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The primary task of WJCC is to rapidly publish high-quality Autobiography, Case Report, Clinical Case Conference (Clinicopathological Conference), Clinical Management, Diagnostic Advances, Editorial, Field of Vision, Frontier, Medical Ethics, Original Articles, Clinical Practice, Meta-Analysis, Minireviews, Review, Therapeutics Advances, and Topic Highlight, in the fields of allergy, anesthesiology, cardiace medicine, clinical genetics, clinical neurology, critical care, dentistry, dermatology, emergency medicine, endocrinology, family medicine, gastroenterology and hepatology, geriatrics and gerontology, hematology, immunology, infectious diseases, internal medicine, obstetrics and gynecology, oncology, ophthalmology, orthopedics, otolaryngology, pathology, pediatrics, peripheral vascular disease, psychiatry, radiology, rehabilitation, respiratory medicine, rheumatology, surgery, toxicology, transplantation, and urology and nephrology.

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RESUME

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II

April 16, 2017 | Volume 5 | Issue 4
Esophageal squamous papilloma lacks clear clinicopathological associations

Bilel Jideh, Martin Weltman, Yang Wu, Calvin H Y Chan

AIM
To determine the prevalence of esophageal squamous papillomas (ESPs) in a tertiary teaching hospital and to assess for any clinical associations, including relations with esophageal squamous cell carcinomas (SCCs).

METHODS
Data from a total of 6962 upper gastrointestinal endoscopies over a five year period were retrospectively obtained and analysed.

RESULTS
ESP was found in sixteen patients (0.23%). Eight (50%) patients had a high body mass index, seven (44%) had history of cigarette smoking. Reflux esophagitis was found in four (25%) patients. All ESPs were solitary with a mean endoscopic size of 3.8 mm and located in the mid to lower esophagus. Human papilloma virus (HPV) was tested in three (19%) patients and was negative. Esophageal SCC was found in seven patients (0.10%) during the same period. None of the specimens were tested for HPV, and none had associated papillomatous changes.

CONCLUSION
ESP is an uncommon tumour with unclear clinical associations and malignant potential.

Key words: Esophagus; Papilloma; Gastroesophageal reflux disease; Human papilloma virus; Squamous cell
Core tip: Esophageal squamous papilloma is a rare endoscopic finding with uncertain clinicopathological associations. They are usually asymptomatic and their aetiology is unknown. A high body mass index and a history of cigarette smoking, both risk factors for gastroesophageal reflux disease, were the most prevalent patient characteristic in our cohort with esophageal squamous papillomas (ESPs), however no definite associations can be established. None of the esophageal squamous cell carcinomas during the same study period progressed from ESP. Long-term longitudinal studies would be valuable to clarify clinical associations and the malignant potential of ESPs in order to establish appropriate management and surveillance strategies.

INTRODUCTION

Esophageal squamous papilloma (ESP) is a rare tumour of the esophagus with a reported prevalence of 0.01% to 0.45%[1-5]. Lesions rarely cause symptoms, and are usually an incidental finding on endoscopy. Typical endoscopic appearance is that of a small, less than 5mm sessile wart-like fleshy nodule (Figure 1) located predominantly in the middle to lower esophagus[1,2]. Larger lesions with a more raised, erythematous appearance have also been described[6]. The aetiology has not yet been established; proposed factors include chronic gastroesophageal reflux disease (GERD), human papilloma virus (HPV) and mucosal trauma[5,7-13]. The clinical associations and malignant potential of these lesions is unknown. Currently, there is no consensus on appropriate management and surveillance strategies for ESPs. In this study we aimed to identify the prevalence of ESPs in an Australian tertiary hospital cohort and to assess for possible clinical associations. We also attempted to assess its association with esophageal squamous cell carcinoma (SCC).

MATERIALS AND METHODS

All patients between June 2010 and March 2015 with ESP and esophageal SCC at a tertiary teaching hospital (Nepean Hospital) were retrospectively identified using the electronic pathology department database. Over this period a total of 6962 upper gastrointestinal endoscopies were performed. Patients were identified and their medical records and endoscopic reports were reviewed and analysed. The clinical information assessed included age, gender, body mass index (BMI), cigarette smoking history and use of acid suppression therapy [proton pump inhibitor (PPI)]. The endoscopic findings comprised the location, size and number of lesions; presence of a hiatus hernia, and presence of reflux esophagitis. Results of HPV testing were noted when performed; histology reports for patients with esophageal SCC during the same period were carefully perused for any papillomatous changes.

RESULTS

Among the 6962 upper gastrointestinal endoscopies performed over the study period, sixteen patients were found to have ESPs giving a prevalence of 0.23%. Patient characteristics are summarised in Table 1. The patients with ESPs comprised of ten (62.5%) females with mean age of 52 ± 16 (SD) years (range 33-83 years). Eight (50%) patients were overweight or obese having BMIs between 25-39; seven (44%) patients were cigarette smokers; three (19%) patients were using regular acid suppression therapy (PPIs). The indications for the endoscopic procedure varied with two of the sixteen patients having the procedure for investigation of GERD and one patient for dysphagia. One patient had evidence of a hiatus hernia, which was small. Reflux esophagitis was found in four (25%) of the sixteen patients. All patients had solitary papillomas; mean endoscopic size of lesions was 3.8 ± 3.2 (SD) mm (range 1-12 mm) and the mean size of histological specimens was 2.9 ± 1.5 (SD) mm (range 1-7 mm). All the papillomas were found in the middle to lower esophagus. Seven (44%) of them were biopsied; seven (44%) were removed with a polypectomy snare and details of the remaining two were not documented. Patients that had lesions biopsied did not have a repeat gastroscopy within the same study period for definitive resection of the lesion. Two (13%) patients had repeat endoscopies following endoscopic snare resection within the same study period and there was no evidence of papilloma recurrence. Helicobacter
Table 1  Patient characteristics with esophageal squamous papilloma

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex (M/F)</th>
<th>Cigarette smoking (Y/N)</th>
<th>BMI</th>
<th>PPI use (Y/N)</th>
<th>Indication for endoscopy</th>
<th>Location of ESP from incisors</th>
<th>No. of ESPs</th>
<th>Endoscopic size of ESP (mm)</th>
<th>Histological size of ESP specimen (mm)</th>
<th>Hiatus hernia (Y/N)</th>
<th>Reflux esophagitis (Y/N)</th>
<th>Helicobacter pylori (positive/ negative)</th>
<th>HPV test (positive/ negative)</th>
<th>Method of ESP resection/sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>F</td>
<td>Y</td>
<td>20</td>
<td>N</td>
<td>Upper GI bleed</td>
<td>Distal</td>
<td>1</td>
<td>Small</td>
<td>2</td>
<td>N</td>
<td>N</td>
<td>Negative</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>85</td>
<td>F</td>
<td>N</td>
<td>19</td>
<td>Y</td>
<td>Dysphagia</td>
<td>20</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>N</td>
<td>Y</td>
<td>Negative</td>
<td>n/a</td>
<td>Snare polypectomy</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>M</td>
<td>N</td>
<td>24</td>
<td>N</td>
<td>Abdominal pain</td>
<td>42</td>
<td>1</td>
<td>Small</td>
<td>4</td>
<td>N</td>
<td>N</td>
<td>Negative</td>
<td>n/a</td>
<td>Snare polypectomy</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>M</td>
<td>N</td>
<td>36</td>
<td>N</td>
<td>Abdominal pain</td>
<td>39</td>
<td>1</td>
<td>Small</td>
<td>5</td>
<td>N</td>
<td>N</td>
<td>n/a</td>
<td>n/a</td>
<td>Hot biopsy</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>F</td>
<td>N</td>
<td>34</td>
<td>Y</td>
<td>GERD</td>
<td>33</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>Y (3 cm)</td>
<td>N</td>
<td>Y</td>
<td>Negative</td>
<td>n/a</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>M</td>
<td>N</td>
<td>30</td>
<td>N</td>
<td>GERD</td>
<td>38</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>N</td>
<td>Y</td>
<td>Negative</td>
<td>Negative</td>
<td>Snare polypectomy</td>
</tr>
<tr>
<td>7</td>
<td>39</td>
<td>F</td>
<td>N</td>
<td>24</td>
<td>N</td>
<td>Bloating</td>
<td>28</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>N</td>
<td>N</td>
<td>Negative</td>
<td>n/a</td>
<td>Biopsy</td>
</tr>
<tr>
<td>8</td>
<td>33</td>
<td>F</td>
<td>N</td>
<td>21</td>
<td>N</td>
<td>Anemia</td>
<td>27</td>
<td>1</td>
<td>Small</td>
<td>3</td>
<td>N</td>
<td>N</td>
<td>Negative</td>
<td>n/a</td>
<td>Snare polypectomy</td>
</tr>
<tr>
<td>9</td>
<td>49</td>
<td>M</td>
<td>Y</td>
<td>30</td>
<td>N</td>
<td>Abdominal pain</td>
<td>Distal</td>
<td>1</td>
<td>Small</td>
<td>3</td>
<td>N</td>
<td>N</td>
<td>Negative</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>10</td>
<td>37</td>
<td>N</td>
<td>24</td>
<td>F</td>
<td>N</td>
<td>Family history of gastric cancer</td>
<td>32</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>N</td>
<td>N</td>
<td>Negative</td>
<td>Negative</td>
<td>Biopsy</td>
</tr>
<tr>
<td>11</td>
<td>54</td>
<td>F</td>
<td>Y</td>
<td>23</td>
<td>N</td>
<td>Variceal screen</td>
<td>35</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>N</td>
<td>N</td>
<td>n/a</td>
<td>n/a</td>
<td>Biopsy</td>
</tr>
<tr>
<td>12</td>
<td>39</td>
<td>M</td>
<td>Y</td>
<td>34</td>
<td>N</td>
<td>Abdominal pain</td>
<td>39</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>N</td>
<td>N</td>
<td>Negative</td>
<td>n/a</td>
<td>Biopsy</td>
</tr>
<tr>
<td>13</td>
<td>81</td>
<td>F</td>
<td>Y</td>
<td>28</td>
<td>N</td>
<td>Diarrhoea</td>
<td>25</td>
<td>1</td>
<td>Small</td>
<td>2</td>
<td>N</td>
<td>N</td>
<td>Negative</td>
<td>n/a</td>
<td>Biopsy</td>
</tr>
<tr>
<td>14</td>
<td>45</td>
<td>M</td>
<td>Y</td>
<td>31</td>
<td>N</td>
<td>Abdominal pain</td>
<td>25</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>N</td>
<td>Negative</td>
<td>n/a</td>
<td>n/a</td>
<td>Snare polypectomy</td>
</tr>
<tr>
<td>15</td>
<td>38</td>
<td>F</td>
<td>Y</td>
<td>N/a</td>
<td>N</td>
<td>Bloating, abdominal pain</td>
<td>25</td>
<td>1</td>
<td>n/a</td>
<td>1</td>
<td>n/a</td>
<td>n/a</td>
<td>Negative</td>
<td>n/a</td>
<td>Biopsy</td>
</tr>
<tr>
<td>16</td>
<td>41</td>
<td>F</td>
<td>N</td>
<td>27</td>
<td>N</td>
<td>Abdominal pain</td>
<td>35</td>
<td>1</td>
<td>12</td>
<td>7</td>
<td>N</td>
<td>N</td>
<td>Negative</td>
<td>Negative</td>
<td>Snare polypectomy</td>
</tr>
</tbody>
</table>

BMI: Body mass index; PPI: Proton pump inhibitor; CRC: Colorectal cancer; GERD: Gastroesophageal reflux disease; HPV: Human papilloma virus; n/a: Not available; ESP: Esophageal squamous papilloma; M: Male; F: Female; Y: Yes; N: No.

pylori was not evident on microscopy in any of the patients. HPV testing was performed on only three patient and all were negative.

Seven patients were observed to have esophageal SCC in the same period, giving a prevalence of 0.10%. Patient characteristics are summarised in Table 2. The group comprised of five (71%) females and with mean age of 71 ± 15 (SD) years (range 50-92 years). Two (29%) patients were overweight, one (14%) patient was underweight with a BMI of 18, and the remaining four (57%) patients had BMIs within healthy range. Three (43%) patients were cigarette smokers. HPV was not tested on any of the specimens. There were no reported papillomatous changes on histological examination.

**DISCUSSION**

In our study the prevalence of ESPs was 0.23% which is consistent with previously published studies[1-5]. The majority of the patients were middle-aged also similar to previous studies in the literature. The female predominance in our cohort is an inconsistent observation compared to previous reports on ESPs[1,7,8,14]. Although GERD has been postulated to be a factor in the aetiology of ESP[5,9,18], only two (12.5%) of our study patients underwent upper endoscopy for GERD. However, we cannot ascertain with any certainty that the other patients did not have GERD. This is supported by the finding of reflux esophagitis in two (12.5%) patients who had the procedure for an indication other than GERD (one for the investigation of anaemia and the other for dysphagia, Table 1).

A high BMI was the most prevalent of the assessed patient characteristics in our study with 50% of patients having a BMI in the overweight-obese range. An association between BMI and ESPs has not been previously demonstrated. However, an elevated BMI is an established risk factor for GERD[16]. The second most prevalent clinical characteristic in the studied patients was a history of cigarette smoking found in seven (44%) patients. Cigarette smoking was not found to be associated with ESP in a previous study[14], but similar to a high BMI, cigarette smoking is a risk factor for the development of GERD[17]. Hiatus hernia is another risk factor for GERD which was observed in one (6.25%) patient in our cohort and it was small-sized.
The mean size and location of ESPs were consistent with previous observations\(^1,2\). They were all solitary and appeared as rounded well delineated sessile wart-like lesions (Figure 1) as traditionally described. Multiple lesions have been observed in some studies\(^3,8,20\).

ESPs were not all removed with therapeutic intent, which is the general recommendation, despite the ambiguity about their malignant potential\(^2,21\). Histological diagnosis remains important due to the endoscopic resemblance to other pathologies including glycogenic acanthosis, verrucoid border of SCC, and verrucous carcinoma\(^2,21\). Case reports of alternative ablative techniques including radiofrequency ablation have been described\(^22\). Recurrence after definitive endoscopic removal is thought to be low\(^2\). This was true for the two patients in our series that had repeat gastroscopies within the same study period and no evidence of papilloma recurrence was found. It is unclear whether other lesions not endoscopically removed were not followed due to lack of well-established management and surveillance guidelines.

Three patients in our cohort had testing for HPV (serotype 16) in the ESP specimen and the results were all negative. Although HPV infection is a proposed aetiological factor since the demonstration of HPV antigens in ESPs\(^2,21\), the extent of the contribution is controversial and most reviews and meta-analyses have addressed this relation. Several systematic reviews and meta-analyses have addressed this relation, concluded that further studies are needed to clarify the association.

This study has several limitations. The study is a retrospective assessment of results which can lead to the possibility of inaccurate and incomplete data. It was performed in a single, tertiary-care institution which can introduce a selection bias. Most patients with ESP did not have follow-up gastroscopies to assess for ESP clearance or recurrence. Finally, the analysis of results is largely descriptive given the low prevalence and small absolute numbers of patients with ESPs making it difficult to draw conclusions on any clinical associations.

In summary, ESPs remains a rare endoscopic finding with uncertain clinicopathological associations. They are usually asymptomatic and their aetiology is unknown. Whilst a high BMI and a history of cigarette smoking, both risk factors for GERD, were the most prevalent patient characteristic in our cohort with ESP, no definite associations can be established. None of the esophageal SCCs during the same study period progressed from ESP. Long-term longitudinal studies would be valuable to clarify clinical associations and the malignant potential of ESPs in order to establish appropriate management and surveillance strategies.

**COMMENTS**

**Background**

Esophageal squamous papilloma (ESP) is a rare tumour with a reported prevalence of 0.01% to 0.45%. It is usually asymptomatic and discovered incidentally on upper endoscopy. The aetiology, clinical associations along with its malignant potential are unknown. The aim of this study was to determine the prevalence of ESps in a tertiary teaching hospital and to assess for any clinical associations, including relations with esophageal squamous cell carcinomas (SCCs).

**Research frontiers**

There are limited studies on ESPs. Gastroesophageal reflux disease (GERD),
human papilloma virus (HPV) and mucosal trauma are proposed aetiological factors. No studies have assessed associations between ESPs and SCCs.

Innovations and breakthroughs
This study identified certain clinical features to be prevalent in patients with ESP including high body mass index and cigarette smoking, which have not been previously described. Also, the SCCs in the study period did not seem to progress from ESPs which may suggest ESP are benign.

Applications
This study contributes to the body of hypotheses surrounding ESP. Large longitudinal studies are required to help clarify clinicopathological associations of ESPs and their malignancy potential in order to establish appropriate management and surveillance strategies.

Peer-review
The authors aimed to identify the prevalence of ESPs in an Australian tertiary hospital cohort and to assess for possible clinical associations and to assess its association with esophageal SCC whose large data from a total of 6962 upper gastrointestinal endoscopies. Well written, well balanced.

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