

Verrucous Carcinoma of the Esophagus: Its Unique Etiology and Association with Human Papilloma Virus

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Abstract

Verrucous carcinoma of the esophagus (VCE) is a rare variant of esophageal squamous cell carcinoma. Most cases of VCE presents as an exophytic, slow-growing mass with a superficial growth pattern. Even when VCE exhibits a characteristic pattern during an endoscopic examination, it is very difficult to make a definitive diagnosis of VCE preoperatively, because biopsy specimens are only characterized by nonspecific acanthosis and hyperkeratosis or parakeratosis associated with inflammation. As well as the characteristics of VCE, the etiology of the disease is even unique. VCE is typically associated with chronic mucosal irritation such as reflux esophagitis, achalasia, and lye ingestion that has resulted in esophageal inflammation or a long-term local disease process in addition to the classic risk factors of nicotine and alcohol consumption. Recent studies had indicated that human papilloma virus (HPV) infection might be associated with VCE. While HPV may be related to VCE initiation, involvement of HPV in the etiology of VCE requires further investigation. VCE's etiology and therapeutic strategy, including the vaccination against HPV, should be established.

Keywords: Verrucous carcinoma, Esophagus, Human papilloma virus

Introduction

Verrucous carcinoma is an extremely rare disease, and it is unique in terms of its appearance, growth pattern, and etiology. In 1948, Ackerman first described verrucous squamous cell carcinoma (VSC) as a variant of oral squamous cell carcinoma [1], and he collected 31 cases of oral neoplasms under the name, "Verrucous Carcinoma of the Oral Cavity." VSC was described as having the following characteristics: slow growing, well-differentiated, irregular surface appearance with a propensity to spread locally, and VSC has subsequently been reported in the mouth, nasal cavity, larynx, glans penis, scrotum, vulva, vagina, cervix, endometrium, urinary bladder, and anorectal region. Verrucous carcinoma of the esophagus (VCE) is a rare variant of esophageal squamous cell carcinoma. In 1967, Minielly et al. described VCE for the first time in a series of five cases [2]. Interestingly, there are reports suggesting an association between VCE and human papilloma virus

(HPV) infection, stating that HPV may be involved in the carcinogenesis of VCE. Although VCE exhibits the same typical appearance and growth patterns as VSC in other organs, because of the paucity of cases neither its etiology nor therapeutic strategies have not been well assessed. In this commentary we reviewed previous reports and discussed VCE, in particular association between its etiology and HPV infection.

Review of the Literature Concerning VCE

We used the keywords "esophagus" and "verrucous carcinoma" to search the literature in the PubMed database during the period from 1983 to 2018 (Table 1). Only 48 cases of VCE (including our case) have been described since Minielly's first report of VCE [2]. Males have predominated, but the proportion of women with VCE (28 males, 18 females, 2 gender unknown) has been higher among esophageal squamous cell carcinoma patients. The male-female ratio is about 3:2, and VCE

No	Author	Year	Age/ Sex	Chief complaint	Past history	Location	1 st diagnosis	Tumor size (cm)	Treat- ment	Prognosis	T	N	M
1	Minielly [2]	1967	58/M	dysphagia	achalasia	upper	benign	9×8.5	OPE	1m dead	3	0	0
2		1967	70/F	dysphagia	diverticulum	upper	VC	large tumor	RT	unknown	N/A	N/A	N/A
3		1967	70/F	dysphagia	achalasia	upper	VC	large tumor	RT	2m dead	4	N/A	N/A
4		1967	36/M	dysphagia	diverticulum	lower	SCC	9×8	OPE	2m dead	4	+	N/A
5		1967	57/M	dysphagia	none	lower	benign	N/A	BSC	5m dead	N/A	N/A	N/A
6	Parkinson [23]	1970	76/M	melena	obstruction	middle	SCC	7.5	BSC	1m dead	1b	0	0
7	Meyerow- itz [24]	1971	45/M	hematem- esis	none	lower	benign	8×5.5	OPE, RT	9m dead	2	N/A	0
8	Sridher [25]	1980	54/M	dysphagia	hiatal hernia	lower	benign	2	OPE	unknown	1b	0	N/A
9	Sakurai [7]	1983	78/M	dysphagia	none	upper	VC	10×5	CT	6m alive	4	N/A	N/A
10	Agha [26]	1984	66/M	dysphagia	acid burn	upper	VC	large tumor	BSC	2m dead	4	N/A	N/A
11	Barbier [27]	1987	50/F	dysphagia	hiatal hernia	lower	VC	N/A	OPE	10m alive	1a	0	0
12	Koerfgen [28]	1988	75/M	dysphagia	traumatic stenosis	lower	benign	N/A	OPE	36m alive	2	0	0
13		1988	54/?	dysphagia	none	lower	benign	6.5×6.5	OPE	18m alive	2	0	0

14	Jasim [29]	1990	79/M	dysphagia	hiatal hernia	lower	benign	9×6	BSC	dead	N/A	0	0
15	Biamond [4]	1991	76/F	dysphagia, dyspnea	RE	middle	benign	15	BSC	1m dead	4	0	0
16	Roach [30]	1993	67/M	dysphagia	achalasia	upper	benign	7	BSC	2m dead	4	0	0
17	Garrard [31]	1994	51/F	dysphagia	none	middle	VC	10	OPE	9m alive	2	0	0
18	Kavin [8]	1996	76/?	odynophagia	none	lower	benign	N/A	BSC	1m dead	N/A	+	N/A
19	Malik [32]	1996	66/M	dysphagia	RE	lower	benign	5×2	OPE	36m alive	2	0	0
20	Tajiri [33]	2000	40/M	none	none	lower	VC	0.6×0.8	EMR	48m alive	1a	0	0
21	Ereno [34]	2001	65/F	dysphagia	none	middle	N/A	11	OPE	N/A	N/A	N/A	N/A
22	Osborn [35]	2003	67/M	dysphagia	achalasia	lower	benign	8×8	OPE	9m alive	2	0	0
23	Devlin [3]	2004	56/F	abdominal pain	none	lower	benign	2.7	OPE	14m alive	1b	0	0
24	Pfitzmann [36]	2004	66/F	N/A	none	lower	N/A	N/A	OPE	N/A	N/A	N/A	N/A
25	Liberale [18]	2005	41/M	chest pain	none	lower	VC	N/A	Anti-ral Tx	6m dead	4	N/A	N/A
26	Na [37]	2009	50/M	dysphagia	RE	middle	VC	7.5×4.8	OPE	6m alive	2	0	0
27	Oh [5]	2009	73/F	dysphagia	RE	upper	benign	3.5	BSC	23m alive	1a	0	0
28	Garcia [38]	2010	71/F	dysphagia	obstruction	middle	benign	3.9×2.5	OPE	N/A	2	0	0

29	Tonna [19]	2010	61/M	dysphagia	none	extensive	benign	10	OPE	12m alive	1b	0	0
30	Munson [39]	2010	63/F	dysphagia	none	extensive	VC	16	CRT	N/A	3	+	0
31	Taniyama [40]	2012	74/M	nausea	none	middle	benign	5	OPE	6m alive	2	0	0
32	Vieira [22]	2013	58/M	dysphagia	none	N/A	benign	N/A	OPE	1m dead	2	0	0
33	Sweetser [41]	2014	61/M	dysphagia	N/A	extensive	N/A	N/A	OPE, CRT	72m alive	2	0	0
34		2014	73/F	dysphagia	N/A	lower	N/A	N/A	CRT	36m alive	N/A	N/A	N/A
35		2014	66/M	dysphagia	N/A	lower	N/A	N/A	OPE	120m alive	1	0	0
36		2014	70/F	dysphagia	N/A	extensive	N/A	N/A	OPE	6m dead	1	0	0
37		2014	71/M	dysphagia	N/A	middle	N/A	N/A	N/A	36m dead	2	0	0
38		2014	57/M	N/A	N/A	lower	N/A	N/A	N/A	N/A	3	0	0
39		2014	75/F	dysphagia	N/A	lower	N/A	N/A	N/A	N/A	1	0	0
40		2014	62/M	dysphagia	N/A	extensive	N/A	N/A	OPE	96m alive	3	0	0
41		2014	63/F	dysphagia	N/A	extensive	N/A	N/A	CRT	12m alive	3	0	0
42		2014	68/M	dysphagia	N/A	extensive	N/A	N/A	OPE, CRT	24m alive	1	0	0
43		2014	62/F	dysphagia	N/A	middle	N/A	N/A	OPE	24m alive	1	0	0
44	Abe [42]	2016	68/M	none	N/A	lower	benign	1	ESD	N/A	1a	0	0
45	Cox [43]	2017	62/M	dysphagia	none	middle	SCC	9.5	OPE	N/A	1b	0	0
46	Hoffmann [44]	2018	61/M	dysphagia	systemic sclerosis	lower	VC	N/A	OPE	24m alive	1b	0	0
47		2018	52/F	dysphagia	none	lower	VC	10	OPE	24m alive	2	0	0
48	Tabuchi [10]	2020	56/F	dysphagia	none	lower	benign	12	OPE	96m alive	3	0	0

Table 1: Reported cases of Verrucous carcinoma of esophagus.

patients' ages (median, 64 years; range, 36-79 years) have been similar to those of esophageal squamous cell carcinoma patients. The most common chief complaint was dysphagia (in 39 (85%) of the 46 cases). The tumors have predominantly been located in the lower third of the esophagus (30 cases, 64%), and their frequent location in the lower-third of the esophagus may be associated with chronic esophageal mucosal inflammation. Almost all patients had a medical history that resulted in esophageal injury or inflammation before the diagnosis of VCE: 90% of the patients have had an associated chronic disease or condition (e.g., achalasia, reflux esophagitis, candida esophagitis, and heavy consumption of nicotine and alcohol).

VCE tumor sizes have been relatively large, but depth of invasion has generally been shallow. In 23 (48% of the 48 cases reported) of the 29 cases in which tumor size was recorded, the tumor measured 5 cm or more in diameter. Tumor invasion has been limited to the muscle layer (T1 and T2): in 68% of the patients in which depth of tumor invasion was recorded, but in seven cases (17%) the tumor was locally advanced (T4). This could be explained by the difficulty of making the diagnosis of VCE. In addition, very low incidence of lymph node metastasis (8%) and distant organ metastasis (0%) have been special characteristics of VCE.

The histopathologic features of VCE include good preservation of the epithelial basement membrane and highly differentiated histology, both of which are important in differentiating VCE from other esophageal carcinomas. However, in the majority of cases, mucosal biopsies were diagnosed as acanthosis, hyperkeratosis, and parakeratosis, and these nonspecific pathological findings make the correct diagnosis of VCE difficult and delay the start of treatment. Using EUS may provide information that is crucial to the diagnostic process [3]. The majority of VCE patients have impressive inflammatory changes that extend deep into the submucosal space and the muscularis propria, and EUS is ideally suited to detecting such changes. Since distorted architecture and local invasion are readily visible by EUS, EUS may make it possible to establish the appropriate diagnosis of VCE.

The histological picture of VCE resembles that of benign squamous cell papilloma. However, VCE tends to be deep-growing and invasive, whereas papilloma tends to grow superficially. Biemond et al. [4] proposed that the presence of infiltration is essential to differentiating VCE from squamous papilloma. It should be noted that some squamous papilloma shows evidence of dysplasia without infiltration. However, because of the limited low-grade nevus cell nest formation and the highly keratinized surface of the tumors, it is not easy to diagnose VCE on the basis of the findings in preoperative biopsy samples. In fact, only 12 (25%) of the 48 cases were diagnosed as

esophageal VC based on the biopsy pathology findings. As Oh et al. have reported, endoscopic mucosal resection (EMR) might be a useful means of making an accurate diagnosis in suspected cases of VCE [5].

Treatment consisted of surgery in 28 cases, chemoradiation therapy in 5 cases, radiotherapy in 3 cases, chemotherapy in 1 case, and best supportive care in 8 cases. Before 1990, all patients had undergone esophageal resection and experienced significant postoperative complications. Surgical treatment after 1990 yielded favorable results because of improvements in surgical procedures and perioperative management in recent years as well as because of the low malignant potentials of VCE. The effectiveness of radiotherapy and chemotherapy, on the other hand, has been very limited [6]. Chemotherapeutic regimens that have been used to treat squamous cell carcinoma have not been effective against VCE. There has been only one report of partial treatment response with bleomycin [7], and new drugs or regimens need to be developed. If a locally advanced tumor stage is the initial diagnosis and surgery is technically possible, esophageal resection should be considered because of the rarity of lymph node metastases and the limited chemo- and radio-sensitivity of VCE.

Association between VCE and Esophageal Mucosal Inflammation

In addition to the classic risk factors of nicotine and alcohol consumption, VCE is typically associated with chronic esophageal mucosal inflammation. Kavin et al. [8] reported a case of VCE in a patient who had chronic esophagitis secondary to a caustic injury as a result of ingesting aerosolized lye and kerosene syrup. After 16 years of serial endoscopic surveillance, a verrucous mass was detected in the distal esophagus, and serial biopsies showed progression from esophagitis to leukoplakia, then to papillary hyperplasia and, finally, to dysplasia. Similar findings had been reported in laboratory rats in which VCE was experimentally induced by prolonged exposure of the esophagus to N-methyl-N-nitrosoaniline [9]. The lesions observed in the rats progressed in stages from acanthosis and hyperkeratosis, to leukoplakia, and then to papillary hypertrophy, and within 500 days the esophageal surface transformed from its normal smooth appearance to having a verrucous exophytic appearance. We also described that candida esophagitis was diagnosed during long-term follow-up period and might be related to the VCE [10]. Thus, esophageal injury or irritation is likely to be a prerequisite for the sequential development of dysplastic changes over time.

Association between VCE and Human Papilloma Virus Infection

HPV infection accounts for approximately more than 5% of the worldwide human cancers [11]. HPV can infect

the stratified epithelia of the skin or mucous membranes of the upper gastrointestinal, respiratory, or anogenital tract, potentially leading to the outcomes such as genital warts and laryngeal papilloma, and sometimes certain cancers. Various types of HPV have been associated with developing cancers in several organs: “low risk” and “high risk” depending on the oncological potential. VSC is uniquely suspected of being related to HPV. HPV infection has been reported to be associated with several cancers, and involvement of HPV in head and neck cancers, particularly oropharyngeal cancer, has recently become clear and been attracting attention. HPV infection due to sexual activity is the cause, and the HPV-positive rate in head and neck cancer patients has been increasing every year [12]. Developing the cancerous lesion after HPV infection may be associated with the immune status of the patients. De Socio et al. has reported a case of HPV-associated lips verrucous carcinoma in HIV-infected male patient [13]. HIV-positive patients have a 2 to 3 times higher prevalence of oral HPV infection than HIV-negative patients. It has also become clearer that HPV infection is the cause of almost all cases of cervical cancer, and HPV vaccination has been introduced worldwide as a means of preventing cervical cancer [14]. HPV may be involved in carcinogenesis [15]. HPV infection causes high expression of oncogenes E6 and E7 in basal cells, promotes proteolysis of tumor suppressor genes p53 and Rb, and inactivates their functions.

There have also been a number of reports of HPV being related to primary laryngeal VC [16]. Also, many studies have addressed a possible association between HPV infection and esophageal dysplasia. Tornesello et al. reported 66 esophageal cancer patients and demonstrated the relatively higher prevalence of HPV infection in well-differentiated squamous cell carcinoma, suggesting a tropism of HPV replication in keratinized tissues [17]. Several investigators have clearly demonstrated the positive association between HPV and VCE [18,19]. There are many HPV genotypes, and genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 are considered to be a high-risk group [20]. Yong et al. reported associations between HPV type 16 and 18 infection and esophageal squamous cell carcinoma [21], and Vieira et al. have demonstrated HPV type 11 infection in endoscopic biopsy specimens of VCE [22]. Tonna et al. detected HPV type 51 deoxyribonucleic acid (DNA) in endoscopic biopsy specimens of VCE by performing polymerase chain reactions, and they stated that the presence of HPV DNA in the endoscopic biopsies raised the possibility that HPV infection underlies the hyperkeratosis and malignant transformation [19]. Liberale et al. [18] reported a case of HPV-positive VCE with esophagobronchial fistula in a 41-year-old man, initially responded to antiviral treatment.

Cappellesso et al. [20], on the other hand, have reported that HPV infection may not be involved in VCE, but,

unlike Vieira et al. and Tonna et al., they tested surgically resected specimens for HPV infection by performing chromogenic hybridization. These different findings might be explained by destruction of HPV DNA in the formalin fixed paraffin embedded (FFPE) tissues of resected specimens, or HPV may have played an initiating role and no longer have been involved once the lesion underwent malignant transformation.

Until recently, no data have been available on the efficacy of the HPV vaccines in preventing HPV infections and its related cancers. However, nowadays, it is well known that vaccination against HPV during childhood and prior to HPV exposure can prevent HPV-associated cervical cancers later in their adult lives. Accordingly, it could be proposed to administer HPV vaccine against VSC including VCE to prevent the acceleration of malignant progression. We should investigate the association between VCE and HPV infection further to understand and successfully treat this disease.

Conclusions

VCE is a rare, well differentiated carcinoma that is slow growing and invades locally. VCE is difficult to diagnose, because histologic examination of mucosal biopsy specimens usually shows only nonspecific inflammatory changes. If VCE is suspected based on the history and clinical findings, we strongly recommend esophagectomy, because distant and lymph node metastasis are relatively rare. HPV may be involved in VCE initiation, and the possible etiological involvement of HPV should be investigated.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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