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Case Report

Sporadic fundic gland polyp with high-grade dysplasia: report of a case and review of the literature

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Abstract: Frequent *CTNNB1* and *APC* mutations in sporadic and syndromic fundic gland polyps, respectively, support that they are likely to be neoplastic. Fundic gland polyps with dysplasia have been revealed to typically have *APC* mutations even in sporadic ones. Dysplasia occurring in fundic gland polyp is much more likely to be associated with patients with familial adenomatous polyposis (FAP) than those without. In particular, high-grade dysplasia is nearly exclusively observed in patients with FAP. Herein, we present the third sporadic case of fundic gland polyp with high-grade dysplasia occurring in a 70-year-old man. Although H. pylori infection was observed, the polyp persisted probably because of its neoplastic nature; fundic gland polyps usually disappear after H. pylori infection. *APC* gene mutation is thought to be present in this case of fundic gland polyp with dysplasia, but *APC* gene mutation alone might not be enough for the development of dysplasia. Further studies are required to elucidate the precise genetic alteration leading to occurrence of dysplasia in sporadic fundic gland polyps.

Keywords: Stomach, fundic gland polyp, high-grade dysplasia, sporadic, β-catenin

Introduction

Fundic gland polyps were once thought to be hamartomas. Along with frequent *CTNNB1* and *APC* mutations described in sporadic and syndromic fundic gland polyps, respectively [1-3], low-grade dysplasia present in 24 to 49% of fundic gland polyps in patients with familial adenomatous polyposis (FAP) support the idea that fundic gland polyps are likely to be neoplastic [4-6]. Although sporadic gastric dysplasia is postulated to be a precursor of carcinoma, it remains uncertain if low-grade dysplasia in a fundic gland polyp increases the risk for the subsequent development of high-grade dysplasia and carcinoma in patients with FAP [7, 8]. Fundic gland polyps with dysplasia have been revealed to have *APC* mutations resulting in nuclear β-catenin accumulation [1, 9], which is consistent with the finding that the frequency of *CTNNB1* mutations is lower in fundic gland polyps with dysplasia compared to fundic gland polyps without dysplasia [6, 9, 10]. Thus, it is considered that *APC* mutations play a role in the formation of fundic gland polyps with dysplasia [10].

Dysplasia occurring in a fundic gland polyp is much more likely to be associated with patients with FAP than those without. In particular, high-grade dysplasia is nearly exclusively observed in patients with FAP [11]. In sporadic cases, fundic gland polyps with low-grade dysplasia have been documented; however, there are only two reported cases of fundic gland polyps with high-grade dysplasia in the English language literature [11, 12]. Herein, we present the third sporadic case of a fundic gland polyp with high-grade dysplasia.

Clinical summary

A 70-year-old man was referred to our hospital for the purpose of endoscopic submucosal dissection (ESD) of two elevated mucosal lesions in the stomach. Laboratory tests revealed he was positive for *Helicobacter pylori*. He has no familial history of FAP. ESD was performed for the two lesions; the gastric mucosa was atro-

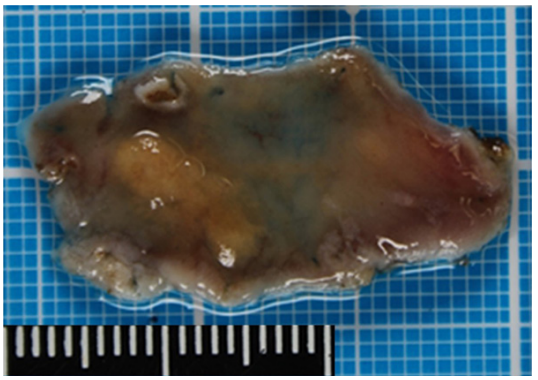

Figure 1. Macroscopic findings. Gross examination reveals a Borrmann IIa-like lesion, measuring 8 × 4 mm.

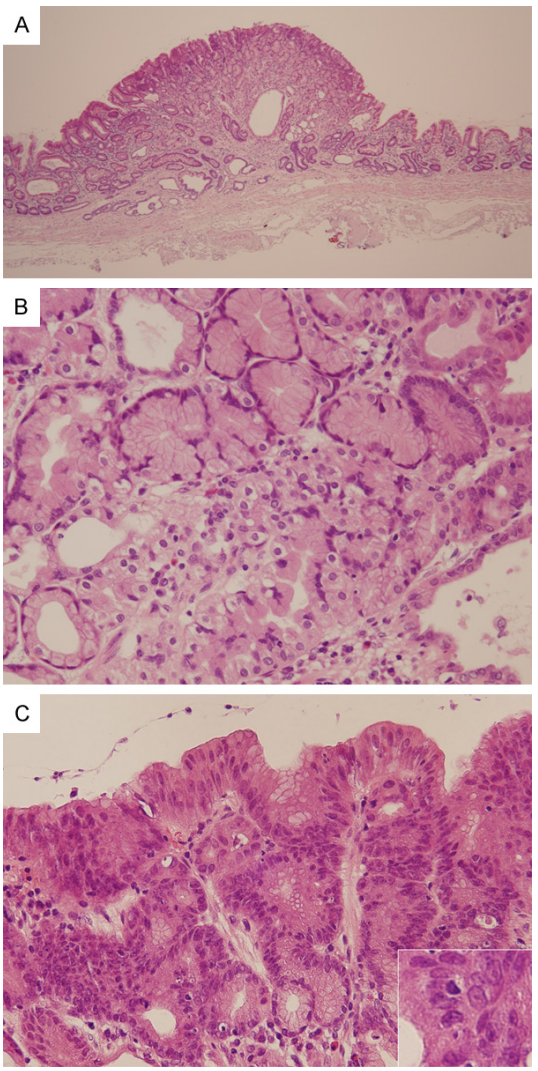

Figure 2. Histological findings. A. An elevated lesion is observed within the background of atrophic mucosa with intestinal metaplasia. B. The lesion is composed of hyperplastic fundic glands with cystic dilatation, which is the cause of elevation of the lesion and allowed it to be recognized as a fundic gland polyp. C. The superficial portion of the polyp is covered by atypical epithelia showing irregularity in architecture, whose nuclei are prominently pseudostratified. Inset: High-power view shows nuclear enlargement and distinct nucleoli of the atypical epithelia.

phic and no other lesion was identified. Pathological diagnosis of one lesion was adenoma, and that of the other lesion was a fundic gland polyp with high-grade dysplasia. Complete resection of the two lesions was achieved and the postoperative course was uneventful.

Pathological findings

For the purposes of this case report, we describe the pathological findings of only the fundic gland polyp with high-grade dysplasia. The other lesion, gastric adenoma, was an ordinary intestinal type of adenoma.

Gross examination revealed a slightly elevated (0-IIa) lesion, measuring 8 × 4 mm (**Figure 1**). On the cut surface, the submucosal layer was unremarkable just beneath the lesion.

Microscopically, the elevated lesion was observed within the background of atrophic mucosa with intestinal metaplasia (**Figure 2A**). The lesion was composed of hyperplastic fundic glands with cystic dilatation, which was the cause of elevation of the lesion and it was recognized as a fundic gland polyp (**Figure 2B**). However, the superficial portion of the polyp was covered by atypical epithelia showing irregularity in architecture, whose nuclei were prominently pseudostratified. Nuclear enlargement and distinct nucleoli were also observed in the atypical epithelia (**Figure 2C**). The resected margins were free of the lesion.

Immunohistochemically, the atypical epithelia was positive for MUC5AC (**Figure 3A**) but was negative for MUC2 (**Figure 3B**) and MUC6. The Ki-67 labeling index was approximately 80% (**Figure 3C**). Diffuse nuclear accumulation of p53 was not observed. Nuclear accumulation of β-catenin was not observed, but there was membranous positivity (**Figure 3D**).

The atypical epithelia were thus regarded as high-grade dysplasia. The pathological diagnosis of fundic gland polyp with high-grade dysplasia was rendered.

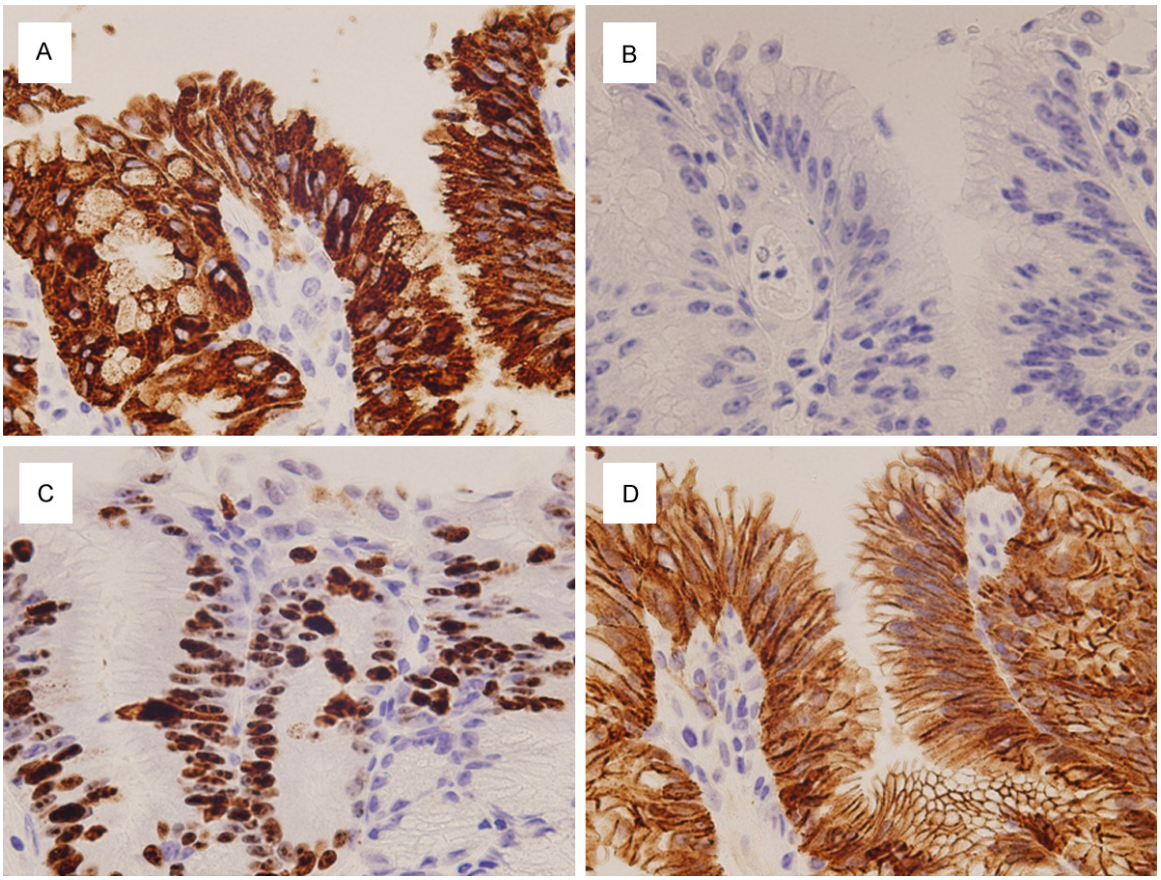

Figure 3. Immunohistochemical findings. A. The atypical epithelia is positive for MUC5AC. B. The atypical epithelia is negative for MUC2. C. The Ki-67 labeling index of the atypical epithelia is approximately 80%. D. Nuclear accumulation of β-catenin is not observed in the atypical epithelia, but there is membranous positivity.

Discussion

CTNNB1 and *APC* gene mutations have been found in fundic gland polyps [13, 14]. Activating *CTNNB1* gene mutations are observed in the majority of sporadic fundic gland polyps; however, *CTNNB1* gene mutations have not been identified in FAP-associated fundic gland polyps. FAP-associated fundic gland polyps have *APC* gene mutations. These findings imply that two distinct types of fundic gland polyps both involve the alteration of the Wnt signaling pathway, in which β-catenin and APC are important proteins.

The inactivation of *APC* due to mutations results in the stabilization of β-catenin; likewise, mutations of the *CTNNB1* gene lead to an accumulation of β-catenin [15]. However, nuclear accumulation of β-catenin is observed in only a minority of fundic gland polyps [16]. One of the possible reasons for this is altered localization of the tumor suppressor tuberin, which could hamper nuclear translocation of β-catenin.

In cases of fundic gland polyps with dysplasia, nuclear accumulation of β-catenin is more often observed than in fundic gland polyps without dysplasia; however, even in fundic gland polyps with dysplasia, its accumulation is observed in only a minority of them. Thus, it is not unexpected that nuclear β-catenin accumulation was not identified in our case.

There is a striking inverse association between fundic gland polyps and *H. pylori*-infected fundal gastritis. Previous studies have revealed the inverse correlation between *H. pylori* infection and fundic gland polyps [17-19]. The biological basis of this relationship has not yet been determined. Thus, further investigation is necessary to see if *H. pylori*-infected fundal gastritis acts to inhibit growth of fundic gland polyps.

H. pylori infection was demonstrated in our case, but one fundic gland polyp was present. A very similar case has been reported previously, in which one fundic gland polyp remained even though *H. pylori* infection took place [19]. Interestingly, only this polyp harbored a *CTNNB1* gene mutation. In other fundic gland polyps that disappeared after *H. pylori* infection, *CTNNB1* gene mutations were not found. These findings imply that fundic gland polyps harboring *CTNNB1* gene mutations are truly neoplastic and will persist irrespective of environmental change. Thus, it is supposed that in our case of a fundic gland polyp with high-grade dysplasia, which should harbor an *APC* gene mutation as was expected due to the reasons mentioned in the section of introduction, the polyp is truly neoplastic and persisted after *H. pylori* infection.

In conclusion, this is the third known sporadic case of fundic gland polyp with high-grade dysplasia. In spite of *H. pylori* infection, the polyp persisted, probably because of its neoplastic nature. *APC* gene mutations are supposed to be present in sporadic cases with dysplasia, but *APC* gene mutation alone might not be enough for the development of dysplasia. Further studies are required to elucidate the precise genetic alteration leading to the occurrence of dysplasia in sporadic fundic gland polyps.

Disclosure of conflict of interest

None.

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