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Potential pitfalls in reporting non-neoplastic gastrointestinal mucosal biopsies

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Summary. Biopsies taken from the gastrointestinal tract (GIT) comprise a significant percentage of the pathologists' routine work. The variable histology and normal components of each organ along the GIT, as well as the different ways of responding to injury among these organs, can cause morphological changes that could result in potential diagnostic pitfalls. Herein, we review the pathological conditions of the GIT that could cause these diagnostic pitfalls. Our aim was to increase awareness among pathologists and trainees regarding these conditions and provide a pragmatic approach to prevent them and achieve a correct diagnosis.

Key words: Gastrointestinal biopsies, Histopathology, Pitfalls, Viral infection, Pancreatic heterotopia, Increased intraepithelial lymphocytes, Inflammatory bowel disease

Introduction

The range of histological normality of the colon has been documented in various publications so that the reporting pathologists will factor that before regarding them as abnormal. For instance, Feakins, on behalf of the British Society of Gastroenterology (BSG) (Feakins and British Society of Gastroenterology), discussed aspects of the histological spectrum of normality and indicated, for example, that plasma cell gradient differences should be considered between various anatomical locations. The overall lamina propria inflammatory cell density in the cecum and ascending colon was higher than elsewhere. Basal plasmacytosis at these sites should not be considered as a marker of chronic inflammatory bowel disease (IBD) unless other definite histopathological features are present.

Two to three intraepithelial neutrophils may reflect bowel preparation artifacts. Nevertheless, the presence of additional factors should trigger the search for other evidence of inflammation (Levine and Haggitt, 1989). A similar situation is observed in cases in which rectal biopsies show significant lymphoid aggregates, often with lymphoid follicles, without any other features of IBD. In a series of 11 cases, none of the patients developed lymphoma or any other significant clinical features. This feature is called the rectal tonsil and is regarded as reactive (Farris et al., 2008).

Based on the above variation within the range of normality, unwary pathologists may fall into the trap of calling these cases nonspecific chronic colitis. This label, which has neither clinical meaning nor significance, has been liberally used by a wide range of specialized and non-specialized pathologists. In one study, the term chronic non-specific colitis was used for normal biopsies without any consistency by expert gastrointestinal pathologists (Theodossi et al., 1994). Jenkins et al. (1997) indicated that using terminology such as non-specific proctitis/colitis may hide the pathologist's difficulty with diagnostic uncertainty and confuse clinical management. A subsequent study of 35 cases originally reported in one department by general histopathologists as non-specific colitis showed, when subsequently reviewed by experienced pathologists, that there were 13 normal cases, two hyperplastic polyps and one solitary ulcer syndrome (Haboubi and Kamal, 2001). This study concluded that "chronic non-specific colitis was used in that department to cover a heterogeneous group of diseases as well as normal biopsies, and the term is meaningless and should be dropped". These studies stimulated BSG recommendations to advise dropping this terminology. There is now a general consensus that the term non-specific colitis should be abandoned.

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Oesophagus

Mucosal ulceration

Various physical, chemical, and infectious agents can cause injury to the oesophagus (Isaacson, 1982; Maguire and Sheahan, 2012). This injury can manifest as mucosal ulceration with regenerative/reactive atypia, which represents a potential diagnostic pitfall and misdiagnosis of cancer (Isaacson, 1982; Noffsinger, 2009; Maguire and Sheahan, 2012).

Severe gastroesophageal reflux disease (GERD) results in ulcerative and reparative changes that result in the formation of atypical endothelial cells and bizarre-looking stromal cells that mimic poorly differentiated carcinomas (Gill at al., 2003; Maguire and Sheahan, 2012). Immunohistochemical staining for cytokeratin can help differentiate these reparative changes from carcinoma.

Regenerating epithelium adjacent to or underneath areas of mucosal ulceration may exhibit architectural and cytological changes that mimic dysplasia. Differentiating regenerative atypia from dysplasia is difficult and has a wide range of inter-observer variability. Some morphological features help to distinguish regenerative atypia from dysplasia. Dysplasia is characterized by an abrupt transition from atypical to non-atypical epithelium without surface maturation (Montgomery at al., 2001; Odze, 2006). The lack of this abrupt transition and the presence of surface maturation are features that favor regenerative atypia. Moreover, in regenerative atypia, cells maintain polarity. The nuclei have smooth contours with mild nuclear pleomorphism and lack of atypical mitotic figures (Montgomery at al., 2001; Odze, 2006; Grin and Streutker, 2014). In dysplasia, there is a loss of cell polarity, and the nuclei show more stratification and hyperchromasia, as well as atypical mitotic figures. The diagnostic utility of immunohistochemical staining in this situation is controversial. P53 protein is one of the more common markers that have been evaluated in this regard (Weston et al., 2001; Reid et al., 2003; Odze, 2006). It has been found that it has low sensitivity and specificity in differentiating regenerative atypia from dysplasia, therefore, many studies do not advocate its use (Reid et al., 2003; Odze, 2006).

Viral infection

Various infectious agents, including fungi and viruses, can affect the oesophagus (Baehr and McDonald, 1994). These are important causes of oesophagitis, especially in immunocompromised patients, such as those with acquired immunodeficiency syndrome (AIDS) or those treated with chemotherapeutic and immunosuppressive agents (Yang et al., 1996; Calore et al., 1997). The oesophagus responds to these infectious microorganisms via mucosal ulceration, neutrophilic infiltration, and inflammatory exudate formation.

The cytopathic effects of viral infections may mimic those of carcinomas and pose diagnostic challenges. Herpes simplex virus (HSV) affects the squamous epithelium and causes pathognomonic cytopathic changes including multinucleation, nuclear moulding, chromatin margination, and dense intranuclear eosinophilic inclusions (Cowdry type A) (Fig. 1) (Wang et al., 2016). On the other hand, Cytomegalovirus (CMV) infects the stromal and endothelial cells. It causes cytomegaly along with characteristic intranuclear and intracytoplasmic basophilic inclusions (Fig. 2) (Theise et al., 1991). Sometimes, not all of these

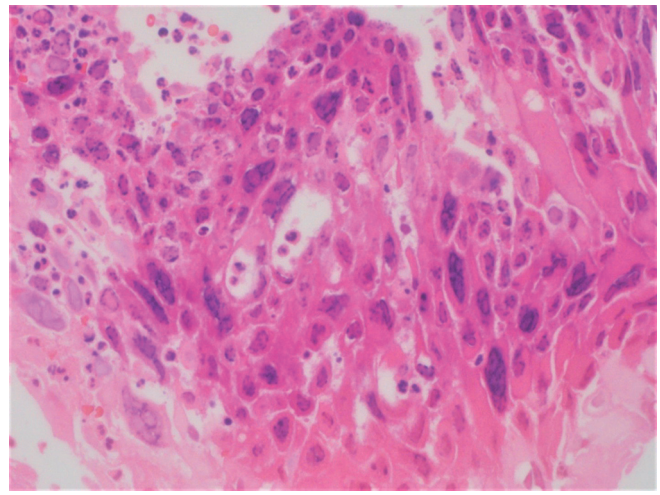

Fig. 1. HSV oesophagitis. Oesophageal squamous mucosa showing cytopathic changes in the form of multinucleation, nuclear moulding and margination of chromatin with intranuclear inclusions. Hematoxylin & Eosin stain. x 200.

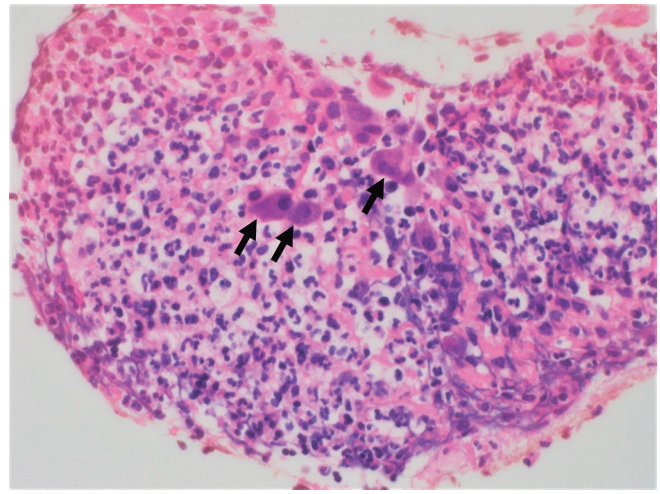

Fig. 2. CMV oesophagitis. Ulcer slough showing cells with cytopathic changes in the form of cytomegaly as well as intranuclear and intracytoplasmic inclusions (arrow). Hematoxylin & Eosin stain. x 200.

morphologic changes are apparent in oesophageal biopsy, and immunohistochemistry for HSV and CMV may be needed to achieve the correct diagnosis (Maguire and Sheahan, 2012).

Crohn's disease

Involvement of the oesophagus in Crohn's disease (CD) is common (Rudolph et al., 2001; Maguire and Sheahan, 2012). Most patients are diagnosed with extraoesophageal CD before the diagnosis of oesophageal involvement (Rudolph et al., 2001). Like severe GERD, CD causes inflammatory changes and mucosal ulceration. The most common histologic finding in oesophageal CD is lymphocyte predominant inflammatory cell infiltrate (Rudolph et al., 2001; Maguire and Sheahan, 2012). This inflammatory cell infiltrate is not limited to the mucosa but characteristically exhibits transmural extension with muscle involvement. This feature is difficult to identify, especially in superficial biopsies. The identification of non-necrotizing epithelioid granulomas is a pathognomonic and useful diagnostic feature; nevertheless, they can only be seen in up to 25% of cases of oesophageal CD (Rudolph et al., 2001). Examining additional tissue levels may aid in revealing these features to avoid misdiagnosing changes in CD as GERD. In addition, clinicopathological correlation with the endoscopic and radiologic findings, which reveal the transmural character of the inflammatory process, is essential to reach a definitive diagnosis.

Stomach and small intestine

Benign signet ring cells infiltrate

Signet-ring cells are morphologically characterized by cytoplasmic mucin, vacuoles, or inclusions that compress crescent-shaped nuclei to the cytoplasmic periphery. These are the hallmarks of signet ring cell adenocarcinoma (Fig. 3). However, epithelial signet ring cells may develop in reactive processes (Wang et al., 2003; Biedrzycki et al., 2005) or in association with non-epithelial neoplasms such as lymphoma arising from mucosa-associated lymphoid tissue (Zamboni et al., 1996). Consequently, they present diagnostic challenges. Table 1 includes a list of GIT diseases associated with non-neoplastic epithelial signet ring cells.

Non-neoplastic epithelial signet ring cells appear to be associated with ulcerations or ischemia, and were limited to the mucosa (Fig. 4). For example, signet ring cells in Peutz-Jeghers polyps have been hypothesized to occur as a result of torsion and ischemia (Chen, 1989). Awareness of the association between non-neoplastic epithelial signet ring cells and degenerated or necrotic mucosa would prevent the potential diagnostic pitfall of malignancy in the GIT.

Non-neoplastic epithelial signet-ring cells express cytokeratins. In the resected specimens, the infiltrative growth pattern is a strong indicator of malignancy (Fig. 5). Careful assessment of the nuclear features of the signet ring cells is essential. The nuclei of signet ring carcinoma cells are larger, more hyperchromatic, and

Table 1. Pathologies of the gastrointestinal tract associated with non-neoplastic epithelial signet ring cells.

1. Pseudomembranous colitis
2. Ulcerative colitis
3. Ischemia
4. Peutz-Jeghers polyps
5. Cystic fibrosis

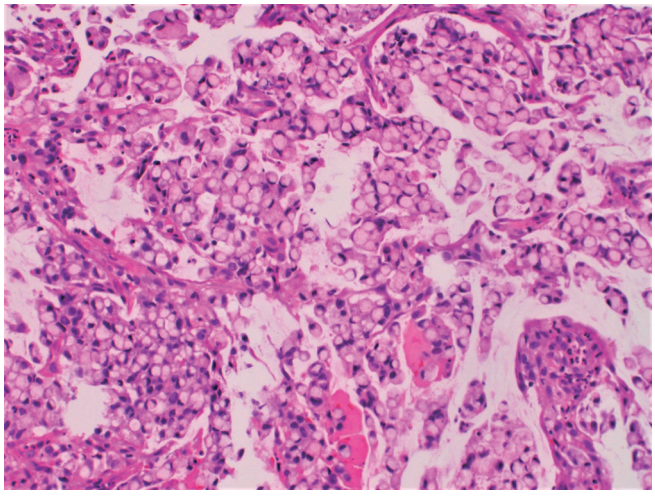

Fig. 3. Signet ring adenocarcinoma. The tumor cells have peripherally located hyperchromatic nuclei with abundant cytoplasmic mucin. Hematoxylin & Eosin stain. x 200.

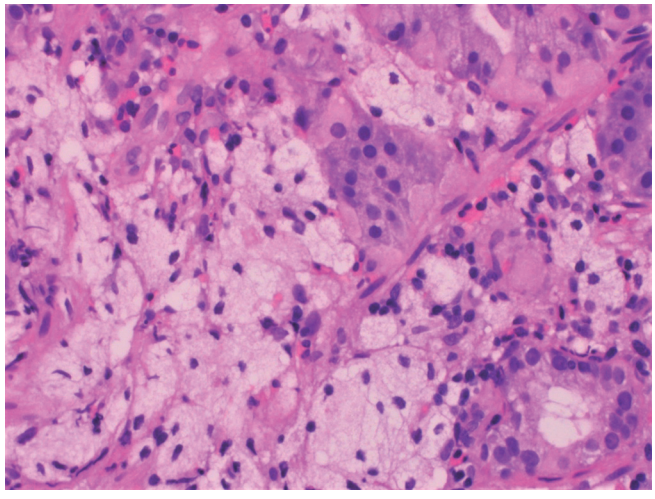

Fig. 4. Non-neoplastic signet ring cells. The cells have bland-looking nuclei with absent hyperchromasia and abundant clear cytoplasm. Hematoxylin & Eosin stain. x 400.

more pleomorphic than the nuclei of non-neoplastic signet ring cells. Moreover, they have single optically clear cytoplasmic vacuole rather than the foamy appearance studded with minute vacuoles found in macrophages. These features may not be apparent in small biopsies, as signet ring cell carcinoma can be cytologically bland. In this setting, distinguishing neoplastic from non-neoplastic epithelial signet-ring cells is challenging. Phenotypic features of signet ring cells may be helpful. In a report on pseudomembranous colitis associated with signet ring cells, Wang et al. (2003) recommended immunohistochemical staining for p53, Ki-67, and E-cadherin in difficult cases. In that study, non-neoplastic epithelial signet ring cells showed strong reactivity for E-cadherin but failed to react with antibodies against p53 and Ki-67. In contrast, the vast majority of neoplastic signet ring cells showed weak or negative staining for E-cadherin and strong reactivity for p53, with a high proliferative index (Ki-67).

Non-neoplastic signet ring cells are not always epithelial in nature; muciphages (i.e., macrophages with mucin in their cytoplasm that can appear packaged in vacuoles) (De Petris et al., 1998), schwannoma cells, and adipocytes (e.g., S100-positive signet ring cells in the subserosa) (Houghton and Herron, 2006) may present as non-neoplastic signet ring cells. Neoplastic signet ring cells have also been reported in numerous extraintestinal neoplasms (e.g. as melanoma, lymphoma, and ovarian tumors). Awareness of the presence of mimickers of malignant signet ring cells and attention to cytomorphological details are necessary for proper interpretation to avoid a potential diagnostic pitfall and unnecessary subsequent surgical resection.

Pancreatic heterotopia

Jean-Schultz reported the first case of pancreatic heterotopia in 1729 (Jiang et al., 2008). The presence of pancreatic tissue outside the pancreas lacks any connection with its anatomical, neural, or vascular connection (de Castro et al., 1946). It has been reported in 1-15% of autopsies (Hill and Lebenthal, 1993).

Most cases are incidental findings given that they are usually undetected and asymptomatic. Symptomatic patients present with abdominal pain, ulceration, bleeding, obstructions, and intussusception. Among symptomatic patients, the peak incidence occurs in the fourth, fifth, and sixth decades of life, with a male-to-female ratio of 3:1. Microscopically, pancreatic heterotopia has been observed in the submucosa, intramuscular, and subserosa (Fig. 6) (Hsia et al., 1999). Owing to the presence of pancreatic heterotopia in intramuscular and subserosal locations, deep biopsy or fine-needle aspiration (FNA) is needed to establish the correct diagnosis (Attwell et al., 2015). Pancreatic heterotopia usually appears as a rounded nodule measuring less than 3 cm (Hsia et al., 1999). It has been found in various locations, most commonly along the GIT (such as gastric antrum, duodenum, jejunum, Meckel diverticulum, and gastroesophageal junction); however, intra-abdominal and extra-abdominal sites have been described (Giorgis and Johnson, 1986; Wang et al., 1996; Hsia et al., 1999; Popiolek et al., 2000; Mourra et al., 2003; Kung et al., 2010).

Four types of pancreatic heterotopia were identified: total heterotopia, exocrine heterotopia (acinar cells only), endocrine heterotopia (islet cells only), and canalicular heterotopia (ducts only) (Fig. 7). When the pancreatic ducts are surrounded by thick muscular bundles, they are called myoglandular hamartomas, adenomyomatous hamartomas, or adenomyomas. Pancreatic heterotopia has diagnostic pitfalls. These include the presence of endocrine heterotopia in the stomach mimicking neuroendocrine tumor (Hammock

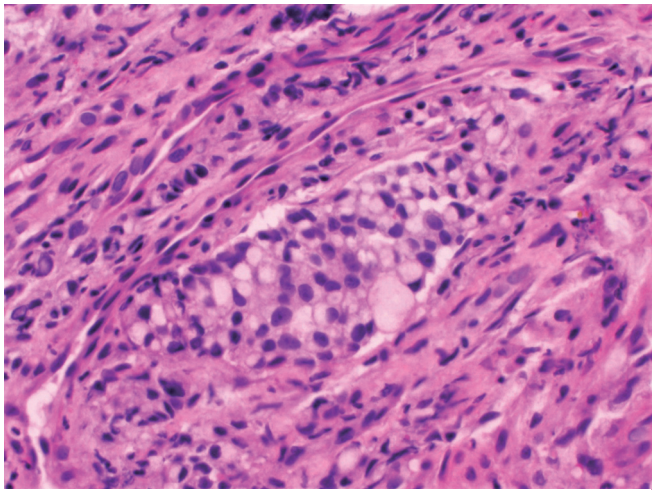

Fig. 5. Signet ring adenocarcinoma. The tumor cells have atypical pleomorphic nuclei and some with prominent nucleoli infiltrating into the muscle, which is a helpful diagnostic feature of malignancy. Hematoxylin & Eosin stain. x 400.

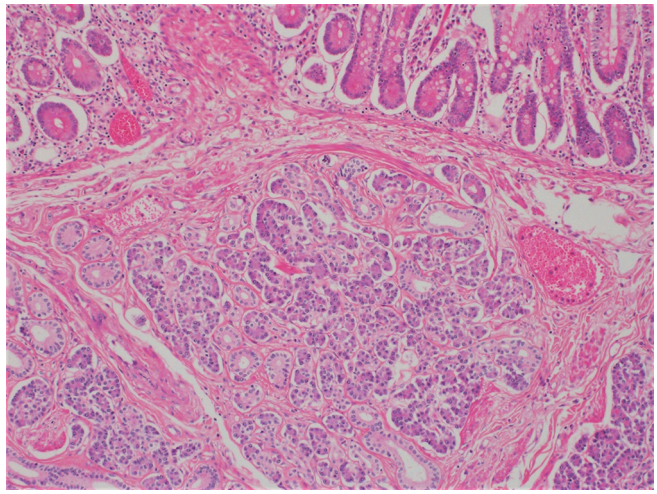

Fig. 6. Pancreatic heterotopia. Photomicrograph depicting a lobule of heterotopic pancreatic tissue in the small intestine at submucosal location. Hematoxylin & Eosin stain. x 100.

and Jorda, 2002), benign heterotopic glands mimicking well-differentiated adenocarcinoma in laparoscopic surgery for a pancreatic mass, duplication cyst mimicking a cystic change in pancreatic heterotopia, and Paneth cells mimicking pancreatic acinar metaplasia in a cytological examination (Cheung and Leong, 1995; Sloots et al., 1999; Chiriatti et al., 2020). As a normal pancreatic tissue, pancreatic heterotopia is vulnerable to pancreatic intraepithelial neoplasms and pancreatic carcinomas (Makhlouf et al., 1999; Zhang et al., 2007). Immunohistochemical staining showed that the epithelial ducts were positive for cytokeratin 7 (CK7) and exocrine acinar cells for trypsin, lipase, and chymotrypsin, while endocrine hormonal islet cells were reactive to insulin, glucagon, and somatostatin, and neuroendocrine cells were reactive to synaptophysin and chromogranin (Lindtner et al., 2007).

Increased intraepithelial lymphocytes (IEL) in the duodenal mucosa with normal villous architecture (lymphocytic duodenosis)

IELs play an important role in the defense against infection (Mayer, 2000; Hayday et al., 2001; Neutra et al., 2001; Cheroutre, 2004). Increased IEL is defined as a count of more than 29 lymphocytes per 100 epithelial cells in 300-500 cells or more than 5 lymphocytes per 20 epithelial cells in 5 well-oriented villous tips (Fig. 8) (Biagi et al., 2004; Jarvinen et al., 2004; Veress et al., 2004). Counting should be away from lymphoid collection because it falsely leads to increased IEL and villous blunting (Dewar and Ciclitira, 2005). Usually, upper endoscopy is performed when a patient presents with abdominal discomfort or pain, weight loss, diarrhea, iron deficiency anemia, persistent vomiting, dysphagia, abdominal distension, and abdominal bloating (Shmidt et al., 2014). Many causes can increase IELs, such as celiac disease (gluten-sensitive enteropathy), Helicobacter pylori infection, peptic injury, bacterial overgrowth, proton pump inhibitor (PPI) use, Crohn's disease, giardiasis, viral gastroenteritis, tropical sprue, cow's milk protein sensitivity, non-steroidal anti-inflammatory drug (NSAID) injury, and some immune conditions (Montgomery and Shearer, 1974; Phillips et al., 1979; Ross and Mathan, 1981; Stern et al., 1982; Klemola, 1988, 1995; Taylor, 1988; Guarino et al., 1995; Ferguson and Kingstone, 1996; Kakar et al., 2003; Chang et al., 2005; Memeo et al., 2005; Brown et al., 2006; Walker et al., 2010). Celiac disease is problematic for endoscopists because the presence of decreased mucosal folds, mucosal nodularity, and mucosal mosaicism is a sensitive but non-specific finding that could also be present in patients with non-celiac disease (Lecleire et al., 2006).

Large intestine and rectum

Primary colonic eosinophilia (PCE) / eosinophilic colitis (EC)

Eosinophils are normally present in the mucosa of the GIT distal to the oesophagus. In the colonic mucosa, the number of eosinophils that are considered normal is controversial; however, there is consensus that their number decreases from the proximal colon to the distal colon (Turner et al., 2017; Walker et al., 2018). The numbers also vary among populations, geographic locations, and cultures. In a recent study by Turner et al., the normal eosinophilic count ranged from 55.7/mm^2 in the right colon to 28.6/mm^2 in the left colon (Turner et al., 2017). Because of this variation in number, what is considered an increase in the eosinophilic content of the

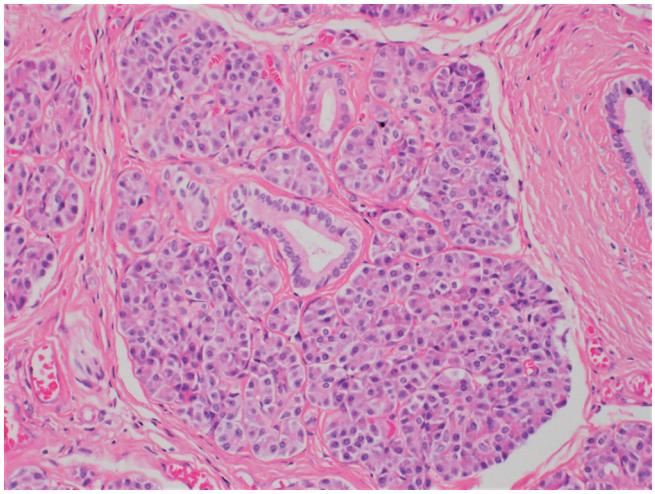

Fig. 7. Pancreatic heterotopia. A well-defined lobule composed of a duct in the center surrounded by acinar cells. Hematoxylin & Eosin stain. x 200.

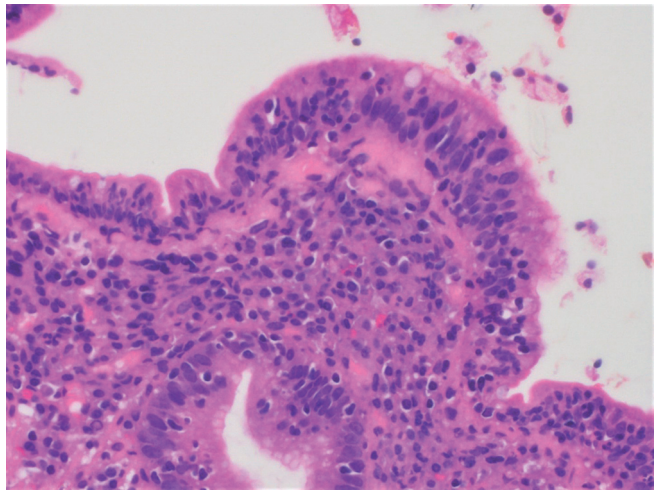

Fig. 8. Lymphocytic duodenosis. Photomicrograph depicting a duodenal mucosal villus with increase in intraepithelial lymphocytes and subtotal villous blunting. Hematoxylin & Eosin stain. x 200.

colonic mucosa is not well-defined. Therefore, histopathological diagnosis of eosinophilic colitis is challenging.

Colonic eosinophilia can occur because of various secondary causes, and parasitic infections are one of the most common causes. Other secondary causes of colonic eosinophilia include inflammatory bowel disease, hypersensitivity to food and drugs, neoplasia, mastocytosis, connective tissue diseases and vasculitis (Alfadda et al., 2011; Abou Rached and El Hajj, 2016; Walker et al., 2018). Once secondary causes are excluded, primary eosinophilia of the colon becomes a rare disease in adults. Patients with PCE/EC can be asymptomatic or present with abdominal pain and diarrhoea (Alfadda et al., 2011; Turner et al., 2017; Walker et al., 2018). Less commonly, they present with malabsorption, weight loss, and intestinal obstruction (Alfadda et al., 2011; Abou Rached and El Hajj, 2016; Giudici et al., 2020). Endoscopic findings are variable and range from normal mucosa to mucosal erythema, erosions, ulcerations, white specks, polyps, or nodules (Alfadda et al., 2011; Abou Rached and El Hajj, 2016; Walker et al., 2018; Giudici et al., 2020). PCE/EC is occasionally associated with peripheral eosinophilia and other atopic conditions.

The histopathological criteria for the diagnosis of PCE/EC are not well defined. In the study performed by Turner et al, they found that patients with well-established clinicopathological diagnosis of EC had eosinophilic mucosal counts that ranged from 166 to 5050/mm^2 (Turner et al., 2017). Odze et al. suggested a density of > 60 eosinophils /10 HPF for the diagnosis of EC (Odze et al., 1993). In addition to the excess number of eosinophils in the lamina propria, the presence of dense aggregates of eosinophils that infiltrate the surface and crypt epithelium with crypt abscess formation, as well as extension into the submucosa and muscularis, are other features that would help in establishing the diagnosis of EC (Fig. 9) (Alfadda et al., 2011; Turner et al., 2017; Walker et al., 2018).

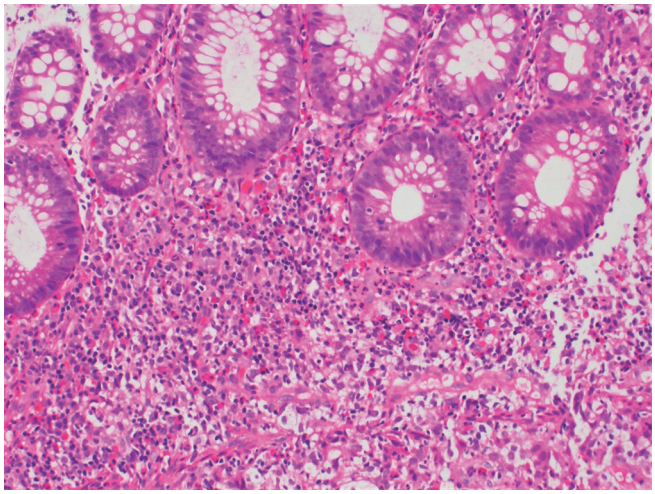

Fig. 9. Eosinophilic Colitis. Photomicrograph showing dense aggregates of eosinophils in the lamina propria of the colonic mucosa that are traversing into the muscularis mucosae. Hematoxylin & Eosin stain. x 200.

In this regard, the terminology used by pathologists is important. It has been suggested that the term "eosinophilic colitis" should be reserved for patients who are clinically symptomatic and/or have significant endoscopic changes, while the descriptive term "primary colonic eosinophilia" should be used for asymptomatic increases in colonic eosinophils after excluding secondary causes (Turner et al., 2017).

Non-steroidal anti-inflammatory drugs (NSAIDs)-induced colonic changes

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used medications and are available as over-the-counter products. They are known to cause various pathologies of the GIT (Russell, 2001; Sostres et al., 2013; Shin et al., 2017; Tai and McAlindon, 2021). The pathophysiology of these changes is mainly related to the inhibitory effects of NSAIDs on cyclooxygenase (COX), which leads to a decrease in prostaglandin (PG) production and the loss of its protective mucosal effects (Russell, 2001; Matsui et al., 2011; Sostres et al., 2013).

NSAID-induced colitis has a nonspecific histological appearance and features overlapping with other colitides (Goldstein and Cineza, 1998; Russell, 2001). This results in mild-to-moderate mucosal inflammation composed of lymphoplasmacytic infiltrates, polymorphonuclear cells, crypt disarray, and focal erosions. These changes fall under the umbrella of "focal active colitis". Other diagnostic considerations for focal active colitis include Crohn's disease, infectious colitis, antibiotic-associated colitis, and acute self-limiting colitis.

Although NSAIDs can cause mild crypt disarray, they do not result in the full-blown crypt architectural distortion that occurs in IBD. Basal plasmacytosis is another feature that is present in IBD but not in NSAID-induced colitis. Non-necrotizing granulomas are a feature of Crohn's disease and are rarely associated with NSAIDs (Goldstein and Cineza, 1998). Given the overlap in microscopic changes between these entities, it is essential to consider NSAID-induced colitis before diagnosing IBD.

NSAIDs also can cause a mild increase in intraepithelial lymphocytes (IELs), and the changes can be misdiagnosed as lymphocytic colitis (Goldstein and Cineza, 1998; Langer et al., 2015). Lymphocytic colitis is a subtype of microscopic colitis in which patients present with chronic non-bloody diarrhea and undergo normal colonoscopy (Langer et al., 2015; Verhaegh et al,. 2016). The diagnosis of lymphocytic colitis depends on the identification of at least 20 IELs per 100 enterocytes located away from lymphoid aggregates and is associated with epithelial damage in the form of

epithelial flattening, mucin depletion, and intracytoplasmic vacuolization (Langer et al., 2015; Verhaegh et al., 2016). Although NSAIDs can cause an increase in IELs, the number of IELs should be sufficient, and the associated epithelial damage should be present to diagnose lymphocytic colitis.

It is essential to mention that NSAIDs had been found to be a major cause for collagenous colitis (Riddell et al., 1992; Goldstein and Cineza, 1998; Langer et al., 2015). Collagenous colitis is another subtype of microscopic colitis, characterized by thickening of the subepithelial collagen plate to more than 10 µm (normal <3 µm) on well-oriented biopsies (Riddell et al., 1992; Langer et al., 2015). It is also associated with surface epithelial damage and detachment as well as an increase in IELs (Riddell et al., 1992; Langer et al., 2015). The foci of increased IELs caused by NSAIDs may represent an early lesion that could progress to lymphocytic/collagenous colitis; however, strict criteria should be applied to diagnose both entities.

One of the pathognomonic pathologies associated with NSAIDs is "diaphragm disease" (Riddell et al., 1992; Price, 2003). NSAIDs result in bowel ulcerations, which may heal through multiple areas of stenosis and result in the formation of these diaphragms (Riddell et al., 1992). The histological features of diaphragm disease are non-specific; however, the disease grossly mimics various pathologies that can cause bowel strictures, such as Crohn's disease, tuberculosis, and lymphoma (Price, 2003). Therefore, biopsy is recommended to rule out more severe disease.

Inflammatory bowel disease (IBD)

Ulcerative colitis versus Crohn's disease

The histopathological diagnosis of IBD is usually a clinicopathological diagnosis and, therefore, is best made at a clinicopathological conference (CPC) when all relevant clinical and imaging data are available. As a complete history is often missing from the histopathology request form, in the interim, the pathologist should issue a preliminary pattern-based report with a differential diagnosis (Haboubi, 2019). IBD is classified into three categories: ulcerative colitis (UC), Crohn disease (CD), and indeterminate colitis (IC). IC cannot be diagnosed using biopsy materials (Satsangi et al., 2006). In one study, when the initial diagnosis of IBD was made without clinical information and subsequently judged against the final diagnosis in the CPC setting, there was a significant difference in favor of CPC-based diagnosis (Haboubi et al., 2004). CD and UC are better differentiated in multiple biopsies than in single biopsies (Bentley et al., 2002). Rectal sparing in UC can be observed if there is local treatment or in the pediatric population. However, when inflammation occurs in the rectal and coecal regions, the so-called coecal patch is accepted as a variant of UC and should not be confused with CD (D'Haens et al., 1997). Granulomas, for instance, are of diagnostic importance only if they are compact and present in the clinical setting of IBD (Fig. 10). Classical teaching of the exclusivity of granulomas to CD is not accurate, as leakage granulomas are not specific to any disease category and can be observed in both UC and CD. Leakage granulomas denote only destructive inflammation of crypts with histiocytic reactions to mucus seepage. Similarly, the presence of 'bare multinucleated' giant cells in the mucosa does not necessarily indicate CD in IBD, as has been reported in UC (Pitt et al., 1993).

Mimics of IBD

As the response to colonic mucosal injuries is fairly limited, there are many histopathological mimics of IBD. Schofield and Haboubi (2020) categorized them into four main categories: infection, iatrogenic, local reaction, and miscellaneous. In the infection category, granulomas are important as they are present in tuberculosis, which is characterized by central caseation necrosis and sarcoidosis, which have granulomatous reactions similar to Crohn's disease but are not associated with other types of inflammatory cell infiltrate or ulceration. In the infection category, the condition of pseudomembranous colitis (PMC) is classically associated with Clostridium difficile infection, but the same features can be seen in acute ischemia and rarely but importantly, amoebic colitis shows the typical organisms lying free amongst the debris in the pseudo membrane, and we have to employ periodic acid-Schiff (PAS) after diastase to recognize the amoebae. In the iatrogenic category of chronic phase radiation bowel disease, crypt distortion and fibrosis of the lamina propria are usually observed, simulating chronic inflammatory

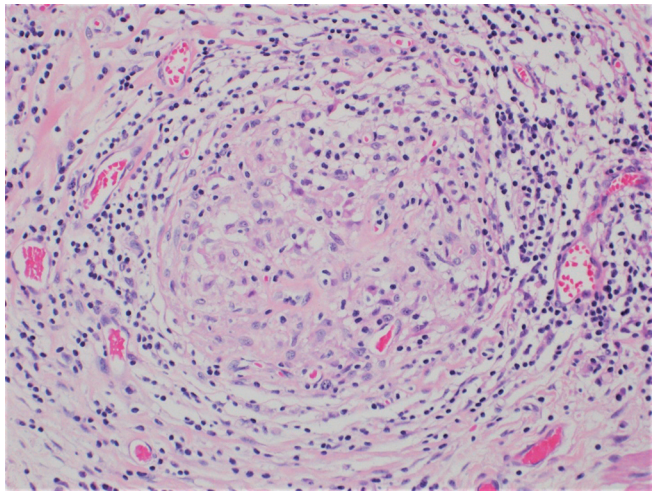

Fig. 10. Non-necrotizing granuloma in Crohn's disease. Photomicrograph shows a well-defined non-necrotizing granuloma composed of epithelioid histiocytes and a few lymphocytes. Hematoxylin & Eosin stain. x 200.

bowel disease. However, focal vascular telangiectasia is not characteristic of IBD (Morris and Haboubi, 2015). In the local reaction category, it is important to focus on segmental colitis-associated diverticular disease (SCADD). This is an uncommon condition seen at the ostia of diverticula and can present in several formats, such as a localized area of inflammation that could mimic UC; it is important to mention that rectal biopsy is normal in cases of SCADD, which helps in differentiating the condition from UC. Occasionally, inflammation in SCADD mimics Crohn's disease with Crohn's-type granulomas. It is also important to emphasize that Crohn's is a clinico-pathological condition, and isolated Crohn's-like lesions in the sigmoid colon, appendix, or gallbladder do not constitute Crohn's disease. However, once such granulomas are observed, it is important for the pathologist to alert the clinician to investigate the rest of the GIT to exclude CD. SCADD sometimes presents endoscopically as a suspicious polyp with histological features of mucosal herniation, such as compartmentalization of diamond-shaped distorted crypts with fibrosis of the lamina propria and proliferation of the muscularis mucosae (Haboubi et al., 2006). In one study, significant thickening of subepithelial collagen-mimicking collagenous colitis was observed (Haboubi and AlQudah, 2012).

Incomplete microscopic colitis (MC)

Microscopic colitis is another strictly clinical pathological condition seen classically in middle-aged women, in which there is watery diarrhea without blood or mucus, associated with normal or near-normal endoscopy, and a specific histological change in which there is either significant deposition of subepithelial collagen of 10 µm or more, known as collagenous colitis, or significant lymphocytic infiltration of the surface epithelium and crypts by 20 lymphocytes or more per 100 epithelial cells, called lymphocytic colitis. In about 6% of cases of MC, the clinical and endoscopic parameters are the same as in classic MC, but the collagen layer is less than 10 µm or the lymphocyte count is less than 20/100 epithelial cells. This condition is called incomplete MC (Sonnenberg and Genta, 2013). Recognizing incomplete variants of MC is important because these patients benefit from the same treatment as classical MC.

Pseudo malignant stromal proliferation

Isaacson divided the atypical cell proliferation observed in the stroma of the GIT into two types. Type-1 is seen only in the stomach and shows atypical epithelial proliferation, while type-2 can be seen throughout the GIT, mainly in the colon. A type-2 Isaacson lesion is an atypical stromal proliferation, which was discussed in detail by Shekitka and Helwig. They described 21 colonic cases with atypical stromal proliferation and confirmed that the tumor was reactive; no sarcoma developed from these lesions. These lesions are usually observed in patients with IBD (mostly ulcerative colitis 'UC') and other chronic illnesses. Immunohisto-chemistry (IHC) revealed fibroblastic/myofibroblastic origin. Misinterpretation of such lesions results in the major resection of benign pathologies (Shekitka and Helwig, 1991).

Type-2 Isaacson lesions can be single or multiple but never fungating masses. Microscopic sections show bizarre, atypical cells close to the ulcer or regenerated mucosa with inflammatory cell infiltration. Mitosis is uncommon in these cells and, if present, is atypical. If high mitotic figures are noted or atypical mitosis is present, the diagnosis should be reconsidered and a proper search for the neoplastic process becomes mandatory. IHC for bizarre cells showed vimentin positivity, with a few positive cases of MSA. Desmin, SMA, CKAE1/AE3, S100, CEA, and EMA are usually negative (lsaacson, 1982; Jessurum et al., 1986).

Multinucleated stromal giant cells of the colonic lamina propria

Various types of multinucleated giant cells, associated with different pathologies, can occur in the colorectum. Bizarre multinucleated stromal giant cells represent a special type of giant cell. Recognition of these cells is essential to avoid the erroneous diagnosis of sarcomas or pseudosarcomatous carcinomas.

Bizarre multinucleated stromal giant cells have been reported to occur in other organs such as urinary tract, lower female genital tract, anus, breast, and skin (Pitt et al., 1993; Wu and Zhao, 2007). In the colon, they can be found in the normal mucosa but are more common in the abnormal mucosa. It has been found that these cells are most commonly associated with polyps, ulcers and inflammatory conditions (Shekitka and Helwig, 1991). It has been suggested that these cells develop in response to local injuries and mucosal irritation. Increased numbers of mast cells have been noted in association with stromal giant cells from other sites (Lloyd et al., 1975; Pitt et al., 1993). The interaction between indigenous stromal cells and mast cells may be related to the development of this type of giant cells. Immunohistochemical and ultrastructural studies have shown that these giant cells exhibit fibroblastic/myo-fibroblastic differentiation (Wu and Zhao, 2007). They are vimentin positive but CD68 negative, a finding that supports a non-histiocytic origin (Pitt et al., 1993; Wu and Zhao, 2007). Morphologically, they are characterized by irregular or stellate shapes. Their nuclei are arranged in a rosette-like or grape-like fashion, and the cells have a small amount of cytoplasm (Fig. 11) (Pitt et al., 1993). The presence of large numbers of these giant cells may provide clues to identify the signs of other associated conditions, including adenomas, ulcerative colitis, and radiation-induced colitis (Pitt et al., 1993; Wu and Zhao, 2007). It has been noted that these giant cells spare the rectum, a finding that could represent a significant histological difference from the

colon (Wu and Zhao, 2007).

Diversion colitis

Morsen et al. were the first to describe diversion colitis as non-specific inflammation in a diverted bowel segment in 1972 (Morson and Dawson, 1972). Glotzer et al. labelled diversion colitis in 1981 (Glotzer et al., 1981). However, the pathogenesis of diversion colitis remains unclear. The most accepted theory is the deficiency of luminal short-chain fatty acids (SCFAs), which are derived from the fermentation of dietary starches by normal bacterial flora (Harig et al., 1989). Another theory is ischemia, which shows that SCFA deficiency increases vascular smooth muscle tunes, leading to ischemia and diversion colitis changes (Villanacci et al., 2007). It most commonly occurs 3-36 months after surgery (Odze and Goldblum, 2015). Histologically, a wide variety of morphological features have been observed, including neutrophilic inflammatory infiltrates with cryptitis and crypt abscess, nodular lymphoid hyperplasia with germinal centers, and crypt architecture distortions (Geraghty and Talbot, 1991; Haque et al., 1993; Villanacci et al., 2007). 87% of diversion colitis cases occur in patients who undergo surgery for inflammatory bowel disease (IBD), whereas 28% occur in patients who undergo surgery for non-inflammatory conditions such as familial adenomatous polyposis (Korelitz et al., 1985). Most patients are asymptomatic, while symptomatic patients present with mucus discharge, bleeding per rectum, and abdominal pain (Glotzer et al., 1981; Komorowski, 1990). After colectomy for ulcerative colitis, the rectal stump area may develop granulomas, fissuring, transmural inflammation, and features resembling those of ischemic and pseudomembranous colitis (Warren et al., 1993). Considering these conclusions, changing the diagnosis of ulcerative colitis to Crohn's would not be appropriate for diverted colonic biopsies (Thorsen, 2007).

Traditional serrated adenoma (TSA) coexistence with other types of polyps

TSA is a rare premalignant colonic polyp with an incidence of 0.06-1.9% colonic polyps (Rosty et al., 2013; Bettington and Chetty, 2015). It usually occurs in patients over 50 years of age, with no sex predilection (Wiland et al., 2014; Bettington et al., 2015). It usually presents as a pedunculated polyp in the rectosigmoid area or as a sessile lesion in the proximal colon (Torlakovic et al., 2008; Bettington et al., 2015). In approximately 50% of cases, other types of polyps may occur with the coexistence of TSA, such as hyperplastic polyps, sessile serrated lesions/polyps, and conventional adenomas (Bettington and Chetty, 2015; Hafezi-Bakhtiari et al., 2015). The gold standard for diagnosis is histopathological examination (Singh et al., 2016). Microscopically, TSA shows a serrated lesion with columnar epithelial cells, eosinophilic cytoplasm, and pencillate nuclei (Figs. 12, 13) (Li and Burgart, 2007). Väyrynen et al. reported the presence of ectopic crypt foci (ECF) as one of the histological features of TSA and defined them as short crypts oriented perpendicular to the main crypt and not reaching the muscularis mucosae. ECF is always present next to villous projections of TSA, but it is rarely present in flat TSA. ECF may also be observed in other types of polyps, such as tubular adenomas (6.5%), tubulovillous adenomas (53.8%), villous adenomas (100%), and traditional serrated adenomas (100%), which can lead to the misdiagnosis of this type of polyp. ECF can also be observed adjacent to colorectal cancer. However, hyperplastic polyps and sessile serrated lesions do not exhibit this feature

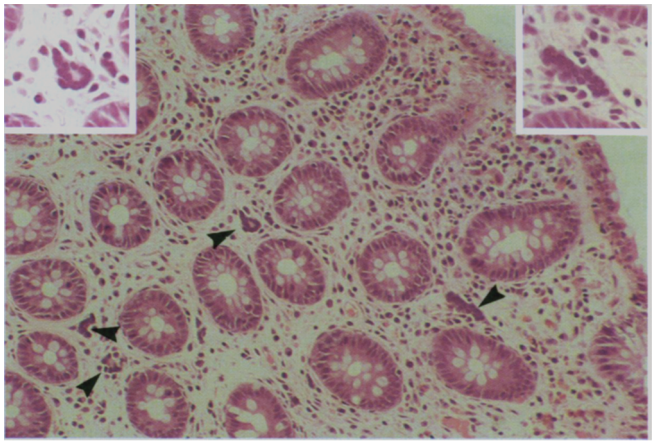

Fig. 11. Multinucleated stromal giant cells (arrowheads). They are located in the lamina propria of the colonic mucosa and have stellate shape and nuclei arranged in grape-like fashion with little amount of cytoplasm. Hematoxilin & Eosin. x 200.

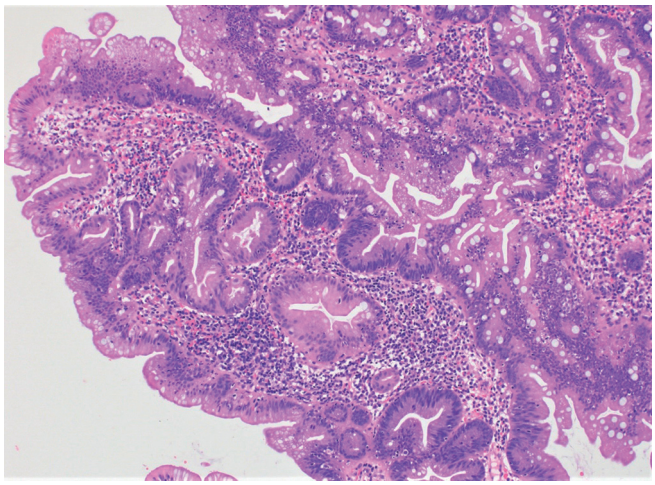

Fig. 12. Traditional serrated adenoma. The crypts are serrated and lined by columnar cells that have eosinophilic cytoplasm. Ectopic crypt foci are present. Hematoxylin & Eosin stain. x 100.

(Väyrynen et al., 2016).

Mucosal prolapse solitary rectal ulcer syndrome (MPSRCUS)

Mucosal prolapse is a condition that was first described by Cruveilhier in the nineteenth century (Cruveilhier, 1830). At that time, it was found to affect the anterior wall of the rectum and was called a solitary rectal ulcer. Later, it was found that this term may not be accurate, as mucosal prolapse lesions can be multiple in up to 30% of cases (Singh et al., 2007; Abid et al., 2012). Ulceration was not required. The histological features are not exclusive to the rectum and can affect other sites, such as the mucosa adjacent to stomas, diverticula, or mass lesions, including adenomas and adenocarcinomas (Singh et al., 2007).

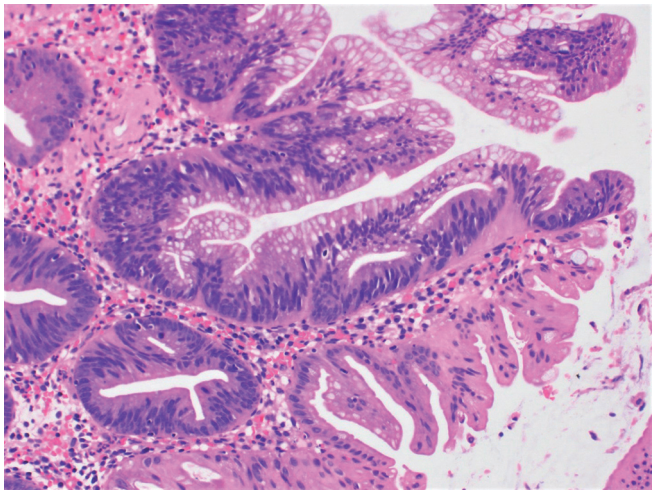

Fig. 13. Traditional serrated adenoma. The cells are eosinophilic and have pencillate nuclei and show low-grade dysplasia in some areas. Hematoxylin & Eosin stain. x 200.

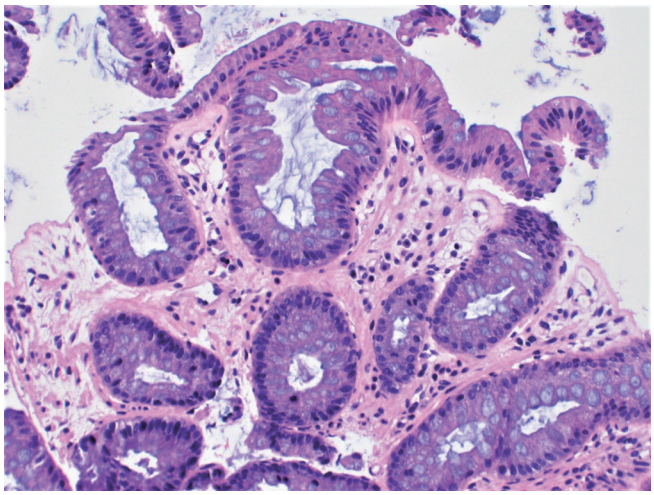

Fig. 14. Mucosal prolapse syndrome. The colonic crypts show hyperplastic changes and the lamina propria is obliterated by fibromuscular hyperplasia. Hematoxylin & Eosin stain. x 200.

The diagnosis of MPSRUS can be challenging, and the presentation of the disease mimics various inflammatory and neoplastic conditions both clinically and endoscopically. Most patients present with rectal bleeding and mucous discharge (Singh et al., 2007; Abid et al., 2012; Sadeghi et al., 2019). A history of constipation and straining during defecation is often present and is characteristic of this condition (Singh et al., 2007; Abid et al., 2012; Sadeghi et al., 2019). The increase in rectal pressure during defecation, as well as direct trauma to the vulnerable rectal mucosa, are believed to be the main mechanisms of disease development (Morio et al., 2005; Sadeghi et al., 2019). Endoscopically, the features of MPSRUS are not specific; most cases manifest as mucosal ulceration. However, non-ulcerative lesions, such as polyps and mucosal erythema, are not uncommon (Singh et al., 2007; Abid et al., 2012). Histopathology is considered the gold standard for confirming the diagnosis and ruling out sinister conditions.

Microscopically, MPSRUS is characterized by a combination of surface mucosal ulceration, fibromuscular obliteration of the lamina propria, hyperplastic crypts with serrated/diamond-shaped architecture, and vascular ectasia (Fig. 14) (Singh et al., 2007; Sadeghi et al., 2019). The presence of ulceration may lead to misdiagnosis of active inflammatory bowel disease; therefore, looking for other signs of chronic IBD is essential to avoid this diagnostic pitfall. Misplacement of the glands into the submucosa in a condition called "colitis cystica profunda" can be misinterpreted as invasive adenocarcinoma. The absence of dysplasia and presence of lamina propria around the misplaced glands are reassuring signs that would prevent the misdiagnosis of adenocarcinoma.

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