

## CASE REPORT

# Squamous papilloma of the proximal oesophagus associated with an inlet patch: a potential aetiological relationship

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### Abstract

Squamous papillomas are rare benign lesions that can be found in the oesophagus. It has been theorised that irritation of the esophageal mucosa leads to squamous papilloma formation. There is evidence to suggest that squamous papillomas of the distal oesophagus are related to irritation due to reflux of gastric acid. In this case report, we describe for the first time a squamous papilloma of the upper oesophagus located just distal to an inlet patch. Inlet patches consist of gastric mucosa located in the proximal oesophagus. They are capable of producing acid. This case raises the possibility that just as squamous papillomas of the distal oesophagus may be related to acid exposure from the reflux of gastric acid, squamous papillomas of the proximal oesophagus may be related to acid exposure from the locally-produced acid of inlet patches.

**Keywords:** Papilloma, oesophagus, gastric mucosa, aetiology, gastric acid

### INTRODUCTION

Squamous papillomas are rare, benign lesions that can be found in the oesophagus.<sup>1,2</sup> The majority of them are located in the distal oesophagus.<sup>3,4</sup> As they are often associated with gastroesophageal reflux disease (GERD), it has been suggested that acid exposure leads to irritation of the lower esophageal mucosa which then promotes squamous papilloma formation.<sup>4</sup>

The cause of squamous papillomas in the proximal oesophagus, however, remains less clear. Studies evaluating for the presence of human papilloma viruses, which have been suggested as a potential cause, have been inconclusive.<sup>3,5,6</sup> In this case report, we describe for the first time a squamous papilloma of the upper oesophagus located near an inlet patch. Inlet patches, also known as heterotrophic gastric mucosa, are located in the proximal oesophagus and are capable of producing acid.<sup>7-9</sup>

### CASE REPORT

A 65-year-old man complained of episodes of non-cardiac chest pain. His past medical history was significant for ischemic heart disease and congestive heart failure. Laboratory studies

were normal with no signs of anemia, as was an electrocardiogram. As part of his evaluation, he underwent a computerised tomography scan of the chest which showed possible esophageal wall thickening. He was therefore referred for gastroenterology evaluation. He denied any heartburn, odynophagia, or dysphagia.

On upper endoscopy, in the very proximal oesophagus, an oval 10 mm patch of mucosa consistent with an inlet patch was identified (FIG. 1A). This diagnosis was confirmed by biopsy (FIG. 1B). A few centimetres distal to the inlet patch, a 2 mm polyp (FIG. 1C) was removed by biopsy forceps. Histological examination confirmed a squamous papilloma (FIG. 2). Immunohistochemical staining for p16 was negative. The remainder of the oesophagus was normal, with no signs of inflammation, oesophagitis, or a hiatal hernia. He has not returned to our gastroenterology clinic for further evaluation since the endoscopy was performed.

### DISCUSSION

Inlet patches are small areas of gastric mucosa located in the upper, cervical oesophagus.<sup>7,8</sup> Their aetiology remains unclear. Traditionally

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FIG. 1: (A) Endoscopic evaluation revealed an oval-shaped patch of tan mucosa (10 x 4 mm in size) consistent with an inlet patch. (B) Histological examination revealed gastric mucosa consistent with an inlet patch. (C) Endoscopic evaluation revealed a 2 mm exophytic polyp in the proximal oesophagus.

they were felt to be asymptomatic, incidental findings. However, over the years, studies have shown that inlet patches can cause symptoms and lead to complications.<sup>7,8</sup> Studies have shown that

inlet patches can produce acid.<sup>9</sup> This can lead to dysphagia from stricture or web formation.<sup>10,11</sup> Additionally, a correlation between inlet patches and throat symptoms, especially globus sensation

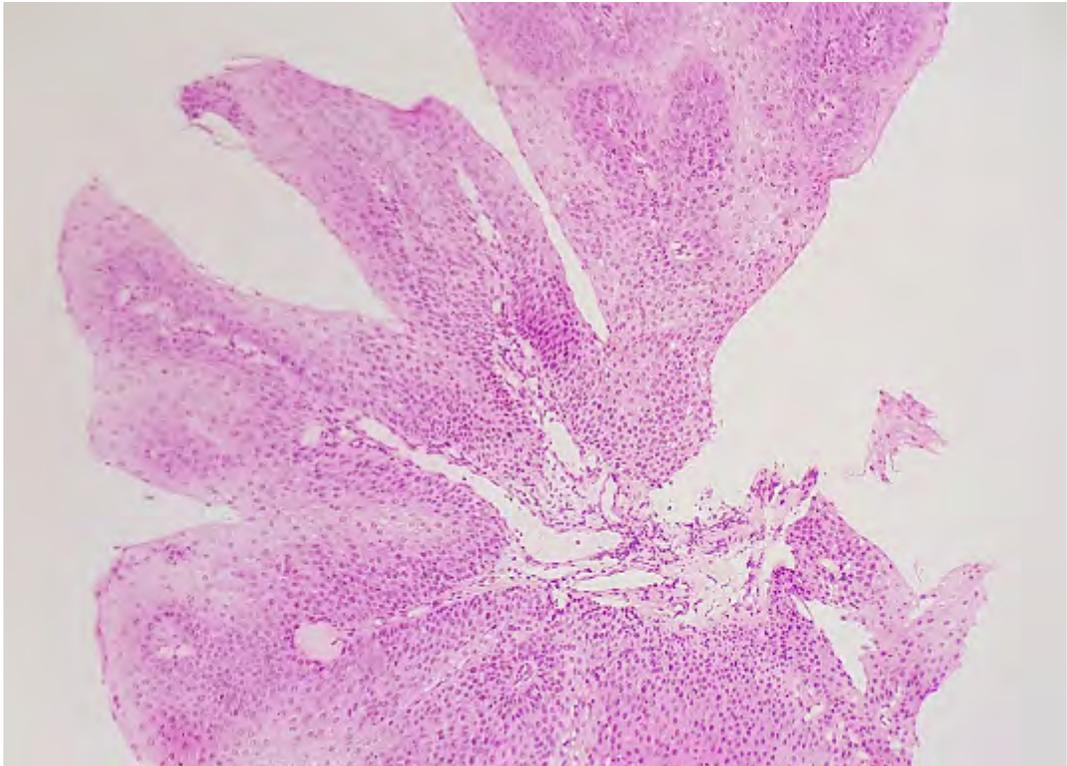


FIG. 2: Histological examination revealed papillary proliferation of non-dysplastic squamous epithelium with fibrovascular cores of lamina propria consistent with a squamous papilloma.

and throat discomfort, has been established based on studies in which the inlet patch has been endoscopically ablated and the throat symptoms subsequently resolve.<sup>12,13</sup>

Oesophageal adenocarcinoma is typically found in the distal oesophagus as it is related to GERD, acid exposure, and Barrett's oesophagus. In the rare cases when it is found proximally, some case reports suggested a relationship to inlet patches.<sup>7,14</sup> This relationship was subsequently confirmed in a study of 398 oesophageal adenocarcinomas.<sup>14</sup> That study found an inlet patch in all 3 (100%) proximal adenocarcinomas, but in just 2 of 395 (0.5%) from the middle or distal oesophagus.

Squamous papillomas of the oesophagus are rare, benign epithelial polyps with an incidence of 0.01-0.45%, and more commonly found in middle-aged men.<sup>1</sup> They are usually incidentally noted on upper endoscopy and rarely cause symptoms. They typically appear as whitish-pink, wart-like exophytic lesions with a size between 2-8 mm.<sup>1,2</sup>

The aetiology of oesophageal squamous papillomas remains unclear.<sup>1,3,15</sup> The most commonly accepted theory is that they arise as a hyper-regenerative response to various mucosal irritants.<sup>3,4</sup> These may include gastroesophageal reflux, trauma from a nasogastric tube or oesophageal dilator, and chemicals. As studies have shown that the majority of squamous papillomas occur in the distal oesophagus and are often noted together with the presence of hiatal hernias or reflux oesophagitis, this has led to GERD being felt to be a key contributor to the formation of these lesions.<sup>4</sup>

An alternative theory proposes a viral aetiology. Animals have shown similar lesions when infected with papilloma viruses.<sup>16</sup> In human studies, some researchers have reported human papilloma virus (HPV) DNA being found within squamous papilloma lesions.<sup>3,6</sup> However, this has not been collaborated in other studies,<sup>5,17</sup> and the association between HPV and squamous papilloma of the oesophagus remains unproven and controversial.<sup>15</sup>

In our case, we performed p16 immunohistochemistry to evaluate for HPV, which returned a negative result. p16, a protein product of a tumour suppressor gene, is considered a surrogate marker for HPV as it is overexpressed in several HPV-related malignancies.<sup>18,19</sup> Definitions of what constitutes a positive p16 stain differ in the literature with  $\geq 70\%$  staining appearing to have the highest sensitivity.<sup>19</sup>

No prior case reports or studies have evaluated if there is a relationship between inlet patches and squamous papillomas. To investigate this hypothesis, we attempted to compare the prevalence of inlet patches in patients with proximal squamous papillomas as compared to those with more distal squamous papillomas. Over a nine-year period, we found that 14 oesophageal squamous papillomas were endoscopically removed at our institution. Similar to other studies, the majority were in the distal oesophagus (nine, 64%), with two in the mid-oesophagus and three in the proximal oesophagus. We reviewed the endoscopy reports of these cases to evaluate if any were associated with an inlet patch. Unfortunately, other than the case presented above, none of the other cases had an inlet patch described in the procedure report.

While this would appear to disprove our theory, inlet patches are notoriously underrecognised on endoscopy as they are located just below the upper oesophageal sphincter, an area that is difficult to visualise.<sup>7</sup> Studies have shown that endoscopists frequently miss them and are ten times more likely to identify them when specifically looking for them.<sup>20</sup> Techniques such as narrow-band imaging also help to identify them. Therefore, the fact that they were not reported in cases of proximal oesophageal squamous papillomas may represent the fact that they are often not seen or reported by endoscopists. To optimally evaluate if this relationship exists, a prospective study would likely be needed, although that may be difficult given the low incidence of squamous papillomas.

In conclusion, we present the first case of a man found to have an inlet patch in the very proximal oesophagus, followed by a squamous papilloma just distal to it. While not proving a relationship, this case does raise the possibility that acid production from an inlet patch may play a role in the formation of proximal oesophageal squamous papillomas. Further studies on this potential causative relationship are warranted.

*Authors' contribution:* DC: concept of study, data collection, writing manuscript. RY: data collection, pathology interpretation. HS: editing manuscript, supervision of study.

*Conflict of interest:* The authors declare no conflict of interest.

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