SHORT REPORT

Suppurative granulomatous inflammation in the ileo-anal pouch

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Abstract
Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is commonly performed for medically refractory ulcerative colitis (UC), however with multiple possible complications, most notably pouchitis, cuffitis, Crohn’s disease of the pouch and irritable pouch syndrome. We present a unique case of suppurative granulomatous inflammation in the ileal pouch mucosa, most likely infective in nature, that is unrelated to recognised causes of such pathology, especially yersiniosis.

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1. Case report

A 19 year-old patient presented with a 3-month history of abdominal pain, bloody diarrhoea and weight loss of 12 kg, and following flexible sigmoidoscopy was diagnosed with ulcerative colitis. Her condition deteriorated despite rectal and oral steroids, and was subsequently admitted with a diagnosis of acute severe ulcerative colitis. Stool cultures were negative for pathogens and Clostridium difficile toxin was not detected. A CT scan confirmed features of severe total colitis with no perforation. She received high dose intravenous steroids but deteriorated rapidly over the next 24 hours and therefore underwent an emergency subtotal colectomy with end ileostomy.

Examination of the surgical resection specimen showed features of fulminant active chronic inflammatory bowel disease, fully in keeping with active chronic ulcerative colitis involving the whole colon. There was deep ulceration related to the fulminant disease and there were the characteristic changes of “backwash ileitis”. There were no stigmata of Crohn’s disease. Whilst the deep ulceration might suggest ‘indeterminate colitis’, overall the changes were regarded as fully in keeping with floridly active ulcerative colitis.

She recovered and remained well, and 10 months following the initial surgery a 20 cm J-pouch was created with a covering loop ileostomy. Her post-operative course was complicated by urinary retention and recurrent urinary tract infections. The
loop ileostomy was closed 4 months later and the patient remained well for the following 2 years. She underwent a pouchoscopy in January 2011 which was normal endoscopically and histologically, with mucosal adaptive changes only seen in biopsies from the ileal pouch. No features to suggest either chronic relapsing pouchitis or Crohn's disease were seen.

Forty-two months after pouch formation, she re-presented with a 5 month history of poor pouch function. Her bowel frequency was 20 times during the day and 2–3 times at night, passing urgent loose stools. She reported abdominal and anal pain with abdominal distension, increasing fatigue and anxiety. Her symptoms markedly improved following an empirical course of ciprofloxacin for possible pouchitis, but returned within 24 hours of drug cessation. Two stool specimens were negative for enteric pathogens and Clostridium difficile. She had no response to a second course of ciprofloxacin, and pouchoscopy was performed. This showed multiple aphthous lesions in the pre-pouch ileal mucosa and in the pouch, with moderate inflammation of the cuff.

Histological assessment of pouch biopsies revealed striking granulomatous inflammation in the pouch mucosa as well as in the pre-pouch ileal mucosa. These granulomatous foci were sited specifically within lymphoid follicles and characterised by well-defined epithelioid cell granulomata with central suppuration (see Figs. 1 and 2). These features were quite distinct from the typical granulomata seen in Crohn's disease and those encountered, not uncommonly, in the pouch mucosa due to adaptive changes. These granulomas were not along the suture line and there were none of the histological features associated with chronic relapsing pouchitis.

A small bowel MR study was performed which showed no evidence of active inflammation in the more proximal small bowel or other features to suggest Crohn's disease. The possibility of Yersinia infection was raised; however stool and serological evaluation (Y. enterocoliticaSerotypes 03, 05:27, 08 and 09; Y. pseudotuberculosisSerotype I to V) was negative. A further pouchoscopy was performed which showed very similar appearance to the first. Histological analysis again showed suppurative granulomatous inflammation. Her stool frequency increased and ciprofloxacin was recommenced along with azithromycin (to cover atypical infections such as atypical TB or cryptosporidium). She improved over the following 4 weeks by which time her pouch function was back to baseline with 5 stools by day and 0 by night with no urgency or incontinence.

2. Discussion

A granuloma is a circumscribed collection of epithelioid histocytes and is a distinctive chronic inflammatory reaction in which the predominant cell type is an activated macrophage with a modified epithelioid-like (epithelioid) appearance. The epithelioid cells are surrounded by a collar of mononuclear leucocytes (predominantly lymphocytes and occasionally plasma cells). Frequently these epithelioid cells fuse to form giant cells in the periphery or sometimes in the centre of the granuloma. Granulomatous inflammation is encountered in a number of chronic immune and infectious diseases. Tuberculosis is the archetypal granulomatous disease and its granuloma or tubercle is the prototype for the immune granuloma. Other causes include sarcoidosis, cat-scratch disease, lymphogranuloma inguinale, brucellosis, syphilis and reactions of irritant lipids.

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice for patients with medically refractory ulcerative colitis (UC) or colitis-associated dysplasia and for patients with familial adenomatous polyposis. About 30–35% of patients with UC eventually require colectomy and most patients elect to have a pouch. The main contra-indications for IPAA include a preoperative diagnosis of Crohn’s disease (CD), absent or decreased anal sphincter muscle tone, and pelvic floor dysfunction.

Complications of the pouch include those related to surgery, inflammatory or infectious disorders, functional disorders, dysplasia or neoplasia. Pouchitis is the most frequent long-term complication of IPAA in patients with UC, with a cumulative incidence of up to 50–60%. Other specific complications include Crohn’s disease of the pouch, cuffitis, and irritable pouch syndrome (IPS). Pouchitis causes increased stool frequency, urgency, incontinence, nocturnal seepage, abdominal cramps, and pelvic discomfort. Abnormal mucosal immune response to altered...
commensal microflora of the pouch (i.e. dysbiosis) is proposed to have a key role in the development of "idiopathic" pouchitis.\cite{3,5,9} There is little consensus as to which risk factors definitively increase the likelihood of developing pouchitis.\cite{3,5,10}

Approximately 20–30% of patients have "secondary pouchitis" with clear secondary identifiable or modifiable aetiologies and triggering factors.\cite{3-5} These include cytomegalovirus (CMV) infection, Candida infection, \textit{Clostridium difficile} infection, ischaemia, autoimmune disorders, radiation, chemotherapy, collagen deposition of the pouch mucosa, and use of NSAIDs.\cite{3,5} Diagnosis of pouchitis is based on symptoms supported by endoscopic and histological abnormalities. The Pouch Disease Activity Index (PDAI) incorporates these variables into a score with a total of greater than or equal to 7 suggestive of pouchitis.\cite{3,5,7}

Suture-line ulcerations are non-specific and common in patients with IPAA and do not necessarily indicate an inflammatory disease. Foreign body granulomas in mucosal biopsies may be mistakenly interpreted as a sign of CD.\cite{4} Granulomas within lymphoid follicles are well described and are a relatively common feature in the ileal reservoir mucosa but they tend to be small, ill-defined and fewer in number unlike in our case which showed large compact well-defined granulomas with central suppuration.\cite{11}

The true incidence of CD of the pouch in patients who undergo surgery for UC is not known, but is reported to be approximately 2.7–13%. The most significant risk factors for CD of the pouch are the preoperative diagnosis of CD or indeterminate colitis (which was not the case for our patient) and being a smoker. Other possible risk factors include longer duration of IPAA and female gender. \textit{De novo} CD of the pouch may develop weeks or years after IPAA even when a reassessment of the original proctocolectomy specimen shows no evidence of CD. Demonstration of small bowel involvement by endoscopy, contrast radiography or cross sectional imaging is helpful to diagnose CD,\cite{4} with video capsule endoscopy being the most sensitive test.\cite{12}

Involvement of the small intestine in inflammatory bowel disease usually indicates Crohn’s disease, but the ileum can be affected in ulcerative in four distinct entities: backwash ileitis, prestomal ileitis, pouchitis and pre-pouch ileitis. Pre-pouch ileitis is continuous inflammation of the terminal ileum (with variable length involved), proximal to the ileal pouch. It is distinct from Crohn’s disease histologically and is often mistaken as Crohn’s disease on endoscopy. In approximately 50% of cases there is concomitant pouchitis.\cite{13}

This case is the first to describe suppurative granulomatous pathology in the ileal pouch mucosa unrelated to recognised causes of such pathology, especially yersiniosis. Indeed the cause remains uncertain but we believe it is likely to be infective in origin. The suppuration was within discrete granulomas, characteristically seen within lymphoid follicles and Peyer’s patches in the ileal mucosa. Such granulomas, without suppuration, are a well-recognised component of the adaptive changes seen in the mucosa of the ileal pouch. In any case of CIBD, Crohn’s disease has to be considered but the original colectomy specimen, the most important specimen to assess as mimicry of the pathological changes of CD, showed no evidence of Crohn’s disease. The feature of central suppuration makes an infective aetiology the most likely possibility, in our view, and, perhaps, an additional reaction to an as yet unknown intraluminal antigen may account for the patient’s symptomatology and the unusual features seen histologically. The complete resolution of symptoms following antibiotics would support its putative infective nature. This case highlights the importance of thorough clinical, endoscopic and histological assessment, before considering the next-line medical treatment in cases of pouchitis.

**Conflict of interest**

There is no financial conflict of interest for any of the authors.

**References**