Differential Diagnosis of Inflammatory Bowel Disease

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Introduction

A diagnosis of inflammatory bowel disease (IBD) is usually suspected in patients with chronic digestive symptoms, especially diarrhea, with or without blood in the stools, abdominal pain, and poor weight gain. Numerous other diseases can have similar symptoms. For some of them, laboratory investigations, endoscopic, and even histological features may be difficult to distinguish from those of ulcerative colitis (UC) or Crohn disease (CD).

In the short term the most important challenge is to rule out an infectious disease. In the long term, the differential diagnosis with other chronic diseases, such as eosinophilic gastroenteropathy, vasculitis, lymphoma, or immunodeficiency syndromes, may cause some difficulties.

In some cases, the possibility of IBD, mostly CD, is considered in a child presenting with abdominal mass, isolated esophagogastroduodenal, or perineal involvement.

Acute Onset Diarrhea

In 10–20 % of adults with IBD, patients present with apparently transient diarrhea, abdominal cramps, and low-grade fever [1]. In this acute onset disease, the diagnoses to be considered are mostly intestinal infection, food allergy, and acute appendicitis.

Intestinal Infection

In the case of acute diarrhea, patients are thought to have *viral gastroenteritis* particularly if they appear to recover promptly. However, prolonged diarrhea, right lower quadrant tenderness, or a slow recovery should alert the physician to the possibility of early IBD, although, in this setting, a *bacterial or parasitic infection* of the intestine is more likely to be responsible for prolonged symptoms. Stool sample should therefore be collected for culture and toxin assay that can identify one of the numerous pathogens responsible for intestinal infection (Table 17.1). According to the age, the severity of symptoms and the type of bacteria, an appropriate antibiotic treatment is then initiated. When no pathogen is present in the stools, an abdominal ultrasound is usually performed. It can show enlarged mesenteric lymph nodes, and thickening of the colonic and/or ileal wall, but these findings can be seen in infectious diseases as well as in IBD. Colonoscopy is then useful, enabling the visualization of colonic lesions and collection of biopsy samples for histology and culture. The endoscopist should describe the lesions precisely without directly stating a final diagnosis of IBD. Besides *Clostridium difficile*, which is responsible for the typical pseudomembranous colitis, infection with numerous bacteria or parasites may lead to colonic lesions, which can be very similar to those of UC or CD [2] (Table 17.2). Moreover, intestinal infection is part of initial manifestations in 10–20 % cases of IBD. When symptoms are severe, it is therefore justified to propose a short-course empiric treatment with ceftriaxone (or ciprofloxacin after 15 years of age), associated with metronidazole.

If laboratory tests and evolution do not confirm the hypothesis of infection, the diagnosis can be changed to IBD because of histological findings. Acute inflammatory changes of cryptitis, and crypt abscesses with neutrophilic infiltration, are not specific and are seen in both entities. The more discriminatory findings in favor of a first manifestation of IBD are the presence of glandular bifurcations and distortions, an infiltration of the mucosa with plasmocytes, and the presence of granuloma [3, 4]. Nevertheless, these findings are rarely seen when endoscopy is performed at an early stage, and, in adults, most acute episodes of colitis remain initially unclassified. Half of these patients will relapse in the following 3 years, leading to a diagnosis of IBD, usually UC [5].

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Table 17.1 Laboratory tests used to detect enteropathogens

Laboratory test	Organism suggested or identified
Microscopic stool examination	
Fecal leukocytes	Invasive or cytotoxin-producing bacteria
Trophozoïtes, cysts, oocysts, or spores	*Giardia lamblia, Entameoba histolytica, Schistosoma mansoni*
Spiral or S-shapped gram-negative bacilli	Campylobacter
Stool culture	
Standard	*Escherichia coli, Shigella, Salmonella, Campylobacter, Yersinia*
Specific selective medium (to be specified to the laboratory)	*Clostridium difficile*, *E. coli* O157:H7
	Aeromonas, Plesiomonas shigelloïdes, Klebsiella oxytoca, Vibrio parahemolyticus
Stool cytotoxicity assay	*Clostridium difficile* (A or B toxin)
Culture of colonic biopsy sample	*Shigella, Salmonella, Campylobacter, Yersinia, Klebsiella oxytoca, E. coli* O157:H7,
PCR on colonic biopsy sample	*Mycobacterium tuberculosis, Cytomegalovirus*
Circulating antibodies	*Shigella, Salmonella, Campylobacter, Yersinia, Entameoba histolytica*

Table 17.2 Main infectious agents responsible for IBD-like lesions during endoscopy

Microorganism	Possible Ileal involvement	Crohn-like aspect	UC-like aspect
Aeromonas	N	+	++
Campylobacter	Y	++	+
Clostridium difficile	N	+	+
Eschericchia coli	N	+	+
Klebsiella oxytoca	N	+	+
Mycobacterium tuberculosis	Y	+++	+
Plesiomonas shigelloides	N	+	+++
Salmonella enteritidis	Y	+	++
Shigella dysenteriae	Y	+	+++
Vibrio parahemolyticus	N	+	+
Yersinia enterocolitica	Y	+++	+
Entamoeba histolytica	N	+	+++
Cytomegalovirus	Y	+	+++

N no; *Y* yes

When the diagnosis is uncertain, one should avoid starting long-lasting anti-inflammatory treatment and be cautious when giving information to the family.

Food Allergy

Food proteins, usually milk or soy, may produce an allergic colitis which is typically encountered in infants under the age of 2 with a family history of atopy [6–8]. Rectosigmoidoscopy usually shows mucosal erythema and nodularity [9], but lesions may include aphtous lesions that mimic UC. The diagnosis of allergy is suspected if an eosinophilic infiltration of the mucosa is present on histology [9, 10]. Patch tests using a panel of the main allergens responsible for food allergy in children can be used to direct the exclusion of the offending protein. A rapid disappearance of symptoms will then confirm the diagnosis [11].

Acute Appendicitis

Acute appendicitis may cause some diarrhea, associated with the classic right lower quadrant pain and tenderness. If there is any doubt or the abdominal tenderness worsens, a laparotomy should be performed to avoid gangrenous or perforated appendicitis. In some rare cases, CD will be discovered because of ileal involvement during operation [12, 13] or at the histological examination of the appendix [14].

Chronic or Recurrent Intestinal Symptoms

Chronic or recurrent intestinal symptoms represent the most frequent presentation of IBD in the pediatric population, and include symptoms such as abdominal pain and diarrhea lasting sometimes for several months or years, especially in CD. This long delay until the diagnosis may be explained by the frequency of these symptoms as up to 10 % of children between 7 and 11 years old seek medical attention for recurrent abdominal pain [15]. The periumbilical location of pain is not pathognomonic for functional abdominal pain since it is present in most children with IBD. In patients with uncomplicated abdominal pain, constipation, lactose intolerance, peptic disease, food allergy, pathology of the urinary tract, or psychosocial causes should be considered and eliminated. The presence of fever, anorexia, weight loss or growth disturbance, perineal involvement, blood in the stools, suggests the possibility of IBD. This diagnosis is strengthened by laboratory investigations showing anemia and increased inflammatory markers (C-reactive protein, erythrocyte sedimentation rate), ultrasound examination of the abdomen showing a thickening of the intestinal wall, or elevated fecal calprotectin [16]. However, these features are not specific to IBD and further investigations are useful to eliminate other diseases (Table 17.3).

Table 17.3 Useful investigations for differential diagnosis of IBD in children with chronic diarrhea

Blood	Polynuclear count and morphologic features
	Lymphocyte count
	FACS enumeration of T and B lymphocytes
	serum electrophoresis
	IgG, A, M
	Total haemolytic complement
	C_3, C_4 concentrations
	anti-neutrophil cytoplasm antibody
	Anti-*Saccharomyces cervisea* antibody
	Anti-transglutaminase antibody
	specific IgE against food allergens
	Anti-bacteria antibody (*Shigella, Salmonella, Campylobacter, Yersinia, Entameoba histolytica*)
Stool	Fecal leukocytes
	Microscopic examination
	Standard and specific medium culture
	Clostridium difficile cytotoxin assay
Skin tests for	Tuberculosis
	Food allergens
Imaging of the abdomen	US examination
	CT-scan or MRI
Endoscopy	Esophagogastroduodenoscopy
	Biopsy for histology
	Ileo-colonoscopy
	Biopsy for histology, bacterial culture, PCR

Intestinal Infection

Even in case of chronic digestive manifestations, an infectious disease remains the most frequent differential diagnosis to be considered [2, 17]. It is therefore important to collect stools for bacterial culture and parasitic pathogens at the initial evaluation of a patient with suspected IBD. Contrary to acute presentation, an anti-microbial treatment is generally not considered until laboratory tests have confirmed a specific infectious disease. According to the pathogen, the part of the gut involved and the symptoms may vary, leading to consideration of either CD or UC (Table 17.2).

Infection with *Yersinia enterocolitica* is usually associated with a mild illness in children [18], but subacute and chronic ileitis or ileocolitis has been reported [18, 19]. This can also be associated with erythema nodosum and polyarthritis. Endoscopic features include aphtoid lesions of the cecum and ileum with round or oval elevations with ulcerations. The ulcers are mostly uniform in size and shape, in contrast to CD [20]. US examination or CT-scan show mucosal thickening and nodular pattern of the terminal ileum and colon that can mimic CD, but also enlarged mesenteric lymph nodes [21]. In contrast to CD, fistula formation and fibrotic stenosis are not observed. Stool or biopsy sample cultures may require a specific enrichment medium, are time-consuming and not always positive. The diagnosis can be made by serology showing an increase (or a very high titer) of antibody titer in two successive sera. However, serology also has false positives (antigenic cross reaction with other bacteria), and false negatives (serology is specific for only three serotypes: *Y. enterocolitica* 03 and 09, and *Yersinia pseudotuberculosis).*

Infection with enteropathogenic and enteroaggregative *Escherichia coli* (EPEC, EAEC) may be responsible for chronic diarrhea in children, especially when they live or travel in developing countries [22, 23].

Infection with *Clostridum difficile* leads to digestive disease ranging from self-limited diarrheal syndrome, to severe pseudomembranous colitis. Sometimes sustained symptoms lead to consideration of the possibility of IBD. *Clostridum difficile* infection must be sought in children receiving antibiotics, especially betalactamins, although it may occur without prior antibiotic therapy. Rectosigmoidoscopy, performed with care and minimal insufflation, reveals the presence of typical yellow–white pseudomembranes in approximately one-third of patients [24] and infection is confirmed by the presence of the toxin A or B in stool. Nevertheless, *Clostridium difficile* infection can occasionally occur in patients with UC or CD, even without the use of antibiotics [25, 26], and stool toxin positivity has been reported in 5–25 % of IBD patients with relapse, mostly after antibiotic exposure [24, 26]. Clinical symptoms are quite similar in both diseases, and it is recommended that stool cytotoxin assay for *C. difficile* be obtained on children with IBD during acute relapses [24].

Giardia intestinalis infection can be associated with chronic diarrhea, abdominal pain, and weight loss [27], which may occasionally lead one to consider the possibility of IBD. Giardia is found in most countries in the world, the prevalence being highest in developing countries. Trophozoites or cysts of *G. intestinalis* can be found in fresh stool specimens or rectal biopsies. In some cases, it may be necessary to examine duodenal aspirations or biopsies. Jejunal morphology may be normal, although partial or even total villous atrophy has been reported [28, 29]. Failure to eradicate Giardiasis can be due to hypogammaglobulinemia or deficit in secretory IgA.

Entamoeba histolytica infection occurs mostly in developing countries. Infection may be asymptomatic or lead to a dysenteric syndrome. Demonstration of *E. histolytica* trophozoites and cysts in stools remains the mainstay of diagnosis. Chronic amoebic colitis could lead to clinical, radiologic, and endoscopic findings that can be indistinguishable from those of IBD [30, 31]. However this differentiation is

important because amoebiasis can become fulminant if the patient is treated with immunosuppressive agents for a presumed IBD [32]. In these chronic manifestations, the parasite can be difficult to find in stools samples or in rectal biopsies, even using a concentration technique. The presence of high titers of antibodies in the serum may then be helpful in the diagnosis of chronic amoebiasis.

Intestinal tuberculosis remains a challenging diagnosis in developing countries, because treatments used for CD may adversely affect tuberculosis [33]. Intestinal tuberculosis involves the ileocecal region more frequently, isolated colonic location being present in only 10–25 % of cases. Symptoms can be very similar to those of CD; these include diarrhea, abdominal pain, fever, weight loss, abdominal mass of the right iliac fossa, and even suppurative perineal lesions. The presence of intramural swelling, mesenteric thickness, stricture or fistula on US examination or CT scan can be encountered in both diseases [34], although the absence or minimal asymmetric thickening of colonic wall and the presence of enlarged necrotic lymph nodes favor the diagnosis of tuberculosis [35–38]. Little data exist regarding the use of magnetic resonance imaging in the diagnosis of intestinal tuberculosis [38]. Nodules, ulcers, and strictures can be seen at ileocolonoscopy, or possibly at enteroscopy in the case of isolated jejunal lesions [39–42], but these lesions can be indistinguishable from those of CD. Usually, intestinal tuberculosis has less than four segments involved, a patulous ileocecal valve, transverse ulcers (longitudinal in CD), and more scars [43]. The characteristics of histologic lesions may also be helpful, needing to perform multiple biopsies [44]: in tuberculosis, granuloma are typically bigger, often confluent, located beneath the ulcerations, and absent in non-inflamed mucosa, and half of them contain caseum. Tuberculin skin test is positive in only 70–80 % of patients with intestinal tuberculosis. The diagnosis may be facilitated by the presence of active pulmonary tuberculosis (but this is only present in 20 % of cases), or ascites, or large lymphadenopathy on imaging [35, 36]. Unfortunately, acid-alcohol-resistant bacilli are very rarely present on direct examination of intestinal biopsies, and culture is positive in only 40 % of cases. PCR for *Mycobacterium tuberculosis* on intestinal biopsies is better, showing an accuracy of more than 80 % for the diagnosis of intestinal tuberculosis [45, 46]. Amplification of insertion element IS6110, that is specific of *M. tuberculosis,* in the fecal samples [47] and the Quantiferon-TB gold, a blood test using an interferon-γ-release assay, look promising tools [48, 49] but their diagnostic value for the diagnosis of intestinal tuberculosis remains to be evaluated. In cases of persistent doubt, empiric treatment with antituberculosis drugs has been proposed in countries where the prevalence of tuberculosis is high, reconsidering diagnosis of CD if the patient's condition does not improve [50]. Nevertheless, this approach is not recommended by others who advise to make every effort to reach an accurate diagnosis before starting specific therapy [33].

Primary intestinal infection with *cytomegalovirus* (CMV) can occur in immunocompromised children but it is exceptionally rare in immunocompetent children [51]. Endoscopy reveals ulcerative and hemorrhagic colitis, and histological examination of the biopsy will confirm the infection with CMV by finding typical intra-nuclear inclusions in the colonic mucosa, associated with immunostaining with a specific antibody. PCR of colonic tissue can also be used to detect viral DNA in the colon, although the significance of a positive result remains unclear in the absence of histological features of CMV disease. The role of this virus in exacerbations of IBD remains under debate: is it only an opportunistic agent present in inflamed tissues, or active infection which really worsens colonic lesions? [52, 53] CMV colitis is rare in CD or mild–moderate UC [53]. In patients with severe and/or refractory UC, local reactivation of CMV can be detected in inflamed colonic tissue in about 30 % of cases, but does not influence the outcome in most studies [53]. Nevertheless, treatment with ganciclovir has allowed some patients with severe colitis to avoid colectomy despite poor response to conventional IBD therapies [54]. It is recommended to test for CMV reactivation via PCR or immunochemistry on colonic biopsies in all patients with severe colitis refractory to immunosuppressive therapy and treat with ganciclovir when CMV is detected [52, 55, 56].

Celiac Disease

Celiac disease is easily recognized in the classic mode of presentation of infants who present with chronic diarrhea, anorexia, failure-to-thrive, and abdominal distension. Presentation is often less typical in older children who complain of abdominal pain, chronic diarrhea, anorexia, short stature, or iron-resistant anemia, symptoms that may also suggest IBD. In this situation, laboratory investigations should include specific antibodies, i.e., anti-transglutaminase and/or anti-endomysium. If these antibodies are positive, the diagnosis of celiac disease will be further confirmed by jejunal biopsy showing total villous atrophy with increased number of intra-epithelial lymphocytes [57].

Eosinophilic Gastroenteropathy

Eosinophilic gastroenteropathy is a rare condition characterized by infiltration of the gastrointestinal tract with eosinophils [58]. Most common symptoms are vomiting, abdominal

pain, and growth failure. Diarrhea associated with rectal bleeding is present in 23 % of cases, especially in infants, and symptoms of protein-losing enteropathy are present in 33 to 100 % of cases [59, 60]. Endoscopic examination may show nodularity, erythema, friability, erosions, and ulcerations in the upper digestive tract and/or in the colon [9, 59, 61]. The diagnosis is strongly suggested by a context of food allergy or the association with hypereosinophilia in the blood, which is present in 70–100 % of cases [59, 61]. The presence of excessive eosinophils in the digestive mucosa will confirm the diagnosis although it may also be encountered in CD. Gastric biopsies may demonstrate eosinophilic gastroenteropathy more consistently, most patients having more than 10 eosinophils per high power field in the antral or duodenal mucosa [59, 62].

Primary or Acquired Immunodeficiency Diseases

The importance of the intestine as an immune barrier is highlighted by the proximity of gut-associated lymphoid tissue to the luminal surface of the gastrointestinal tract, an external environment which is rich in microbial pathogens and dietary antigens. Significant gastrointestinal disorders, leading to chronic diarrhea, malabsorption, and failure-to-thrive, are frequently present in primary or acquired immunodeficiency diseases [63] (Table 17.4). The most frequent diseases are recurrent, persistent, and severe or unusual infections [64]. Disturbance of the immune system in the gut may also lead to autoimmune diseases, excessive production of IgE, or malignancies [65, 66].

Table 17.4 Gastrointestinal manifestations in the main immunodeficiency syndromes

Immunodeficiency syndrome	Gastrointestinal manifestations
Predominantly antibody defects	
X-linked agammaglobulinemia IgA deficiency Common variable immunodeficiency	Persistent rotavirus, *Campylobacter* or *Giardia* infection Bacterial overgrowth Gluten-sensitive enteropathy Food allergies Nodular lymphoid hyperplasia Autoimmune diseases Chronic non-specific colitis Malignancies (gastric cancer, lymphoma) Crohn disease
Predominantly cellular defects	
Severe combined immunodeficiency Acquired immunodeficiency syndrome Combined immunodeficiency Wiskott–Aldrich syndrome DiGeorge's syndrome	Severe, persistent opportunistic infections Graft-versus-host disease Persistent viral, parasitic, fungal or bacterial infections HIV enteropathy Malignancies Chronic non-specific colitis
Defects of phagocytic function	
Congenital neutropenia Chronic granulomatous disease CD11/CD18 leukocyte adhesion molecule deficiency Glycogen storage disease type 1b Hermansky-Pudlak syndrome	Severe bacterial infections Chronic diarrhea with malabsorption Stomatitis, perineal abcesses Crohn-like colitis

Immunodeficient patients may present with chronic non-specific enterocolitis, characterized at jejunal biopsy by subtotal villous atrophy with acute and chronic inflammatory cell infiltration of the lamina propria [64, 67–69]. This chronic non-specific enteropathy is non-sensitive to a gluten-free diet and occurs in several immunodeficiency disorders, affecting humoral response (X-linked agammaglobulinemia, IgA deficiency, common variable immunodeficiency), T-cell function (Wiskott–Aldrich syndrome, acquired immuno deficiency syndrome), or both (combined immunodeficiency). In some cases, strictures of the intestine may develop [67–70]. In these patients it is important to rule out infection with opportunistic bacteria or parasites, and also with more common pathogens, such as rotavirus, adenovirus, and picornavirus [64].

Enterocolitis that resembles CD is mostly associated with defects of phagocytic function. Patients with chronic granulomatous disease may present with chronic colitis, perirectal abscesses and fistulas, and antrum narrowing [71, 72]. The similarity with CD also includes endoscopic appearance, radiographic abnormalities, and even histologic features showing granulomas and giant cells in the digestive mucosa. Nevertheless, a paucity of neutrophils, an increased number of eosinophils, eosinophilic crypt abscesses, pigmented macrophages, and nuclear debris suggest chronic granulomatous disease [73]. Patients with CD11/CD18 leucocyte adhesion molecule deficiency, a rare disorder of phagocytic function, present with oral and perineal involvement that may be mistaken for CD. These manifestations include stomatitis with pharyngitis, gingivitis with parodontitis, ischiorectal abscesses, and distal ileocolitis [74]. Other disorders of neutrophils, such as glycogen storage disease type 1b and the Hermansky-Pudlack syndrome [75], and also IgA deficiency and acquired immunodeficiency syndrome may be associated with chronic colitis that resembles IBD [63, 76].

In patients presenting with digestive involvement resembling CD, a history of delayed umbilical cord separation (2 or 3 weeks), recurrent infections, and a young age, should alert the clinician to the possibility of an immunodeficiency disease and lead to prompt referral.

Autoimmune Enteropathy

Autoimmune enteropathy is characterized by severe persistent diarrhea associated with circulating auto-antibody against gut epithelial cell and/or another auto-immune disorder [77, 78]. It may be an X-linked familial disease which includes polyendocrinopathy (IPEX syndrome) [79–81]. Although the colon is frequently involved [79, 82, 83], the lesions are predominant in the small intestine, with inflammatory cell infiltration of the mucosa, and subtotal or total villous atrophy [79, 80, 83], leading to secretory, protracted diarrhea in the first months of life [84, 85]. Nevertheless, antibodies to colonic epithelial cells have been also found in patients with UC [86], and 10 % of IBD patients suffer from one or more auto-immune diseases [87], leading to some diagnostic difficulties in the older child.

Intestinal Neoplasm

Patients with *intestinal lymphoma* often present with chronic digestive symptoms, such as abdominal pain, distension, and/or diarrhea. Ultrasound examination show a thickening of the intestinal wall, and/or narrowing of the lumen of the gut, which can be very similar to CD [88]. Extension of the lesions is more precisely seen with a CT scan of the abdomen, and upper digestive endoscopy and ileo-colonoscopy are mandatory to provide an histologic confirmation. Nevertheless, if the lesions are limited to part of the small intestine, the biopsy may require an enteroscopy or even a surgical procedure, by coelioscopy or laparotomy. Predisposing conditions for intestinal lymphoma in children include inherited or acquired immunodeficiency syndromes, immunosuppressive therapy, and Epstein-Barr Virus infection [89]. In developing countries, Mediterranean lymphoma is characterized by the proliferation of IgA-secreting B lymphocytes. The diagnosis is usually suspected because of the presence of alpha heavy chain in the serum [90].

Vasculitis Disorders

Henoch–Schoenlein purpura (HSP) is a frequent vasculitis, involving the gut, skin, joints, and kidney. Diagnosis is easily made in a child presenting with typical skin purpura. Gastrointestinal symptoms, i.e., colicky abdominal pain and bleeding, may precede the skin rash by a number of days, and some cases of isolated duodenojejunitis without purpura have been described [91].

In other less frequent systemic vasculitis, such as periarteritis nodosa [92, 93], Wegener granulomatosis [94], Behcet's disease [95, 96], and lupus arteriosus [97], intestinal involvement can lead to chronic abdominal pain associated with bleeding. Endoscopic and histological findings may be very similar to CD, even with the presence of granuloma. Extra-digestive manifestations, especially neurological, respiratory, renal, and cutaneous lesions suggest systemic vasculitis [98] (Table 17.5). On the other hand, extra-intestinal vasculitis can complicate IBD, involving the retina, brain,

Table 17.5 Extra-digestive manifestations and useful investigations for the diagnosis of systemic vasculitis in children with digestive symptoms resembling Crohn disease

Vasculitis	Extra-digestive manifestations	Investigations
Periarteritis nodosa	Multiple neuritis Myositis Arterial hypertension Skin ulcerations and gangrene	Skin, muscle biopsy Angiography
Wegener granulomatosis	Epistaxis, sinusitis, otitis, hearing loss Stridor, hoarseness Cough, wheezing, dyspnea, hemoptysis Necrotizing glomerulonephritis Skin ulcerations and gangrene Conjunctivitis, uveitis, optic neuritis Pseudotumor cerebri	Thoracic CT-scan c-ANCA Nasal mucosa biopsy
Behcet's disease	Buccal aphtous lesions Genital ulcers Uveitis Thrombophlebitis Menigoencephalitis	HLA-B5
Lupus arteriosus	Typical facial erythema Myocarditis, pericarditis, endocarditis Pleuropneumonitis Glomerulonephritis Thrombophlebitis Hemolytic anemia and thrombopenia Keratoconjunctivitis, retinitis	Antinuclear antibody Anti-DNA antibody

skin, muscle, joints, and lung [99–104]. Nevertheless, the differentiation between primary systemic vasculitis and IBD can be clinically challenging, but is important because their treatments and outcome are different [105]. The confirmation of the vasculitis process is more often evident on extra-intestinal biopsies (skin, muscle, kidney) than on intestinal biopsies, and on angiography showing aneurysms and caliber variation of visceral arteries [93].

Abdominal Mass

The discovery of an abdominal mass has been found to reveal ileocolic CD in some adults and children [106–108]. Ultrasound examination and CT scan of the abdomen are first-line investigations which will exclude extra-digestive malignant tumors, such as lymphoma, sarcoma, nephroblastoma, or neuroblastoma. When the mass is developed from the digestive tract, glandular lymphoma or adenocarcinoma of the colon, although rare in children, can be suspected [109–111]. Radiologic findings may be very similar in some benign lesions, like leiomyoma, pseudoinflammatory tumor, or tuberculosis [112, 113]. Nevertheless, surgical exploration is generally required, leading to correct diagnosis after histologic examination of the excised tumor. Intestinal tuberculosis may be a challenging diagnosis because histologic findings may be very similar to those of CD, although granuloma are typically larger and contain caseum in the case of tuberculosis [44]. Polymerase chain reaction for *Mycobacterium tuberculosis* should be systematically performed [45, 46].

Isolated Esophagogastroduodenal Involvement

Esophagogastroduodenal involvement is present in about 25 % of children with CD, usually discovered during upper digestive endoscopy with systematic biopsies, performed at initial work-up [114–116]. More rarely, patients may present with symptoms suggestive of peptic disease, including epigastric burning pain and early satiety, these often being relieved by antacids or antisecretory treatment [117, 118]. Endoscopy can show heterogenous lesions, but a bamboo-joint like appearance is suggestive of CD [115, 117, 119, 120]. Uncommonly, CD patients present with an isolated gastric or duodenal ulcer [118]. In the case of long-lasting symptoms, altered growth rate, the possibility of CD should be kept in mind and a biopsy of the edge of the ulcer looking for the presence of granulomas should be performed [114, 115, 117].

Isolated Perineal Disease

Skin tags, anal fissures, and perianal fistulae or abscesses are frequent in infants who are in diapers and/or have a history of constipation with hard stools.

Such perianal lesions also occur in half of patients with CD, mostly in the context of colonic inflammation [121]. These lesions may precede other manifestations of intestinal disease in about one-third of these patients [122]. In adolescents, perianal lesions can be severe [123, 124], hidden, and unrecognized for several months. The diagnosis of CD should then be considered in the case of extensive or refractory perianal lesions occurring in older children. Confirmation of diagnosis will be obtained by the presence of granuloma on biopsies of perianal lesions that required surgery, and/or colonoscopy that will show colitis [122, 124]. More rarely, severe perineal lesions can be seen in tuberculosis [125], disorders of phagocytic function of polynuclear neutrophil [71], apoptosis deficiency [126], or occur after trauma or sexual abuse [127, 128].

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