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ASSESSMENT OF THE RISK OF MALIGNANCY BASED ON THE HISTOMORPHOLOGICAL AND IMMUNOHISTOCHEMICAL CHARACTERISTICS OF GASTRIC POLYPS

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Abstract: Gastric polyps (GPs) are increasingly common. On upper endoscopy, they should be examined with white light and occasionally chromoendoscopy, and their morphology classified according to the Paris classification. Most GPs have a typical endoscopic appearance and can be associated with diseases like Helicobacter pylori infection. Histological examination is necessary for an accurate diagnosis. While most polyps are non-neoplastic and do not require treatment, some carry a risk of malignancy or are already malignant. Therefore, understanding the diagnosis, classification, and management of GPs is crucial for patient prognostication. Our new classification categorizes GPs into "good", "bad", and "ugly" based on their likelihood of becoming malignant. We aim to provide descriptions of the endoscopic appearance, pathology, treatment, and follow-up for different GPs, as well as clinical management flowcharts.

Keywords: Gastric polyps, Fundic gland polyps, Hyperplastic polyps, Adenomas, Neuroendocrine tumors, Early gastric cancer

General information.

During upper gastrointestinal endoscopy, gastric polyps are frequently encountered, however, most are benign. Despite this, it is crucial that endoscopist have a thorough understanding of diagnostic approaches, management strategies, and screening protocols, particularly for polyps with neoplastic potential. We have developed a new classification system for gastrointestinal polyps based on their likelihood of becoming malignant, categorizing them into "good", "bad", and "ugly" groups. This classification aims to assist clinicians in managing and treating polyps effectively.

INTRODUCTION

Gastric polyps (GPs) are luminal lesions that arise above the mucosal surface. This simple definition encompasses a wide range of lesions with varying histology and neoplastic potential. The detection of GPs is becoming increasingly common in clinical practice, with an estimated current incidence of 6% of upper gastrointestinal endoscopic procedures in the United States. This trend likely underestimates the actual occurrence, as the majority of GPs are asymptomatic, reflecting the widespread access to esophago-gastroduodenoscopy (OGD) in recent years.

During an OGD, it is important to thoroughly examine the gastric mucosa and any polyps encountered using white light and narrow band imaging (NBI) to classify their morphology according to the Paris classification. Chromoendoscopy may be used in some occasions. Most GPs have a typical endoscopic appearance in the stomach and can be associated with diseases such as Helicobacter pylori (H. pylori) infection, autoimmune gastritis, or inherited polyposis syndrome. However, it is essential to conduct histological examination of GPs and the surrounding mucosa for an accurate assessment and diagnosis. While most polyps are non-neoplastic and do not necessitate treatment, some GPs pose a risk of malignancy or are already malignant at the time of endoscopic examination. Therefore, a deep understanding of the diagnosis, classification, and management of GPs is crucial for patient prognostication.

It can be a complex task for clinicians to classify and manage GPs due to uncertainties about lesion characterization, sampling, treatment necessity, therapy type, and long-term monitoring. It is crucial not to underestimate lesions with malignant potential and to treat them appropriately. As such, our new classification of gastrointestinal polyps is based on categorizing them into three groups according to their likelihood of becoming malignant: "Good" [polyps that generally do not progress to cancer, such as fundic GPs (FGPs), inflammatory fibroid polyps (IFPs), and ectopic pancreas (EP)], "bad" [polyps that pose a risk of malignancy, such as large hyperplastic polyps, adenomas, type 1 and 2 neuroendocrine tumors, and hamartomatous polyps (HaPs)], and "ugly" [the most aggressive and invasive polyps, such as type 3 neuroendocrine tumors and early gastric cancer (EGC)]. We aim to provide descriptions of the endoscopic appearance, pathology, treatment, and follow-up for different gastrointestinal polyps, as well as a clinical management flowchart.

Inclusion criteria are polyps with generally no progression to cancer such as: FGPs, IFPs, and ectopic pancreatic tissue.

FGPs

FGPs are the most commonly encountered type of GPs, constituting about 80% of all GPs. While FGPs are typically sporadic, they can also occur in conjunction with polyposis syndromes like familial adenomatous polyposis (FAP) or MUTYH-associated polyposis (MAP). Given the rarity of FAP and MAP patients, in addition to the low likelihood of developing gastric cancer, both types of FGPs have been categorized as "good" polyps. However, there is a slight variation in the management of syndromic and non-syndromic patients, particularly regarding the common occurrence of dysplasia in FGPs associated with FAP.

Sporadic FGPs are closely related to the use of proton-pump inhibitors (PPIs). PPIs increase serum gastrin levels which leads to polyps consisting of large fundic gland cysts with parietal, chief, and some mucous cells. PPIs administration increases the size and number of FGPs while the withdrawal of PPIs leads to regression of FGPs, emphasizing the link between PPIs consumption and FGPs development. It has been noted that the incidence of H. pylori infection is very low in patients with FGPs. In contrast, it has been linked to FGPs regression, suggesting a protective role of H. pylori in reducing FGPs occurrence.

Sporadic FGPs are more common in middle-aged woman, possibly due to hormonal imbalances during menopause. They grow in the gastric body or fundus, are often multiple, less than 8 mm in diameter, isochromatic, and a sessile shape with a smooth surface (Figure 1). On NBI, dot-shaped crypt regular openings with dense regular vessels can be visible. Sporadic FGPs are generally regarded as benign lesions, but rarely (1%-6% of cases) they are associated with dysplasia of the overlying foveolar epithelium with very slow progression to cancer. The surrounding mucosa is generally normal appearing or shows signs of PPIs

The suggested management of sporadic FGPs on OGD is to take biopsies of one or more representative FGPs, while carefully inspecting the remaining polyps. When a polyp displays an atypical morphology or is larger than 1 cm, ulcerated, or located in the antrum, the best course of action is to remove it to confirm the diagnosis and eliminate the possibility of dysplasia. Although bleeding from FGPs is rare, it can be treated with polyp resection and PPIs therapy discontinuation. Periodic surveillance for sporadic FGPs is not typically recommended.

Syndromic FGPs often develop at an earlier age, sometimes even in those less than 20 years old, and this occurs without distinction between genders. In cases where FGPs are associated with FAP/MAP, it has been reported that dysplasia occurs in up to 54% of cases. Nevertheless, the risk of developing malignancy in these cases remains low. In over 90% of cases, syndromic FGPs manifest as multiple growths (more than 20) and primarily affect the gastric body. Similar to sporadic FGPs, they are generally sessile and have an average size of

less than 6 mm. The endoscopic appearance of syndromic FGPs without carcinoma is indistinguishable from that of sporadic FGPs. However, certain characteristics such as redness, irregular surface, depressed areas, erosions, and irregular vessels under NBI have been associated with FGPs containing carcinoma. It is recommended to conduct endoscopic surveillance for syndromic FGPs, although the optimal timing for this surveillance has not yet been standardized.

To summarize, when FGPs are detected on OGD, inspect them with white light and if needed, chromoendoscopy. If polyps are found in the antrum, size larger than 1 cm, red appearing, irregular surface, depressed areas, erosions and/or irregular vessels are present, remove them or take biopsies. Moreover, in patients with more than 20 FGPs, FGPs in the antrum, and onset of FGPs prior to 40 years, it is necessary to perform colonoscopy to rule out the possibility of polyposis syndrome. Reduction, discontinuation of PPIs therapy, or switching to a different PPI can be considered in patients with multiple FGPs and hypergastrinemia, or in cases of anemia caused by FGPs.

IFPs

IFPs are an extremely rare entity, representing less than 0.1% of all GPs. They generally arise within the submucosa of the gastrointestinal tract and penetrate through the lamina propria leading to bulging of the mucosal layer. They may originate from dendritic cells.

IFPs are more commonly small (< 15 mm) and located in the antrum of older adults. In the majority of cases, IFPs are asymptomatic, however, large IFPs can cause early satiety, gastric outlet obstruction, or ulcerate the overlying mucosa causing bleeding and anemia. On OGD they appear as solitary, sessile or pedunculated, sometimes ulcerated polyps and typically have a solid pale tan cut surface. On endoscopic ultrasonography (EUS) they present as a homogeneous hypoechoic mass originating from the second or third layer without involvement of the fourth layer and without a capsule. On histology, IFPs display a proliferation of spindle cells with an eosinophilic-rich inflammatory infiltrate and mutations in the platelet-derived growth factor receptor alpha gene that may lead to a misdiagnosis of gastrointestinal stromal tumour (GIST). The stroma in most lesions is positive for CD34 but negative for CD117.

Diagnosis of IFPs is typically confirmed through histopathological analysis, as they do not have a pathognomonic endoscopic appearance, and only 10% are diagnosed in the preoperative setting with endoscopic biopsy or EUS.

Endoscopic resection of IFPs is generally not associated with a risk of recurrence. Furthermore, since IFPs are considered benign, surveillance is not recommended. However, in sporadic cases, IFPs have been reported to be malignant which may necessitate scheduled follow-ups.

EP

EP is a rare congenital anomaly characterized by aberrant pancreatic tissue that lacks direct vascular or neural connections with the true pancreas. This anomalous tissue can be found in various locations throughout the body, including the gastrointestinal tract, biliary system, liver, lung, mediastinum, and brain. In the gastrointestinal tract, it is most commonly located in the gastric antrum and the prepyloric region on the greater curvature or posterior wall, followed by the duodenum and jejunum. EP tissue can originate from the mucosa, muscularis mucosae propria, submucosa, or muscularis propria.

The majority of gastric EPs are typically asymptomatic and are usually discovered incidentally during OGD. They generally do not require any treatment or ongoing monitoring. However, in some instances, they may manifest with symptoms such as bleeding or pain, and there have been reported cases of gastric outlet obstruction, resembling hypertrophic pyloric stenosis, in both adults and children. Malignant transformation of EP is rare. During OGD, EP

typically appears as a submucosal nodule covered by normal mucosa with an umbilicated shape(Figure 2). However, when lacking central dimpling, EP can be indistinguishable from other submucosal lesions such as GIST, gastrointestinal autonomic nerve tumors and carcinoid tumors. In these cases, EUS with endoscopic-guided fine needle aspiration plays a pivotal role in making an accurate diagnosis

Histologically, EPs are classified into four distinct categories according to Fuentes's classification. The most common tissue type of EP is similar to that found in the normal pancreas, containing all cellular components such as acini, ducts, and pancreatic islet cells. The second histological type consists only of ducts, the third of acini (exocrine cells), and the fourth of pancreatic islet cells (endocrine cells). Asymptomatic gastric EPs do not require any treatment or follow-up.

THE BAD

In this class we identify polyps with a low risk of malignancy such as hyperplastic polyps, adenomas, type 1 and 2 neuroendocrine tumors, and HaPs.

Hyperplastic polyps

Gastric hyperplastic polyps (GHPs) are common epithelial polyps found in the stomach, with an incidence ranging from 15% in areas where H. pylori infection is less common to 75% in populations with widespread H. pylori infection. GHPs are a reactive response to chronic inflammatory stimuli, primarily caused by H. pylori infection, as well as chronic atrophic gastritis, pernicious anemia, stomas, and sites of ulcers and erosions.

GHPs shows no predilection towards males or females; however, they most commonly affect individuals in the middle to late stages of life. On OGD, GHPs can appear in various forms, ranging from smooth to lobulated, and can be either sessile or pedunculated, with sizes generally less than 2 cm, although larger dimensions of up to 12 cm have been reported. They typically have a reddish surface and often show erosions, particularly as they grow in size (Figure 3). The morphological characteristics of GHPs can make it challenging to distinguish them from polypoid foveolar hyperplasia or gastric adenomatous polyps, underscoring the need for biopsy sampling. The antrum is the most commonly affected site in the stomach (60%), although GHPs can occur in any area of the stomach, including the cardia. They may appear as solitary growths or, more commonly, as multiple growths. Over time, their size can remain stable or increase, especially in the presence of the inflammatory agent. Conversely, the eradication of H. pylori infection significantly increases the rate of GHPs elimination by more than 20 times, as shown in a meta-analysis

GHPs are usually asymptomatic and are found incidentally on OGD. However, they can cause bleeding when eroded, or intermittent gastric outlet obstruction when pedunculated and prolapsing from the antrum into the bulb. Microscopically, GHPs are characterized by elongated, dilated, branching, distorted, cystic foveolar glands with mucinous cytoplasm and an inflamed stroma.

GHPs have long been considered to be benign growths, however, their development within a background of chronic inflammation may increase the risk of neoplastic transformation, following the adenoma-carcinoma sequence. On histological examination, 15% of GHPs exhibit intestinal metaplasia, while nearly 5% show signs of dysplasia, and cancer is present in less than 1%. Notably, GHPs larger than 1 cm, displaying a pedunculated morphology, arising in individuals who have undergone gastrectomy, or coexisting with other neoplastic lesions, are all factors that predispose GHPs to neoplastic transformation. When examining GHPs, it is essential to extensively sample the surrounding mucosa to rule out H. pylori infection, atrophy, metaplasia, or dysplasia, especially when they show characteristics of underlying chronic inflammatory conditions.

All polyps greater than 5 mm in size should be removed endoscopically and all patients with H. pylori infection should be adequately treated to eradicate the infection. Surveillance after removal of GHPs should be based on polyp histology (i.e., dysplasia) and cancer risk due to concurrent H. pylori infection, autoimmune gastritis, family history of gastric cancer, migrants from areas with high gastric cancer incidence and operative link of gastritis assessment stage. Furthermore, it is advisable to conduct a follow-up endoscopy three to six months after polyp resection to ensure that there are no residual GHPs and that H. pylori has been successfully eradicated.

CONCLUSION

In this article we have made an overview of the most frequently encountered classes of GPs, presenting a new classification based on potential malignant evolution that can guide clinicians in polyp management. We provide an overview of clinical presentation, diagnosis, treatment, and follow up. Additionally, we offer a practical approach with flowcharts.

One challenge of this classification is the complexity of categorizing GPs into distinct malignancy classes, as seemingly benign polyps could contain precancerous areas that have the potential to develop into cancer. To address this issue, we have chosen to categorize polyps with a low likelihood of malignancy as "good", those with a moderate likelihood as "bad", and those with a high likelihood as "ugly".

The challenge lies in accurately identifying polyps based on their morphology and endoscopic appearance, often requiring histological examination for diagnosis. Additionally, consensus on assessing submucosal invasion during endoscopy remains difficult, particularly in Western countries. This challenge may lead to both overtreatment and undertreatment when planning resections. Furthermore, treatment should be tailored to each individual patient, considering not only polyp-related factors but also the patient's characteristics and clinical history. Lastly, clinical guidelines do not always clearly define surveillance protocols.

Given that GPs are frequently encountered in clinical practice, it is essential for endoscopists to be knowledgeable in the diagnosis and classification of polyps. This information not only guides treatment but also reflects prognosis. Additionally, evaluating the surrounding mucosa to characterize the environment in which the polyp has developed is crucial for accurate diagnosis. Therefore, endoscopists should perform biopsies not only on the polyps themselves but also on the surrounding tissue. We believe that a thorough and conscious examination during OGD can enhance the stratification of GPs based on their risk of malignancy, thereby ensuring appropriate therapy when required and avoiding unnecessary surveillance. Ultimately, this approach can reduce mortality and morbidity rates while optimizing resource utilization.

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