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Case Series

Delayed Anastomotic Failure After Chemoradiation: A Delay in Diagnosis or Late Presentation? – A Case Series

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ABSTRACT

Anastomotic leak after colorectal surgery can result in serious morbidity for certain patients. The rate of clinically significant anastomotic leak after colon resection ranges from 1.8% to 11.9%. Risk factors include male sex, steroids, smoking, perioperative blood transfusion, malnutrition, and a low anastomosis. However, the effect of pre-operative chemoradiation therapy (CRT) on rates of anastomotic leak is controversial. Specifically, late leaks, which are defined as those that occur greater than 30 days after surgery, are sparsely described in current literature. Recent evidence suggests that CRT may contribute to the presentation of late anastomotic leaks. In this case series, we report our experience with three patients who received CRT and developed varying presentations of a late anastomotic leak. Therefore, our experience supports the consideration of late anastomotic leaks as a separate entity in colorectal surgery. While pre-operative CRT may increase risk for postoperative anastomotic leak overall, further exploration into the relationship between preoperative CRT and late anastomotic leaks is warranted.

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Introduction

Anastomotic leak can be a devastating, and sometimes fatal, complication for patients undergoing bowel surgery [1-4]. The rate of clinically significant anastomotic leak (AL) after colorectal surgery ranges from 1.8%-11.9% and certain factors, such as male sex, steroids, smoking, perioperative blood transfusion, malnutrition and a low anastomosis, are known to increase the risk of AL [1, 3, 5-14]. There have been many published studies and reports documenting these risks including Tortorelli *et al.* who published a retrospective review of 475 patients who underwent low anterior resection for rectal cancer, which reported a 9% symptomatic leak rate with tumors less than 6 cm from the anal verge and intraoperative transfusions identified as statistically significant risk factors [12]. However, whether or not pre-operative chemoradiation therapy (CRT) increases the risk of colorectal anastomotic failure remains controversial [5, 7, 12, 13, 15]. In a single-institution retrospective analysis with 123 patients undergoing elective rectal surgery, Hayden *et al.* found that neoadjuvant CRT was associated with an increased risk for anastomotic complications, including stenosis

and leakage or abscess [16]. However, Milgrom *et al.* found that neoadjuvant CRT was not associated with an increased risk of morbidity and Chang *et al.* determined that pre-operative CRT did not increase the risk of AL in their patients in a propensity matched retrospective study [5, 15, 17].

Much of the current literature only describes leaks that occur less than 30 days from surgery, but recently Lim *et al.* published a retrospective study of 141 rectal adenocarcinoma patients who developed AL in which they compared risk factors and presentation of early (i.e., <30 days) vs late (i.e., >30 days) AL [18]. Interestingly, they found that radiotherapy was the only significant independent factor predisposing the patients to a late leak [18]. We observed three patients who presented with anastomotic leaks well beyond the immediate 30-day period post-operatively. These patients had undergone pre-operative CRT and presented with AL months to years after their operations. In our effort to better understand this subset of patients, we present this review detailing the presentation, clinical course, and management of these patients who presented with delayed AL. The following is presented in accordance with the CARE reporting checklist.

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Case Presentation

Case 1

A 57-year-old man with a past medical history of diabetes mellitus, coronary artery disease that required a coronary artery bypass graft, hypertension, and a smoking history of 24 pack-years with the past 15 years tobacco-free was found to have a stage II (cT3N0M0) moderately differentiated rectal adenocarcinoma in the distal rectum. Seven weeks after completing neoadjuvant CRT, the patient underwent low anterior resection (LAR) and diverting loop ileostomy. During the surgery, the patient had a positive air-leak test on the left lateral aspect of the anastomosis treated by an omental pedicle flap and drainage. Final pathology revealed well to moderately differentiated adenocarcinoma associated with calcifications, 1.2 cm, extending into the muscularis propria, 0/15 lymph nodes with tumor cells (ypT2N0M0). The pathologist noted an ulcer in the area previously filled by tumor, which is an indicator of adequate response to neoadjuvant CRT. The patient then underwent adjuvant chemotherapy with Xelox. During this time, he was noted to have some hematochezia, which was treated with mesalamine enemas. Three months after surgery, the patient had a colonoscopy, which demonstrated an ulcer just proximal to the anastomosis. In addition, contrast enema revealed a leak. Six weeks later, the patient underwent another contrast enema which failed to demonstrate a leak but was notable for a slight irregularity of the rectal wall at the anastomosis in the region of the previously seen extravasation. As there was no evidence of persistent leak, the patient underwent reversal of his ileostomy.

Four months after his ileostomy reversal, the patient underwent another colonoscopy that revealed a new ulceration. Repeated biopsies of the ulcer did not demonstrate tumor recurrence. There was concern that this new ulcer, 8.5 months after the LAR, was a developing anastomotic dehiscence and the patient was counseled to undergo another diverting ileostomy, which he refused. Over the next three years, the patient was

surveyed with colonoscopies and exams, which demonstrated progression of the ulcer. During this time, the patient only complained of rectal bleeding, which intermittently improved with mesalamine enemas as well as pentoxifylline and Vitamin E. Then, three years after his initial surgical resection, the patient presented to the office complaining of fevers associated with abdominal and rectal pain. He was found to have a complete dehiscence of his anastomosis and pelvic sepsis requiring an emergent exploratory laparotomy and end colostomy. Interestingly, although this patient had a high risk of anastomotic failure given the operative details, the interval period between initial surgery and the need for fecal diversion was significant. Post-operatively, the patient did well.

Case 2

An 88-year-old man with a past medical history significant for adenocarcinoma of the rectum, presented with pelvic pain, left hip pain, bright red blood per rectum and fecal incontinence for several weeks. Six years prior to presentation, the patient received neoadjuvant CRT, and underwent a LAR with diverting colostomy and subsequent colostomy reversal for his rectal cancer. On physical exam, he was noted to have perineal tenderness to palpation and a concern for pelvic abscess. A subsequent CT scan demonstrated a 7x4x9 cm presacral air and fluid-filled collection in direct communication with the rectum. The collection was associated with a tract of air and fluid, which extended laterally and inferiorly along the left pubic rami and ischial tuberosity (Figure 1). The patient subsequently underwent an exam under anaesthesia (EUA), flexible sigmoidoscopy, exploratory laparotomy and diverting loop colostomy and washout. The surgeons noted a complete disruption of the colorectal anastomosis with a large presacral abscess. The patient's immediate post-operative course was complicated by left ischial osteomyelitis and presacral abscesses treated with intravenous antibiotics, repeated EUAs and washout procedures of the pelvis.



Figure 1: Depicted is the axial (left) and coronal (right) cuts of a CT scan of the pelvis showing extraluminal air and fluid tracking inferiorly and laterally, suggestive of an anastomotic dehiscence.

One year later, the patient presented with fevers and chills and was diagnosed with an intra-abdominal abscess with tracking to the left gluteal region. This was treated with drainage via intra-abdominal catheter and antibiotics. Two months after, the patient presented with similar complaints, and was again diagnosed with a pelvic abscess. This time he was taken to the operating room for an EUA and excision of a

portion of the internal and external anal sphincter in an attempt to provide better drainage as the patient had a relatively stenotic anus. Over the next several months, the patient continued to have recurrent pelvic abscesses treated with drainage catheters placed by interventional radiology. Infectious disease was consulted and eventually, as the collections became progressively smaller and the patient was no longer

presenting with signs and symptoms of sepsis, they recommended to simply survey the collections or treat with drainage without antibiotics. The patient died of pneumonia three years after his initial presentation at the age of 91. At the time of the last documented visit, the patient was admitted for a urinary tract infection and doing well in terms of his pelvic collections.

Case 3

A 79-year-old man with a history of diabetes mellitus, hypertension, prostate cancer treated with radiation therapy, and rectal cancer that was treated at an outside institution presented with lethargy for two to three months and syncope, as well as left leg pain for two to three weeks. Five years prior to his presentation, he completed neoadjuvant chemotherapy with FOLFOX followed by radiation treatment. He also underwent a LAR with diverting ileostomy that was complicated by a pelvic hematoma requiring urgent takeback for control of pelvic bleeding. Postoperatively, he developed an anastomotic leak that was treated with endoluminal vacuum therapy. Ultimately, the dehiscence healed, and the patient did well in the five-year surveillance period but decided not to reverse his ileostomy. At time of presentation to our hospital, CT scan of the abdomen and pelvis showed a 10 cm air and fluid-filled collection immediately posterior to the rectum in the presacral space with extension into the left proximal thigh, consistent with an abscess due to an anastomotic breakdown.

The patient underwent a CT-guided drain placement with evacuation of 140 mL of purulent fluid and was started on antibiotic therapy. Due to a persistent collection, another drainage catheter was placed but ultimately the patient required transrectal drainage. He was discharged to a long-term care facility. Unfortunately, the patient was re-admitted two weeks later for multifocal pneumonia and a persistent presacral collection treated with repeat transrectal drainage. The rectal wound was treated with negative pressure wound therapy and showed improvement over the course of his hospitalization. However, the patient deteriorated, and he died due to complications from multi-drug resistant pneumonia that had developed.

Discussion

As demonstrated above, our patients had different clinical presentations and courses, yet all three had the interesting characteristic of presenting 'late' or 'delayed' after having received pre-operative CRT. Two of the three patients primarily complained of leg and hip pain, which can distract providers from working up bowel-related issues, making a high level of suspicion even more critical given the associated morbidity.

Although, CRT is an established therapy in the treatment of rectal cancer, it is not without consequence [19]. There are well known immediate side effects such as fatigue, gastrointestinal disturbances, cytopenia, and delayed consequences, such as radiation enteritis and intestinal strictures [18, 19]. Our experiences with these three patients highlights delayed or late anastomotic failure as another potential consequence and an entity that surgeons and oncologists need to be aware of as a leak can have dire consequences [2, 3]. As Caulfield and Hyman noted, they were 'surprised' by the presence of late leaks (defined as >45 days post-operatively) in two of their 30 patients in their retrospective review of anastomotic leaks after LAR [4]. August *et al.*

hypothesized that the development of AL likely involves disruption of collagen, as local hypoxia can lead to impaired hydroxylation of proline and lysine residues, and resultant poor collagen formation [2]. Other studies have noted that the development of a late leak may be driven by the presence of an anastomotic leak or technical error at the time of the original operation [6, 10, 11]. However, one would surmise that this would be more likely to contribute to an early rather than late leak.

All three of our patients appear to be late leaks (occurring more than 1 month after surgery) with delayed clinical manifestations rather than cases of delayed diagnosis. In the case of the first patient, despite a small leak at the time of the operation, there was no clinical or radiographic evidence of a leak just prior to his ileostomy reversal. Furthermore, when there was a suspicion of a complication after his ileostomy reversal, it was a small ulcer and took three years to progress to a complete dehiscence and pelvic sepsis with minimal clinical complaints from the patient. And, by report, our second and third patients did not have any known complications with their initial operations and lived five years or more without any overt clinical issues. One would imagine that if these cases were simply a delay in diagnosis, the patients would have had more clinical symptoms that would progress over weeks, not years. Additionally, the long period of time between surgery and pelvic sepsis suggests that the cause of their leaks was an insidious process – perhaps chronic, progressive ischaemia as a result of fibrosis from CRT in the setting of surgically altered vasculature [2, 19].

The slow progression of such a process would also explain why our patients ultimately had complete dehiscence of their anastomosis and pelvic sepsis, despite clinically appearing relatively well prior to their more urgent presentations. The subclinical component to their disease process may be part of the pathophysiology of late leaks in patients who undergo preoperative CRT. Unfortunately, no individual papers have enough evidence to publish any statistically significant findings. Despite the lack of clear evidence as to whether pre-operative CRT leads to an increased risk of postoperative anastomotic leaks, there is growing awareness of a potentially separate entity of late dehiscence in colon and rectal surgery. Further studies should be done to elucidate any unique risk factors in the development of late anastomotic leaks.

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Ethical Statement

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standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013).

Consent

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