Case report

Streptococcus pyogenes peritonitis: a rare, lethal imitator of appendicitisMatthew Johnson,¹ Ashley Bartscherer,¹ Ellis Tobin,² Marcel Tafen¹¹Department of Surgery, Albany Medical College, Albany, New York, USA²Upstate Infectious Disease, Albany, New York, USA

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SUMMARY

Streptococcus pyogenes is a common cause of infection. Since 2010, the Centers for Disease Control has noted a 24% rise in invasive *S. pyogenes* infections with a mortality rate of 10%. We present a case series and review of the English literature. Two patients presented with findings concerning for appendicitis, each underwent laparoscopic appendectomies. Both had diffuse peritoneal inflammation without appendicitis, cultures grew *S. pyogenes* and both recovered with appropriate antibiotics. Thirty cases were identified in a review of the English literature. The average age was 27 years, 75% were in women, 9% were immunocompromised, 15% had rashes and 88% underwent surgical intervention. Previous work identified female gender, immunosuppression and preceding varicella infection as risk factors for invasive *S. pyogenes*. Given the similarities to appendicitis, early suspicion can influence antibiotic therapy and possibly improve outcomes.

BACKGROUND

Streptococcus pyogenes is a gram-positive coccus harbouring the Lancefield group A antigen that causes a wide variety of potentially lethal infections.¹ Invasive *S. pyogenes* infections include sepsis, empyema, endocarditis, osteomyelitis, necrotising fasciitis, surgical wound infections, endometritis and peritonitis.² Between the years 2010 and 2015, the Centers for Disease Control reported an approximately 20% increase in invasive *S. pyogenes* infections and an attributable mortality rate of 10%.^{3–5} Only 5% of invasive *S. pyogenes* infections were due to primary peritonitis in a nationwide review of paediatric invasive *S. pyogenes* cases in Finland.⁶ Without a high index of suspicion for *S. pyogenes* infections, clinicians may be more likely to misdiagnose the patient and delay crucial antimicrobial therapy. The study was approved by the institutional review board and reviewed two patients with primary *S. pyogenes* peritonitis treated at a tertiary academic medical centre along with 30 cases presented in the literature in an attempt to better define this rare, poorly understood disease process.

CASE PRESENTATION

Case 1

A 14-year-old male patient presented to an outside hospital with 3 days of worsening right lower quadrant pain and associated nausea, vomiting and subjective fever. His examination was significant

for diffuse abdominal tenderness with rebound and guarding, worst in the Right lower Quadrant (RLQ). On hospital day 1, the patient was noted to have a fever of 38°C and leucocytosis ($25 \times 10^9/L$) with 46% bands. An initial urinalysis was unremarkable. A CT abdomen and pelvis demonstrated a 9 mm rim enhanced, fluid filled appendix and small amount of free pelvic fluid. The patient was started empirically on ertapenem in preparation for the operating room. On hospital day 2, the patient underwent a laparoscopic appendectomy which revealed hyperaemic bowel and grossly purulent free fluid in the abdomen and pelvis as well as a normal appearing appendix that was removed. The pathology report showed minimal amount of grey fibrinous exudate that may be consistent with acute appendicitis. Nineteen hours after the operation, the patient met criteria for severe sepsis: febrile to 38°C, leucocytosis (white cell count $17.4 \times 10^9/L$) and acute kidney injury (creatinine increased from 1.0 to 1.8 mg/dL) with oliguria. Gram stain of peritoneal fluid found gram-positive cocci in round pairs and chains, Remel Streptex Rapid Latex Agglutination Test identified the isolate as containing the Lancefield group A antigen and no further testing was completed. The patient was transferred to our centre's paediatric intensive care unit and clindamycin was added to the antibiotic regimen. The formal culture was sensitive to ampicillin, penicillin, ceftriaxone, clindamycin, erythromycin, vancomycin, linezolid and levofloxacin.

Case 2

A 52-year-old female patient presented to the emergency department with 3 days of right lower quadrant abdominal pain associated with nausea, vomiting, poor oral intake, fever of 38.9°C and leucocytosis ($20.9 \times 10^9/L$) with 84% neutrophils. Her abdomen was tender to palpation at McBurney's point with no rebound tenderness or guarding. In the emergency department there was initial concern for urinary tract infection based on a urinalysis that showed 2+ leucocyte esterase and 10–20 white cell count per high-powered field. Oral sulfamethoxazole/trimethoprim was initiated empirically. A CT abdomen and pelvis was obtained for evaluation of persistent abdominal pain, and it revealed a 1 cm dilated, fluid filled appendix and an 8.5×8.5 cm heterogenous pelvic mass at the level of the cervix. Appendicitis with abscess was suspected, and she was taken to the operating room on hospital day 2 for laparoscopic evaluation. Inspection of the pelvis showed an inflamed

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right ovary with mucopurulent fluid involving the tip of the appendix, which had a normal appearing base. The appendix was removed, and a further inspection showed no extension of the inflammation beyond the lower right quadrant. Pelvic fullness, corresponding to the large pelvic mass seen on CT, was appreciated in the retroperitoneum low in the pelvis, contiguous with the cervix. Gynaecology evaluated the patient in the operating room and determined that the mass was inflammation of the right ovary and fallopian tube secondary to appendicitis. A drain was placed in the pelvis, the abdomen was irrigated and closed. The pathology report showed chronic active periappendicitis, with no primary appendiceal inflammation. Peritoneal fluid and endocervical cultures showed gram-positive cocci in pairs and chains. Gynaecology had noted a normal cervix on their initial evaluation, and the infection was determined to be unrelated to cervicitis. Postoperative antibiotics initially consisted of piperacillin–tazobactam and linezolid. She was transitioned to ampicillin–sulbactam on hospital day 4 at the recommendation of infectious disease consultant after identification of *S. pyogenes* was confirmed via the Bruker Biotyper matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) system (MALDI identification score: 2.415) with secondary confirmation using the pyrrolidonyl arylamidase test. However, no formal sensitivity testing was conducted on either peritoneal or endocervical cultures.

OUTCOME AND FOLLOW-UP

Both patients did well with focused antibiotics, the young man in our first case recovered after his tumultuous course and was discharged on hospital day 5 with a 5-day course of levofloxacin. The middle-aged woman in our second case did well with the tailored antibiotic regimen, she was treated in the hospital for 6 days and then discharged on hospital day 7 with an 8-day course of amoxicillin–clavulanic acid. Both patients are doing well as of the writing of this report with no complications related to their infection or operation.

DISCUSSION

Literature review

We completed a review of the English literature as of March 2018 in the NCBI PubMed database using the search terms ‘Streptococcus pyogenes OR Group A Streptococcus AND primary peritonitis’. Additional cases were found by cross-referencing the references of the previously identified papers. Cases were excluded if there was a clearly identified primary aetiology of peritonitis prior to diagnosis such as peritoneal dialysis, hepatic ascites or known pelvic inflammatory disease. A total of 30 cases were identified and 32 total cases were reviewed including our two patients (table 1). Patient demographics and common findings are outlined in table 2.

Discussion

Primary bacterial peritonitis is a rare cause of acute abdomen and can be difficult to diagnose because it presents sporadically in previously healthy individuals with symptoms similar to those of appendicitis.⁷ Multiple global surveillance studies have indicated that invasive *S. pyogenes* infections have been increasing in incidence over the past two decades.^{4 6 8–10} Invasive *S. pyogenes* infections can cause significant morbidity and mortality, with a mean case fatality in affluent countries ranging from 8% to 16%, rates similar to those caused by invasive meningococcal disease.⁸

Since *S. pyogenes* is not a part of the normal gastrointestinal flora, it is rarely a cause of intra-abdominal infection. However,

our literature review revealed multiple case reports documenting a primary peritoneal *S. pyogenes* infection, many with symptoms mimicking that of appendicitis, as seen in table 1. Due to the similar symptoms shared between *S. pyogenes* peritonitis and appendicitis, distinguishing between the two can be difficult. Since the literature suggests that patients with appendicitis should undergo surgery within the first 72 hours of symptom presentation to minimise the risk of perforation, there is a narrow window of time to identify *S. pyogenes* infection and distinguish it from appendicitis.¹¹ Previous work has highlighted the importance of proper radiological interpretation of CT scans and ultrasounds to prevent unnecessary surgical intervention in this patient population.¹²

We performed a literature review of *S. pyogenes* peritonitis evaluating medical history, suspected diagnosis, rash, imaging findings and surgical intervention. Several cases have illustrated that *S. pyogenes* peritonitis can originate from the appendix itself; however, there are also many reported cases, similar to our two patients, in which the aetiology is unclear. Review of the literature has identified female gender, immunosuppression and preceding varicella infection as risk factors for developing primary *S. pyogenes* peritonitis.^{6 13 14} It has been hypothesised that women are at greater risk due to retrograde passage of organisms through the genital tract.⁷ This is a possible aetiology in our second case. However, one of our patients and approximately a quarter of the cases identified in the literature were men. Additionally, a number of women did not have associated genitourinary or gynaecologic sources of *S. pyogenes*. There must be additional mechanisms leading to the peritoneal invasion by *S. pyogenes*, although these are not clear based on our review.

Immunosuppression, specifically HIV infection, appears to be a risk factor for invasive *S. pyogenes* disease in adults. Several case reports have documented primary *S. pyogenes* peritonitis in immunocompromised patients. One case report has documented primary *S. pyogenes* peritonitis in a 15-year-old female patient with HIV, in which the appendix was normal on surgical examination.⁶ Two other cases of *S. pyogenes* peritonitis in adult males with HIV were also reported.^{13 14} However, neither of our patients were immunosuppressed, and further studies should look into immunosuppression related risk factors for developing *S. pyogenes* peritonitis.

Finally, preceding varicella infection was seen in 13% and 15% of paediatric invasive *S. pyogenes* infections in national surveys of Canada and Finland, respectively.^{6 15} Although the authors did not propose a reason why this association exists, the viral infection may simply act as a nidus for haematogenous spread.⁶ While 15% of patients identified in our literature review had a rash, dermatologic findings can be associated with toxic shock syndrome, varicella infection or other aetiologies. Additionally, it was not always clear whether this symptom preceded or was secondary to the infection. Finally, neither of our patients had a rash during the course of their illness. Thus, we feel that the presence or absence of a rash is not helpful in identifying patients with *S. pyogenes* peritonitis.

The therapy for *S. pyogenes* varies based on the tissue affected and the clinical presentation. The choice of antibiotics provided to the patient varied in our literature review, but generally included broad spectrum beta-lactam antibiotics. However, invasive *S. pyogenes* infections are best treated with combination therapy including clindamycin and beta-lactam antibiotics¹⁶ as monotherapy with beta-lactam has been associated with increased mortality.¹⁷ The decreased efficacy of beta-lactam monotherapy was initially described as the ‘Eagle effect’ and recent studies

Table 1 Published case studies on primary *Streptococcus pyogenes* peritonitis

Case study	Age and gender	Suspected diagnosis	Rash	Imaging	Surgery	Initial antibiotics	Follow-up antibiotics
Woods and Mason ¹⁹	15-year-old female	–	No	CT: thickened small bowel and ascending colon, small amount of free fluid in pelvis	Laparotomy	Clindamycin	None
Moskovitz <i>et al</i> ²⁰	39-year-old female	Appendicitis	No	None	Laparoscopy	Levofloxacin and metronidazole	Ceftriaxone and ampicillin–sulbactam
Tufarelli <i>et al</i> ²¹	27-year-old male	Appendicitis	No	CT: dilated blind RLQ loop of bowel consistent with appendicitis	Appendectomy	Cefotetan	Vancomycin, ampicillin, metronidazole and gentamicin
Sanchez and Lancaster ²²	34-year-old male	–	No	CT: normal	Laparoscopy	Piperacillin–tazobactam	Penicillin G and clindamycin
Gillespie <i>et al</i> ²³	3-year-old female	–	No	X-ray: ileus	Laparotomy	Ampicillin, gentamicin and clindamycin	Penicillin G and clindamycin
Kanetake <i>et al</i> ²⁴	40-year-old male	Appendicitis	Yes	CT: distention of the small intestine	Laparotomy	Unspecified	None
Dann <i>et al</i> ²²	8-year-old female	Appendicitis with partial/early small bowel obstruction	No	CT: intraperitoneal fluid, dilated small bowel loops, peritoneal enhancement, could not identify normal appendix	Laparotomy	Unspecified	None
Dann <i>et al</i> ²²	6-year-old female	Primary bacterial peritonitis	No	CT: complex ascites with diffuse peritoneal enhancement, no appendicitis	Laparoscopy	Unspecified	None
Dumas <i>et al</i> ²⁵	51-year-old female	Appendicitis	No	Chest X-ray: negative; abdominopelvic scan: 10 cm diameter appendix	Coelio-surgery	Ceftriaxone and metronidazole	Penicillin G and ceftriaxone
Sewery and Bryant ²⁶	7-month-old female	Small bowel obstruction	No	Abdominal radiography: dilated duodenum with edematous folds and termination of flow	Laparotomy	Ceftriaxone and metronidazole	Penicillin G
Tilanus <i>et al</i> ²⁷	39-year-old female	Pelvic inflammatory disease	Yes	CT: thickened right psoas muscle surrounded by fatty infiltration and a large amount of free fluid in the peritoneal cavity	None	Amoxicillin–clavulanic acid, clindamycin and gentamicin	Benzylpenicillin and clindamycin
Saha <i>et al</i> ²⁸	23-year-old female	Appendicitis	No	CT: left sided adnexal mass with moderate amount of free fluid	Laparotomy	Unspecified	None
Haap <i>et al</i> ²⁹	27-year-old male	Bowel obstruction	No	US: fluid in Morrison's pouch; gallstones CT: edematous alteration of small intestine; segmental colitis of transverse colon and perirectal oedema	Laparotomy	Piperacillin–tazobactam ciprofloxacin and metronidazole	None
Legras <i>et al</i> ³⁰	32-year-old female	Urinary tract infection	No	CT: free peritoneal fluid, most abundant in the pelvis	Laparotomy	Gentamicin and ofloxacin	Ceftriaxone, metronidazole and levofloxacin
Demitrack ³¹	3-year-old female	Appendicitis	Yes	CT: diffuse ileus and ascites	Appendectomy	Ampicillin, gentamicin and clindamycin	Penicillin G and clindamycin
Holden <i>et al</i> ³²	14-year-old female	Appendicitis	No	US: no appendix visualisation	Laparoscopy	Metronidazole and ciprofloxacin	Meropenem and clindamycin
Preece <i>et al</i> ³³	17-year-old female	Appendicitis	No	Unknown	Laparoscopy	Benzylpenicillin	Doxycycline, metronidazole and phenoxymethylpenicillin
Park <i>et al</i> ³⁴	29-year-old female	Appendicitis	No	CT: edematous swelling of intestinal wall and ascites with peritoneal enhancement	Laparoscopy	Ampicillin–sulbactam	Penicillin G and metronidazole
Cheung <i>et al</i> ³⁵	16-month-old male	Small bowel obstruction	No	CT: small bowel obstruction and large ascites	Laparotomy	Ampicillin, gentamicin and metronidazole	Penicillin G and clindamycin
Nogami <i>et al</i> ³⁶	40-year-old female	Adverse reaction to chemotherapy	No	CT: ascites, no perforation	Laparotomy	Meropenem and vancomycin	Ampicillin–sulbactam

Continued

Table 1 Continued

Case study	Age and gender	Suspected diagnosis	Rash	Imaging	Surgery	Initial antibiotics	Follow-up antibiotics
Patel <i>et al</i> ³⁷	6-year-old male	Gastroenteritis, perforated appendix, peritonitis	No	Chest X-ray: negative	Laparotomy	Cefuroxime, gentamicin and metronidazole	None
Filan and Abbas ³⁸	7-year-old male	Gastroenteritis, appendicitis	No	CT: free fluid and two intra-abdominal abscesses	Laparoscopy	Piperacillin-tazobactam	None
Min <i>et al</i> ³⁹	51-year-old female	Gastritis	No	CT: diffusely distended and thickened whole stomach with intraperitoneal fluid	Laparotomy	Unspecified	None
Kaneko <i>et al</i> ⁴⁰	28-year-old female	–	No	CT: edematous swelling of the intestinal wall with dense fat infiltrations in the pelvic cavity but no marked free air or ascites	None	Vancomycin and piperacillin-tazobactam	Penicillin G and clindamycin
Abellan Morcillo <i>et al</i> ⁴¹	60-year-old female	–	No	CT: minimal amount of free intraperitoneal fluid with no other findings	Laparoscopy	Amoxicillin-clavulanic acid	Clindamycin and a third-generation cephalosporin
Yokoyama <i>et al</i> ⁴²	40-year-old female	Intra-abdominal haemorrhage or formation of a pelvic abscess	Yes	CT: uterine fibroids, ascites and thickening of the peritoneum	Laparotomy	Azithromycin	Meropenem
Chomton <i>et al</i> ⁴³	10-year-old female	Primary peritonitis and toxic shock syndrome	Yes	Abdominal ultrasound: free peritoneal fluid	Laparoscopy	Cefazolin, cefotaxime and clindamycin	None
Iitaka <i>et al</i> ⁴⁴	26-year-old female	Peritonitis	No	CT: large amount of free fluid in the peritoneal cavity consistent with a peritonitis; no free air	Paracentesis	Meropenem	Piperacillin-tazobactam and clindamycin
Iwata and Iwase ⁴⁵	66-year-old female	Enteritis of unknown origin	No	CT: small bowel dilation without ischaemic signs and mild pelvic ascites	None	Meropenem	Ampicillin-sulbactam and clindamycin
Ledger ⁴⁶	46-year-old female	Appendicitis, ectopic pregnancy and enteritis	No	CT: intra-abdominal stranding consistent with peritonitis	None	Benzylpenicillin	None
Case 1	14-year-old male	Appendicitis	No	CT: free fluid in the pelvis suspicious for early appendicitis	Laparotomy	Ertapenem	Piperacillin-tazobactam
Case 2	52-year-old female	Appendicitis	No	CT: 1 cm dilated, fluid filled appendix and a large heterogeneous pelvic mass at the level of the cervix	Laparotomy	Sulfamethoxazole-trimethoprim	Piperacillin-tazobactam and linezolid

Table 2 Characteristics and demographics of the literature review

Average age	27	
Rash	5	15%
Female gender	24	75%
Immunocompromised status	3	9%
	HIV	2 6%
	Chemotherapy	1 3%
Underwent surgical intervention	28	88%
	Total cases	32

have shown antibiotics that work at the ribosomal level are important in the management of invasive *S. pyogenes*.^{17 18}

CONCLUSION

The incidence of invasive *S. pyogenes* infection has increased significantly over the last decade. We reviewed 32 total cases of *S. pyogenes* peritonitis, including two treated at our own institution. Female gender, immunosuppression and preceding varicella infection have been suggested as possible risk factors for developing *S. pyogenes* peritonitis. Female gender predominated in the literature; however, the exact mechanism remains evasive. Nevertheless, the essential components of managing this patient population effectively include awareness, early suspicion and early initiation of appropriate antibiotic therapy.

Learning points

- *Streptococcus pyogenes* can cause invasive disease including primary peritonitis.
- Keys to the management of *S. pyogenes* infection include awareness and early initiation of appropriate antibiotics.

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