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Classification, differential diagnosis, and diagnosis of pouchitis

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A B S T R A C T

Evaluation of patients with ileal pouch-anal anastomosis after total proctocolectomy who present with symptoms suggestive of pouchitis requires a systematic approach. Although idiopathic pouchitis is the most common cause of symptoms, evaluation for possible secondary causes of pouch inflammation and for potential disease mimickers is essential. After appropriate testing and assessement of response to treatment, disease can be classified based on response to antibiotics and as idiopathic or secondary. A systematic approach and the use of different modalities of testing including pouch endoscopy, pathology and imaging, should lead to an appropriate diagnosis and a well-planned treatment plan. A proposed algorithm for evaluation of symptomatic patients will be outlined.

Introduction

Restorative proctocolectomy has become the standard of care for the majority of patients with ulcerative colitis requiring surgery. Outcomes after this surgery are excellent but one of the most frequent complications is the development of pouchitis. Up to 50% of patients with ulcerative colitis and ileal pouch-anal anastomosis (IPAA) will develop pouchitis, often within the first 2 years after closure of a diverting ileostomy.[1] In this review, we will discuss the classification, differential diagnosis, and diagnosis of pouchitis all of which are key factors in guiding appropriate management of patients presenting with pouch inflammation.

Classification

The term “pouchitis” is generally used to refer to inflammation of a surgically created ileal pouch. There are many conditions that can lead to ileal pouch inflammation and thus further classification is important especially as it impacts clinical management. Pouchitis can be classified into several categories but most important among these are duration and frequency of symptoms, etiology, and response to antibiotic treatment (Table 1).[1,2]

Initial classification for patients presenting with pouchitis can be determined based on duration and frequency of symptoms. Acute pouchitis is considered as symptoms of less than 4 weeks duration while chronic pouchitis symptoms last 4 or more weeks.[1,2] Frequency of symptoms can be classified as infrequent/self-limited when there are fewer than 3 episodes per year while relapsing pouchitis is defined as 3 or more episodes per year or recurrence of symptoms within 1 month of stopping antibiotics.[1] Next, one should consider etiology of the underlying symptoms, which will usually require diagnostic testing to help classify. The majority of cases of pouchitis are idiopathic in etiology and typically can be managed with antibiotics. However, there is increasing recognition of secondary causes of pouch inflammation including infectious etiologies, Crohn's disease, autoimmune, nonsteroidal anti-inflammatory drug related, pelvic sepsis and anatomic problems.[2] These secondary causes can cause symptoms that mimic those of idiopathic pouchitis but require different management; they will be discussed in further detail later. Finally, as most patients with pouchitis respond to antibiotics, a further classification based on antibiotic response can be helpful. Antibiotic-responsive pouchitis occurs frequently and responds to 2 weeks of antibiotics; antibiotic dependent pouchitis requires frequent or long-term antibiotics for relapsing symptoms; antibiotic-refractory pouchitis does not respond to a 4-week course of a single antibiotic.[1,2]

It is important to recognize that these classification categories are not mutually exclusive. For example, relapsing pouchitis can be considered a form of chronic pouchitis that may be antibiotic-responsive or antibiotic refractory. Similarly, chronic antibiotic-refractory pouchitis can be idiopathic or secondary in etiology.[2]

To develop a better understanding of the different classification types of pouchitis, it is helpful to further distinguish between idiopathic and secondary causes of pouchitis. Idiopathic pouchitis is the most common form of pouch inflammation and its epidemiology, etiology, and pathogenesis are discussed in detail in other

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Table 1
Classification of pouchitis.

Etiology:
- Idiopathic
- Secondary (Table 2)

Duration of symptoms:
- Acute: less than 4 weeks
- Chronic: 4 or more weeks

Frequency of symptoms:
- Self-limited/infrequent: less than 3 episodes per year
- Relapsing:
  - 3 or more episodes per year
  - Recurrent symptoms within 1 month of stopping antibiotics

Response to antibiotics:
- Antibiotic responsive: responds to 2 weeks of antibiotics
- Antibiotic dependent: requiring long-term antibiotics
- Antibiotic refractory: no response to antibiotics

sections of this seminars issue. There is a strong pathogenic role of gut microbiota and dysbiosis in idiopathic pouchitis and the most common presentation is that of an acute pouchitis with rapid response to a short course of antibiotics.[3,4] In cases with recurrent symptoms, further classification based on the frequency of symptoms and antibiotic response as listed earlier is helpful. Among patients who develop chronic antibiotic-refractory pouchitis, 20–30% will have identifiable underlying etiologies and thus are classified as having secondary pouchitis.[5] It is essential to recognize these secondary causes of pouchitis as management and treatment decisions will be altered. In the rest of this section, we will review some of the key different types of secondary pouchitis.

Secondary causes of pouchitis

Clostridium difficile associated pouchitis

Clostridium difficile developing as a superimposed infection in patients with inflammatory bowel disease has become a significant problem.[6] In particular, *C. difficile* infection in patients with IPAA has been increasingly recognized.[7–10] In a study of 196 consecutive patients with IPAA presenting with more than 4 weeks of increased stool frequency, 11% tested positive for *C. difficile* on stool PCR testing.[10] It is also important to note that colonization with this organism may occur as suggested by a study in which the organism could be detected by ELISA testing in patients undergoing routine pouch endoscopy with no pouch inflammation.[7]

The symptoms of *C. difficile* infection in IPAA can be similar to those in idiopathic pouchitis but among those with *C. difficile* additional systemic symptoms such as fever, weight loss, and leukocytosis may be present.[9] Similar to *C. difficile* arising in IBD, *C. difficile* associated pouchitis typically does not lead to development of pseudomembranes.[5,9]

There are no controlled trials for medical treatment of *C. difficile* in IPAA patients but first line treatment with vancomycin rather than metronidazole has been suggested.[9] This mirrors recent expert recommendations to consider vancomycin as first line therapy in patients with inflammatory bowel disease and superimposed *C. difficile*. There has been one case report of successful use of fecal microbiota transplantation for relapsing *C. difficile* infection in a patient with IPAA.[11]

Autoimmune pouchitis

Chronic antibiotic-refractory pouchitis (CARP) can be a difficult disease to manage. There is increasing evidence of an association of a subgroup of CARP with an underlying autoimmune etiology including associations with higher rates of autoantibodies such as perinuclear antineutrophil cytoplasmic antibody and antimicrosomal antibody and with primary sclerosing cholangitis and autoimmune disorders.[12–15] Patients who have at least one underlying autoimmune disorder such as psoriasis, rheumatoid arthritis, and autoimmune thyroid disease among others have been shown to have a 2-fold increased risk of developing CARP.[14] More recently, an immunoglobulin G4 (IgG4)-associated pouchitis has been described in a subgroup of patients with CARP including findings of high serum IgG4 levels and of tissue infiltration of IgG4 positive plasma cells on pouch biopsies.[16,17] In a multivariate analysis of 150 symptomatic IPAA patients, the presence of antimicrosomal antibody and increased IgG4-expressing plasma cell tissue infiltration were shown to be strong, independent risk factors for the development of CARP.[15]

It is not clear whether the presence of autoantibodies, other autoimmune disorders, and elevated IgG4 are causal or merely an epiphenomenon, but these associations have led to the description of an autoimmune pouchitis. This condition should be particularly suspected in patients with CARP who have other autoimmune disorders or evidence of autoantibodies. Further evaluation of IgG4 levels in serum and pouch biopsies can be helpful. Recognizing this condition is important as these patients are likely to require immunosuppressive agents for treatment.[5,18]

Ischemic pouchitis

It has been postulated that some cases of chronic pouchitis may be due to underlying chronic ischemic factors leading to hypoperfusion.[18] This was initially considered when an asymmetric pattern on pouch endoscopy with inflammation of only one limb of the pouch and sparing of the other limb with a sharp demarcation between inflamed and noninflamed portions was described and theorized to be due to underlying ischemia.[19] There are limited studies related to this but it has been theorized that factors such as mesenteric tension of vessels at the time of pouch creation, excessive weight gain after surgery, and development of portal vein thrombosis can predispose to a chronic low flow state that leads to a chronic, ischemic type of pouchitis.[18] Supporting this theory is a study that used tonometry at the time of IPAA surgery to estimate intramucosal pH as a measure of intramucosal acidosis suggestive of hypoperfusion.[20] The authors found that low intramucosal pH suggestive of hypoperfusion was associated with increased risks of acute pouchitis and local septic complications.[20]

More work needs to be done to better define and understand this condition but a hypoperfusion/ischemic etiology for pouchitis should be considered in patients with CARP who have asymmetric inflammation of the pouch noted at the time of pouch endoscopy. Typical patterns include inflammation along 1 limb of the pouch with sparing of the other limb or inflammation of only the distal aspect of the pouch, and linear ulcers along suture lines.[18] There is a sharp demarcation between inflamed and noninflamed portions of the pouch. Management of this condition is not clear cut but may require pouch revision surgery.

Crohn's disease of the pouch

The diagnosis of Crohn's disease after patients undergo IPAA for an initial diagnosis of ulcerative colitis or indeterminate colitis has been increasingly recognized with a frequency of 3–19%.[21,22] It is not clear whether Crohn's disease developing in an ileal pouch represents Crohn's that was not recognized prior to surgery or whether it is a de novo process developing in an altered anatomic and microbial environment.[23] Making such a diagnosis can be challenging as there are no uniform diagnostic criteria and because surgically related fistulizing and stricturing complications can have similar presentations.[2] A diagnosis of Crohn's disease of the pouch