Ocular and extraocular sebaceous carcinomas: A retrospective study with emphasis on the presence of *in situ* lesion and discussion and review of the histogenesis of extraocular sebaceous carcinoma

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Abstract. Sebaceous carcinoma (SC) is a rare carcinoma classified as ocular or extraocular. Ocular SC is believed to arise from the meibomian glands or the glands of Zeis. However, the origin of extraocular SC is controversial because there is no evidence of carcinoma arising from pre-existing sebaceous glands. Several hypotheses about the origin of extraocular SC have been proposed, including one suggesting an origin from intraepidermal neoplastic cells. Although extraocular SCs have been shown to occasionally comprise intraepidermal neoplastic cells, no study has investigated whether intraepidermal neoplastic cells possess sebaceous differentiation. The present study analyzed the clinicopathological features of ocular and extraocular SC, with an emphasis on the presence of *in situ* (intraepithelial) lesions. It retrospectively reviewed the clinicopathological features of eight patients with ocular and three patients with extraocular SC (eight women and three men; median age, 72 years), respectively. *In situ* (intraepithelial) lesions were observed in four of the eight ocular SC cases and one of the three extraocular SC cases and an apocrine component was noted in one patient with ocular SC (seboapocrine carcinoma). In addition, immunohistochemical analyses showed that the androgen receptor (AR) was expressed in all ocular SCs and two of the three extraocular SC cases. Adipophilin expression was observed in all ocular and extraocular SC. *In situ* lesions of extraocular SC showed positive immunoreactivity for both AR and adipophilin. The present study is the first to demonstrate sebaceous differentiation in *in situ* lesions of extraocular SC. The possible origin of extraocular SC is speculated to be the progenitor cells present in the sebaceous duct or interfollicular epidermis. The results of the present study and reported cases of SC *in situ* indicate that extraocular SC also arises from intraepidermal neoplastic cells.

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Abbreviations: SC, sebaceous carcinoma; ADP, adipophilin; AR, androgen receptor

Key words: sebaceous carcinoma, extraocular sebaceous carcinoma, *in situ* lesion, histogenesis, seboapocrine carcinoma

Introduction

Sebaceous carcinoma (SC) is a rare skin carcinoma characterized by sebocytic differentiation (1,2). SC is classified according to the location of the tumor as ocular or extraocular (1,2). While ocular SC comprises ~75% of all SC cases, 10-30% of both ocular and extraocular SC patients have a risk of tumor-related mortality (1,2). Ocular SC is considered to arise from the meibomian glands, modified sebaceous glands present in the tarsal plates of the upper and lower eyelids and the glands of Zeis, which are also sebaceous glands located in the eyelashes. *In situ* SC lesions are frequently observed within the pre-existing sebaceous glands of the meibomian glands or the glands of Zeis (3). However, the pathogenesis of extraocular SC remains to be elucidated because no *in situ* SC lesions within the pre-existing sebaceous glands of extraocular skin tissues have been observed to date (4).

The origin of extraocular SC is an issue that needs to be addressed in the field of dermatopathology. Several hypotheses have been proposed about the histogenesis of extraocular SC. Boecker *et al* (5,6) hypothesized that progenitor cells ($p63^+$/keratin 5^+) present in the sebaceous ducts or the interfollicular epidermis could be the cells of origin of some parts of extraocular SC based on immunohistochemical analyses. The authors also speculated that some extraocular SCs may originate from intraepidermal pluripotent neoplastic cells because a relatively large proportion of extraocular SC in their series had a 'full-thickness intraepidermal neoplasia' (5). In addition, the latter possibility is supported by the presence of reported cases of SC *in situ* and SC arising from squamous intraepidermal neoplasia (actinic keratosis or Bowen's disease) (7-17). These

in situ neoplastic SCs in a few cases show positive immunoreactivity for adipophilin (ADP) (7,11), which is a useful sebaceous differentiation marker that shows reactivity for intracellular lipid droplets. ADP expression has also been reported in non-SCs in various organs (18-20). Thus, sebaceous differentiation must be defined by considering both typical histopathological features and ADP immunoreactivity. However, the expression of ADP and androgen receptor (AR), which is also a useful marker for sebaceous differentiation, has not been reported in intraepidermal neoplastic cells present in extraocular SC in most of the previously reported extraocular SCs.

In addition, although most SCs do not exhibit follicular or apocrine differentiation, extremely rare cases of SC with apocrine differentiation (seboapocrine carcinoma) have been reported (21-25). This phenomenon is not unexpected based on the common embryological origin of the folliculosebaceous-apocrine unit (23). To date, only five cases (two ocular and three extraocular) have been reported in English-language literature (21-25).

The present study retrospectively reviewed the clinicopathological features of ocular and extraocular SC experienced in the Osaka Medical and Pharmaceutical University (Takatsuki, Japan), with an emphasis on the presence of *in situ* SC lesions and apocrine differentiation and discussed and reviewed the histogenesis of extraocular SC.

Materials and methods

Patient selection. The present study selected consecutive patients with SC who underwent biopsy and/or surgical resection at the Osaka Medical and Pharmaceutical University Hospital between January 2001 and December 2020. Accordingly, 11 patients with ocular (eight patients) and extraocular (three patients) SC were included in the present study.

This retrospective, single-institution study was conducted in accordance with the principles of the Declaration of Helsinki and the study protocol was approved by the Institutional Review Board of Osaka Medical and Pharmaceutical University Hospital (approval nos. 2020-124 and 2022-212). All data were anonymized. The Institutional Review Board waived the requirement for informed consent because of the retrospective study design, as medical records and archived samples were used with no risk to the participants. In addition, the present study did not include minors. Information regarding this study, such as the inclusion criteria and opportunity to opt-out, was provided through the institutional website (https://www.ompu.ac.jp/u-deps/path/img/file9.pdf).

Histopathological analysis. Biopsied and/or surgically resected specimens were fixed in 10% formalin at room temperature for 24-48 h, sectioned (3-5 mm), dehydrated in ethanol and xylene at room temperature, embedded in paraffin (60˚C), and stained with hematoxylin and eosin for 5 min each at room temperature. A minimum of two researchers independently evaluated histopathological features.

Immunohistochemical analyses. Tumor tissues were fixed in 10% formalin at room temperature for 24-48 h, dehydrated in ethanol and xylene at room temperature, and embedded in paraffin (60˚C). The 4-μm tumor tissue sections then underwent immunohistochemical staining using autostainers (Discovery Ultra System; Roche Diagnostics; Leica Bond-III; Leica Biosystems GmbH), according to the manufacturer's instructions. Sections were incubated with mouse monoclonal antibodies against ADP (cat. no. AP125; 1:100 dilution; Progen Biotechnik GmbH), AR (cat. no. AR441; 1:100 dilution; Dako; Agilent Technologies, Inc.), keratin 5/6 (cat. no. D5/16B4; 1:100 dilution; Dako; Agilent Technologies, Inc.), Ki-67 (cat. no. MIB-I; 1:150 dilution; Dako; Agilent Technologies, Inc.), p53 (DO-7; 1:50 dilution; Dako; Agilent Technologies, Inc.) and p63 (cat. no. 4A4; 1:50 dilution; Dako; Agilent Technologies, Inc.) for 20 min at room temperature. Secondary antibodies were pre-diluted and were used to incubate the sections for 8 min at room temperature [Optivew DAB Universal Kit (cat. no. 518-111427; Roche Diagnostics) and Novolink Max Polymer Detection System (cat. no. RE7140-K; Leica Biosystems GmbH)]. Then two researchers independently evaluated the results of the immunohistochemical staining.

Results

Patient characteristics. Table I summarizes the clinicopathological features of the study cohort. This study included eight women and three men. The median patient age was 72 years (range: 50-90 years). The cohort comprised eight and three patients with ocular and extraocular SC, respectively. The extraocular SC was located on the cheek, fingers, or scalp.

Histopathological features. Table I summarizes the histopathological characteristics observed in this study. The typical histopathological features of SC were as follows: an infiltrative variable-sized nodular proliferation of basaloid neoplastic cells with large round-to-oval nuclei and occasional scalloped nuclei (Fig. 1A). Occasional necrosis was observed within the nodules. Some neoplastic cells had a clear cytoplasm and multi-vacuoles were characteristically observed in the cytoplasm of the neoplastic cells (Fig. 1A). *In situ* (intraepithelial) lesions were noted in four of the eight ocular SC cases and one of the three extraocular SC cases (the two remaining extraocular SC cases showed no intraepithelial lesion; Fig. 1B for ocular SC and Fig. 1C for extraocular SC). Mild solar elastosis was noted in the dermis around the tumor in an extraocular SC case with *in situ* lesions. In addition, no neoplastic cells were present within the pre-existing sebaceous glands in any of the extraocular SC.

An apocrine component was observed in one patient with ocular SC (patient 3). The tumor was composed of SC (~70% of the tumor) and apocrine carcinoma components (~30%). The SC component comprised variable-sized nodular proliferations of basaloid cells (Fig. 1D). *In situ* (intraepithelial) lesions in the SC were also observed. An irregularly shaped glandular formation was observed with continuity of the above-mentioned SC component (Fig. 1D). These neoplastic glandular cells had large round-to-oval nuclei containing small nucleoli and mitotic figures were frequently observed (Fig. 1E). Decapitation was also noted (Fig. 1E). Accordingly, the latter component was considered to be an apocrine carcinoma component; thus, a diagnosis of seboapocrine carcinoma was made.

Table I. Clinicopathological and immunohistochemical characteristics of ocular and extraocular sebaceous carcinomas.

A, Ocular sebaceous carcinoma

Characteristic	Age, years	Sex	Location	*In situ* component	Apocrine component	Adipophilin	Androgen Receptor	p53	Ki-67 labelling index, %
Patient 1	50	Female	Eyelid	-	-	+	+	+	20
Patient 2	83	Male	Eyelid	-	-	+	+	-	15
Patient 3	79	Female	Eyelid	+	+	+	+	+	50
Patient 4	82	Female	Eyelid	-	-	+	+	+	25
Patient 5	71	Female	Eyelid	+	-	+	+	+	80
Patient 6	72	Female	Eyelid	-	-	+	+	+	15
Patient 7	80	Female	Eyelid	+	-	+	+	-	10
Patient 8	66	Female	Eyelid	+	-	+	+	-	20

B, Extraocular sebaceous carcinoma

Characteristic	Age, years	Sex	Location	*In situ* component	Apocrine component	Adipophilin	Androgen Receptor	p53	Ki-67 labeling index, %
Patient 9	90	Female	Cheek	-	-	+	+	+	35
Patient 10	68	Male	Finger	+	-	+	+	+	10
Patient 11	65	Male	Scalp	-	-	+	-	+	15

Table II. Clinicopathological features of extraocular sebaceous carcinomas *in situ* and sebaceous carcinomas arising from squamous intraepidermal neoplasm.

First author/s, year	Patients	Age, years	Sex	Location	Associated squamous lesion	Sebaceous carcinoma	AR expression	ADP expresion	(Refs.)
Namiki *et al*, 2018	Patient 1	67	Male	Abdomen	Bowen's disease	*in situ*	ND	+	(7)
Misago *et al*, 2015	Patient 2	85	Female	Cheek	Actinic keratosis	invasive	ND	+	(8)
Misago *et al*, 2015	Patient 3	82	Female	Cheek	Actinic keratosis (bowenoid)	invasive	ND	+	(8)
Aung *et al*, 2014	Patient 4	60	Male	Forehead	Squamous cell carcinoma *in situ*	*in situ*	ND	ND	(9)
Aung *et al*, 2014	Patient 5	70	Male	Neck	Actinic keratosis	*in situ*	ND	ND	(9)
Aung *et al*, 2014	Patient 6	85	Female	Cheek	Actinic keratosis	*in situ*	ND	ND	(9)
Ishida *et al*, 2013	Patient 7	67	Female	Buttock	Bowen's disease	invasive	+	+	(10)
Ishida *et al*, 2012	Patient 8	60	Male	Neck	Actinic keratosis	*in situ*	+	+	(11)
Nakashima *et al*, 2010	Patient 9	83	Female	Cheek	Actinic keratosis	invasive	ND	+	(12)
Ansai *et al*, 2000	Patient 10	75	Female	Temple	Actinic keratosis	*in situ*	ND	ND	(13)
Ansai *et al*, 2000	Patient 11	81	Female	Cheek	Actinic keratosis	invasive	ND	ND	(13)
Escalonilla *et al*, 1999	Patient 12	76	Female	Vulva	Bowen's disease	invasive	ND	ND	(14)
Oka *et al*, 1990	Patient 13	81	Female	Upper arm	Squamous cell carcinoma *in situ*	*in situ*	ND	ND	(15)
Jacobs *et al*, 1986	Patient 14	89	Female	Vulva	Bowen's disease	invasive	ND	ND	(16)
Fulling *et al*, 1981	Patient 15	74	Male	Cheek	Squamous cell carcinoma *in situ*	*in situ*	ND	ND	(17)

ADP, adipophilin; AR androgen receptor; ND, not performed.

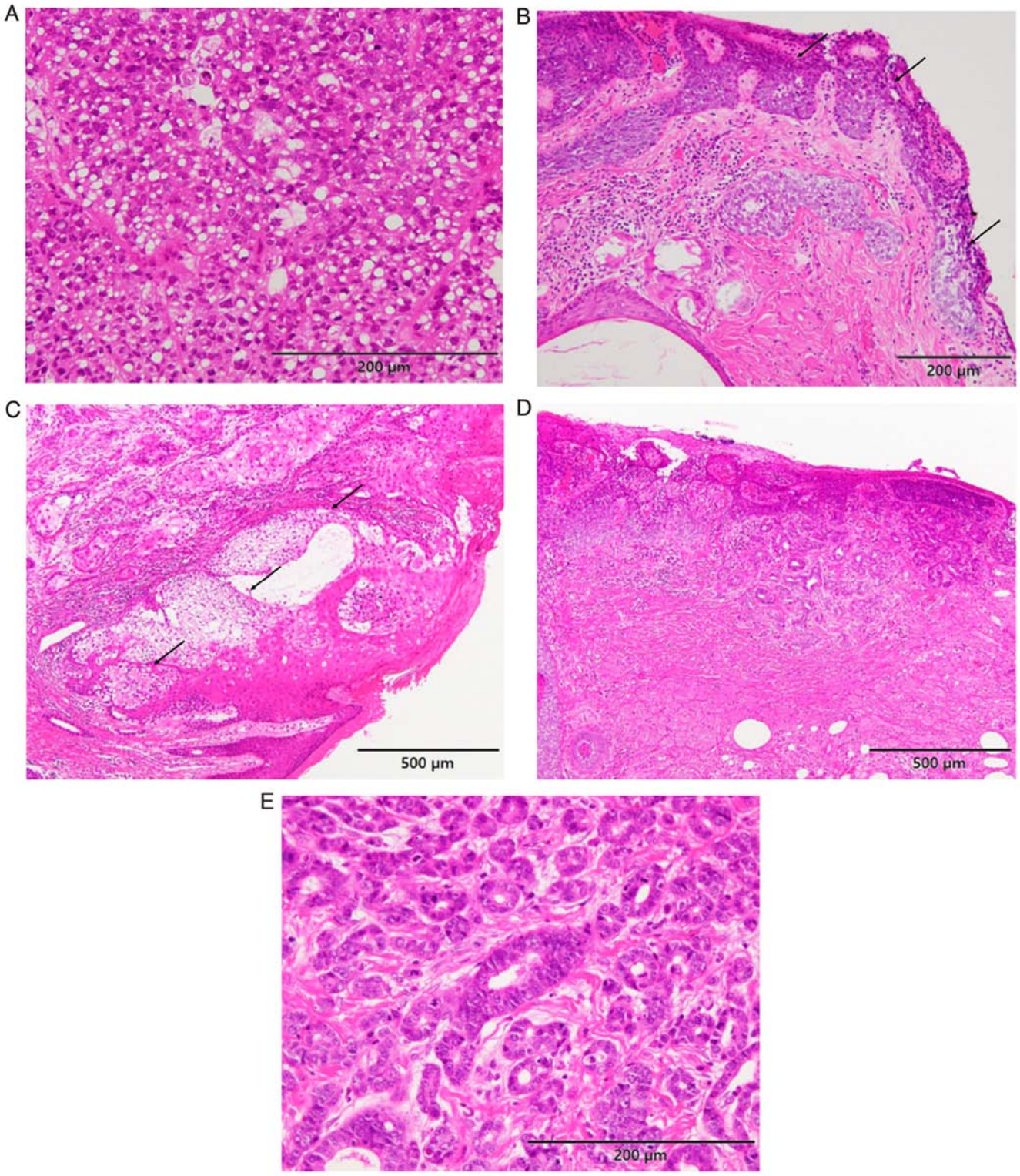

Figure 1. Histopathological features of sebaceous carcinoma. (A) Proliferation of the neoplastic cells with large round-to-oval nuclei, some of these cells showed scalloped features and multivacuolated cytoplasm (hematoxylin and eosin; magnification, x400). (B) *In situ* (intraepithelial) lesion noted in ocular sebaceous carcinoma (arrows) (hematoxylin and eosin; magnification, x200). (C) *In situ* (intraepidermal) lesion observed in extraocular sebaceous carcinoma (arrows) (hematoxylin and eosin; magnification, x100). (D) Seboapocrine carcinoma of the eyelid (Patient 3). Solid proliferation of sebaceous carcinoma component (left side) and infiltrative growth with glandular formation (right side) are present (hematoxylin and eosin; magnification, x100). (E) Apical snouts are observed in the apocrine carcinoma component (hematoxylin and eosin; magnification, x400).

Immunohistochemical features. AR expression was observed in all eight patients with ocular SC and two of the three patients with extraocular SC (Fig. 2A). In addition. ADP expression was observed in all patients with ocular and extraocular SC (Fig. 2B). Fig. 2C shows positive immunoreactivity for AR and ADP in an *in situ* (intraepidermal) lesion of extraocular SC (Patient 10). In seboapocrine carcinoma, ADP expression was present in both the invasive and *in situ* (intraepithelial)

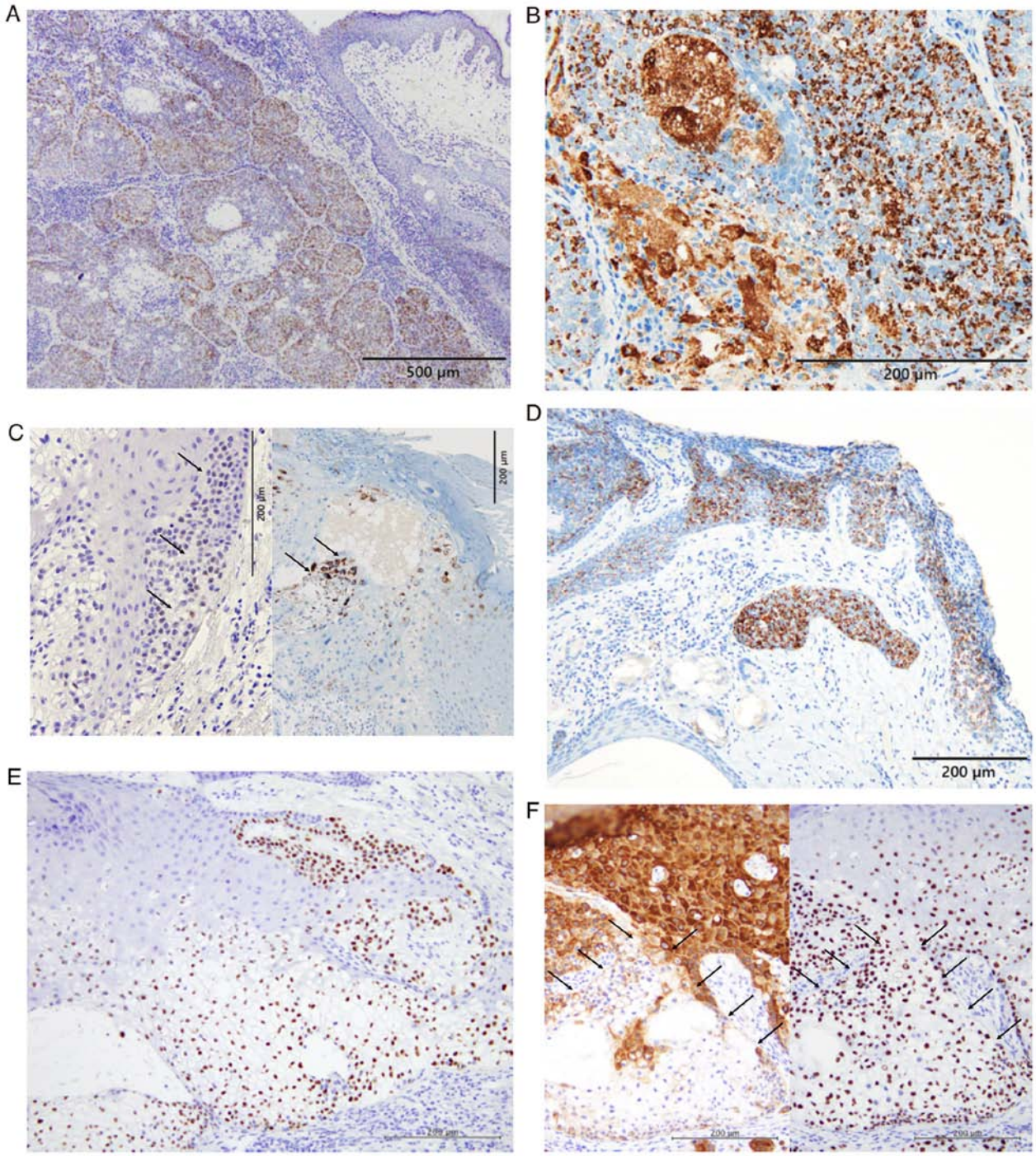

Figure 2. Immunohistochemical features of sebaceous carcinoma. (A) The androgen receptor is expressed in almost all of the neoplastic cells (magnification, x100). (B) Diffuse-positive immunoreactivity for adipophilin (magnification, x400). (C) Androgen receptor (left side) and adipophilin (right side) were positive in *in situ* (intraepidermal) neoplastic cells of extraocular sebaceous carcinoma (arrows; magnification, x400 for the androgen receptor; magnification, x200 for adipophilin). (D) Adipophilin was expressed in a diffused manner in both the in situ (intraepithelial) and invasive components of ocular sebaceous carcinoma (magnification, x200). (E) p53 overexpression is noted in *in situ* (intraepidermal) neoplastic cells of extraocular sebaceous carcinoma (note: No overexpression was observed in the non-neoplastic epidermal cells; magnification, x200). (F) Focal keratin 5/6 expression (left) and diffuse p63 expression (right) are observed in *in situ* (intraepidermal) neoplastic cells of extraocular sebaceous carcinoma. Non-neoplastic epidermal keratinocytes show positive immunoreactivity for keratin 5/6 and p63 [Arrows indicate *in situ* (intraepidermal) neoplasm; magnification, x200].

components of the SC (Fig. 2D). p53 overexpression was noted in all three extraocular SCs and five of the eight ocular SCs (Fig. 2E) (Table I). Diffuse expression of p63 and focal expression of keratin 5/6 were observed in an *in situ* (intraepidermal) lesion of extraocular SC (Patient 10; Fig. 2F). The median Ki-67 labelling index was 20% for ocular (range: 10-80%) and 15% for extraocular SC (range: 10-35%).

Discussion

The present study comprehensively reviewed the histopathological and immunohistochemical characteristics of eight ocular and three extraocular SC cases. *In situ* (intraepithelial) lesions were noted in four of eight ocular and one of three extraocular SC cases and the neoplastic cells in these *in situ*

Table III. Clinicopathological features of seboapocrine carcinoma.

First author/s, year	Patients	Age, years	Sex	Location	Size, cm	Outcome	(Refs.)
Ishida and Okabe, 2012	Patient 1	61	Male	Eyelid	2.1x1.5	Alive with disease 38 months	(21)
Misago and Narisawa, 2001	Patient 2	60	Male	Eyelid	3x2	Not available	(22)
Kazakov *et al*, 2007	Patient 3	84	Male	Shoulder	4x3	No evidence of disease 6 months	(23)
Pinheiro and Lopes, 2019	Patient 4	76	Female	Scalp	3x1.7	No evidence of disease 29 months	(24)
Afroz *et al*, 2013	Patient 5	54	Male	Nose	2.5x2	No evidence of disease 5 years	(25)

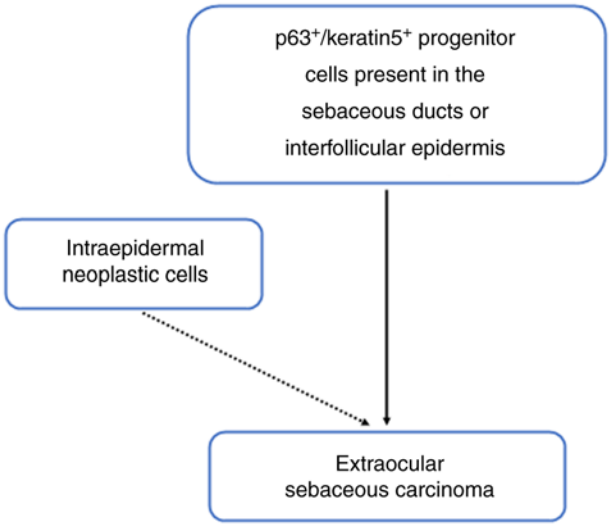

Figure 3. Possible schematic of the histogenesis of extraocular sebaceous carcinoma. Sebaceous carcinoma may arise from the p63+/keratin 5+ progenitor cells present in the sebaceous duct or interfollicular epidermis. Intraepidermal neoplastic cells may be the origin of extraocular sebaceous carcinomas, especially those with intraepidermal squamous neoplasia.

lesions, including extraocular SC, showed sebaceous differentiation. It is recognized that ocular SC arises from the meibomian glands or the glands of Zeis and the presence of *in situ* lesions is not uncommon (1,3). However, the origin of extraocular SC remains to be elucidated and has been a controversial topic (4,5). Boecker *et al* (5,6) proposed a model of sebaceous gland development and the histogenesis of sebaceous gland neoplasms. According to their model, mature sebocytes and ductal cells arise from p63+/keratin 5+ progenitor cells and extraocular sebaceous tumors may also arise from p63+/keratin 5+ progenitor cells. Thus, these progenitor cells present in the sebaceous ducts or the interfollicular epidermis could be the cells of origin of some parts of extraocular SC (Fig. 3) (5,6). However, some cases of extraocular SC might arise from the epidermis because, albeit rare, SC *in situ* or SC (*in situ* or invasive) arising from squamous intraepidermal neoplasm (actinic keratosis or Bowen's disease) have been reported (7-17). Table II summarizes the clinicopathological features of the previously reported SC *in situ* and SC arising from a squamous intraepidermal neoplasm of the extraocular sites. Of 15 patients, eight and seven had *in situ* and invasive SC associated with squamous intraepidermal neoplasms, respectively, and more than half of these lesions occurred in sun-exposed regions.

The frequency of the presence of *in situ* (intraepidermal) lesions of extraocular SC remains to be elucidated, although Boecker *et al* (5) reported that four of the six cases of extraocular SC had full-thickness intraepidermal neoplasia and three of the six cases also had actinic keratosis. However, information on whether these intraepidermal lesions showed sebaceous differentiation was not available. Notably, ADP expression, for which >95% of extraocular SC showed positive immunoreactivity (5), was observed in two cases of SC *in situ* (7,11) and AR expression, for which >80% of ocular and extraocular SC showed positive immunoreactivity (5,26), was also noted in one case of SC *in situ* (11). In the present study, one of the three extraocular SC had intraepidermal neoplasia (*in situ* lesion) overlying the invasive SC and this lesion showed sebaceous differentiation (both AR and ADP expression). In addition, these intraepidermal neoplastic cells showed diffuse positive immunoreactivity for p63 and focal positive immunoreactivity for keratin 5/6. Although this finding did not directly indicate that intraepidermal neoplastic cells of extraocular SC arise from p63+/keratin 5+ progenitor cells, these intraepidermal neoplastic cells might have the characteristics of these progenitor cells. Accordingly, these results suggest that a proportion of extraocular SC may arise from intraepidermal neoplasia. Therefore, additional analyses of extraocular SC, especially the presence of intraepidermal neoplasia and sebaceous differentiation in these intraepidermal lesions, are required to clarify the histogenesis of extraocular SC.

Recently, the results of whole-exome sequencing have shown that three distinct mutational patterns were present in SC; ultraviolet (UV)-damaged signature, microsatellite instability profiles and pauci-mutational signature (27). Ocular SC shows pauci-mutational signature, whereas extraocular SC exhibits UV-damaged, microsatellite instability and pauci-mutational signatures (27). Accordingly, the genetic backgrounds of ocular and extraocular SCs are different (27). In addition, SC showing UV-damaged signatures occurs in the extraocular sites and its transcriptional changes resemble those of cutaneous squamous cell carcinoma. Therefore, it has been hypothesized that UV-damaged extraocular SC arises from the subpopulation of intraepidermal keratinocytes or the superficial portion of the folliculosebaceous unit, which

is vulnerable to UV damage, following the same mechanism of cutaneous squamous cell carcinoma (27). Although data on the genetic changes of SC accompanying intraepidermal squamous neoplasia are not available, these tumors may show UV-damaged signatures. Additionally, p53 overexpression was noted in all extraocular SCs in the present cohort (by contrast, it was observed in five of the eight ocular SCs, although both extraocular and ocular SCs showed high proliferative activities). Therefore, intraepidermal pluripotent neoplastic cells may be the origin of a portion of extraocular SC. According to these findings, the results of the present study and the reported cases of SC *in situ* and SC arising from intraepidermal squamous neoplasms, some parts of the extraocular SC may arise from intraepidermal neoplastic cells.

In some rare cases, SC can show apocrine differentiation, namely seboapocrine carcinoma (23,24). However, only five cases of extraocular and ocular SCs with sebaceous differentiation (three extraocular and two ocular SCs) have been reported in the literature (21-25). These findings are consistent with the common embryonic origin of the folliculosebaceous-apocrine unit (23). The tumor in one patient with ocular SC presented in the present study is the third reported case of ocular seboapocrine carcinoma. Table III summarizes the clinicopathological features of the previously reported cases of this type of rare carcinoma. These findings suggest that the frequency of apocrine differentiation in SC may be higher at the extraocular site as ~75% of SCs occur in the ocular region.

The present study has some limitations. Although SC is a rare carcinoma, this study was a retrospective, single-institution analysis with a small sample size. Therefore, the frequency of *in situ* (intraepithelial) lesions may be biased and additional multi-institutional studies with larger sample sizes are required to clarify the pathogenesis of extraocular SC.

In conclusion, extraocular SC may arise from progenitor cells present in the sebaceous duct or the interfollicular epidermis and intraepidermal neoplastic cells with pluripotency for sebaceous differentiation may also be the origin of extraocular SC.

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Availability of data and materials

All data generated and analyzed in this study are included in this published article.

Authors' contributions

DT and MI conceived and designed the present study, performed histopathological and immunohistochemical analyses. DT, MI, EY, KU and YH performed acquisition and analysis of data. DT and MI drafted of the manuscript; tables and figures. DT and MI confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the Institutional Review Board of Osaka Medical and Pharmaceutical University (approval nos. 2020-124 and no. 2022-212). All data were anonymized. The Institutional Review Board waived the requirement for informed consent because of the retrospective design of the study with no risk of identity exposure for the patients. This study did not include minors.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Dubovy S, Eberhart CG and Vemuganti G: Sebaceous carcinoma of the conjunctiva and caruncle. In: WHO Classification of Tumours of the Eye. 4th Edition. IARC, Lyon, pp25-26, 2018.
2. Wick MR, Cree IA, Kazakov DV, Lazar AJ, Michal M, Sangüeza OP, Singh R, Wood BA and Zembowicz A: Sebaceous carcinoma. In: WHO Classification of Skin Tumours. 4th Edition. IARC, Lyon, pp211-212, 2018.
3. Rao NA, Hidayat AA, McLean IW and Zimmerman LE: Sebaceous carcinomas of the ocular adnexa: A clinicopathologic study of 104 cases, with five-year follow-up data. Hum Pathol 13: 113-122, 1982.
4. Kazakov DV, Kutzner H, Spagnolo DV, Rütten A, Mukensnabl P and Michal M: What is extraocular cutaneous sebaceous carcinoma in situ? Am J Dermatopathol 32: 857-858, 2010.
5. Boecker W, Reusch M, Mielke V, Reusch U, Hallermann C, Loening T, Tiemann M and Buchwalow I: Twenty-eight cases of extraocular sebaceous carcinoma: A correlative clinicopathological and immunohistochemical analysis of extraocular sebaceous carcinomas and benign sebaceous gland tumors. Am J Dermatopathol 43: 93-102, 2021.
6. Boecker W, Reusch M, Mielke V, Reusch U, Loening T, Tiemann M and Buchwalow I: Spatial analysis of p63, K5 and K7 defines two groups of progenitor cells that differentially contribute to the maintenance of normal sebaceous glands, extraocular sebaceous carcinoma and benign sebaceous tumors. J Dermatol 46: 249-258, 2019.
7. Namiki T, Miura K, Yokozeki H and Ansai SI: Bowen disease with sebaceous differentiation: A case report and immunohistochemical analysis of adipophilin and cytokeratin 1. Am J Dermatopathol 40: 841-845, 2018.
8. Misago N, Kuwashiro M, Tsuruta N and Narisawa Y: Sebaceous carcinoma in association with actinic keratosis: A report of two cases with an immunohistochemical study. J Dermatol 42: 616-620, 2015.
9. Aung PP, Batrani M, Mirzabeigi M and Goldberg LJ: Extraocular sebaceous carcinoma in situ: Report of three cases and review of the literature. J Cutan Pathol 41: 592-596, 2014.
10. Ishida M, Iwai M, Yoshida K, Kagotani A and Okabe H: Sebaceous carcinoma associated with Bowen's disease: A case report with emphasis on the pathogenesis of sebaceous carcinoma. Int J Clin Exp Pathol 6: 3029-3032, 2013.
11. Ishida M and Okabe H: Intraepidermal sebaceous carcinoma occurring concurrently with actinic keratosis. J Cutan Pathol 39: 731-732, 2012.
12. Nakashima K, Adachi K, Yamasaki A, Yamada N, Yoshida Y and Yamamoto O: Sebaceous carcinoma with actinic keratosis. Acta Derm Venereol 90: 196-198, 2010.

13. Ansai S and Mihara I: Sebaceous carcinoma arising on actinic keratosis. Eur J Dermatol 10: 385-388, 2000.
14. Escalonilla P, Grilli R, Cañamero M, Soriano ML, Fariña MC, Manzarbeitia F, Sáinz R, Matsukura T and Requena L: Sebaceous carcinoma of the vulva. Am J Dermatopathol 21: 468-472, 1999.
15. Oka K and Katsumata M: Intraepidermal sebaceous carcinoma: Case report. Dermatologica 180: 181-185, 1990.
16. Jacobs DM, Sandles LG and Leboit PE: Sebaceous carcinoma arising from Bowen's disease of the vulva. Arch Dermatol 122: 1191-1193, 1986.
17. Fulling KH, Strayer DS and Santa Cruz DJ: Adnexal metaplasia in carcinoma in situ of the skin. J Cutan Pathol 8: 79-88, 1981.
18. Yoshikawa K, Ishida M, Yanai H, Tsuta K, Sekimoto M and Sugie T: Prognostic significance of adipophilin expression in biopsy specimens of patients with triple-negative breast cancer. Oncol Lett 23: 127, 2022.
19. Hashimoto Y, Ishida M, Ryota H, Yamamoto T, Kosaka H, Hirooka S, Yamaki S, Kotsuka M, Matsui Y, Yanagimoto H, *et al*: Adipophilin expression is an indicator of poor prognosis in patients with pancreatic ductal adenocarcinoma: An immunohistochemical analysis. Pancreatology 19: 443-448, 2019.
20. Fujimoto M, Matsuzaki I, Yamamoto Y, Yoshizawa A, Warigaya K, Iwahashi Y, Kojima F, Furukawa F and Murata SI: Adipophilin expression in cutaneous malignant melanoma. J Cutan Pathol 44: 228-236, 2017.
21. Ishida M and Okabe H: Sebaceous carcinoma with apocrine differentiation (seboapocrine carcinoma). Pathol Int 62: 438-440, 2012.
22. Misago N and Narisawa Y: Sebaceous carcinoma with apocrine differentiation. Am J Dermatopathol 23: 50-57, 2001.
23. Kazakov DV, Calonje E, Rütten A, Glatz K and Michal M: Cutaneous sebaceous neoplasms with a focal glandular pattern (seboapocrine lesions): A clinicopathological study of three cases. Am J Dermatopathol 29: 359-364, 2007.
24. Pinheiro JAF and Lopes JMPB: Periocular sebaceous carcinoma with apocrine differentiation: A case report and review of the literature. Int J Surg Pathol 27: 432-436, 2019.
25. Afroz N, Zaidi N and Rizvi SAR: Sebaceous carcinoma with apocrine differentiation: A rare entity with aggressive behavior. Indian J Pathol Microbiol 56: 408-410, 2013.
26. Na HY, Choe JY, Shin SA, Choung HK, Oh S, Chung JH, Park M and Kim JE: Proposal of a provisional classification of sebaceous carcinoma based on hormone receptor expression and HER2 status. Am J Surg Pathol 40: 1622-1630, 2016.
27. North JP, Golovato J, Vaske CJ, Sanborn JZ, Nguyen A, Wu W, Goode B, Stevers M, McMullen K, Perez White BE, *et al*: Cell of origin and mutation pattern define three clinically distinct classes of sebaceous carcinoma. Nat Commun 9: 1894, 2018.