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ORIGINAL PAPER

Prevalence and Clinical Implications of Positive Serum Anti-Microsomal Antibodies in Symptomatic Patients with Ileal Pouches

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Abstract
Background and aim Autoimmune disorders (AID) have been shown to be associated with chronic antibiotic-refractory pouchitis (CARP). The role of anti-microsomal antibodies in ileal pouch disorders has not been investigated. The aims of the study were to investigate the prevalence of positive anti-microsomal antibody in symptomatic patients with ileal pouches and to investigate its clinical implications.
Methods A total of 118 consecutive symptomatic patients with ileal pouches were included between January and October 2010. Anti-microsomal antibodies were measured at the time of presentation. Demographic, clinical, and laboratory characteristics were compared between patients with positive and negative anti-microsomal antibody.
Results There were 14 patients (11.9%) with positive serum anti-microsomal antibody. The mean age of patients in the antibody positive and negative groups were 41.8±14.4 and 42.0±14.0 years, respectively (p=0.189). All 14 patients in the antibody positive group (100%) had some form of AID, as compared to 20 patients (19.2%) in the antibody negative group (p<0.001). Four (28.6%) patients in the antibody positive group had at least one AID in addition to Hashimoto's thyroiditis in contrast to four (3.8%) in the antibody negative group (p=0.003). In addition, five (35.7%) patients had associated primary sclerosing cholangitis (PSC) in the antibody positive group compared to nine (8.7%) in the antibody negative group (p=0.012). Eleven patients (78.6%) in the antibody positive group required steroids for treatment of pouch related symptoms in contrast to 26/104 (25%) patients in the antibody negative group (p=0.002).
Conclusions Anti-microsomal antibodies were common in pouch patients presenting with symptoms. Patients with positive anti-microsomal antibodies were much more likely to have concurrent AID and PSC. These patients were more likely to require therapy with steroids.

Keywords Autoimmune · Anti-microsomal · Pouchitis · Primary sclerosing cholangitis

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Abbreviations

AID	Autoimmune disorders
AIP	Autoimmune pancreatitis
CD	Crohn's disease
CARP	Chronic antibiotic refractory pouchitis
IBD	Inflammatory bowel disease
IPAA	Ileal pouch-anal anastomosis
NSAID	Non-steroidal anti-inflammatory drug
PSC	Primary sclerosing cholangitis
PDAI	Pouchitis Disease Activity Index
TSH	Thyroid stimulating hormone
UC	Ulcerative colitis

Introduction

Autoimmune disorders (AID) have been shown to be more common in patients with inflammatory bowel disease (IBD) than in those without IBD, suggesting that they may share common etiopathogenetic factors.[1] Some patients with chronic pouchitis do not respond to routine antibiotic therapy, which is termed chronic antibiotic-refractory pouchitis (CARP).[2] The predominant theory on etiopathogenesis of pouchitis is dysbiosis and its associated abnormal mucosal immune response,[3] as the majority of patients with pouchitis respond favorably to antibiotic therapy.[2] Other factors, including autoimmunity, may contribute to refractory pouchitis. Our previous study showed that the presence of AID was associated with a 2-fold increase in the risk for CARP.[2]

Previous epidemiologic studies and case reports/series have reported an association between thyroid disorders and IBD.[4–6] The association appears to be stronger with ulcerative colitis (UC) than with Crohn's disease (CD). Other investigations have found alterations in thyroid physiology and anatomy in the form of thyroid enlargement by ultrasound in patients with IBD who did not have clinical signs or symptoms of thyroid dysfunction.[7] Similarly, in a previous study, increased iodide uptake and increased daily fractional turnover of thyroxine in IBD patients was seen as compared with controls.[8] However, the role of thyroid disorders in patients with ileal pouch-anal anastomosis (IPAA) is not clear.

In our clinical practice, we found that antimicrosomal antibody was often present in patients with concurrent AID and IPAA and patients with pouchitis in this setting frequently did not respond to traditional antibiotic therapy. These observations lead us to embark on our current project with the hypothesis that anti-microsomal antibody-mediated autoimmunity may contribute to the disease process in some patients with pouchitis. The aims of this study were to investigate the prevalence of positive serum anti-microsomal antibodies in symptomatic patients with ileal pouches and to characterize clinical features of pouch disorders in these patients.

Patients and Methods

Patients

The study involved consecutive symptomatic patients presenting to the Pouchitis Clinic from January to October 2010. Patient's demographic and clinical data were retrieved from the IRB approved, prospectively maintained database. Patients were divided into two groups: those with positive anti-microsomal antibody and those with negative anti-microsomal antibody.

Inclusion and Exclusion Criteria

Inclusion criteria were patients with IPAA for underlying UC with symptoms of frequency, urgency and abdominal cramps. Exclusion criteria were IPAA patients with a preoperative diagnosis of familial adenomatous polyposis and patients with pouch dysfunction secondary to structural abnormalities, surgical causes, and cuffitis.

Clinical, Endoscopic, Laboratory, and Histologic Evaluation

Demographic, clinical, endoscopic, and histologic data were reviewed. As a part of our routine clinical practice, all symptomatic patients underwent an outpatient pouch endoscopy with biopsy. Examination under anesthesia, contrast pouchography, computed tomography enterography, or magnetic resonance imaging of the pelvis was performed when CD of the pouch was suspected. The modified Pouchitis Disease Activity Index (mPDAI) scores (range 0–12 points) were calculated to define pouchitis.[9,10]

Other laboratory tests which were abstracted from the database were thyroid stimulating hormone (TSH). Anti-microsomal antibody was measured by immunoenzymatic assay and antibody level greater than 9 IU/ml was indicative of a positive test.

Definitions of Variables

CARP was defined as pouchitis (mPDAI ≥5 points) that does not respond to a 4-week antibiotic course of a single antibiotic (metronidazole 20 mg kg^{-1} day^{-1} or ciprofloxacin 500 mg bid).[11] The diagnosis of CD of the pouch was defined by ulcerated lesions of the small bowel or afferent limb without diffuse pouchitis (excluding backwash pouchitis) that persisted after ≥4 weeks of antibiotic therapy or by ulcerated strictures in the distal small bowel or pouch inlet with concurrent ulcers or inflammation of the afferent limb.[12] Those criteria were applied after the exclusion of non-steroidal anti-inflammatory drug (NSAID) use at the time of diagnosis.

Demographic and clinical variables were defined as follows: "smoking": ever consumption of ≥7 cigarettes per week since the surgery; "family history of inflammatory bowel IBD": CD or UC in first-degree relatives; "duration of UC": the time interval between UC diagnosis and pouch construction; "duration of pouch": the time interval between completion of IPAA with ileostomy closure and entry into the study; "extensive colitis": endoscopic, macroscopic, or microscopic disease extending proximal to the splenic flexure; "indeterminate colitis": a histopathological diagnosis on proctocolectomy specimens that defied a clear distinction between CD and UC; "indication for proctocolectomy": the primary reason for the surgery based on clinical presentation

and preoperative diagnostic studies; "use of NSAID": regular use of NSAID more often than weekly at the entry into the current study; "primary sclerosing cholangitis (PSC)": the presence of intra- or extrahepatic bile duct abnormalities documented on endoscopic retrograde cholangiopancreatography and/or magnetic resonance cholangiopancreatography (the patients with PSC may or may not undergo orthotopic liver transplantation); "autoimmune mediated disorders": including adult-onset asthma, psoriasis, rheumatoid arthritis, autoimmune thyroid disease, autoimmune pancreatitis (AIP) and vitiligo.

Statistical Analysis

Descriptive statistics were computed for all factors in both the study and the control group. This included mean and percentiles for continuous factors and frequencies for categorical factors. Associations with categorical variables were done by Fisher's exact test. Associations with quantitative and ordinal variables were performed by Student's *t*-test or Wilcoxon's rank sum test as appropriate.

Results

Demographic and Clinical Characteristics

The basic demographic and clinical information including duration of the pouch, type of pouch, preoperative and postoperative use of biologics and immunomodulators,

Table 1 Comparison of patients with and without microsomal antibody

Factor	Anti-microsomal antibody positive group (n=10)	Anti-microsomal antibody negative group (n=114)	p Value
Mean age (years)	41.8±14.4	42.0±14.0	0.19
Mean duration of IBD before pouch (years)	9.4±6.2	9.1±8.2	0.858
Mean duration of pouch (years)	8.4±7.7	9.0±6.8	0.763
Male gender	7 (50.0%)	54 (51.9%)	0.881
Caucasian race	13 (92.9%)	104 (100%)	0.118
Tobacco consumption			
Active	3 (21.4%)	9 (8.65%)	0.153
Past	0 (0%)	3 (2.88%)	1.000
Family history of IBD	3 (21.4%)	20 (19.2%)	1.000
J Pouch	13 (92.9%)	100 (96.2%)	0.474
Stage of pouch surgery			0.754
1	1 (7.1%)	2 (1.9%)	
2	11 (78.6 %)	73 (70.2%)	
3	1 (7.1%)	24 (23.1%)	
4 or redo pouch	1 (7.1%)	5 (4.8%)	
Colectomy for refractory IBD	10 (71.1%)	91 (87.5%)	
Extensive colitis	13 (92.9%)	99 (95.2%)	0.78
Toxic megacolon	1 (7.1%)	14 (13.5%)	1.000
Pre-op diagnosis			
Ulcerative colitis	14 (100%)	95 (91.4%)	0.596
Indeterminate colitis or Crohn's colitis	0 (0%)	9 (8.7%)	
Post-operative immunomodulator use	0 (0%)	8 (7.7%)	0.593
Post-operative biologic use	0 (0%)	4 (3.8%)	1.000
Post-operative steroid use	11 (78.6%)	26 (25.0%)	0.002
Pouchitis responded to steroids	11 (100%)	17 (65.8%)	0.03
Extraintestinal manifestations	8 (57.1%)	47 (45.2%)	0.569
Primary sclerosing cholangitis	5 (35.7%)	9 (8.7%)	0.012
Presence of autoimmune disorders in addition to Hashimoto thyroiditis	4 (28.6%)	4 (3.8%)	0.003
Antibiotic responsive pouchitis	3 (21.4%)	59 (56.7%)	0.02
Chronic antibiotic refractory pouchitis	7 (50.0%)	26 (25.0%)	0.06
Crohn's disease of the pouch	4 (28.6%)	19 (18.3%)	0.579

presence of concomitant AID, comorbidities, and duration of IBD are summarized in Table 1.

There were 14 patients (11.9%) with positive anti-microsomal antibody. Among the 14 patients in the antibody positive group, six patients had a previous diagnosis of hypothyroidism and Hashimoto thyroiditis and were on thyroxine supplement therapy at the time of their initial Pouch Clinic visit. The other eight patients were diagnosed with positive anti-microsomal antibodies after presenting to the Pouch Clinic with symptoms of pouch dysfunction, and were newly diagnosed with Hashimoto thyroiditis. Among the eight patients, three patients were euthyroid on further testing with free thyroxine and TSH; and five patients were diagnosed with hypothyroidism secondary to Hashimoto's thyroiditis and were started on thyroxine after the visit. In all, there were 11 patients with hypothyroidism and three patients with euthyroid status in patients in the antibody positive group.

The mean age of patients in the antibody positive and antibody negative groups were 41.8+14.4 and 42.0+14.0 years, respectively (p=0.189). There was no difference in the extent of colitis or the indication for colectomy prior to IPAA surgery between the two groups. All 14 patients in the antibody positive group (100%) had some form of concurrent AID including Hashimoto's thyroiditis as compared to 20 patients (19.2%) in the antibody negative group (p<0.001). Furthermore, four (28.6%) patients in the antibody group had at least one more concurrent AID in addition to Hashimoto's thyroiditis in contrast to four (3.8%) in the antibody negative group (p=0.003). The AID seen in these four patients were vitiligo in one, rheumatoid arthritis in one, psoriasis in one, and autoimmune pancreatitis in one. Moreover, five (35.7%) patients had concurrent PSC in the antibody positive group compared to nine (8.7%) in the antibody negative group (p=0.012). Seven patients (50%) in the antibody positive group had CARP vs. 26 (25.0%) in the antibody negative group (p=0.06). Four patients (28.6%) in the antibody positive group and 19 patients (18.3%) in the antibody negative group had CD of the pouch (p=0.579).

Treatment

Oral administration of topically active corticosteroids (i.e. budesonide) has routinely been used in treating refractory pouchitis and/or autoimmune-associated pouchitis. Among the patients with positive anti-microsomal antibody, 11 (78.6%) required budesonide for control of pouch-related symptoms, while in the control group, 26 (22.8%) patients required budesonide (p=0.002). Of the patients who required budesonide, all 11 patients (100%) responded clinically to budesonide and required them for maintenance therapy as compared to 17/26 (65.4%) who responded clinically and required budesonide for maintenance therapy (p=0.03).

Discussion

In this study, we investigated the prevalence and clinical implications of seropositive anti-microsomal antibody in patients with pouch dysfunction. A variety of factors may contribute the initiation, development, and progression of pouchitis including genetic predisposition, dysbiosis, altered mucosal immunity, and colonic metaplasia due to fecal stasis.[5] Autoimmune factors may play a role in the pathogenesis of pouchitis, particularly in CARP and CD of the pouch.[2] Our study showed that approximately 12% of symptomatic patients at our Pouch Clinic had seropositive anti-microsomal antibody. There was clustering of AID and PSC in patients with seropositive anti-microsomal antibody. Patients with positive anti-microsomal antibody with symptoms of pouchitis were much more likely to respond to budesonide than controls. We did not find significant association between the presence of the antibody and CARP which might have resulted from type II error.

Microsomal antibodies are directed against components of thyroid microsomes, in particular peroxidase. Thyroid peroxidase in fact accounts for virtually all of the antigenic determinants reacting with the autoantibodies commonly termed as anti-microsome.[13] Anti-microsomal antibodies are present in Hashimoto's thyroiditis, Graves' disease, hypothyroidism, atrophic thyroiditis, and are sometimes increased in the elderly. In addition to the above mentioned etiologies, the prevalence of autoantibodies for thyroid antigens, like anti-microsomal antibody, is as high as 30% in patients with other AID, such as Sjogren's syndrome and systemic lupus erythematosus.[14,15] Although anti-microsomal antibodies are elevated in a number of AIDs, they are the most useful measurement for detecting autoimmune thyroid diseases (Hashimoto thyroiditis).[16] In this study, 11/14 patients with positive antibody were hypothyroid and were on medications. The remaining three patients were euthyroid at the time of the study. These three patients did not show any evidence of Sjogren's syndrome or systemic lupus erythematosus. These patients did not have any coexisting AID and had a normal TSH. Although euthyroid at present, these patients are at risk of developing hypothyroidism on follow-up.[17] Development of overt hypothyroidism occurs at a rate of 4–5% per year in adults with elevated TSH and antithyroid antibodies, and a rate of 2% per year in patients with antithyroid antibodies alone.[17] None of our patients with anti-microsomal antibodies were hyperthyroid. Nevertheless, hyperthyroidism can present with diarrhea and can confound the picture with pouchitis. Hence screening for thyroid dysfunction in patients with

IPAA presenting with increased frequency of bowel movements is required.

A recent population-based study from England has highlighted the coexistence of AID in patients with either Graves' disease or Hashimoto's thyroiditis.[18] The frequency of another AID was 9.7% in Graves' disease and 14.3% in Hashimoto's thyroiditis index cases ($p=0.005$). There were higher prevalences of Addison's disease (10-fold higher) and pernicious anemia (3-fold higher) in those with Hashimoto's thyroiditis, than the subjects with Graves' disease. Rheumatoid arthritis was the most common coexisting AID.[16] Relative risks of almost all other autoimmune diseases in Graves' disease or Hashimoto's thyroiditis were significantly increased (pernicious anemia, systemic lupus erythematosus, Addison's disease, celiac disease, and vitiligo). IBD was also more common in female patients with Graves' disease, but did not reach significance in patients with Hashimoto's thyroiditis. Similarly we found a clustering of AID in patients with positive anti-microsomal antibody which points to the autoimmune nature of their pouchitis. There was also a trend towards increased prevalence of CARP in anti-microsomal antibody positive group. Rheumatoid arthritis was seen in 1/14 patients with anti-microsomal antibody. Patients in the antibody positive group were treated with budesonide rather than antibiotics and the response rate was also higher highlighting the role of autoimmunity in the pathogenesis of pouch dysfunction.

A study from Sweden revealed thyroid diseases in 8.4% of the 119 patients with PSC.[19] Similarly, in a study from the Mayo Clinic, the prevalence of thyroid dysfunction in PSC was 11% at initial evaluation.[20] In the study group, three patients had PSC. It would be very hard to discern whether the positive anti-microsomal antibodies were related to PSC or CARP or was just an "innocent bystander." PSC was more common in patients with a positive anti-microsomal antibody highlighting the role of autoimmunity. The relationship of CARP, PSC and thyroid antibodies points to the common pivotal role of autoimmunity in the pathogenesis of these diseases. The overlap of immune response in IBD and autoimmune thyroid disease has been previously studied. One study found the immune response of both autoimmune thyroid disease and IBD to be polyclonal by examining immunoglobulin and T cell antigen receptor gene rearrangement.[21] Autoimmune thyroiditis and UC are speculated to be Th2-mediated disease processes because both are associated with the production of autoantibodies. Alterations in T-cell immunity with imbalance between proinflammatory and immunoregulatory cytokines have been described in pouchitis patients.[5] Thus the relationship between anti-microsomal antibodies and pouchitis warrants further investigation.

The findings of this study have several clinical implications. Patients with positive anti-microsomal antibodies may develop a distinct subtype of pouchitis. Whether patients with IPAA are prone to develop autoimmune thyroid disorders is not known. We had reported a case of de novo celiac disease after IPAA surgery.[22] De novo AID has been reported in patients with bowel-anatomy-altering surgeries, such as in Whipple's procedure.[23] In fact, eight of 14 patients had newly diagnosed autoimmune thyroid disease after the evaluation at our Pouchitis Clinic. We speculated that altered bowel anatomy in IPAA patients may predispose them to development of AID. On the other hand, concurrent AID[2] and PSC[24] may impact the disease course of pouchitis. By definition, patients with CARP were refractory to traditional antibiotic therapy. Thus some patients with CARP or even CD of the pouch with positive anti-microsomal antibodies might be considered to be treated with targeted therapies including steroids or biologics. Serum assay of anti-microsomal antibodies is routinely available in clinical labs. The finding of positive anti-microsomal antibodies may help direct a proper therapy for the patients with pouchitis as well as exploration for concurrent thyroid disease in patients with IPAA. There was also a trend for CARP in microsomal antibody positive patients; however, it did not reach statistical significance.

This study has several limitations. The study population was recruited from a subspecialty Pouch Clinic. This might have had referral or selection biases with patients being refractory to routine treatment and the data would be difficult to be extrapolated to the general pouch population. Our study cohort did not have a long-term follow-up to see the natural course of the disease. Statistical significance was not achieved in certain parameters including the presence of CARP. The small sample size of the study group precluded meaningful multivariable analysis. We are continuing to recruit patients to generate a larger sample size for future multivariable analyses.

In summary, approximately 12% of pouch patients presenting with symptoms of pouch dysfunction to our clinic had positive anti-microsomal antibody. Patients with positive anti-microsomal antibodies were much more likely to have concurrent AID and PSC. Further study to investigate the usefulness of testing patients with pouch dysfunction for anti-microsomal antibody is required.

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Specific author contributions Study concept, data monitoring and paper preparation—Udayakumar Navaneethan.
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