editions from 2002 to 2017 [19-22], SCIS was not even mentioned in any of their classifications of sebaceous neoplasms.

Beside the flat SCIS (see below for detail), which has been called by some as SCIS and considered as an exceedingly rare phenomenon, Chen was the first one who pointed out the existence of other histologic types of SCIS and proposed to establish SCIS as a concept and diagnostic entity [23-24].

Like the definition for any other type of carcinoma in situ, the definition of SCIS would be a sebaceous neoplasm with these microscopic features:

- (1) Architectural findings of confinement, namely, no invasive growth, indicating neoplastic cells still confined in epithelium (within surface epithelium, infundibular epithelium,

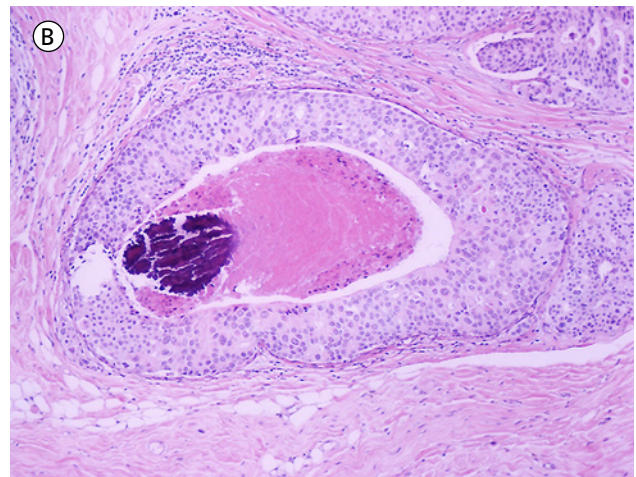
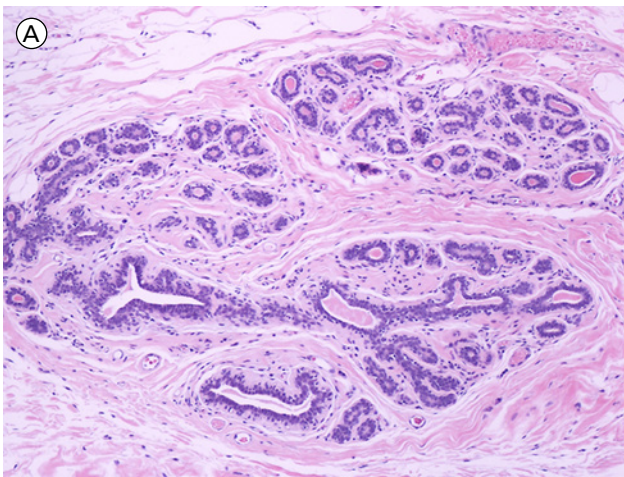


Figure 1. (A) Normal breast tissue showing terminal duct lobules (H&E stain). (B) Ductal carcinoma in situ of breast, solid type, with central necrosis and calcifications. Note that the ductal carcinoma in situ forms expansile nodules completely distorting and effacing the original breast epithelial structure (H&E stain). [Copyright: ©2017 Komforti et al.]

sebaceous gland, sebaceous duct, and/or follicular epithelium); and

- (2) Cytological attributes of malignancy, i.e. presence of nuclear atypia, enlarged nuclei, hyperchromasia, increase of nucleus to cytoplasm ratio, decrease of differentiation, increase of mitotic activity and necrosis in the form of individual cells or necrosis en masse.

Of note, carcinoma in situ can certainly grow very large and render the original epithelial structure unrecognizable. That is often the case for ductal carcinoma in situ of the breast, which can form a palpable mass (Figure 1A & B). Thus, the histopathologic diagnosis of carcinoma in situ can still be made even the original epithelial structure is distorted or unrecognizable.

Regarding the origin of sebaceous neoplasm, Kazakov et al. stated that “whereas in periorbital sebaceous lesions, it is accepted that sebaceous lesions arise from Meibomian glands and glands of Zeis, sebaceous glands elsewhere in the skin practically never appear to give rise to a sebaceous carcinoma” [25]. It is true no one knows for sure the exact origin of sebaceous neoplasm. But one can be certain that it must originate from epithelium, namely, epidermis, follicular epithelium or sebaceous gland. Among these elements, it is reasonable to believe sebaceous neoplasm originates from sebaceous gland. If one accepts that ocular sebaceous neoplasm arises from sebaceous gland (Meibomian as well as Zeis glands), there is no reason to reject the notion that extraocular or cutaneous sebaceous neoplasm arises from cutaneous sebaceous gland, which is actually identical to Zeis sebaceous gland in the eyelid.

SCIS has a number of different histopathologic expressions. In our opinion, there are three histopathologic types, namely, flat, nodular and cystic types.

The flat type of SCIS refers to proliferation of malignant sebocytes within surface epithelium (epidermis or conjunc-

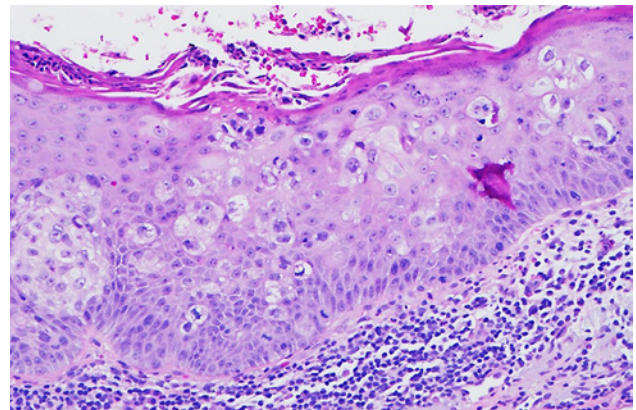


Figure 2. Sebaceous carcinoma in situ, flat type, showing proliferation of atypical neoplastic sebocytes within epidermis (H&E stain). [Copyright: ©2017 Komforti et al.]

tiva) with no evidence of underlying sebaceous carcinoma or nodular/cystic SCIS (Figure 2). Flat SCIS can only be diagnosed after excluding pagetoid involvement of surface epithelium by either underlying sebaceous carcinoma or nodular/cystic SCIS. Flat SCIS is a rare lesion and often reported in the literature under the term of intraepithelial or epidermotropic sebaceous carcinoma [25-27]. Some authors call this variant as superficial type of sebaceous carcinoma [15].

The nodular type of SCIS is the most common type of SCIS. Nodular SCIS is located in the dermis and/or subcutis with or without surface epithelial involvement, has a multilobulated (Figure 3A-C) or solid nodular configuration (Figure 4A-C). The lesion is well circumscribed with smooth border. There is no desmoplastic stromal response or any features of infiltrative growth.

The cystic type of SCIS is located in the dermis and usually extends into subcutis. It consists of an encapsulated or well-defined cystic sebaceous lesion with smooth outer border lined by multiple layers of neoplastic sebocytes (Figure 5A & B).

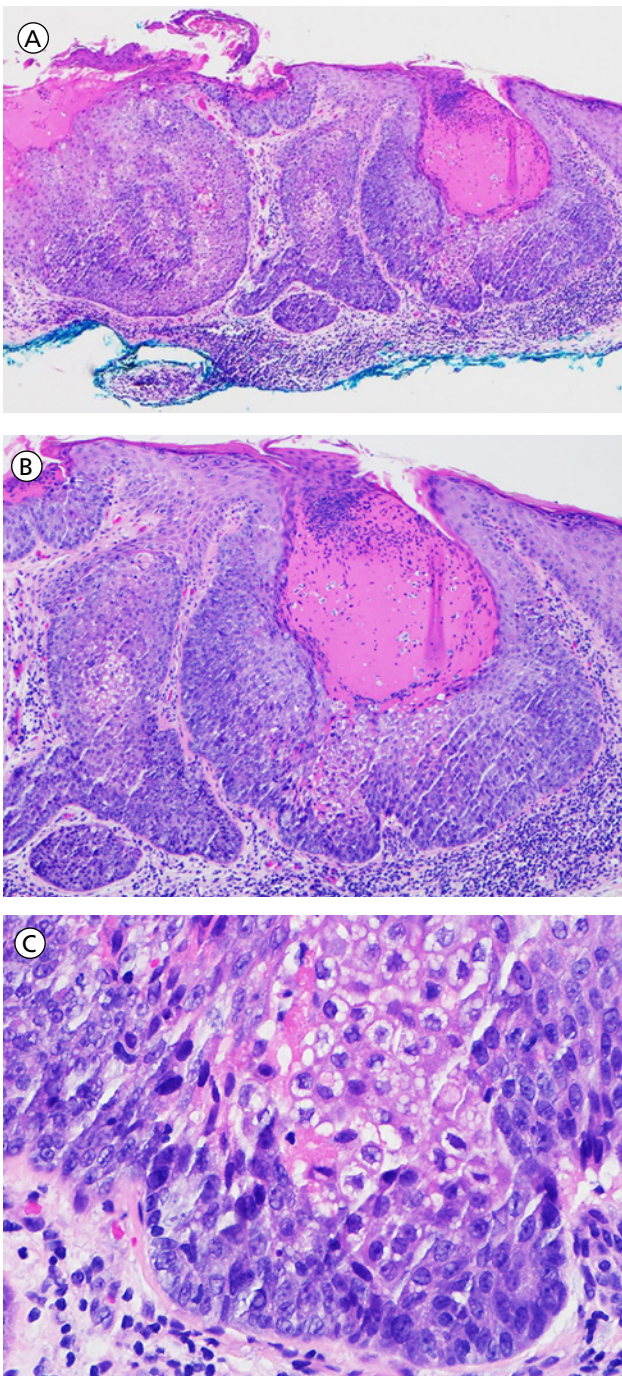


Figure 3. (A) Low power view of sebaceous carcinoma in situ, multilobulated nodular type (H&E stain). (B) Intermediate power view of sebaceous carcinoma in situ, multilobulated nodular type (H&E stain). (C) High power view of sebaceous carcinoma in situ, multilobulated nodular type (H&E stain). [Copyright: ©2017 Komforti et al.]

Well- and moderately-differentiated nodular/cystic SCIS was called sebaceous adenoma initially by early authors [3, 28] and subsequently has been called this way by many up to this day. However, in an article published in 1998, Nussen and Ackerman revised this concept and stated that the so-called sebaceous adenoma is not a benign neoplasm but sebaceous carcinoma [29]. This notion was upheld by them in another article published in 1999 [30] and subsequently in the second edition of a book devoted to neoplasms with

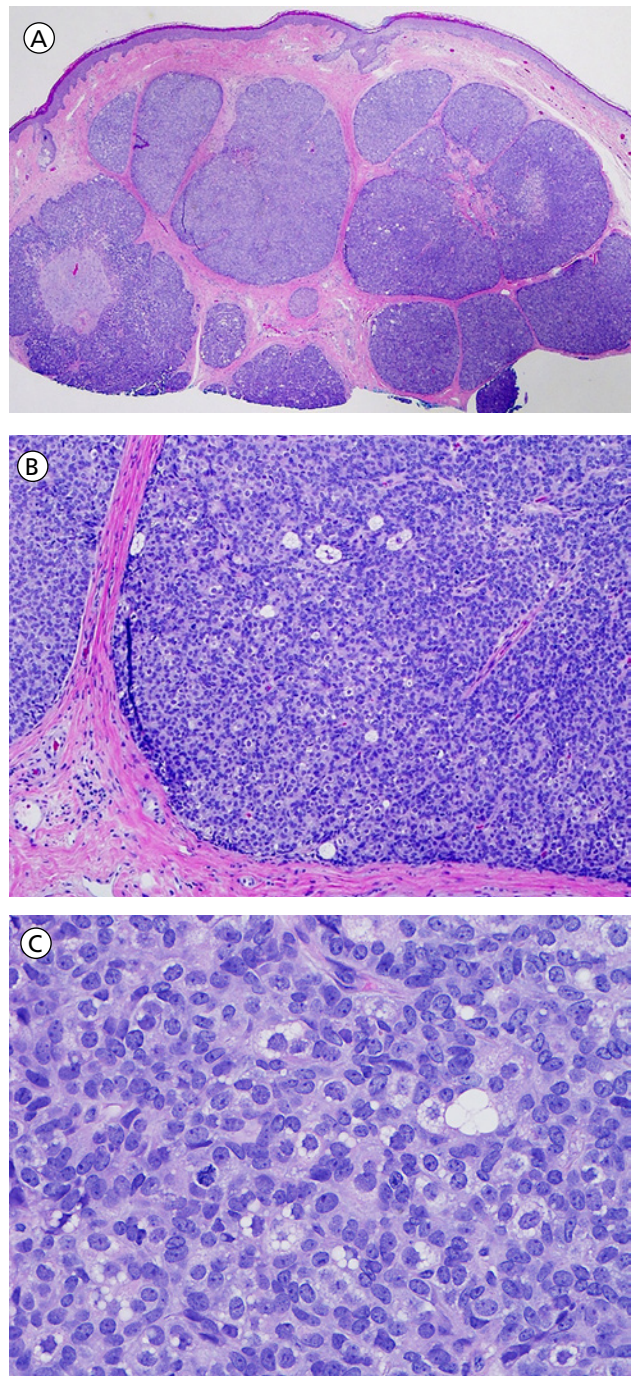


Figure 4. (A) Low power view of sebaceous carcinoma in situ, solid nodular type (H&E stain). (B) Intermediate power view of sebaceous carcinoma in situ, solid nodular type (H&E stain). (C) High power view of sebaceous carcinoma in situ, solid nodular type (H&E stain). [Copyright: ©2017 Komforti et al.]

sebaceous differentiation published in 2009 [26]. Although this view has been accepted by some, it is not shared by many others in the field of dermatopathology. In an essay published in 2010, Chen proposed a different view and asserted that the so-called sebaceous adenoma is really SCIS based on the above-mentioned definition of SCIS [23].

On the other hand, poorly differentiated or high nuclear grade nodular/cystic SCIS is often misinterpreted as sebaceous carcinoma or so-called unclassifiable sebaceous neoplasm.

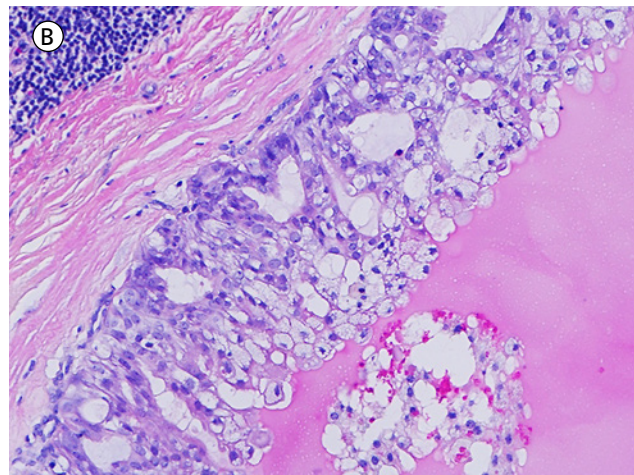
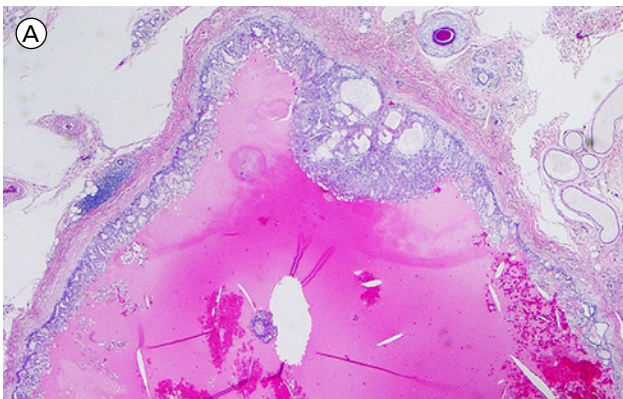


Figure 5. (A) Low power view of sebaceous carcinoma in situ, cystic type (H&E stain). (B) Intermediate view of sebaceous carcinoma in situ, cystic type (H&E stain). [Copyright: ©2017 Komforti et al.]

For example, one of the sebaceous lesions interpreted as low-grade sebaceous carcinoma in a recent article by Kacerovska et al. is clearly SCIS based on the photomicrographs the authors presented (well-defined lobulated lesion with no evidence of invasion; Figure 4 in that article) [31]. Other examples include five cases of sebaceous neoplasms with architectural features of benignancy and cytologic features of malignancy reported by Kazakov et al., who stated that “the classification of such lesions as sebaceoma (with atypia) or sebaceous carcinoma remains unresolved” [32]. This opinion was in contrast to that of Resnik, who reviewed the manuscript as well as glass slides of the five neoplasms under discussion and did not agree with the authors’ assessment that these lesions cannot be classified as either sebaceoma or sebaceous carcinoma [33]. In Resnik’s opinion, four out of the five cases represented sebaceous carcinoma and one sebaceoma. Kramer and Chen had yet another view. Based on the architectural features of benignancy (well-circumscription with smooth border of lobules with no invasive growth) and cytological features of malignancy (presence of nuclear atypia, increased mitotic figures including atypical ones, and necrosis), Kramer and Chen thought most if not all of the five sebaceous neoplasms presented by Kazakov et al. are actually examples of SCIS [24].

In summary, as one can see from above SCIS is a valid concept and diagnostic entity. The histopathological criteria for diagnosing such lesion are clear, precise and understandable. Recognizing SCIS as a diagnostic entity can certainly prevent misinterpreting this kind of lesions as others, thus avoiding under or over treatment.

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