Inflammatory Bowel Disease

Chapter 5

Dilemmas and Pitfalls in Diagnostic Evaluation of Inflammatory Bowel Disease: A Review on the Available Armamentarium for Diagnosis

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1. Introduction

Inflammatory Bowel Disease (IBD) can be broadly divided into Ulcerative Colitis (UC) and Crohn's Disease (CD), with 10-15% patients showing overlapping features of both, termed as Indeterminate Colitis (IC). In practice, however, the diagnosis is never straightforward, and a plethora of conditions of varying severity, including both benign and malignant diseases, have remarkably similar presentation and features as any of the IBD spectrum.

In the present chapter, we highlight the common mimics of IBD that make the diagnosis and management of this entity difficult. The differences are highlighted across clinical presentation and laboratory parameters, imaging features, endoscopic findings, and pathological findings.

2. Common Differentials

The most common conditions mimicking IBD are listed in **(Table 1)**. While some of them can usually be differentiated from IBD based on clinical features, that is not always the case, and as a result, patients require all the above mentioned investigations to arrive at a

diagnosis [1].

Table 1: Conditions mimicking IBD

Conditions mimicking IBD
Infective colitides
Pseudomembranous colitis
Ischemic enteritis and colitis
Radiation enteritis and colitis
Irritable bowel syndrome
Colorectal cancer
Intestinal tuberculosis
Chronic nonspecific ulcers of small intestine {CNSU}
Cryptogenic multifocal ulcerous stenosing enteritis {CMUSE}
Eosinophilic gastroenteritis
Intestinal Behcet disease

3. Clinical Presentation

Since the origin of medicine, clinical findings have been given the utmost importance for diagnosing a disease. The same key applies to differential diagnosis of IBD. A multitude of clinical hints are available to a good clinician to rule out differentials. Clinico-epidemiological profile of the patients, demographics, dietary habits and general medical condition of the patient all provide hints to diagnosis and are discussed next.

UC is more common in whites and in jewish population. Nonsmokers are at risk and so are patients with positive family history. It commonly presents with bleeding per rectum (90%-95%) [2], mucus per rectum, diarrhea, abdominal pain (65%) and tenesmus. The presentation varies with the severity and extent of disease, ranging from long duration of loose stools with mucus and weight loss to toxic megacolon with severe sepsis in acute severe disease [2]. Abdominal or pelvic pain of unkown origin is also one of the rare presentations of UC. Many times, infective etiology may prompt investigations and diagnosis of asymptomatic UC and in these scenarios, it is important to suspect this co-existence of disease to avoid missing the diagnosis.

CD, on the other hand, has abdominal pain as the dominant symptom (80-85%), and weight loss (60%) and chronic diarrhea with mucus and blood (40-50%) are encountered less frequently [3]. More importantly, CD presents with small bowel predominant disease and hence mucus per rectum and tenesmus are less common than UC. Also, CD can present with perianal predominant disease as atypical or recurrent/refractory perianal abscess, complex fistulas or fissures/ulcers. CD can also affect upper gastrointestinal tract and presents with dyspepsia, nausea, vomiting or severe epigastric pain. Up to 25% patients of IBD can present with extra-intestinal manifestations such as oral ulcers, arthralgia, skin rashes or ocular symptoms before diagnosis of IBD [4-6].

In India and in other lower socioeconomic areas, intestinal tuberculosis {TB} is the most common differential diagnosis of CD and less commonly UC. The disease most commonly affects the age group 20-50 years of age and the presentation can be with an ileocecal mass, appendicitis, small bowel obstruction or nonspecific abdominal pain, colic, nausea, vomiting, anorexia, loss of weight and fever with an evening rise, high grade with chills and rigors [7]. These patients often have concomitant pulmonary/extrapulmonary TB or a past history of treated or incompletely treated TB or a positive case in their family or close community. These rarely present with colorectal involvement and hence, rarely confused with UC [8].

History of recent travel to endemic areas for infections such as *Entameba histolytica*, consumption of contaminated food/water, history of contact and presence of more affected members in family or close community provide a hint towards infective colitis. These patients present with abdominal pain, diarrhea, fever, generalized fatigue and malaise and may or may not have blood in stools [9]. Hemorrhagic colitis is a fatal form of Enterohemorrhagic Escherichia coli {EHEC} infection and is an important differential for acute severe toxic colitis due to ulcerative colitis as well as ischemic colitis. Immunocompromised patients (human immunodeficiency virus infection or prolonged steroid intake or chemotherapy/malignancy patients or patients post-transplant on immunosuppression) are at risk for infective colitis, most commonly due to cytomegalovirus and some opportunistic parasites such as isospora and cyclospora [11].

Patients with prolonged hypotensive states, patients with history of peripheral arterial insufficiency/cerebrovascular or coronary insufficiency, obesity, diabetes and hypertension with risk factors for thromboembolic arteriopathy, patients with hypercoaguable states, pregnancy, patients on long term steroids or oral contraceptives are all at risk for arteriovenous thromboembolic or vasospastic events which can lead to ischemic enteritis {Embolic>Non-occlusive vasospastic > thrombotic > venous thrombotic} or ischemic colitis {Vasospastic > thromboembolic} [11]. These patients presenting with symptoms such as postprandial pain and fullness, who are afraid to eat owing to this pain, have weight loss and malabsorption in chronic ischemia which can progress to intestinal obstruction due to stricture formation. On the other hand, acute ischemic event can present with persistent and severe abdominal pain, abdominal distension and gastrointestinal bleeding which can be confused with acute severe colitis.

Behcet's disease [12] is a chronic, relapsing and remitting systemic vasculitis which can be neurologic/ocular/intestinal or vascular types or may be a combination of all these. It can present in a wide variety of symptoms owing to this multisystem involvement. Neurological symptoms such as stroke/papillitis/papilledema, ocular symptoms such as scleritis/episcleritis/anterior or posterior uveitis/retinitis, vascular manifestations such as endocarditis/myocarditis/pulmonary arteritis/arthritis and triad of recurrent oro-oculo-genital aphthoid ulcers can be

the presenting features in these patients that help in differentiating intestinal Behcet's disease from CD as the abdominal symptoms are otherwise identical to CD. The most common site involved here is ileocecal valve and most common differential is CD amongst other causes of ileocecal ulcers.

CNSU [13] and CMUSE [14] are relatively newer disease entities that affect the proximal ileum more than terminal ileum and are differential diagnosis for CD. CNSU affects young females who most commonly present with long standing symptoms of hypochromic, microcytic anemia and/or growth retardation. They rarely have any other symptoms such as diarrhea, hematochezia or fever. On the other hand, CMUSE is more common in males and presents with diarrhea, weight loss and edema. It also has a chronic, relapsing course and can present with recurrent intestinal obstruction due to unexplained small intestinal strictures. There are no signs of infection or inflammation in these patients.

Drug history is also very important as in patients with symptoms of enterocolitis, a history of antibiotics/chemotherapy drugs suggest a possibility of pseudomembranous colitis. On other hand, history of allergic diseases, especially food allergy with similar presentation points to a differential diagnosis of eosinophilic gastroenteritis. In eosinophilic enteritis, periumbilical pain, nausea, vomiting and diarrhea occur with mucosal involvement, obstruction occurs when the muscularis is involved, whereas subserosal and serosal involvement can lead to ascites or pleural effusion {Klein classification for the extent of involvement} [15].

Two other important differentials for ulcerative colitis are solitary rectal ulcer syndrome (SRUS) and endometriotic involvement of rectosigmoid junction. SRUS is a misnomer and these patients have history of functional constipation with pelvic floor dyssynergy that results in single or multiple anterior rectal ulcers with/out inflammation and occasional rectal polyps. The disease is limited to the last 10-12 cm of rectum. Endometriosis of rectosigmoid junction is a rare condition presenting with recurrent pelvic pain or intestinal obstruction. The condition is peculiar because the endometriotic deposits here are not under hormonal influence and hence, the symptoms are not cyclical.

Irritable Bowel Syndrome (IBS) is a functional bowel disorder (FBD) characterized by chronic recurrent abdominal pain associated with defecation, accompanied by abdominal distension or bloating and changes in bowel habits (constipation, diarrhea, or a combination of both). The diagnostic criteria are: Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of 1) Relation to defecation, 2) Associated with a change in frequency of stool or 3) Associated with a change in form (appearance) of stool. The criteria should be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis [17].

The diagnosis of IBS should be made based on the following 4 key features: clinical

history; physical examination; minimal laboratory tests; and, when clinically indicated, a colonoscopy or other appropriate tests. Abdominal pain, usually in the lower abdomen, is an essential feature. Abnormal stool frequency (>3 bowel movements/day and <3 bowel movements/week), abnormal stool form, excessive straining during defecation, urgency, incomplete evacuation,and mucus with bowel movements, although common in IBS, are not specific. IBS can further be subdivided into subtypes as: IBS with predominant constipation (IBS-C): >25% constipation, <25% diarrhoea, IBS with predominant diarrhoea (IBS-D): <25% constipation, >25% diarrhoea, IBS with mixed bowel habits (IBS-M): >25% constipation, >25% diarrhoea and IBS unclassified (IBS-U): Patients who meet diagnostic criteria for IBS but whose bowel habits cannot be accurately categorized into 1 of the 3 groups above [16].

Female gender, age <50 years, exacerbation by meals, presence of GI (dyspepsia) and non-GI (headache, cystitis, psychosocial stress, insomnia, dyspareunia) symptoms, and absence of alarming features (bleeding PR without haemorrhoids/fissure, weight loss, anaemia, family history of colorectal cancer) strongly support a diagnosis of IBS [17-19]. A thorough physical examination, including anorectal examination, is mandatory to exclude organic causes of symptoms.

4. Laboratory Investigations

In differential diagnosis of the above mentioned diseases, laboratory investigations play a small yet important role. Blood investigations lack specificity and accuracy for diagnosis of UC and CD. Fecal biomarkers have been identified that are fairly sensitive and specific for these conditions. The most well studied and most significant ones of these are fecal calprotectin and fecal lactoferrin [1]. A cut off of fecal calprotectin more than 50 µgm/g stool is fairly accurate in appropriate clinical setting for diagnosis of UC. IBD serology is not mandatory for diagnosis due to low sensitivity and specificity. When performed, anti-saccharomyces cerevisiae antibodies {ASCA} are positive in CD (sensitivity 57%, specificity 98.1%) whereas p-Anti-nuclear cytoplasmic antibodies {pANCA} are positive in UC (sensitivity 63%, specificity 92.5%) [20].

A diagnosis of TB can be supported by a lot of investigations such as tuberculin skin test {Mantoux test}, lymphocytosis, raised erythrocyte sedimentation rate, hypoalbuminemia and interferon gamma release assay {IGRA} [21]. Stool cultures for acid-fast bacilli and stool TB Polymerase chain reaction {PCR} have extremely low sensitivity. IGRA and Mantoux test cannot differentiate between latent infection and active TB and hence, are of uncertain clinical significance. In appropriate clinical setting, endoscopic mucosal biopsy evaluation by histopathology as well as TB PCR may help in diagnosis [22].

Investigations to establish a diagnosis of IBS include a complete blood count (CBC) to exclude anaemia or elevated leucocyte count, and C-reactive protein and faecal calprotectin

which are highly sensitive for IBD. Inflammatory markers, including faecal calprotectin, may not be useful in patients with constipation symptoms. Thyroid function tests, serologic tests for celiac disease, and stool analysis, should be individualized [17].

Stool culture, stool routine and microscopy are important to rule out infective colitis which may be individually responsible for the symptoms or may co-exist with IBD. Stool assay for toxin A/B are to be performed in cases with suspicion of Clostridium difficile colitis [23]. Blood culture, serology for anti-salmonella antibodies are helpful for enteric fever. Long standing anemia and multiple positive fecal occult blood tests in a young female patient points towards CNSU. Peripheral eosinophilia is present in patients with eosinophilic gastroenteritis. Elevated lactate, metabolic acidosis, and leucocytosis point towards bowel ischemia and gangrene. These patients need to be worked up for thrombophilic states such as factor V leiden mutation, prothrombin gene mutation, antiphospholipid antibody syndrome, etc.

5. Endoscopy Findings and Role in Differential Diagnosis

After a proper clinical history, physical examination and appropriate laboratory investigations, the most important part of investigation is endoscopy ± biopsy and imaging. The sequence of these investigations depend on the clinical situation, however, most patients undergo a non-invasive investigation first followed by endoscopy.

5.1. Aims of Endoscopic Assessment

- Diagnosis of inflammatory bowel disease

- Distinguish between ulcerative colitis and crohn's disease

- Monitor the grade the extent and severity of disease

- Assess the response to treatment

- Assess the exacerbations and document remissions following treatment

- Identify complications and surveillance for malignancy

- Therapeutic role of endoscopy

5.2. Endoscopic methods of assessment

- Colonoscopy with mandatory ileal intubation

- Flexible Sigmoidoscopy

- Esophagogastroduodenoscopy {OGDscopy}

- Capsule Endoscopy

- Balloon enteroscopy – single/double balloon for small bowel evaluation

- Spiral enteroscopy for small bowel evaluation

- Endoscopic Ultrasonography

Here, we will keep our discussion to diagnostic features of IBD and the differential diagnosis. Ulcerative colitis has continuous, circumferential mucosal and submucosal inflammation that extends from rectum proximally. The endoscopic findings are hyperemic and erythematous colorectal mucosa with a sharp demarcation at the proximal limit between the normal and the involved mucosa [24]. Uneven, irregular fine or rough granular mucosa is seen which bleeds on touch. Also, the normal mucosal vascular pattern is lost due to mucosal and submucosal edema. Ulcers in UC are superficial and are surrounded by inflamed mucosa. Stricture in UC and polyps should be evaluated to rule out adenomas.

In atypical cases, up to 40% patients with UC can have skip lesions whereas around 10% cases can have rectal sparing. Some patients may have colorectal disease with isolated appendiceal orifice inflammation. Patients can have backwash ileitis characterized by mild inflammation in terminal ileum due to incompetent ileocecal valve. However, the inflammation is not as severe as in CD. These cases are difficult to characterize as either CD or UC based only on endoscopic findings.

CD is characterized endoscopically by skip lesions, longitudinal, serpigenous ulcers with transmural inflammation most commonly in terminal ileum. The ulcers are usually located at the site of mesenteric attachments to bowel. Aphthous ulcers are also seen in CD. Coalescing ulcers result in a cobblestone appearance. In CD, ileal involvement is patchy, deep and more than cecal inflammation with discrete ulcers and chronic disease can result in strictures [3, 25]. OGDscopy is important in CD and can show solitary or multiple longitudinal ulcers/ erosions of esophagus and/or aphthous ulcers in gastric antrum, gastric body and/or part 2 of duodenum.

Differential diagnosis for ulcers in terminal ileum can be done with help of some of the endoscopic features specific to each disease. Intestinal tuberculosis most commonly affects the ileocecal junction and presents with small and shallow to large and deep but transversely oriented ulcers in terminal ileum. The ulcers more commonly has circumferential >serpigenous arrangement. Scars, strictures or pseudpolyps can be seen in TB too. Patulous ileocecal valve is more common in TB than CD. However, apart from the finding of transverse orientation of ulcer, none of the other endoscopic finding is characteristic of TB [26,27].

CNSU and CMUSE also have endoscopic findings of ileal ulcers. CNSU presents with

sharply demarcated flat proximal ileal ulcers in circumferential or oblique alignment which when heal, produce spiral stenosis that looks in endoscopy like a coiled spring. CMUSE has multifocal, superficial ulcers in small bowel, most commonly in terminal ileum [13,14]. These ulcers never progress to cobblestoning, adhesions, fistula or fissure formation and remain confined to mucosa and submucosa. Gastroduodenal and/or colonic superficial ulcers are also common in CNSU.

Intestinal Behcet's disease is characterized by presence of aphthous ulcer which is a single and usually less than 5 round or oval, white ulcer with red peripheral rim of 2-15 mm size and usually is deep ulcer in ileocecal area. The erythematous rim is nodular and elevated with normal surrounding mucosa and base covered in exudates. This description of ulcer is known as volcano-type ulcer [28]. The ulcer usually heals without scarring. The characteristic ulcer pattern, absence of anorectal and distal colonic lesions and well defined discrete border of the ulcer help identifying Behcet's disease over CD.

Pseudomembranous colitis is characterized endoscopically by well defined, yellowish white plaques ranging from 1 mm – 2 cm in diameter which cover the distal colon and rectum most commonly. Occasionally, the disease can extend into proximal colon. Bowel preparation can remove the pseudomembranes, and hence, if this disease is suspected, the colonoscopy is recommended without bowel preparation [23].

Infective colitis has non-specific endoscopy findings such as mucosal erosions, edema, punctate hemorrhages and mucoid exudates. Enteric fever shows longitudinal ulcers in terminal ileum. Typhoid affects the right colon very rarely and in those cases can be confused with CD. Similarly, Yersinia colitis and amebic colitis affect the right colon in 70% cases with pathognomonic flask shaped ulcers, whereas it affects rectosigmoid in 30% cases. Yersinia has a characteristic octopus sucker shaped ulcer with mucosal elevation in ileocecal area [29]. Yersinia can also present with mesenteric lymphadenopathy.

On the other hand, campylobacter colitis and shigella colitis affects rectosigmoid area and can be differentiated from UC by absence of severe desquamation and presence of uneven discrete lesions in rectosigmoid mucosa. Also, shigella colitis presents initially with watery diarrhea which gradually decreases and changes to stool with blood, mucus and tenesmus. Solitary rectal ulcer syndrome also presents a single ulcer in the rectum or can have multiple ulcers or polyps [29].

Chronic ischemic enteritis or colitis will present with a stricture in the characteristic watershed locations such as jejunum, splenic flexure or rectosigmoid junction. The stricture can be concentric, short or long and single or multiple. In acute cases, mucosa appears edematous, ulcerated and/or haemorrhagic. Severe cases can have transmural necrosis and/or gangrene. Thus, endoscopic findings help in differential diagnosis of a lot of diseases that have clinical

presentation confusing with IBD.

6. Pathological Dilemmas in Diagnosis of IBD

Biopsy diagnosis is one of the crucial steps in diagnosis, further management, assessment of response and for prognostication of IBD. Many types of colitis mimic the histological features of IBD and therefore, it is important to distinguishing between them. The morphological features include endoscopic features and histopathological findings of multiple labelled biopsy specimens from different parts of colorectum [30,31].

Various lesions mimicking IBD pathologically are as shown in table 2

Table 2: IBD mimics in pathology

Indeterminate colitis
Reparative change in IBD mimicking dysplasia
Dysplasia associated lesion or mass (DALM) versus adenoma
Morphologic variants of ulcerative colitis with crohn's-like features.
•   Backwash ileitis
•   Upper GI tract involvement
•   Superficial fissuring ulcers and aphthous ulcers
•   Transmural inflammation
•   Granulomas
•   **Iatrogenic procedure/ manoeuvres mimicking IBD**
❖   Diversion colitis and defunctioned rectum
❖   Ileal reservoirs or pouchitis
❖   Drugs
Other forms of colitis mimicking IBD
•   Microscopic / lymphocytic colitis
•   Diverticular disease associated colitis
•   ischemic enterocolitis and Bechet's syndrome
•   Radiation colitis
Infections
Polyposis disorder mimicking IBD
❖   Solitary rectal ulcer syndrome
❖   Inflammatory cap Polyposis
❖   Juvenile Polyposis
Others
•   Malignant lymphoma
•   Eosinophilic infiltrate of the gut
•   Chronic Granulomatous Disease (CGD)
•   Graft vs host disease
•   Mass lesion
•   Common variable immunodeficiency

It is important to distinguish between ulcerative colitis from crohn's disease, because their

management differs and both have different clinical behaviour. The pathological distinguishing features between Ulcerative colitis and Crohn's disease are as shown in **table 3. Figure 1** shows the pathological characteristics of ulcerative colitis.

Table 3: Pathological differences between ulcerative colitis and crohn's disease [1,2,3,4,5]

Features	Ulcerative colitis	Crohn's disease
Macroscopic		
Disease involvement	Continuous and diffuse; left sided and involves mucosa and submucosa	Segmental with skip areas. Predominantly right sided and involves transmurally
Rectal involvement	Always present(adult)	Can be involved
Perianal disease	Rare	Present 75%
Ileal involvement	Occasional 15% (backwash ileitis) not more than 10 cms	Common
Serositis	Absent (except in fulminant colitis)	Present
Fat wrapping	Usually absent	Frequently present
Fistulas and sinuses	Absent	Present
Microscopic		
Discrete mucosal ulcers	Absent (except in fulminant colitis)	Present
Mucosal edema	Usually absent	Present
Fissures	Rare, in fulminant colitis superficially located	Present , located deep
Granulomas	Absent, except crypt related.	Common
Mucosal regeneration and crypt atrophy, abnormal crypt architecture	Frequent	Minimal
Mucosal inflammation and architectural involvement	Diffuse	Focal
Cytoplasmic mucin	Diminished	Maintained
Lymphoid aggregates	Rare	Frequent
Paneth cell metaplasia	Sometimes present	Absent
Pyloric gland metaplasia	Rare	Common in crohn's enteritis.

6.1 Indeterminate colitis

The diagnosis is restricted to the cases showing overlapping pathological features, in which it is difficult to differentiate between Ulcerative colitis and Crohn's disease even after the surgically resected specimen is examined. Its prevalence is less than 15% of IBD cases. Most common pathological presentation is a case showing all features of Ulcerative colitis with superficial fissures initially, most of which, on follow up behave like ulcerative colitis with fewer having the biological behaviour of Crohn's disease [30,31].
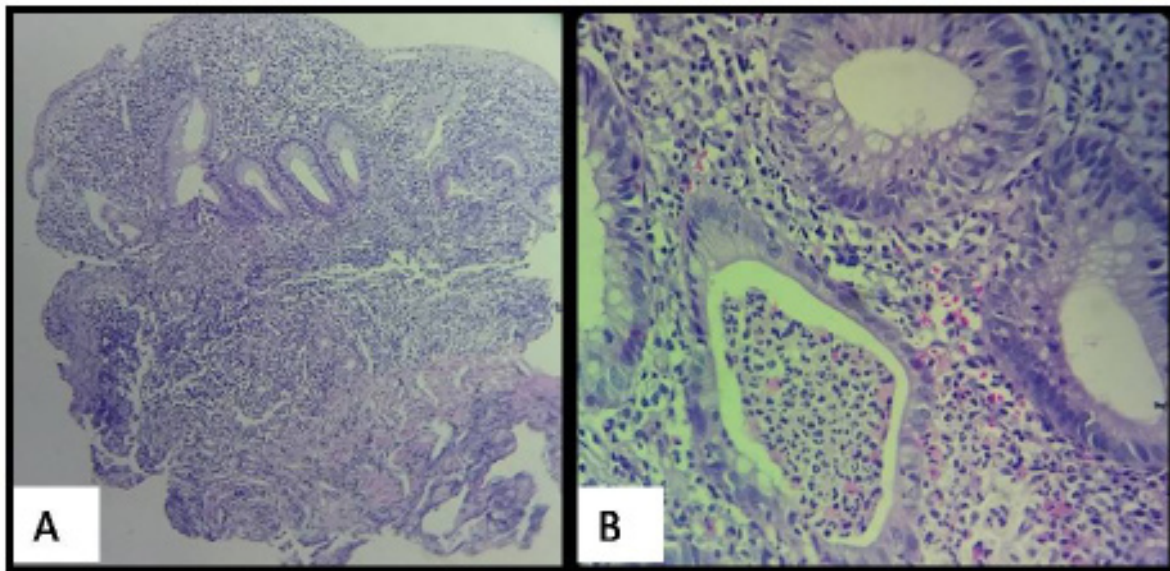
Figure 1: Ulcerative colitis. [A] The microscopic diagnosis is based on diffuse dense inflammation, architectural changes that are marked loss and mild distortion of crypts.(H & E X 100). [B] Chronic active phase showing crypt abscess and cryptitis (H & E 400X)

6.2 Reparative change in IBD mimicking dysplasia [31,32]

The important features differentiating the two entities are as follows **(Table 4)**

**Table 4:** Differentiating features between dysplasia and reparative change

Characteristic	Dysplasia	Reparative change
Loss of nuclear polarity	Present (in high grade)	Absent
Glandular complexity (cribriform change and luminal bridging)	Present (in high grade)	Absent
Nuclear enlargement	Mild to severe	Mild
Nuclear pleomorphism, hyperchromasia, irregular nuclear contours	Mild to severe	Absent / mild
Nuclear stratification and crowding	Mild to severe	Absent / mild
Inflammatory infiltrate	Mild to moderate	Moderate
High N:C ratio	Moderate to severe	Absent / mild
Cytoplasmic eosinophilia	Absent	Mild

6.3 DALM verses adenoma

It is important to distinguish these two entities as DALM **(Table 5 and Figure 2)** is associated with a higher risk for malignancy even when the dysplasia is of low grade. It is therefore, an indication for colectomy [31].

Table 5: Differentiating features between adenoma and DALM

Features	Adenoma	DALM
Age	Usually more than 40yrs	Usually less than 40 yrs
Endoscopic appearance Pedunculated polyp	Present	Present or absent
Stalk base region and biopsy of adjacent colonic mucosa	Negative for dysplasia	Dysplasia seen.
If the lesion is in an area unaffected by ulcerative colitis then adenoma is favoured.		
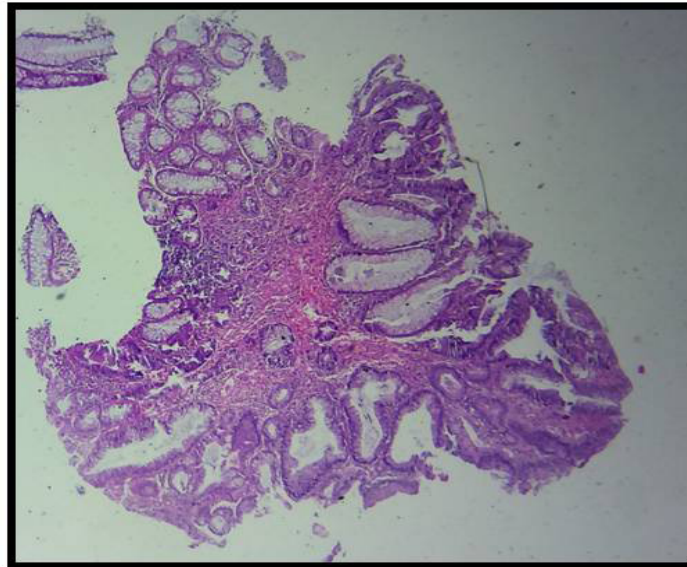
Figure 2:DALM: Rectal polyp, showing mildly dysplastic epithelial lining with adjacent epithelium showing changes of Ulcerative Colitis (H& E 100X)

6.4 Morphologic variants of Ulcerative colitis with Crohn's-like features

6.4.1 Backwash ileitis

It important to recognise this entity as, this can be misdiagnosed as Crohn's disease. It is seen in approximately 15% of cases with pancolitis and is generally associated with incompetent ileocaecal valve causing regurgitation of colonic content. The inflammation is mild, patchy and limited to mucosa. It is not associated with stricture or thickening and other features of Crohn's disease such as granulomas, deep fissures and submucosal inflammation are absent [31,33].

6.4.2 Upper GI tract involvement

Very rarely in UC, duodenal involvement is present and is represented by diffuse inflammation, thickening of duodenum and fistula [34]. Gastric involvement in UC shows superficial plasmacytosis, basal mixed inflammation and focal gastritis [35]. These patterns of involvement, in the absence of granulomas can be categorised as UC. However as these changes are fairly nonspecific, a diagnosis of UC has to be established, elsewhere in the colon [34].

6.4.3 Aphthous ulcers

It is a shallow irregular ulcer or mucosal erosion, located over a lymphoid follicle. It is characteristic of CD. However, in one study aphthous like ulcer were present in 17 % of cases with UC. It can also be seen in other conditions like infectious colitis, diversion colitis and diverticular disease [31,33,36].

6.4.4 Transmural inflammation

Transmural mononuclear inflammation can be seen in cases of UC, with fissuring ulcers extending to deep submucosa and superficial muscularis propria. It can also be seen in toxic megacolon with prominent myocyte necrosis and serosal inflammation.

6.4.5 Granulomas [2]

Two types of granulomas are seen in UC [31].

• Crypt related - Damaged crypt causing extravasation of mucin causing histiocytic collection in surrounding mucosa.

• Deep seated foreign body granulomas usually associated with fulminant colitis.

Such granulomas need to be differentiated from epithelioid granulomas seen in case of Crohn's disease.

6.4.6 Iatrogenic procedure/ manoeuvres mimicking IBD

6.4.6.1 Diversion colitis and defunctioned rectum [3,9,10]

When part of rectum or colon is surgically placed out of the fecal stream for any reason, it acquires histological changes of defunctioning. It is probably related to loss of exposure to essential fatty acids and physiological response to stasis. It occurs in patients with defunctioned large intestine for disorders like colorectal cancer, diverticular disease, Hirschsprung's disease.

The defunctioned rectum shows acute and chronic inflammation, architectural distortion, transmural inflammation, fissures, lymphoid hyperplasia and poorly formed granulomas, mimicking Crohn's disease. In such cases the clinical history is critical, so also if any histological examination of the rectum, colon prior to fecal stream diversion is available [32,37,38].

6.4.6.2 Pouchitis [3,4,9,10]

In some operations requiring total proctocolectomy, one of the late complications of pouch construction for patients with UC or familial adenomatous polyposis is pouchitis.

It is primary chronic relapsing inflammation of the pouch and can be acute or chronic. In some patients, unresponsive pouchitis may develop as a complication and this mimics CD. Microscopically it shows acute on chronic inflammation, atrophy of villi and elongation of crypts.

Rare cases show transmural inflammation and granulomas formation. In these case, if the colectomy was done for UC, the original case should be re-examined to exclude the possibility of a true CD, which can be seen in 2 to 7% of patients [32,33,37,38].

6.4.6.3 Drugs

Various drugs causes active inflammation of the large bowel which includes non-steroidal anti-inflammatory drug (NSAIDS) causing mucosal damage, occasional granulomas and IBD like changes. It can be differentiated by increased intraepithelial lymphocytes and epithelial cell apoptosis and history of drug intake, with regression of symptoms and microscopic features on cessation of the drug [38,39].

Antineoplastic drugs such as 5-flurouracil cause acute colitis. Epithelial necrosis is an important feature in the acute phase. Crypt regeneration and distortion are seen in the resolving phase, mimicking ulcerative colitis.

6.4.7 Other forms of colitis mimicking IBD

6.4.7.1 Microscopic / lymphocytic/collagenous colitis [32,33,37,38]

Microscopic colitis is defined only by its microscopic abnormality, with normal endoscopy findings and clinical complaints of watery diarrhoea. It includes two entities: lymphocytic colitis and collagenous colitis.

The characteristic features of lymphocytic colitis are as follows

• Increase in intraepithelial lymphocytes ≥ 25/ 100 epithelial cells. {Normal ≤ 6 / 100 epithelial cells}.

• Mucin depletion and decreased cell height which implies surface epithelial damage.

• Relatively preserved crypt architecture.

• The lamina propria shows increased in lymphocytes, plasma cells, eosinophils and mast cells {usually clustered at crypt bases}.

The characteristic features of collagenous colitis are as follows

• Subepithelialy located thickened collageneous bands > 10 micrometre. {normal< 7 micrometer}.

• The collageneus layer may extend into the lamina propria with irregular lower border. Normally the lower edge of basement membrane should be sharp and distinct.

• The presence of chronic inflammation can suggest an IBD. However, the absence of mucosal architectural distortion and atrophy differentiate it.

2 to 5 % of cases show aberrant histology including ulcers, crypt abnormalities, paneth cell metaplasia, inflammatory membranes and occasional cryptitis. Histology of both these entities do not correlate with the symptoms, response to treatment or outcome and no patient with this aberrant histology has yet developed IBD [32].

6.4.7.2 Ischemic enterocolitis and Bechet's syndrome

In chronic ischemic bowel disease, stricture development may mimic CD grossly. However superficial epithelial damage, lamina propria showing hemosiderin laden macrophages, fibrosis and relative absence of chronic inflammation differentiate it from IBD.

Behcet's disease is a multisystem disorder, which can affect the intestine. Ulceration is an important feature. It can be diffuse or limited to the ileocaecal region. Colitis in Bechet's syndrome shows mucosal cobblestoning,apthous ulcers and sometimes granulomas can also be seen. Presence of characterstic perivascular inflammation, necrotizing vasculitis and absence of transmural inflammation and lymphocytic aggregates differentiate it from CD [32,38].

6.4.7.3 Radiation colitis

This can cause architectural distortion, crypt atrophy, mucin depletion and chronic inflammation mimicking IBD. Other features of obliterative arteritis with hyalinization of vessel wall, vascular ectasia and submucosal and intramural fibrosis with the history of radiation exposure help in differentiating it from IBD [37].

6.4.8 Infections [32,38,39]

The differentiating features between IBD and infective colitis are as shown in **Table 6**.

**Table 6:** Differentiating features between Infective colitis, UC and CD

Feature	Infective colitis	UC	CD
Diffuse change	Sometimes present	Present	Sometimes present
Focal change	Usually present	Absent	Usually present
Architectural abnormality	Focal	Diffuse	Focal
Neutrophils in lamina propria	Usually present	Absent	Absent
Granulomas	Absent	Absent	Present

6.4.8.1 Granulomatous inflammation simulating crohn's disease is seen in the following conditions:

• Tuberculosis (TB) is the most common cause of granulomas associated. The mucosal architectural changes with crypt distortion, crypt loss, cryptitis and crypt abscess is a close mimic of IBD. It is the prominence of granulomas that subtly indicate a tubercular etiology. Florid coalescent granulomatous inflammation with extensive caseous necrosis is the most definitive feature favouring TB. In 50% of intestinal tuberculosis, acid fast bacilli can be identified on special stains, in which case the diagnosis of TB is definitive.

• Yersiniosis – Relative lack of transmural inflammation and granulomas exhibiting central necrosis favours yersiniosis.

• Other conditions with identifiable organism in granulomatous inflammation include schistosomiasis, deep mycoses and larval infestation.
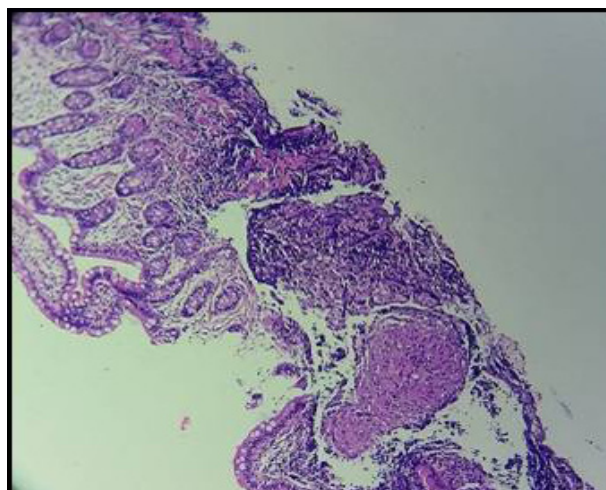
Figure 3: Mimic of Crohn's disease: ileal biopsy showing single large granuloma with adjacent ileum showing relatively preserved architecture. (H & E 100X)

6.4.8.2 Viral infections [32,38]

In immunosuppressed patients, infection by Cytomegalovirus(CMV), Herpes simplex virus (HSV) and cryptosporidiosis mimic active UC. CMV causes necrotizing gut injury

secondary to vasculitis. HSV infects distal rectum causing ulceration and microscopy shows ulceration with acute inflammation in lamina propria with cryptitis and crypt abscess. In the rectum, HSV inclusions are not seen. Characteristic inclusion bodies, multinucleated giant cells, demonstration of organism and their typical cytopathic changes help in differentiating from IBD.

Amoebic colitis can also causes crypt distortion [36]. Clostridium difficile causes early patchy changes, with epithelial cell degeneration, and later on regenerative crypt architectural changes, can be seen.

6.4.9 Others

6.4.9.1 Solitary rectal ulcer syndrome (SRUS) (Figure 4)

It is an endoscopically and pathologically defined entity. It occurs in the anterior wall of rectum, in relatively young patients with female preponderance. Histological features can mimic IBD because of marked crypt distortion with crypt atrophy seen in IBD.

In SRUS, crypt hyperplasia and elongation is seen. The inflammatory cells are scant. Fibromuscular replacement of the lamina propria is seen. These features help in differentiating it from IBD [36,37].
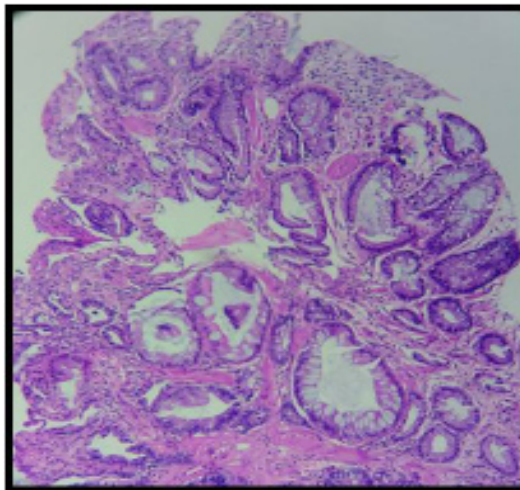
Figure 4: Mimic of IBD, (SRUS): Rectal biopsy showing architectural distortion with fibromuscular replacement of lamina propria (H &E 100X).

6.4.9.2 Malignant lymphoma

In high grade small and large cell lymphoma of B and T cell type, deep destructive ulceration is seen, which can mimic Crohn's disease specially in cases with few neoplastic cells and numerous eosinophils. In such cases immunohistochemistory can help to differentiate the two [38].

Rarely UC can coexist with a malignant lymphoma. Large bowel primary malignant lymphoma is one of the rare yet known complications of chronic ulcerative colitis.

6.4.9.3 Eosinophilic colitis

Eosinophilia of the intestine can be seen in several conditions eg- parasitic infestation such as strongyloides stercoralis or eosinophilic colitis in which marked eosinophilic infiltrate of the mucosa is seen without architectural distortion or eosinophilic gastroenteritis and peripheral blood eosiniphilia [37,38].

In the quiescent phase of UC, eosinophils can be the prominent inflammatory infiltrate. Crypt architectural abnormality would help to differentiate it from eosinophilic colitis.

6.4.9.4 Chronic Granulomatous Disease (CGD)

This is autosomal recessive disorder. When complicated by colitis it can mimic CD. Presence of histiocytes containing lipid vacuoles and pigment helps in the differentiation. In CD leucocyte bactericidal activity is normal [38].

6.4.9.5 Graft versus host disease

Acute graft vs host disease causes crypt epithelial apoptosis, crypt distortion and atrophy. Chronic inflammation may be mild or absent. In chronic graft vs host disease crypt architectural abnormality with or without fibrosis is seen. Here history would help in differentiation [39].

6.4.9.6 Mass lesion

In subserosal or intramural mass (eg- carcinoma, diverticular disease, endometriosis) the overlying mucosa due to pathological distortion may show features resembling IBD [39].

6.4.9.7 Common variable immunodeficiency

In absence of or with mild chronic inflammation with crypt atrophy and distortion with or without fibrosis is seen in common variable immunodeficiency. The mild or absent chronic inflammation differentiates this condition from IBD [39].

7. Radiological Imaging modalities for IBD

7.1 X-ray

- Not very useful for primary diagnosis of IBD.

- Useful for imaging in complicated IBD

  - Perforation: visible extraluminal air/free air under diaphragm
  - Toxic megacolon: Diameter of transverse colon > 6cm

- Extra-intestinal manifestations

  - Spondyloarthropathy evaluation

  - Immunosuppression induced pneumonia

- To rule out tuberculosis before starting infliximab

7.2 Fluoroscopic imaging {Barium meal follow through, barium enteroclysis for small bowel and barium enema for large bowel} [40]

- **Findings on fluoroscopy of small bowel**

  - Ulcerative colitis: Patulous, incompetent IC valve with nodular ileitis

  - Crohn's disease: Stenotic ileocecal junction with luminal narrowing and ileal ulcerations. Fat wrapping is radiologically seen as bowel loop angulation and kinking. Cobblestone appearance is seen due to transverse and longitudinal ulcerations and strictures are seen in chronic disease.

  - **Limitations**

    - Invasive procedure and not definitive.

    - Patient intolerance to oral contrast and rapid distension in enteroclysis.

    - No extraluminal information is obtained. Inadequate bowel distension in small bowel follow through.

    - Limited availability especially in peripheral centers.

    - Limited experience of radiologists

- **Findings on Barium enema [Large bowel]**

  - Barium enema is performed when clinical suspicion of ulcerative colitis is high and helps in differentiation between ulcerative colitis and crohn's disease.

  - Ulcerative colitis: Continuous involvement, rectum is involved early, aphthous ulceration and lead pipe pattern due to loss of haustrations and widening of presacral space > 20 mm

  - Crohn's disease: Skip pattern, rectum may be spared or involved late, cobblestone pattern and strictures

    Table 7 highlights the differences between barium enema and colonoscopy for diagnosis of inflammatory bowel disease

Table 7: Differences in utility of barium enema and colonoscopy for diagnosis of IBD

Barium enema	Colonoscopy
Noninvasive	Invasive
Indirect and subjective evaluation of mucosa	Direct objective mucosal evaluation,
Doubtful reproducibility	Reproducible
Screening modality	Diagnostic modality
Strictures are not a limitation and proximal loops can be visualized using dilute barium suspension	Strictures may limit the study
Biopsy cannot be done	Biopsy can be done simultaneously
Less complications	Perforation rate 1 in 5000
Less costly	Expensive

7.3 Ultrasound abdomen and pelvis

It does not play a major role in diagnosis of inflammatory bowel disease. Wall thickening of bowel and loss of gut signature may be seen in crohn's disease.

7.4 Computed tomography [CT] enterography and CT enteroclysis [41]

It is now preferred over fluoroscopy studies as it has a rapid scan time with multiplanar reformatting options and also provides extraluminal information. CT enteroclysis similar to barium enteroclysis requires a nasojejunal tube placement for contrast instillation. Enterography is hence preferred except for cases of partial obstruction wherein, enteroclysis is the procedure of choice.

Neutral contrast is now favored over iodinated contrast because it is tasteless so more palatable, mucosal enhancement by intravenous contrast can be adequately visualized with neutral contrast whereas it is obscured with iodinated contrast. Stricture evaluation is better with iodinated contrast. Oral contrast is followed by intravenous low osmolar contrast such as iohexol to look for bowel wall enhancement and extraluminal findings.

In cases of suspected bowel obstruction or perforation, positive oral contrast is preferred as transit across the perforation site is identified better with positive contrast. Also, after the diagnosis of rectal IBD on colonoscopy, the extraluminal findings can be better evaluated with CT with positive rectal contrast. Pattern of disease [skip versus continuous], submucosal extent, ulceration, lymphadenopathy, and presence of fistula can be evaluated

Findings on CT

• In acute cases, colonic/small bowel wall thickening and edema is seen

• Mucosal hyperenhancement, mesenteric inflammation and increased vascularity are seen in the form of fat stranding and 'comb sign' at the mesenteric edge of the bowel

- Fistula/perforation/abscess are better evaluated

- Fibrostenotic strictures can be seen and evaluated

- Chronic cases show mesenteric fat proliferation known as creeping fat sign and submucosal fat infiltration

- Gross bowel distension with bowel wall thinning and/or pneumatosis are seen in toxic megacolon

CT enterography allows more interobserver agreement, is reproducible, is widely available and can be used in children without prolonged sedation. Also, the scan time is short, radiologists are more familiar with the procedure and scan readings, cost is less when compared to magnetic resonance [MR] enterography and the scan can be done in patients with claustrophobia or patients with MR sensitive implants/devices. Limitation is contrast induced complications such as nephropathy or allergy and radiation exposure in follow up of cases.

7.5 MR enterography [42]

MR enterography is helpful in follow up of the cases to look for disease activity. Also, frequent follow up scans are feasible as there is no radiation in MR and non-contrast T1, T2, diffusion and cine images are good enough to provide a lot of information. Important MR sequences are

- T2 steady state free precession [SSFP] sequence helpful for bowel wall edema

- Post contrast T1 imaging is used for mucosal hypervascularity and comb sign

- Dynamic cine T2 imaging is useful for distinguishing between peristalsis and stricture

- T2 fat saturated sequences [Short tau inversion recovery {STIR}/ Spectral and inversion recovery {SPAIR}] are also useful for better evaluation of bowel wall edema, abscess and fistula.

- Diffusion weighted imaging will show restricted diffusion in areas of active inflammation and abscess. This is seen in T2 sequences without contrast.

Findings on MR [42]

- Active disease – Mucosal edema on T2 and mucosal hyperenhancement and transmural enhancement on post contrast T1 images.

- Inflammatory strictures are T2 hyperintense whereas fibrotic strictures are T2 hypointense.

- MR pelvis is the gold standard for imaging of perianal fistula due to better evaluation of tracts as well as the relationship of the fistula with the sphincter complex.

- MR is also a means to evaluate mucosal healing in response to treatment.

- MR cholangiopancreaticography[MRCP] helps in evaluation of primary sclerosing cholangitis.

Table 8 summarizes the role of radiology in diagnosis of IBD.

Table 8: Role of different imaging modalities on diagnosis of IBD

Small bowel disease	o CT enterography is first line o Capsule endoscopy if no evidence of obstruction and/or enteroscopy if required o CT enteroclysis useful in cases of suspicious partial small bowel obstruction
Large bowel disease	□ Colonoscopy for diagnosis □ CT to look for pattern of involvement and for evaluation of extra-luminal disease
Acute abdomen	o X-ray to rule out perforation/ toxic megacolon o If megacolon, CT done without positive oral or rectal contrast o If no megacolon, CT done with positive oral and/or rectal positive contrast to look for fistula or abscess. o This is continued till intravenous urography phase if ureteric stricture or fistula is suspected in cases with hydronephrosis
For follow up of cases on treatment	MR enterography
For sacroiliac and hip joint	MR of the involved area
Biliary system	MRCP
Perianal disease	MR pelvis

7.6 Differential diagnosis based on imaging findings

7.6.1 Crohn's disease

Stratified enhancement of the intestinal wall with wall thickness > 3 mm is the most characteristic finding in CD. This is also known as mural stratification sign which is because of hyperenhancing mucosa and muscularis on CECT and hypoenhancingsubmucosa. This becomes reverse with a hyperintensesubmcosa on T2 MR imaging. MR also shows mesenteric edema and inflammation is the form of T2 hyperintense mesentery and CECT/MR can also show nodes, sinuses, fistulas or sinuses. Sacculations of intestinal wall due to compensatory dilatation of antimesenteric wall due to fibrosis and shortening at the mesenteric side of the bowel wall are a feature of chronic CD along with the presence of fat wrapping/ creeping fat. Imaging will also reveal extra-intestinal manifestations such as primary sclerosing cholangitis, gallstones, pancreatitis, arthropathy and portal vein thrombosis amongst others.

7.6.2 Ischemic enteritis/ colitis

Splenic flexure, rectosigmoid junction and jejunum are the most common sites involved in ischemic enterocolitis. Thumb printing is the most common sign described for ischemic colitis.

Target sign, bowel wall thickening and pericolonic infiltration and stranding is also common on CT. Stricture suggests chronic disease and location of the stricture in an appropriate clinical setting suggests ischemia as the cause. Penumatosis, portal gas or free air suggests ischemic gangrene/ perforation and are surgical emergencies. Imaging can also hint towards possible cause for ischemia with the help of CT angiography which has now replaced conventional angiography for diagnosis. Arterial thrombus and embolus can be visualised as meniscus sign or planar defect on angiography whereas prolongation of arterial phase can be seen in patients with vasospastic states. Phlebosclerosis is suggested by presence of calcification in the venous system. Presence of target sign, absence of long segment stricture and absence of mucosal hyperenchancement suggest the presence of ischemic bowel disease.

7.6.3 Intestinal tuberculosis

Being most common type of abdominal tuberculosis (90%) [43], Ileocecal tuberculosis often shows abdominal lymphadenopathy with mesenteric lymphadenopathy being the most common of them [44]. Generalised lymphadenopathy involving peripancreatic, periportal and periaortic lymphadenopathy is seen in generalised disease. Early disease may show enhancing mucosa associated wall edema and thickening which later form strictures. Associated symmetrical wall thickening of IC valve and adjacent cecal wall is often seen in early intestinal tuberculosis which often confuses with radiological findings of Crohn's disease, malignancy or lymphoma however in advanced stage associated mesenteric inflammation along with clumping of bowel can be seen in as high as 45% patients [45]. Multifocal bowel involvement can often mimic skip lesions of Crohn's disease. Isolated TB involving colon is relatively less common which can mimic ulcerative colitis. Important differences between CD and TB are shown in **Table 9**

Table 9: Differences in imaging characteristics of CD and intestinal TB

CD	TB
Long segment small bowel involvement at more than 4 sites is characteristic with eccentric strictures	Short segment ileocecal> small bowel involvement is seen at less than 4 sites with concentric strictures
Comb sign and fat wrapping is common	Comb sign and fat wrapping is uncommon
Lymphadenopathy is uncommon and reactive	Lymphadenopathy is common with necrotic nodes
Omentum is rarely involved and ascites is not common	Omentum is frequently involved and ascites is common
Cobblestoning pattern, deep ulcers, enterocutaneous fistulas are common	Cobblestoning pattern, deep ulcers, enterocutaneous fistulas are uncommon

7.6.4 Intestinal Behcet's disease

The most common site of involvement is ileocecal region. Double contrast barium examination is better than single contrast and shows the characteristic deep collar button shaped lesions with ring like protrusion. It very rarely presents as ileocecal mass when, only the pathological findings can differentiate it from the other diagnostic mimics. On contrast

enchanced CT, the bowel wall appears thickened with/out a mass and a central ulceration may be present in the mass. The involved segment enhances brightly on IV contrast administration. The absence of significant lymphadenopathy and peri-enteric stranding helps in differentiation from malignancy and other inflammatory bowel diseases [46].

Other sites of involvement are rare. There is no specific pattern of involvement in other organs such as esophagus, stomach or proximal small bowel but, deep penetrating ulcers in an appropriate clinical setting should raise a suspicion of Intestinal Behcet's disease. The disease can also present in its complicated form with perforation, hemorrhage, peritonitis or fistula [47].

7.6.5 Pseudomembranous colitis

Pseudomembrane may be visible on double contrast barium study. Findings on CT that support the diagnosis include the accordion sign that presents due to trapping of oral contrast in between the thickened edematous folds, shaggy mucosal outline and/or bowel wall thickening. Other findings such as grossly dilated colon in cases of toxic megacolon, thumb printing due to ischemic colitis and pericolonic stranding can be present as in other inflammatory bowel diseases [48].

7.6.6 CNSU, CMUSE and infective colitis

These diseases are diagnosed based on history, endoscopy and biopsy and/or cultures and radiology does not have a role in establishing a diagnosis.

8. Conclusion

From the above discussion, it is clear that correlation between clinical features, laboratory parameters, radiologic and endoscopic findings, and histopathological examination, is the key to overcome the diagnostic dilemmas and hence, all these features should be used to arrive at a diagnosis in all cases suspected to have IBD.

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