An analysis of histopathological features of Crohn's disease in surgical specimens

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Research article

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Abstract

Background

The diagnosis of Crohn's disease is challenging. This study aimed to compare the histological features of Crohn's disease and non-Crohn's disease (i.e., other intestinal inflammatory diseases) in surgical specimens to identify histologic features for differential diagnosis.

Methods

We evaluated patients who were diagnosed with Crohn's disease (n = 171) and non-Crohn's disease (n = 215) between 2010 and 2015 and underwent surgical bowel resection. The frequency of histological features in surgical resection specimens were compared between these two patient groups.

Results

Transmural inflammation, subserosal lymphoid aggregates, fissures or sinus-like structures, granulomas or granuloma-like nodules, abnormalities of the enteric nervous system, and mucosa structure alterations (i.e., *muscularis mucosae* thickening or mucosal atrophy with pseudopyloric gland metaplasia) were more frequent in Crohn's disease than non-Crohn's disease ($p < 0.001$ for all). A set of 3 of the above pathological features had a specificity of 93.5% for Crohn's disease. Some of the above histologic features were further grouped as chronic inflammatory change that includes granulomas or granuloma-like nodules, lymphoid aggregates in the *muscularis propria* or subserosa, fissures or sinus-like structures, and architectural abnormality (i.e., the presence of abnormal enteric nervous system and/or mucosa structure alterations). A combination of transmural inflammation, chronic inflammatory change, and architectural abnormality had a sensitivity of 92.4% and a specificity of 97.7% for Crohn's disease.

Conclusions

A combination of transmural inflammation, chronic inflammatory change, and architectural abnormality in surgical bowel resection specimens is diagnostic for Crohn's disease.

Background

Gut inflammatory bowel disease (IBD) is a group of chronic gastrointestinal disorders characterized by relapsing and remitting idiopathic inflammation of the gastrointestinal tract. The two most common types of IBDs are ulcerative colitis and Crohn's disease (CD). The diagnosis of CD is confirmed by clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical investigations[1]. The European Crohn's and Colitis Organisation (ECCO) consensus has proposed a diagnostic criteria for CD in surgical specimens. CD can present as the following microscopic features in

surgical specimens: transmural inflammation aggregated inflammatory pattern and transmural lymphoid hyperplasia; submucosal thickening (expansion by fibrosis–fibromuscular obliteration and inflammation); fissure; sarcoid granuloma (including in lymph nodes); abnormalities of the enteric nervous system (submucosal nerve fiber hyperplasia and ganglionitis); and relatively unchanged epithelia–mucin preservation [1]. Thus it has been suggested that a diagnosis of CD can be made in surgically resected bowel samples when three of the above features are present in the absence of granulomas, or when an epithelioid granuloma is present with one other feature provided that specific infections are excluded [1, 2]. However, although this set of diagnostic criteria plays an important role in CD diagnosis in surgically resected bowel specimens, its sensitivity and specificity have not been investigated. The incidence of CD has been steadily increasing in China in recent years [3]. Large-scale multicenter studies examining the diagnostic sensitivity and specificity are needed to validate the above diagnostic criteria.

This study aimed to review the histologic features of CD in surgically resected bowel specimens and validate the sensitivity and specificity of a combination of the examined histologic features for CD diagnosis.

Methods

Study design and patients

We evaluated 171 and 215 patients who were diagnosed with CD and non-CD, respectively, between 2010 and 2015 and who underwent surgical bowel resection. The patients were identified using the pathology database at Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University. Those with tumor or acute intestinal infarction were excluded. All included patients underwent intestinal surgery and were followed up for at least 12 months.

Clinical diagnosis

CD diagnosis was confirmed by clinical, endoscopic, radiological, and histological examinations [1]. The clinical diagnosis of infectious colitis was based on positivity of the pathogenic organism, and symptom relief and endoscopy healing after 6 months of antibiotic therapy without recurrence. Other causes of enteritis such as intestinal perforation, diverticulum, chronic obstruction, fistula, mesenteric arteriovenous thrombosis, appendicitis, vascular malformation, Behçet's disease, abdominal cocoon, ectopia, mucosal prolapse, eosinophilic enteritis, and necrotizing enterocolitis were diagnosed based on clinicohistologic features.

Microscopic analysis

Surgical pathology reports and slides were retrieved and reviewed by two pathologists for the following histological features: transmural inflammation, transmural lymphoid aggregates, fissures and related structures, granulomas (including granulomas in lymph nodes) and granuloma-like nodules,

abnormalities of the enteric nervous system, *muscularis mucosae* thickening, mucosal atrophy, and pseudopyloric gland metaplasia. They were defined as follows:

1. Transmural inflammation: the presence of varying degree of chronic inflammatory cells such as lymphocytes and plasma cells in all layers of the bowel wall (Figure 1A).
2. Transmural lymphoid aggregates: the presence of lymphoid aggregates, with or without germinal centers, anywhere in the bowel wall, from the mucosa to the subserosa (Figure 1A). The linear distribution of lymphoid aggregates were referred to as “the string of beads” (or “Crohn’s rosary”) (Figure1B) [4,5,6]. Transmural lymphoid aggregates were divided into two types according to the distribution: submucosa and beyond submucosa (involving *muscularis propria* or subserosa). Further, frequent lymphoid aggregates were defined as 3 or more per low power field [7].
3. Granulomas and granuloma-like nodules: a granuloma was defined a discrete collection of at least five epithelioid cells (activated histiocytes with homogeneous eosinophilic cytoplasm), with or without accompanying multinucleate giant cells, in the bowel wall or lymph nodes [8,9] (Figure 2A-B). Caseation should be absent. Histiocytic reaction around a ruptured crypt or isolated multinucleate giant cell were excluded. The granuloma-like nodules were composed of non-epithelioid histiocytes without multinucleated giant cells and with clear boundaries. The granuloma-like nodules in the mucosa were excluded. (Figure 2C-F).
4. Fissures and related structures: fissures were identified as deep, flask-shaped, or knife-like ulcers that extended into the submucosa or *muscularis propria* and were lined by plump fibroblasts, many neutrophils, histocytes and even foreign body giant cells (Figure 3A-B). Abscess was a localized collection of pus surrounded by inflamed tissue (Figure 3C). Sinuses were formed by fissuring ulcers extending into or through the colonic wall and usually communicating with other fissuring ulcers extending laterally to produce a complex network. Sinuses that did not demonstrate an opening to intestinal lumen in slides, but have long or complex configuration were referred to as “sinus-like structures” (Figure 3D) [4]. Epithelium may be found in the sinus-like structures (Figure 3E) [4,10].
5. Abnormalities of the enteric nervous system: this was defined as the presence of large, abnormal, irregular nerve bundles throughout the submucosa, *muscularis propria* or subserosa (Figure 4A-C). Perineural chronic inflammation may be seen.
6. *Muscularis mucosae* thickening: this was defined as increased thickness of *muscularis mucosae* due to hyperplasia and/or fibrosis. In some cases, the submucosa was present (Figure 5A), whereas it was obliterated in some cases (Figure 5B).
7. Mucosal atrophy: this was defined as chronic mucosal change such as villous atrophy and crypt distortion with chronic inflammatory cells (especially lymphocytes and plasma cells) in the lamina propria (Figure 5C).
8. Pseudopyloric gland metaplasia: this was defined as the presence of small clusters of small round glands in deep mucosa with clear neutral mucinous cytoplasm (Figure 5D).

Statistical analysis

The c2 and Fisher's exact probability tests were used to evaluate differences in the frequency of the histological parameters between the CD and the non-CD group. Statistical analysis comparing trends between different parameters was performed using Kendall-tau. All statistical analyses were performed using IBM SPSS Statistics Version 19.0 (IBM Corporation, Armonk, NY, USA). A *p* value of <0.05 was considered statistically significant.

Results

Clinical features

Patients in the CD group were significantly younger during surgical bowel resection than patients in the non-CD group (mean age 35±11.5 years (range, 15–64 years), vs 56±17.9 years (range, 1–96 years), *p*<0.001). There was no significant difference in the male:female ratio between the CD and the non-CD group (1.71 vs. 1.91, *p*=0.117). Non-CD included intestinal perforation (n=57), diverticulum (n=39), chronic intestinal obstruction (n=31), ulcerative colitis (n=13), special infectious diseases (14), fistula (n=12), mesenteric arteriovenous thrombosis (n=7), appendicitis (n=7), vascular malformation (n=5), ectopia (n=5), and other miscellaneous or unknown etiologies (n=25) (Table 1).

Table 1. Clinicodemographics and clinical diagnosis in CD and non-CD patients

	CD group (N=171)	Non-CD group (N=215)
Age (mean ± SD), year	35±11.5	56±17.9
Male to female ratio	108:63	141:74
Type of surgical specimens		
Small intestine resection	63	101
Ileocecal resection	84	40
Colon resection	15	73
Small and large intestine resection	9	1
Type of enteropathy		
Intestinal perforation	N/A	57
Diverticulum	N/A	39
Chronic intestinal obstruction	N/A	31
Ulcerative colitis	N/A	13
Special infectious disease	N/A	14
Tuberculosis	N/A	5
EB virus	N/A	5
Yersinia	N/A	4
Fistula	N/A	12
Mesenteric arteriovenous thrombosis	N/A	7
Appendicitis	N/A	7
Vascular malformation	N/A	5
Ectopia (stomach, pancreas)	N/A	5
Behçet's disease	N/A	1
Abdominal cocoon	N/A	1
Mucosal prolapse	N/A	1
Eosinophilic enteritis	N/A	1
Necrotizing enterocolitis	N/A	1
Uncertain etiology	N/A	20

Abbreviations: CD: Crohn's disease; non-CD: other forms of enteritis except Crohn's disease; SD: standard deviation; EB virus: Epstein-Barr virus

Histological features

The histological features in CD and non-CD are shown in Table 2. The frequency of transmural inflammation was significantly higher in CD resection specimens than in non-CD resection specimens (100% vs. 35.6%, $p<0.001$). There was no significant difference in the rate of submucosal lymphoid aggregates (4/171 (2.3%) vs in 8/215 (3.7%), $p=0.560$), but lymphoid aggregates in the *muscularis propria* or subserosa were significantly more frequent in CD cases (89.5% vs 7.0%, $p<0.001$).

Table 2. Histological features of the surgically resected bowel specimens by group

Histological parameters	CD group (N=171)	Non-CD group (N=215)	*p* value
Transmural inflammation	171/171 (100%)	70/215 (32.6%)	0.000
Transmural lymphoid aggregates			
Submucosa	4/171 (2.3%)	8/215 (3.7%)	0.560[a]
Muscularis propria or subserosa	153/171 (89.5%)	15/215 (7.0%)	0.000
Granulomas and granuloma-like nodules			
Granuloma-like nodules	20/171 (11.7%)	0/215 (0%)	0.000[a]
Granulomas	121/171 (70.8%)	14/215 (6.5%)	0.000
Granulomas or granuloma-like nodules	141/171 (82.5%)	14/215 (6.5%)	0.000
Fissures and related structures			
Fissures	94/171 (55.0%)	18/215 (8.4%)	0.000
Abscesses	31/171 (18.1%)	47/215 (21.7%)	0.364
Sinus-like structures	80/171 (46.8%)	4/215 (1.7%)	0.000[a]
Fissures or sinus-like structures	125/171 (73.1%)	22/215 (10.2%)	0.000
Abnormalities of the enteric nervous system	81/171 (47.4%)	7/215 (3.3%)	0.000
Muscularis mucosae thickening			
Submucosa presence	28/171 (16.4%)	1/215 (0.5%)	0.000[a]
Submucosa obliteration	110/171 (64.3%)	1/215 (0.5%)	0.000[a]
Submucosa presence or obliteration	138/171 (80.7%)	2/215 (0.9%)	0.000[a]
Mucosa structural alterations			
Mucosal atrophy	170/171 (99.4%)	49/215 (22.8%)	0.000
Pseudopyloric gland metaplasia	150/171 (87.7%)	20/215 (9.3%)	0.000
Mucosal atrophy with pseudopyloric gland	149/171	16/215 (7.4%)	0.000

metaplasia	(87.1%)

[a]: Fisher's exact probability tests

Abbreviations: CD: Crohn's disease; non-CD: other forms of enteritis except Crohn's disease

Granulomas were significantly more present in CD cases than in non-CD cases (121/171 (70.8%) vs. 6.5%, $p<0.001$). There were 6/171 (3.5%) CD patients who had granulomas only in the lymph nodes. Granuloma-like nodules were present in 20/171 (11.70%) of CD cases but none of the 215 non-CD cases ($p<0.001$).

Fissures (55.0% vs. 8.4%, $p<0.001$) and sinus-like structures (46.8% vs. 1.9%, $p<0.001$) were more frequent in CD cases. Meanwhile the frequency of abscesses was not significantly different (18.1% vs. 21.9%, $p=0.364$).

Muscularis mucosae thickening with intact submucosa (16.4% vs. 0.5%, $p<0.001$) or obliterated submucosa (64.3% vs. 0.5%, $p<0.001$) was also more common in CD than in non-CD cases.

Abnormalities of the enteric nervous system were more common in CD than in non-CD cases (47.4% vs. 3.3%, $p<0.001$). Mucosal atrophy (99.4% vs. 22.8%, $p<0.001$) and pseudopyloric gland metaplasia (87.7% vs. 9.3%, $p<0.001$, respectively) were also significantly more common in CD.

Correlation analysis revealed a significant correlation between *muscularis mucosae* thickening and mucosal atrophy (Kendall's tau_b correlation coefficient 0.753, $p<0.001$). Therefore, we combined them into one pathological index, that is, mucosa structure alterations (*muscularis mucosae* thickening or mucosal atrophy with pseudopyloric gland metaplasia), and this feature was more common in CD patients than in non-CD patients (93.0% [159/171] vs. 7.9% [17/215], $p<0.001$).

Further analysis revealed that the presence of at least 3 of the 6 studied features (transmural inflammation, lymphoid aggregates in the *muscularis propria* or subserosa, granulomas or granuloma-like nodules, fissures or sinus-like structures, abnormalities of the enteric nervous system, and mucosa structure alterations (*muscularis mucosae* thickening or mucosal atrophy with pseudopyloric gland metaplasia)) had a sensitivity of 98.8% and a specificity of 93.5% for distinguishing CD from non-CD cases (Table 3).

Table 3. Diagnostic value of two composite histological features in distinguishing CD from non-CD cases

No. of histological features	CD	Non-CD	Se (%)	Sp (%)	PPV%	NPV%
³3 of 6 histological features[a]	169/171	14/215	98.8	93.5	92.4	99.0
Transmural inflammation + ³1 feature of chronic inflammation changes[b]+ ³1 feature of architectural abnormalities[c]	158/171	5/215	92.4	97.7	96.9	94.2

[a]: The 6 histological features were as follows: transmural inflammation; granulomas or granuloma-like nodules; lymphoid aggregates in the *muscularis propria* or subserosa; fissures or sinus-like structures; abnormalities of the enteric nervous system; mucosa structure alterations (*muscularis mucosae* thickening or mucosal atrophy with pseudopyloric gland metaplasia)

[b]: The chronic inflammatory changes were as follows: granulomas or granuloma-like nodules; lymphoid aggregates in the *muscularis propria* or subserosa; fissures or sinus-like structures

[c]: The architectural abnormalities were as follows: abnormalities of the enteric nervous system; mucosa structure alterations (*muscularis mucosae* thickening or mucosal atrophy with pseudopyloric gland metaplasia)

Abbreviations: CD: Crohn's disease; non-CD: other forms of enteritis except Crohn's disease; No.: number; Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value

Then, we simplified the 5 studied histological features other than transmural inflammation into two categories: (1) chronic inflammatory changes and (2) architectural abnormalities. Chronic inflammatory changes were characterized by the presence of granulomas/granuloma-like nodules, lymphoid aggregates in the *muscularis propria* or subserosa, and/or fissures/sinus-like structures. Meanwhile, architectural abnormalities were characterized by the presence of abnormalities of the enteric nervous system and/or mucosa structure alterations (*muscularis mucosae* thickening or mucosal atrophy with pseudopyloric gland metaplasia). A combination of transmural inflammation, chronic inflammatory changes, and architectural abnormalities had a sensitivity of 92.4% and specificity of 97.7% for distinguishing CD from non-CD cases.

Discussion

The diagnosis of CD is based on a combination of clinical, endoscopic, radiological, and histological parameters. Although the ECCO consensus had proposed diagnostic recommendations for Crohn's surgical specimens, no study has evaluated its diagnostic value [1]. Although previous studies have reported the histological features in Crohn's surgical specimens [11, 12], thus far, no study has compared the histological features between CD and non-CD. In the present study, we investigated the combination of histological features that can be useful for differential diagnosis of CD from other forms of enteritis.

Univariate analysis showed that transmural inflammation, lymphoid aggregates in the *muscularis propria* or subserosa, granulomas or granuloma-like nodules, fissures or sinus-like structures, abnormalities of

the enteric nervous system, mucosa structure alterations (e.g., *muscularis mucosae* thickening or mucosal atrophy with pseudopyloric gland metaplasia) are diagnostic for CD, consistent with previous studies [11, 12]. Other features such as abscesses and submucosal lymphoid aggregates were of little value in distinguishing CD and non-CD. Granulomas are characteristic findings in CD and have been reported to be present in 52–75% of resection specimens [11, 13, 14, 15]. In line with the literature, granulomas were found in 70.8% of CD cases (including 6 cases whose granulomas were only in the lymph nodes) in this study.

We also compared the frequency and characteristics of granuloma-like nodules between CD and non-CD cases and found that they were only present in CD, although the overall frequency was low (11.7%). These results indicate that the presence of granuloma-like nodules in the submucosa and beyond in surgically resected specimens could indicate CD and thus the specimen should be thoroughly investigated for further evidence.

Hypertrophy of nerve fibers accompanied by infiltration of chronic inflammatory cells is the most primary abnormality of the enteric nervous system. Although nerve hypertrophy is found in less than 50% of CD cases, it has high specificity as it only occurs in 3.3% of non-CD cases. Thickening of the *muscularis mucosae* by hyperplasia or fibrosis with or without submucosal obliteration is also common in surgical specimens of CD. The results showed that regardless of whether the submucosa was obliterated or not, *muscularis mucosae* thickening in a surgically resected bowel specimen should prompt careful search for more evidence of CD.

We further examined two combinations of the six histologic features examined in this study, namely, (1) transmural inflammation; (2) lymphoid aggregates in the *muscularis propria* or subserosa; (3) granulomas or granuloma-like nodules; (4) fissures or sinus-like structures; (5) abnormalities of the enteric nervous system; and (6) mucosa structure alterations (*muscularis mucosae* thickening or mucosal atrophy with pseudopyloric gland metaplasia). The results showed that the presence of at least 3 of the above 6 features in the surgically resected bowel specimens had a sensitivity of 98.8% and specificity of 93.5% for distinguishing CD from non-CD cases.

Further, we evaluated the diagnostic value of the combination of transmural inflammation, one chronic inflammatory change (i.e., granulomas/granuloma-like nodules, lymphoid aggregates in the *muscularis propria* or subserosa, or fissures or sinus-like structures), and one structural abnormality (i.e., abnormalities of the enteric nervous system or mucosa structure alterations that include *muscularis mucosae* thickening or mucosal atrophy with pseudopyloric gland metaplasia). This simplified combination had a sensitivity of 92.4% and a specificity of 97.7% in diagnosing CD. The 5 non-CD cases misclassified as CD using this combination included 2 cases of tuberculosis, 1 case of ulcerative colitis, 1 case of chronic obstruction, and 1 case of uncertain etiology. Chronic active Epstein-Barr virus infective enteritis may present with CD-like features such as transmural inflammation, fissuring ulcers, and lymphoid aggregates in intestinal wall[16]. However, all five cases of chronic active Epstein-Barr virus

infective enteritis in this study were correctly classified as non-CD cases using this simplified combination.

The strengths of our study include the relatively large sample size from a single tertiary medical center with expertise in IBD care. This allowed for a relatively uniform tissue sampling of the surgically resected specimens. Further, all patients were followed up for at least 12 months. In addition, all slides were independently reviewed in detail by two pathologists experienced in IBD pathology. However, our study also had some limitations that need to be considered when interpreting the findings. First, data availability and quality were limited to those available within the medical records. For example, some cases lacked detailed information on medical treatment prior to surgical bowel resection. In addition, macroscopic features were not thoroughly documented in the surgical pathology report and thus could not be included in this study. Further, all patients were from a tertiary medical center, and this may have introduced referral bias. Accordingly, conclusions from this study may not be applicable to other practice settings. Finally, slides were only reviewed by two pathologists. Despite these limitations, we believe that this study is valuable because it provides important information for CD diagnosis in surgically resected bowel specimens. Large-scale prospective studies are needed to confirm our findings and to standardize the diagnosis of CD in surgically resected bowel specimens, which would be important and particularly relevant in developing countries where the incidence of CD is increasing but the pathological expertise needs to be improved.

Conclusion

Our study highlights the histological features prevalent in surgically resected CD bowel diseases. In addition to clinical, endoscopic, and radiographic information, a combination of histologic features including transmural inflammation, chronic inflammatory changes, and architectural alterations in surgically resected bowel specimens helps distinguish CD from non-CD.

Abbreviations

IBD: Inflammatory bowel disease; CD: crohn’s disease; ECCO: European Crohn’s and Colitis Organisation; non-CD: other forms of enteritis except Crohn’s disease; SD: standard deviation; EB virus: Epstein-Barr virus; No.: number; Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value.

Declarations

Acknowledgements

Not applicable.

Authors’ contributions

ZJ and TF made substantial contributions to the conception and design of this study; YF wrote the manuscript; JX, TZ, JJ kindly provided some advices; QC provided the clinical advices; ZJ and XL revised the manuscript for important intellectual content; ZJ gave final approval to submit the manuscript for publication.

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Availability of data and materials

All data generated or analyzed during this study are included in the article.

Ethics approval and consent to participate

The retrospective study was approved by the ethics committee of our hospital (NO. 20180226-51). Individual consent was not necessary according to local ethical regulation in a retrospective investigation based on the hospital data management system as performed here.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

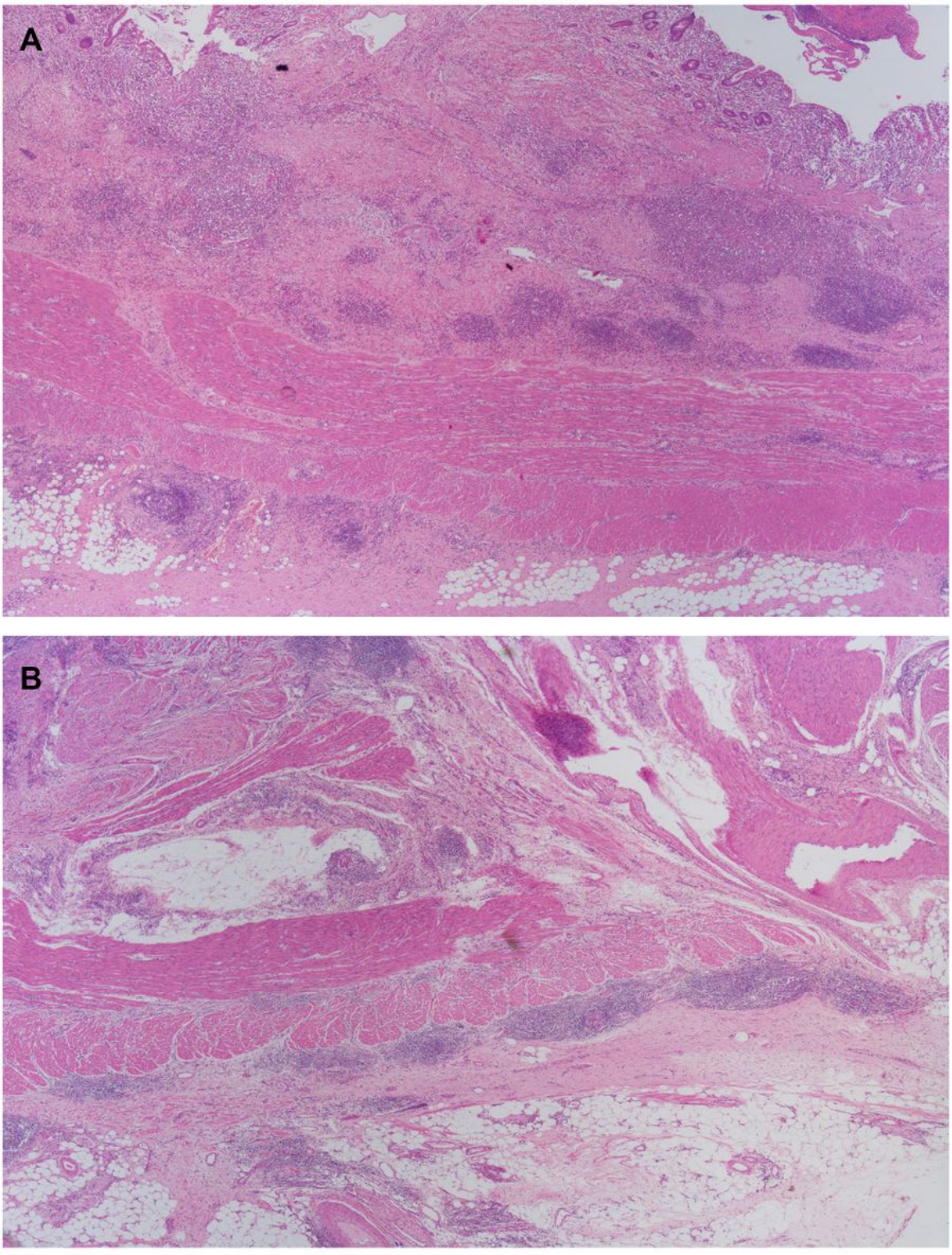

Figure 1

Transmural inflammation and transmural lymphoid aggregates. (A) Transmural inflammation and lymphoid aggregates HE×20. (B) “The string of beads” in the subserosa HE×20.

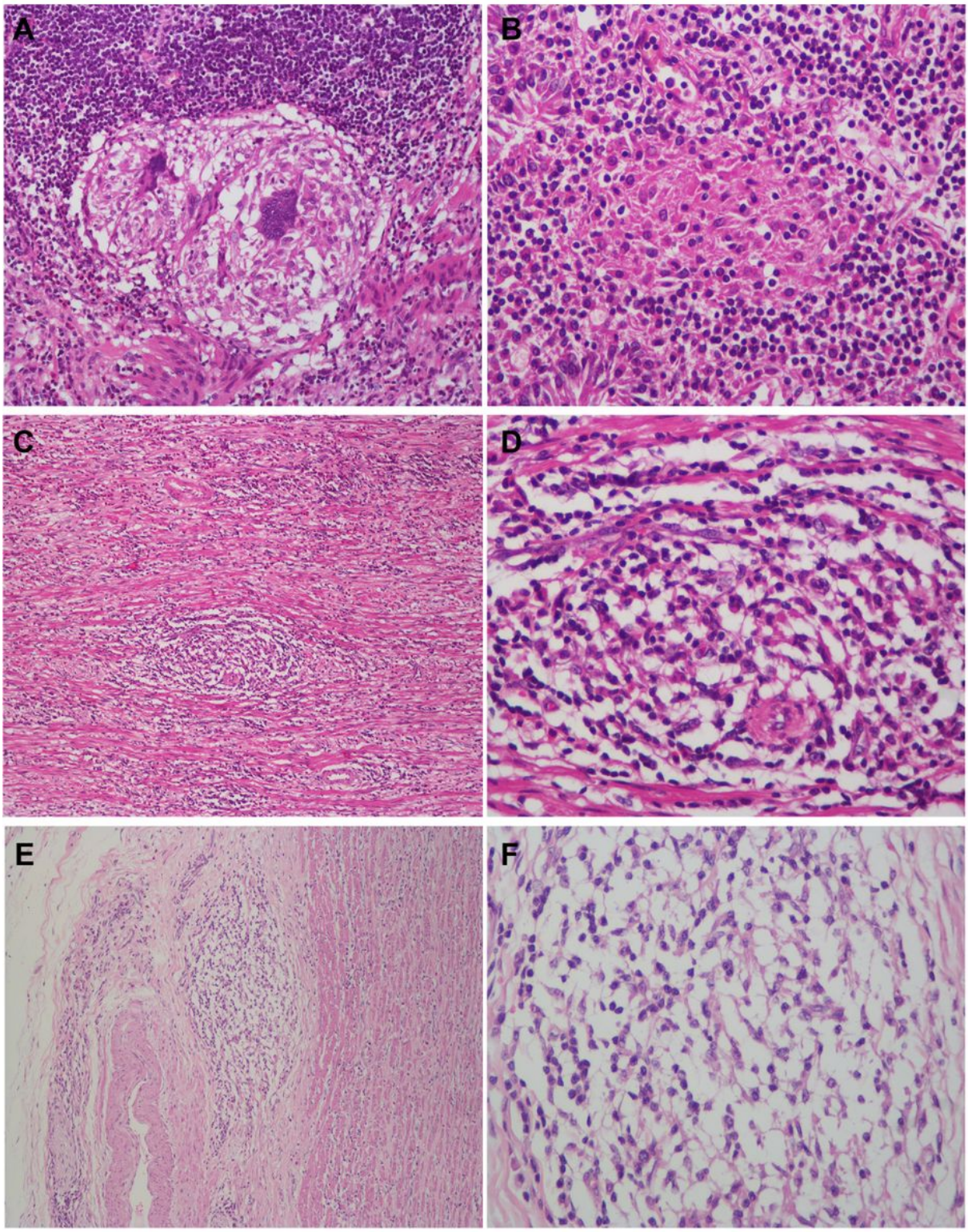

Figure 2

Granulomas and granuloma-like nodules. Granuloma is a discrete collection of epithelioid cells (activated histiocytes with homogeneous eosinophilic cytoplasm), with accompanying multinucleate giant cells HE×200 (A), or without accompanying multinucleate giant cells HE×40 (B). Granuloma-like nodule is a well-defined nodule of non-epithelioid histiocytes in the muscularis propria (C HE×100, D HE×400) and subserosa (E HE×100, F HE×400).

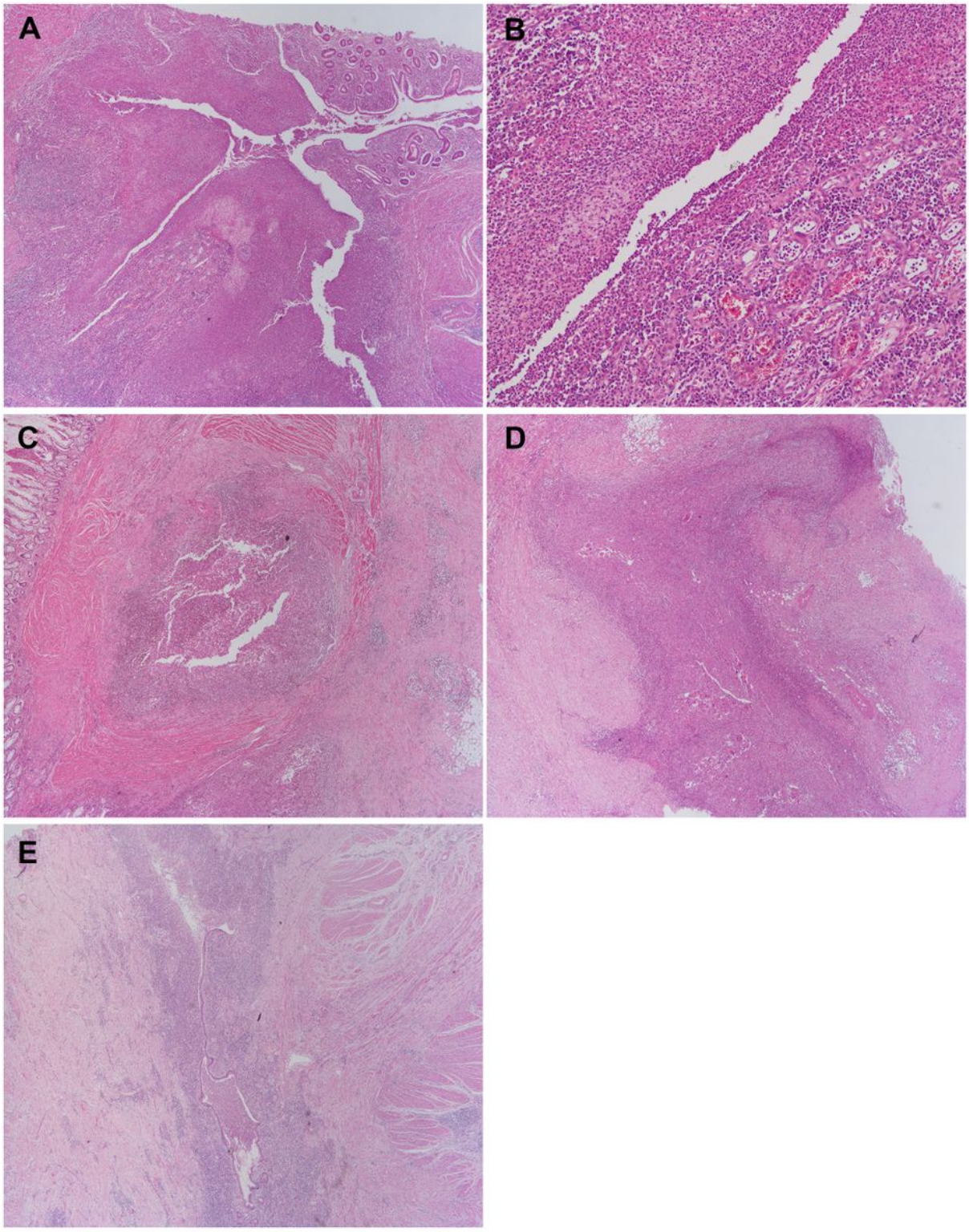

Figure 3

Fissures and related structures. Fissures are deep, flask-shaped, or knife-like ulcers that extend into the submucosa HE×20 (A) and is lined by numerous neutrophils HE×100 (B). Abscess is a localized collection of pus surrounded by inflamed tissue HE×20 (C). Some sinuses do not demonstrate an opening to intestinal lumen on slides, but those with long or complex configurations are considered a sinus-like structure HE×20 (D). Sometimes, epithelium lines the sinus-like structure HE×20 (E).

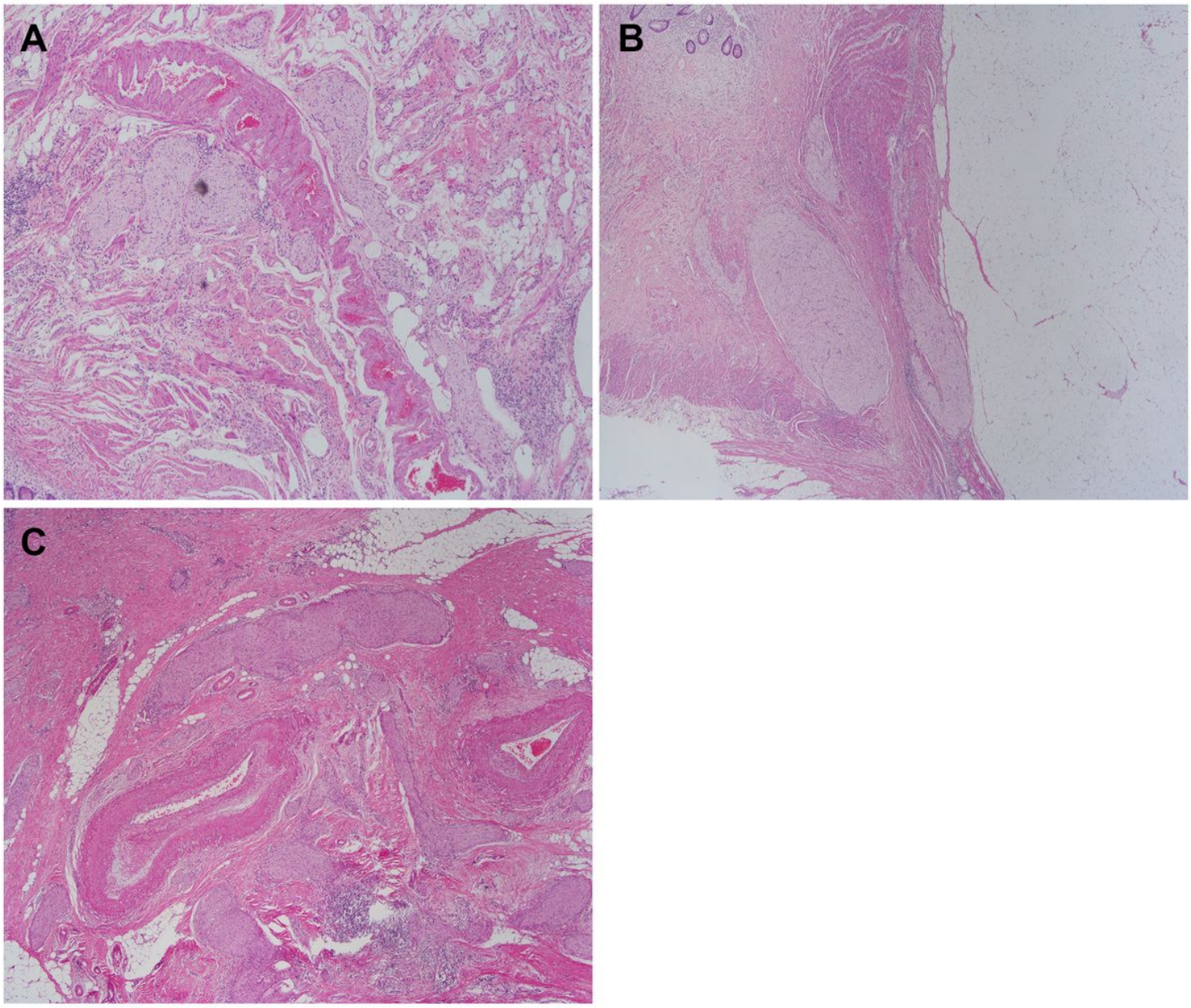

Figure 4

Abnormalities of the enteric nervous system. Large, abnormal, and irregular nerve bundles are present in the submucosa HE×40 (A), muscularis propria HE×20 (B), or subserosa HE×20 (C).

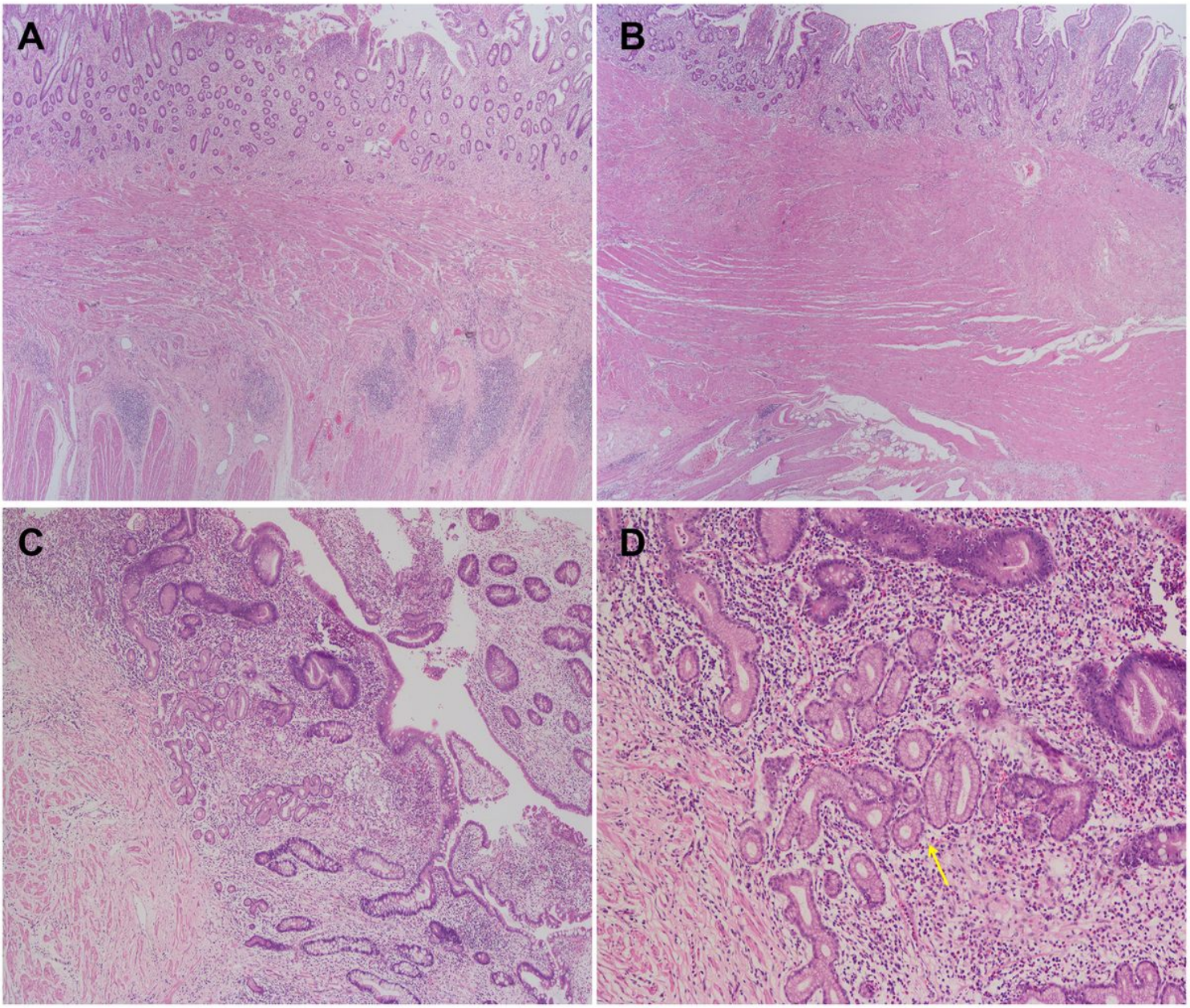

Figure 5

Architectural abnormalities. Muscularis mucosae is thickened by hyperplasia or fibrosis. Sometime, the submucosa is still present HE×20 (A), or obliterated HE×20 (B). Mucosal atrophy with pseudopyloric gland metaplasia (arrow) (C HE×40, D HE×100).