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BRIEF REPORT

A first case of primary gastric verrucous carcinoma with isolated squamous epithelium in the stomach

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Abstract

Primary gastric squamous cell carcinoma (SCC) is a rare histological subtype of gastric cancer. Here, we report the first case of primary gastric verrucous carcinoma (VC), a well-differentiated variant of SCC. Gastroscopy revealed a papillary polypoid lesion at the posterior wall of the upper gastric body and isolated squamous epithelium at the greater curvature of the fornix in a 78-year-old woman. Endoscopic submucosal dissection was performed. Microscopically, the lesion comprised very well-differentiated squamous epithelium with minimal atypia and exhibited coarse papillary structure and bulbous epithelial downgrowth with submucosal invasion. Conventional SCC or adenocarcinoma components were not included, and the lesion was surrounded by the metaplastic intestinal mucosa. Human papillomavirus infection was not detected. Although the pathogenesis of primary gastric SCC remains controversial, here, the disease is suggested as having originated from squamous epithelium. Knowledge of primary gastric VC and difficulty in diagnosing it using surface biopsy is necessary.

Keywords Gastric cancer · Squamous cell carcinoma · Verrucous carcinoma · Squamous metaplasia

Introduction

Primary gastric squamous cell carcinoma (SCC) is a rare histological subtype of gastric cancer considering background mucosa covered by glandular epithelium. Its pathogenesis is still controversial, but there are several hypotheses [1, 2]. Verrucous carcinoma (VC) is a rare, well-differentiated variant of SCC characterized by exophytic papillary structure, sharply circumscribed deep margin, minimal cytological atypia, low metastatic potential, and good prognosis [3, 4]. VC is most commonly located in the oral cavity, and only a few cases in the tubal gut originating from the esophagus have been reported [3–6]. Here, we report the first case of primary gastric VC, an important one to understand the pathogenesis of the disease as it presents with concomitant squamous epithelium in the stomach.

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Case presentation

A 78-year-old woman presented to our hospital with minimal hemoptysis after a papillary polypoid lesion was identified by gastroscopy. She had a history of hypertension and surgery for uterine leiomyoma and appendicitis. She never smoked and drank one glass of wine per day. There was no family history of cancer. The physical examination results were unremarkable, and laboratory data and tumor markers, including CEA, SCC, and CYFRA, were within normal limits. Gastroscopy revealed a papillary polypoid lesion at the posterior wall of the upper gastric body (Fig. 1a). This lesion was stained with Lugol's iodine solution, indicating that it was covered in squamous epithelium. The stain also identified flat squamous epithelium at the greater curvature of the fornix (Fig. 1b) and posterior wall of the cardia (Fig. 1c). These flat squamous epithelia separated from the lesion, although the flat squamous epithelium at the posterior wall continued to the esophageal squamous epithelium. The background gastric mucosa showed severe atrophy, and the fundic gland mucosa could

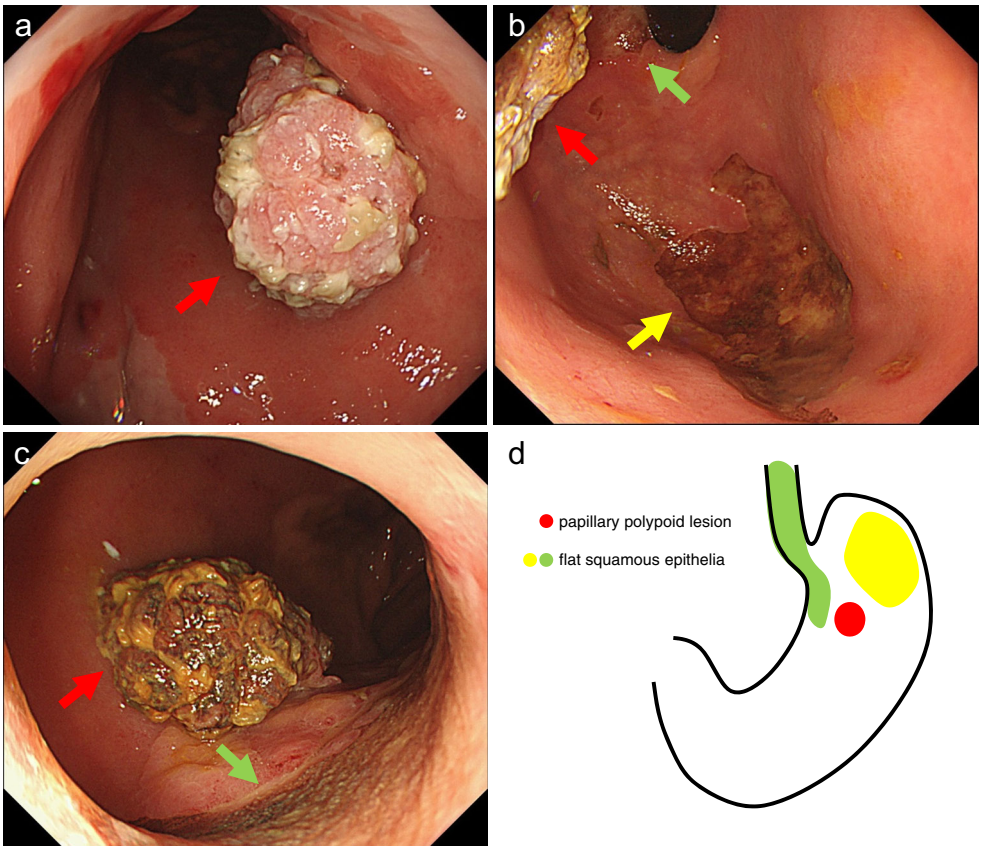

Fig. 1 **a** Gastroscopy revealed a papillary polypoid lesion at the posterior wall of the upper gastric body (red arrow). **b** Flat squamous epithelia stained by Lugol's iodine solution were identified at the greater curvature of the fornix (yellow arrow) and posterior wall of the cardia (green arrow). The former was separated from the lesion and esophageal squamous epithelium. **c** The latter was also separated from the lesion, but continued to the esophageal squamous epithelium. **d** The schema of endoscopic findings

not be detected. The endoscopic finding of the esophagus was normal. Figure 1d shows a scheme of the endoscopic findings. An endoscopic ultrasound detected the absence of submucosal invasion, and a computed tomography scan revealed no lymph node or distant metastases. A biopsy of the lesion revealed an atypical squamous epithelium, in which it was difficult to distinguish between neoplastic and reactive change, and the flat squamous epithelium at the greater curvature of the fornix was squamous epithelium without atypia. An endoscopic submucosal dissection was performed for a therapeutic diagnosis.

Macroscopically, the lesion was 25 × 25 mm in size, well-circumscribed, and of rough, brown surface (Fig. 2). A loupe view of the cross section showed coarse papillary structure and bulbous downward elongation of the epithelial rete ridges (Fig. 3a). Microscopically, the lesion consisted of thick, keratinizing, and well-differentiated squamous epithelium, and some parts contained hyperkeratosis and/or parakeratosis (Fig. 3b). Overall, nuclear atypia was minimal (Fig. 3c), and mitotic figures were rare. The stroma interface was generally smooth, but solid nest invasions were scarcely observed (Fig. 3d). Erosion was scattered and neutrophils infiltrated the entire lesion. Some bacteria and *Candida* cells were attached to the surface of the lesion, but *Helicobacter pylori* was absent in both the lesion and the background gastric mucosa. Koilocytosis was not detected on the surface of the lesion. The background gastric mucosa showed severe atrophy similar to the endoscopic findings. Intestinal metaplasia was observed in most parts, and the fundic gland mucosa was focally concentrated. The lesion was also surrounded by the metaplastic intestinal mucosa (Fig. 3e), and the contiguity of the non-neoplastic squamous epithelium was not observed. No evidence of recurrence or metastasis was detected 1.5 years after the endoscopic treatment.

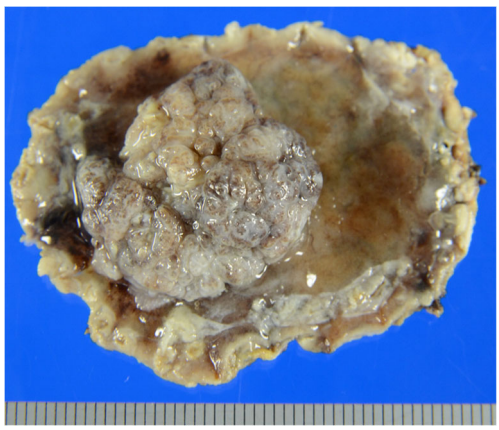

Fig. 2 Macroscopically, the lesion was 25 × 25 mm in size, well-circumscribed, and of a rough, brown surface

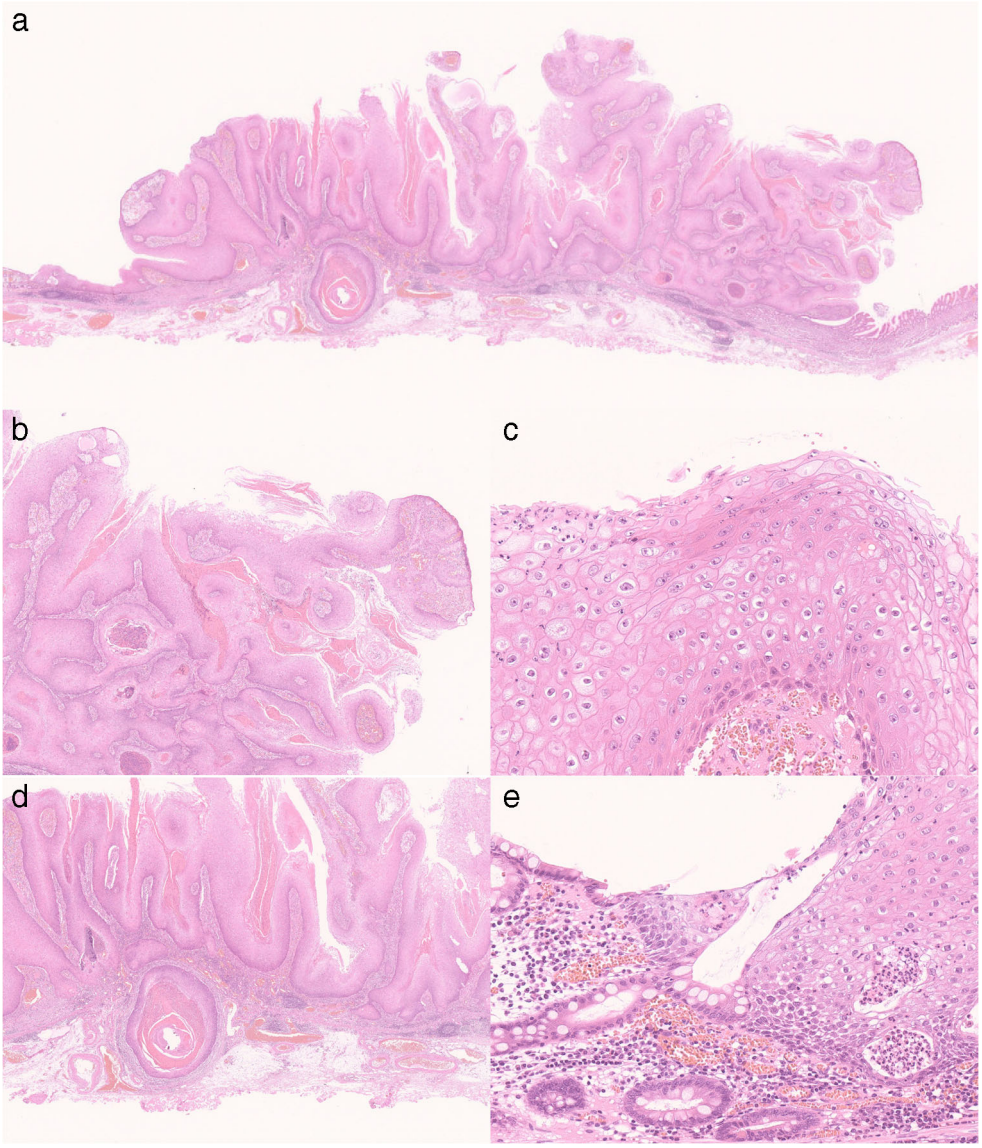

Fig. 3 **a** A loupe image showed coarse papillary structure and bulbous elongation of the epithelial rete ridges. **b** Microscopically, the lesion consisted of a thick, well-differentiated squamous epithelium. **c** Overall, nuclear atypia was minimal. **d** The stroma interface was generally smooth, but there were a few solid nest invasions observed. **e** Most areas of the lesion were surrounded by the metaplastic intestinal mucosa

These histological findings were similar to VC in other organs, such as the skin and oral cavity. Other histological subtypes accompanying conventional SCC or adenocarcinoma were not included, although the specimen was sliced at intervals of approximately 3 mm. The tumor invaded the surface submucosal layer with only a few lymphovascular tumor invasions. We performed immunohistochemical and cytogenetic analyses to detect human papillomavirus (HPV) infection. Immunohistochemically, anti-HPV antibody (clone 4C4, 1:15; Novocastra, Newcastle, UK) was negative, and p16 (clone E6H4, 1:4; Roche Diagnostics K. K., Tokyo, Japan) was weakly and focally positive. In situ hybridization was performed using an HPV III High Risk Probe (Roche Diagnostics K. K.) to detect high-risk HPV (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66) and an HPV Low Risk Probe (Roche. Diagnostics K. K.) to detect low-risk HPV (types 6 and 11), but both were negative. These findings suggest no association with HPV infection.

Discussion

Less than 100 cases of primary gastric SCC have been reported [1, 2], many of which are single case reports, and its incidence ranges from 0.04 to 0.7% [1]. According to Wakabayashi et al., a review of 56 cases of primary gastric SCC in Japan showed that the mean age of diagnosis was 64.7 ± 1.7 years (ranging from 29 to 81 years), and the male-to-female ratio was 44:12 [2]. The most common location was the upper third of the stomach (57%), and the most frequent class was type 2 (43%). In more than 50% of cases, the depth of invasion was T4a (14%) or T4b (45%), and surgical curability was poor. Although not all cases in the English literature mention tumor differentiation, to our knowledge, neither primary gastric VC nor gastric cancer with a VC component has been reported. Therefore, this is the first case report of its kind. VC is a rare, well-differentiated variant of SCC first reported by Ackermann et al. in 1948 [7]. Most

commonly located in the oral cavity, it also occurs throughout the body covered in squamous epithelium in various sites of the head and neck, esophagus, genitalia, and skin [3–6]. VC is histologically characterized by an exophytic papillary structure consisting of thick, well-differentiated squamous epithelium, bulbous elongated rete ridges, sharply circumscribed deep margin, and minimal cytological atypia [3, 4]. It has been surmised that VC has insufficient metastatic potential and shows a good prognosis, although it can destroy adjacent tissue and local recurrence is often observed [3, 4]. The etiology of VC is still unclear. In head and neck cases, an association has been found between VC and tobacco smoking [3, 8]. Furthermore, HPV infection has been identified in some cases of VC [3, 9]. These etiologies, however, did not apply here. Part of VC has a conventional SCC component characterized by higher degrees of cytologic atypia and an infiltrative margin, also called hybrid verrucous-squamous carcinoma or hybrid tumors [8, 10]. These cases should be treated as comparably staged conventional SCC due to a higher tendency of local recurrence and a distinct metastatic potential [8, 10]. As described in other organs [5], the diagnosis of VC by surface biopsy is very difficult due to its benign cytological appearance and ambiguity of invasion. Deeper biopsy or therapeutic endoscopic treatment may be required for diagnosis.

Squamous epithelium does not exist in the gastric mucosa in nature, and the pathogenesis of primary gastric SCC is still controversial. The three main theories include as follows: (1) squamous differentiation in a preexisting adenocarcinoma, (2) origination from a metaplastic squamous epithelium or nests of ectopic squamous epithelium, and (3) origination from undifferentiated multipotent stem cells [1, 2]. Mori et al. concluded that adenocarcinoma occurs first and later differentiates into adenosquamous carcinoma (ASC) by squamous metaplasia. They hypothesize that some cases of SCC include ASC with predominant SCC components based on the detection of small foci in the adenocarcinoma through reexamination of slices initially diagnosed as pure SCC and the nonexistence of ASC in early gastric cancers [11]. Recently, however, an early gastric cancer consisting of pure SCC as in the present case was reported, and these two instances cannot be explained by current theories [12].

The existence of squamous epithelium is not widely recognized. Different terms such as squamous metaplasia and ectopic squamous epithelium have been used to describe squamous epithelium, but their distinctions were obscure [1, 2]. Oide et al. reviewed 11 cases of gastric squamous metaplasia and indicated its tendency to occur in the lesser curvature of the cardia in elderly individuals. Five of the 11 cases presented with SCC [12, 13]. These cases suggest that primary gastric SCC is derived from a metaplastic squamous epithelium. Chronic inflammation, mucosal injury, and repair have been considered to be associated with the gastric squamous metaplasia, but there is a wide range of conditions that might be associated with gastric squamous metaplasia right from common conditions, including *Helicobacter pylori*–associated gastritis or peptic ulcers, to special conditions, including corrosive acid burns, chronic syphilitic gastritis, or gastric tuberculosis, and in some cases, there are no causal conditions in the stomach [13, 14]. At least, the present case had no special conditions, but the pathogenesis of the gastric squamous metaplasia remains unclear.

Some authors have considered that undifferentiated multipotent stem cells directly differentiate into SCC, but it is difficult to prove that the cancer originates from stem cells [1, 15].

In this case, there is no direct evidence for the pathogenesis due to the lack of an adenocarcinoma component and the contiguity of non-neoplastic squamous epithelium. However, considering the low possibility that adenocarcinoma transformed into well-differentiated SCC, it being an early cancer, and the existence of isolated squamous epithelia in the stomach, origination from those squamous epithelia is plausible.

In conclusion, we have reported the first case of primary gastric VC. Origination from squamous epithelium was considered, but further study regarding the pathogenesis of primary gastric SCC is necessary. Knowledge of primary gastric VC and difficulty in diagnosing it using surface biopsy is necessary. During diagnosis, pathologists should pay attention to the coexistence of a conventional SCC component.

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Authors' contributions RY drafted the manuscript. RS and KM provided clinical details. SH, NN, TM, and TH evaluated the histological findings. SH edited and reviewed the manuscript. All authors gave final approval for publication.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from the patient included in the study.

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