Peutz-Jeghers (PJ) syndrome (PJS) is an autosomal dominant disease characterized by gastrointestinal polyposis and pigmented spots on the skin of the fingertips and the mucous membranes of the lips and oral cavity [1-5]. The representative polyps seen in this syndrome are hamartomatous polyps with distinct pathologic features of extensive smooth muscle proliferation and an elongated arborized pattern of polyp formation, called PJ polyps [6]. PJ polyps occur most frequently in the jejunum, followed by the ileum and duodenum, and are occasionally found in the stomach, large intestine, and even the nostrils.

By age 20 years, patients with PJS have a 1-2% risk of developing malignancy in the gastrointestinal tract, pancreas, breast, testis, ovaries, or cervix. Cancer prevalence increases to 30% by age 50 and to 80% by age 70. In addition, the incidence of intussusception due to small intestinal polyps is 15% by age 10 and 50% by age 20. Thus, surveillance for malignant diseases...
and polyps in the small intestine is vital in patients with PJS [3]. In this context, prompt histopathologic diagnosis of PJ polyps and early intervention are essential.

In our prior study, we retrospectively investigated 14 Japanese patients with PJS who were treated at 6 hospitals to determine the prevalence of cancer in this patient population [7]. During the review process, we observed that gastric polyps were less frequently diagnosed as PJ polyps than were polyps in the small intestine. In addition, to our knowledge, the endoscopic characteristics of gastric polyps in patients with PJS have not been fully investigated. In this study, we review 11 patients with PJS and summarize the endoscopic and pathologic findings of their gastric polyps.

Methods

Letters of inquiry for patients with PJS were sent to five collaborating institutions from the Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences. Patients with clinically diagnosed PJS were selected for inclusion in the study. PJS was diagnosed when the patient met any of the following clinical criteria: two or more histologically confirmed PJ polyps; any number of PJ polyps detected in a person whose family history included one close relative with PJS; characteristic mucocutaneous pigmentation in a person whose family history included one close relative with PJS; and any number of PJ polyps in a person who also had characteristic mucocutaneous pigmentation [8-10]. Finally, 15 patients diagnosed with PJS between January 1990 and January 2020 were identified and registered in the study. Of these, 3 patients did not undergo esophagogastroduodenoscopy. Another patient underwent esophagogastroduodenoscopy and histopathologic examination of the gastric polyps in a facility other than the collaborating institutions. Consequently, we retrospectively reviewed and analyzed the endoscopic and histopathologic features of gastric polyps in the remaining 11 patients with PJS, in addition to their clinical background characteristics. Of the 11 patients examined in this study, 10 were also participants in our previous study [7].

The present study was approved by the Ethics Committee of Okayama University Hospital (No. 2004-019) and adhered to the Declaration of Helsinki.

Results

The characteristics of the enrolled patients and the endoscopic and pathologic features of their gastric polyps are listed in Table 1. The patient group included 7 men and 4 women. Mean age at diagnosis of PJS was 27 years (range, 6-60 years). We observed that the patients' gastric polyps could be mainly classified into 2 types: (i) solitary or sporadic polyps > 5 mm, reddish in color with a sessile or semi-pedunculated morphology; and (ii) multiple sessile polyps ≤ 5 mm with the same color tone as the peripheral mucosa. In this study, 10 patients who underwent esophagogastroduodenoscopy had either or both types of polyps in the stomach: 8 patients (72.7%) had both types, 1 patient (9.1%) had the first type of polyp only, and 1 patient (9.1%) had the second type of polyp only. The remaining patient had no gastric polyps (9.1%). No patients had pedunculated polyps in the stomach.

Among the 9 patients with solitary or sporadic polyps > 5 mm with a reddish color, 2 were histopathologically diagnosed by endoscopic mucosal resection; the diagnosis was PJ polyp in 1 patient (Fig. 1) and PJ polyp and hyperplastic polyp in 1 patient (Fig. 2). In the remaining 7 patients with solitary or sporadic polyps > 5 mm with a reddish color, histopathologic analysis was performed using endoscopic biopsy alone, and the diagnosis was hyperplastic polyps in all these patients (Fig. 3A). Based on the irregular architecture of the muscularis mucosae, a PJ polyp wads suspecte in 1patient (case 7). However, a definitive diagnosis could not be made because extensive smooth-muscle proliferation was not confirmed in the biopsy specimen.

Among the 9 patients with multiple polyps ≤ 5 mm with the same color tone as the peripheral mucosa (Figs.3B and 4), 5 did not undergo histopathologic evaluation. Biopsy sampling was performed in the remaining 4 patients, and the diagnosis was fundic gland polyps in 3 patients, and hyperplastic polyps in 1 patient (Fig. 5). Endoscopic findings other than polyps in the stomach were atrophic gastritis in 3 patients, and gastric ulcer and atrophic gastritis in 1 patient.

Among the 11 patients with PJS, 3 had been taking proton pump inhibitors (Table 1). Six patients underwent tests to detect Helicobacter pylori infection: 2 were positive for H. pylori, while 4 were negative. All but 1 of the 11 patients (case 2) underwent both enteroscopy and colonoscopy in addition to esophagogastroduode-
The enteroscopy methods used were double balloon enteroscopy alone (n = 5), video capsule enteroscopy alone (n = 2), both double-balloon and video capsule enteroscopy (n = 2), and intraoperative enteroscopy during laparotomy (n = 1). Locations of PJ polyps other than the stomach included the ileum (n = 6), large intestine (n = 6), jejunum (n = 5), and duodenum (n = 2). Mucocutaneous pigmentation was observed in 9 patients. Patients with mucocutaneous pigmentation had multiple polyps ≤ 5 mm with the same color tone as the peripheral mucosa, while the remaining 2 patients without mucocutaneous pigmentation did not have polyps ≤ 5 mm.

Notably, one of the patients (case 11) was misdiagnosed with familial adenomatous polyposis at the age of 58. The patient underwent multiple colonoscopies from

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age at PJS diagnosis (years)</th>
<th>Sex</th>
<th>Solitary or sporadic polyps &gt;5 mm with a reddish color</th>
<th>Multiple polyps ≤ 5 mm with the same color tone as the peripheral mucosa</th>
<th>Other features</th>
<th>Oral intake of PPI</th>
<th>H. pylori infection</th>
<th>Location of PJ polyps other than the stomach</th>
<th>Mucocutaneous pigmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>M</td>
<td>Present; EMR: PJ polyp and hyperplastic polyp</td>
<td>Present; no histopathologic examination</td>
<td>None</td>
<td>No</td>
<td>NA</td>
<td>Duodenum</td>
<td>Present</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>M</td>
<td>Present; EMR: PJ polyp</td>
<td>Present; no histopathologic examination</td>
<td>None</td>
<td>No</td>
<td>NA</td>
<td>None*</td>
<td>Present</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>M</td>
<td>Present; biopsy: hyperplastic polyp</td>
<td>Present; biopsy: fundic gland polyp</td>
<td>None</td>
<td>No</td>
<td>Negative</td>
<td>Duodenum, ileum</td>
<td>Present</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>M</td>
<td>Absent</td>
<td>Present; no histopathologic examination</td>
<td>None</td>
<td>No</td>
<td>Negative</td>
<td>Ileum, large intestine</td>
<td>Present</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>M</td>
<td>Present; biopsy: hyperplastic polyp</td>
<td>Present; biopsy: fundic gland polyp</td>
<td>Atrophic gastritis</td>
<td>No</td>
<td>NA</td>
<td>Jejunum, ileum, large intestine</td>
<td>Present</td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>M</td>
<td>Present; biopsy: hyperplastic polyp</td>
<td>Present; biopsy: hyperplastic polyp</td>
<td>None</td>
<td>No</td>
<td>Negative</td>
<td>Large intestine</td>
<td>Present</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
<td>F</td>
<td>Present; biopsy: hyperplastic polyp, suspected of PJ polyp</td>
<td>Present; no histopathologic examination</td>
<td>None</td>
<td>No</td>
<td>NA</td>
<td>Jejunum, ileum, large intestine</td>
<td>Present</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
<td>M</td>
<td>Absent</td>
<td>Atrophic gastritis</td>
<td>Yes</td>
<td>Positive</td>
<td>Ileum, large intestine</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>52</td>
<td>F</td>
<td>Present; biopsy: hyperplastic polyp</td>
<td>Present; biopsy: fundic gland polyp</td>
<td>None</td>
<td>No</td>
<td>Negative</td>
<td>Jejunum, large intestine</td>
<td>Present</td>
</tr>
<tr>
<td>10</td>
<td>57</td>
<td>F</td>
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<td>Absent</td>
<td>Yes</td>
<td>Positive</td>
<td>Jejunum</td>
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<td></td>
</tr>
<tr>
<td>11</td>
<td>60</td>
<td>F</td>
<td>Present; biopsy: hyperplastic polyp</td>
<td>Present; no histopathologic examination</td>
<td>Atrophic gastritis</td>
<td>Yes</td>
<td>NA</td>
<td>Jejunum, ileum</td>
<td>Present</td>
</tr>
</tbody>
</table>

PJS, Peutz-Jeghers syndrome; PPI, proton pump inhibitor; PJ, Peutz-Jeghers; M, male; F, female; EMR, endoscopic mucosal resection; NA, not available.

*This patient did not undergo enteroscopy or colonoscopy.
Images of a PJ polyp observed in case 2. A reddish-color polypoid lesion >5 mm was identified in the gastric body (A). Pathologic analysis of the endoscopic mucosal resection specimen revealed smooth muscle fibers surrounding the lobulated clusters of gastric crypts (B & C), which are characteristic features of PJ polyps.

Fig. 2 Images of a PJ polyp and a hyperplastic polyp observed in case 1. Two reddish-color polypoid lesions >5 mm were removed by endoscopic mucosal resection. One polyp in the gastric body (A) showed an arborizing pattern of smooth muscle proliferation (B & C) and was diagnosed as a PJ polyp. The other polyp was diagnosed as a hyperplastic polyp (D–F).

Fig. 3 Images of gastric polyps observed in case 9. Endoscopic biopsy was performed for a solitary polyp >5 mm with a reddish color, which was diagnosed as a hyperplastic polyp (A). This patient had multiple polyps ≤5 mm with the same color tone as the peripheral mucosa (B). Biopsy examination revealed that these gastric polyps were fundic gland polyps (C).
age 48-58, and was diagnosed with polyps in the colon. Endoscopic mucosal resection was performed for the colonic polyps, and the histopathologic diagnosis was adenoma. Esophagogastroduodenoscopy performed when the patient was aged 58 years showed diffuse gastric polyps ≤ 5 mm, consistent with the typical endoscopic morphology of fundic gland polyps (Fig. 4). In addition, esophagogastroduodenoscopy and biopsy revealed adenoma of the duodenal papilla. As diffuse gastric fundic gland polyps and adenoma of the duodenal papilla are well-known features of familial adenomatous polyposis, we considered that familial adenomatous polyposis was the most probable diagnosis. However, video capsule enteroscopy performed at age 60 revealed pedunculated polyps in the small intestine. Polypectomy under double-balloon enteroscopy resulted in the histopathologic diagnosis of PJ polyps in the small intestine. Physical examination revealed pigmentation on the palmoplantar skin of the lips. Thus, PJS was finally diagnosed.

**Discussion**

Hamartomatous polyps in the gastrointestinal tract with extensive smooth muscle proliferation and an elongated arborized pattern of polyp formation (i.e., PJ polyps) are one of the chief manifestations in patients with PJS [11,12]. PJ polyps are predominantly observed in the small intestine, whereas it is known that polypoid lesions are often found in the stomach of

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**Fig. 4** Images of gastric polyps observed in case 11. The patient had adenomas in the duodenum and colon. In addition, esophagogastroduodenoscopy revealed diffuse fundic gland polyps in the stomach. Because of the diffuse gastric fundic gland polyps and gastrointestinal adenomas, the patient was initially misdiagnosed with familial adenomatous polyposis.

**Fig. 5** Diagram showing polyp types in the stomach and their histopathological diagnosis. PJ, Peutz-Jeghers; EMR, endoscopic mucosal resection.
patients with PJS. Bartholomew et al. reviewed 182 patients with PJS, and reported that polyps were most frequently found in the small intestine (96.2%), followed by the colon (29.1%), rectum (24.2%), and stomach (24.2%) [13]. In another study investigating 222 Japanese patients with PJS, the prevalence of gastric polyps was relatively high (48.6%), whereas the small intestine was involved in 64.0%, the colon in 53.2%, and the rectum in 32.0% of patients [14]. Although gastric polyps have been observed in not a few patients with PJS, and the histopathology of gastric polyps in these patients has been explored in several reports, to our knowledge, the endoscopic features have not been sufficiently investigated thus far.

In the present study, polyps were observed in the stomachs of 10 out of 11 patients with PJS (90.9%). The prevalence was higher than in previous articles, which reported rates of 24.2% [13] and 48.6% [14]. We consider that the difference was likely due to the surveillance methods; endoscopy examinations were performed in our study, while barium-based fluoroscopy and macroscopic observation of the resected specimen were mainly performed in the previous reports, which were conducted in the 1950s [13] and 1970s [14]. Although proton pump inhibitor use is known to cause polypoid lesions in the stomach such as fundic gland polyps, hyperplastic polyps, multiple white and flat elevated lesions, and cobblestone-like mucosa [15], only 3 of our patients had been taking proton pump inhibitors, and 1 of them had no gastric polyps. Thus, we consider that the high prevalence of gastric polyps observed in the present study was a manifestation of PJS itself.

Definitive diagnosis of PJ polyps was made in only 2 patients who underwent endoscopic resection of gastric polyps >5 mm, whereas this type of polyp was diagnosed as hyperplastic in the other patients who underwent endoscopic biopsy alone. We speculate that endoscopic biopsies provide too small a sample for the histopathologic detection of extensive smooth-muscle proliferation, a crucial feature for the diagnosis of PJ polyps. Thus, endoscopic resection of gastric polyps >5 mm is required for the histopathologic identification of PJ polyps. However, physicians should be aware that gastric polyps >5 mm may be diagnosed as hyperplastic polyps even in endoscopically resected specimens, as seen in our case 1. Therefore, we consider that biopsy or resection of intestinal polyps, rather than gastric polyps, is more appropriate for the histopathologic diagnosis of PJ polyps.

The presence or absence of mucocutaneous pigmentation corresponded to the presence or absence of multiple polyps ≤5 mm with the same color tone as the peripheral mucosa in the stomach. Nine patients with mucocutaneous pigmentation had polyps ≤5 mm. Conversely, 2 patients without mucocutaneous pigmentation did not have polyps ≤5 mm. These results suggest that mucocutaneous pigmentation predicts concomitant gastric polyps ≤5 mm. However, a relatively small number of patients were included in this study, and further studies are needed to investigate the relationship between clinical manifestation and types of gastric polyps.

Another important implication of the present study is that multiple fundic gland polyps can be found in the stomach of patients with PJS, and these features may lead to a misdiagnosis. As previously described, fundic gland polyps are the most common gastric polyps in patients with familial adenomatous polyposis [16]. Thus, PJS patients with multiple fundic gland polyps may be misdiagnosed with familial adenomatous polyposis unless they have pedunculated PJ polyps in the gastrointestinal tract. The surveillance protocols differ between patients with the 2 conditions because they are characterized by risk for malignant progression of different tumors: most patients with familial adenomatous polyposis develop colorectal cancer if the polyps are left untreated, whereas patients with PJS have an increased risk of developing cancers of various organs such as the breast, colorectum, pancreas, stomach, testicles, ovaries, lung, and cervix [17, 18]. In this context, endoscopic detection and pathological diagnosis of PJ polyps and physical examinations of mucocutaneous pigmentation are important to differentiate PJS from familial adenomatous polyposis. Correct diagnosis is crucial for the appropriate management of patients with gastrointestinal polyposis, as well as their relatives, since both PJS and familial adenomatous polyposis are autosomal dominant genetic disorders.

This study had several limitations. First, although we recruited patients from six institutions, only 11 were enrolled owing to the rarity of this disease. A nationwide survey of patients with PJS is required to reveal the true prevalence and distinctive features of gastric polyps in patients with this disease. Second, the presence of STK11/LKB1 germline mutations, which are specific
for PJS, was not investigated. In Japan, unfortunately, genetic testing is virtually unavailable in clinical settings, as it is not covered by health insurance.

In conclusion, we retrospectively investigated the endoscopic and histopathologic features of gastric polyps in 11 patients with PJS. We found 2 types of polyps in the stomach: (i) solitary or sporadic polyps >5 mm and reddish in color with a sessile or semi-pedunculated morphology; and (ii) multiple sessile polyps ≤5 mm with the same color tone as the peripheral mucosa. Both hyperplastic and PJ polyps were included in the first type of polyps, and PJ polyps were diagnosed only when the polyps were endoscopically resected. Thus, endoscopic resection of gastric polyps >5 mm is required for the histopathologic identification of PJ polyps. Fundic gland polyps and hyperplastic polyps were included in the second type of polyps, and care should be taken not to confuse the multiple fundic gland polyps of PJS with those of familial adenomatous polyposis. We believe that a better understanding of the endoscopic features of gastric polyps in patients with PJS will lead to accurate and prompt diagnosis.

References


