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Review Article

Histomorphology and Molecular Profiling of Well-Differentiated Squamous Cell Carcinoma of the Esophagus Including its Unusual Variants

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Abstract

Esophageal verrucous squamous cell carcinoma and esophageal carcinoma cuniculatum are rare variants of extremely well-differentiated squamous cell carcinoma. These rare tumors share similar risk factors and clinical presentations with conventional esophageal squamous cell carcinoma. However, these tumors have distinct morphological features, molecular mutation profiles, and clinical outcomes. Diagnosis of esophageal verrucous squamous cell carcinoma and esophageal carcinoma cuniculatum can be challenging, requires high clinical suspicion, and often can only be diagnosed on a deep mucosal biopsy or resection specimen. Surgical treatment or endoscopic resection can be curative in early disease. This review presents the histomorphology and molecular profiling of the conventional type and the rare variants of the esophageal well-differentiated squamous cell carcinoma.

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Introduction

Esophageal cancer is the seventh most common cancer and the sixth most common cause of cancer-associated death worldwide, with an overall 5-year survival rate ranging from 15% to 25%.[1,2] There are two major types of esophageal epithelial cancer: esophageal squamous cell carcinoma (ESC) and esophageal adenocarcinoma. Compared to esophageal adenocarcinoma, ESC has a much higher incidence rate (5.2 vs. 0.7 cases per 100,000 persons per year),[3] accounting for approximately 80–90% of the total esophageal cancer cases worldwide each year.[4,5] Notably, the incidence rate of ESC varies greatly among continents and countries, with the highest incidence rates observed in eastern to central Asia, along the Indian Ocean, along the coast of Africa, and in Uruguay in South America.[4–6]

Similar to squamous cell carcinoma in other parts of the body, ESC can be classified into three major categories: well-differentiated (Grade 1), moderately differentiated (Grade 2), and poorly differentiated (Grade 3). Among these, well-differentiated ESC frequently presents a diagnostic challenge, especially if only a small biopsy sample is available. This is even more true for some rare variants of well-differentiated ESC. This review will present histomorphological features and updates on the molecular abnormalities in conventional well-differentiated ESC and two emerging variants of well-differentiated ESC: verrucous squamous cell carcinoma (VC) and esophageal carcinoma cuniculatum (CC).

Conventional well-differentiated squamous cell carcinoma

Conventional well-differentiated ESC most commonly occurs in the middle third of the esophagus, followed by the lower third, and rarely the upper third.[7] Dysphagia, chest pain, and weight loss are the most common clinical symptoms and signs. Notably, the presence of symptoms frequently indicates an advanced tumor stage. The most important risk factors are smoking and alcohol consumption. Other risk factors include achalasia, caustic injury, poor oral hygiene, low socioeconomic status, and nutritional deficiency.[2,8,9] Genetics also plays a role in the carcinogenesis of ESC. For example, an autosomal dominantly-inherited form of hyperkeratosis *palmaris et plantaris*, known as "tylosis with esophageal cancer," is associated with focal thickening of the palmoplantar skin and an increased lifetime risk of ESC. Tylosis with esophageal cancer is caused by mutations in the *RHBDF2* gene located at 17q25.1.[10]

The correlation between human papillomavirus (HPV) and

Keywords: Esophageal squamous cell carcinoma; Verrucous carcinoma; Esophageal carcinoma cuniculatum; Histology; Molecular profiling.

Abbreviations: CC, esophageal carcinoma cuniculatum; EEM, esophageal epidermoid metaplasia; ESC, esophageal squamous cell carcinoma; HPV, human papillomavirus; NGS, next-generation sequencing; PH, pseudoepitheliomatous hyperplasia; SCCIS, squamous cell carcinoma *in situ*; TCGA, The Cancer Genome Atlas; VC, verrucous squamous cell carcinoma.

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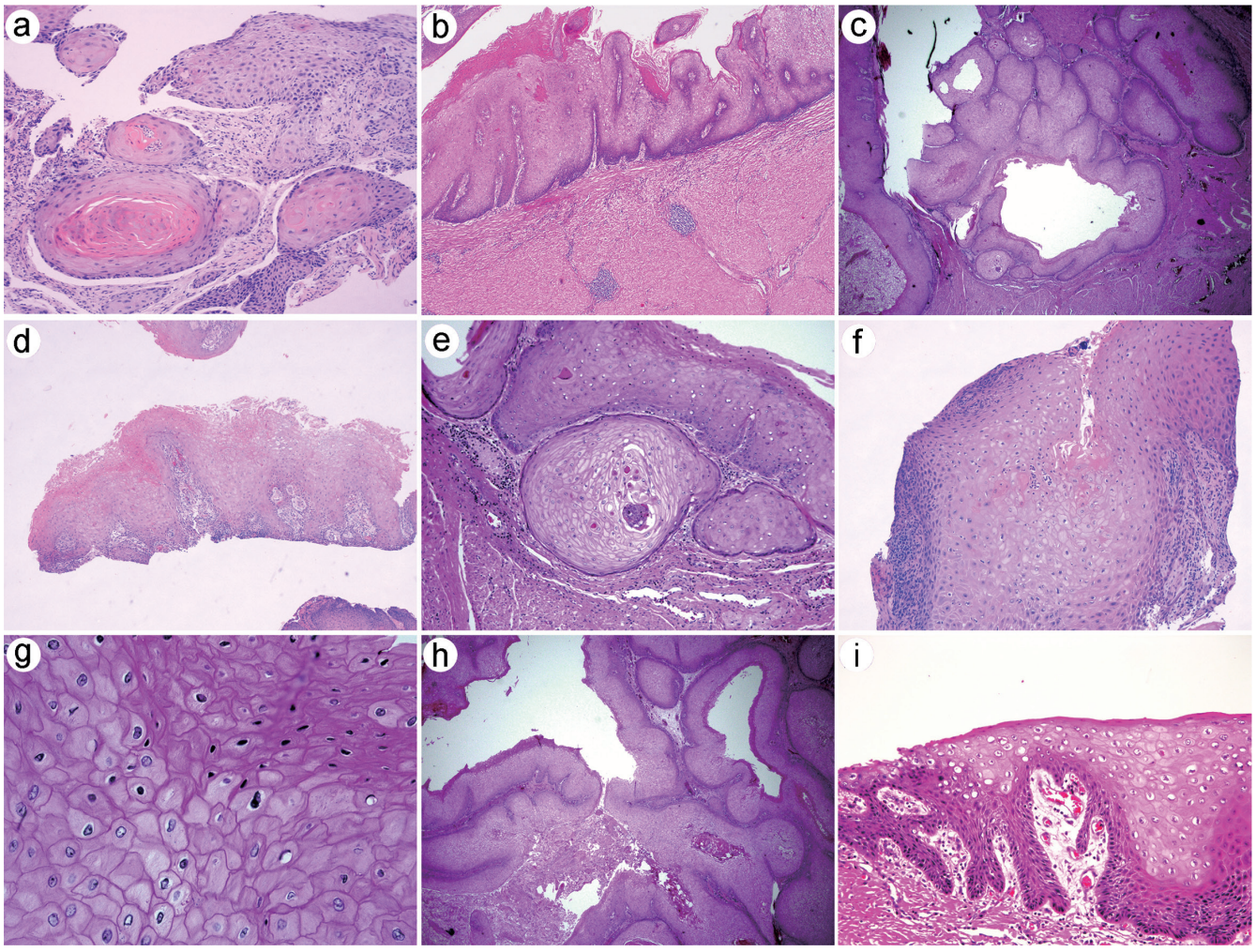

Fig. 1. Well-differentiated squamous cell carcinoma of the esophagus. (a–c) Representative H&E staining images showing conventional esophageal squamous cell carcinoma (a) (200×), verrucous squamous cell carcinoma (b) (200×), and esophageal carcinoma cuniculatum (c) (200×); (d–h) Common morphological features of esophageal carcinoma cuniculatum, including hyperkeratosis (d) (100×), deep keratinization (e) (200×), acanthosis and intraepithelial neutrophils (f) (200×), koilocyte-like cells (g) (400×), and keratin cyst/burrow (h) (200×); (i) "Normal" squamous mucosa adjacent to the invasive esophageal carcinoma cuniculatum (200×).

ESC carcinogenesis is still controversial. There is evidence showing the presence of HPV-16 (11.67%) and HPV-18 (1.82%) in ESC tumor samples, and HPV-16 is likely associated with the risk of ESC.[11] A serological study also supports the role of HPV-16 infection in the occurrence of ESC in a high-incidence area of China.[12] Interestingly, unlike oropharyngeal or cervical squamous cell carcinoma, p16 expression is not a reliable marker for the HPV infection status in ESC.[13] Shuyama *et al.* reported a large proportion of ESC samples carrying an integrated HPV-16 genome in a specific Chinese region with a very high ESC incidence rate. However, only a small number of HPV-16 copies were present in tumor cells, and there was no evidence of HPV-16 E6 and/or p16 protein expression.[14] These findings potentially argue against the oncogenic role of HPV infection in ESC.

Unlike poorly-differentiated ESC, which commonly presents as nested basaloid tumor cells with or without central necrosis, well-differentiated ESC resembles normal squamous epithelium and typically contains enlarged tumor cells with abundant eosinophilic cytoplasm, minimal cytological atypia, and infrequent mitotic figures (Fig. 1a). Intercellular bridges and keratinization are also common findings. It is crucial to identify evidence of invasion to establish a diagnosis of well-differentiated ESC, especially the presence of abnormal keratinization or "keratin pearl" formation in infiltrative atypical squamous cells. Desmoplasia, the stromal reaction with the growth of edematous fibrous connective tissue around the tumor, is a common feature of invasive squamous cell carcinoma. Notably, desmoplasia may not be seen in early invasive tumors. Some additional essential clues of invasive squamous cell carcinoma include downward tumor growth (pushing border of the atypical squamous epithelium excessively extending into the stroma), irregular and complex epithelial branching, abnormal squamous maturation, and paradoxical keratinization. Attention should be drawn to areas showing irregular epithelial/stromal interfaces in the otherwise rounded pushing border since these areas likely represent early stromal invasion with tiny tongues of neoplastic cells breaking through the basement membrane.

Pseudoepitheliomatous hyperplasia (PH) is a major mimicker of well-differentiated ESC. PH can present as an intraluminal protruding mass lesion with histological findings resembling ESC, namely a prominent squamous epithelial proliferation with an infiltrative growth pattern (Fig. 2f). PH

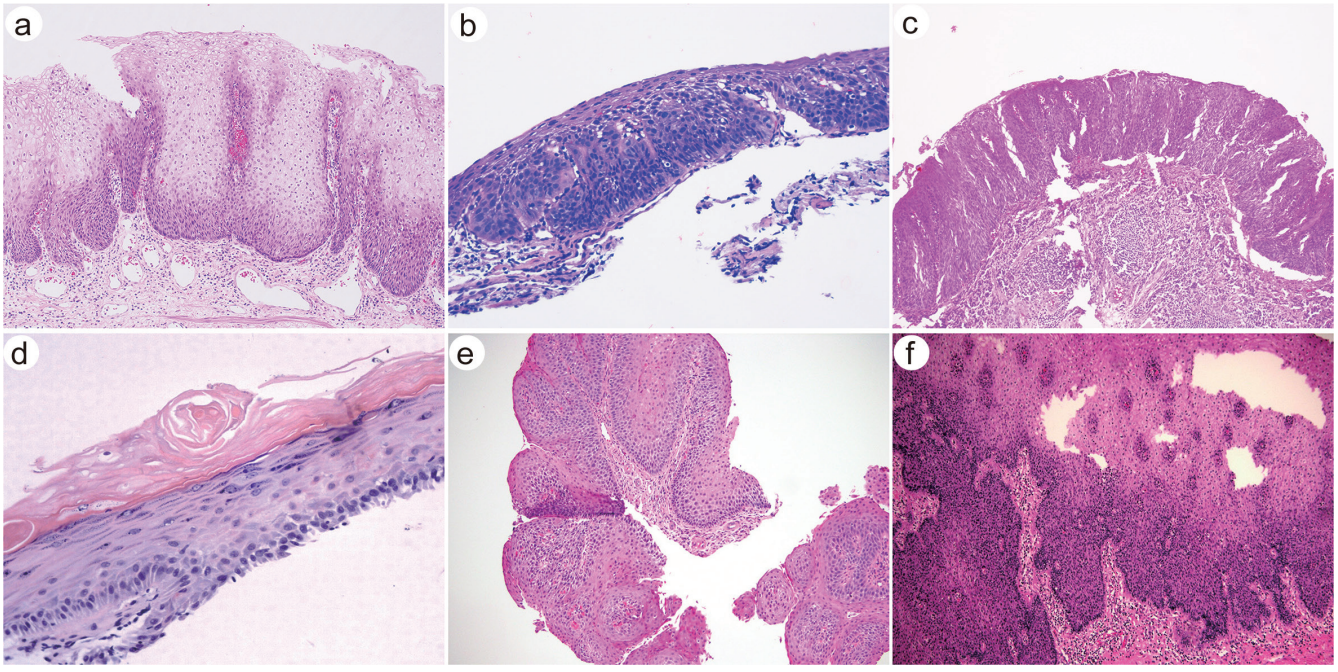

Fig. 2. Precursor lesions and mimics of esophageal well-differentiated squamous cell carcinoma. (a–d) Representative H&E staining images showing precursor lesions of esophageal well-differentiated squamous cell carcinoma, including low-grade squamous dysplasia (a), high-grade squamous dysplasia (b), squamous cell carcinoma in situ (c), and esophageal epidermoid metaplasia (d); (e–f) Representative H&E staining images showing mimics of esophageal well-differentiated squamous cell carcinoma, including squamous papilloma (e) and pseudoepitheliomatous hyperplasia (f). (a–f, 200×).

especially needs to be considered when it occurs alongside other disease processes such as granular cell tumor, infections, or trauma.[15,16] The lack of atypical features, maintained epithelial maturation, and the recognition of the underlying condition are critical in making the correct diagnosis and avoiding unnecessary treatment.

Squamous dysplasia is commonly considered the precursor lesion of well-differentiated ESC. Similar to oropharyngeal or cervical squamous dysplasia, esophageal squamous dysplasia can be graded with either a 3-tier system (mild dysplasia: involving lower 1/3 of the epithelium; moderate dysplasia: involving lower 2/3 of the epithelium, and severe dysplasia: extending to upper 1/3 of the epithelium) or a 2-tier system (low-grade dysplasia: involving lower 1/2 of the epithelium; high-grade dysplasia: involving more than ½ of the epithelium or less than 1/2 of the epithelium but with severe cytological dysplasia) (Fig. 2a, b). The term "squamous cell carcinoma *in situ*" (SCCIS) is usually reserved for full-thickness dysplasia without evidence of superficial maturation (Fig. 2c). However, additional forms of esophageal SCCIS have been reported. For example, pagetoid SCCIS is characterized by the presence of enlarged neoplastic cells predominantly involving the basal layer of the squamous epithelium, with pagetoid spread into the superficial half of the epithelium.[17,18]

Esophageal epidermoid metaplasia (EEM) has been proposed as a potential precursor lesion for squamous dysplasia and ESC.[19] EEM is a rare condition characterized by white plaques on endoscopy, therefore often referred to as "esophageal leukoplakia." Histologically, EEM shows hyperorthokeratosis with a granular cell layer, similar to the cutaneous squamous epithelium (Fig. 2d).[20,21] Kamboj *et al.* identified that 25% (10 of 40) of patients with an EEM diagnosis had squamous neoplasia diagnosed (before, at, or after EEM diagnosis).[20] Cottreau *et al.* also reported an increased prevalence of EEM in patients with squamous neoplasms.[22] In addition, a study with targeted next-generation sequencing (NGS) revealed that 67% of the samples with EEM (12 of 18) carried gene mutations commonly associated with ESC, including *TP53*, *PIK3CA*, *EGFR*, *MYCN*, *HRAS*, and *TERT* promoter (Table 1).[23,24] The mutation rate of *TP53* in EEM was 55.5%, similar to the mutation rate of 68.5% in one study of intraepithelial squamous neoplasia,[25] supporting it as a potential precursor of conventional ESC.[23]

Multiple large-scale comprehensive studies have identified recurrent genetic alterations in ESC, including *TP53*, *PIK3CA*, *NOTCH1*, and *FAT1* (Table 2).[24,26–33] ESC also harbors frequent genomic amplifications of *CCND1* and *SOX2* and/or *TP63*.[34] The *TP53* mutation has been the most common genetic alteration identified in ESC (60% to 92%), followed by *NOTCH1* mutation (8% to 32%) and *PIK3CA* mutation (5% to 17%).[26] Notably, *NOTCH1* and *PIK3CA* mutations are associated with distinct clinical outcomes in ESC and have been proposed to be mutually exclusive.[32] ESC harboring *NOTCH1* mutations were associated with well-differentiated, early-stage malignancy with a lower frequency of lymph node metastasis. However, these patients often failed to respond to chemotherapy and had a short survival time. On the other hand, patients with *PIK3CA* mutations had a better response to chemotherapy and a longer survival time.[32] The Cancer Genome Atlas (TCGA) has subclassified ESC into three major subtypes. ESC subtype 1 is characterized by alterations in the NRF2 pathway, which regulates the response to oxidative stressors and chemotherapy agents. This subtype has frequent *SOX2* and/or *TP63* amplification and Hippo-YAP pathway activation (*YAP1* amplification and *VGLL4* deletion). ESC subtype 2 is characterized by frequent mutations in *NOTCH1*, *ZNF750*, *KDM6A* and *KDM2D*, *CDK6* amplification, and inactivation of *PTEN*. This subtype is frequently associated with prominent leukocyte infiltration. ESC subtype 3 showed

Table 1. Potential precursor lesions for squamous cell carcinoma in the esophagus

Entity	Defining feature	Other features	Molecular abnormalities (frequency)	Associated squamous cell neoplasm
Esophageal epidermoid metaplasia	Presence of granular layer	Acanthotic squamous mucosa, superficial hyperorthokeratosis	*TP53* (55.5%); *PIK3CA* (11.1%); *EGFR* (11.1%); *MYCN* (5.6%); *HRAS* (5.6%); *TERT* promoter (5.6%)[23]	Squamous dysplasia, conventional squamous cell carcinoma
Non-invasive squamous component adjacent to invasive verrucous carcinoma	Exophytic growth with verruciform architecture	Preserved epithelial maturation, abrupt keratinization, lack of nuclear overlapping or atypia	*SMARCA4; FBXW7; NOTCH1*	Verrucous carcinoma
"Normal" mucosa in the esophagus harboring invasive esophageal carcinoma cuniculatum (Fig. 1i)	None	Slightly thickened squamous mucosa	*NOTCH3; NOTCH4; ROS1; FLT1; POLE; SDHA; TLR2; CSF1R*[24]	Carcinoma cuniculatum

no evidence of alterations in cell cycle-related genes. This subtype is likely esophagus specific and is characterized by changes predicted to activate the PI3K pathway.[34] How this TCGA molecular subtyping will influence personalized cancer management still awaits further investigation.

Verrucous squamous cell carcinoma

Esophageal verrucous squamous cell carcinoma (VC) is a rare and distinct variant of well-differentiated ESC. The term "verrucous squamous cell carcinoma" was first used in 1948 by Ackerman to describe a type of well-differentiated squamous cell carcinoma of the oral cavity.[35] It has been reported in various sites, including the foot,[36,37] head, neck,[38–40] urinary bladder,[41] and female genital tract.[42–44] Verrucous carcinoma of the esophagus was first described by Minielly *et al.* in 1967.[45] Until now, about 135 VC cases have been reported in 82 publications.[46] In a systemic review of the reported VC cases, the male to female ratio was about 2:1. The patients' ages ranged from 30 to 90 years old, with a median age of 65. Twenty-seven percent of the patients had a significant history of alcohol and tobacco use.[46] The medical history was often significant for gastroesophageal reflux disease, chronic esophageal irritation, achalasia, esophageal diverticulum, caustic injury, esophageal stricture, *Candida* esophagitis, and hiatal hernia. Most patients were symptomatic at the time of diagnosis, with dysphagia and weight loss being the most common symptoms, followed by odynophagia, hematemesis, cough, and anemia.[46–48] The association between VC and HPV subtypes (HPV-51 and HPV-11) has been proposed in some early studies.[49,50] However, in a case series of 9 VC patients, none of the cases demonstrated HPV infection.[51]

VC possesses some unique clinical features. It usually presents as a slow-growing lesion in the lower third of the esophagus with infrequent lymph node metastasis. The lesion is commonly described as a white, exophytic, or wart-like mass lesion, hence the name "verrucous".[52–57] The lesion is usually localized but can be diffuse and involve the entire esophagus.[58] Unfortunately, VC usually presents at an advanced tumor stage. Therefore, the prognosis is very poor. The mortality is primarily attributed to local invasion into adjacent organs such as the lung and pleura, in addition to surgical complications.[59] The development of broncho-esophageal fistula has been reported.[60] Respiratory complications are considered the primary cause of death in advanced cases. The tumor shows aggressive local invasion; however, distal metastasis has never been reported so far.[54]

On endoscopic ultrasound, VC was generally described as an area of localized hypoechoic wall thickening. In some cases, the tumor invasion into the deeper layers of the esophageal wall could also be appreciated.[46]

Due to the lack of cytological atypia, VC remains a diagnostic dilemma, especially on superficial endoscopic biopsy samples. These biopsy specimens generally show prominent chronic and acute inflammation with or without *Candida* organisms. The squamous mucosa usually shows nonspecific papillary architecture, hyperkeratosis, parakeratosis, and acanthosis with no evidence of significant dysplasia or malignancy (Fig. 1b). The tumor cells have pale eosinophilic cytoplasm, mildly hyperchromatic nuclei, and occasional keratinization or koilocytic changes.[61] The full-thickness biopsy or endoscopic resection specimen may reveal tumor invasion as broad nests with pushing borders.

In such cases, squamous papilloma may be a diagnostic consideration. However, unlike VC, squamous papilloma tends to grow superficially without evidence of deep growth or invasion (Fig. 2e). The definitive diagnosis of VC can be challenging to make, even with repeated biopsies. It frequently requires deep, full-thickness biopsy or endoscopic mucosal resection. Therefore, there can be a delay of months to years between initial presentation and diagnosis. Endoscopically, the lesion can sometimes be described as a whitish plaque. Due to the frequent superimposed *Candida* infection in VC cases, this may lead to a misdiagnosis of refractory *Candida* esophagitis[62] and cause a significant delay in diagnosis and management. The treatment options include esophagectomy, endoscopic resection (endoscopic mucosal resection and endoscopic submucosal dissection), and radiation.

Isidro *et al.* reported the first molecular study on VC.[33] Unlike conventional ESC, *TP53* mutations were much less likely to be detected in VC. Copy number variants for *CDKN2A*, *CDKN2B,* and *CCND1* were significantly less frequent in VC than in conventional ESC. In contrast, VC frequently harbored *SMARCA4* missense mutations or in-frame deletions. Therefore, VC is not only morphologically distinct but also a genetically distinct variant of ESC. The *TP53* and *SMARCA4* mutation signatures significantly differ between VC and conventional ESC.[46] These may provide aid when dealing with challenging cases.

A precursor lesion to verrucous carcinoma in the esophagus is not well defined yet. A non-invasive component of verrucous carcinoma adjacent to invasive verrucous carci-

Table 2. Histomorphology and molecular abnormalities of well-differentiated esophageal squamous cell carcinoma

Entities	Location	Premalignant lesion(s)	Defining features	Other features	Genes (frequency)	Type of abnormalities	Associated features
Conventional well-differentiated squamous cell carcinoma	Mid esophagus	Squamous dysplasia, esophageal epidermoid metaplasia	Infiltrative growth of atypical epithelium showing obvious keratinization	Single cells and small nests, abnormal keratinization, variable pleomorphism, increased mitotic activity, abnormal mitoses, variable tumor necrosis, desmoplastic stroma	*TP53* (60–90%)[26]	Mutations	N/A
					NOTCH1 (8–32%)[26]	Mutations	Well-differentiated, less chemo-sensitive, shorter survival[32]
					PIK3CA (5–17%)[26]	Mutations	More chemo-sensitive, longer survival[32]
					FAT1	Mutations	N/A
					CCND1	Amplifications	N/A
					SOX2	Amplifications	N/A
					TP63	Amplifications	N/A
Verrucous carcinoma	Distal esophagus	Not well characterized	Exophytic growth of bland squamous epithelium, lack of nuclear atypia, pushing invasion	Verruciform architecture, preserved epithelial maturation, abrupt keratinization, lack of nuclear overlapping, occasional koilocyte-like changes, absent or low mitotic activity, fibrotic and inflamed stroma	*SMARCA4* (5 of 6 cases) [33]	Missense mutations or in-frame deletions	N/A
					FBXW7 (3 of 6 cases)	Mutations	N/A
					GNAS (3 of 6 cases)	Mutations	N/A
					KMT2D (3 of 6 cases)	Mutations	N/A
					ROS1 (2 of 6 cases)	Mutations	N/A
					PIK3CA (2 of 6 cases)	Mutations	N/A
					NOTCH1 (2 of 6 cases)	Mutations	N/A
					TP53 (much less frequent)	Mutations	N/A
					CDKN2A, CDKN2B, and *CCND1* (much less frequent)	Copy number variants	N/A
Carcinoma cuniculatum	Distal esophagus	Not well characterized	Presence of furrows on macroscopic examination, endophytic growth of bland squamous epithelium, keratin cysts/ burrows, lack of nuclear atypia	Hyperkeratosis, deep keratinization, acanthosis, dyskeratosis, koilocyte-like cells, intraepithelial neutrophils, neutrophilic microabscesses, mild cytologic atypia, absent or low mitotic activity, pushing or infiltrative invasion	*NOTCH1* (3 of 5 cases)[24]	Mutations	N/A
					TP53 (2 of 5 cases)	Mutations	N/A
					PIK3CA (1 of 5 cases)	Mutations	N/A
					KRAS (1 of 5 cases)	Mutations	N/A
					HRAS (1 of 5 cases)	Mutations	N/A
					SETD2 (1 of 5 cases)	Mutations	N/A
					TLR2 (1 of 5 cases)	Mutations	N/A

N/A: not available.

noma depicted in one paper demonstrated exophytic growth with verruciform architecture, preserved epithelial maturation, abrupt keratinization, and lack of nuclear overlapping or atypia.[33] Sequencing of the non-invasive squamous component showed nearly identical mutations in *SMARCA4*, *FBXW7*, and *NOTCH1* (Table 1) compared to the invasive squamous component.[33] Cases 2 and 3 in this series showed the morphology of carcinoma cuniculatum in the deep portion of the lesion with keratin-filled cysts. Both cases showed mutated *SMARCA4*, *FBXW7*, and *NOTCH1* but wild-type *TP53*.[33]

Esophageal carcinoma cuniculatum (CC)

Carcinoma cuniculatum is a rare variant of extremely well-differentiated squamous cell carcinoma. Carcinoma cuniculatum was first described in the skin as a variant of squamous cell carcinoma peculiar to the foot.[63] Subsequently, non-cutaneous carcinoma cuniculatum cases have been reported in many different organ systems, including the esophagus,[53,64–68] head, neck,[69–73] cervix,[74] and penis.[75] Carcinoma cuniculatum was initially considered to be a special type of VC. Both tumors are extremely well-differentiated SCC with bland histology and have similar clinical presentations. However, due to its distinctive growth pattern and architecture, CC has been recognized as a unique variant of well-differentiated ESC. Compared to VC, CC may have a better prognosis with a lower percentage of T4 tumor stage (11.1% vs. 41.6%) and lower mortality (22.2% vs. 66.7%).[66]

De Petris *et al.* reported the first two esophageal CC cases in 2005.[64] Until now, fewer than 20 cases have been published in the literature.[53,64–68] In the reported CC cases, the median age was about 63 years (range, 40–77 years), with a male to female ratio of 2:1.[53] Dysphagia is the most common complaint. Other clinical symptoms and signs include regurgitation, diarrhea, weight loss, chest and epigastric pain, and melena.[63,66] About 70% of the patients have a significant smoking history, and about one-third have chronic alcohol abuse.[63,66] Unlike conventional ESC, which is more commonly seen in the middle third of the esophagus, CC mainly involves the distal esophagus and gastroesophageal junction.

Macroscopically, a common feature of CC is the presence of burrows on the tumor surface reminiscent of those dug by rabbits and therefore called "cuniculi".[66] The tumor growth patterns include obstructive, ulcerative, and warty lesions. Esophageal wall invasion was reported in at least 73.3% of the cases.[53] About half of the CC cases showed a mixed endophytic and exophytic growth pattern, and the differential diagnosis would therefore include VC and well-differentiated ESC with verrucous features. Only rare cases showed a pure endophytic pattern of growth, and for such cases, inverted papilloma and intramural pseudodiverticula should be excluded before rendering the diagnosis of CC.[66]

CC is a variant of extremely well-differentiated ESC (Fig. 1c). An early pathological diagnosis on endoscopic mucosal biopsy is quite challenging. As a result, most reported cases could only obtain correct histological diagnosis with endoscopic or surgical resection specimens. To improve early diagnosis, Landau *et al.* have proposed some common morphological features of CC: hyperkeratosis, deep keratinization, acanthosis, dyskeratosis, intraepithelial neutrophils, neutrophilic microabscesses, koilocyte-like cells, mild cytologic atypia, and keratin cysts/burrows (Fig. 1d–h).[66] By assigning one point for each morphological feature, a semiquantitative histologic evaluation system for CC has been validated.[67] The mean histologic score for the CC tumor biopsies was 6.66 (SD, 1.88), compared to the mean score of 1.93 (SD, 1.75) for the benign esophageal mucosal biopsies. Based on this study, the authors have proposed a cutoff value of 7 for CC diagnosis on biopsy specimens that could significantly improve the diagnostic sensitivity and specificity for the endoscopic mucosal biopsy in CC cases.[67] A preoperative diagnosis of CC using this histologic scoring system was confirmed on esophagectomy specimens in two patients.[68] However, extensive studies are needed to validate its diagnostic use in clinical practice.

Some hot spot somatic mutations in *NOTCH1*, *TP53*, *PIK3CA*, *KRAS*, *HRAS*, *SETD2,* and *TLR2* genes have been identified in CC tumor samples through NGS.[24] Although the mutations in *TP53*, *NOTCH1,* and *PIK3CA* genes are also among the common mutations in conventional ESC tumor samples, there is a significant enrichment of *NOTCH1* and *PIK3CA* gene mutation in CC tumors. Specifically, the majority (62% to 86%) of the conventional ESC cases have wild-type expression of the *NOTCH1* and *PIK3CA* genes.[26–31] However, CC tumors show frequent *NOTCH1* mutation (60%, three out of five cases in the study cohort).[24] Conventional ESC with *NOTCH1* gene mutation is significantly associated with well-differentiated, early-stage tumors without lymph node metastasis. These tumors also frequently have a poor response to chemotherapy.[32] Whether the presence of frequent *NOTCH1* gene mutations is associated with the unique histological features and clinical behaviors in CC tumors still awaits further clarification. The study also demonstrated identical deleterious mutations between the non-invasive and invasive CC components, supporting the use of molecular testing on superficial endoscopic mucosal biopsy samples to establish a preoperative diagnosis for challenging CC cases.[24]

The presence of koilocyte-like cells is one of the histological features of CC (Fig. 1g). However, there was no significant expression of p16 on immunohistochemistry in one study,[76] and *in situ* hybridization for HPV subtypes (6, 11, 16, 18, 31, 33, and 51) were negative in all the cases tested.[64,66] *TP53* mutation was detected in 40% of CC cases (2 of 5 cases) in a recent NGS study,[24] which suggests a potential use for p53 immunohistochemistry to assist in the diagnosis of CC on an endoscopic mucosal biopsy sample.

The curative treatment for CC is surgical resection. Unlike conventional ESC, which has a five-year survival rate of approximately 20%, the prognosis of CC has been excellent. Landau *et al.* have reported a median survival of 84 months even in advanced tumor cases. The indolent clinical course is likely associated with the lack of lymph node metastasis.[66]

Precursor lesions leading to CC are not well-defined yet. Acanthotic squamous epithelium with abnormal keratinization is noted immediately adjacent to CC.[24] The "normal" appearing mucosa adjacent to the "acanthotic squamous epithelium" showed recurrent somatic gene mutations (Fig. 1i) (Table 1), indicating a field effect.[24] Additional studies are needed to further characterize the precursor lesions of CC histomorphologically and molecularly.

The relationship between conventional ESC, VC, and CC remains unclear. There are overlapping histologic features among conventional well differentiated ESC, VC, and CC, and this may attribute to the partially overlapping genetic alterations (Table 2). Further intra- and inter-observer studies are needed to identify a relatively pure population of VC and CC so that their subtle precursor lesions can be characterized, diagnosed, and treated prior to the development of locally advanced carcinoma.

Conclusions

VC and CC are morphologically and genetically distinct variants of extremely well-differentiated ESC. Together with con-

ventional well-differentiated ESC, these entities often pose diagnostic challenges due to their lack of significant cytologic atypia and distinct histological findings. Unfortunately, misdiagnosis is common for these rare variants. Improving awareness of these variants since early diagnosis often leads to complete curative resection, avoiding late complications and mortality. High clinical suspicion and close collaboration among specialists, including gastroenterologists, pathologists, radiologists, and surgeons, are required to achieve timely diagnosis and proper management. In recent years, *TP53* wild-type squamous intraepithelial neoplasia has been increasingly recognized in the vulvar and anal region. We hope that in the future, *TP53* wild-type squamous intraepithelial neoplasia in the esophagus will be characterized, diagnosed, and treated prior to the development of locally advanced carcinoma.

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Conflict of interest

Liu X has been an editorial board member of the *Journal of Clinical and Translational Pathology* since November 2021. The authors have no other conflicts of interest related to this study.

Author contributions

Yin F, Zheng W, Amofa-Ho, and Liu X collected and analyzed the data, made the Tables and Figures, and wrote and finalized the manuscript. All authors have approved the final manuscript.

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