



Original Article

Ulcerative Colitis: Beyond the Basics and Customary

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Abstract

Background: *Involvement of the upper gastrointestinal tract by inflammatory bowel disease was thought to be a feature of Crohn's disease, whereas ulcerative colitis was considered to be limited to the colon.*

Methods: *We studied 7 cases of inflammatory bowel disease over a period of 15 months in Bhagalpur district of Bihar, India, which involved the upper GI tract. Patients presenting with typical symptoms were investigated further. They underwent a an array of tests based on guidelines for confirmatory diagnosis.*

Results: *Those patients who had colonoscopic findings suggestive of ulcerative colitis and the diagnosis of which was reiterated by other confirmatory tests were subjected to upper GI endoscopy. The cases were positive for fecal calprotectin level and were also pANCA positive. The endoscopic and histopathological exam agreed to the diagnosis of ulcerative colitis in the upper gastrointestinal tract.*

Conclusion: *Patients with involvement of upper GI, against the popular belief should have ulcerative colitis in its differential diagnosis.*

Keywords: *Ulcerative colitis, Endoscopy, Upper Gastrointestinal tract, fecal calprotectin.*

Introduction

Involvement of the upper gastrointestinal tract by inflammatory bowel disease was thought to be a feature of Crohn's disease, whereas ulcerative colitis was considered to be limited to the colon. We studied 7 cases of inflammatory bowel disease over a period of 15 months in Bhagalpur district of Bihar, India, which involved the upper GI tract.

Method

Patients presenting with rectal bleeding, tenesmus, crampy abdominal pain were

investigated further. They underwent a complete blood count exam, CRP, serum electrolyte levels, tests to ascertain the liver and kidney functions. Fecal microbiological examination, to rule out any infective pathology. Fecal calprotectin level was sought to confirm the inflammatory state of gastrointestinal tract. Upper GI endoscopic examination and colonoscopy along with guided biopsies followed by its histopathological examination was also performed. A sample for serological markers pANCA and ASCA were also sent.

Results

Those patients who had colonoscopic findings suggestive of ulcerative colitis and the diagnosis of which was reiterated by other confirmatory tests were subjected to upper GI endoscopy. The cases were positive for fecal calprotectin level and were also pANCA positive. We found following features, the edematous mucosa, erythema, loss of vascular markings, and mucosal friability. More severe cases were associated with erosions, ulcers, and spontaneous bleeding. Mucosal atrophy were seen at places. Histopathology of the specimen from upper GI showed diffused plasmacytosis. These findings were very well suggestive of ulcerative colitis in upper gastrointestinal tract and negated the fact that UC is confined only to the lower GI tract. Patients with involvement of upper GI, against the popular belief should have ulcerative colitis in its differential diagnosis.

Discussion

Ulcerative colitis appears with complex interplay between genetics and environmental factors, which results in continuous chronic mucosal inflammation of the rectum and the colon proximally. India is projected to have one of the highest disease setbacks of IBD across the globe. The holistic genetic risk and microbial signature in Indian IBD patients are similar to those of patients in the West as established by the similar incidence of IBD in second-generation Indian immigrants and corresponding perturbations in the structural and functional component of gut microbiota in Indian studies.

Site of Affection

Extent and site of inflammation holds the key for the choice of management, drug delivery to be chosen and probability of having dysplasia and colorectal carcinoma which in turn influences the schedule for surveillance. For instance, topical therapy by the means of

suppositories or enemas is of choice for proctitis and left-sided colitis, respectively, on the other hand oral therapy [often combined with topical therapy] is apt for extensive colitis. The patients with extensive colitis have highest risk of developing colorectal carcinoma¹.

Pattern of Disease²

It is always advocated to ascertain the existence of active colitis by flexible sigmoidoscopy and biopsy before starting therapy, this excludes the unexpected mimics such as cytomegalovirus [CMV] colitis, rectal mucosal prolapse, Crohn's disease, malignancy, or even irritable bowel syndrome and haemorrhoids. Further, patients with suspected active disease warrant stool cultures that includes *Clostridium difficile* toxin assay to exclude enteric infection. The microscopic infection is also very important. In covert UC, chronic inflammatory cell infiltrates are present in biopsy specimens and crypt architectural irregularities could be seen. More than half of the patients with acute inflammatory cell infiltrate relapse within a year.

Warning Bells of Severity

Clinically the number of stools per day, presence or absence of blood in stool, pulse rate, temperature, hemoglobin concentration and ESR have been used to earmark the severity of the disease activity in ulcerative colitis (Montreal classification of disease activity in UC). Not consistent with the popular belief acute phase C-reactive protein [CRP] is not as useful in UC as it is in Crohn's disease for the estimation of disease progression, on the other hand none amongst elevated ESR, elevated serum procalcitonin, and low albumin levels have been demonstrated to be superior to CRP. The most researched stool markers are faecal calprotectin and lactoferrin. These are of value for both

diagnosing and defining the severity of disease because these have a good parallelism with endoscopic indices, relapse, and response to treatment. Calprotectin has therefore gained name as a marker of relapse of IBD. It must be however be reiterated that, none of aforementioned markers are specific for UC, since they mostly represent active colonic inflammation.

Remission

It has been loosely defined as having a stool frequency less than 3 times per day which is not admixed with blood and there is no endoscopic evidence of mucosal involvement.

The Earlier the Worst

The patient who acquire the disease early in life have a more aggressive course requiring more robust immunomodulator therapy and even surgery. All the available therapies for UC have shown an comparable efficacy in children when compared with adults. The visible higher risk of dysplasia and colorectal carcinoma in patients with early onset UC almost certainly vocalizes the duration of disease, this risk is further escalated by the presence of primary sclerosing colangitis.

UC which is equally prevalent in both the sexes, appears basically in late adolescence and early adulthood. The inflammation characteristically kicks start in the rectum and extends proximally in a continuous, confluent, and concentric manner to affect a variable extent of the colon, or its entire mucosal surface. The proximal exploitation of inflammation may aggravate or regress over time, but after disease regression the extent of inflammation tends to correlate with the degree of previous episodes in the event of relapse.

Remarkably, the notion that UC represents continuous colonic inflammation has, been challenged by reports of a rectal sparing variant and peri-appendiceal patchy

inflammation. As a matter of fact patients with UC have been found to be involving the upper GI which was thought to be seen only in chrons disease. A vast majority of patients with UC bleed per rectum. The occurrence of other associated symptoms generally reflect the intensity of mucosal disease, and may fluctuate according to disease extent. Persistent loose stool for more than 6 weeks inclines the diagnosis towards UC instead of any infective cause. Affected individuals may also have rectal urgency, tenesmus, mucopurulent exudate, nocturnal defaecation, and crampy abdominal pain. On the other hand, patients with proctitis usually present with rectal bleeding, urgency, tenesmus, and sometimes severe constipation. A perianal fistula in most occasions are due to chrons disease, but its presence doesn't always exclude a diagnosis of ulcerative colitis. The onset of UC is usually gradual and progressive ; symptoms are frequently present for weeks or even months before medical guidance is sought after. About 1/6th of the patients presents with very severe symptoms systemic symptoms including weight loss, fever, tachycardia, nausea, and vomiting.

Risk Factors for Ulcerative Colitis

1st degree relatives of the patients with UC have a increased chance of acquiring the disease (incidence rate ratio [IRR]: 4.08; 95% CI: 3.81–4.38) Tobacco surprisingly protects against and reduces the severity of UC, but as a matter of fact the overall natural course of the disease remains the same. On the other hand those who have quit, have 70% higher risk of developing the disease, which is often more extensive and resistant to the treatment. If the patient has ever suffered from appendicitis and mesenteric lymphadenitis during childhood or adolescence it makes them less vulnerable to UC. Non-selective non-steroidal anti-inflammatory drugs [NSAIDs] supposedly exacerbate the disease.

Investigations and Procedures to Diagnose the Disease³

CBC (may reveal thrombocytosis, anemia and leucocytosis), CRP (which may correlate well with the severity), Serum Electrolytes, Liver function tests and fecal microbiological investigations (to exclude common pathogens, specially *C. difficile*) are to be done at presentation. Faecal calprotectin is an precise marker of colonic inflammation. Supplementary tests may be tailored according to the medical history, for illustration the examination of fresh, warm stool samples for amoebae or other parasites. Endoscopic examination [flexible sigmoidoscopy or colonoscopy] along with histological analysis are required at diagnosis and may be required to confirm disease relapse. A plain abdominal radiograph should be performed to exclude colonic dilatation [≥ 5.5 cm] and to approximate the level of disease and look for features that predict response to treatment. The proximal extent of disease broadly correlates with the distal distribution of faecal residue. The occurrence of mucosal islands [representing residual mucosa isolated by surrounding ulceration] or more than two gas-filled loops of small bowel is associated with a poor response to treatment. Endoscopic criteria for severe colitis include haemorrhagic mucosa with deep ulceration, mucosal detachment on the edge of these ulcerations, and well-like ulceration, all of which can be assessed by flexible sigmoidoscopy.

Microbial Investigations

Healthcare setup associated *C. difficile* infection is a compounding health issue that has been associated with higher mortality. Reactivation of CMV can occur in UC⁷, specially in immunosuppressed patients with severe colitis it can be the culprit behind severe refractoriness and relapse. It should be excluded in patients who relapse while receiving immunosuppressant therapy⁵.

Biomarkers

The most widely calculated serological markers are perinuclear antineutrophil cytoplasmic antibodies [pANCA] and anti-*Saccharomyces cerevisiae* antibodies [ASCA]. Usually, pANCA are detected in up to 65% of patients with UC and in less than 10% of patients with Crohn's. Given the current limited sensitivity of these markers, their routine use for the diagnosis of UC and for therapeutic decisions is not clinically warranted.

Several neutrophil-derived proteins such as calprotectin, elastase, lysozyme, and lactoferrin have been evaluated as markers of intestinal inflammation in IBD. Amongst these, faecal calprotectin appears to be the most sensitive. As with all faecal tests, calprotectin lacks the specificity to categorize between different types of inflammation; nevertheless, it represents a useful non-invasive marker in the follow-up of UC patients.

Endoscopic Features

Endoscopic changes typically initiate at the anal verge and extend proximally in a continuous, confluent, and concentric fashion. The delineation between inflamed and normal areas is usually clear and may occur abruptly within millimetres. Granularity, vascular pattern, ulceration, and bleeding and/or friability have been reported to envisage the global appraisal of endoscopic severity. The Ulcerative Colitis Endoscopic Index of Severity [UCEIS] evaluates the vascular pattern and the presence of bleeding and ulceration, each with 3 or 4 levels of severity. The endoscopic features of mild inflammation are erythema, vascular congestion, and at least partial loss of the visible vascular pattern. Moderately active colitis is characterized by a complete loss of vascular pattern, blood adherent to the surface of the mucosa, and erosions, often with a coarse granular appearance and mucosal friability [bleeding to

light touch In contrast to Crohn's disease, ulcers in severe UC are always entrenched in inflamed mucosa. The presence of deep ulceration is a poor prognostic sign.

Colonic Stricture

In long-standing UC, a colonic stricture signals an increased risk for CRC and requires vigilant histological assessment. To diagnose UC with certainty at least 2 biopsies from 5 different locations that must include the rectum and ileum is warranted.

Features in Microscopy⁶

Not all the microscopic features found in UC are observed in early stage disease; only about 20% of patients show crypt distortion within 2 weeks of the first symptoms of colitis. The dissimilarity from infectious colitis [acute self-limiting colitis], which is characterized by preserved crypt architecture and acute inflammation, is thus a matter of prime concern. Focal or diffuse basal plasmacytosis has been documented as the most primitive feature with the highest predictive value for UC diagnosis. Initially distribution pattern of basal plasmacytosis is focal, but may eventually change into a diffuse pattern throughout the disease course. Widespread mucosal or crypt architectural distortion, mucosal atrophy, and an irregular or villous mucosal surface appear later during the evolution of disease [at least 4 weeks after presentation]. A decreasing gradient of inflammation from distal to proximal favors a diagnosis of ulcerative colitis. Treatment may change the classical distribution pattern of inflammation. Awareness of these treatment-related effects is important in the evaluation of biopsies from treated patients to avoid misdiagnosis.

Conclusion

Contrary to the popular belief that UC is confined to the reign of lower GI tract, we found the upper GI infiltration in cases we studied. This study is of conviction that upper gastrointestinal system should not be ignored in UC to avoid unwarranted sequels.

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