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REVIEW ARTICLE

Ileocecal thickening: Clinical approach to a common problem

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Abstract

Ileocecal thickening (ICT) is a common finding on radiological imaging. It can be caused by a variety of inflammatory, infectious, or neoplastic conditions, and evaluating a patient of ICT can be a challenging task. Intestinal tuberculosis (ITB), Crohn's disease (CD), and adenocarcinoma are the most common causes. Enteric bacterial infections, cytomegalovirus, histoplasmosis, amebiasis, systemic vasculitis, lymphoma, etc. should be suspected in appropriate clinical settings. However, it could often be a spurious or nonspecific finding. A thickness of more than 3 mm in a normally distended small bowel is usually considered abnormal. Detailed evaluation of imaging of the site and extent of thickening; the degree and pattern of thickening; and the associated findings, such as degree of fat stranding, fibrofatty proliferation, adjacent lymph nodes, and solid organ involvement, should be performed. Ileocolonoscopy is an important tool for diagnosing and obtaining samples for tissue diagnosis. Histopathology is usually the gold standard for diagnosis, although—not uncommonly—findings could be nonspecific, and reaching a definitive diagnosis is difficult. As such, a systematic approach with the integration of clinical, biochemical, radiological, endoscopic, histological, and other laboratory tests is the key to reaching a diagnosis. In this article, we review the causes of ICT and present a clinical approach for the management of ICT.

Introduction

Ileocecal thickening (ICT) is a common radiological finding that is being increasingly recognized due to increased access to imaging.[1] The etiology of ICT is varied, and reaching a definitive diagnosis can be a challenging task for even an astute clinician. Moreover, the two important differentials of ICT are intestinal tuberculosis (ITB) and Crohn's disease (CD), and differentiation between them itself is an eternal enigma.[2] A systematic approach with the integration of clinical, biochemical, radiological, endoscopic, histological, and ancillary tests is the key to reaching a diagnosis. In this article, we review the causes of ICT and present a clinical approach for its management.

Ileocecal region-pathophysiological significance

The ileocecal (IC) region comprises the cecum, appendix, ileocecal valve, and the terminal ileum.[3] These structures are closely placed near each other, and as such, they may be contiguously involved in disease process, thereby creating a diagnostic dilemma. The ileocecal area can be involved by diseases localized to that segment of the bowel, diseases involving the gastrointestinal system in general, or systemic diseases. The ileocecal area is an area of physiological stasis, increased absorptive area, decreased digestive function, and abundant lymphoid tissue and M cells, and as such, it is the most common area of the gastrointestinal tract involved by pathological process.[4,5]

Definition of ICT

ICT is usually measured on computed tomographic (CT) scan (Fig. 1a–d). The wall thickness on CT scan varies depending on the distension of the lumen. Normal thickness of an adequately distended small bowel wall is usually 1–2 mm.[6] In a partially collapsed bowel, the thickness may be 2–3 mm. However, some authors have used a thickness of 2–3 mm as the upper limit of normal.[7,8] With regard to colonic wall thickness, it can vary from 1 to 2 mm when the lumen is adequately distended and up to 5 mm when the lumen is collapsed.[9] As such, it is commonly agreed that a thickness of more than 3 mm in a normally distended small bowel should be usually considered abnormal.[6–9] However, it should be kept in mind that the clinical relevance of a concentrically, evenly, symmetrically thickened, and homogeneously enhancing bowel wall must be interpreted with caution.

Causes of ICT

The ileocecal area could be involved by a variety of conditions, including benign or malignant tumors, infections, inflammatory conditions, ischemia, etc. However, ICT can also be a spurious finding, without any underlying cause. In various studies on bowel wall thickening, a normal ileocolonoscopy has been found

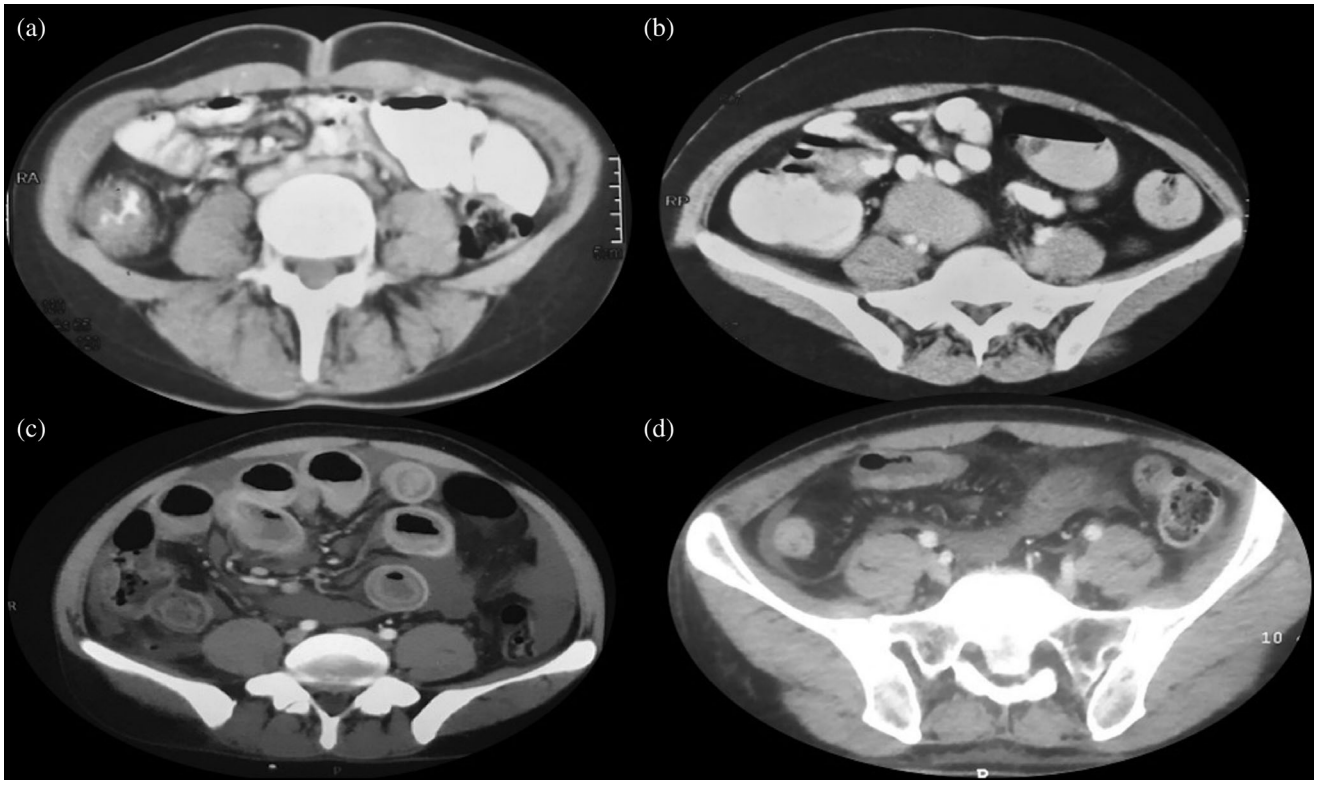

Figure 1 Computed tomographic images showing (a) asymmetrical mural thickening of the cecum in a patient with intestinal tuberculosis; (b) asymmetrical mural thickening of the terminal ileum in a patient with intestinal tuberculosis; (c) mural thickening of cecum and multiple other places in the small intestine with halo sign in a patient with eosinophilic enteritis; and (d) mural thickening of the cecum and part of colon with fat stranding and increased vascularity consistent with comb sign in a patient with Crohn's disease.

Table 1 Various etiological factors of ileocecal thickening[1,19–41]

Common causes	Uncommon causes	Rare causes
• Tuberculosis[2,34,35] • Crohn's disease[2,36] • Adenocarcinoma[20,21,33] • Cecal diverticulitis,[37,38] appendicitis • Bacterial ileocolitis[19,30]—Shigella, Salmonella, Campylobacter, *Clostridium difficile*, Yersinia • Ameboma/iasis[22] • Lymphoma[31]	• Ischemic[32] • *Mycobacterium avium* complex[19] • Systemic vasculitis • Histoplasmosis[27,28] • CMV[39,40] Other tumors- carcinoid, GIST, metastasis, lipoma • Typhlitis[41]	• Eosinophilic gastroenteritis[25,26] • Endometriosis[24] • Bauhin's Ileocecal valve syndrome[23] • Lipomatosis of IC valve[21,23] • IgG4-related disease of ileocecal area[29]

CMV, cytomegalovirus; GIST, gastrointestinal stromal tumors; IC, ileocecal.

in 18–33% cases.[1,10–12] As such, not all cases of ICT have a pathological cause. Moreover, some patients may have nonspecific ileitis. Such patients have ulceration or nodularity on ileocolonoscopy but in the absence of significant symptoms, can be followed up without any definite treatment.[13]

Tuberculosis (TB) is often reported as the most common cause of ICT in tropical countries.[1] CD is another important cause of ICT. Although CD is thought to be more common in North America and Europe, its incidence in Asian countries has been increasing.[14,15] The ileocecal area is the most common site for the involvement of both ITB and CD.[14,16–18] In immunocompromised and posttransplant patients, apart from TB, other etiologies such as cytomegalovirus (CMV), enteric bacterial infections, fungal infections (mucormycosis, aspergillosis, histoplasmosis etc), ischemic necrosis of cecum, and lymphoma should be considered.[19] Malignancy in the ileocecal area is an important cause of ICT, especially in the elderly.[20,21]

In a study on symptomatic ICT from north India, ITB (present in 48% cases) was found to be the most common cause. CD was found in 20% cases, and adenocarcinoma was found in 2% cases. Ileocolonoscopy was normal in 18% cases, whereas in 4% cases, both colonoscopy and histology were normal. In 26% of cases, histopathology showed nonspecific changes, and the

patients were asymptomatic on follow up without any treatment.[1] The various causes of ICT are listed in Table 1.[1,19–41]

Clinical evaluation

Clinical correlation is often required to arrive at the final diagnosis as the imaging findings are often nonspecific, and the histology could remain noncontributory. The most common clinical presentation is right lower quadrant abdominal pain.[1] History regarding onset and duration of symptoms and the presence of associated features such as diarrhea, anorexia, weight loss, fever, immunocompromised status, contact history of TB, etc. helps in narrowing the differential diagnosis.

In a patient with ICT presenting with any combination of symptoms such as abdominal pain, diarrhea, hematochezia, fever, weight loss, and intestinal obstruction, ITB and CD remain the most important diagnostic consideration.[2] Presence of lung involvement, ascites, lump abdomen, fever, and night sweats are more common in ITB, whereas diarrhea, hematochezia, perianal disease, and extraintestinal manifestations are more common in CD.[2] History of contact with a TB patient or coexisting pulmonary ITB point towards TB. The duration of symptoms at presentation is also longer in CD compared to ITB.[18]

Presentation with right lower quadrant mass with anorexia, weight loss, and symptoms of anemia in an elderly patient should warrant consideration of malignancy. Adenocarcinoma is the most common malignancy leading to a constellation of these symptoms. Intestinal obstruction is more common in left-sided colon cancer, but cecal carcinoma can act as a lead point for intussusception.[20,31] A long history of inflammatory bowel disease and family history of carcinoma colon are also pointers to underlying colon cancer.[42] Ileum and cecum are the most common sites for involvement of primary gastrointestinal lymphoma, accounting for 18–26% of cases.[43,44] They most commonly present with abdominal pain and abdominal mass. Other symptoms include vomiting, anorexia, and gastrointestinal bleeding.[44–46]

Infectious ileocolitis other than ITB usually has a short duration and could present acutely with diarrhea, right lower quadrant pain, fever, and vomiting. Immunocompromised patients are more prone to infectious ileocolitis. However, at times, diarrhea may be mild or absent, and the clinical picture may mimic acute appendicitis. Yersinia ileocolitis can especially have a chronic course and even cause abscesses in the right lower quadrant of the abdomen, mimicking CD or appendicitis.[19,30] In immunocompromised patients, CMV infection can present with constitutional symptoms, such as pain, diarrhea, and blood in stools.[39] Amoebic colitis predominantly presents with bloody diarrhea, abdominal pain, fever, and weight loss.[47] The onset of symptoms may be gradual, and the presence of several weeks of symptoms prior to presentation is common. In around 1.5% cases, invasive amebiasis can lead to the formation of ameboma (a mass of granulation tissue) in the cecum or ascending colon.[48] Such patients can present with lump abdomen mimicking carcinoma colon.[22]

Diverticulitis and appendicitis usually present with acute severe right lower quadrant pain, with fever, nausea, and vomiting.[37] Isolated ischemic cecal necrosis is uncommon. Such patients usually have some predisposing conditions, such as hypertension, diabetes mellitus, atherosclerosis, vasculitis, atrial fibrillation, cardiopulmonary bypass surgery, chemotherapy, etc. It usually presents with abdominal pain, diarrhea, and bleeding per rectum. Ischemic colitis should always be considered whenever any patient with predisposing factors presents with acute right iliac fossa pain.[32]

Systemic vasculitis most commonly presenting with ileocecal involvement is Behcet's disease. It is commonly seen in the Mediterranean belt, with gastrointestinal involvement seen in 1–50% of cases.[49,50] Gastrointestinal (GI) symptoms include, in decreasing frequency, abdominal pain, diarrhea, bleeding, and fever. Extraintestinal symptoms include recurrent oral and genital ulcers, papulopustular lesions of skin, and uveitis.[50] The ileocecal area can also be involved as a part of clinical manifestation of other vasculitis. The possibility of vasculitis should be considered in young patients with symptoms suggestive of mesenteric ischemia.

Radiological evaluation

ICT can be diagnosed by radiological investigation such as ultrasound, CT scan, or magnetic resonance imaging (MRI). As mentioned above, a wall thickness above 3 mm is considered to be significant in a well-distended bowel. However, knowledge of other factors, such as site of involvement, extent of thickening, degree of thickening, pattern of thickening (symmetrical *vs* asymmetrical), and pattern of bowel wall enhancement, and associated findings, such as degree of fat stranding, fatty proliferation, adjacent lymph nodes, and solid organ involvement, is necessary to narrow down the differentials.[51]

Mild (<2 cm) and symmetric thickening is common in inflammatory (CD, radiation), ischemic, and infectious (TB, Yersinia, Salmonella, Campylobacter, etc.) causes, whereas marked (>2 cm) and asymmetric thickening is common in malignant conditions. Infectious and ischemic processes could, at times, be an exception to this rule and can present with marked bowel thickening (Fig. 1a,b).[52] Diverticulitis, adenocarcinoma, and appendicitis usually present with focal thickening (<10 cm long). Segmental thickening (10–30 cm) is usually found in lymphoma, CD, ischemic causes, and infectious ileocolitis, whereas diffuse thickening is common in vasculitis, infiltrative disorders, eosinophilic enteritis (Fig. 1c), and infectious ileocolitis. It is also important to look at the enhancement pattern of the bowel wall. Homogenous attenuation is commonly seen in lymphoma, small adenocarcinoma, submucosal hemorrhage, localized infarction, CD (due to transmural fibrosis), and chronic radiation enteritis.[8,53–55] Ischemic, infectious, and inflammatory (CD, ulcerative colitis, vasculitis, radiation enteritis) causes could show heterogenous and stratified (double halo or target pattern) enhancement.[6,8,56] A stratified enhancement pattern usually excludes malignancy. Heterogenous mixed attenuation (irregular areas of low attenuation near areas of high attenuation) can be seen in large adenocarcinoma and gastrointestinal stromal tumors (GISTs).

Inflammatory and malignant causes are the predominant causes of ICT. It is important to differentiate between the two groups. Table 2 shows the radiological differentiation between the two categories.[21,51–56]

Table 2 Radiological features used to discriminate benign and malignant causes of ileocecal thickening[21,51–56]

	Favors Malignant etiology	Favors Inflammatory etiology
Pattern of ICT	Irregular, asymmetric	Regular, symmetrical
Length of involvement	Short segment	Long segment (exception lymphoma)
Wall thickness	Greater (>3 cm)	Usually <2 cm
Attenuation pattern	Homogenous or mixed attenuation.	Stratified attenuation
Lymphadenopathy	Adjacent lymph nodes, necrotic, large	Adjacent lymph node may be present, usually homogenous (exception tuberculosis)
Perienteric fat stranding	Usually absent	Could be present
Transition of thickening	Abrupt transition from abnormal to normal	Gradual transition from abnormal to normal

ICT, ileocecal thickening.

Radiologically, both ITB and CD present as symmetrical thickening of the ileocecal region. However, multiple and long-segment eccentric strictures with mural stratification, interbowel fistulae, perianal fistulae, increased mesenteric vascularity (Fig. 1d), and fibrofatty proliferation favor CD over TB. On the contrary, the presence of ascites, omental involvement, abdominal cocoon formation, bulky abdominal lymphadenopathy, and enteroliths suggest ITB over CD.[57–59]

Adenocarcinomas usually present as short-segment marked thickening of cecum without a stratified pattern or fat stranding.[55] It can be associated with the thickening of terminal ileum in up to 10% of patients, with the thickening occurring due to tumor extension in about two-third of cases and due to edema and congestion in the remaining one-third.[60] Adenocarcinoma of ileum, although uncommon, can present as an annular lesion. Carcinoid tumor of the ileum and appendix can also sometimes present as ICT. The usual feature on imaging is a hypervascular wall thickening or a hyperattenuating submucosal mass with calcification at times.[61]

Radiologically, ileocecal lymphoma usually present as marked, symmetrical, circumferential bowel wall thickening that enhances poorly and has homogeneous attenuation. Ulceration and cavitation is common.[54] They can be heterogeneous in appearance, being a nodular, polypoidal, infiltrating, ulcerated, or exophytic mass. GISTs of the ileocecal area manifest as a well-circumscribed exophytic mass.[62] Lipoma of the ileocecal area presents as a asymmetric mass, whereas in lipomatosis, the valves are symmetrically enlarged.[23,63] The radiological finding of ischemic bowel varies as it progresses from ischemia to infarction. An ischemic bowel wall shows circumferential thickening and may show a target sign. In other cases, thickened wall without enhancement may be seen.[53]

On CT images, infectious ileocolitis usually shows circumferential mural thickening of the distal ileum and cecum and may be accompanied by mesenteric lymph nodal enlargement. It can be occasionally complicated by perforation or fistulization.[64] Neutropenic enterocolitis is commonly seen in immunocompromised patients and also presents with a similar picture. However, associated pericolic fluid collection and pneumatosis coli are common.[41] The cecum is the most common site affected in intestinal amebiasis, involved in 90% of cases.[48] Less commonly, the distal ileum may be involved in severe cases.[48] The cecum becomes concentrically thickened and can take a conical shape. Sparing of terminal ileum may help to differentiate it from ITB and CD. Ameboma may present as asymmetric or symmetric thickening of cecum and ileocecal mass.[22,48] In Behcet's disease, the CT could show concentric thickening of bowel wall with marked contrast enhancement, polypoid mass, or both. However, in patients without complications, only minimal perienteric or pericolonic changes are seen.[65]

Laboratory evaluation

Laboratory investigations are the next step in narrowing down the differential diagnosis. Anemia is nonspecific and can be seen in TB, CD, malignancy, lymphoma, etc. Anemia is usually multifactorial, with iron deficiency (due to blood loss from mucosal lesions), megaloblastic (due to vitamin B12 deficiency resulting from terminal ileal involvement), and chronic disease contributing to the causation.[66] Leucocytosis can be seen in infectious ileocolitis.

C-reactive protein (CRP) can be elevated in TB, CD, or any inflammatory condition.[67] CRP is also important in monitoring response to antitubercular therapy (ATT). In a study, it was shown that, in patients demonstrating a lack of decline of CRP with ATT, an alternative diagnosis should be considered.[67] Elevated stool calprotectin is nonspecific and suggests an inflammatory cause of diarrhea. The Mantoux test and interferon gamma release assay (IGRA) are useful for diagnosis of TB. A systemic review and meta-analysis showed that IGRA had a sensitivity of 81% and specificity of 85% when differentiating TB and CD.[68] However, it cannot discriminate active TB from past infection. Serology for antisaccharomyces cerevisiae (ASCA) has also been used to differentiate TB and CD. The sensitivity and specificity of this test has been shown to be 33 and 83%, respectively, in a meta-analysis.[68] Carcinoembryonic antigen (CEA) is a tumor marker for colon carcinoma. However, its predictive value for diagnosis in asymptomatic disease is low. It is mainly used for preoperative staging and postoperative follow up and not for the diagnosis.[69,70] Lactate dehydrogenase (LDH) may be increased in lymphoma. Stool examination is an important, low-cost tool that can help in the diagnosis of many infectious causes of ICT, such as amebiasis. The role of polymerase chain reaction (PCR)-based testing in the diagnosis of infectious ileocolitis is not entirely clear, although its use has been reported to be helpful in the diagnosis of ITB. Stool culture is also of help in the diagnosis of salmonellosis.

Endoscopy

Ileocolonoscopy and obtaining tissue for histopathology are the key investigations to reaching a definite diagnosis. Transverse ulcers (Fig. 2a) with patulous ileocecal valve (2B) and contagious involvement of ileum and cecum are more suggestive of TB, whereas longitudinal ulcers (Fig. 2c), aphthous ulcers, skip lesions, cobblestoning appearance, multiple segment involvement, and

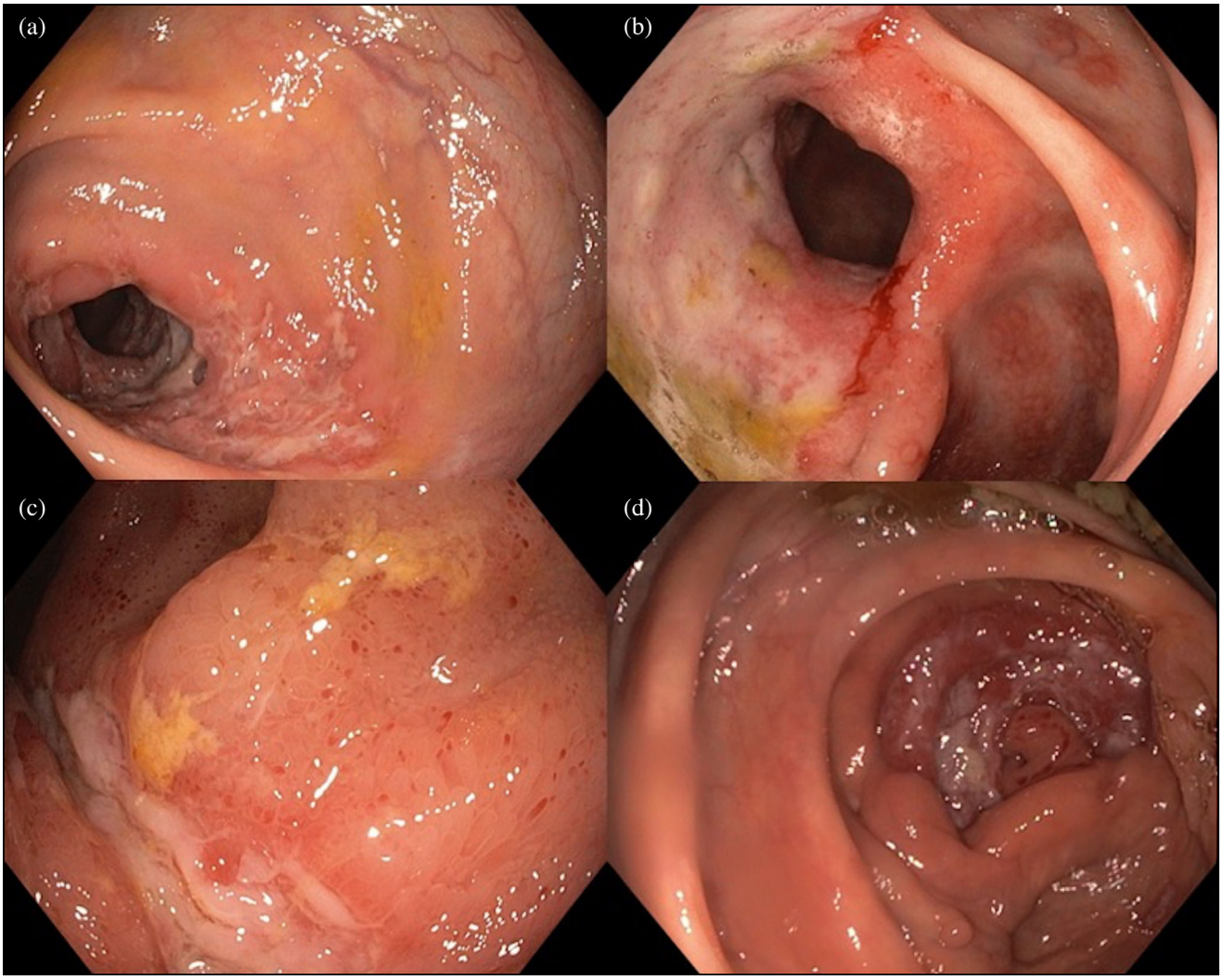

Figure 2 Colonoscopic images showing (a) circumferential ulceration in the cecum in a case of intestinal tuberculosis; (b) gaping ileocecal valve with a large ulcer in the ileocecal region in a patient with intestinal tuberculosis; (c) linear ileal ulcer in a patient with Crohn's disease; and (d) multiple amoebic cecal ulcers in a patient who also had amoebic liver abscess.

perianal fistulae are more common in CD.[2,18] Infective diseases like enteric fever and amebiasis (Fig. 2d) can also present with ulcers of varying sizes in ileocecal region, and lower gastrointestinal bleeding. On colonoscopy, carcinoma colon usually presents as a polypoidal or ulceroproliferative mass. It may also involve the ileocecal valve. Lymphoma can have a heterogeneous appearance on endoscopy. It can present as an annular or exophytic tumor, ulcer or multiple polyps.[71] In cases not accessible by colonoscopy, capsule endoscopy may be required to evaluate the ileum. However, this modality has the limitation of not being able to acquire tissue for diagnosis.

Histology

Histology is the gold standard for diagnosis. Tissue samples are usually obtained by colonoscopic biopsy; however, fine-needle aspiration with cytological analysis or percutaneous core tissue biopsy may be used in some cases. The presence of granulomas on microscopy may be found both in ITB and CD. However, large, confluent, multiple (>5 granulomas per site) granulomas with the presence of lymphocyte cuffing and submucosal location favor ITB over CD. Caseation necrosis is pathognomic of ITB, whereas crypt-centered inflammation, such as pericryptal granulomas and focally enhanced colitis, are suggestive of CD.[72]

Microscopically, colonic adenocarcinoma is characterized by medium- to large-sized abnormal glands (variable size and configuration) with moderate desmoplastic stroma. Inspissated eosinophilic mucus and cellular debris fill the glandular lumina, resulting in dirty necrosis.[73] The histopathology of lymphoma depends on its subtype. Diffuse large B cell lymphoma (DLBCL), the most common subtype, shows diffuse infiltration of medium to large lymphoid cells with oval to round vesicular nuclei and 2–4 nucleoli. Mantle cell lymphoma shows infiltration with small lymphoid cells with irregular nuclei.[74] Immunohistochemistry helps to differentiate different subtypes.

Amoebic colitis exhibits flask-shaped ulcers with undermining of normal mucosa and necroinflammatory exudates, with the organisms showing foamy cytoplasm and round and eccentric nucleus with erythrophagocytosis. Microscopically, ameboma shows abundant granulation tissue, inflammatory cells, edema, and live organism.[47] Histoplasmosis show lymphohistiocytic infiltrates involving the mucosa and submucosa with ulcerations. Discrete granulomas and giant cells can also be seen in some cases. Periodic acid-Schiff (PAS) staining demonstrates the presence of intracellular uniform, ovoid, uninucleate yeast with eccentrically placed nuclei and peripheral halo, suggestive of histoplasma.[28] Bacterial enterocolitis usually shows nonspecific neutophilic inflammation, cryptitis, crypt abscesses, and absence of basal plasmacytosis. Salmonella typhi predominantly shows mononuclear cell infiltration with paucity of neutrophils. Yersinia enterocolitica is associated with epithelioid granulomas with prominent lymphocyte cuffing.[30] Owl's eye intranuclear and basophilic granular intracytoplasmic inclusions are seen in CMV infection.[39]

Treatment

Treatment of ICT depends on the underlying etiology. Differentiating TB and CD is important for management. If TB is misdiagnosed as CD, the patient is at the risk of flare due to the immunosuppressants used for CD. Similarly, treatment with ATT in patients with CD causes them to be at risk of drug resistance, adverse effects of drugs, delay in treatment, and flare of CD. Tuberculosis is managed with the standard four antitubercular drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide). CD is treated with immunosuppressant and biologicals. Sometimes, even with extensive evaluation, it may not be possible to differentiate between the two entities. In such a situation, a recommendation is made to start empirical ATT in regions endemic for tuberculosis, and diagnosis of CD is considered after a failed response to ATT.[14] In a study from India, it was shown that, after 3 months of therapy, 93.6% of ITB patients showed response to ATT compared to 38.2% cases of CD. Mucosal healing after treatment was seen in all patients with ITB and only 5% with CD.[75] In addition, another study suggested that both partial and complete early mucosal response (evaluated at 2 months after starting ATT) suggest underlying ITB.[76] As such, it was suggested that colonoscopic examination should be repeated at 2 months, and the possibility of CD or multidrug-resistant TB should be considered if there is no change or worsening of symptoms.[75,76] Surgery is the treatment of choice for carcinoma colon. The use of adjuvant or neoadjuvant chemotherapy/radiotherapy/immunotherapy depends on the stage of the disease.[77]

In conclusion, ICT can be caused by a variety of conditions. Differentiating between malignancy and inflammatory condition is the first step in evaluation. ITB and CD are the key

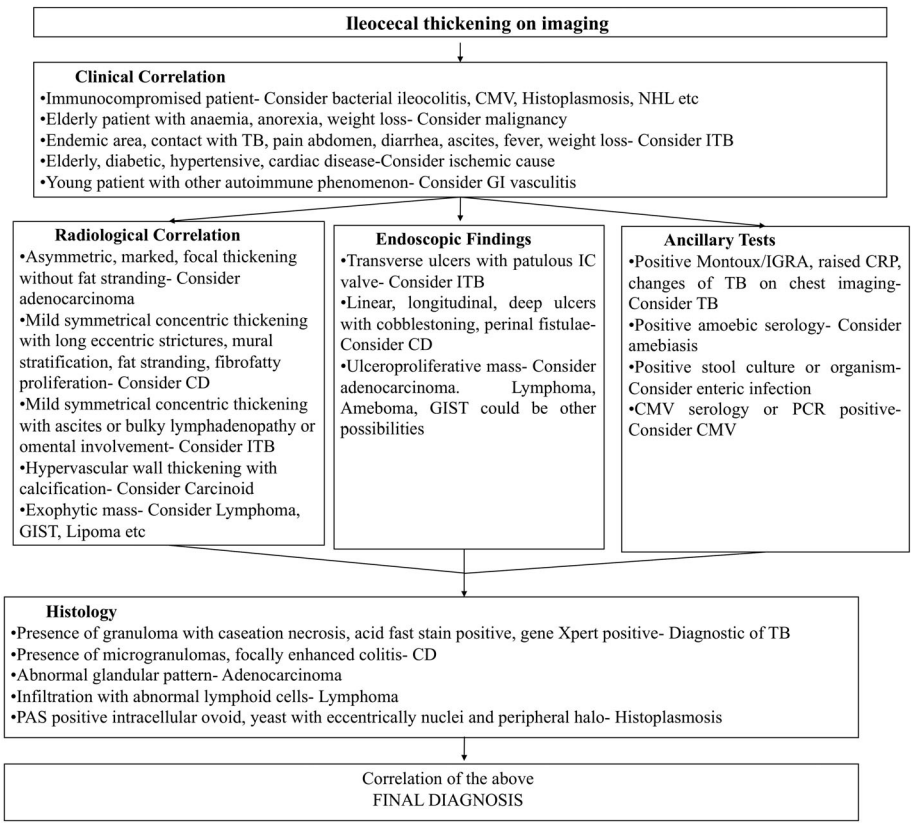

Figure 3 Flow chart depicting the integrative approach to evaluation of patients with ileocecal thickening. CD, Crohn's disease; CMV, cytomegalovirus; GI, gastrointestinal; GIST, gastrointestinal stromal tumors; IC, ileocecal; IGRA, interferon gamma release assay; ITB, intestinal tuberculosis; NHL, Non-Hodgkin Lymphoma; PAS, Periodic Acid Schiff; PCR, polymerase chain reaction; TB, tuberculosis.

differentials in the inflammatory category. However, in tropical and underdeveloped countries and in immunocompromised patients, other infections should be considered. Ischemia and vasculitis should be suspected in appropriate settings as outlined above. Figure 3 shows a systematic approach to the management of a case of ICT. In conclusion, a systematic approach with the integration of clinical, biochemical, radiological, endoscopic, histological, and ancillary tests is the key to reaching a diagnosis.

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