Review Article

Esophageal carcinoma cuniculatum: a narrative review to understand this rare and commonly misdiagnosed variant of well-differentiated esophageal squamous cell carcinoma

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Background and Objective: Esophageal carcinoma cuniculatum (CC) is a rare variant of a well-differentiated squamous cell carcinoma (SCC). Unlike other forms of esophageal cancers, CC of the esophagus is difficult to diagnose on endoscopic biopsies. This can lead to a delay in the diagnosis and increases morbidity. We reviewed the available literature to shed light on the etiopathogenesis, diagnosis, treatment, and outcomes of this disease. Our aim is to create a better understanding of this rare disease entity and contribute to a timely diagnosis to reduce the associated morbidity and mortality.

Methods: Extensive review of PubMed, Embase, Scopus, Google Scholar was conducted. We identified the published literature on Esophageal CC from inception till date. We report epidemiological trends, clinical presentation, diagnostic and treatment strategies to correctly identify the cases to reduce the likelihood of a missed diagnosis of esophageal CC.

Key Content and Findings: Associated risk factors for esophageal CC are chronic reflux esophagitis, smoking, alcohol consumption, immunosuppression, and achalasia. Dysphagia is the most common presentation. Primary diagnostic modality is an esophagogastroduodenoscopy (EGD), but diagnosis can be easily missed. To favor an early diagnosis, a histological scoring system has been proposed by Chen *et al.* where authors describe specific histological features that appear to be common based on the numerous mucosal biopsies examined from patients with CC.

Conclusions: A high clinical suspicion for the disease along with close endoscopic follow-up with repeat biopsies is needed for an early diagnosis. Surgery remains the gold standard for treatment and is associated with a favorable prognosis when the patients are diagnosed early.

Keywords: Esophageal carcinoma; esophageal carcinoma cuniculatum (esophageal CC); dysphagia

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Introduction

Carcinoma cuniculatum (CC) is a rare variant of a well-differentiated squamous cell carcinoma (SCC). CC was first described in the plantar skin by Aird *et al.* in 1954 as an unusual variant of a SCC of the skin in a 64-year-old man who presented with a forefoot swelling (1,2). This disease was initially considered a variant of a verrucous carcinoma (VC); however, the World Health Organization

Table 1 Summary search strategy

Items	Specification
Date of search	Inception to 1/20/2022; updated search on 12/12/2022
Databases and other sources searched	PubMed, Embase, Scopus, and Google Scholar
Search terms used	Carcinoma AND Cuniculatum AND Esophagus (see *Table S1* for additional search term used for the individual databases)
Timeframe	Inception till 12/12/2022
Inclusion and exclusion criteria	Inclusion criteria: articles published in the English literature and human subjects
	Exclusion criteria: articles published in languages other than English, non-human subjects, and other close variants of SCC not CC
Selection process	Two independent reviewers conducted the initial database search using the defined search terms. Consensus was achieved in cases of disagreement by a third independent reviewer

SCC, squamous cell carcinoma; CC, carcinoma cuniculatum.

(WHO) has come to recognize it as a unique variant of a well-differentiated SCC (3,4). CC has a distinctive histomorphology characterized by burrowing channels lined by well-differentiated squamous epithelium (5,6). This hallmark has been described in cutaneous and non-cutaneous sites, such as the oral mucosa and the pharynx (7). However, only several cases involving the esophagus have been reported in the English literature starting in 2005 (2,3,8-15). Esophageal CC is often diagnosed at a locally advanced stage contributing to the patients' overall morbidity (10). Unfortunately, the rarity of the disease and difficulty in the preoperative diagnosis has led to a delayed or missed diagnosis. Here, we review the available literature on esophageal CC to shed light on the epidemiology, clinicopathological features, diagnostic challenges, treatment, and prognosis. We present this article according to standardized guidelines set forth by the Narrative Review reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-22-37/rc).

Methods

Search strategies were developed for PubMed, Embase, Scopus, and Google Scholar databases from inception till date (*Table 1*). The search was conducted in March 2022 using controlled vocabulary and keywords (Table S1). An updated search was carried out in December 2022. Two independent researchers reviewed each article to ensure they met inclusion criteria and excluded duplicates. Reference of articles included were examined to capture articles missed in previous searches.

Inclusion criteria: articles published in the English literature and containing human subjects were included. Abstracts of interests on esophageal CC were identified and full articles were obtained.

Exclusion criteria: articles published in languages other than English, non-human subjects, and other close variants of SCC and not CC were excluded.

Potential risk factors, clinical presentations, diagnostic evaluations, histopathological findings, treatment, and disease prognosis were evaluated and reported.

Search results

A total of 11 full articles on esophageal CC were identified. These included case reports, case series, and retrospective studies on esophageal CC. A total of 28 patient cases were identified. *Table 2* contains a list of all publication on esophageal CC cases, patient characteristics, symptoms at presentation, endoscopic findings and staging, pathological staging, and mortality. The article by Yin *et al.* [2022] was included because it contained important sociodemographic information and pathological staging of disease (16) despite missing information on clinical presentation, potential risk factors, endoscopic and biopsy findings, diagnostic modalities, and patient outcomes. A decision was made to exclude the article by Landau *et al.* [2012] because it contained duplicate cases reported by Chen *et al.* in 2013 (*Table 2*) (7,8).

Epidemiology of esophageal CC

The most frequent CC site is the skin, particularly the soles

Table 2 Cases of esophageal carcinoma caniculatum published in the English literature until 2022

Author	Number of cases	Cases	Age/sex	Clinical presentation	Associated factors	CT/PET scan	EGD findings	Location	Biopsies	Endoscopic stage	Pre-surgical diagnosis/ diagnosis	Surgery	Chemo/ radiation	Final stage	Follow-up	Mortality	Recurrence/ progression
Yin *et al.*, 2022 (16)	5	1	58/F	–	–	–	–	–	–	–	–	Yes	–	ypT3N0	–	–	–
		2	37/F	–	–	–	–	–	–	–	–	Yes	–	pT3N0	–	–	–
		3	67/F	–	–	–	–	–	N/A (EMR)	–	–	–	–	N/A	–	–	–
		4	73/F	–	–	–	–	–	Yes	–	–	–	–	N/A	–	–	–
		5	67/M	–	–	–	–	–	Yes	–	–	–	–	N/A	–	–	–
Liu *et al.*, 2020 (2)	2	1	67/M	Dysphagia (solids and liquids) + weight loss	–	Esophageal thickening/avid mass	Villous, nodular partially obstructive mass	GEJ	Yes	T3N2Mx	Yes (endoscopic biopsies)/ esophageal CC	Yes	Neoadjuvant chemotherapy + radiation	Surgery/ypT3N0Mx	1 month	No	No
		2	62/M	Chest pan + dysphagia + weight loss	–	Esophageal thickening/avid mass	5 cm partially obstructing + friable mass lesion	Distal esophagus	Yes	T3N1Mx	Yes (endoscopic biopsies)/ esophageal CC	Yes	Neoadjuvant chemotherapy + radiation	Surgery/ypT3N0Mx	36 months	No	No
Fatima *et al.*, 2020 (14)	1	1	86/M	Dysphagia to solids+ weight loss	Smoking (previous history)	–	Keratinized esophageal mucosa + papillary + filiform protrusion	Distal esophagus	–	–	Yes (EMR)/well differentiated SCC/CC	No	Treated with cryotherapy	–	–	–	–
Lai *et al.*, 2019 (3)	2	1	74/F	Dysphagia + weight loss	Smoking	Esophageal thickening+ stenosis/ no lymphadenopathy	Pseudomembranous lesions + lumen stenosis	Distal esophagus	No	–	No/esophagitis dissecans superficialis	Yes	–	Surgery/T3N0	6 months	No	No
		2	46/M	Dysphagia + melena + severe anemia	Smoking	–	Stenotic lesion	Distal esophagus	Yes	–	Yes (endoscopic biopsies)/well differentiated SCC	Yes	No	Surgery/T4N0	9 months	No	No
Dick *et al.*, 2018 (9)	1	1	52/M	Dysphagia + chest discomfort	Reflux esophagitis + smoking	Esophageal wall thickening at GEJ + lymphadenopathy/ partially obstructing esophageal cancer + lymphadenopathy	Papillary and nodular esophageal mass	GEJ	Yes	T4N3M0	No/nonspecific (bland squamous epithelium + mild cytoplasmic atypia + granulomatous changes+ lymphocytosis)	Yes	No	Surgery/pT2N0	15 months	No	No
Koch *et al.*, 2018 (12)	1	1	68/M	Dysphagia + weight loss	–	Avid mass with no evidence of spread	Firm mass	GEJ	Yes	T3N0M0	No/reactive changes (atypical squamous proliferation)	Yes	No	Surgery/No wall invasion/N0	–	No	–
Goh *et al.*, 2014 (13)	1	1	72/M	Dysphagia + weight loss	Smoking	Tumor in esophagus	Irregular tumorous lesion	Distal esophagus	No	–	No/hyperplastic changes	No	–	–	14 months	No	No
Coman *et al.*, 2014 (15)	1	1	65/F	–	–	Esophageal mass, no lymphadenopathy	Large circumferential partially obstructing mass	22–30 cm	Yes	–	Yes (subsequent ESD)/ esophageal CC	Yes	No	Surgery/T1bN0	–	–	–

Table 2 (*continued*)

Table 2 (*continued*)

Author	Number of cases	Cases	Age/sex	Clinical presentation	Associated factors	CT/PET scan	EGD findings	Location	Biopsies	Endoscopic stage	Pre-surgical diagnosis/ diagnosis	Surgery	Chemo/ radiation	Final stage	Follow-up	Mortality	Recurrence/ progression
Chen *et al.*, 2013** (7)	11	1	48/F	Dysphagia + weight loss	–	–	Nodular mass	16–28 cm	–	Wall invasion. Thickening of all layers	Yes (EMR)/ esophageal CC	–	–	–	19 months	No	–
		2	67/F	Dysphagia	–	–	Obstructing mass	12–30 cm	–	N/A	Yes (EMR)/ esophageal CC	–	–	–	8 months	Yes (tracheal recurrence)	–
		3	63/M	Dysphagia + weight loss	Smoking (72 pack years)	–	Warty stenosis	Distal	Yes	N/A	Yes (endoscopic biopsies)/invasive SCC	Yes	–	–/Adventitia and lungs invasion/N0	0	Yes (V fib)	–
		4	73/M	Change in bowel habits	–	–	Mass	Distal/GEJ	Yes	N/A	No/esophagitis with candida	Yes	–	–/adventitia/N0	214 months	Yes (–)	–
		5	40/M	Dysphagia + weight loss	Smoking (8.5 pack years)	–	Fond like mass	Distal	Yes	T1N0M0	Yes (endoscopic biopsies)/invasive well differentiated carcinoma	Yes	–	Surgery/ adventitia/N0	12 days	Yes (ARDS)	–
		6	46/M	Dysphagia + weight loss + chest pain	Smoking (50 pack years)	–	Fungating + ulcerating mass	Distal	Yes	T2N0M0	No/ulcer with acute inflammatory changes and atypical squamous epithelium	Yes	–	Surgery/muscularis propria/N0	157 months	No	–
		7	62/M	Epigastric pain + regurgitation	Smoking (45 pack years)	–	Ulcerated mass	Distal EGJ	Yes	T3N1M0	No/active esophagitis	Yes	–	Surgery/muscularis propria/N0	49 months	Yes (empyema + respiratory failure)	–
		8	44/M	Dysphagia + weight loss + GERD	Smoking (30 years)	–	Fungating and friable mass	Distal	Yes	T3N1	No/fungal esophagitis/ parakeratosis and atypical maturation changes	Yes	–	Surgery/ adventitia/N0	87 months	No	–
		9	63/M	Dysphagia	Smoking (40 pack years)	–	Polypoid obstructing	Distal	Yes	T3N1M0	No/fungal esophagitis	Yes	–	Surgery/muscularis propria/N0	68 months	Yes (metastatic lung cancer)	–
		10	48/F	Dysphagia + weight loss	Smoking (3 pack years)	–	Polypoid, ulcerating	25 cm	Yes	N/A	Yes (endoscopic biopsies)/SCC	Yes	–	Surgery/muscularis propria/N0	84 months	No	–
		11	72/F	Dysphagia + odynophagia	–	–	Wary lesion	25–27 cm	Yes	T1N0M0	No/esophagitis + fungal organism present	Yes	–	Surgery/3 tumors mucosal ×2 and submucosal ×1/N0	48 months	No	–
De Petris *et al.*, 2005 (11)	2	1	73/M	Dysphagia + weight loss	Smoking (60 packs) + alcohol	Stricture, no adenopathy	Verrucous lesion + stricture + ulceration	Distal	Yes	Distorted architecture + diffuse hypoechoic thickening	No/–	Yes	–	Surgery/muscularis propria/N0	12 months	No	–
		2	58/M	Dysphagia + weight loss	Smoking	Mass at GEJ no adenopathy	Mass	GEJ	Yes	–	No/–	Yes	–	–	7 months	No	–
Long *et al.*, 2020 (10)	1	1	63/F	Dysphagia + weight loss	GERD + smoking	Mass in distal esophagus and proximal stomach/no lymph node	Inflammatory and, fungating lesion	Lower third of esophagus + extending into cardia	Yes	T3N1M0	Yes (EMR)/esophageal CC on multiple biopsies	No (declined/ poor surgical candidate)	Chemotherapy + radiation	–	17 months	Yes (progressive disease)	Yes

**, article from Chen *et al.* [2013] contained 11 cases which included 9 cases from previously reported case-series by Landau *et al.* [2012] (7,8). CT, computed tomography; PET, positron emission tomography; EGD, esophagogastroduodenoscopy; F, female; M, male; N/A, not available; EMR, endoscopic mucosa resection; GEJ, gastroesophageal junction; CC, carcinoma cuniculatum; ESD, endoscopic submucosal dissection; SCC, squamous cell cancer; ARDS, acute respiratory distress syndrome; GERD, gastroesophageal reflux disease; N0, no lymph node involvement.

of the feet. Occurrence of CC has also been reported in non-cutaneous sites such as the oral cavity (gingiva, tongue, buccal mucosa) (6,13,17-23), esophagus (8,11), larynx (24), and nails (25). CC involving the oral cavity has been reported in a broad age range (9–87 years). Esophageal involvement was uncommon: fewer than 30 cases have been reported in the English literature. Because of this disease's rarity and the difficulty in the preoperative diagnosis, its exact incidence and risk factors remain relatively unknown.

Esophageal CC tends to be found predominantly in males with a male to female ratio of 3:1 (22). Chen *et al.* have reported that 63% (7 of 11) of the cases were in males (7). Similarly, a 2019 review by Lai *et al.* has indicated that 64% (11 of 17) of the cases were in males (3).

Esophageal CC has been reported over a wide age range. In an extensive review study, Lai *et al.* reported an age range of 40–77 years with a median age of 63 years at diagnosis (3). The oldest patient with esophageal CC reported in the English-language literature was in an 82-year-old man who presented with a 6-year history of dysphagia (14).

Pathogenesis of esophageal CC

Rare examples of cutaneous CC have been described earlier in longstanding neuropathic ulcers secondary to leprosy (26), plantar keratoderma (27) and necrobiosis lipoidica (28). However, the exact etiopathogenesis of esophageal CC remains unclear. Potential risk factors of esophageal CC are chronic reflux esophagitis, smoking, alcohol consumption, immunosuppression, and achalasia (8).

A history of reflux or previous use of reflux medications has been reported in approximately 53–73% of diagnosed cases (3,7). Chen *et al.* reported active esophagitis on endoscopic biopsies in 72.7% (8 of 11) of the examined cases. However, most of these cases were diagnosed as fungal esophagitis or associated changes. Despite a high prevalence of gastroesophageal reflux symptoms in patients with esophageal CC, the exact role of gastroesophageal reflux disease (GERD) in the etiopathogenesis of CC is unclear, as biopsies do not consistently show evidence of chronic esophageal injury (11).

Smoking appears to be a consistent risk factor in most cases (2,3); studies have reported the prevalence of smoking to be 64–67% among patients with esophageal CC (3,7). This may indicate that patients with esophageal CC with a substantial smoking history warrants a high vigilance regarding synchronous or metachronous SCC in the aerodigestive and respiratory tracts. Alcohol consumption has a relatively weaker association and has been reported at much lower rates in patients with esophageal CC (3,7).

A linkage between CC and human papillomavirus (HPV) type-11 has been suggested previously; this is believed to be site specific and has been reported only in cutaneous sites (29). Goh *et al.* have reported of no significant expression of p16 according to immunohistochemistry, thus arguing against high-risk HPV as an etiological factor (13). This finding is consistent with other reports of CC in extracutaneous sites that have not demonstrated any association with HPV (8,11). Landau *et al.* and De Petris *et al.* have analyzed numerous diagnosed cases through chromogenic *in situ* hybridization for HPV and immunostaining. These cases were negative for both low- and high-risk HPV (8,11), thus further refuting the involvement of HPV in the pathogenesis of esophageal CC.

Clinical and endoscopic findings in patients with esophageal CC

Dysphagia (either long-standing or progressive) appears to be the most common presentation of patients with esophageal CC (3,7,8). In a 2019 review of 15 cases by Lai *et al.*, dysphagia was found in approximately 80% (12 of 15) of cases (3), similarly to previously reported rates (8).

GERD, particularly at the time of diagnosis, has been reported in 53–73% of cases (3,7,8). Weight loss has been reported in 66% (10 of 15) of diagnosed cases (3).

The preliminary modality for evaluating patients with an esophageal pathology is an esophagogastroduodenoscopy (EGD). Most cases of esophageal CC presented with a mass on EGD (7,12). In a review of 15 patients, Lai *et al.* have reported endoscopic growth patterns: stenosis or obstruction in approximately 40%, ulcerative patterns in approximately 33%, and warty patterns in 20% of diagnosed cases (3). The tumor appears to primarily affect the distal part of the esophagus (3,7). Lai *et al.* have reported that the distal esophagus was affected in 75% (10 of 15) of cases (3), and the gastroesophageal junction (GEJ) was affected in the remaining one-third (5 of 15). Chen *et al.* have reported similar frequencies in the distal esophagus and GEJ. However, they have also reported involvement of the cervical and/or mid-esophagus in approximately one-third (36%, 4 of 11) of examined cases (7).

Histological findings in esophageal CC

Histologically, CC is characterized by a diverse pattern of

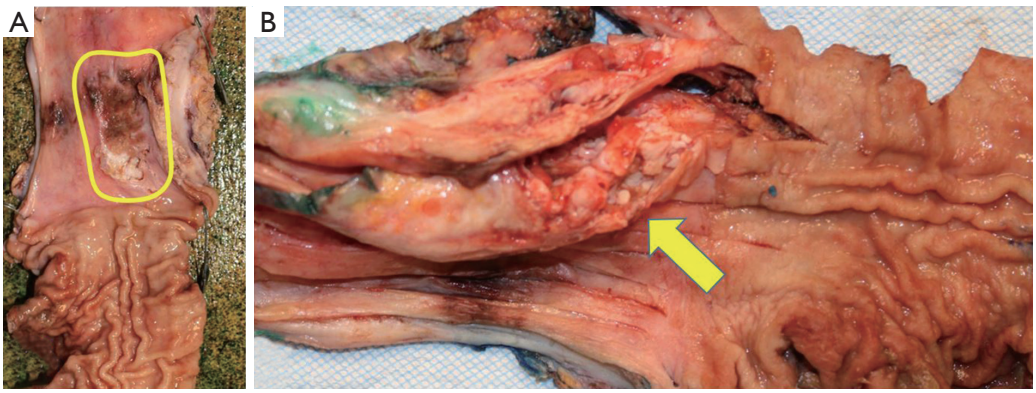

Figure 1 Macroscopic specimen. (A) A large partially ulcerated reddish white esophageal lesion is identified with focal verruciform exophytic growth pattern (yellow circle). (B) Serial sectioning revealed that the lesion deeply invades the esophageal wall with a burrowing penetrating growth pattern (yellow arrow). Image courtesy: Xianzhong Ding, MD, PhD (Chief of Gastrointestinal and Liver Pathology, Loyola University Medical Center, Maywood, IL, USA).

hyperkeratosis, acanthosis, dyskeratosis, deep keratinization, intraepithelial neutrophils, neutrophilic micro-abscesses, focal cytologic atypia, koilocyte-like cells, and keratin-filled cysts/burrows (*Figures 1,2*) (3,7,8,11,13,15). Lai *et al.* have observed the presence of hyperkeratosis, dyskeratosis, acanthosis, cysts or burrows, and deep keratinization in 100% of the reviewed cases; furthermore, authors observed intraepithelial neutrophilic micro-abscesses in 93.3% of cases (3). In a similar review conducted by Landau *et al.*, the presence of hyperkeratosis, acanthosis, dyskeratosis, abnormal keratinization, and intraepithelial neutrophils was noted in 100% of examined cases, while intraepithelial neutrophilic micro-abscesses occurred in 91% (10 of 11) of cases (8).

Preoperative diagnosis on the basis of mucosal biopsies obtained through EGD is highly challenging because of the bland cytology and the presence of inflammation (2,7-9). Presurgical diagnosis is difficult but can be suspected in endoscopic specimens if the biopsy obtained is sufficiently deep and adequately oriented (3), with a squamous proliferation devoid of cytological atypia and a non-aggressive pattern of invasion (3). Difficulties in presurgical diagnosis have often led to a misdiagnosis of esophageal CC as an active esophagitis, candida esophagitis, papilloma, esophageal Crohn's disease, or an inconclusive diagnosis (7,8,13,15).

Prior studies have proposed a histologic scoring system to aid in the diagnosis with mucosal biopsies (2,7,8). Thirty-five esophageal mucosal biopsies from 25 upper endoscopies in 11 patients with a resection-validated diagnosis of esophageal CC have been evaluated and compared with 92 esophageal biopsies from 69 patients with a benign diagnosis (7). All biopsies were assessed for the presence of hyperkeratosis, acanthosis, dyskeratosis, deep keratinization, intraepithelial neutrophils, neutrophilic micro-abscess, focal cytologic atypia, koilocyte-like cells, and keratin-filled cysts/burrows, which are the typical findings in patients with esophageal CC. Each feature, if present, was assigned 1 point, and final histologic score was calculated for each biopsy by adding the points. A cut off score of 7 for endoscopic mucosal biopsies from an esophageal mass greatly improved the diagnostic sensitivity to 57% and specificity to 100%. Early recognition of the histopathologic features can improve the pre-surgical diagnosis of esophageal CC (10). The use of this scoring system needs to be validated in other prospective studies.

Diagnosis of esophageal CC from endoscopic biopsies is difficult but possible (14). Several cases have been reported to be diagnosed in specimens through an endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), the latter of which has enabled successful tumor staging (2,7,10,15). However, the use of these techniques to either diagnose or stage disease has not been validated, and specimens obtained from EMR can be inconclusive and non-diagnostic (10). Long *et al.* have reported a case in which EMR was performed on an area of congested and inflamed mucosa with a fungating mass in the distal esophagus: initial histologic evaluation of a simple biopsy specimen revealed six of the characteristic features of esophageal CC, but findings were not sufficient for the diagnosis. A subsequent EMR, on the other hand, met the cutoff of 7, and the most distinguished characteristic feature was burrowing channels

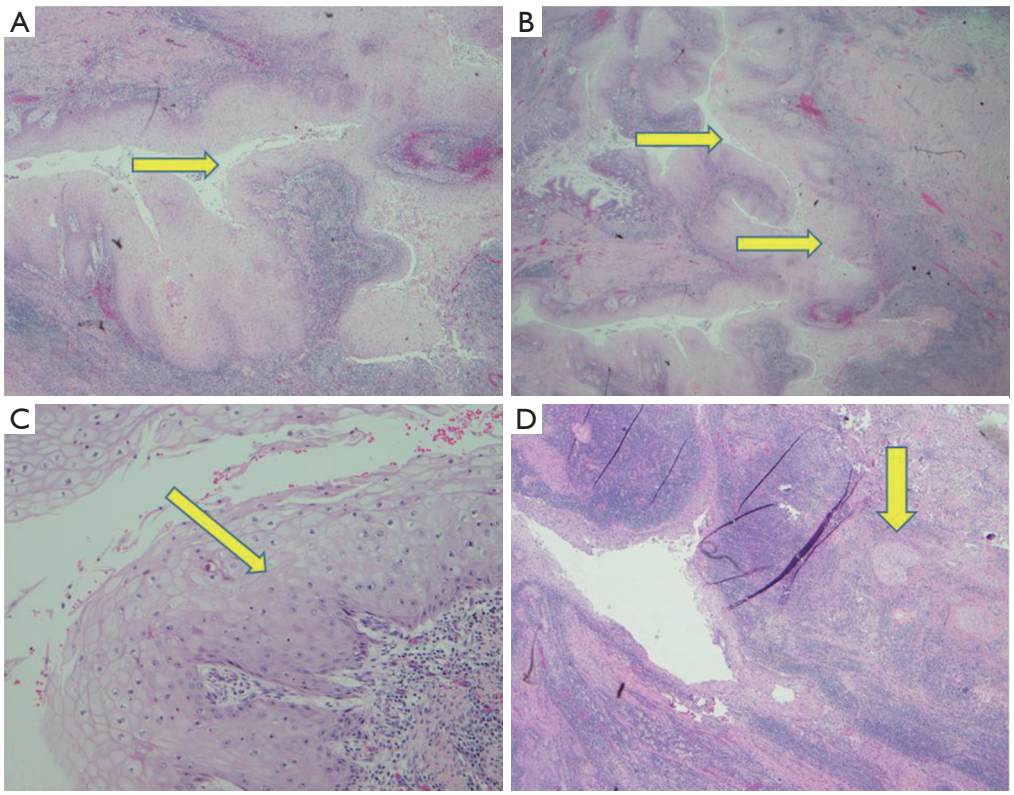

Figure 2 Microscopic section (hematoxylin and eosin stains). (A) The lesion is composed of a well-differentiated stratified squamous epithelium forming multiple, complex, branching keratin filled crypts (yellow arrow). (B) Crypts exhibit the characteristic burrowing pattern (yellow arrows). (C)Tumor cells in the crypts have mild cytological atypia and rare mitotic figures limited to basal and parabasal layers (yellow arrow). (D) The tumor islands invade esophageal adventitia adjacent to large nerve bundles (yellow arrow). Magnification: (A,B,D) ×40, (C) ×200. Image courtesy: Xianzhong Ding, MD, PhD (Chief of Gastrointestinal and Liver Pathology, Loyola University Medical Center, Maywood, IL, USA).

lined by well-differentiated squamous epithelium (10).

The common differential diagnoses for esophageal CC are VC and benign papilloma (11). Differentiating VC from CC has been suggested to be essential because of the local invasion and potentially faster growth of VC (11). VC usually presents as a T4 disease (7,8,30) in comparison to CC and is associated with a poor prognosis and a higher mortality (31,32). Squamous papilloma are rare benign lesions with endophytic patterns that are difficult to distinguish from the extremely well-differentiated squamous carcinomas (11). Another uncommon differential diagnosis suggested for esophageal CC with an endophytic growth pattern is esophageal intramural pseudo diverticulosis (8).

Treatments of esophageal CC

The preferred treatment for esophageal CC is surgical excision. Radical surgery is typically curative because of the aggressive nature of the tumor. Advanced local aggressiveness does not correspond to contextual systemic involvement (3). The role of perioperative endoscopic ultrasound (EUS) in staging remains unclear and may be limited. Landau *et al.* have reported inaccurate assessment of lymph node involvement and tumor depth in 50% (3 of 6) of cases. They suggested that stromal inflammation and mural fibrosis are likely to be responsible for over-staging of the disease (8). Endoscopic submucosal dissection has been examined as a therapeutic alternative to surgery but has shown limited success, owing to the severe submucosal fibrosis from tumor invasion encountered during the procedure (15). The roles of other ancillary treatment modalities such as radiotherapy and chemotherapy are not well defined, but these modalities have been used as primary treatments. Long *et al.* have reported an initial

response to chemoradiation treatment in a poor surgical candidate with uT3N1M0 disease (10). However, disease progression occurred within 3 months, and death occurred at 15 months (10). Surgical excision of the tumor by esophagectomy provides long-term survival even in T3 tumors and continues to be the best therapeutic modality available for the treatment of esophageal CC.

Evolution and prognosis of esophageal CC

Patients with isolated CC usually have a favorable prognosis. Post-surgical resection outcomes in patients with esophageal CC appear to be generally better than those in patients with other types of esophageal cancer (3). Although the diagnostic route of CC can be arduous and exacerbated by surgical complications from deeply invasive tumors, the tentative prognosis appears to be quite favorable, on the basis of the 9 patient cases published by Landau *et al.* (8). Seven patients who received esophagectomy were followed for a median duration of 84 months and showed no disease recurrence, despite evidence of invasion of the muscularis propria. However, in all these cases, there were no lymph node involvement, suggesting that these tumors are indolent and do not metastasize, although can be locally aggressive (10). Two other case reports of patients with esophageal CC have shown no recurrence or metastasis after a 14 months follow-up (11,13). The role of neoadjuvant chemoradiation therapy prior to surgery remains unclear (2,10). Prognosis with treatment primarily involving chemoradiation, rather than surgical resection, is less certain (10).

Conclusions

Esophageal CC is a rare variant of a well-differentiated SCC associated with dysphagia and weight loss. It is more common in men than women and is associated with smoking. This condition is difficult to diagnose from endoscopic biopsies due to the nonspecific inflammatory and hyperkeratotic changes, which unfortunately leads to a delay or missed diagnosis. However, a semiquantitative method has been proposed based on specific histopathologic findings to enable a presurgical diagnosis from endoscopic biopsies. A high index of clinical suspicion for the disease is necessary along with close endoscopic follow-up with repeated biopsies for an early diagnosis and treatment. Histologic findings seen in esophageal CC include hyperkeratosis, acanthosis, dyskeratosis, deep keratinization, intraepithelial neutrophils, neutrophilic micro-abscess, focal cytologic atypia, koilocyte-like cells, and keratin-filled cyst/burrows. Surgery remains the gold standard for treatment and is associated with a favorable prognosis. The need for neoadjuvant chemoradiation is unclear and needs to be further studied.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tgh.amegroups.com/article/view/10.21037/tgh-22-37/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Search terms

Database	Search terms
PubMed	"(Esophageal) AND (Carcinoma cuniculatum)", "(Carcinoma cuniculatum) AND (Esophageal)", "(Esophageal) AND (Cuniculatum)"
Embase	"Esophageal carcinoma cuniculatum OR (esophageal AND ('carcinoma'/exp OR carcinoma) AND cuniculatum)"
Scopus	Carcinoma AND cuniculatum AND esophagus
Google Scholar	Allintitle: Esophagus "carcinoma cuniculatum"
	Allintitle: "Esophageal carcinoma cuniculatum"
	Exact phrase: "Esophageal carcinoma cuniculatum"

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