



SEBACEOUS CARCINOMA: CORRELATION OF HISTOMORPHOLOGY WITH IMMUNOHISTOCHEMICAL FINDINGS

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ABSTRACT

Background: Sebaceous carcinoma is a rare malignant adnexal neoplasm that predominantly affects the periocular region and may mimic other epithelial malignancies. Immunohistochemistry is particularly useful when sebaceous differentiation is inconspicuous. The present study aimed to evaluate the histomorphological features of sebaceous carcinoma and correlate them with immunohistochemical findings.

Materials and Methods: A retrospective descriptive study was conducted on 10 histopathologically confirmed cases of sebaceous carcinoma. H&E-stained sections were evaluated for tumour architecture, differentiation, sebaceous differentiation, nuclear pleomorphism, hyperchromasia, mitotic activity, necrosis and infiltrative growth. Immunohistochemical expression of adipophilin, epithelial membrane antigen (EMA), androgen receptor (AR) and Ber-EP4 was assessed using a semiquantitative composite scoring system.

Results: The mean age was 62.4 ± 11.8 years, with 60% of patients aged >60 years and 60% being female. The upper eyelid was the commonest tumour site (40%). Nuclear pleomorphism was present in all cases, while lobular/irregular architecture, hyperchromasia, sebaceous differentiation and increased mitotic activity were observed in 90%, 90%, 80% and 80% respectively. Infiltrative growth was present in 70% and necrosis in 50%. Adipophilin and EMA showed positivity in 90% of cases, followed by AR in 80% and Ber-EP4 in 30%. AR positivity was observed in all well/moderately differentiated tumours but in only one poorly differentiated tumour ($p=0.067$). Adipophilin was positive in all cases with morphological sebaceous differentiation ($p=0.20$).

Conclusion: Histomorphology remains fundamental for diagnosis, while adipophilin and EMA provide valuable immunohistochemical support. An integrated morphological and immunohistochemical approach is particularly useful in diagnostically challenging and poorly differentiated sebaceous carcinomas.

KEYWORDS: Sebaceous Carcinoma, Sebaceous Differentiation, Adipophilin, Epithelial Membrane Antigen, Androgen Receptor, Immunohistochemistry, Histomorphology.

Introduction

Sebaceous carcinoma (SC) is a rare malignant adnexal neoplasm characterized by sebaceous differentiation. It most commonly occurs in the periocular region, particularly involving the meibomian glands and glands of Zeis, although

extraocular lesions may arise in the head, neck, trunk, and other cutaneous sites[1]. Despite its rarity, SC is clinically important because of its potential for local invasion, recurrence, and regional or distant metastasis.

Sebaceous carcinoma is a rare cutaneous malignancy

worldwide, with population-based studies reporting age-adjusted incidence rates of approximately 0.07–0.18 per 100,000 person-years, with most tumours arising in the head and neck region[2]. In India, sebaceous carcinoma shows a relatively higher proportion among eyelid malignancies than in Western populations; Indian series have reported it as one of the commonest malignant eyelid tumours, with frequencies ranging from approximately 37% to 56% in selected studies[3].

Histologically, sebaceous carcinoma demonstrates considerable morphological variation depending on the degree of sebaceous differentiation. Well-differentiated tumours may show recognizable sebocytes with abundant pale or vacuolated cytoplasm, whereas poorly differentiated lesions may predominantly consist of basaloid or atypical epithelial cells with only focal evidence of sebaceous differentiation[4]. The tumour cells may be arranged in lobules, nests, cords, or irregular infiltrative groups. Cytological features supporting malignancy include nuclear pleomorphism, hyperchromasia, prominent nucleoli, increased mitotic activity, atypical mitoses, and infiltrative growth into the surrounding tissue[5].

The differential diagnosis of sebaceous carcinoma includes several cutaneous adnexal and epithelial malignancies, particularly basal cell carcinoma and squamous cell carcinoma. In poorly differentiated lesions, the characteristic sebaceous cytoplasmic features may be inconspicuous, making diagnosis based solely on routine histomorphology difficult. Recognition of subtle sebaceous differentiation is therefore essential, and immunohistochemistry can provide valuable additional evidence in diagnostically challenging cases[6].

Immunohistochemical examination is useful for demonstrating sebaceous differentiation and supporting the diagnosis when morphological findings are equivocal. Markers such as adipophilin, androgen receptor, epithelial membrane antigen and selected cytokeratins have been studied in sebaceous neoplasms. Adipophilin is particularly useful for highlighting intracellular lipid droplets, while androgen receptor may demonstrate nuclear staining in sebaceous neoplasms[7]. However, immunohistochemical findings should always be interpreted in conjunction with the architectural and cytological features rather than relying on a single marker in isolation.

The present study focuses on the correlation of the morphological features of sebaceous carcinoma with its immunohistochemical profile. The study emphasizes the identification of characteristic tumour architecture, cytological atypia and sebaceous differentiation on histopathological examination, together with the corresponding immunohistochemical staining pattern. Such an integrated approach can improve diagnostic accuracy, particularly in poorly differentiated lesions where conventional histomorphology alone may not be sufficient.

Materials and Methods

Study Design

A retrospective descriptive study was conducted to evaluate the histomorphological features of sebaceous carcinoma and correlate them with the corresponding immunohistochemical findings.

Study Sample Size

The study included 10 histopathologically confirmed cases of sebaceous carcinoma with adequate representative tumour tissue and available immunohistochemical findings.

Study Area

The study was conducted in the Department of Pathology at a Tertiary Hospital in South India, using the available histopathology and immunohistochemistry records and representative tissue sections.

Inclusion Criteria

- Histopathologically confirmed cases of sebaceous carcinoma.
- Cases with adequate representative tumour tissue.
- Cases with corresponding immunohistochemical findings available for evaluation.

Exclusion Criteria

- Inadequate or poorly preserved tissue sections.
- Cases without representative tumour tissue.
- Cases lacking corresponding immunohistochemical findings.
- Cases without a definitive diagnosis of sebaceous carcinoma.

Histopathological Evaluation

Hematoxylin and eosin (H&E)-stained sections were reviewed for tumour architecture, degree of differentiation, sebaceous differentiation, cellular morphology, nuclear pleomorphism, mitotic activity, necrosis and infiltrative growth pattern. The histological findings were documented and correlated with the immunohistochemical results.

Immunohistochemistry

The immunohistochemical panel included commonly used markers for sebaceous carcinoma, namely adipophilin, epithelial membrane antigen (EMA), androgen receptor (AR) and Ber-EP4. These markers have been evaluated in published sebaceous carcinoma studies and are useful in supporting sebaceous differentiation and distinguishing sebaceous carcinoma from common mimics such as basal cell carcinoma and squamous cell carcinoma.

Where available, additional markers such as GATA3 and TRPS1 may be evaluated as supplementary markers.

Histomorphological-Immunohistochemical Correlation

The immunohistochemical findings were correlated with

the histomorphological features in each case, particularly the degree of sebaceous differentiation and tumour differentiation. The diagnostic contribution of individual markers and their overall concordance with morphology were assessed.

Assessment Tools

Histomorphological assessment was performed using haematoxylin and eosin (H&E)-stained sections under a light microscope. The evaluated parameters included tumour architecture, degree of differentiation, sebaceous differentiation, nuclear pleomorphism, mitotic activity, necrosis and infiltrative growth pattern.

Immunohistochemical expression was assessed using a Semi-quantitative Immunohistochemical Scoring System, based on the percentage of positive tumour cells and staining intensity. The percentage of positive cells was scored as 0 (No staining), 1 (<5% positivity), 2 (5–50% positivity) and 3 (>50% positivity), while staining intensity was scored as 0 (negative), 1 (weak), 2 (moderate) and 3 (strong). The two scores were added to obtain a composite score ranging from 0 to 6. This approach has been used in published studies evaluating immunohistochemical markers in sebaceous neoplasms[8].

For adipophilin, the pattern of immunoreactivity was additionally documented as vesicular/membranous or granular cytoplasmic staining, as the staining pattern may aid in recognizing intracellular lipid droplets and supporting sebaceous differentiation.

Ethical Considerations

Ethical Committee clearance was obtained before the commencement of the study and the declaration of Helsinki Protocols were followed.

Statistical Analysis

Data were analyzed using appropriate descriptive and inferential statistical methods. Categorical variables were expressed as frequency and percentage [n (%)],

while continuous variables were expressed as mean $\pm$ standard deviation or median with range, as appropriate. Associations between histomorphological features and immunohistochemical expression were assessed using the Chi-square test or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant.

Results

Table 1, depicts the demographic and clinical profile of the 10 study cases, with a mean age of 62.4 ± 11.8 years and female predominance. The upper eyelid was the most frequent tumour site, while right and left-sided lesions were equally represented.

Table 2, shows the major histomorphological features of sebaceous carcinoma, with nuclear pleomorphism being universal and lobular/irregular architecture, hyperchromasia, sebaceous differentiation and increased mitotic activity being frequent findings. Most tumours were moderately differentiated, while infiltrative growth was observed in 70% of cases.

Table 3, depicts the immunohistochemical expression profile, with adipophilin and EMA showing the highest positivity (90%), followed by AR (80%) and Ber-EP4 (30%). Adipophilin also demonstrated the highest mean composite immunohistochemical score (4.9 ± 1.3).

Table 4, shows the relationship between tumour differentiation and AR expression, showing positivity in all well/moderately differentiated cases compared with 33.3% of poorly differentiated cases. Although a trend toward reduced AR expression in poorly differentiated tumours was observed, the association was not statistically significant ($p=0.067$).

Table 5, depicts the correlation between histomorphological sebaceous differentiation and adipophilin expression, with all eight cases showing sebaceous differentiation being adipophilin positive. However, the association did not reach statistical significance ($p=0.20$), likely reflecting the limited sample size.

Table 1: Demographic and Clinical Characteristics of the Study Cases

Parameter	Category	n (%)
Age (years)	Mean $\pm$ SD	62.4 ± 11.8
Age group	≤ 60 years	4 (40.0)
	> 60 years	6 (60.0)
Sex	Male	4 (40.0)
	Female	6 (60.0)
Tumour site	Upper eyelid	4 (40.0)
	Lower eyelid	3 (30.0)
	Other periocular site	3 (30.0)
Laterality	Right	5 (50.0)
	Left	5 (50.0)

Table 2: Histomorphological Features of Sebaceous Carcinoma

Histomorphological feature	Present, n (%)	Absent, n (%)
Lobular/irregular tumour architecture	9 (90.0)	1 (10.0)
Sebaceous differentiation	8 (80.0)	2 (20.0)
Nuclear pleomorphism	10 (100.0)	0 (0.0)
Hyperchromasia	9 (90.0)	1 (10.0)
Increased mitotic activity	8 (80.0)	2 (20.0)
Necrosis	5 (50.0)	5 (50.0)
Infiltrative growth	7 (70.0)	3 (30.0)
Tumour differentiation		
Well differentiated	2 (20.0)	—
Moderately differentiated	5 (50.0)	—
Poorly differentiated	3 (30.0)	—

Table 3: Immunohistochemical Expression in Sebaceous Carcinoma

IHC marker	Positive, n (%)	Negative, n (%)	Mean composite score $\pm$ SD
Adipophilin	9 (90.0)	1 (10.0)	4.9 $\pm$ 1.3
EMA	9 (90.0)	1 (10.0)	4.7 $\pm$ 1.4
Androgen receptor (AR)	8 (80.0)	2 (20.0)	4.2 $\pm$ 1.5
Ber-EP4	3 (30.0)	7 (70.0)	1.8 $\pm$ 1.6

Table 4: Correlation of Tumour Differentiation with Androgen Receptor Expression

Tumour differentiation	AR positive, n (%)	AR negative, n (%)	p-value
Well/Moderately differentiated (n=7)	7 (100.0)	0 (0.0)	0.067
Poorly differentiated (n=3)	1 (33.3)	2 (66.7)	
Total (n=10)	8 (80.0)	2 (20.0)	

Table 5: Correlation of Histomorphological Sebaceous Differentiation with Adipophilin Expression

Sebaceous differentiation	Adipophilin positive, n (%)	Adipophilin negative, n (%)	p-value
Present (n=8)	8 (100.0)	0 (0.0)	0.20
Absent (n=2)	1 (50.0)	1 (50.0)	
Total (n=10)	9 (90.0)	1 (10.0)	

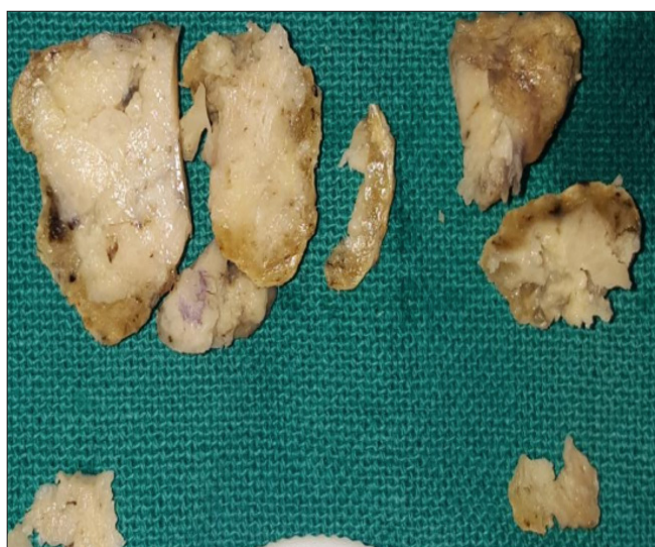


Image 1. Gross specimen showing grey white to brown areas of tumor tissue with areas of necrosis

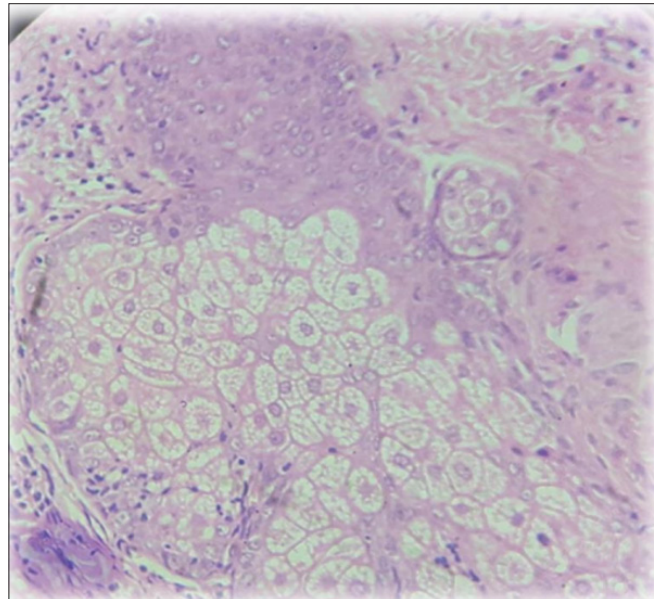


Image 2. Histopathological image of lobules showing sebaceous cells with foamy cytoplasm and surrounding undifferentiated cells

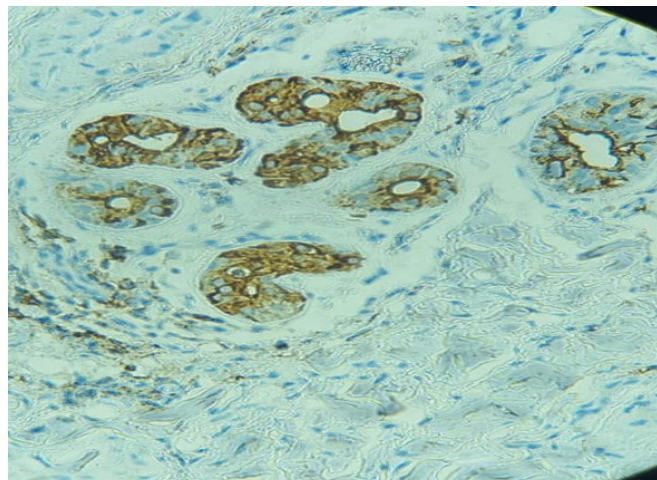


Image 3. IHC (epithelial membrane antigen) showing membranous positivity

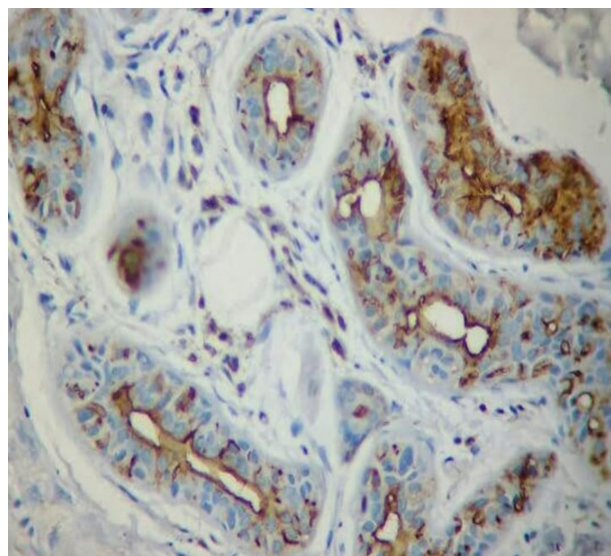


Image 4. Immunohistochemical staining showing prominent brown immunoreactivity within tumour cells surrounding luminal structures in a higher-power view

Discussion

Sebaceous carcinoma is an uncommon but clinically important malignant adnexal neoplasm, with the periocular region being the predominant site of involvement. In the present study of 10 histopathologically confirmed cases, the mean age was 62.4 ± 11.8 years, with a higher proportion of patients aged >60 years (60%). Females constituted 60% of the cases, while males accounted for 40%. The tumour predominantly involved the upper eyelid (40%), followed by the lower eyelid (30%) and other periocular sites (30%), with equal right- and left-sided involvement. Histomorphologically, lobular/irregular tumour architecture was observed in 90% of cases, sebaceous differentiation in 80%, nuclear pleomorphism in all cases, hyperchromasia in 90%, increased mitotic activity in 80%, necrosis in 50%, and infiltrative growth in 70%. Most tumours were moderately differentiated (50%), followed by poorly differentiated (30%) and well-differentiated (20%). These findings emphasize that although recognizable sebaceous differentiation is an important diagnostic feature, significant cytological atypia and infiltrative behaviour may coexist, particularly in less differentiated tumours.

The immunohistochemical findings in the present study demonstrate the usefulness of a panel-based approach for supporting the diagnosis of sebaceous carcinoma. Adipophilin showed the highest positivity, being expressed in 9 of 10 cases (90%), with a mean composite score of 4.9 ± 1.3 . This observation is comparable with the findings of Plaza et al.[9], who reported adipophilin positivity in all 27 sebaceous carcinomas studied and concluded that adipophilin was a sensitive and reliable marker for demonstrating sebaceous differentiation. EMA was also positive in 90% of cases in the present study, with a mean composite score of 4.7 ± 1.4 , which is consistent with the earlier observations of Ansai et al.,[10] who demonstrated EMA positivity in their series of extra-ocular sebaceous carcinomas. Similarly, Sinard [11] reported focal EMA expression in 10 of 11 ocular sebaceous carcinomas. Thus, the high expression of adipophilin and EMA in the present study supports their value as useful ancillary markers in sebaceous carcinoma, particularly when the diagnosis is difficult on morphology alone.

Androgen receptor (AR) was positive in 8 of 10 cases (80%) in the present study, with a mean composite score of 4.2 ± 1.5 . Although AR expression was frequent, its association with tumour differentiation did not reach statistical significance ($p = 0.067$). All seven well- and moderately differentiated tumours showed AR positivity, whereas only one of three poorly differentiated tumours was positive. This pattern suggests that AR expression may be retained more consistently in better differentiated sebaceous carcinomas, with reduced expression in poorly differentiated lesions, although the present sample size was insufficient to establish

a statistically significant association. Plaza et al.[9] reported AR expression in 9 of 27 sebaceous carcinomas, indicating variable sensitivity across studies. The relatively higher AR positivity observed in the present series may therefore reflect differences in tumour composition, sample size, staining methodology, or interpretation criteria. Nevertheless, the findings support the use of AR as a complementary marker rather than as an isolated diagnostic marker.

Ber-EP4 showed comparatively limited expression in the present study, being positive in only 3 of 10 cases (30%), with a mean composite score of 1.8 ± 1.6 . This relatively low expression is in agreement with the study by Plaza et al.[9], in which Ber-EP4 was positive in only 7 of 27 sebaceous carcinomas (25.9%). The limited sensitivity of Ber-EP4 in sebaceous carcinoma is diagnostically relevant because Ber-EP4 is frequently associated with basal cell carcinoma and therefore its interpretation requires appropriate morphological and immunohistochemical correlation. The findings of Sinard[11] also highlight the importance of using a panel rather than a single marker, as ocular sebaceous carcinoma, basal cell carcinoma and squamous cell carcinoma may demonstrate overlapping expression of individual epithelial markers. The present results therefore reinforce that strong or frequent expression of adipophilin and EMA is more supportive of sebaceous differentiation, whereas Ber-EP4 positivity alone should not be considered diagnostic of sebaceous carcinoma.

The correlation between morphology and immunohistochemistry in the present study further supports the complementary role of these approaches. All eight cases showing histological sebaceous differentiation were positive for adipophilin, whereas among the two cases without morphologically evident sebaceous differentiation, one was adipophilin positive and one was negative; although this association did not reach statistical significance ($p = 0.20$), the finding demonstrates that adipophilin expression may identify sebaceous differentiation even when it is not readily appreciable morphologically. This observation is particularly relevant to poorly differentiated tumours, in which conventional microscopic recognition of sebaceous differentiation may be challenging. The recent study by Yu et al.[12], evaluating TRPS1, GATA3 and adipophilin in a large cohort of sebaceous carcinoma and its common mimics, further emphasized the importance of an immunohistochemical panel, particularly in poorly differentiated lesions. Their findings suggested that combining TRPS1, GATA3 and adipophilin improved diagnostic discrimination compared with individual markers. Although supplementary markers such as TRPS1 and GATA3 were not systematically evaluated in the present series, the current findings similarly demonstrate that integration of histomorphology with multiple immunohistochemical markers, particularly adipophilin and EMA, provides a more reliable diagnostic strategy than reliance on a single marker.

Conclusion

Sebaceous carcinoma predominantly affected older individuals and showed a clear predilection for the periocular region, particularly the upper eyelid. Nuclear pleomorphism, sebaceous differentiation, hyperchromasia, increased mitotic activity and infiltrative growth were the major histomorphological findings. Adipophilin and EMA showed the highest immunohistochemical positivity (90% each), supporting their diagnostic utility in sebaceous carcinoma. AR expression was more frequent in well/moderately differentiated tumours, whereas Ber-EP4 showed limited positivity. Correlation of histomorphology with an appropriate immunohistochemical panel improves diagnostic confidence, particularly in cases with limited or poorly differentiated sebaceous differentiation.

Limitations

The study was limited by its small sample size of 10 cases, which may restrict the generalizability of the findings. The retrospective design was dependent on the availability and completeness of existing histopathology and immunohistochemistry records. The absence of a comparative group of other eyelid malignancies limited assessment of the diagnostic specificity of individual immunohistochemical markers. Larger prospective studies with appropriate comparison groups are required to validate these findings.

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None

Conflict of Interest

None

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