Differential Diagnosis

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Abstract

Although often clinical symptoms and first investigations arouse the suspicion of inflammatory bowel disease (IBD), clinical features, such as diarrhea, abdominal pain, or rectal bleeding, are not specific for either CD or UC. As no single diagnostic criterion proves IBD, and several other diseases can mimic CD or UC, accurate patient profiling, including patient history, endoscopy, lab investigations, ultrasound, and MRI is needed to make the final diagnosis.

Differential diagnosis varies with the type of symptoms, site of involvement, and the duration of symptoms and includes, e.g. irritable bowel syndrome, colon cancer, celiac disease, and infection disorders, but also rare diseases such as auto-immune enteropathy.

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9.1 Introduction

Inflammatory bowel diseases (IBD) are characterized by a chronic inflammatory reaction of the gastrointestinal tract and beyond. The inflammatory reaction is a nonspecific response of the bowel to diverse attacks on its integrity and can be triggered by many different causes. At the first manifestation of an IBD, however, it is not always easy to distinguish between Crohn's colitis (CD) and ulcerative colitis (UC). To date, there is no test that serves as a gold standard for the diagnosis of the IBD. Therefore, a confirmation of the diagnosis of CD/UC remains a major clinical challenge.

If a patient presents with symptoms that are suggestive of an IBD, the patient history is very important and should include a detailed history of the symptoms, personal and family history, travel history, smoking status, and medication intake (especially NSAIDs, ergotamine, digoxin, and penicillamines). Symptoms such as abdominal pain, chronic diarrhea, rectal bleeding, and family history of IBD and iron-deficiency anemia are suspicious of IBD. However, often the clinical situation is less typical. The immense range of differential diagnoses varies with the type of symptoms, site of involvement, and the chronicity.

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9.2 Differential Diagnosis According to the Type of Symptoms

A summary of possible differential diagnosis of IBD patients is given in Tables 9.1 and 9.2.

Table 9.1 Differential diagnosis of ileitis

Infection	Yersinia enterocolitica
	Yersinia pseudotuberculosis
	Mycobacterium tuberculosis
	Mycobacterium avium-intracellulare complex
	Typhlitis
	Histoplasma capsulatum
	Salmonella
	Cryptococcosis
	Anisakiasis
	Actinomycosis israelii
Inflammation	Appendicitis, Appendiceal abscess
	Cecal diverticulitis
Gynecologic	Pelvic inflammatory disease
	Tuboovarian abscess
	Ovarian cyst or tumor
	Endometriosis
	Ovarian torsion
	Ectopic pregnancy
Neoplasm	Cecal or small bowel (ileal) adenocarcinoma
	Lymphoma
	Lymphosarcoma
	Carcinoid tumor
	Metastatic cancer
Drug-related	Nonsteroidal antiinflammatory drug-related ulcer or stricture
	Ischemic: oral contraceptives, ergotamine, digoxin, diuretics, antihypertensives
Vascular	Ischemia
	Vasculitides: Polyarteritis nodosa, Churg-Strauss syndrome, Takayasu's arteritis, Wegener's granulomatosis, lymphomatoid granulomatosis, giant cell arteritis, rheumatoid arthritis vasculitis, thromboangiitis obliterans, Henoch-Schönlein purpura
	Systemic lupus erythematosus
	Behçet's syndrome
Infiltrative	Eosinophilic gastroenteritis
	Amyloidosis
Lymphoid nodular hyperplasia	
Torsion of the appendiceal epiploica	
Ileitis associated with spondyloarthropathy	
Backwash ileitis in ulcerative colitis	
Radiation enteritis	
Bacterial overgrowth	

Early symptoms are often mild and nonspecific and abdominal problems are frequently misinterpreted as *irritable bowel syndrome* (IBS). There are no typical symptoms with which a distinction between functional vs. organic disorder can be made without a doubt. In patients with diarrhea, a number of different causes must be ruled out by the combination of patient history,

Table 9.2 Differential diagnosis of colitis and proctitis

Colitis
Ulcerative colitis
Crohn's colitis
Indeterminate colitis
Acute self-limited colitis
Segmental colitis associated with diverticular disease
Diverticulitis
Infections
Cytomegalovirus
Shigella
Campylobacter
Clostridium difficile
Salmonella
Aeromonas (Plesiomonas), Amebiasis
Enterohemorrhagic Escherichia coli (EHEC)
Mycobacterium tuberculosis
Yersinia enterocolitica
Schistosomiasis
Strongyloides
Ischemic colitis
Behcet's disease
Microscopic colitis
Collagenous colitis
Lymphocytic colitis
Radiation colitis
Diversion colitis
Chronic granulomatous disease
Graft-vs.-host disease
Gastrointestinal sarcoidosis
Eosinophilic gastroenteritis
Drug-related (NSAIDs, gold, penicillamine)
Proctitis
Prolapse
Solitary rectal ulcer
Trauma
Chemical injury
Infection
Herpes simplex type II
Neisseria gonorrhoeae
Syphilis (Treponema pallidum)
Lymphogranuloma venereum
Chlamydia trachomatis
Whipworm infestation
Ulcerative proctitis
Crohn's proctitis

clinical examination, laboratory, endoscopy, histology, and potentially radiology. Chronic abdominal pain with alternation of bowel habits (diarrhea and constipation) indicates an IBS while nocturnal diarrhea (esp. when with blood or pus), fever, and weight loss are rarely functional and are suspicious of different organic disorders such as IBD, infectious and neoplastic diseases. The stool marker *calprotectin* is useful to distinguish functional (normal values) versus organic disorder. However, this inflammation parameter can also increase with infections, NSAID therapy, and neoplasms. In addition, *lactose intolerance* presents itself with symptoms of abdominal discomfort and diarrhea in combination with flatulence typically after ingestion of milk-containing products. On a lactose eliminating diet, the symptoms resolve completely which helps to distinguish it from other causes.

Elevated bowel frequency and loosening stool consistency are the most common symptoms of IBD. *Acute diarrhea* can also be seen in *ischemic colitis* or *infectious* enterocolitis but in these cases there are no antecedent changes in the intestinal habits in the patient history. A detailed history of the onset and frequency of symptoms is therefore important for the interpretation of the histological findings in order to distinguish between IBD and other intestinal inflammations. In addition to the patient history and calprotectin, further *stool analyzes* are recommended to exclude Salmonella, Shigella, Campylobacter, EHEC, Yersinia, and parasites. Clostridium difficile toxin should be measured particularly in cases with previous antibiotic therapy; microbiological analysis from intestinal biopsies can also be helpful since, for example, CMV can mimic CD in immunocompromised patients. With elderly patients chronic diarrhea is suspicious of *microscopic colitis* (mean age of diagnosis 65 years) and should be excluded histologically. Furthermore, *laxative abuses* must be considered and should be included in the patient history.

Abdominal pain is the second most common symptom of IBD. Many patients with ileocecal *CD* report pain in the *right lower abdomen*, which is often increased after eating. Other pain localizations indicate different areas of inflammation. Patients suffering from *UC* report mostly localized cramping in the *left lower abdomen* that increases before defecation and improves thereafter. Tenesmus (a distressing but ineffectual urge to evacuate the rectum) indicates *proctitis*. *Sexually transmitted diseases* including herpes virus, Neisseria gonorrhoeae, Chlamydia trachomatis, and syphilis must also be considered in patients who suffer from tenesmus. If tenesmus is associated with hematochezia, a *rectal prolapse* should be ruled out.

Blood and mucus discharge is suggestive of a UC or some *infectious colitis* such as EHEC and Entamoeba. Rectal bleeding due to bowel *endometriosis* is rare; in these cases, patients often report changes in bowel habit, and bowel cramping which may be cyclic. Other reasons for rectal bleeding include *hemorrhoidal disease, diverticular bleeding,* and *ischemic colitis*.

Weight loss can be caused by eating disorders like *bulimia or anorexia nervosa* (often in combination with vomitus) and must always be considered since IBD is frequently diagnosed in young adult patients. With elderly patients, *malignancy* is a more frequent cause of weight loss.

9.3 Differential Diagnosis Depending on the Localization of the Inflammatory Changes

Ileitis In addition to many other diseases, Crohn's disease causes pain in the right abdomen, with or without diarrhea. In many cases, imaging assays such as ultrasound or CT can identify or exclude *appendicitis* or *gynecological diseases* as a cause. CT can also detect thickening of the ileum, lymphadenopathy, fistulae, or stricture. However, the CT findings alone should never lead to the diagnosis of Crohn's disease since it is not pathognomonic. *Medications* (oral anticonceptives, ergotamines, digoxin, and NSAID), the *Henoch-Schönlein purpura* (immunoglobulin A vasculitis), and infections can cause the same clinical manifestation. *Infectious diseases* with acute ileitis resembling CD can be due to *Yersinia*, tuberculosis, and amebiasis.

Proctitis Not only CD and UC but also a *rectal prolapse* or *sexually transmitted diseases* such as herpes virus, Neisseria gonorrhoeae, Chlamydia trachomatis, and syphilis can cause proctitis.

Colitis Many *infectious agents* can cause acute self-limited colitis (ASLC) which usually heals within 2 weeks but, in some cases, can last over 6 weeks. Ruling out infectious colitis with stool samples is essential; however, due to a low sensitivity of those tests, a negative culture result still does not exclude an infection. If no pathogen can be detected, the histological findings are even more important. An *ischemic colitis* leads to symptoms and histological changes which can mimic IBD colitis, particularly UC; this typically occurs in elderly patients with cardiovascular risk factors or atrial fibrillation. *Microscopic colitis* can lead to chronic diarrhea especially in elderly patients with an inconspicuous endoscopic image. The diagnosis is made via histological examination. The distinction between *diverticulitis* and a segmental CD is often difficult because strictures, fistulae, and abscesses may occur in both entities. Crohn's colitis should always be considered a differential diagnosis in the evaluation of ulcerative colitis since the therapy strategy differs. *Suspicious of CD* are sparing of the rectum, ileitis, perianal disease, fistulas, absence of bleeding, and histological findings like granulomas and focality of inflammation. An MRI of the small bowel or a capsule endoscopy can help to detect further lesions of the small bowel and a gastroscopy for upper intestinal involvement of CD.

Extraintestinal Manifestations Extraintestinal manifestations may indicate an IBD but are not pathognomonic. Aphthous/ulcerous stomatitis is also seen in patients with Behçet's syndrome where oral aphthae recur at least three times in one year in combination with other features like recurrent genital aphthae, eye and skin lesions, and a positive pathergy test. Further extraintestinal manifestations include peripheral arthritis; ankylosing spondylitis/axial arthropathies can occur also with other causes like rheumatological diseases. Skin lesions such as erythema nodosum, pyoderma gangrenosum, or papulonecrotic skin lesions are also not pathognomonic. For example, pyoderma gangrenosum, a neutrophilic dermatosis with painful inflammatory skin ulcers, is also associated with hematologic disorders and arthritis. Erythema nodosum can be seen in patients with malignancies (lymphoma), vasculitis, medications (oral contraceptives), or sarcoidosis.

9.4 Summary

Inflammatory bowel diseases (IBD) are characterized by a chronic inflammatory reaction of the gastrointestinal tract similar to those that are triggered by many different causes. The immense range of differential diagnoses varies with the type of symptoms, site of involvement, and the duration of symptoms. Therefore, a detailed patient history is essential. In combination with the clinical examination, laboratory, endoscopy, histology, and potentially radiology, a number of different causes must be excluded before the diagnosis of an IBD can be made.

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