Review Article

Intestinal inflammation markers in inflammatory bowel disease

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ABSTRACT

During the past few decades, extensive researches were conducted to identify serological markers in patients with inflammatory bowel disease (IBD) that can reliably diagnose and monitor disease activity and help in predicting relapses. To date, several serological markers have been identified. This review will address the different serological markers and their clinical significance and applicability in medical practice. Serological markers include antibodies against microbial antigens, peptide antigens, autoantibodies, and basic inflammatory markers. Some serological markers such as anti-*Saccharomyces cerevisiae* antibodies (ASCA) and antibodies against exocrine pancreas (PAB) help the confirmation of the diagnosis of IBD to differentiate it from other non-IBD. Perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and ASCA can distinguish Chron's disease and ulcerative colitis. Certain markers can aid stratification of Chron's disease including antibodies to *Pseudomonas fluorescens* associated sequence I2 (Anti-I2), antibodies to bacterial flagellin (Anti-CBir1), ASCA, and antibodies to outer membrane porin C (Anti-OmpC). ASCA and pANCA can predict disease response to therapeutic agents (e.g. Infliximab). ASCA can also unaffected family members at risk of developing Chron's disease.

Keywords: Inflammatory bowel disease, Markers, Markers of inflammation

INTRODUCTION

Inflammatory bowel diseases (IBD) are a group of heterogenous disorders characterized by immune-mediated chronic inflammation of the gastrointestinal tract. Crohn's disease (CD) and ulcerative colitis (UC) represent the two major types of inflammatory bowel diseases, and they affect about two million individuals in the United States.[1] Ulcerative colitis (UC) characteristically affects the mucosa of the colon, whereas Chron's disease (CD) can affect any part of the intestinal mucosa from the oral cavity to the anal lining.

Although ulcerative colitis (UC) and Crohn's disease have different characteristic features, about 15% of patients cannot be definitely diagnosed as either type, and they are classified as 'intermediate colitis' or 'unclassified inflammatory bowel disease' (IBDU).[2] Inflammatory bowel diseases (IBD) occur due to immune-mediated destruction of intestinal epithelial integrity and lymphocytic differentiation. Genetic predisposition is proposed to be responsible for activation of the inflammatory process encountered in inflammatory bowel diseases.[3]

Patients with inflammatory bowel disease (IBD) often manifest with non-specific gastrointestinal symptoms such as abdominal pain and cramping, diarrhoea alternating with constipation, bleeding per rectum, passage of pus in stools, tenesmus, nausea, and vomiting. These are often associated with fever, malaise, weight loss, and sometimes extra-intestinal symptoms including uveitis, arthritis, or hepatic impairment. Inflammatory bowel disease (IBD) are associated with a higher mortality rate than the general population and a higher risk of malignancy especially colorectal cancer, small bowel adenocarcinoma, intestinal lymphoma, anal cancer, and cholangiocarcinoma.[4,5]

BIOMARKERS OF INFLAMMATION IN INFLAMMATORY BOWEL DISEASE

During the past few decades, researchers have extensively studied the pathophysiology of inflammatory bowel disease. The current body of evidence proposes that inflammatory bowel disease results from immune-mediated destruction of intestinal mucosa due to inappropriate activation of immune system by the commensal intestinal microbiota. This activation is thought to be genetically-predisposed. However, and exact pathophysiology of such activation remains elusive.[6] It is thought that the immune-mediated response encountered in patients with inflammatory bowel disease is an autoimmune reaction, suggested by the involvement of extra-intestinal organs such as the skin, the joints, and the eyes), and this immune response is triggered by normal commensal bacteria inhabiting the intestine such as *Escherichia coli*.[7]

Many serological markers have been studied during the last few years aiming at identifying an ideal specific marker that can reliably confirm the diagnosis, detect individuals at risk for the disease, objectively measure disease activity, and provide a prognostic tool for future relapses. However, to date, researchers could not prove a certain marker to be ideal. Many markers have been studied with each of them having advantages and disadvantages that will be addressed in this review.[8] The serological markers found in serum of patients with inflammatory bowel disease are of four types: antibiotics against microbial antigens, autoantibodies against self-antigens, peptide antibodies, and basic inflammatory markers. Antibodies against microbial antigens include anti-*Saccharomyces cerevisiae* antibodies (ASCA), antilaminaribioside carbohydrate antibodies (ALCA), antibody to outer membrane porin C (Anti-OmpC), antichitobioside carbohydrate antibodies (ACCA); anti-laminarin antibodies (Anti-L), anti-mannobioside carbohydrate antibodes (AMCA), anti-chitin antibodies (Anti-C), antibody to bacterial flagellin (Anti-Cbir1), and antibody to *Pseudomonas* fluorescens- associated sequence I2 (Anti-I2),[9] Autoantibodies include anti-neutrophil cytoplasmic antibodies (pANCA), antibodies against exocrine pancreas (PAB), and antibodies to goblet cells (GAB).[9] Peptide antibodies include Anti-cocktail

multiple antigenic peptide antibody and Anti-TCP antibody.[10] Basic inflammatory markers include C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and faecal Calprotectin.[8]

ANTIBODIES AGAINST MICROBIAL ANTIGENS

Anti-Saccharomyces cerevisiae antibodies (ASCA)

One of the prominent anti-glycan antibodies that targets the epitopes on the cell wall of bacteria and fungi. These antigens are thought to stimulate the immune system after the fungi colonize in the intestinal lumen leading to antibodies formation that attack self-antigens through molecular mimicry mechanisms. These antibodies can be detected via standardized enzyme linked immunosorbent (ELISA) and immunofluorescence (IIF).[11]

Antilaminaribioside carbohydrate antibody (ALCA)

Another newly discovered antibody that belongs to the antiglycan antibodies targeting cell wall epitopes of microbiota that was found in serum of 20%-40% of patients with Chron's disease and 10% of patients with ulcerative colitis.[12]

Antichitobioside carbohydrate antibody (ACCA)

Another novel antiglycan antibody that targets chitobioside carbohydrate on organisms' cell wall. Similar to ALCA, it is more prevalent among patients with Chron's disease than ulcerative colitis.[12]

Antibody to outer membrane porin C (Anti-OmpC)

Antibodies targeting the *Escherichia coli* outer-membrane protein, and detected in 55% of patients with Chron's disease and 10% of patients with ulcerative colitis.[10]

Antibody to bacterial flagellin (Anti-Cbir1)

Antibodies against flagellin proteins present on the surface of motile bacteria which is highly antigenic.[10]

Antibody to Pseudomonas fluorescens- associated sequence I2 (Anti-I2)

An antibody that targets *Pseudomonas fluorescens* component I2 that is detected in 55% of patients with Chron's disease and 10% of patients with ulcerative colitis.[9]

AUTOANTIBODIES

Anti-neutrophil cytoplasmic antibodies (pANCA)

Perinuclear ANCA antibodies that are found in patients with vasculitis such as Wagner's granulomatosis could be

isolated from 60%-70% of patients with ulcerative colitis and 10%-15% of patients with Chron's disease.[10]

Antibodies against exocrine pancreas (PAB)

Those are antibodies against trypsin-sensitive protein in pancreatic secretions that are detected in 20%-40% of patients with Chron's disease and 5% of patients with ulcerative colitis.[13]

Antibodies to goblet cells (GAB)

Antibodies against goblet cells of intestinal wall were also detected in patients with inflammatory bowel disease with figures of around 45% in ulcerative colitis and up to 30% in Chron's disease.[9]

PEPTIDE ANTIBODIES

Anti-cocktail multiple antigenic peptide antibody

New antibodies against four peptides (Cocktail multiple antigenic peptides, cocktail MAP) were recently detected in sera of about 44% of patients with Chron's disease not ulcerative colitis.[14]

Anti-TCP antibody

Antibodies against a novel peptide called TCP peptide could be detected by ELISA in 61.7% of patients with Chron's disease and 7.3% of patients with Ulcerative colitis.[15]

BASIC INFLAMMATORY MARKERS

C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and faecal Calprotectin were used during the past decades to monitor inflammatory disease activity and detect relapse. However, because they are non-specific and with the emergence of various novel antibodies, the use of these markers is not condemned.[8]

SIGNIFICANCE OF SEROLOGICAL MARKERS IN INFLAMMATORY BOWEL DISEASE

I- Diagnosis of inflammatory bowel disease (IBD versus Non-IBD)

Some serological markers, particularly ASCA and PAB for Chron's disease, have a high specificity to inflammatory bowel disease that ranges from 75 to 99%. However, they cannot be used solely for absolute confirmation of diagnosis or exclusion of inflammatory bowel disease. This is due to the presence of these markers in other diseases. For instance, ASCA and PAB were found in up to 60% and 23% of patients with celiac disease, respectively.[16,17]

II- Differentiation between Chron's disease and ulcerative colitis

To date, even with the multiple serological markers discovered in patients with inflammatory bowel disease, no single marker could be proven to confirm the diagnosis of the disease. However, using a combination of markers, particularly pANCA and ASCA can help in diagnosis of ulcerative colitis and Chron's, and in assessing the risk of intermediate colitis to develop a clearly defined phenotype of inflammatory bowel disease. Negative pANCA/positive ASCA-positive was found to have a 95% predictive value for Chron's disease, whilst positive pANCA/negative ASCA had a predictive value of 90% for ulcerative colitis.[18]

III- Stratification of IBD

Over time, Chron's disease can evolve and progress from an inflammatory non-stricturing and non-fistulizing phenotype to aggressive structuring or penetrating phenotypes. Such progression was found to be positively associated with certain serological markers. Chron's disease patients who progressed to more aggressive phenotypes were positive to anti-I2, anti-CBir1, anti-OmpC, or ASCA. Furthermore, those who were seropositive for more than one of these serological markers were more prone to develop aggressive disease phenotypes.[19,20]

IV- Treatment decision

Some researchers reported that certain medications used in treatment of inflammatory bowel disease were not effective in patients with certain serological markers. For instance, Chron's disease patients who have positive pANCA antibodies and negative ASCA antibodies do not respond to Infliximab.[21] Also, Chron's disease patients with positive anti-OmpC and positive anti-I2 were found to be good responders to antibiotics.[22]

V- Detecting population at risk for IBD

In family studies, the most proven serological marker that was found to have a potential prognostic value in first-degree family members who are at risk for developing inflammatory bowel disease. ASCA was found to be significantly higher among first-degree relatives of patients with Chron's disease than individuals from the general population, with figures of 20-25% and 0-10% among both groups, respectively.[23] Other markers were also reported to be positively correlated with an increased risk of developing Chron's disease among unaffected family members of known patients. These markers included ASCA, AMCA, ALCA, ACCA, anti-CBir1, anti-OmpC, and Anit-I2).[24]

CONCLUSION

Serological markers have been studies extensively during the past few decades to detect their clinical usefulness in patients with inflammatory bowel disease. Various serological markers have been identified, and they were classified into four groups: antibodies against microbial antigens, peptide antigens, autoantibodies, and basic inflammatory markers. Some serological markers such as anti-*Saccharomyces cerevisiae* antibodies (ASCA) and antibodies against exocrine pancreas (PAB) help the confirmation of the diagnosis of IBD to differentiate it from other non-IBD. Perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and ASCA can distinguish Chron's disease and ulcerative colitis. Certain markers can aid stratification of Chron's disease including antibodies to *Pseudomonas fluorescens* associated sequence I2 (Anti-I2), antibodies to bacterial flagellin (Anti-CBir1), ASCA, and antibodies to outer membrane porin C (Anti-OmpC). ASCA and pANCA can predict disease response to therapeutic agents (e.g. Infliximab). ASCA can also unaffected family members at risk of developing Chron's disease.

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