Clinical significance of pathologic abnormalities in biopsy samples from the appendiceal orifice

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Aims: Appendiceal orifice mucosa often appears inflamed endoscopically, even when other colonic segments appear normal. Histological findings in biopsy samples taken from endoscopically abnormal mucosa may simulate a variety of inflammatory colitides. We performed this study to evaluate the clinical implications of inflammatory changes isolated to the appendiceal orifice.

Methods and results: In this double cohort study, biopsy samples from 26 histologically abnormal appendiceal orifices were reviewed. Twenty-five control cases were culled from endoscopically normal ($n = 11$) and abnormal ($n = 14$) appendiceal orifices that were histologically normal. Histological findings were correlated with presentation, medication history, findings at other colonic sites and clinical outcomes. Study cases displayed active inflammation ($n = 12$), chronic active inflammation ($n = 13$) or features simulating collagenous colitis ($n = 1$). Eighteen patients had biopsies taken from other colonic sites; these revealed benign polyps ($n = 10$) or displayed active ($n = 4$) or chronic active ($n = 4$) inflammation. All patients with findings isolated to the appendiceal orifice were asymptomatic at most recent clinical follow-up. Four of eight (50%) of the patients with inflammation in other biopsy samples were ultimately diagnosed with ulcerative colitis, in keeping with the well-established role of the appendix as a 'skip lesion' in that disorder. Control patients presented for screening colonoscopy ($n = 19$), iron deficiency anaemia ($n = 3$) or change in bowel habits ($n = 3$) and none reported gastrointestinal symptoms upon follow-up, regardless of the endoscopic appearance of the appendiceal orifice.

Conclusion: Isolated inflammation of the appendiceal orifice mucosa should not be regarded as a feature of evolving inflammatory bowel disease or other types of chronic colitis.

Keywords: active inflammation, appendix, chronic inflammation, microscopic colitis, ulcerative colitis

Introduction

The endoscopic appearance of the appendiceal orifice may reveal underlying appendiceal disorders, including neoplasms and appendicitis.[1,2] It may also reflect inflammatory disorders of the lower gastrointestinal tract. For example, the appendix is a well-established 'skip lesion' in patients with ulcerative colitis that may exhibit endoscopic and histological features of chronic active colitis in patients with distal disease, even when the right colon is not involved.[3] It is not surprising, therefore, that some gastroenterologists have a low threshold for sampling abnormal-appearing appendiceal orifice mucosa during endoscopic examination.[4]

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We have observed that the appendiceal orifice often has an irregular endoscopic appearance, even when the remainder of the colon appears normal. In our experience, histological features in these biopsy samples may simulate a variety of colitides, including inflammatory bowel disease, active colitis, and microscopic colitis. The clinical importance of these findings is often unclear. We performed this double cohort study to investigate the implications of inflammatory patterns in biopsy samples from the appendiceal orifice in the absence of other histological abnormalities.

Materials and methods

CASE SELECTION

All cases with biopsy samples of the appendiceal orifice submitted during a 2-year period (August 2018–August 2020) were reviewed. Patients undergoing screening colonoscopy or who reported recent onset of gastrointestinal signs and symptoms were considered for the study. Those with inflammatory changes in biopsy samples from the appendiceal orifice formed the study group. Samples of polypoid mucosa that featured inflammatory changes were included; however, biopsy samples from polypoid mucosa that proved to harbour benign neoplasms or lymphoid aggregates were excluded. Patients with an established clinical history of inflammatory bowel disease or other chronic colitis were also excluded. Demographic information, endoscopic findings and clinical information were extracted from the electronic medical record following approval by the institutional review boards (IRB) of the participating institutions (IRB number: 2019-10513, approval date: 08/05/2019; IRB code: HUM00143268, approval date: 3/12/2019). Controls were culled from patients with biopsy samples taken from the appendiceal orifice that showed normal histology.

HISTOLOGICAL REVIEW

Cases were assessed for active inflammation (neutrophilic cryptitis, crypt abscesses, erosion, lamina propria neutrophils) and chronic inflammation (basal lymphoplasmacytosis, architectural distortion). A microscopic colitis pattern was regarded as intraepithelial lymphocytosis (> 20 lymphocytes per 100 colonocytes), depletion of surface epithelial mucin and/or thickened subepithelial collagen ≥10 μm. The reviewing pathologists (C.A.C., N.C.P., M.W.) were blinded to clinical information and original diagnoses.

CLINICAL FOLLOW-UP

Histological findings were correlated with endoscopic impression, gastrointestinal symptoms at the time of colonoscopy and at follow-up visits and medication history. Cases without clinical follow-up were included in histological results, but were excluded from analysis of clinical outcomes.

STATISTICAL ANALYSIS

Differences among outcomes for patients with inflammatory findings isolated to the appendiceal orifice versus those who also had similar findings at other sites are expressed as relative risk (RR). χ^2 and *t*-tests were used to compare study and control groups regarding clinical features.

Results

Twenty-six patients formed the study cohort (M/F = 3/23, average age = 56 years). Their clinical and pathological features are summarised in Table 1.
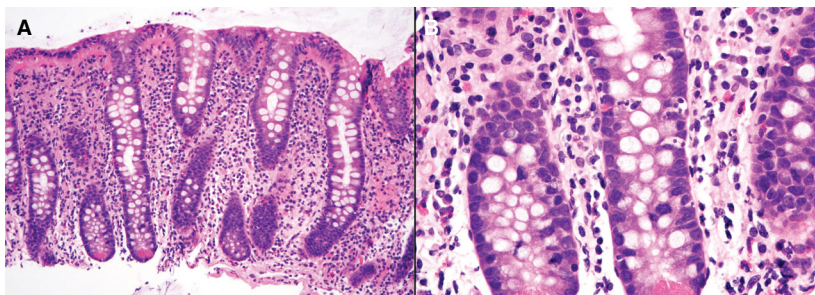
Twelve cases showed active inflammation (Figure 1A,B). Patients in this group presented for screening colonoscopy ($n = 9$), rectal bleeding ($n = 2$) and iron deficiency anaemia ($n = 1$). Two of these patients had undergone appendectomy. Endoscopically, these appeared as nodular ($n = 5$), congested ($n = 3$), polypoid ($n = 3$) or normal ($n = 1$) mucosa. Six patients had endoscopic polyps at other sites, which proved to be hyperplastic ($n = 4$) or normal ($n = 2$). One patient had erythematous nodular mucosa in the rectosigmoid colon ($n = 1$), which revealed chronic active inflammation. The remainder of the colon appeared normal in the other five cases.

Clinical follow-up was available for seven of these patients (interval: range = 1–13 months, mean = 4 months), six of whom reported symptom resolution or remained asymptomatic. Four of these patients were known to regularly use non-steroidal anti-inflammatory drugs (NSAIDs). The patient with chronic active inflammation in the rectosigmoid colon reported recurrent rectal bleeding that improved with mesalamine treatment; he was ultimately diagnosed with ulcerative colitis. The five cases without follow-up included patients who presented for screening colonoscopy ($n = 3$), rectal bleeding ($n = 1$) and anaemia ($n = 1$).

Thirteen cases showed chronic active inflammation as defined above (Figure 2). Clinical presentation in these cases included rectal bleeding ($n = 4$), change

Table 1. Clinical and pathological features of study cases and controls

Features	Acute inflammation (n = 12)	Chronic active inflammation (n = 13)	Collagenous colitis (n = 1)	Controls (n = 25)
Male: Female	1:11	2:11	0:1	2:3
Average age (years)	56	58	64	61
Endoscopic features at the appendiceal orifice				
Polyps	3	0	0	2
Congestion	3	6	1	9
Nodularity	5	5	0	3
Ulcer	0	1	0	0
Normal	1	1	0	11
Endoscopic features at other sites				
Polyps	6	4	1	21
Nodularity	1	3	0	0
Ulcers	0	4	0	0
Normal	5	2	0	4
Pathologic findings in other samples				
Active inflammation	0	4	0	0
Chronic active inflammation	1	3	0	0
Polyps	4	4	1	13
Normal	2	2	0	8
Outcome				
Asymptomatic at last follow-up	6	9	1	25
Ulcerative colitis	1	3	0	0
Unknown	5	1	0	0

Figure 1. Crypt architecture and lamina propria cellularity are normal in this biopsy sample from a congested appearing appendiceal orifice (**A**). Active cryptitis is present (**B**). No symptoms developed in this patient.

in bowel habits ($n = 3$) and screening colonoscopy ($n = 6$). One patient in this group had a past surgical history of appendectomy. Endoscopic abnormalities at the appendiceal orifice included congested ($n = 6$), nodular ($n = 5$) or ulcerated mucosa ($n = 1$); one case had normal-appearing mucosa. Four patients had adenomas and/or hyperplastic polyps at other sites. The remainder of the colon appeared normal in two patients. None of these six patients reported gastrointestinal symptoms at their follow-up appointments (interval range = 1–48 months, mean = 26 months).

Seven patients (Figure 3A) also had biopsies taken from ulcerated or nodular mucosa in the ascending ($n = 2$), transverse ($n = 1$), rectosigmoid ($n = 1$) colon or rectum ($n = 3$) that also revealed active inflammation with (Figure 3B) ($n = 3$) or without ($n = 4$) features of chronicity. Clinical follow-up
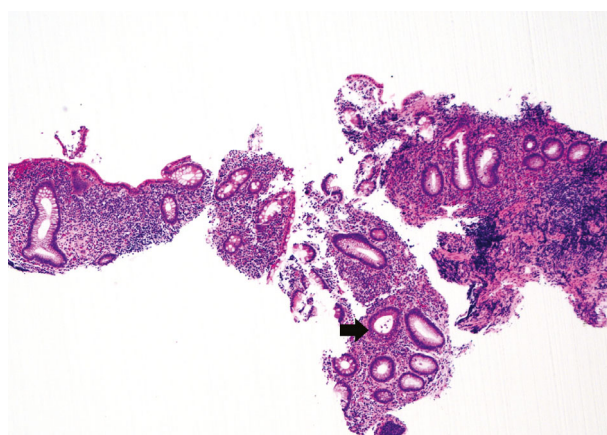

Figure 2. Biopsy samples of a nodular appendiceal orifice displays lymphoplasmacytosis of the lamina propria with active cryptitis (arrow) and architectural distortion, simulating inflammatory bowel disease. There were no other endoscopic findings and the patient was asymptomatic at last clinical follow-up.

(interval range = 1–38 months, mean = 12 months) revealed that three patients reported resolution of symptoms with either dietary modifications (two cases of diarrhoea), or linaclotide in one case of constipation. These three patients did not have features of chronicity in other biopsy samples. Two of these patients with resolution of symptoms were known to use NSAIDs regularly. The remaining four of the seven patients reported recurrent blood per rectum ($n = 3$) or lower abdominal pain ($n = 1$). Three of these patients had features of chronic inflammation in concurrent specimens and one did not. The former three were ultimately diagnosed with ulcerative colitis and reported symptom improvement with mesalamine therapy. No further follow-up was available for the last patient.

The RR of developing ulcerative colitis for patients with chronic active inflammation at the appendiceal orifice as well as active or chronic active inflammation at other sites compared to those who only showed that pattern at the appendiceal orifice was 3. The RR of developing ulcerative colitis combining the patients with active or chronic active inflammation at the appendiceal orifice and at other sites versus either of those findings isolated to the appendiceal orifice was 5.

Features of collagenous colitis, including thickened subepithelial collagen and surface epithelial mucin depletion were present in one sample (Figure 4A,B). The biopsy was taken from an appendiceal orifice that appeared erythematous in a patient who presented for colon cancer screening. The rest of the colon showed multiple polypoid lesions which proved to harbour tubular adenomas ($n = 2$), hyperplastic polyps ($n = 2$) and an inflammatory-type polyp ($n = 1$). No biopsy samples were taken of flat mucosa, as other abnormal areas were not identified in the rest of the colon. This patient was using multiple medications, including NSAIDs and proton-pump
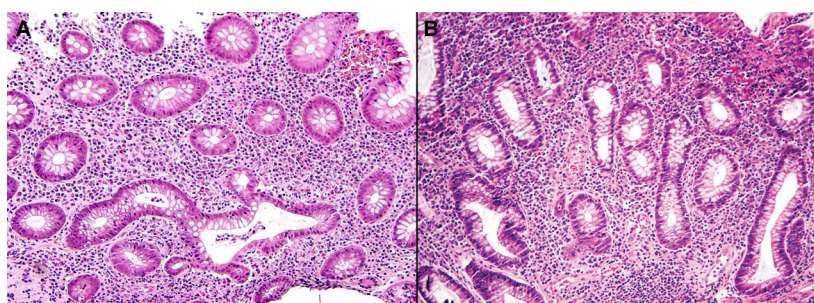
Figure 3. Chronic active inflammation is present at the appendiceal orifice (**A**) and in biopsies from the rectum (**B**) in a patient who was later diagnosed with ulcerative colitis. [Colour figure can be viewed at wileyonlinelibrary.com]
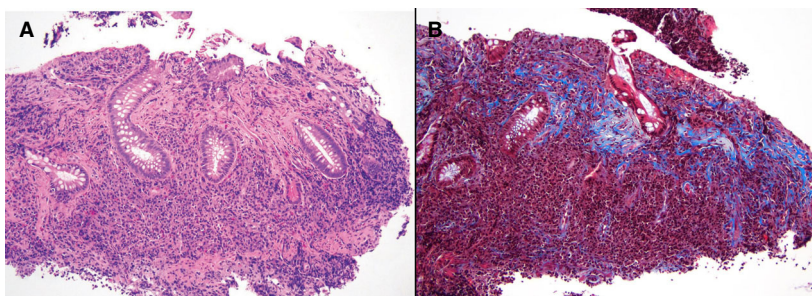
Figure 4. One case displayed increased chronic inflammation in the lamina propria with thickened subepithelial collagen (**A**) prompting the pathologist to order a trichrome stain (**B**) and raising concern for collagenous colitis. [Colour figure can be viewed at wileyonlinelibrary.com]

inhibitors (PPIs) intermittently, and remained asymptomatic at most recent follow-up (21 months). No history of appendectomy was reported for this patient.

Patients in the control cohort (n = 25) included 10 men and 15 women, with an average age of 61 years. This did not vary significantly from the study group (P = 0.2). Biopsy samples were taken from endoscopically normal-appearing (n = 11) or abnormal (n = 14) appendiceal orifices, all of which revealed normal histology. Endoscopic abnormalities reported in this group included congested (n = 9), nodular (n = 3) or polypoid (n = 2) mucosa. These patients presented with anaemia (n = 4), bowel habit changes (n = 3) or for colon cancer screening (n = 18). Three patients in this group had undergone appendectomy, and four patients were known to use NSAIDs regularly. No statistically significant differences were found between study cases and controls regarding prior appendectomy (P = 1) or NSAID use (P = 0.5). Biopsy samples of polyps were taken from other sites in the colon in twenty-one patients. These contained normal mucosa or lymphoid aggregates in eight patients. The other thirteen patients had benign polyps (adenoma = 9, hyperplastic polyp = 7, inflammatory-type polyp = 1). All patients in the control group were asymptomatic upon clinical follow-up (interval: range = 1–24 months, mean = 9 months). The follow-up interval did not differ significantly from the study group (P = 0.9).

Discussion

We performed this study to characterise the histopathological spectrum of inflammatory changes isolated to the appendiceal orifice and understand their clinical implications. We observed that findings in appendiceal orifice biopsies may raise a broad differential diagnosis, including active colitis, inflammatory bowel disease and microscopic colitis. Patients with inflamed appendiceal orifice mucosa who did not have colitis in biopsies taken from other sites either remained asymptotic or symptoms resolved by their most recent follow-up appointment. We conclude that, in the absence of inflammation elsewhere in the colon, these features are not a harbinger of subsequent disease development.

The relationship between appendiceal inflammation and inflammatory bowel disease is complex. It is well established that patients who undergo appendectomy are at decreased risk for development of ulcerative colitis, possibly due to the role of inflammatory cells in the appendix in mucosal immune response.[5] The appendix is involved as a 'skip lesion' in 15–85% of patients with ulcerative colitis otherwise limited to the left colon.[6–8] This may be seen endoscopically as a red patch, granularity or friability involving the appendiceal orifice with or without caecal inflammation ('caecal patch').[9,10] Most authors report that appendiceal orifice inflammation develops concurrently or after the onset of distal colitis and shows a similar degree of disease activity.[11,12] One published series by Park et al. suggests that appendiceal orifice inflammation may precede the development of ulcerative colitis. These authors followed 19 patients with appendiceal orifice inflammation and no established diagnosis of ulcerative colitis for a mean duration of 18 months, and reported that five (25%) developed ulcerative colitis.[13] Of these, two had endoscopic evidence of segmental or patchy colitis at the time of original colonoscopy. The authors did not report on results of other biopsy samples taken, if any, either from normal appearing or colitic mucosa, raising the possibility that some would have had evidence of ulcerative colitis elsewhere in the colon. In our series, the only patients diagnosed with ulcerative colitis during the follow-up interval (n = 4) had inflammation in concurrent biopsy samples taken from other

colonic sites and had persistent symptoms of rectal bleeding or abdominal pain after colonoscopy.

Another series by Ladefoged et al. detected inflammation in 4 of 53 (8%) appendiceal orifice biopsy samples in patients without colitis at other sites.[4] Interestingly, these authors reported that inflammation was mild and cryptitis and erosions were only seen in patients with inflammatory bowel disease. This differs from our findings, in that we observed cryptitis, erosion, architectural distortion and basal lymphoplasmacytosis in 13 cases, but only 3 proved to be indicative of inflammatory bowel disease. Our findings suggest that chronic active inflammation at the appendiceal orifice is not limited to patients with inflammatory bowel disease. We speculate that some of these cases may have been in the resolving stages of active colitis, which is known to show features more typically associated with chronicity late in its course. Ladefoged et al. also specifically analysed patients with microscopic colitis, noting that appendiceal orifice mucosa may also be affected.[4] Our series included only one patient with features simulating microscopic colitis at the appendiceal orifice, but the patient did not have evidence of the disease elsewhere and did not develop symptoms on follow-up.

Finally, Ekanayaka et al. recently reported on a series of six patients with chronic active inflammation limited to the caecum (isolated caecal patch lesion).[14] These patients presented with chronic diarrhoea and/ or rectal bleeding or chronic abdominal pain. All had endoscopically apparent abnormal mucosa limited to the caecum and spanning 1–5 cm. The patches appeared as erythematous, granular mucosa with loss of vascular pattern. Appendiceal orifices, in our study, similarly often appeared congested and nodular, but were also frequently polypoid, probably due to protrusion of the appendiceal orifice in its normal state. In keeping with our findings, Ekanayaka et al. reported normal or unrelated pathology in biopsies taken from other colonic sites. Two patients in the series reported regular use of NSAIDs, and their inflammation subsided after drug cessation. The authors conclude that NSAIDs are one potential cause of the isolated caecal patch lesion. We believe that NSAIDs may also cause inflammation limited to the appendiceal orifice. Of the remaining four patients in the series by Ekanayaka et al., one had an established history of ulcerative colitis that was in remission, one subsequently developed ulcerative colitis and two were treated for ulcerative colitis empirically, but had not developed clinical evidence of ulcerative colitis at the time of publication. Thus, for one patient in the series, the isolated caecal patch lesion preceded ulcerative colitis development. This differs from our findings, in that we did not find isolated inflammation of the appendiceal orifice to be predictive of subsequent ulcerative colitis. It is possible that inflammation that is limited only to the area immediately surrounding the appendiceal orifice lacks clinical implications associated with that involving the caecum. An alternative hypothesis is that our series of 26 cases was underpowered to detect any that would subsequently develop into ulcerative colitis.

The aetiology of active inflammation in study cases is unclear. Given the self-limited course of symptoms, the main considerations include infections and medication induced injury.[15,16] Unfortunately, stool cultures and polymerase chain reaction (PCR) for microorganisms were not performed on the patients in this study. Four patients with this pattern were taking NSAIDs, as were two with chronic active inflammation, and one patient with thickened subepithelial collagen. As mentioned above, NSAIDs are a known cause of gastrointestinal inflammation of a variety of histological patterns, and may account for the findings in these patients.[17] Non-specific inflammatory changes due to bowel preparation are another possible explanation, and would account for the asymptomatic presentation of most patients in this group.[18] Although our study did not include patients who were undergoing colonoscopy after conservative management of acute appendicitis, it should be noted that appendicitis may persist or recur in the interval before definitive surgery. Chronic and/or active inflammation may also be seen histologically in that setting.[19]

Our series includes the largest group of patients, to our knowledge, with appendiceal orifice inflammation in the absence of other colonoscopic and/or histological findings. Its retrospective nature resulted in a lack of follow-up in six study cases; however, all available follow-up indicates that abnormalities limited to the appendiceal orifice mucosa rarely have clinical implications. They may lend themselves to overinterpretation, especially when chronic inflammation is present. We recommend that pathologists interpret these findings with particular caution when unassociated with abnormalities in the rest of the colon. Comments in pathology reports should reflect the isolated and likely self-limited nature of these findings.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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