

## Primary Sebaceous Carcinoma of Esophagus

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### Abstract

**Background:** Sebaceous Carcinoma (SC) is an uncommon neoplasm that usually occur in the skin of head and neck region with a predilection of periocular sites. This tumor is thought to arise from sebaceous glands in the skin and thus may arise anywhere on the body where these glands exist. However, the non-cutaneous SC in where the sebaceous glands are anatomically absent have also been reported sporadically, and the pre-existing ectopic sebaceous glands are speculated to be the basis of its origination. Though ectopic sebaceous glands are not uncommon in esophagus, primary SC in esophagus has not been reported thus far.

**Methods:** We report one space-occupying lesion of the esophagus in a 66-year-old man. Clinical and radiological data were collected; the tumor morphology and immunohistochemical pattern were analyzed. Related literatures were reviewed.

**Results:** The tumor cells diffusely expressed P40, CK5/6, AR and P53, and EMA staining highlighted the sebocytes with a foam-like pattern in cytoplasm. With the auxiliary immunohistochemical staining, we finally made an unequivocal diagnosis of SC.

**Conclusion:** SC is a rare entity in esophagus which have not been reported before and may bring up diagnostic puzzles to pathologists. The tumor morphology is complex and with a similar immunohistochemical expression profiles just like SC reported in other sites. This unique tumor occur in esophagus extends the spectrum of extraocular, extracutaneous SC from existing case reports.

**Keywords:** Sebaceous carcinoma; Esophagus; Ectopic sebaceous glands; Muir-torre syndrome, Immunohistochemistry

### Introduction

Sebaceous Carcinoma (SC) is a rare malignant tumor derived from the sebaceous glands that arises most commonly in the head and neck region, with a predilection of periocular sites [1]. By historical convention, SC is placed into two anatomic groups, periocular or extraocular, because of an alleged dissimilarity in the behavior of the lesions in those two categories [2]. In addition to the skin of head and neck, extraocular SC can also occur in trunk, genitals, and extremities [3]. Extracutaneous SC in where the sebaceous glands anatomically absent have also been reported, such as the oral cavity, salivary glands, lacrimal gland, pharyngeal, lung, breast, uterine cervix etc [4-11]. Here we report one space-occupying lesion in esophagus in an old man. The combination of morphological and immunohistochemical findings confirmed the diagnosis of SC, just similar to those described in other sites, and the regional lymph node metastasis was found. The patient was evaluated for orbital, cutaneous, head and neck regions, no other primary SC was found, which excluded the possibility of SC metastasized to esophagus. Due to the complexity of its morphology and the rarity of this site that had never been reported before, making an accurate and confident diagnosis may be a great challenge. Herein, we described the morphology and immunohistochemical expression pattern of this tumor, and systematically reviewed the recent progress in the diagnosis and molecular research of SC, with purpose of improving the understanding of this tumour by pathologists.

### Materials and Methods

#### Clinical presentation

A 66-year-old male patient with no tobacco smoking and alcohol abuse history was admitted to our hospital because of dysphagia without obvious causes 20 days ago, especially when eating coarse and

overheated food. Gastroscopy showed a space-occupying lesion in the anterior wall 36 cm-40 cm away from the incisors, accounting for about 60% of the cavity. The tissue was brittle and easy to bleed (Figure 1A). CT scan displayed obvious thickening of the wall of the lower esophagus and local lumen stenosis (Figure 1B). The biopsy showed moderate to severe dysplasia of esophageal squamous epithelium or carcinoma *in situ*. The patient then underwent surgical therapy of radical esophagectomy *via* a left thoracotomy and ligation of thoracic duct.

#### Histochemical staining

The excised specimen was fixed in formalin and embedded in paraffin. Immunohistochemical staining was performed using an Envision system (Dako Envision) and DAB chromogen. The following antibodies against P40, CK5/6, CK7, AR, Epithelial Membrane Antigen (EMA), Ber-EP4, P53, Her-2, Ki-67 and mismatch repair protein (MLH1, MSH2, MSH6 and PMS2) were used at their recommended dilution. Special stainings of Alcian blue and PAS were also performed. The lipid staining was not performed due to the fresh frozen tissues could not be obtained.

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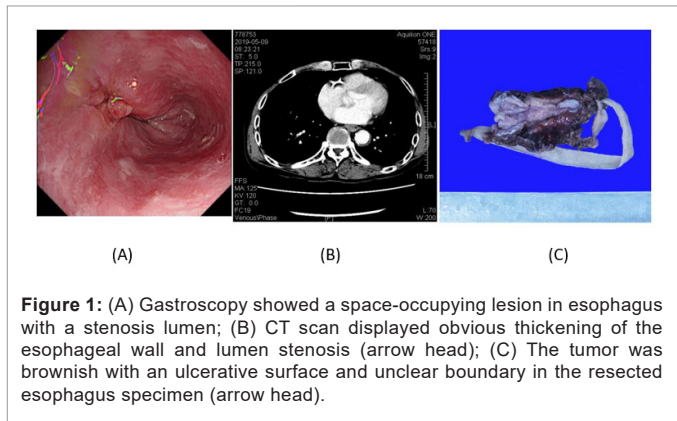
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## Results

### Gross features

The resected esophagus specimen was measured 10 cm long. A brownish tumor with ulcerative surface and unclear boundary measuring 5 cm × 3 cm in diameter was noted in the middle of the section. The tumor had a hard texture and white to tan cut-surface, which infiltrated the whole layer of the esophageal wall (Figure 1C).



**Figure 1:** (A) Gastroscopy showed a space-occupying lesion in esophagus with a stenosis lumen; (B) CT scan displayed obvious thickening of the esophageal wall and lumen stenosis (arrow head); (C) The tumor was brownish with an ulcerative surface and unclear boundary in the resected esophagus specimen (arrow head).

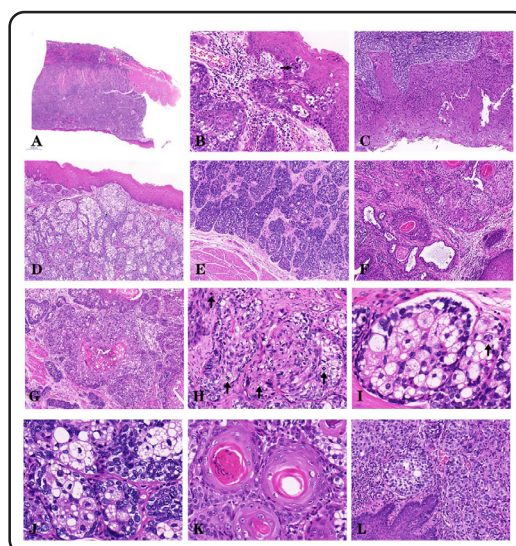
### Pathologic findings

Microscopically, the tumor cells presented a lobulated or nested arrangement, and the sizes were varied, demonstrating an infiltrative growth in the whole layer of the esophageal wall (Figure 2A). Intraepithelial spread with a pagetoid pattern or bowenoid pattern were observed locally. Some of the tumor nests were very similar to sebaceous lobules, the tumor cells with moderate to marked nuclear atypia (Figures 2B-2D). While some of the tumor nests were composed mainly of

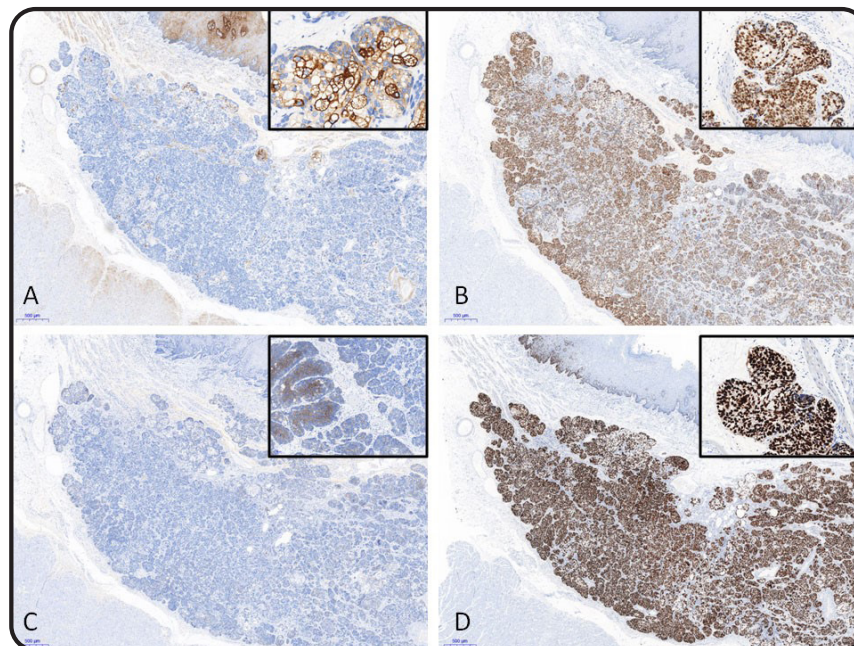
basaloid cells with none or scanty sebaceous differentiated cells (Figure 2E). Glandular differentiation and squamous differentiation were also observed occasionally (Figure 2F), “comedonecrosis” was apparent in the central aspects of some tumor lobules (Figure 2G). Under a high-power microscope, the tumor cells were obviously heteromorphic and mitotic, and pathological mitoses were also observed (Figure 2H). There were four types of cellular morphology: (1) Sebaceous differentiated cells with abundant multivesicular or clear cytoplasm and round, oval or irregular nucleus, which was the hallmark of SC lesions (Figure 2I); (2) basaloid cells that originated from the outer germinal cells of the secretory alveoli, the percentage of which was inversely correlated with the level of differentiation. These cells had a high nuclear-to-cytoplasmic ratio, and mainly distributed in the periphery of tumor nests (Figure 2J); (3) epidermoid cells with formation of keratin pearls or keratohyaline granules in the cytoplasm (Figure 2K); (4) and basosquamous cells, which showed the intermediate cytoplasmic features of the basaloid and epidermoid types, with the cytoplasm of basophilic (Figure 2L).

### Histochemical findings

Immunohistochemistry and special stainings were performed and compared with published descriptions, and the results were similar to prior published reports regarding SC in other sites. The tumor cells diffusely expressed P40, CK5/6, AR (Figure 3A) and P53 the overexpression of p53 indicate a p53 mutant type, the EMA staining highlighted the sebocytes with a foam-like pattern in cytoplasm, which was unique in sebaceous tumors (Figure 3B); The Ber-EP4 was expressed focally and confined to the basaloid cells only (Figure 3C); The CK7 and Her-2 were absolutely negative. The Ki-67 showed a proliferation index of about 50% (Figure 3D); No deletion of mismatch repair proteins of MLH1, MSH2, MSH6 and PMS2 was observed. Special stainings of Alcian blue and PAS were negative in the clear and vacuolated areas, which confirmed the absence of mucus and glycogen in cytoplasm.



**Figure 2:** Histopathologic spectrum of sebaceous carcinoma. (A) The tumor infiltrated in the whole layer of the esophageal wall; (B) Intraepithelial spread with pagetoid pattern and (C) bowenoid pattern; (D) Tumor nests with a morphological similarity to sebaceous lobules; (E) Tumor nests were composed mainly by the basaloid cells with scarce sebaceous differentiation; (F) The squamous differentiation and occasionally appeared glandular structures; (G) “Comedonecrosis” in the center of the lobules; (H) The tumor cells were obviously heteromorphic and mitotic. Four types of cellular morphology; (I) Sebaceous differentiated cells with abundant multivesicular or clear cytoplasm one pathological mitosis was denoted; (J) Basaloid cells showed a high nuclear-to-cytoplasmic ratio, and mainly distributed at the periphery of the tumor lobules; (K) Epidermoid cells with formation of keratin pearls or keratohyaline granules in the cytoplasm; (L) The basosquamous cells with an intermediate cytoplasmic features of the basaloid and epidermoid types.



**Figure 3:** Representative immunohistochemical staining of sebaceous carcinoma. (A) The tumor cells diffusely expressed AR; (B) The EMA stain highlighted the sebocytes with a foam-like pattern in cytoplasm; (C) The Ber-EP4 expressed focally and confined to the basaloid cells only; (D) The Ki-67 showed a proliferation index of about 50%.

## Discussion

SC is a rare and aggressive malignancy, most commonly occur in the 60-79 age group, with a median age of 72 years (SEER database), and no significant gender difference [12]. According to US and Dutch data, about 26%-27% SC are ocular, 55%-69% occur elsewhere on the head and neck, and 5%-18% elsewhere on other sites of the body [13]. The rare sites include throat, lung, uterine cervix, penis, breast, etc. However, no case of SC occur in esophagus had never been reported before, here we present the first case.

The origin of extracutaneous SC in different location is not exactly the same. SC of parotid gland is originate from the pluripotential cells distributed in the blind-ending intercalated and striated ducts, which can differentiate into sebaceous that secondary to obstruction or inflammation, or congenital presence of sebaceous differentiation [14]. SC in oral cavity is thought to arise from salivary gland elements or ectopic sebaceous glands, that is fordyce's spots, which are usually found in buccal mucosa, soft palate, upper lip, or gingiva, etc [15]. SC in uterine cervix may occur on the basis of the pre-existing ectopic sebaceous glands in this site [16]. The ectopic sebaceous glands in esophagus, an organ of endodermal origin, were occasionally reported, and with a prevalence rate of about 0.05% in an asymptomatic population [17-19]. Two hypotheses have been postulated. One suggests that ectopic sebaceous glands arise from metaplasia of esophageal mucous glands (a gland with the phenotype of salivary gland), while the other hypothesis suggests a congenital misplacement of the esophagus when the organ was developing from the endoderm. The increasing evidences suggesting that they originate as a result of an acquired metaplastic process [20-22]. There was one case of ectopic esophagus sebaceous glands in the setting of esophageal cancer [23], however, the ectopic

esophageal sebaceous glands are known to have no malignant potential in previous literature [18]. In our case, the tumor tissue together with the surrounding esophageal specimen were completed sampled. Neither ectopic sebaceous glands nor sebaceous metaplasia of mucous gland was observed. Maybe the ectopic or metaplasia hypothesis could not elaborate the histogenesis of esophageal SC convincingly. Notably, the simultaneous presence of dysplasia or canceration in esophageal epidermis promote us to present a scenario that whether the SC was originated from the malignant transformation of keratinocytes or pluripotent stem cells in the basal layer of epidermis? Whatever, more evidences based on the cases accumulation and molecular genetic analyses are needed to elaborate the neoplastic process in esophageal SC.

Recent genetic studies propose that SC arise from multiple pathway and the distinct tumorigenesis depend upon the anatomic site in where the tumor arises, and the defined molecular-genetic subtypes may potentially paving a way for targeted treatment and personalised medicine in future [24,25]. The four main subtypes identified are summarized as follows: Low mutation burden SC that mainly occur in the head and neck region, especially the periorbital: (1) SC with RB1 and TP53 mutations and (2) SC with transcriptionally active High-Risk Human Papillomavirus (HR-HPV) infection [26]. Extraocular SC with high mutation burden, including (3) mismatch repair-deficient (dMMR) SC and (4) UV-damage SC [27]. The different mutation type may be related to an unique histopathological feature to some extent. For example, UV-damage SC is more invasive in growth pattern with a poorly differentiation. On the other hand, the pathologists can infer the possibility of dMMR-related SC based on the anatomical site (extraocular tumors) and histopathological features (basaloid-like tumors without invasive boundary and with more differentiation) in

some cases [28].

Once the diagnosis of SC is made, the test for Microsatellite Instability (MSI) by immunohistochemistry should be performed as a primary screening for Muir-Torre Syndrome (MTS). Lesions demonstrating a loss of nuclear staining for MMR gene products (MLH1, MSH2, MSH6 and PMS2) should be subject to testing with MSI gene locus assays to confirm the diagnosis of MTS. It is a variant of Hereditary Nonpolyposis Colorectal Cancer (HNPCC) syndrome, characterized by sebaceous neoplasms and visceral malignancies, with the most common of colorectal adenocarcinoma [29]. Correct diagnosis may be lifesaving for patients with MTS and their at-risk relatives who will benefit from early and close tumor surveillance [30]. In our case, there were no deletion of mismatch repair proteins and no history of other visceral tumors, indicating that the tumorigenesis was not related to microsatellite instability. While the over-expression of P53 suggests that the p53 gene mutations may play a critical role during the tumorigenesis.

Morphologically, SC encompasses a broad variety of morphologic features, ranging from well differentiated sebaceous neoplasms to highly undifferentiated tumors. Several growth patterns such as lobular, trabecular, papillary, and BCC-like can be recognized, with the lobular pattern is the most common [31]. The rippled arrangement like carcinoid was occasionally observed [32]. A combination of two or more of the above patterns can be seen in one single lesion. The occasionally presented “comedonecrosis” in the center of the cellular nests may correspond to foci of exaggerated holocrine secretion rather than true necrosis [33]. SC can also form ductal or cystic structures within the central of the lobules which indicate the sebaceous ducts differentiation. The cellular nests are separated by fibrovascular stroma that is usually devoid of desmoplastic changes, and the peripheral palisading arrangement, clefting and mucinous stroma are not evident. Intraepithelial spread, which can be pagetoid or bowenoid in pattern is not uncommon [34].

Cytologically, the sebaceous differentiated tumor cells (sebocytes) are characterized by vacuolated or clear cytoplasm, which is the hallmark for sebaceous tumors including SC. In well-differentiated lesions, they locate mainly in the center of the cellular nests with an outer zone of basaloid cells. However, the sebocytes may be obscure in poorly-differentiated lesions, and the pleomorphic basaloid cells with a high nuclear to cytoplasmic ratio, nuclear pleomorphism, numerous mitoses and basophilic cytoplasm constitute the major component. In addition, two other cell types that is epidermoid and basosquamous cells are also observed in some lesions. Epidermoid cells display scattered dyskeratotic cells, nonkeratinizing cellular whorls or even obvious keratinization, which may lead to foreign body response; while the basosquamous cells demonstrate a intermediate cytoplasmic feature of the basaloid and epidermoid cell types, in which the cytoplasm is basophilic.

Histopathological diagnosis maybe challenging in high grade lesions. In a retrospective study of 40 cases, the first diagnosis of SC was made only in 22.8% of the cases, with the most erroneous diagnoses to be Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC), and the misdiagnosis rates were 27.5% and 25% respectively [35]. Identification of sebocytes is the key morphologic clue to this entity. Special stainings for lipid such as oil red O or Sudan dyes were traditionally used, but their practicability were limited by the use of fresh frozen tissues. Immunostainings on paraffin-embedded sections demonstrate obvious advantage in diagnosis of SC, and a proposed panel including AR, EMA, CK7 and Ber-EP4 was usually used to

differentiate SC from its mimics [13]. The EMA stain demonstrates a distinctive immunoreactivity pattern that it stains around each of the many vesicles comprising the vacuolated cytoplasm. The neoplastic sebocytes are potentially labeled for Androgen Receptor (AR) in about 81.0% of the cases. About 50%-75% of SC are positive for CK7 according to the reported researches, but the CK7 was not expression in our case, which was perhaps related to the specific location that this tumor origin. Ber-EP4 is not expressed in about 74%-94% cases, but if they do, the staining is usually focal. Although these markers are highly sensitive for sebaceous differentiation, the specificity is not enough to distinguish true sebaceous differentiation. The emergence of adipose differentiation related proteins like adipophilin and perilipin as both sensitive and specific marker of sebaceous differentiation have greatly improved diagnostic accuracy in this regard. Another useful marker of nuclear factor XIIIa (AC-1A1) has similar sensitivity and specificity in the diagnosis of SC, but it is worth noting that reactivity with an unknown nuclear antigen only detected by the AC-1A1 clone. The mutation of P53 together with increased Ki-67 proliferation index (estimated 38%-72% for SC) could help differentiate SC from benign sebaceous tumors [36-39].

The differential diagnoses to be considered include BCC, SCC and Mucoepidermoid Carcinoma (MEC). BCC is the most frequent histopathological diagnosis obtained in the first assessment of SC cases. When accompanying with sebaceous differentiation (BCCSD), the situation will be more complex. According to the literature, regardless of sebaceous differentiation, BCC or BCCSD should have typical histopathologic features which is different from SC, namely: (1) Aggregations of basal-like cells with sparse cytoplasm; (2) cells at the periphery of aggregations are columnar and are arranged in a palisade pattern; (3) clefts between aggregations of neoplastic cells and adjacent stroma, and (4) absence of pagetoid spread or Bowen-like disease in the epidermal lesion margin. BCC are positive for Ber-EP4, and negative for EMA, AR and adipophilin, only if there is the foci of sebaceous differentiation. The second differential diagnosis is SCC. Since SCC is the most common malignancy in esophagus and may sometimes present a clear change in cytoplasm (namely Glycogen-Rich Clear Cell SCC), and the SC can also demonstrate squamous differentiation in morphology, the overlap between them increase the difficulty to diagnosis. In SCC, the PAS positive and diastase labile in clear cells conform the presence of glycogen other than lipids. What is more, SCC is negative for AR and adipophilin which can distinguish it from SC. Although not as common in esophagus, MEC should also be considered as an additional differential diagnosis. MEC is characterized by the presence of an intimate mixture of squamous cells, mucus-secreting cells, and “intermediate” cells in varying proportions. In the mucus-secreting cells which may similar to sebocytes, the alcian blue and mucicarmine stains are positive, and immunohistochemistry demonstrate a positive stain for CK7 and negative stain for P63, CK5/6, AR and adipophilin.

## Conclusion

A panel of immunohistochemical stains is recommended because different combinations of immunoprofiles characterize these entities, of which EMA, Ber-Ep4, AR, and adipophilin appear to be the most useful. In this paper, we report for the first time about one case of SC occurring primarily in the esophagus, which expands the existing spectrum of noncutaneous SC according to the documents. It is easy to be misdiagnosed as BCC, SCC or MEC due to their overlap in morphology. A comprehensive analysis of histological features and the combined usage of appropriate immunohistochemical markers

are helpful for the diagnosis. The prognosis of esophageal sebaceous carcinoma remains to be observed, and more cases and further molecular pathological analysis are needed to elaborate its histological origin and pathogenesis.

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### Patient Consent for Publication

Acquired.

### Contributorship Statement

Idea and design: Chang Zhao and Ye Jiang; Acquisition of data: Wenwen Luo, Yiwang Zhang; S search: Jiani Wang and Na Cheng; Writing and polishing: Nana Zhang and Jing Zhou.

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