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Actinomyces in Crohn's-like appendicitis

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Actinomyces in Crohn's-like appendicitis

Aims: Appendicitis with a Crohn's-like histological appearance generally raises concern for Crohn's disease, *Yersinia* infection, and interval appendectomy. *Actinomyces* infection is a recognised 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 five cases. Two patients had interval appendectomy. Histological features showed Crohn's-like appendicitis in 16 cases, with moderate to marked fibrosis and granulomas in seven cases. The other four cases had less consistent histological findings. None of the patients developed Crohn's disease during the follow-up interval (median, 37 months).

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

Keywords: *Actinomyces*, appendicitis, appendix, Crohn's disease, granuloma

Introduction

Some cases of chronic appendicitis have histological features that resemble those of Crohn's disease, including granulomas, transmural inflammation, and fibrosis. Historically, these were believed to represent Crohn's disease limited to the appendix, but it is now well known that Crohn's disease develops in other segments of the bowel in <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 species are Gram-positive non-acid-fast anaerobic filamentous bacteria. The organisms colonise stagnant areas of the gut, including the mouth, the caecum, and the appendix. They also frequently colonise the uterus in women using an intrauterine device (IUD). *Actinomyces israelii* is the species that is 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 intrathoracic (15–20%).[1]

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Intra-abdominal actinomycosis is usually preceded by a perforated viscus, most often the appendix. There is also an association with IUD use. It occurs most often in adolescence up to middle age, mirroring the incidence of appendicitis.[1] The incidence is decreasing because of there being fewer cases of perforated appendicitis, and because of 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 'sulphur granules'. Microscopically, sulphur granules consist of colonies of filamentous bacteria that are Gram-positive and also Gomori methenamine silver (GMS)-positive. The colonies may show the Splendore–Hoeppli phenomenon, which is the deposition of proteins creating radiating club-shaped projections. Polymicrobial infection is common, and it is speculated that *Actinomyces* species are pathogenic only when they act synergistically 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* species 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, not all pathologists were aware of this association, and had never noted *Actinomyces* in appendix specimens. At those institutions, review of cases of chronic or granulomatous appendicitis showed that several had *Actinomyces*, raising the possibility that actinomycotic appendicitis was an under-recognised 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, in order to understand whether the presence of *Actinomyces* was associated with a particular histological appearance in these appendices.

Materials and methods

Twenty cases were identified in a variety of ways. Nine cases were identified during routine surgical pathology examination at Envoi Specialist Pathologists, Royal Brisbane and Women's Hospital (seven cases), and the University of Chicago (two cases). Three cases were identified in the consultation files of the authors (J.M., G.Y.L., and L.L.). Eight cases were found through retrospective review: we performed a search of the surgical pathology databases of Massachusetts General Hospital, Envoi Specialist Pathologists and the 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 morphological appearance of 'sulphur granules'. GMS and/or Brown–Hopps stains were used to confirm the presence of *Actinomyces* in some cases if they had not been applied at the time of initial diagnosis (GMS stain in four cases, Brown–Hopps stain in three cases, and both stains in two cases). All cases with granulomas also had acid-fast bacillus stains performed, and these were negative. All cases were reviewed for features of Crohn's-like appendicitis: granulomas, lymphoid hyperplasia, transmural inflammation, periappendiceal fibrosis, and mucosal inflammatory activity, including ulcers and fissures. The number of *Actinomyces* colonies and whether there was faecal material acting as scaffolding for the colonies were noted. Clinical information was obtained from medical records review. The paraffin blocks for seven cases were sent to the University of Washington Molecular Diagnostic Laboratory for identification of *Yersinia* by polymerase chain reaction (PCR) with 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 those with diagnostic terms that included Crohn's disease in the differential diagnosis of an appendicitis, or for those 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 the degree of lymphoid hyperplasia, and the presence of transmural inflammation, granulomas, xanthogranulomatous inflammation, periappendiceal fibrosis, and faecaliths. Comparisons of features between the control groups and the 20 cases of actinomycotic appendicitis were tested for significance with the chi-square test. In addition, a group of 100 consecutive routine appendectomy specimens obtained at the Massachusetts General Hospital were reviewed to determine the

frequency with which *Actinomyces* species occur in routine appendectomy specimens.

The study was approved by the Massachusetts General Hospital IRB committee (2016P001581/MGH; 27 July 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 years). 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 one patient presented with fever and emesis only. Five patients presented with chronic abdominal pain, generally described as lasting for several weeks or a month; all of them had radiological study findings that demonstrated an inflammatory mass in the appendix, for which the differential diagnosis included a neoplasm of the appendix. Two patients had undergone 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 previously 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 being inflamed in all cases, and, in some cases, as being dilated. An inflammatory mass was described in five patients, four of whom underwent hemicolectomy, and one of whom had a caecal cuff resection. The remaining patients underwent appendectomy only.

The presence of *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 pathological 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, the presence of *Actinomyces* was not noted by the pathologist, and was not included in the differential diagnosis. The two cases of interval appendectomy were diagnosed as granulomatous appendicitis resulting from interval appendectomy. *Yersinia* was not ruled out pathologically or clinically in any case at the time of diagnosis. However, PCR performed for this study using broad-range bacterial 16S RNA gene primers, using the paraffin blocks in seven cases, gave negative results in all seven cases.

Follow-up information was available for 15 cases, including the 12 patients whose pathology report specifically noted the presence of *Actinomyces*, although follow-up included only the postoperative month in two patients and was <1 year for another two patients. Four patients received antibiotics specifically for *Actinomyces*, with three 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 anastomosis 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 pain, and was given antibiotics at that time, for an unknown duration. Three patients were not known to have been specifically treated for *Actinomyces*. Of 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).

HISTOLOGICAL FEATURES OF CASES OF CROHN'S-LIKE APPENDICITIS WITH *ACTINOMYCES*

Sixteen cases had a similar appearance (Figure 1), with moderate to marked periappendiceal fibrosis, mucosal lymphoid hyperplasia, transmural lymphoid aggregates, and, in seven of these cases, granulomas. The most conspicuous feature in several of these cases was the degree of periappendiceal fibrosis, which was marked in seven cases, although, in three cases, it was relatively mild. The fibrosis was often

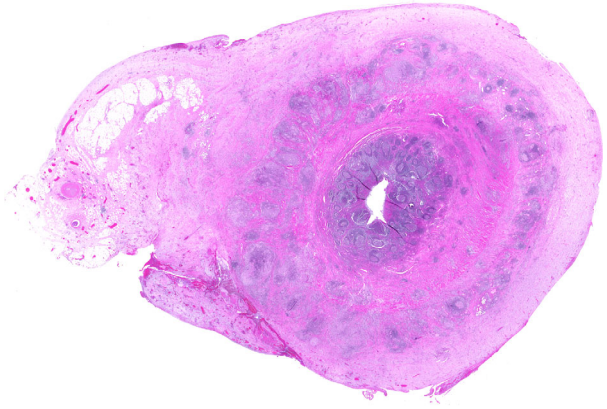

Figure 1. Whole mount section from a case of Crohn's-like appendicitis with *Actinomyces*. Note the marked fibrosis with encasement of adipose tissue, resulting in a markedly thickened appendix.

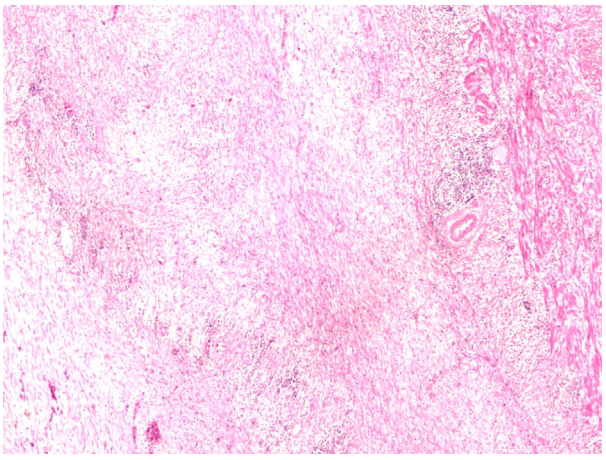

Figure 2. Subserosa in a case with *Actinomyces* in the appendix. The muscularis is on the right side of the image. Note the marked periappendiceal fibrosis in the subserosa. [Colour figure can be viewed at wileyonlinelibrary.com]

circumferential, creating a rind-like appearance, with encasing of fat lobules and, in two 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 hyalinised 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 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 the outer aspect of the muscularis propria (Figure 4). In eight of the 16 cases, lymphoid aggregates drifted into the periappendiceal fibrous tissue (Figure 5).

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

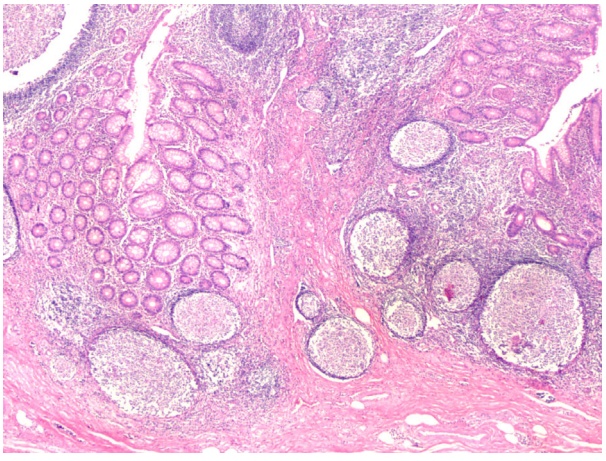

Figure 3. Mucosal lymphoid hyperplasia with numerous reactive follicles in a case of actinomycotic appendicitis. [Colour figure can be viewed at wileyonlinelibrary.com]

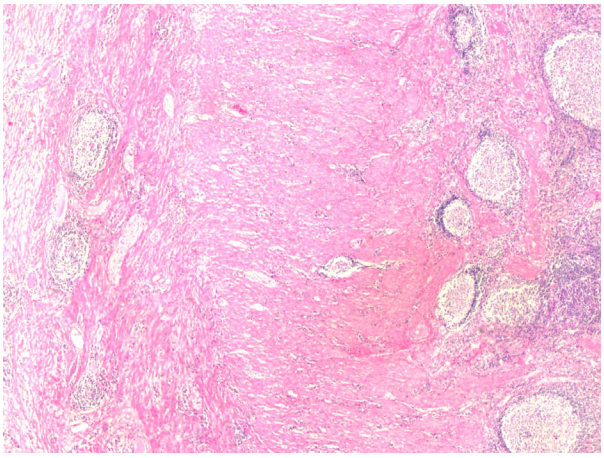

Figure 4. Transmural inflammation in a case of Crohn's-like appendicitis resulting in a Crohn's-like rosary on the outer aspect of the muscularis propria (left). Mucosal lymphoid hyperplasia is also evident on the right. [Colour figure can be viewed at wileyonlinelibrary.com]

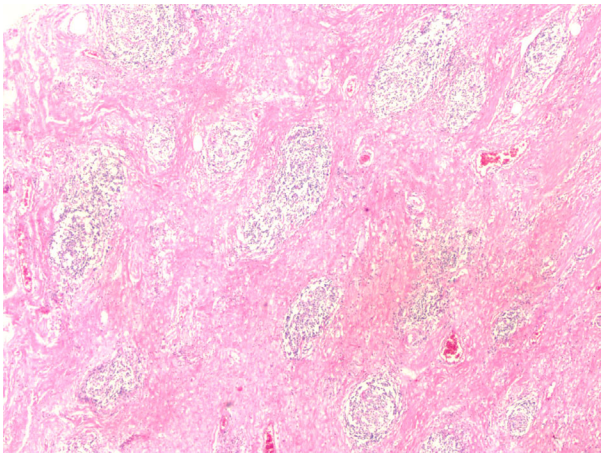

Figure 5. Subserosal tissue in a case with *Actinomyces* in the appendix. Note the dense fibrosis with lymphoid follicles scattered throughout the fibrotic tissue. [Colour figure can be viewed at wileyonlinelibrary.com]

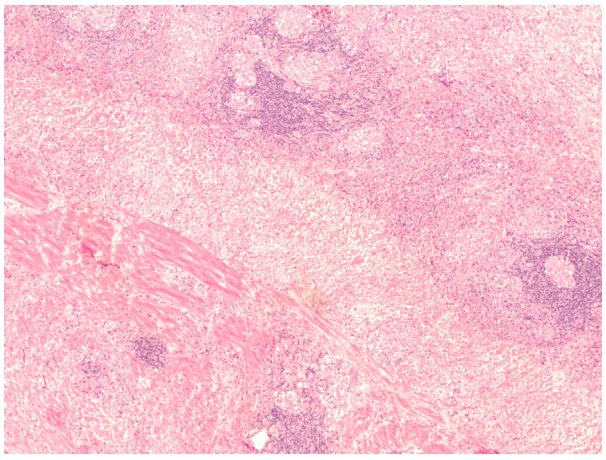

Figure 6. Several epithelioid granulomas localised in lymphoid nodules. [Colour figure can be viewed at wileyonlinelibrary.com]

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

Four cases had fewer of the features detailed above, but had 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 periappendiceal 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 one case, the organisms were seen in the lumen and in a submucosal abscess. In eight cases, the organisms were seen only in the lumen, admixed with a purulent exudate, but without ulceration of the underlying mucosa. The Splendore–Hoeppli phenomenon was present focally in two cases. The bacterial colonies formed around faecal material or hair in eight cases, and, in another five cases, some colonies were present around faecal material and others were not. The remaining cases did not have faecal 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 faecal material. Some cases had a single large colony (often with faecal 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 *Actinomyces* colonies were usually present in only one or two tissue blocks, even in cases with several blocks of tissue. When histochemical stains were performed, GMS stain proved to be more reliable for staining the organisms than Brown–Hopps stain.

The two patients who had undergone interval appendectomy both had Crohn's-like appendicitis but with only mild (one case) or at most moderate (one 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 significant transmural inflammation. Both had a single large *Actinomyces* colony in the lumen adherent to faecal material. Neither had xanthogranulomatous inflammation.

CONTROL GROUP OF *ACTINOMYCES*-NEGATIVE APPENDICES

The 60 *Actinomyces*-negative appendices used to compare the histological features with those of Crohn's-like appendicitis with *Actinomyces* comprised 22 cases of Crohn's disease for which a right colectomy or total colectomy had been performed, 34 cases of interval appendectomy, and four cases of idiopathic granulomatous appendicitis (Table 1). 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 two cases showed widespread ulceration. Only four appendices showed moderate to marked lymphoid hyperplasia, and the others had limited or mild lymphoid hyperplasia. Transmural inflammation was at least focally present in nine cases. Periappendiceal fibrosis was absent in most cases or mild at most, and only three cases had moderate periappendiceal fibrosis. Nine cases had granulomas, but, in six cases, they were rare or focal. Four harboured faecaliths, but none had filamentous bacteria coating the faecal matter.

Among the 34 interval appendectomy specimens, half of the cases had either no significant mucosal activity (14 cases) or focal mild activity (three 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

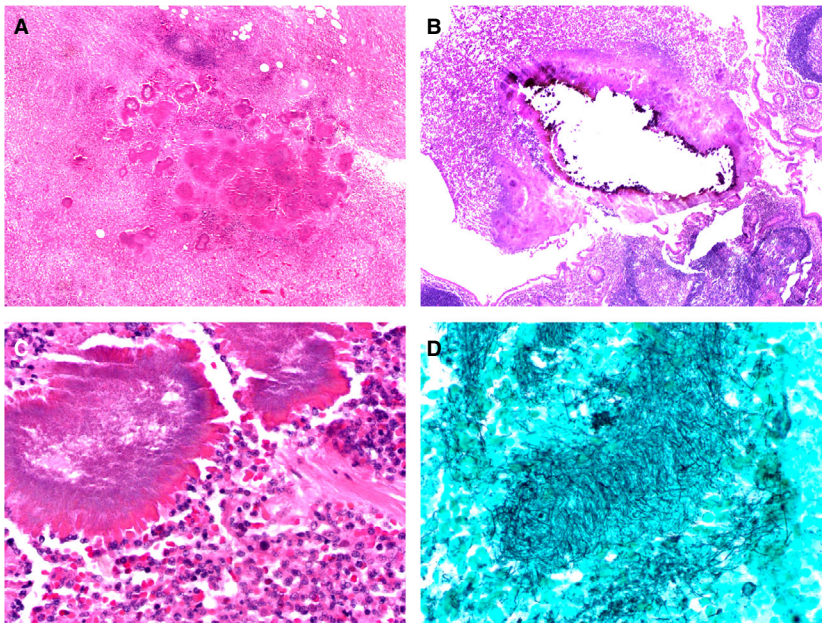

Figure 7. *Actinomyces* in cases of Crohn's-like appendicitis. **A,** An aggregate of *Actinomyces* colonies. **B,** Low-power view of a single large colony of *Actinomyces* surrounding faecal material. **C,** High-power view of *Actinomyces* with the Splendore–Hoeppli phenomenon, consisting of radiating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

focal and mild in four. Thirty of 34 cases had mild or no periappendiceal fibrosis, and only four cases had moderate (three cases) or marked (one case) periappendiceal fibrosis. Twenty-six cases showed no granulomas; eight showed granulomas (two 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 five had faecaliths, and none showed the presence of *Actinomyces*. Various other alterations were seen in some cases, including submucosal abscess, haemorrhagic or granulation tissue-like adhesions, and mucosal attenuation or atrophy.

In the four cases of idiopathic granulomatous appendicitis, 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 three cases and moderate but focal in one case. Three cases had granulomas and the last case had xanthogranulomatous inflammation. None had a faecalith.

After exclusion of the idiopathic group, because of small numbers of cases, comparison between the other two groups and the *Actinomyces* group showed that the degrees of lymphoid hyperplasia and transmural inflammation were greater in the cases with *Actinomyces*, and the degree of fibrosis was greater in actinomycotic appendicitis than in the cases of either 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 two. In one case, a 12-year-old boy had a dilated appendix with focal deep ulceration and acute appendicitis and oedema. 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, and a focal perforation with suppuration; a large *Actinomyces* colony was present in the lumen, with sloughed epithelium and neutrophils.

Discussion

Rarely, an inflamed appendix may show histological features that resemble those of 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

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

	Crohn's-like appendicitis with *Actinomyces*	Appendix from a patient with resected Crohn's disease	Interval appendectomy specimen	Idiopathic granulomatous appendicitis
Total	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
Faecalith				
Absent	12	18	29	0
Present	8	4	5	4

All *P*-values are in comparison with the Crohn's-like appendicitis with *Actinomyces* group.
*$P < 0.01$–0.001.
†$P < 0.05$–0.01.
‡$P < 0.00005$.
§$P < 0.0005$.

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; its presence is often associated with marked fibrosis that can create concern for an appendiceal tumour. In several of our cases, the presence of *Actinomyces* was only noted at retrospective review, suggesting that *Actinomyces* is an under-recognized cause of Crohn's-like appendicitis. Pathologists 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, because microbiological studies are often not performed and often not successful in isolating *Actinomyces*.

The concept of Crohn's disease limited to the appendix was once generally accepted, on the basis of the histological 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 <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, whereas 60 control cases were negative.[9] The histological 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 cases of *Yersinia* infection,[9,10] but are neither sensitive nor specific. Although *Yersinia* infection is often considered in cases of granulomatous appendicitis, it is difficult to prove because serological diagnosis is challenging, the organism is difficult to culture, and it is typically not included in routine stool culture examination in most microbiology laboratories; furthermore, histological evaluation for the organism by the use of special stains is insensitive. Although PCR can be attempted, it is insensitive in paraffin-embedded tissue, and is almost 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 periappendiceal abscesses, and appendectomy after a few months. In 1997, Mazziotti *et al*. reported granulomatous appendicitis in three 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 that 11 cases had Crohn's-like features, including mural thickening, transmural lymphoid hyperplasia, and crypt distortion.[12] Xanthogranulomatous inflammation was found in eight cases. These changes were uncommon in the control group in their series. We had two patients who had undergone an interval appendectomy, but who also had *Actinomyces* on faecal 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 eight of the cases, an appendiceal neoplasm was considered in the differential diagnosis on the basis of radiological 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 greater degrees of lymphoid hyperplasia and transmural inflammation in these appendices than are seen in patients with actual Crohn's disease or 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 that seen in Crohn's disease itself or in most cases of interval appendectomy. Others have also noted the marked fibrosis and induration that characterises actinomycotic appendicitis,[14–16,19] and several case reports have described 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 ileocaecal region, and is commonly preceded by a perforated viscus, most often the appendix. Actinomycosis is characterised by 'wooden' desmoplastic fibrosis that often raises concerns for cancer.[1,3] Long-term penicillin therapy is indicated in patients with chronic actinomycosis, as the antibiotic has poor penetrance into the fibrotic inflammatory mass.

In several reported cases of appendiceal actinomycosis, long-term antibiotic therapy was initiated because of concerns for the development of abdominal actinomycosis.[3,13,14,16] However, some of the cases we have encountered went undiagnosed until retrospective review, and there seem to have been no negative consequences for those patients. Others were treated for up to 12 months with antibiotics, because

of the pathological 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 is generally not perforated. Probably, appendectomy and routine postoperative antibiotic coverage is sufficient for these patients. Nevertheless, 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* colonises 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 that *Actinomyces* does not colonise the appendix in sufficient numbers to form cotton wool colonies in most patients. In those two cases, the features were not those of chronic Crohn's-like appendicitis. In two of our cases, the histological 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 characterised 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 those with marked fibrosis. It is possible that *Actinomyces* in an appendix left *in situ* after appendicitis and treated with interval appendectomy may cause a more dramatic fibrosing Crohn's-like appearance than is seen for interval appendectomies without *Actinomyces*. We tested seven 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 of this, *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 histological 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, 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 greater degrees 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 faecal 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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