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INFLAMMATORY FIBROID POLYP: CLINICAL, MORPHOLOGICAL AND IMMUNOHISTOCHEMICAL FEATURES

In order to study the clinical, morphological and immunohistochemical features of inflammatory fibroid polyp, a literature review was conducted. It was found that inflammatory fibroid polyp is one of the rare benign tumors of the gastrointestinal tract, the clinical picture of which depends on the size, location and complications. The complexity of diagnosis is due to its morphological similarity to malignant tumors of the gastrointestinal tract. Immunohistochemical testing is used to exclude malignancy. It was found that inflammatory fibroid polyp is characterized by pronounced diffuse expression of CD34, reactions to DOG1, CD117, S-100 are negative.

Keywords: inflammatory fibroid polyp; stomach; Vanek's tumor; immunohistochemical study

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Introduction. Inflammatory fibroid polyp (IFP) is a rare benign mesenchymal [17] polypoid lesion [4] arising in the mucosa and submucosa throughout the gastrointestinal tract [8] and characterized by the proliferation of vascular-rich fibrous tissue [14] and an eosinophilic infiltrate [4].

These tumors account for 0.1% [8] to 3.0% of all gastric polypoid lesions and are often discovered incidentally during endoscopic examination [2].

The most common organ affected by VFP is the antrum of the stomach (66%-75%) [2, 17], the second most common organ affected is the small intestine (18%-20%), the third is the colon, which accounts for 8.4%, and the rest of the gastrointestinal tract is affected less frequently (less than 3% in total) [14], the gallbladder (1%) [2, 18], the esophagus (1%), the duodenum (1%), and the appendix (<1%). However, the ileum is the

most common site where these polyps cause intussusception [2, 4].

According to the studies by Garmpis et al. [14], when VFP develops in the esophagus, its lower third is most often affected and almost always the lower esophageal sphincter or cardia. In the stomach, after the antral section, the pyloric/prepyloric section (15%), cardia (7%), body of the stomach (4%), then the pylorus and lastly the fundus of the stomach are most often affected [8, 14].

Although a relatively rare disease in clinical practice, VFP has a serious impact on the gastrointestinal function and physical health of patients [19].

The purpose of the study: analysis of publications devoted to the study of clinical, morphological and immunohistochemical features of inflammatory fibroid polyp.

Materials and methods. In this review, we examined the literature devoted to the study of inflammatory fibroid polyp. The search was conducted in the electronic databases PubMed, Web of Science, Google Scholar for 2015-2025. The key words for the search included: inflammatory fibroid polyp, stomach, Vanek's tumor, immunohistochemical study.

A microscopic method was also used, conducted on the basis of the OGBUZ "Belgorod Pathoanatomical Bureau" during our own studies. The material was fixed for 24 hours in 10% neutral buffered formalin, then it underwent histological processing in a closed-type histoprocessor Thermo Scientific Excelsior AS (sequential dehydration, degreasing and impregnation of tissue with paraffin). From the manufactured paraffin blocks,

4- μ m-thick sections were made using a semi-automatic rotary microtome Thermo Scientific HM340e. Sections were stained with hematoxylin and eosin, and for immunohistochemical studies, antibodies produced by Cell Marque (USA) were used: CD34 (clone QBEnd/10), CD117 (clone YR145), DOG1 (clone SP31), S-100 (clone 4C4.9). To obtain images, a Hamamatsu nanozoomer s60 scanner was used.

Results and discussion. Inflammatory fibroid polyps are one of the least common benign tumors localized in the submucosa of the gastrointestinal tract [14].

For the first time, VFP was described as "polypoid fibroma" in 1920 by Konjetzny [1]. In 1949, J. Vanek published a description of 6 cases of similar formations in the American Journal of Pathology [5], called them "submucous granuloma of the stomach with eosinophilic infiltration" and interpreted them as a reactive process, probably of inflammatory origin [5, 8, 14, 18]. Later, in 1953, E. Helwig and A. Ranier first introduced the term inflammatory fibroid polyp [8], which became widespread [14]. Also in the literature there are synonyms for the name VFP, such as "Vanek's tumor", granuloblastoma, neurofibroma, hemangiopericytoma, polypoid myoendothelioma, myxoma, submucous fibroma, hemangiopericytoma [12].

The etiology of VFP remains unclear [7, 13, 14], but it may be associated with chemical, physical, metabolic factors and *Helicobacter pylori* infection [3, 7, 12], as well as allergic reactions, autoimmune processes, genetic/familial predisposition [8, 14], or as an excessive reaction of the body to an unknown irritant [4, 14].

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In turn, it should be noted that the exact pathogenesis of CFP also remains unclear [20]. Yang et al. believe that it can range from reactive lesions with eosinophilic infiltration to tumor lesions [18]. Recent studies in the field of molecular biology [7] have shown that CFPs are often associated with mutations in the platelet-derived growth factor receptor α (*PDGFRA*) gene [3, 7, 8], in exons 12 and 18, and, less commonly, in exon 14 [5]. A number of authors have suggested that CFPs are neoplastic lesions caused by these mutations [7, 20], and not simply inflammatory lesions [20]. Thus, in the fifth edition of the World Health Organization classification of tumors of the digestive system 2019, CFPs are classified as benign tumors of the gastrointestinal tract.

VFP occurs in a wide age range, but most often with a peak incidence from 50 to 70 years of age [4, 5, 8, 12, 14, 18], and is extremely rare in children [4, 5, 15]. This pathology more often affects women (the ratio of women to men is 1.3:1) [8, 14, 16].

Most researchers believe that in most cases, VFP is asymptomatic, but some formations can gradually increase in size and cause complications [5, 7, 12, 14, 20, 21] or be accompanied by vomiting, nausea [14], a feeling of early satiety in the stomach [8], abdominal pain, bleeding from the gastrointestinal tract (large polyps usually collapse and ulcerate superficially) [5], acute abdomen [11, 14, 16, 18]. Severe iron deficiency anemia [3, 4, 14], intussusception or obstruction are also possible if VFP is localized in the small intestine [5, 20].

It should be noted that the clinical picture depends on the size, location and complications [3, 5, 11, 13, 21]. Thus, weight loss [5], epigastric pain and bleeding are the most common symptoms of gastric VFP, while colicky abdominal pain with constipation and bloating are the most common symptoms of intestinal VFP [11]. When localized in the esophagus, it causes dysphagia [5, 6].

Macroscopically, VFPs are small, clearly defined, submucosal formations on a stalk or sessile, arising in the submucosal layer, usually covered by normal mucosa, and protruding into the lumen of the organ; in ¼ of cases, ulceration of the mucosa located above is possible [3, 5, 7, 12]. VFPs can spread to the muscularis propria and even to the serous membrane [7] and be single or multiple [2]. The size of most formations varies from 1 to 12 cm [20], reaching 0.2–20 cm in diameter, but usually have a diameter of 2 to 5 cm [5].

Despite their benign nature, these tumors can mimic other malignancies, so an accurate diagnosis is essential for proper treatment [3]. Histologically, VFPs may resemble gastrointestinal stromal tumors (GISTs), leiomyomas, or other gastrointestinal stromal tumors [7]. GISTs are potentially malignant tumors with varying risks of progression, while VFPs have a favorable prognosis.

According to microscopic examination, the VFP is a submucous formation [17], with a clear border at the level of the muscularis propria [5] and consisting of mononuclear spindle-shaped or stellate stromal cells, edematous stroma with thin-walled blood vessels [3, 12], around which are located the surrounding proliferating fibroblasts [4, 8, 9] with long thin cytoplasmic processes located around the vessels and mucous glands [5], forming a disordered or spiral structure [2]. Mixed inflammatory infiltration is also characteristic, but mainly represented by eosinophils [3, 9, 12, 20] and lymphocytes [7], but plasma cells and histiocytes are also noticeable [5]. Blood vessels are irregularly shaped with muscular walls of varying thickness [8]. Proliferating cells are homogeneous, with abundant cytoplasm and pale rod-shaped nuclei [7]. Spindle-shaped cells proliferate in the submucosa and rarely penetrate the muscularis propria [17]. Mucosal lesions occur in 89% to 93.5% of cases [4]. Thus, some glands may be cystically dilated and inverted into the submucosa, muscularis propria, and tumor stroma. The epithelium of the glands is without atypia, characterized by pronounced hyperplasia and elongation with twisting, expansion, and deformation [18].

Tumor cell nuclei have smooth contours, oval or spindle-shaped, finely granular chromatin, and small nucleoli. The cytoplasm is scanty/elongated and amphiphilic. Mitoses are rare but may occasionally be present in deeper parts of the lesion. Atypical mitoses are never seen [5].

In turn, Righetti et al. [21] believe that, depending on the part of the gastrointestinal tract in which they arise, VFPs look different. Thus, in the stomach, VFPs arise at the base of the proper plate of the mucous membrane, spreading and destroying the muscular layer of the mucous membrane. In turn, Buda et al. [5] believe that the involvement of the proper muscular layer in VFPs of the stomach is rare. They have less pronounced stromal edema and therefore seem denser compared to VFPs in the ileum [21]. According to the authors, in the stomach, as a rule, there is a pronounced perivascular

orientation of various cells, and eosinophil infiltration is more pronounced than with VFP localization in the ileum. Intestinal VFPs are intramural growths that press on the muscularis mucosa, eventually destroying it and penetrating the mucosa, often causing ulceration. They destroy the submucosa and the muscularis propria, often penetrating the mesentery [15]. Tumor growth into the mucosa leads to separation of the gastric glands, which leads to disruption of their structure and atrophy [5].

Our study is consistent with the authors' opinion, since the VFP consists of spindle-shaped and stellate stromal cells with a large number of thin-walled blood vessels and pronounced inflammatory infiltration by eosinophils (Fig. 1 a, b).

In the differential diagnosis of VFP, it is necessary to exclude other spindle cell lesions, such as inflammatory fibrosarcoma, spindle cell carcinomas, gastrointestinal stromal tumors (GIST), schwannomas, perineuromas, and inflammatory myofibroblastic tumors. For this purpose, immunohistochemical examination is necessary [2, 17]. Differentiation without immunohistochemistry is difficult, especially between VFP and GIST, because GIST also occurs in the stomach and often appears as polypoid formations. In the intestine, these tumors can manifest as intussusception, like VFP [2].

In turn, Abboud et al. [2] believe that VFP differs from gastrointestinal stromal tumors in its morphology, submucosal origin, and clinical course, although both of these pathologies have common mutational subtypes of the *PDGFRA* gene.

SCFs are very characterized by pronounced eosinophil infiltration and diffuse positivity for CD34 and vimentin [2, 7, 14], while GISTs are positive for CD117 and DOG1, while SCFs are not [2, 3, 8, 14, 17]. Schwannomas are positive for the S100 protein, while almost all GISTs and smooth muscle cell tumors are negative for the S100 protein [10]. Inflammatory myofibroblastic tumors are positive for anaplastic lymphoma kinase (ALK) and negative for CD34 [17], and desmin is present in leiomyomas [3]. It should be noted that the S-100 protein allows us to exclude tumors with neural differentiation. Solitary fibrous tumor also responds to CD34, but it rarely occurs in the gastrointestinal tract (GIT) and is not associated with inflammation [5]. Desmoid tumors consist of spindle-shaped or stellate cells and are negative for DOG1, S-100 protein [10]. Desmoid tumors also have nuclear expression of beta-catenin, which is not observed in HFP.

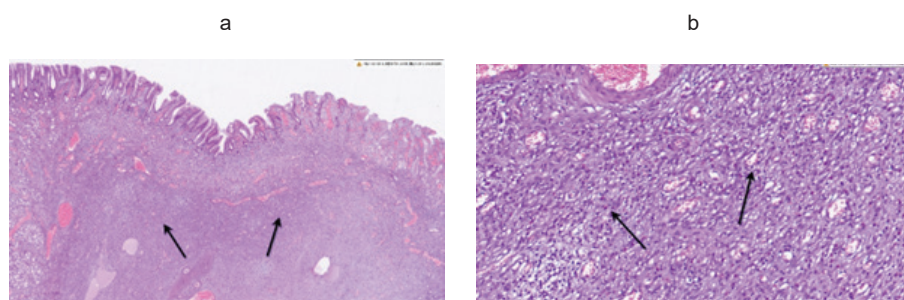


Fig. 1. Inflammatory fibroid polyp of the stomach in a patient born in 1969: a – the specimen shows a tumor-like formation located under the gastric mucosa; b – the tumor-like neoplasm consists of spindle-shaped and stellate stromal cells with a large number of thin-walled blood vessels and pronounced inflammatory infiltration by eosinophils. Magnification a x25, b x200, staining: hematoxylin and eosin

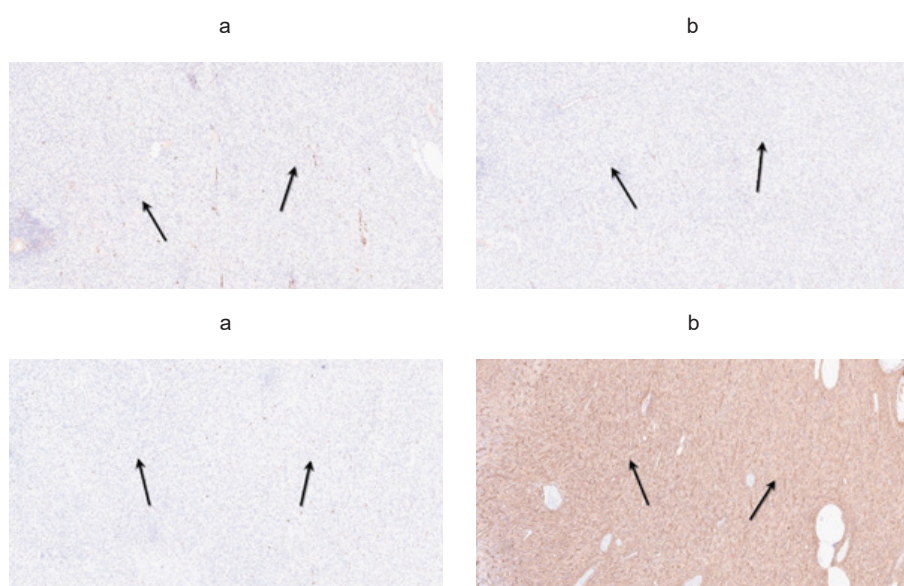


Fig. 2. Inflammatory fibroid polyp of the stomach in a patient born in 1969: a – there is no expression of S-100 in the cells of the neoplasm (staining: S-100), b – there is no expression of DOG1 in the cells of the neoplasm (staining: DOG1), c – there is no expression of CD117 in the cells of the neoplasm (staining: CD117), d – pronounced diffuse cytoplasmic expression of CD34 is determined in the cells of the neoplasm (staining: CD34). Magnification x50

Gastric leiomyomas, both morphologically and immunohistochemically, in some cases can resemble VFP; they are characterized by a diffuse pronounced reaction to α -smooth muscle actin (α -SMA) and desmin [10].

The results of our immunohistochemical study are consistent with the results of other authors, thus, pronounced diffuse expression of CD34 is determined, reactions to DOG1, CD117, S-100 are negative (Fig. 2 a- d).

It should be noted that the results of the studies by Harima et al. [17] indicate that in some cases, VFPs can behave as locally aggressive neoplasms with infiltrative growth and can recur after incomplete resection.

Conclusion. The results of the analysis showed that inflammatory fibroid polyp is one of the rare benign tumors of the gastrointestinal tract, the clinical

picture of which depends on the size, location and complications. Despite the benign nature, these tumors can imitate other malignant neoplasms, so for the correct treatment, it is extremely important to make an accurate diagnosis and here immunohistochemistry is of decisive importance, which we confirmed with our study.

The authors declare no conflict of interest in the submitted article.

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