Anti–*Saccharomyces cerevisiae* Antibodies Are Associated With the Development of Postoperative Fistulas Following Ileal Pouch-Anal Anastomosis

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Although serologic testing for perinuclear antineutrophil cytoplasmic antibodies (pANCA) and anti–*Saccharomyces cerevisiae* antibodies (ASCA) is reportedly useful in distinguishing ulcerative colitis (UC) from Crohn's disease (CD), there are few and conflicting reports assessing their utility in predicting postoperative complications after ileal pouch-anal anastomosis (IPAA). We examined the associations between postoperative complications such as pouchitis or fistulas and pANCA and ASCA antibodies in a group of patients who underwent IPAA for UC. We conducted a retrospective chart review of 34 patients initially diagnosed with UC (four of these patients had a diagnosis of indeterminate colitis) who underwent IPAA by a single surgeon, and who had pANCA and ASCA antibody levels measured during their clinical course. Study patients were assigned to four groups based on the pattern of antibody reactivity: pANCA+/ASCA− (16 patients), pANCA−/ASCA+ (nine patients), pANCA+/ASCA+ (five patients), and pANCA−/ASCA− (four patients). The median length of follow-up was 16 months (3–144 months). None of the patients (0 of 16) who were pANCA+/ASCA− had their preoperative diagnosis of UC changed after a median follow-up of 14 months (3–118 months). Of the nine patients with a preoperative diagnosis of UC who were pANCA−/ASCA+, four patients (44%) had their diagnosis changed postoperatively to CD based on clinical findings, with a median follow-up: 15 months (5–98 months). Of 16 patients who underwent IPAA and who were pANCA+/ASCA−, 15 of 16 (93.75%), were free of fistulas postoperatively, with a median follow-up of 14 months (3–118 months). Of nine patients with a preoperative diagnosis of UC who underwent IPAA and who were pANCA−/ASCA+, four of nine (44%; $p = 0.04$) developed fistulas postoperatively, with a median length of follow-up of 55 months (15–67 months). No relationship between serologic profiles or antibody titer levels and the development of pouchitis was identified. In a cohort of patients undergoing IPAA for UC, serologic profiles may be useful in identifying patients at risk of postoperative fistula formation. Patients who were pANCA−/ASCA+ were at increased risk for the development of fistulas postoperatively compared to patients who were pANCA+/ASCA−, and were also more likely to have their diagnosis changed postoperatively to CD. A larger study is needed to validate these observations. (J GASTROINTEST SURG 2006;10:1060–1064)

KEY WORDS: pANCA, ASCA, ileal pouch-anal anastomosis, fistulas

The vast majority of patients with inflammatory bowel disease (IBD) can be classified as having either ulcerative colitis (UC) or Crohn's disease (CD). However, the diagnosis remains indeterminate in 10–15% of patients.[1,2] In some patients who require urgent colectomy, pathologic examination of the resected colon may not yield a definitive diagnosis of either UC or CD. For most patients without clinical, endoscopic, or radiologic evidence suggestive of CD and in whom the final pathology is indeterminate, it is a common surgical practice to perform an ileal pouch-anal anastomosis (IPAA).[3] Total proctocolectomy with IPAA has become the surgical treatment of choice for most patients with refractory ulcerative

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colitis.[2,4] Approximately 5–13% percent of IPAA procedures are performed in patients whose primary diagnosis is revised at some point after surgery from UC to CD.[2,5] These patients are thought to be at increased risk for postoperative complications, such as pouchitis, fistula formation, and pouch failure.[5–8]

The reported cumulative risk of developing pouchitis in all UC patients undergoing IPAA approaches 25–50% after 10 years.[2,6] The reported pouch failure rate (resulting in a permanent stoma) in patients with postoperative fistulous complications associated with the diagnosis of CD approximates 30%.[2,8]

Since clinical, endoscopic, radiologic, and histological evidence is sometimes still not enough to differentiate between UC and CD, attempts have been made to utilize specific serologic markers. In 1990, an IBD-specific anti-neutrophil cytoplasmic antibody with perinuclear highlighting (pANCA) was first described and has been associated with UC.[2] Antibodies to baker's and brewer's yeast, anti−*Saccharomyces cerevisiae* antibody (ASCA), have been described in patients with Crohn's disease.[2,9–15] The sensitivity and positive predictive value for combining the pANCA−ASCA assay to differentiate between UC and CD have been reported as approximately 60–70% and 94–96%, respectively.[9–15]

Some studies have suggested that the pANCA test might be useful in predicting pouchitis postoperatively in UC patients undergoing IPAA and that high titer levels of pANCA might be predictive of chronic pouchitis, although other studies have contradicted these findings.[16–19] To date, there have been no studies looking at the combination of the pANCA and ASCA serology with regard to their association with postoperative complications. Thus, the aim of this study was to examine the utility of pANCA and ASCA antibodies in a group of patients who underwent IPAA for UC to determine if there were associations with postoperative complications, such as pouchitis or fistulas.

MATERIAL AND METHODS

From the patient records of a single general surgeon at our institution (J.M.B.) with more than 20 years of experience in performing over 750 IPAA operations, 34 patients were identified for this study. All patients in the study had a preoperative diagnosis of UC (30 patients) or IC (four patients), underwent IPAA for refractory ulcerative colitis, and had serologic testing for pANCA and ASCA antibodies performed by Prometheus Laboratories (www.prometheus-labs.com). Thirteen patients had the serologic testing performed preoperatively and 21 patients had the testing postoperatively.

Study Subject Data Collection

In reviewing each patient's chart retrospectively, the following information was gathered: date of original diagnosis of UC; results of serologic testing; date of colectomy or date of bowel resection; date of IPAA; pathologic diagnosis; the incidence and frequency of pouchitis, and fistula formation; and, the final clinical diagnosis based on last follow-up visit. Information regarding the serologic results that was recorded included ASCA IgG, ASCA IgA, and pANCA antibody titer levels, the date of the test, and the Prometheus interpretation of the serologic pattern of reactivity.

Serum ANCA presence was determined by Prometheus Laboratories using a fixed ELISA assay. Levels were determined relative to a Prometheus laboratory standard consisting of pooled sera obtained from well-characterized pANCA+ UC patients. Sera with circulating antineutrophil cytoplasmic IgG antibody exceeding the normal reference range value were termed "ANCA positive" (ANCA+). Numeric values below the normal reference range were termed "ANCA negative" (ANCA−). ANCA+ sera were further subtyped via indirect immunofluorescence staining to determine the ANCA neutrophil binding pattern. Sera exhibiting the characteristic perinuclear highlighting which then lost this characteristic staining pattern when first treated with DNase were termed "pANCA+."[20]

Serum ASCA expression was performed by Prometheus Laboratories using a fixed ELISA assay. Results were expressed as ELISA units (EU/ml). Levels were determined and results expressed as ELISA units (EU/ml) relative to a Prometheus Laboratory standard that were derived from a pool of patient sera with well-characterized CD found to have reactivity to this antigen. Sera exhibiting ASCA reactivity (IgG and/or IgA) exceeding the normal reference range were termed "ASCA positive" (ASCA+).[21]

We used the diagnosis established at the time of the last postoperative office visit, which was based on symptoms, endoscopy, and histology, as our gold standard. This diagnosis was associated with the results of the serologic testing for each patient. This study was reviewed and approved by the Institutional Review Board at the Boston Medical Center.

Patient Population

Patients included in this study underwent IPAA from 1980 to 2002 and had serologic studies drawn