

Prevalence of esophageal squamous papilloma (ESP) and associated cancer in northeastern France

Authors

Marie-Caroline d'Huart^{1,*}, Jean Baptiste Chevaux^{1,*}, Aude Marchal Bressenot², Nicolas Froment³, Lucine Vuitton⁴, Séverine Valmary Degano⁵, Clotilde Latarche⁶, Marc André Bigard¹, Alain Courrier⁷, Hervé Hudziak¹, Stéphane Koch⁴, Eric Kull⁷, Laurent Peyrin-Biroulet¹

Institutions

Institutions are listed at the end of article.

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Corresponding author

Laurent Peyrin-Biroulet, MD, PhD

Inserm U954 and Department

of Hepatogastroenterology

Nancy University Hospital

Allée du Morvan

54511 Vandœuvre-lès-Nancy

France

peyrinbiroulet@gmail.com

Background and study aims: Esophageal squamous papilloma (ESP) is a rare lesion. The aims of this study were to assess the prevalence of ESP in northeastern France and the risk of associated squamous cell carcinoma (SCC).

Patients and methods: The charts of 78 patients who were diagnosed with ESP between January 2005 and February 2013 at three hospitals in northeastern France were reviewed.

Results: A total of 55 305 endoscopies were performed and 78 ESP were diagnosed (0.01%). Patients with ESP included 44 males (56.4%), 34 females (43.6%); median age 50, interquartile range (IQR) 19–86. Median follow-up was 21 months (IQR 0–91 mo) and median time between first and second endoscopy was 7 months (IQR 0.5–74 mo). Of the total number of patients, 35 (44.9%) had a second endoscopy. Main endoscopy indication was dyspepsia (24.4%). Most ESP were isolated (93.6%) and located at distal esophagus (27 cm, IQR 16–40 cm). Median size was 3 mm

(IQR 1–20 mm). ESP-associated endoscopic lesions were hiatal hernia in 12 patients and esophagitis in 11 patients. Endoscopic treatment was mainly excisional biopsies (60.3%). Human papillomavirus (HPV) was not detected in the 6 patients with available data. Low dysplasia was found in 2 ESP. During follow-up endoscopies, 2 SCC were detected in 2 different patients; the first SCC was located at the previous resection site of the ESP and the second had a different location. Prevalence of associated cancer was 1.3%.

Conclusion: Prevalence of ESP in northeastern France is similar to that previously reported. Endoscopic findings were also broadly the same as in previous reports. The occurrence of dysplasia and SCC should strongly encourage the endoscopist to totally remove the ESP and to start an endoscopic surveillance, given the potential risk of malignant transformation.

Introduction

Esophageal squamous papilloma (ESP) is a rare epithelial tumor that was first described by Adler et al. in 1959 [1]. Less than 200 cases have been reported so far [2]. ESP prevalence ranges from 0.01 to 0.45% according to endoscopic series [2–4]. It is more frequent in middle-aged males [5]. ESP is usually asymptomatic and mostly discovered as an incidental finding during upper gastrointestinal endoscopy [2, 6]. It is usually located at distal esophagus and resembles a single small, whitish, and elevated sessile lesion [2, 5, 7]. Multiple forms like papillomatosis [8, 9] and giant esophageal papilloma up to 5 cm have been described in the literature [10]. Its endoscopic aspect is usually characteristic but not pathogno-

monic [2]. Hence, the diagnostics depend on histological findings in order to differentiate it from acanthosis, hypergranulosis, and hyperkeratosis [11].

The pathogenesis of ESP is not well known [7]. Chronic mucosal irritation due to chemical and mechanical factors [5, 7, 12] and human papillomavirus (HPV) infection [2, 12] may contribute to its development. Prevalence of HPV-positive ESP varies between 0 and 87.5% [12, 13].

ESP is considered a benign neoplasia [12]; however, recent reports highlighted the potential malignant evolution of these lesions [12, 14–19]. In most of the reported cases, squamous cell carcinoma (SCC) developed on giant ESP or on squamous papillomatosis [14–19]. Overall, the risk of cancer in patients with ESP has yet to be determined.

* These authors contributed equally.

License terms



The aims of this retrospective study were to assess the prevalence of ESP in northeastern France and the risk of associated SCC.

Material and methods

Inclusion criteria

All consecutive patients who underwent an upper gastrointestinal endoscopy at Nancy University Hospital, Besançon University Hospital, and Metz Mercy Hospital between January 2005 and February 2013 were included in the study. Endoscopic samples were fixed in formalin and sent to the pathology unit of each hospital; and histological diagnoses were made based on: fingerlike projections of tissue lined by an increased number of squamous cells, uninflamed fibrovascular core containing small blood vessels with conserved normal cellular orientation, and normal differentiation without signs of cytological atypia.

Patients

The following variables were recorded by reviewing the medical charts of every patient diagnosed with an ESP and all endoscopic procedures performed during follow-up: (1) patient characteristics: sex, age, active smoker, chronic alcohol consumption, proton-pump inhibitors treatment, immunosuppressive therapies, past history of cancer (especially ear nose throat [ENT], esophageal, anal, gynecological); (2) endoscopic findings: date of upper gastrointestinal endoscopy, indications (dyspepsia, dysphagia, anemia, liver cirrhosis, etc.), number of ESP, size of ESP, distance from the incisors, appearance (sessile or pedicle), consistency (soft or hardened), color (whitish or other), treatment (biopsy [tissue sampling], excisional biopsy [complete resection], polypectomy, mucosectomy, argon plasma coagulation), endoscopic ultrasound, Lugol iodine chromoendoscopy, associated lesions (hiatal hernia, esophagitis, Barrett esophagus, gastric ulcer, cancer); and (3) histological findings: dysplasia, SCC, and associated HPV infection.

If HPV detection was performed on tissue samples, histological methods of detection and HPV subtype were collected.

Latest update on the patient corresponded to the latest endoscopic follow-up available. If the patient underwent only one endoscopy, which was the one used to establish the diagnosis of

the ESP, information about SCC occurrence was obtained from patient's general practitioner.

Statistical analysis

Statistical analysis looked at the prevalence rate of ESP among endoscopies performed; and baseline characteristics were analyzed with median and interquartile range (IQR). Analyses were performed using SAS (SAS, Version 9.3, Cary, NC, USA). Only descriptive analyses were performed.

Results

Prevalence

Among the 55 305 upper gastrointestinal endoscopies performed between January 2005 and February 2013, 78 patients were diagnosed with ESP. The prevalence rate of ESP was 0.01 %.

Baseline characteristics of the 78 patients

At time of diagnosis of ESP, patients included 44 males (56.4%), 34 females (43.6%); median age 50, IQR 19–86. Of the 78 patients, 30 were active smokers (45.5%) and 13 had chronic alcoholism (20%). Treatment with proton-pump inhibitors was reported in 22 cases (31.4%) and an immunosuppressive therapy in 4 cases (5.5%). A total of 4 patients had past histories of ENT or esophageal cancers (5.3%) (1 SCC of the esophagus, 1 gastric cardia adenocarcinoma, 1 SCC of the vocal cords, and 1 SCC of the mouth floor) (● [Table 1](#)).

Endoscopic findings at diagnosis of esophageal squamous papilloma

Indications for endoscopy were dyspepsia in 19 cases (24.4%), followed by cirrhosis surveillance (15.4%), dysphagia (7.7%), and anemia (5.1%). Median distance between dental arch and ESP was 27 cm (IQR 16–40 cm). Most ESP were isolated (93.6%). Median size of ESP was 3 mm (IQR 1–20 mm). ESP numbering 17 were macroscopically pedicle (73.9%), most often soft (80%), and whitish (91.7%). Chromoendoscopy using Lugol iodine was performed in 3 cases. ESP-associated lesions were hiatal hernia in 12 patients, esophagitis in 11 patients, Barrett esophagus in 4 patients, and gastric ulcer in 3 patients. An echoendoscopy was performed in only 1 case. Only biopsies were performed in 27

	Patient n (%)	
Baseline clinical characteristics	Active smoker	30/66 (45.5%)
	Chronic alcoholism	13/66 (20%)
	Proton-pump inhibitors consumption	22/70 (31.4%)
	Immunosuppressive therapy	4/73 (5.5%)
	ENT or esophageal cancer	4/75 (5.3%)
	Anal or gynecological cancer	1/75 (1.3%)
	Other cancer	10/75 (13.3%)
Baseline endoscopic characteristics	Pedicle lesion	17/23 (73.9%)
	Sessile lesion	6/23 (26.1%)
	Soft lesion	4/5 (80%)
	Hardened lesion	0/5 (0%)
	Whitish lesion	11/12 (91.7%)
Endoscopic management	Biopsy	27/78 (35%)
	Excisional biopsy	47/78 (60%)
	Polypectomy	2/78 (2.6%)
	Mucosectomy	2/78 (2.6%)
	APC	3/78 (3.8%)

Table 1 Baseline characteristics.

Abbreviations: APC, argon plasma coagulation; ENT, ear nose throat.

Table 2 Endoscopic follow-up.

	Second endoscopy	Third endoscopy
Patient number	35	30
ESP number	15	3
Initial ESP	8	2
Recurrent ESP	3	0
Metachronous ESP	4	1

Abbreviation: ESP, esophageal squamous papilloma.

cases (34.5%). In the remaining cases, ESP were removed using excisional biopsies in 47 cases (60.3%), diathermic snare in 2 cases (2.6%), and mucosectomy technique in 2 patients (2.6%). Resection was completed by endoscopic argon plasma coagulation (APC) in 3 patients (3.8%). Endoscopic management was at the discretion of the endoscopist.

Follow-up data

Median follow-up was 21 months (IQR 0–91 mo). Median time between first and second endoscopy was 7 months (IQR 0.5–74 mo). Of the total number of patients, 35 (44.9%) had a second endoscopy and 15 of these had ESP (Table 2). There were 8 initial ESP not removed during the previous upper gastrointestinal endoscopy; 3 were recurrent ESP at the same location after initial endoscopic management; and 4 were metachronous lesions at a different location. Endoscopic treatments at a second upper gastrointestinal endoscopy were: excisional biopsy (n=6), biopsy (n=4), mucosectomy (n=1), and APC (n=5). A third endoscopy was undergone by 30 patients and 3 of these had ESP. Already known and not removed during the previous upper gastrointestinal endoscopy were 2 ESP, and 1 ESP was a metachronous lesion. Altogether, 15 lesions were adequately removed with a negative endoscopic follow-up.

After ESP endoscopic resection, 41 patients (52.6%) had no upper gastrointestinal endoscopy and/or no clinical follow-up. For every patient, the general practitioner was contacted directly by phone and asked about SCC occurrence. A second upper gastrointestinal endoscopy without ESP recurrence was reported in 1 patient, and 20 patients had no other upper gastrointestinal endoscopy during follow-up but did not develop cancer of the esophagus. For the 20 remaining patients, the general practitioner could not be contacted.

Human papillomavirus diagnosis

HPV detection was performed for only six lesions (7.7%). The techniques of detection were hybridization in five lesions and immunohistochemical (IHC) techniques in one case. No HPV was detected among the six lesions.

Dysplasia and squamous cell carcinoma occurrence

Low-grade dysplasia was found in two ESP. Of these two patients, one had a normal upper gastrointestinal endoscopy 6 months later, and the other one had developed a SCC of the esophagus with low-grade dysplasia at the same location as the previous ESP. Hence, prevalence of SCC associated with ESP was 1.3%. A second case of SCC was diagnosed at the same time as ESP, but at a different site. The first case of SCC concerned a 75-year-old man with alcoholic liver cirrhosis and a past history of smoking. The first upper gastrointestinal endoscopy was performed in 2002, and found a small lesion between 32 and 34 cm from the dental arch. Biopsies were performed and found an ESP with low-grade dys-

plasia. A control upper gastrointestinal endoscopy performed 1 month later with Lugol iodine chromoendoscopy found no ESP recurrence. A control endoscopy 2 years later found a 1-cm sessile lesion at the same place, which was a SCC treated with mucosectomy 1 month later. Histological analysis revealed a microinvasive SCC with high-grade dysplasia. Surveillance by endoscopy with Lugol iodine chromoendoscopy and biopsies showed no ESP and no cancer recurrence 1 month later. A new upper gastrointestinal endoscopy was performed 3 months later with Lugol iodine chromoendoscopy and showed two areas of nonstaining at 29 and 31 cm from the dental arch. Pathological examination revealed ESP with no HPV in situ hybridization. After endoscopic treatment, several surveillance gastroscopies were performed at 1 and 3 years and did not find ESP or SCC recurrence. The second case concerned a 75-year-old man presenting with a sudden dysphagia in March 2012. He was a heavy smoker with an alcohol consumption evaluated at 20 gm per day. A cervical and chest computed tomography (CT) scan showed a thickening of the thoracic esophagus. An endoscopic evaluation was performed and revealed a nonstenosis tumor involving one third of the circumference between 19 and 24 cm from the dental arch, and a likely ESP at 36 cm from the dental arch. Biopsies of the proximal lesion confirmed the diagnosis of SCC and those of the distal lesion found an ESP. Concerning the SCC of the esophagus, the patient had chemo-radiotherapy from July 2012 to September 2012. An upper gastrointestinal endoscopy performed in January 2013 found only a scar aspect of the third superior esophagus; all biopsies were negative. In this case, the ESP was distant from the SCC location.

Discussion

ESP prevalence has been reported in only a few series and has varied from 0.01 to 0.45% [2, 3, 5]. Most of these studies were European and mainly conducted in Italy [2, 20] (Table 3). In our study, the ESP prevalence was 0.01% and was similar to that found by Mosca et al. in Italy in 2001 [2]. The majority of our patients were middle-aged males. These data are consistent with previous reports [2, 5, 7]. Endoscopic characteristics of ESP were broadly similar to previous reports: single, small (3 mm), soft, and whitish, located at the distal esophagus [2, 5, 7, 12, 18]. ESP shape in our study was different, with more pedicle than sessile lesions [2, 5]. As in our study, ESP is usually removed endoscopically by using excisional biopsy or diathermic snare [2].

Pathogenesis of ESP is unknown. Two etiological factors have been proposed [2, 7, 21]. The first one is chronic mucosal irritation [5, 7, 12] due to chemical and mechanical factors such as reflux disease [6, 20], minor trauma [2] (endoscopic injection sclerotherapy [22], self-expanding metal stent [23]), alcohol consumption, or cigarette smoking [4]. In our study, dyspepsia was the main indication (24.4%) of the upper gastrointestinal endoscopy, and 22 patients were treated with proton-pump inhibitors. Peptic esophagitis and Barrett esophagus were found in 15 patients and were the main associated lesions visualized during upper gastrointestinal endoscopy. ESP location was mostly in the distal esophagus (27 cm, IQR 16–40 cm) as in most of the other studies [7]. These findings raise the possibility that gastrointestinal reflux is an etiological factor of ESP.

The second etiological factor may be HPV infection [2, 12]. Its relevance remains unclear [7]. HPV is an epitheliotropic virus that is sexually transmitted [12, 24, 25]. It belongs to a heterogeneous

Table 3 Prevalence of esophageal squamous papilloma (ESP) in the literature.

Author	Date of publication	Country	Upper endoscopy number	ESP number	ESP prevalence
Takeshita et al. [5]	2006	Japan	17 387	38	0.20%
Szántó et al. [38]	2005	Hungary	59 056	172	0.29%
Mosca et al. [2]	2001	Italy	7 618	9	0.01%
Talamini et al. [4]	2000	Italy	18 534	42	0.35%
Chang et al. [13]	1991	Finland	18 000	12	0.07%
Orłowska et al. [39]	1994	Poland	36 500	24	0.05%
Spinelli [40]	1989	Italy	11 932	9	0.07%
Sablich et al. [3]	1988	Italy	8 095	35	0.45%
Fernández-Rodríguez et al. [6]	1986	Spain	14 900	6	0.04%
Toet et al. [31]	1985	The Netherlands	3 100	4	0.12%
Franzin et al. [20]	1983	Italy	20 000	15	0.08%
Morini et al. [41]	1980	Italy	1 789	6	0.34%

Table 4 Prevalence and types of human papillomavirus (HPV).

Author	Date of publication	Country	Number of ESP	Prevalence of HPV (technique)	Subtypes of HPV
Bohn et al. [12]	2008	Mexico	19	85.7% (PCR), 87.5% (ISH)	6 and 11
Takeshita et al. [5]	2006	Japan	38	10.5%	NR
Szántó et al. [38]	2005	Hungary	26	46.2% (PCR)	High risk
Mosca et al. [2]	2001	Italy	9	0%	
Talamini et al. [4]	2000	Italy	42	4.8%	NR
Lavergne and de Villiers [33]	1999	Germany and Norway	11	63.6%	6
Woo and Yoon [43]	1996	Korea	10	10% (ISH)	NR
Poljak et al. [34]	1995	Poland	29	3.6%	6
Al-Sohaibani and Al-Rashed [44]	1995	Saudi Arabia	10	0% (IHC)	
Carr et al. [35]	1994	USA	17	4.3%	6 and 11
Odze et al. [7]	1993	Canada	33	50%	16
Chang et al. [13]	1991	Finland	12	0%	
Fontolliet et al. [42]	1991	Switzerland	33	18.1% (ISH)	31, 33, and 35

Abbreviations: ESP, esophageal squamous papilloma; IHC, immunohistochemical; ISH, in situ hybridization; NR, not reported; PCR, polymerase chain reaction.

Table 5 Squamous cell carcinoma (SCC) associated with esophageal squamous papilloma (ESP).

Author	Date of publication	Country	Sex	Age	Clinical signs	Maximal size	Histological diagnosis	HPV
Van Cutsem et al. [14]	1992	NR	Male	NR	NR	NR	NR	Positive
Waluga et al. [15]	2000	Poland	Male	28	Dysphagia and loss of weight	1.5 cm	Squamous papilloma	NR
Reynoso et al. [16]	2004	USA	Female	74	Occasional dysphagia	NR	Squamous papilloma and SCC in situ	Negative
Attila et al. [17]	2009	Canada	Male	70	Dysphagia and epigastralgia	NR	Papilloma	Negative
Borgulya et al. [19]	2011	Germany	Female	72	Progressive dysphagia and reflux	NR	Papilloma and SCC	NR
Donnellan et al. [18]	2012	Canada	Female	64	NR	2 cm	Papilloma and SCC on the biggest lesion	NR

Abbreviations: HPV, human papillomavirus; NR, not reported.

group of DNA viruses with many identified subtypes [2,26,27]. Two categories have been defined: low-risk HPV, which does not cause cancer (e.g., HPV subtypes 6 and 11), and high-risk or oncogenic HPV, which can cause cancer (e.g., HPV subtypes 16 and 18) [27]. It is established that HPV, in particular oncogenic subtypes 16 and 18, is responsible for the majority of cervical cancers

[28]. More recently, HPV infections have been found to cause cancer of the oropharynx [29, 30]. Syrjanen et al. first demonstrated an association of HPV with ESP in 1982 [21]. The prevalence of HPV-positive ESP varies between 0 and 87.5% in the literature [2, 12, 13] (Table 4). Some investigators have failed to identify HPV in ESP by either polymerase chain reaction (PCR) or in situ

hybridization (ISH) [2,3,13,31,32]. In the study by Takeshita et al., the ratio of HPV positive ESP was 10.5%, and the identified HPV subtype was type 6 [5]. Odze et al. found HPV in 50% of their ESP tested and subtype 16 was the most frequent [7]. HPV 6 and 11 are the main subtypes found to be associated with ESP [12, 33–35]. In our study, no HPV sequences were detected by using ISH or IHC methods. These methods are not the most sensitive to detect HPV [5]. Moreover, these results must be analyzed with caution because of the small sample size. The implications of other etiological factors [6,7,20], unknown HPV subtypes [2], and undetectable HPV subtypes due to low concentration [2, 16] have been proposed over the past years.

HPV-mediated progression from papilloma to carcinoma is well accepted in the cervix, anogenital region, and larynx [16]. The role of HPV in the esophageal carcinogenesis is still debated [36, 37]. ESP is usually considered a benign lesion [2,6,15]. There is much debate as to whether it is a premalignant lesion [2, 12, 15]. A better knowledge of the natural history is needed to assess the risk of SCC in case of ESP. The malignant potential of ESP has been described in six patients [14–19] (Table 5). The first case was reported by Van Cutsem et al. in 1992 [14]. The cases concern three females [16,18,19] and three males [14,15,17]. All SCC were developed on an esophageal papillomatosis [14–19]. Presence of HPV was negative in two out of three patients [14, 16, 17]. Surgical treatment was performed in most of the cases [15,16, 17]. There is no scientific evidence to support an increased risk of SCC and no consensus for endoscopic surveillance. In our study, two cases of low-grade dysplasia and two cases of SCC were observed. In one case, SCC was located at the same location as ESP with low-grade dysplasia that was described previously. Endoscopic treatment was successful and no HPV was detected. In the other case, SCC had arisen at a different site from ESP. Importantly, these SCC occurred in patients with a current or past history of alcoholic consumption or smoking, which are known to be risk factors for SCC [4]. From our findings, we can conclude that SCC prevalence was 1.3% in this case series. Our data support the fact that ESP may be associated with SCC and should require specific endoscopic survey [18].

No risk factor for cancer occurrence has been described in the literature; however, some authors have proposed that large or multiple ESP has malignant potential [16, 17]. In our study, low-grade dysplasia was found in two biopsies. In the first case, ESP was single and small (10 mm), and in the second case there were two ESP but their sizes were not specified. Only one SCC developed on ESP. This ESP was unique and its size was not specified on the endoscopy report. No risk factors for SCC-associated ESP could be studied because of the low prevalence of this event in our population.

Limitations of our study include its retrospective design, with no systematic endoscopic follow-up. This underscores the lack of consensus on endoscopic surveillance with different practices among endoscopists. Because only ESP confirmed histologically were collected and included, this could have underestimated its prevalence; some endoscopists overlook small lesions of the esophagus without performing any biopsy. Moreover, multiple biases such as the selected population, the indications of endoscopy, the experience of the operator, the decision to biopsy, and the endoscope used could have influenced ESP prevalence. However, more than 55 000 consecutive endoscopy reports have been reviewed, which allows a valid assessment of ESP prevalence. Because of the small number of SCC cases, different strategies for ESP (biopsy, excisional biopsy, polypectomy, etc.), and different

endoscopic surveillance, it was difficult to accurately investigate the risk of ESP-associated SCC in our population.

Conclusion

In conclusion, ESP prevalence in northeastern France is similar to that previously reported. No link with HPV was found, although this finding should be interpreted with caution due to the small-size tested samples. Endoscopists should be aware of potential malignant development in ESP, encouraging total removal and endoscopy surveillance. Large prospective cohorts are needed to further investigate the natural history of ESP.

Competing interests: None

Institutions

¹ Inserm U954 and Department of Hepatogastroenterology, Nancy University Hospital, Vandoeuvre-lès-Nancy, France

² Department of Pathology, Nancy University Hospital, Vandoeuvre-lès-Nancy, France

³ Department of Pathology, Metz Mercy Hospital, Metz, France

⁴ Department of Hepatogastroenterology, Besançon University Hospital, Besançon, France

⁵ Department of Pathology, Besançon University Hospital, Besançon, France

⁶ Inserm CIC-EC CIE6, Vandoeuvre-lès-Nancy, France and Department of Epidemiology and Clinical Evaluation, Nancy University Hospital, Vandoeuvre-lès-Nancy, France

⁷ Department of Hepatogastroenterology, Metz Mercy Hospital, Metz, France

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