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Article type : Original Article

Actinomyces in Crohn's-like appendicitis

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Abstract

AIMS: Appendicitis with a Crohn's-like histologic appearance generally raises concern for Crohn's disease, Yersinia infection, and interval appendectomy. Actinomyces is a recognized cause of chronic appendicitis that can histologically mimic Crohn's disease.

METHODS AND RESULTS: We report on 20 cases of appendicitis with Crohn's-like histological features that were due to Actinomyces. Most patients presented with acute or chronic abdominal pain. Imaging studies suggested a mass in 5 cases. Two patients had interval appendectomy. Histologic features shows Crohn's-like appendicitis in 16 cases with moderate to marked fibrosis and granulomas in 7 cases. The other 4 cases had less consistent histologic findings. None of the patients developed Crohn's disease during the follow up interval (median 37 months).

CONCLUSIONS: Actinomyces can be associated with a Crohn's-like appendicitis with marked fibrosis, transmural inflammation, lymphoid hyperplasia, and granulomas.

Key words: Appendix, appendicitis, Crohn's disease, granuloma, Actinomyces

Acknowledgements:

Bela A. Horvath: Original collection of cases, histologic review, writing manuscript

Elena Maryamchik: Review of histology, collection of controls, updating manuscript

Gregory C. Miller: Provision of cases and clinical history, edit manuscript

Ian S. Brown: Provision of cases and clinical history, edit manuscript

Namrata Setia: Provision of cases and clinical history, edit manuscript

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Laura Lamps: Provision of cases and clinical history, edit manuscript

Gregory Y. Lauwers: Provision of cases and clinical history, edit manuscript

Eric Rosenberg: edit manuscript and adjudication of antibiotic and clinical issues

Joseph Misdraji: Project oversight, collecting cases, manuscript writing and editing.

Introduction

Some cases of chronic appendicitis have histologic features that resemble Crohn's disease, including granulomas, transmural inflammation, and fibrosis. Historically, these were believed to represent Crohn's disease isolated to the appendix, but it is now well-known that Crohn's disease develops in other segments of the bowel in less than 10% of these patients. Therefore, Crohn's-like appendicitis is usually not Crohn's disease. Pathologists faced with such a case typically generate a differential diagnosis, with leading considerations being Yersinia infection and interval appendectomy.

Actinomyces are gram-positive non-acid-fast anaerobic bacteria that exhibit filamentous growth. The organism colonizes stagnant areas of the gut, including the mouth, the cecum, and the appendix. They also frequently colonize the uterus in women using an intrauterine device (IUD). *A. israelii* is the species most often implicated in human infection. Actinomycosis is a chronic infection caused by Actinomyces that is often cervicofacial (>50% of cases) but can also be intra-abdominal (20%) or intra-thoracic (15-20%).[1] Intra-abdominal actinomycosis is usually preceded by a perforated viscus, most often the appendix. There is also an association with IUD. It occurs most often in adolescent to middle aged patients, mirroring the incidence of appendicitis.[1] The incidence is decreasing due to fewer cases of perforated appendicitis and antibiotic coverage.[2]

Actinomycosis is associated with aggressive desmoplastic fibrosis that is described as "wooden" and often raises concern for malignancy.[3] The pathognomonic finding is pus that contains yellow to white to brown granules, known as "sulfur granules". Microscopically, sulfur granules consist of colonies of filamentous bacteria that are Gram positive and also with GMS. The colonies may show Splendore-Hoeppli phenomenon, which is the deposition of proteins creating radiating club-shaped projections. Polymicrobial infection is common, and it is speculated that Actinomyces are pathogenic only when they synergistically act with other bacteria.[1]

During routine casework, a few of the authors encountered cases of Crohn's-like appendicitis in which the appendix had Actinomyces sp. in the lumen, and the marked fibrosis produced a mass lesion or firmness of the appendix that raised clinical concern for cancer. Because of these cases, pathologists at those institutions were sensitive to the presence of Actinomyces in some cases of appendicitis and routinely examined appendices, particularly those with a Crohn's-like appearance, for Actinomyces. However, pathologists are not all sensitized to this association, and had never noted Actinomyces in appendix specimens. At those institutions, review of cases of chronic or granulomous appendicits showed that several had Actinomyces, raising the possibility that Actinomycotic appendicitis was an under-recognized cause of chronic Crohn's-like appendicitis.

The goal of this study was to describe our experience with Actinomyces in Crohn's-like appendicitis. We also sought to assess whether colonies of Actinomyces were frequent in routine appendicitis, to understand whether the Actinomyces was associated with a particular histologic appearance in these appendices.

Methods

Twenty cases were identified through a variety of means. Nine cases were identified during routine surgical pathology examination at Envoi Specialist Pathologists, Royal Brisbane and Women's Hospital (7 cases), and University of Chicago (2 cases). Three cases were identified in the consultation files of the authors (JM, GYL, LL). Eight cases were found through retrospective review: we performed a search of the surgical pathology databases of Massachusetts General Hospital, Envoi Specialist Pathologists, and University of Chicago for appendicitis with unusual terms in the pathology report, such as granuloma, granulomatous, xanthogranulomatous, chronic, transmural, and fibrosis. To be included, a case had to have convincing Actinomyces colonies, which were defined as filamentous bacteria in "cotton wool" colonies, consistent with the morphologic appearance of "sulfur granules". Gomori methenamine silver (GMS) and/or Brown-Hopps stains were performed to confirm Actinomyces in some cases if they had not been done at the time of initial diagnosis (GMS stain in 4 cases, Brown-Hopps stain in 3 cases, both stains in 2 cases). All cases with granulomas also had AFB stains performed and were negative. All cases were reviewed for features of Crohn's-like appendicitis: granulomas, lymphoid hyperplasia, transmural inflammation, peri-appendiceal fibrosis, and mucosal inflammatory activity including ulcers and fissures. The number of Actinomyces colonies and whether there was fecal material acting as scaffolding for the colonies was noted. Clinical information was obtained from medical records review. The paraffin block for 7 cases was sent to University of Washington Molecular Diagnostic Laboratory for identification of Yersinia by PCR using broad-range, bacterial 16S rRNA gene primers.

A control group of 60 appendices was evaluated. This group was derived by searching the surgical pathology files between 2012 and 2017 for cases of Crohn's disease in which an appendix was available for review, for diagnostic terms that included Crohn's disease in the differential diagnosis of an appendicitis, or for which the term interval appendectomy was used in the pathology report. The control group was divided by indication into three groups: known Crohn's disease, interval appendectomy, and idiopathic granulomatous appendicitis. The control group was evaluated for features of Crohn's like appendicitis, including degree of lymphoid hyperplasia, the presence of transmural inflammation, granulomas, xanthogranulomatous inflammation, periappendiceal fibrosis, and the presence of fecalith. Comparisons of features between the control groups and the 20 cases of Actinomycotic appendicitis was tested for significance using Chi square. In addition, a group of 100 consecutive routine appendectomy specimens performed at the Massachusetts General Hospital were reviewed to determine the frequency with which Actinomyces occurs in routine appendectomy specimens.

The study was approved by the Massachusetts General Hosptial IRB committee (2016P001581/MGH; July 27, 2016).

Results

Clinical Characteristics of cases of Crohn's-like appendicitis with Actinomyces

The patient cohort included 11 females and 9 males. The median age was 25.5 years (range 4 – 67). Clinical information was available for 19 of 20 cases. Eleven patients presented with acute abdominal pain, with or without other signs of acute appendicitis, such as fever or nausea, and 1 patient presented with fever and emesis only. Five patients presented with chronic abdominal pain, generally described as lasting several weeks or a month; all of them had radiologic studies that demonstrated an inflammatory mass in the appendix, for which the differential included a neoplasm of the appendix. Two patients had a an interval appendectomy. One of these patients experienced several months of abdominal pain and radiology suggested a phlegmon. This patient received intravenous long-term antibiotics before undergoing appendectomy. The other patient had an episode of appendicitis 3 months prior that was treated with antibiotics. At the time of surgery, the patient still had a palpable abdominal mass. None of the patients had a history of Crohn's disease.

Intraoperatively, the appendix was noted as inflamed in all cases and, in some cases, dilated. An inflammatory mass was described in 5 patients, 4 of whom underwent hemicolectomy, and one had a cecal cuff resection. The remaining patients had appendectomy only.

Actinomyces was noted in the pathology report in 12 cases, although in one case it was included as one of many possible explanations for the pathologic findings. Several cases were diagnosed as granulomatous appendicitis with the usual differential diagnosis (Crohn's disease, *yersiniosis*, and interval appendectomy) or as chronic appendicitis; in these cases, Actinomyces was not noted by the pathologist and not included in the differential diagnosis. The two cases of interval appendectomy were diagnosed as granulomatous appendicitis due to interval appendectomy. Yersinia was not ruled out pathologically or clinically in any case.

Follow-up information was available in 15 cases, including the 12 patients whose pathology report specifically noted Actinomyces, although follow up included only the post-operative month in 2 patients and was less than 1 year for another 2 patients. Four patients received antibiotics specifically for Actinomyces, with 3 of them receiving a 12-month course. One of the patients who received a 12-month course of antibiotics presented 3.2 years later with abdominal pain and a small amount of intraperitoneal free air; a biopsy of the anatomosis showed non-specific inflammation and the patient was treated with antibiotics to prevent intraperitoneal actinomycosis. Four patients had a week-long course of antibiotics only. One other patient presented 2 weeks after appendectomy for abdominal patin, and was given antibiotics at that time, for unknown duration. Three patients were not known to have been specifically treated for Actinomyces. For the patients who had at least 6 months of follow up, none developed Crohn's disease, with a follow up interval of 7 months to 9.5 years (median 37 months).

Histologic Features of cases of Crohn's-like appendicitis with Actinomyces

Sixteen cases had a similar appearance (Figure 1), with moderate to marked peri-appendiceal fibrosis, mucosal lymphoid hyperplasia, transmural lymphoid aggregates, and, in 7 of these cases, granulomas. The most conspicuous feature in several of these cases was the degree of peri-appendiceal

fibrosis, which was marked in 7 cases, although in 3 cases it was relatively mild. The fibrosis was often circumferential, creating a rind-like appearance, with encasing of fat lobules and, in 2 cases, a lymph node. However, in some cases, the fibrosis was segmental or eccentric around the lumen. The quality of fibrosis was variable; the pattern ranged from hyalinized hypocellular stroma, to a more cellular, storiform appearance, to a fascicular fibromatosis-like appearance, with a few cases showing more than one appearance in different sections (Figure 2). In one case, there was focal fat necrosis and xanthogranulomatous reaction focally.

Another frequent finding was mucosal lymphoid hyperplasia,(Figure 3) which was moderate to marked in 12 of the 16 cases. Transmural lymphoid aggregates were present in all 16 cases, often creating a "Crohn's-like rosary" appearance with lymphoid aggregates abutting on the outer aspect of the muscularis propria (Figure 4). In 8 of the 16 cases, lymphoid aggregates drifted into the peri-appendiceal fibrous tissue (Figure 5).

Six of the 16 cases had epithelioid non-necrotizing granulomas, ranging from a few to numerous. The case with a cecal cuff resection had a granuloma in the cecal cuff, and in one case, granulomas were also found in a lymph node. The granulomas were occasionally present within the germinal centers of mucosal lymphoid tissue (Figure 6), but were also found in and beyond the muscularis propria.

Fifteen of the 16 cases had mucosal inflammatory activity, with or without ulceration. In 6 cases, mucosal ulceration was associated with fissuring or a flask-like configuration. In another 2 cases, mural abscesses were present. Two cases had pseudopyloric metaplasia.

Four cases had less of the features detailed above, but with other unusual features. One case showed a purulent fissure with moderate lymphoid hyperplasia, weak transmural inflammation, and focal appendiceal fibrosis. Another case showed mucosal ulceration with only limited lymphoid hyperplasia and peri-appendiceal fibrosis; however, there was a submucosal granuloma with suppuration. The third case showed circumferential ulceration, with areas of transmural granulation tissue, but also mucosal lymphoid hyperplasia, transmural lymphoid aggregates, and segmental moderate fibrosis. The least impressive case had only mucosal lymphoid hyperplasia.

Actinomyces colonies were seen in all cases (Figure 7), but in slightly different contexts. The organisms were overlying ulcers or fissures in 11 cases. In 1 case, the organisms were seen in the lumen and in a submucosal abscess. In 8 cases, the organisms were only seen in the lumen, admixed with purulent exudate, but without ulceration of the underlying mucosa. Splendore-Hoeppli phenomenon was present focally in two cases. The bacterial colonies formed around fecal material or hair in 8 cases, and in another 5 cases, some colonies were around fecal material and others were not. The remaining cases did not have fecal material admixed with the bacterial colonies. The number of colonies ranged from one to several. The most common pattern was a single large colony around fecal material. Some cases had a single large colony (often with fecal material) accompanied by several smaller ones, and some cases had a few small colonies often aggregating in the same area. It is worth noting that colonies of Actinomyces were usually present in only 1 or 2 tissue blocks, even in cases with several blocks of tissue. When

histochemical stains were performed, GMS proved to be more reliable at staining the organisms than Brown-Hopps.

The two patients with interval appendectomy both had Crohn's-like appendicitis but with only mild (1 case) or at most moderate (1 case) fibrosis. Both had granulomas in lymphoid follicles, and one of the cases had many granulomas. In both, the mucosal lymphoid tissue appeared dense but only the more fibrotic one had signficiant transmural inflammation. Both had a single large colony of Actinomyces in the lumen adherent to fecal material. Neither had xanthogranulomatous inflammation.

PCR for Yersinia using broad-range, bacterial 16S rRNA gene primers returned negative for bacterial DNA in all 7 cases tested.

Control group of Actinomyces-negative appendices (Table 1)

The 60 cases of Actinomyces-negative appendices used to compare the histologic features with Crohn's like appendicitis with Actinomyces included 22 cases of Crohn's disease for which a right colectomy or total colectomy had been performed, 34 cases of interval appendectomy, and 4 cases of idiopathic granulomatous appendicitis. Among the 22 cases of Crohn's disease with an appendix in the resection specimen, the appendix most often showed no significant mucosal activity or only focal activity, but 2 cases showed widespread ulceration. Only 4 appendices showed moderate to marked lymphoid hyperplasia and the others had limited or mild lymphoid hyperplasia. Transmural inflammation was at least focally present in 9 cases. Periappendiceal fibrosis was absent in most cases or mild at most, and only 3 cases had moderate periappendiceal fibrosis. Nine cases had granulomas, but in 6 cases they were rare or focal. Four harbored a fecalith but non had filamentous bacteria coating the fecal matter.

In the 34 interval appendectomy specimens, half of the cases had either no (14 cases) significant mucosal activity or focal mild activity (3 cases). The other half had at least focal erosions or ulcers. No lymphoid hyperplasia or weak lymphoid hyperplasia was seen in 18 cases whereas 16 cases had moderate to marked lymphoid hyperplasia. Transmural inflammation was noted in 17 cases but was focal and mild in 4. Thirty of 34 cases had mild or no periappendiceal fibrosis, and only 4 cases had moderate (3 cases) or marked (1 case) periappendiceal fibrosis. 26 cases showed no granulomas; 8 showed granulomas (2 only focally) often in lymphoid cuffs and one of these showed focal necrosis. Xanthogranulomatous inflammation was seen in 13 cases (one of which had numerous well-formed granulomas as well). Only 5 had a fecalith and none had Actinomyces. Various other alterations were seen in some cases, including submucosal abscess, hemorrhagic or granulation tissue-like adhesions, and mucosal attenuation or atrophy.

In the 4 cases of idiopathic granulomatous appendicits, the appendix showed varying mucosal activity with erosion or ulceration, and mild to moderate lymphoid hyperplasia in all cases. Three of the cases showed transmural lymphoid hyperplasia. However, fibrosis was only mild in 3 cases and moderate but focal in 1 case. Three cases had granulomas and the last case had xanthogranulomatous inflammation. None had a fecalith.

Excluding the idiopathic group due to small numbers of cases, comparison between the other two groups and the Actinomyces group showed that the degree of lymphoid hyperplasia and transmural inflammation was greater in the cases with Actinomyces, and the degree of fibrosis was greater in Actinomycotic appendicitis than in either the cases of true Crohn's disease or interval appendectomy. Conversely, interval appendectomies were much more likely to show xanthogranulomatous inflammation.

One hundred consecutive appendectomy specimens:

Among the group of 100 consecutive cases of appendicitis, Actinomyces was detected in 2. In one case, a 12 year old boy had a dilated appendix with focal deep ulceration and acute appendicitis and edema. Cotton wool colonies were noted in the lumen admixed with neutrophils, near the ulcer. The second case was a 67 year old man with symptoms of acute appendicitis, whose appendix was dilated with mucosal hyperplasia, diverticula, a focal perforation with suppuration; a large colony of Actinomyces was present in the lumen with sloughed epithelium and neutrophils.

Discussion

Rarely, an inflamed appendix may show histologic features that resemble Crohn's disease, including periappendiceal fibrosis, lymphoid hyperplasia, transmural lymphoid aggregates forming a "string of pearls" or "Crohn's-like rosary", fissuring ulcers, and granulomas. Among the differential diagnostic possibilities for Crohn's-like appendicitis, two entities have gained most attention: Yersinia infection and interval appendectomy. As we have shown in this observational study, Actinomyces may be the cause of Crohn's-like appendicitis; it is often associated with marked fibrosis that can create concern for an appendiceal tumor. In several of our cases, Actinomyces were only noted at retrospective review, suggesting that Actinomyces is an under-recognized cause of Crohn's-like appendicitis. Patholoigists evaluating a case of granulomatous appendicitis should submit the whole appendix, and examine the lumenal contents, as cotton wool colonies can appear in only one or two sections and Actinomyces is unlikely to be identified by other means in these cases since microbiologic studies are often not performed and are often not successful in isolating Actinomyces.

The concept of Crohn's disease limited to the appendix was once generally accepted based on histologic resemblance of some cases of granulomatous appendicitis to Crohn's disease. However, the clinical presentation was often acute or subacute abdominal pain and these patients did not present with long-term symptoms of Crohn's disease.[4-6] More significantly, whereas Crohn's disease often recurs after surgical resection of a diseased segment of intestine, patients with Crohn's-like appendicitis develop Crohn's disease in other intestinal segments in less than 10% of cases.[7, 8]

The differential diagnosis of Crohn's-like appendicitis or granulomatous appendicitis includes several infections, although some, such as tuberculosis or parasitic infection, are uncommon in Western populations. In 2001, Lamps et al. used PCR to identify pathogenic strains of Yersinia in 10 of 40 cases of

granulomatous appendicitis, while 60 control cases were negative.[9] The histologic features in those cases shared characteristics with Crohn's disease and with Actinomycosis, including granulomas with lymphoid cuffs, transmural granulomas, lymphoid hyperplasia, transmural lymphoid follicles, mural fibrosis, and mucosal ulcers. Suppurative granulomas can be seen in Yersinia[9, 10] but are neither sensitive nor specific. Although Yersinia infection is often considered in cases of granulomatous appendicitis, it is difficult to prove, since serologic diagnosis is challenging, the organism is difficult to culture and typically not part of the routine stool culture examination in most microbiology laboratories, and histologic evaluation for the organism by special stains is insensitive. Although PCR can be attempted, it is insensitive in paraffin-embedded tissue and is virtually never performed in routine practice in cases of granulomatous appendicitis.

Perhaps the most common cause of granulomatous appendicitis in developed countries is interval appendectomy, which refers to the conservative management with antibiotics of perforated appendicitis with peri-appendiceal abscess, and appendectomy after a few months. In 1997, Mazziotti et al. reported granulomatous appendicitis in 3 of 17 interval appendectomy specimens.[11] Several years later, Guo and Greenson described a case-control series of interval appendectomy specimens, and found that 13 of 22 cases had granulomas (usually within lymphoid follicles), and 11 cases had Crohn's-like features, including mural thickening, transmural lymphoid hyperplasia, and crypt distortion.[12] Xanthogranulomatous inflammation was found in 8 cases. These changes were uncommon in the control group in their series. We had two patients who had an interval appendectomy, but who also had Actinomyces on fecal material within the lumen.

As we have shown in our cases, Crohn's-like appendicitis may be associated with Actinomyces within the lumen or within granulation tissue of ulcerated mucosa. Our cases presented as either chronic or acute appendicitis (in two patients followed by antibiotic therapy and interval appendectomy), and in 8 of the cases, an appendiceal neoplasm was considered in the differential diagnosis based on radiologic and/or operative findings of a mass-like enlargement of the appendix. Most reported patients with Actinomycotic appendicitis also presented with acute or subacute appendicitis.[3, 13-17] A palpable mass may be present.[14, 15, 18] The features most often described are those that overlap with Crohn's disease, including granulomas, transmural inflammation, lymphoid hyperplasia, and ulceration/abscesses.[3, 13, 16] In our cases, we found a greater degree of lymphoid hyperplasia and transmural inflammation in these appendices when compared to actual Crohn's disease or to interval appendectomies. One of the distinguishing features of Actinomycotic appendicitis may be the marked fibrosis, which can create concern for malignancy, and distinguishes this entity from Yersiniosis. In our series, this feature was significantly different from Crohn's disease itself or from most cases of interval appendectomy. Others have also noted the marked fibrosis and induration that characterizes Actinomycotic appendicitis,[14-16, 19] and several case reports describe Actinomycotic appendicitis mimicking malignancy[2, 3, 16, 19]

The significance of making a diagnosis of Actinomycotic appendicitis rests in part on preventing the development and spread of intra-abdominal Actinomycosis. Intra-abdominal actinomycosis often affects the ileocecal region and is commonly preceded by a perforated viscus, most often the appendix. Actinomycosis is characterized by "wooden" desmoplastic fibrosis that is often concerning for cancer.[1, 3] Long-term penicillin therapy is indicated in chronic actinomycosis since the antibiotic has poor penetrance into the fibrotic inflammatory mass.

In several reported cases of appendiceal Actinomycosis, long-term antibiotic therapy was initiated out of concern for developing abdominal actinomycosis.[3, 13, 14, 16] However, some of the cases we have encountered went undiagnosed until retrospective review, and there seems to have been no negative consequences for those patients. Others were treated up to 12 months with antibiotics based on the pathologic finding of Actinomyces, but whether this was necessary is uncertain. Whether Crohn's-like Actinomycotic appendicitis is likely to develop into abdominal actinomycosis is uncertain, as the organisms are in the lumen of a fibrotic appendix that generally is not perforated. Probably, appendectomy and routine postoperative antibiotic coverage is sufficient treatment for these patients. Still, because intra-abdominal actinomycosis can be difficult to treat once it is established, a conservative approach may be warranted, especially if there is evidence of appendiceal disruption or perforation.

The determination of causality in our cases is difficult. Actinomyces colonizes stagnant areas of the bowel, and an argument could be made that the Actinomyces is a bystander in appendicitis. However, we found Actinomyces colonies in only 2% of consecutive appendectomy specimens, suggesting Actinomyces does not colonize the appendix in sufficient numbers to form cotton wool colonies in most patients. In those 2 cases, the features were not those of a chronic Crohn's-like appendicitis. In 2 of our cases, the histologic findings could be explained by interval appendectomy. However, many cases of interval appendectomy have xanthogranulomatous inflammation which was unusual and limited in our Actinomyces cases. Also, most cases of interval appendectomy in our control group were not characterized by marked periappendiceal fibrosis. However, these entities might not be mutually exclusive. Culture of an interval appendectomy specimen is essentially never performed, and the bacterial flora may differ in appendices with granulomas or ones with marked fibrosis. It is possible that Actinomycoses in an appendix left in situ after appendicitis and treated by interval appendectomy may cause a more dramatic fibrosing Crohn's-like appearance than interval appendectomies without Actinomyces. We tested 7 cases for Yersinia, and all of them yielded no bacterial DNA by PCR. Although Yersinia DNA was not detected, neither was other bacterial DNA, indicating that the sensitivity of PCR-based assays for bacterial DNA is compromised in paraffin embedded tissue. In practice, the determination of Yersinia infection is best performed on fresh tissue. Regardless, Yersinia infection generally does not produce the dense fibrosis typical of Actinomyces. Ultimately, the diagnosis of Actinomycotic appendicitis requires identification of the organism in the proper histologic context of

chronic appendicitis with significant fibrosis and possibly Crohn's-like features, and exclusion of interval appendectomy as the cause of the findings.

In summary, a Crohn's-like appendicitis can be associated with Actinomyces in the appendix, suggesting that this organism is responsible for some cases of chronic appendicitis. Furthermore, the presence of Actinomyces produces a more dramatic Crohn's like appearance with a greater degree of lymphoid hyperplasia and transmural inflammation, and most significantly, marked fibrosis, which can create the impression of malignancy. The role of Actinomyces in Crohn's-like appendicitis may be more significant than previously appreciated, because the organism is frequently overlooked when it is admixed with fecal material. Although none of the patients in our series developed abdominal Actinomycosis, a diagnosis of Actinomycotic appendicitis may help to explain an unusual pattern of appendicitis that otherwise might lead to concern for Crohn's disease, and may also alert clinicians to the possibility of abdominal Actinomycosis should symptoms recur.

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Figure legends:

Figure 1. Whole mount section from a Crohn's-like appendicitis with Actinomyces. Note the marked fibrosis with encasement of adipose tissue, resulting in a markedly thickened appendix.

Figure 2. Subserosa in a case of Actinomyces of the appendix. The muscularis is on the right side of the image. Note the marked peri-appendiceal fibrosis in the subserosa.

Figure 3. Mucosal lymphoid hyperplasia with numerous reactive follicles in a case of Actinomycotic appendicitis.

Figure 4. Transmural inflammation in a case of Crohn's-like appendicitis resulting in a Crohn's-like rosary on the outer aspect of the muscularis propria (left). Mucosal lymphoid hyperplasia is also evident on the right.

Figure 5. Subserosal tissue in a case of actinomyces of the appendix. Note the dense fibrosis with lymphoid follicles scattered throughout the fibrotic tissue.

Figure 6. Several epithelioid granulomas localized in lymphoid nodules.

Figure 7. Actinomyces in cases of Crohn's-like appendicitis. A) An aggregate of Actinomyces colonies; B) Low power view of a single large colony of Actinomyces surrounding fecal material material; C) High power view of Actinomyces with Splendore-Hoeppli phenomenon, consisting of radiating clubs of eosinophilic material; D) GMS stain highlights the filamentous bacteria in the colonies.

Table 1. Histological features in cases of Crohn's-like appendicitis with Actinomyces compared to resected Crohn's appendices, interval appendectomy specimens, and idiopathic granulomatous appendicitis specimens.

	Crohn's like appendicitis with Actinomyces	Appendix in resected Crohn's colitis	Interval appendectomy specimen	Idiopathic granulomatous appendicitis
Number	20	22	34	4
Lymphoid Hyperplasia				
None or mild	5	16**	18*	1
Moderate to marked	15	6	16	3
Transmural lymphoid aggregates				
Absent	2	13****	17*	1
Focal or poorly developed	3	8	4	0
Present	15	1	13	3
Periappendiceal fibrosis				
None or mild	5	19***	30****	3
Moderate	8	3	3	1
Marked	7	0	1	0
Granulomas				
Absent	12	13	26	1
Rare	3	6	2	0
Few to many	5	3	6	3
Xanthogranulomatous inflammation				

Absent	20	19	21**	3
Present	0	3	13	1
Fecalith				
Absent	12	18	29	0
Present	8	4	5	4

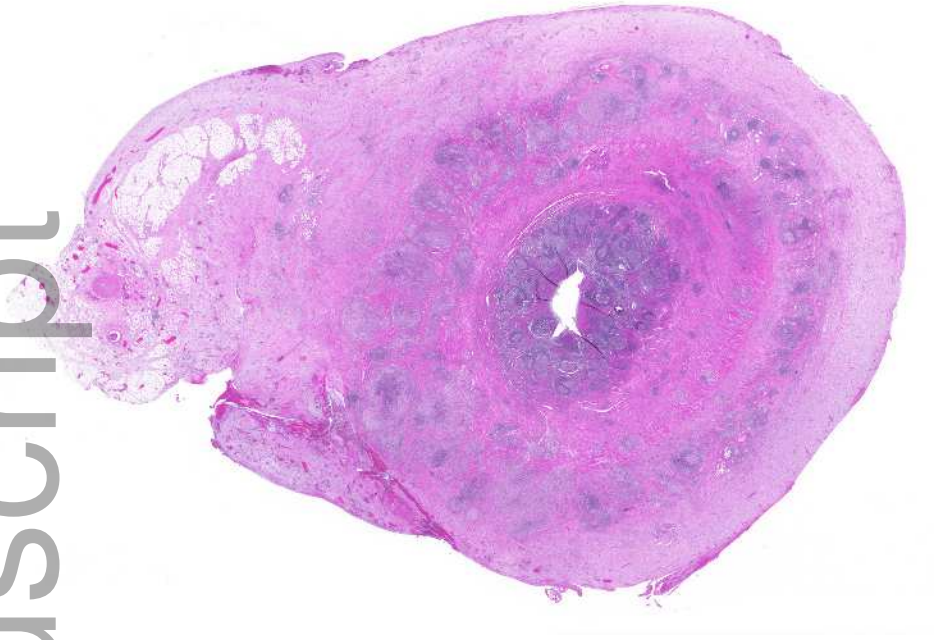
All p values are in comparison to Crohn's like appendicitis with Actinomyces group.

*p < 0.05-0.01

** p < 0.01-0.001

*** p < 0.0005

**** p < 0.00005



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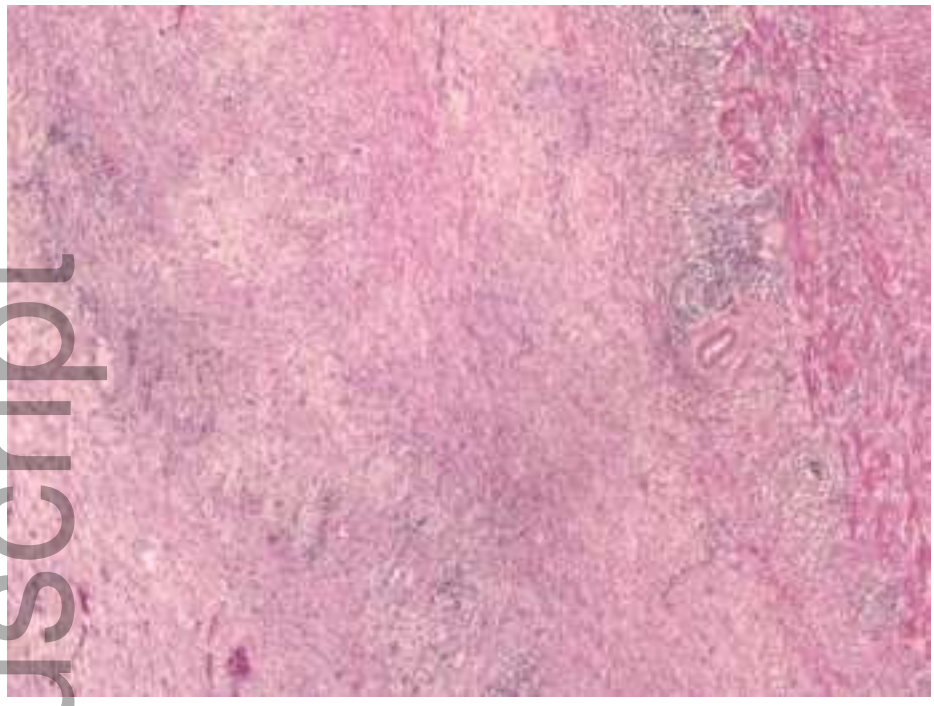

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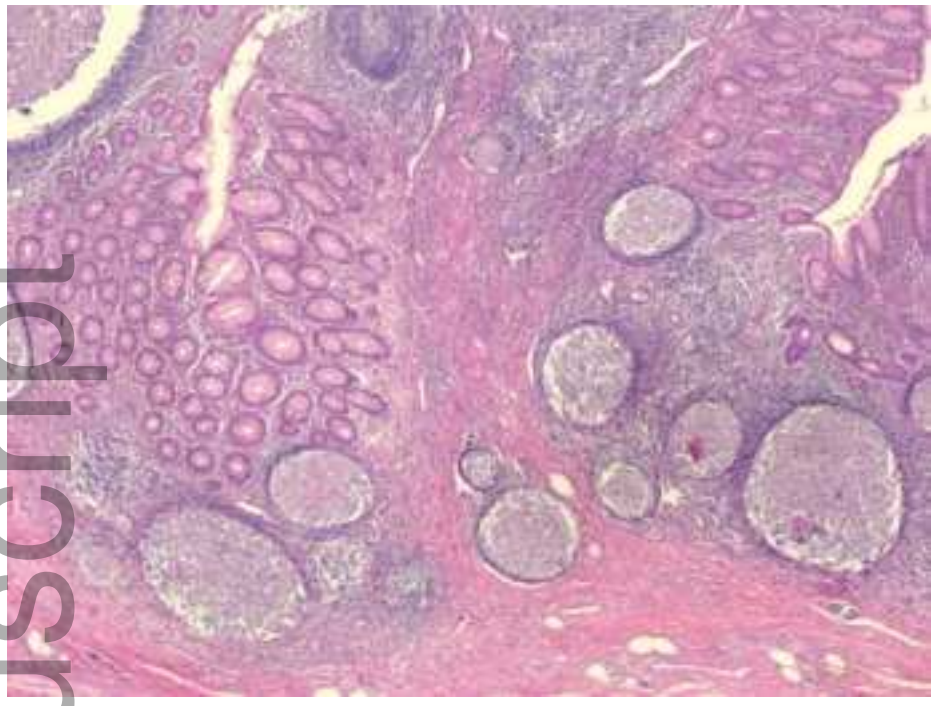

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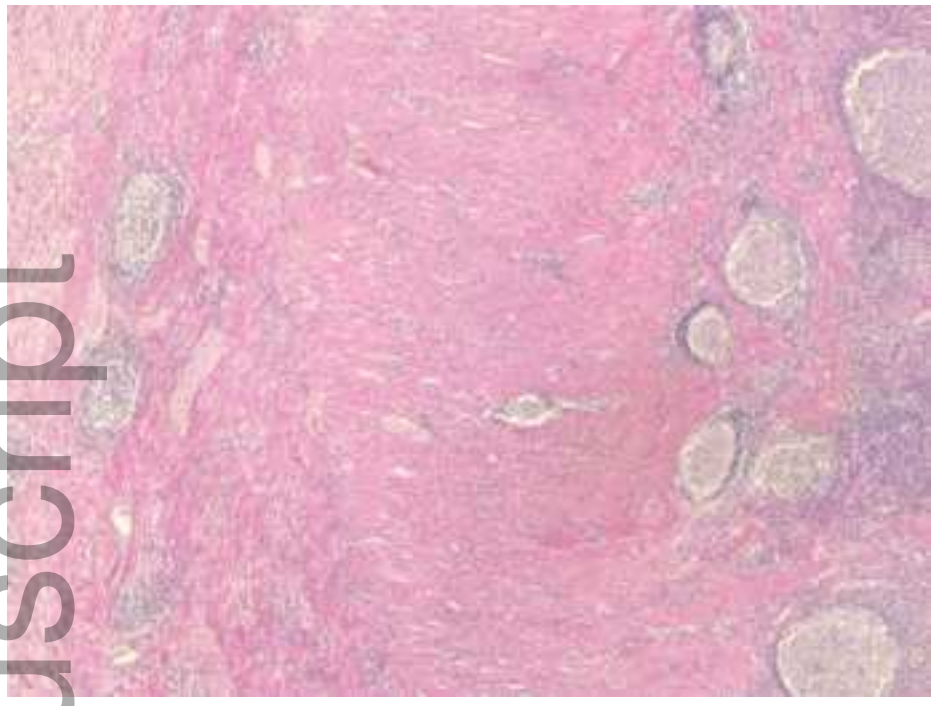

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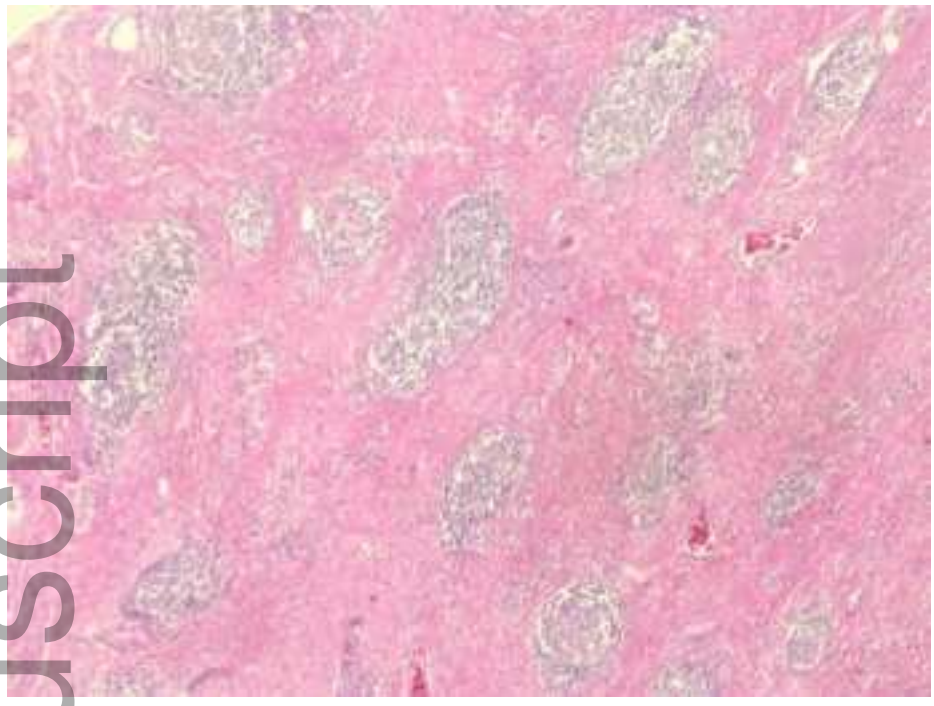

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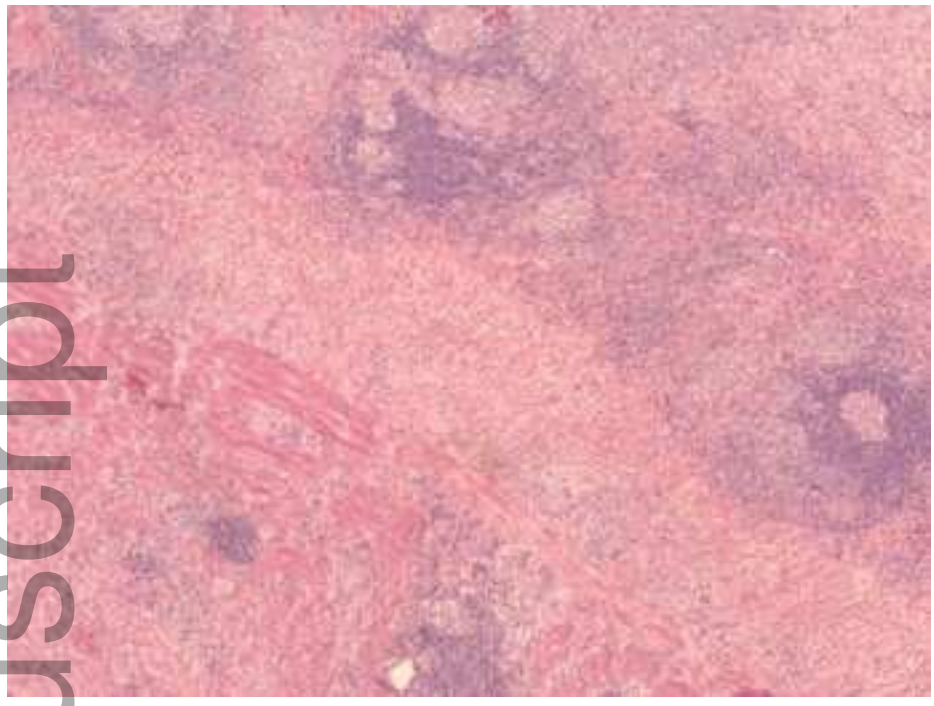

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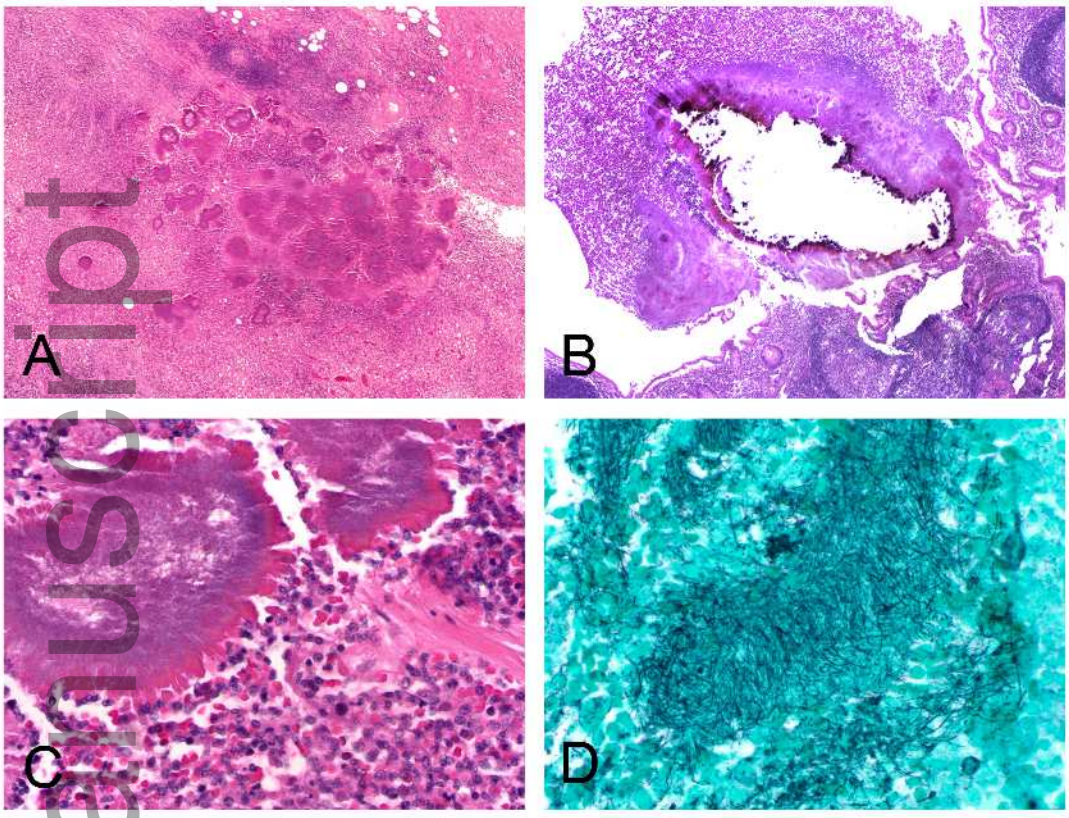

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