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Epithelial gastric polyps

Polipy nabłonkowe żołądka

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Abstract

Gastric polyps are lesions projected above the mucosal surface, which are detected in approximately 1–6% of upper gastrointestinal endoscopies. Based to their shape, polyps are classified as pedunculate, semi-pedunculate, sessile and flat. Depending on the histopathological type, some of them have the potential to transform into adenocarcinoma. Polyps can be of epithelial and non-epithelial origin. The first group, which is discussed in greater detail in this paper, includes fundic gland polyps, hyperplastic, adenomatous and hamartomatous polyps. Non-epithelial polyps include stromal tumours, leiomyomas, fibrous inflammatory polyps, fibroids, fibromyomas, lipomas, ectopic pancreas, neuroendocrine tumours, neuromas, and some vascular lesions. Multiple polyps in patients under the age of 40 years require more extensive diagnosis for hereditary polyposis syndromes, which are associated with an increased risk of gastric cancer, as well as other gastrointestinal and extra-gastrointestinal malignancies. In recent years, there has been a clear decrease in the proportion of hyperplastic polyps and an increase in the proportion of fundic gland polyps among all gastric polyps, which is probably related to the increased use of proton pump inhibitors and a reduced incidence of *Helicobacter pylori* infections. About 90% of gastric polyps are detected accidentally and usually do not cause clinical symptoms, but large polyps may be responsible for anaemia, bloody stools, abdominal pain, and even pyloric obstruction, which may be manifested by vomiting, severe flatulence, lack of appetite or progressive weight loss.

Keywords: gastric polyps, gastroscopy, gastric cancer

Streszczenie

Polipy żołądka to zmiany uwypuklające się ponad powierzchnię błony śluzowej, które są wykrywane w około 1–6% endoskopii górnego odcinka przewodu pokarmowego. Ze względu na kształt polipy dzieli się na uszypułowane, półuszypułowane, przysadziste i płaskie. W zależności od typu histopatologicznego niektóre z nich cechują się potencjałem transformacji w kierunku gruczolakoraka. Polipy mogą być pochodzenia nabłonkowego i nienabłonkowego. Do pierwszej grupy, szerzej omawianej w tej pracy, należą polipy z gruczołów sklepienia żołądka, hiperplastyczne, gruczolakowate i hamartomatyczne. Z kolei do polipów nienabłonkowych zaliczają się guzy stromalne, mięśniaki gładkokomórkowe, włókniste polipy zapalne, włóknaki, włókniakomięśniaki, tłuszczaki, trzustka ektopowa, guzy neuroendokrynne, nerwiaki i niektóre zmiany naczyniopochodne. Mnogie polipy występujące u pacjentów w wieku poniżej 40. roku życia wymagają pogłębienia diagnostyki w kierunku dziedzicznych zespołów polipowatości, które wiążą się ze zwiększonym ryzykiem rozwoju raka żołądka, innych nowotworów złośliwych przewodu pokarmowego, a także nowotworów pozajelitowych. W ostatnich latach obserwuje się wyraźny spadek udziału polipów hiperplastycznych wśród wszystkich polipów żołądka i wzrost udziału polipów z gruczołów sklepienia żołądka, co jest prawdopodobnie związane ze zwiększonym stosowaniem leków z grupy inhibitorów pompy protonowej i obniżeniem częstości zakażeń *Helicobacter pylori*. Polipy żołądka w ponad 90% przypadków są wykrywane przypadkowo i zazwyczaj nie powodują objawów klinicznych, lecz duże polipy mogą być odpowiedzialne za niedokrwistość, obecność krwi w stolcu, bóle brzucha, a nawet niedrożność odźwiernika, która może się manifestować wymiotami, nasilonymi wzdęciami, jądłowstrętem czy postępującą utratą masy ciała.

Słowa kluczowe: polipy żołądka, gastroskopia, rak żołądka

FUNDIC GLAND POLYPS

Fundic gland polyps (FGP), also known as Elster's cyst, are the most commonly diagnosed gastric polyps in developed countries. Depending on the population, they account for 16–51% of all histopathological diagnoses of benign epithelial gastric polyps (BEGP)⁽¹⁾. FGPs accounted for up to 77% of polypoid lesions in a study in 120,000 patients⁽²⁾. Macroscopically, FGPs are mostly sessile with a smooth and shiny surface, usually surrounded by normal mucosa of the same colour. Single FGPs are rare; usually, there are several of them and they are small, <1 cm in diameter^(3,4). They are located almost exclusively in the fundus or body of the stomach. Considering the pathogenesis of FGPs, they can be classified as sporadic, associated with long-term use of proton pump inhibitors (PPIs) and associated with familial adenomatous polyposis (FAP).

Sporadic and PPI-associated FGPs are usually detected in patients 40–70 years of age and are more common in women^(2,4). FAP-associated FGPs develop in younger individuals (<40 years), are much smaller and occur with almost equal frequency in both sexes^(4–6).

Sporadic FGPs develop as a result of activating mutations of β -catenin, which is one of proteins of the *APC*/ *β -catenin/Tcf* and *Wnt* pathways. Although such mutations are found in cancer cells, this type of polyps contains almost no dysplastic foci^(4,5). The same mechanism generates PPI-associated polyps. Local effects of increased levels of gastrin during PPI therapy is one possible explanation of mutations^(4,7). Martin et al. showed in their meta-analysis that 15.1% of patients on PPI therapy were affected by FGPs⁽⁸⁾. These polyps often regress after PPI discontinuation⁽⁷⁾.

FAP is an autosomal dominant disorder caused by germline mutations in the *APC* gene. It has an incidence of approximately 1:8,000 in the general population. Patients with FAP are characterised by a significantly increased risk of colorectal cancer, as well as other malignancies, such as osteomas or foetal hepatocellular carcinoma⁽⁹⁾. FGPs in FAP develop as a result of *APC* somatic mutation. They are found in 12.5–84% of patients with FAP, which is much more often than sporadic FGPs (0.8–1.9% of gastroscopies). Low-grade dysplasia can occur in up to 25% of FAP-associated FGP cases⁽⁶⁾. Colonoscopy is needed in these patients. The risk of dysplasia and gastric cancer in non-polypoid syndrome patients with FGP is very low (<1%)^(4,10).

Since FGPs have a characteristic macroscopic picture, they can be diagnosed already during endoscopy, especially when performed by an experienced endoscopist. However, specimens for histopathological examination from at least one, preferably the largest, polyp should be collected during the first endoscopic examination to confirm the diagnosis and exclude dysplasia. Polyps >1 cm in diameter should be removed completely due to the increased risk of dysplastic foci^(1,10).

In patients on chronic PPIs who are diagnosed with large polyps (>1 cm), discontinuation or dose reduction, if possible, and monitoring of the size of the polyps are recommended. In the event of polyp size reduction, the same type of PPI should not be resumed, but should be switched to another PPI, at the lowest effective dose, or to agents from the class of histamine H₂-receptor blockers⁽¹⁾ (Fig. 1).

GASTRIC HYPERPLASTIC POLYPS

Gastric hyperplastic polyps (GHP) are endothelial polyps arising from mucin-producing cells⁽¹¹⁾. In their analysis of over 120,000 patients undergoing upper gastrointestinal (GI) endoscopy, Carmack et al. showed that GHPs account for 14.3% of all polyps found during gastroscopy, which makes them the second most common type of gastric polyp after FGPs⁽²⁾. They are slightly more common in women and in the elderly^(2,12,13).

GHPs are usually small, sessile, or flat, with smooth or lobular surface. Up to 72% of all GHPs have a diameter <1 cm, and only 4% of these polyps have a diameter >3 cm⁽¹²⁾. Large polyps tend to be pedunculated with clustered or granular surface. In some cases, the mucosa that covers the GHP erodes, forming erosions that can cause chronic bleeding and iron deficiency anaemia in some patients. Narrow band imaging (NBI) endoscopy allows the visualisation of dense clusters of irregular capillaries on the surface of the polyp, which is a hallmark of GHP. Hyperplastic polyps usually develop as single lesions (68–78%), although they can also be multiple, e.g. in Ménétrier's disease (hypertrophic gastritis) or in hyperplastic polyposis syndrome, a rare autosomal dominant disorder⁽¹¹⁾. GHPs are located mainly in the antral part (60%), less often in the gastric body or fundus⁽¹²⁾. In some cases, GHPs may be accompanied by other types of gastric polyps, most often FGPs⁽²⁾.

Fig. 1. Fundic gland polyp

The cause of proliferation of mucin-producing epithelial cells remains unknown. It is presumed that the proliferation is the result of the regenerative processes of the gastric mucosa in response to damage. The main factors responsible for the development of GHPs include chronic gastritis associated with *H. pylori* infection and autoimmune metaplastic atrophic gastritis (AMAG), which can lead to Addison–Biermer anaemia. Other aetiological factors for GHPs include chemical and reactive gastropathy, dilation of the gastric antrum (the so-called watermelon stomach, gastric antral vascular ectasia, GAVE) or Zollinger–Ellison syndrome⁽¹²⁾. Chronic atrophic mucositis related to *H. pylori* infection, chemical or reactive gastropathy and AMAG were found in 25%, 21% and 12% of patients with GHP, respectively. GHPs arise from normal mucosa in only 15% of cases⁽¹²⁾. The involvement of repair processes in the pathogenesis of GHPs is also evidenced by the location of GHPs near gastric ulcers, erosions or a gastroenterostomy⁽¹¹⁾.

H. pylori increases the expression of cyclooxygenase-2 (COX-2), interleukin 1 β (IL-1 β) and hepatocyte growth factor (HGF) in mesenchymal cells. These factors trigger local inflammatory reaction and stimulate the mitotic activity of epithelial cells, increasing cell turnover^(14,15). As a result of *H. pylori* infection, the gastric mucosa is infiltrated by macrophages, which, when activated, produce IL-1 β , which in turn activates fibroblasts and increases the expression of the mitotic factor HGF⁽¹⁵⁾. The importance of *H. pylori* infection in the pathogenesis of GHPs may be confirmed by reports on polyp size reduction or complete regression as a result of effective eradication of *H. pylori* infection, occurring in up to 80% of patients with these polyps^(14–17).

The percentage of GHPs among all polyps detected during upper GI endoscopy has changed in recent years. Studies show an increase in the number of gastric polyps with a percentage decrease in the incidence of GHPs and an increase in the incidence of FGPs^(18–21). It has been suggested that a reduction in the number of *H. pylori* infections associated with the pathogenesis of GHPs and the widespread use of PPIs, which in turn is associated with the formation of FGPs, are the cause of this phenomenon^(2,21).

Hyperplastic polyps rarely transform into carcinomas. Research indicates that dysplasia may be present in 1.9–19% of GHPs, although such a large range may be the result of various histopathological criteria adopted by researchers^(3,10). The incidence of adenocarcinoma ranges from 0.6 to 2.69%^(22,23). Since GHPs arise from inflamed gastric mucosa, it is important to assess the mucosa surrounding the polyp. Abraham et al. found intestinal metaplasia in the gastric mucosa in 37%, dysplasia in 2%, and adenocarcinoma in 6% of GHP cases⁽¹²⁾. Some studies even suggest that GHP is associated with a greater risk of dysplasia and neoplasia of the gastric mucosa than the polyp itself^(11,24).

The size of the polyp is the most frequently mentioned risk factor for GHP neoplastic transformation. There is an increased carcinogenic risk for a polyp head >20 mm in diameter⁽³⁾. For this reason, it is suggested to remove all GHPs >5 mm in diameter⁽²⁵⁾. In addition to the size of the polyp, other potential risk factors for neoplastic transformation include the presence of antibodies against the gastric parietal cells, hypergastrinemia, female sex, or AMAG⁽²³⁾.

Due to the risk of dysplasia and cancer in the gastric mucosa surrounding GHPs, it is recommended to collect specimens from the gastric mucosa according to the Sydney protocol, i.e. five sections (two from the gastric antrum and body, and one from the gastric angle area)⁽¹¹⁾. The specimens should be subject to histological evaluation according to the risk stratification system for gastric cancer arising from atrophic mucositis (Operative Link for Gastritis Assessment, OLGA).

Endoscopic surveillance after polypectomy should include patients with dysplasia in the polyp (upper GI endoscopy after one year) or early gastric cancer (after one year and then after 3 consecutive years)⁽¹¹⁾. Follow-up examinations are also recommended in patients with an increased risk of gastric cancer – OLGA III and IV (every 1–2 years) and patients who, in addition to GHPs, have dysplastic mucosa outside the polyp (every 1–3 years)^(3,11) (Fig. 2).

ADENOMATOUS POLYPS

Adenomatous polyps account for 3–26% of all polyps, with similar rates in women and men^(1–3). Although they can be found in any gastric location, about 50% of these polyps are located in the antral part, less commonly in the angular or fundic part^(13,26). These are usually single lesions (>80%) with lobular structure and smooth surface, soft, sessile, and different in colour than the surrounding atrophic and smooth mucosa^(13,27).

Adenomas usually arise from atrophic gastric mucositis (35%) and intestinal metaplasia (29.6%), which is both

Fig. 2. Hyperplastic gastric polyp

a precursor lesion and a high-risk factor for adenoma⁽¹³⁾. They are less commonly associated with *H. pylori* infection (9.3%)^(2,13).

The risk of malignant transformation increases for polyps >2 cm in diameter and is estimated at 28.5–40% for villous adenomatous polyps and 5% for tubular adenomatous polyps⁽¹⁾. Synchronous malignancy develops in 30% of patients with adenomas⁽³⁾. Also, an increased risk of gastric adenocarcinoma at different time points after the diagnosis of an adenomatous polyp (non-synchronous cancers) has been reported. The risk of cancer increases with age, with similar frequency in women and men^(1,2,27). The risk of cancer in the polyp is estimated at about 10% and is 5 times higher than in GHPs and two times higher than for the peri-GHP mucosa⁽¹¹⁾.

Gastric adenomas usually cause no clinical symptoms except for situations when ulceration and bleeding from the polyp occur. Since adenomatous polyps are preinvasive lesions, they must be removed completely⁽¹³⁾. Also, the entire gastric mucosa should be investigated for lesions and if found, specimens should be collected for histopathology^(1,13).

After polyp removal, the patient should be monitored endoscopically: endoscopic follow-up should be performed after 6 months for incompletely resected polyps or high-grade dysplasia and after a year in other cases. Eradication treatment of *H. pylori* should also be performed, and its efficacy should be confirmed⁽¹⁾. There is a relationship between the presence of gastric and colorectal adenomas, therefore a colonoscopy is indicated⁽²⁸⁾ (Fig. 3).

HAMARTOMATOUS POLYPS

Gastrointestinal hamartomatous polyps most often arise from the mucosa, although they may originate from tissues of all three germ layers. They are composed of cells and tissues found in a given organ, but they develop in a disorderly manner. These polyps are divided into sporadic polyps, which are most often single lesions and are not associated with the risk of carcinogenesis, and polyps in hereditary polyposis syndromes, such as Peutz–Jeghers syndrome, juvenile polyposis syndrome or Cowden syndrome.

Peutz–Jeghers syndrome

Peutz–Jeghers syndrome is an autosomal dominant disease caused by a germline mutation in the *STK11/LKB1* gene, with an incidence of 1:8,300 to 1:200,000^(29,30). This syndrome is associated with an increased risk of cancers, especially in the breast and the GI tract. This risk significantly increases in individuals over the age of 50 years⁽²⁹⁾. Dermal and mucosal pigmentation lesions located in the perianal area, on the lips, in the oral cavity and the nostrils, on the skin of fingers, hands and feet, which may regress with age, are characteristic for

Peutz–Jeghers syndrome^(10,29). The polyps are most common in the small intestine, slightly less common in the colon and the stomach, and they can also be located outside the GI system (in the urinary bladder, bronchi, gall bladder)^(10,29,30). They have a characteristic microscopic picture, and they macroscopically resemble GHPs. They can cause overt bleeding or latent anaemia, and intussusception if located in the small bowel. As part of cancer surveillance, the first endoscopy in asymptomatic patients diagnosed with Peutz–Jeghers syndrome should be performed at the age of 8 years and repeated every 1–3 years if polyps are found. If no lesions were detected in the first examination, another gastroscopy is performed after the patient turns 18 years and is then repeated every 1–3 years. Polyps with suspicious morphology or a diameter >1 cm should be removed⁽³¹⁾.

Juvenile polyposis syndrome

Juvenile polyposis has an incidence of 1:100,000 to 1:160,000⁽³⁰⁾. The disorder is caused by a germline *BMPRIA* or *SMAD4* mutation and is inherited in an autosomal dominant pattern. The polyps are most commonly found in the colon, rectum, and stomach, with cancers developing in these locations. Patients with *SMAD4* mutation are more likely to develop gastric polyps, gastric cancer, and have a tendency to develop hereditary haemorrhagic telangiectasia (HHT)^(30,31). Single, pedunculated antral polyps, 3–20 mm in size are most typical and common in juvenile polyposis, although they can also be located throughout the stomach and have a diverse morphology⁽¹⁰⁾. Due to the >50% risk of malignant transformation of the polyp, patients undergo endoscopic surveillance, and screening depends on the detected mutation⁽¹⁾. For asymptomatic individuals with *SMAD4* mutation, it is recommended to initiate surveillance after the age of 18 years, with endoscopic follow-up every 1–3 years, depending on the size and number of polyps. For asymptomatic patients with *BMPRIA* mutation, who are less likely to develop

Fig. 3. Gastric adenoma

gastric polyps, gastroscopy is performed for the first time after the age of 25 years and should also be repeated at 1–3-year intervals⁽³¹⁾.

Cowden syndrome

Cowden syndrome is an autosomal dominant disorder, with a germline mutation inactivating the suppressor *PTEN* gene found in 80% of patients. It has an incidence of 1:200,000 to 1:250,000, is more common in women, and is usually diagnosed between 20 and 30 years of age^(10,32). The diagnosis is based on the pathognomonic clinical criteria, which include Lhermitte–Duclos disease, trichilemmoma, oral fibromas, keratosis of the hands and feet, as well as major and minor criteria. Hamartomatous polyposis of the intestine, which are included in the minor criteria, are almost always found in the rectum and the sigmoid colon and are less likely to involve the entire GI tract, including the stomach. The simultaneous presence of several histological types of polyps, with predominant hamartomatous polyps, is typical for Cowden syndrome. They differ in size, with a diameter from 1 mm to up to a few centimetres (most often ≤ 5 mm)⁽³²⁾. Macroscopically, they are similar to hyperplastic and inflammatory polyps, and therefore are sometimes misdiagnosed⁽³³⁾. Since gastric polyps in Cowden syndrome are extremely unlikely to undergo neoplastic transformation, endoscopic surveillance is not necessary. However, the disorder predisposes to other malignant neoplasms, breast, thyroid, and endometrial cancer in particular. For this reason, annual imaging and clinical examinations involving these organs are recommended from the moment the patient reaches a certain age^(1,10,32).

CONCLUSIONS

Gastric polyps are usually asymptomatic; hence they are detected accidentally during gastroscopy for another reason. Fundic gland polyps are most common in developed countries, while hyperplastic polyps in areas where *H. pylori* infection is still common. Hyperplastic polyps >5 mm in diameter, FGPs >10 mm in diameter, and all adenomas should be removed during endoscopy. FGPs may be classified as sporadic, PPI-associated and FAP-associated. These polyps pose a negligible risk of carcinogenesis. In the case of hyperplastic polyps arising from inflamed mucosa, it should be remembered that carcinogenesis may also occur in the mucosa outside the polyp; therefore it is necessary to collect a biopsy sample as well as to use eradication treatment for *H. pylori* infection if needed. Adenomatous polyps, arising from atrophic inflammation and intestinal metaplasia, are benign lesions, but with a high potential for progression to adenocarcinoma; therefore they should be completely removed with a thorough assessment of the entire gastric mucosa with a biopsy from suspicious sites. Although hamartomatous polyps developing in polyposis syndromes are rare, they should not be ignored.

Conflict of interest

The authors do not declare any financial or personal links to other persons or organisations that could adversely affect the content of this publication or claim rights thereto.

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