REVIEW

Diagnosis of bowel diseases: The role of imaging and ultrasonography

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Abstract

Examinations with a visualisation of the anatomy and pathology of the gastrointestinal (GI) tract are often necessary for the diagnosis of GI diseases. Traditional radiology played a crucial role for many years. Endoscopy, despite some limitations, remains the main technique in the differential diagnosis and treatment of GI diseases. In the last decades, the introduction of, and advances in, non-invasive cross-sectional imaging modalities, including ultrasound (US), computed tomography (CT), positron-emission tomography (PET), and magnetic resonance imaging, as well as improvements in the resolution of imaging data, the acquisition of 3D images, and the introduction of contrast-enhancement, have modified the approach to the examination of the GI tract. Moreover, additional co-registration techniques, such as PET-CT and PET-MRI, allow multimodal data acquisition with better sensitivity and specificity in the study of tissue pathology. US has had a growing role in the development and application of the techniques for diagnosis and management of GI diseases because it is inexpensive, non-invasive, and more comfortable for the patient, and it has sufficient diagnostic accuracy to provide the clinician with image data of high temporal and spatial resolution. Moreover, Doppler and contrast-enhanced ultrasound (CEUS) add important information about blood flow. This article provides a general review of the current literature regarding imaging modalities used for the evaluation of bowel diseases, highlighting the role of US and recent developments in CEUS.

INTRODUCTION

Endoscopy remains the main technique for the diagnosis of gastrointestinal (GI) tract diseases because it allows a direct visualisation of the mucosa and the possibility of taking samples for histological analysis. Moreover, in recent years, improvements in endoscopic techniques have also made it possible to use endoscopy for interventions in some diseases of the GI tract. However, endoscopy has some limitations due to its invasiveness and the difficulty of examining the small bowel, and it does not allow the visualisation of extra-intestinal structures that may be involved.

For many years, traditional radiological techniques played a crucial role in the diagnosis of small bowel diseases. In the last decades, the introduction of, and improvements in, non-invasive cross-sectional imaging tech-

niques including ultrasound (US), computed tomography (CT), positron-emission tomography (PET) and magnetic resonance imaging (MRI), have changed the diagnostic approach to the GI tract[1]. The high resolution of imaging data, ability to acquire 3D images, enhancement of tissues and additional co-registration techniques (PET-CT, PET-MRI) have improved the diagnostic classification of tissue pathology and performance in terms of sensitivity, specificity and accuracy, depending on the specific method and equipment used, the section of the GI tract investigated, the patient's constitution and preparation, and the type of pathology being studied[2].

In the last two decades, among the cross-sectional imaging techniques, US has had a growing role in the development and application of techniques for the diagnosis of GI diseases because it is cheap, non-invasive, and more comfortable for the patient, and it has sufficient diagnostic accuracy to provide the clinician with high temporal and spatial resolution image data. Moreover, Doppler and contrast-enhanced ultrasound (CEUS) contribute important information about blood flow.

This article provides a general review of the current literature regarding imaging modalities used for the evaluation of bowel diseases, highlighting the role of US and recent developments in CEUS.

CONVENTIONAL RADIOLOGICAL EXAMINATIONS

Plain-film radiography remains the first-line of investigation in the acute setting. Non-contrast radiography is useful in the initial assessment of various GI diseases, including bowel perforation, obstruction, volvulus, and toxic megacolon[3].

When detailed luminal evaluation is required, fluoroscopic barium or water-soluble single- and double-contrast studies are the modalities of choice. These techniques are able to visualise transit time, peristalsis, luminal emptying and pathological changes such as stenosis, dilatation, luminal filling defects and external compression. Moreover, double-contrast examinations allow detailed visualisation of the mucosa and the detection of inflammatory and neoplastic changes in the intestine[4].

Barium swallow studies remain the main investigational tool for dysphagia, allowing direct evaluation and inspection of the oesophageal mucosa and gastro-oesophageal junction, an objective measurement of oesophageal contractibility, assessment of reflux and identification of the presence of strictures, pouches, and hiatal hernia[5]. With respect to the small intestine, fluoroscopic imaging techniques such as small bowel barium follow-through and conventional enteroclysis are able to detect subtle mucosal abnormalities such as fistulous tracts, adhesions and, more rarely, intraluminal lesions. Functional information about transit time and peristalsis can also be ascertained.

Water-soluble, single-contrast oral studies are gener-

ally performed in the immediate post-operative period to assess anastomotic integrity, due to the potential for free intra-abdominal barium to induce peritonitis[6].

However, fluoroscopic imaging has several disadvantages: first, it only allows indirect detection of alterations of the small bowel, with no information on deeper wall layers and extramural disease extension; and second, its sensitivity for detecting marginal changes is low compared to direct inspection of the mucosa.

CROSS-SECTIONAL IMAGING

Computed tomography

The development of multi-detector computed tomography (MD-CT) scanners with rapid acquisition of thin slices and multi-planar reconstructions allows a detailed investigation of intestinal loops[7]. In particular, non-contrast-enhanced CT scanning is replacing plain-film radiography in the evaluation of acute abdominal disease such as intestinal perforation or obstruction[8]. Intravenous contrast enhancement together with distension of the intestinal lumen by water or positive contrast agents is very useful in the detection of inflammatory and neoplastic intestinal pathologies (fistula, abscess, and phlegmon) as well as in the evaluation of extra-intestinal involvement (mesenteric lymph nodes)[9].

MD-CT colonography, also known as virtual endoscopy, is a new technique to study the large intestine that is able to detect colonic polyps greater than 6 mm with a similar accuracy to conventional colonography[10-12]. Similar to CT, it is also important in the detection of extra-colonic pathology[13,14].

For these reasons, this technique may replace traditional double-contrast examinations as a non-invasive screening test or in acute colonic inflammatory processes when other approaches are contraindicated due to the high perforation risk[2].

MRI

MRI is generally considered the gold standard examination for TNM staging of rectal cancers because it allows an exact visualisation of the rectal wall and perirectal fat infiltration[15].

Moreover, MRI is the preferred technique in inflammatory bowel diseases (IBD) because it is able to examine the entire small intestine without radiation hazards[9,16]. It can detect luminal (stenosis and fissures), mural (wall thickening and wall enhancement after gadolinium administration) and exoenteric (mesenteric inflammation, fibrofatty proliferation, lymph adenopathy, hypervascularity, abscesses and fistulas) pathologies[16-20]. In particular, MRI is more sensitive than other techniques in the evaluation of anorectal fistulas[20].

Finally, the administration of intravenous contrast agent and the consequent detection of hypervascular areas are useful in distinguishing between active and inactive disease[17,21,22].
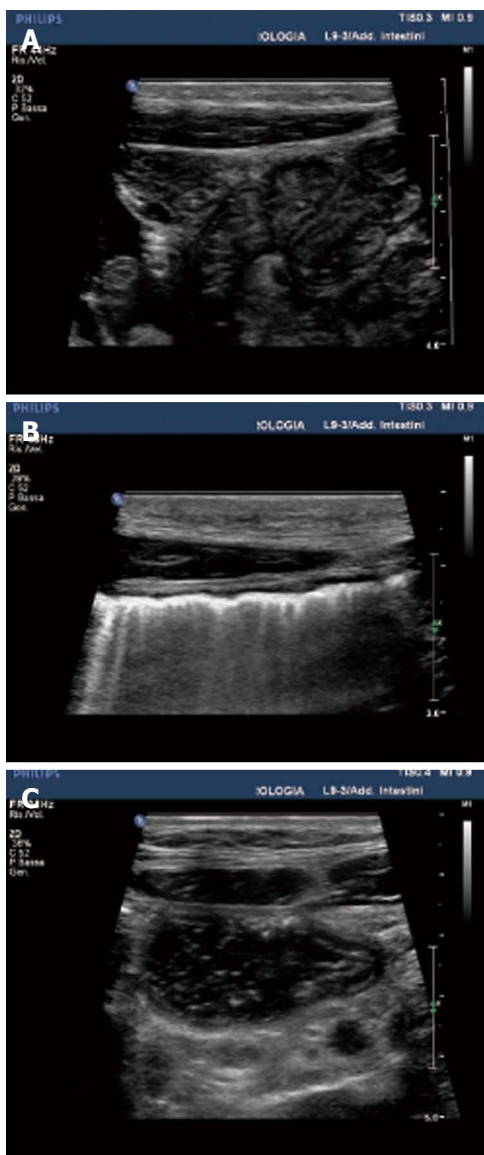
Figure 1 Sonographic appearance of normal bowel. A: Mucus pattern: collapsed bowel containing only a highly reflective core of mucus with target appearance on a transverse section; B: Gas pattern: only the proximal side of the bowel wall is visible due to beam attenuation by gas; C: Fluid pattern: the bowel is filled with fluid and faeces with a tubular appearance on a longitudinal section.

US

Among the cross-sectional imaging techniques, US is less invasive, more comfortable for the patient and has a significant diagnostic accuracy[23].

The normal bowel wall appears as a multi-layered area with hyperechoic bowel contents at the centre. Five distinct layers can be observed on sonography: an inner hyperechoic layer, the interface between the mucosa and the bowel contents; a second hyperechoic layer, the deep mucosa; a third hyperechoic layer, the submucosa; a fourth hypoechoic layer, the muscle proper; and a last outer hyperechoic layer, the serosa and the serosal fat[24].

The average wall thickness of the normal gut is 2-4 mm and the US appearance depends not only on the structure of the individual segment but also, more im-portantly, on its contents and degree of distension. The bowel may be collapsed, containing only a small amount of mucus (mucus pattern), or it may contain fluid or gas (respectively, fluid and gas patterns). The mucus pattern appears as a target with a highly reflective core of mucus. The fluid pattern gives a tubular appearance on a longitudinal section and a rounded pattern on a cross-section. In the gas pattern, only the proximal side of the bowel wall is visible due to beam attenuation by gas (Figure 1).

The jejunum has valvulae conniventes, which produce a ladder pattern, and the ileum has a smooth, featureless wall. The site of the studied bowel must also be inferred from the location of the bowel loop.

The large bowel wall thickness is < 4 mm; it has similar characteristics to the small bowel, but it can be distinguished by its location in paracolic regions and by the presence of haustra.

Similar to the other cross-sectional imaging techniques, US is able to evaluate intestinal findings, such as the bowel wall (in particular, its thickness, layers and perfusion), peristalsis, compressibility, rigidity and extra-intestinal structures, such as perienteric fatty tissues, mesenteric lymph nodes and adjacent organs[25-29].

US and bowel diseases

The most frequent pathological aspects found by sonography in intestinal diseases are wall thickening, mucosal abnormalities, the absence of peristalsis, mesenteric thickening, lymph node enlargement, vascular alterations, and extra-intestinal complications[30].

Morphological changes of the bowel wall

Bowel-wall thickening can be found in inflammatory, infectious, ischemic (but only in later stages) and neoplastic diseases. Usually, in inflammation and infections, the wall thickening is regular with preserved stratification, whereas in tumours, the thickness is irregular with loss of normal stratification[31] (Figure 2).

IBD: Crohn's disease and ulcerative colitis: The classic sonographic feature of Crohn's disease (CD) is the "target" sign on transverse images, which means a strong echogenic centre surrounded by a relatively sonolucent rim of more than 5 mm. In a longitudinal section, the sonographic feature is the "sandwich" sign. In CD, transmural inflammation or fibrosis can lead to complete circumferential loss of the typical gut wall layers, which results in a thick hypoechoic rim more than 5 mm. Strictures appear as marked thickenings of the gut wall with a fixed hyperechoic narrowed lumen, dilatation and hyperperistalsis of the proximal gut[32] (Figure 3).

In expert hands, the distribution of frank lesions of inflammatory bowel disease can be determined with a sensitivity of 73%-87%[33]. In ulcerative colitis, the sensitivity reaches 89%, and the specificity reaches 100%[34].

Differentiation between CD and ulcerative colitis based on sonographic findings is based on the location of the disease, the presence of skip lesions and the
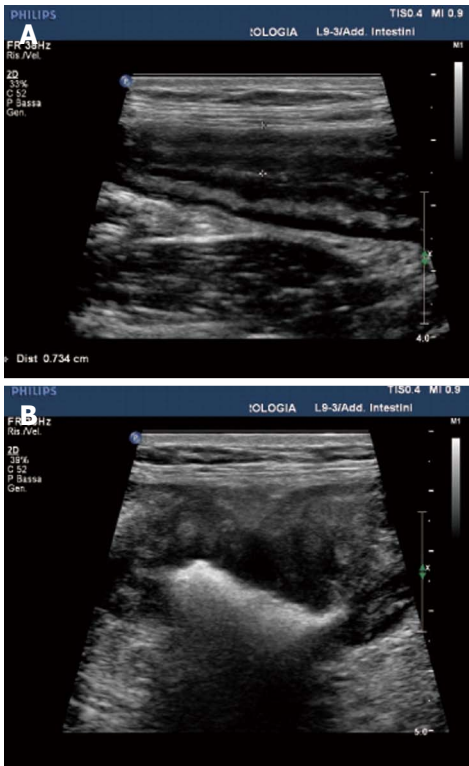
Figure 2 Wall thickening. A: Inflammatory thickening: regular, with preserved wall stratification; B: Neoplastic thickening: irregular with "pseudokidney appearance".

Figure 3 Stenosis in patients with Crohn's disease. A: B-mode aspect: narrow lumen with dilatation of the upstream segments; B: The presence of vascular signals on power Doppler indicates the inflammatory nature of stenosis.
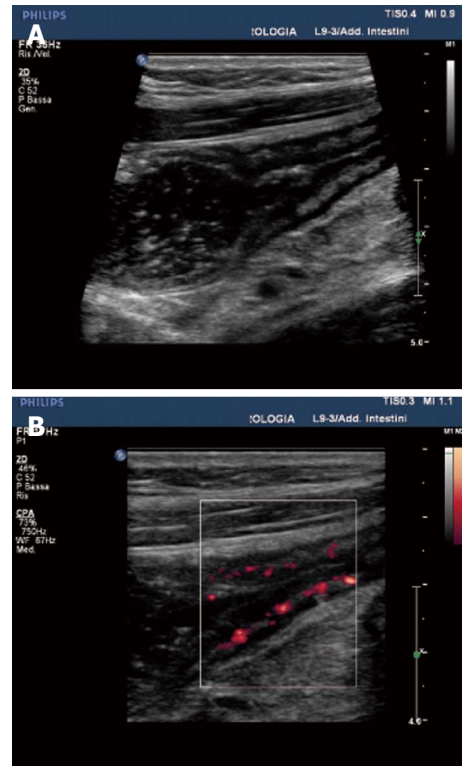
presence of pericolic abscesses. Bowel-wall thickening is usually less marked in ulcerative colitis with preserved stratification. However, definitive differential diagnosis is difficult on transabdominal sonography[35-37].

Acute terminal ileitis: Acute terminal ileitis is frequently caused by Yersinia species but also by Campylobacter and Salmonella. Tuberculous enteritis and Behcet's disease may also affect the ileo-caecal region.

The reported sonographic features include hypoechogenic mural thickening of the terminal ileum and caecum between 6 and 10 mm, with hypoechoic swollen ileal folds in the edematous mucosa, and these findings should be related to clinical and laboratory data[38,39].

Appendicitis: The typical finding of acute appendicitis on a transverse cross-section is the target sign with a hyperechoic centre, an inner hyperechoic ring and an external, thicker hypoechoic ring. In sagittal images, the inflamed appendix is seen as a blind-end, non-compressible tubular structure. Focal or circumferential loss of the inner layer of echoes usually indicates gangrenous inflammation and ulceration of the submucosa. Several studies achieved sensitivities of 80%-93% and specificities of 94%-100% in the sonographic workup of acute appendicitis[40,41].

Graded compression sonography has gained widespread acceptance as a useful technique for the examination of patients with atypical signs of appendicitis[42].

The diagnosis can be established with confidence if the appendix is non-compressible, shows no peristalsis, and measures more than 6 mm in diameter on axial images, and if compression leads to a localised pain response[43].

A statistically significant association has been found between perforation and two sonographic findings: loculated pericaecal fluid and loss of the echogenic submucosa[44].

Small bowel tumours: The gut is the most common extranodal site of lymphoma after the stomach[45]. Eighty percent of gastrointestinal lymphomas have B-cell origins. In patients with underlying coeliac disease, however, a T-lymphocyte origin predominates. In most patients, the US appearance is characterised by transmural hypoechoic wall thickening up to 4 cm in diameter with loss of normal stratification and a central hypoechoic region. This pattern is known as the "pseudokidney" sign[46,47].

Isolated mucosal involvement is rare and leads to hyperechoic thickening of the mucosa. Sonographic patterns favouring the diagnosis of a non-Hodgkin's lymphoma over adenocarcinoma are transmural, circumferential, hypoechoic wall thickening with preserved peristalsis, lack of intestinal obstruction, involvement of a long stretch of the gut and the presence of multiple prominent lymph nodes[48].

Carcinoid is the most frequent small bowel tumour and occurs in 80% of cases in the distal ileum. Usually,
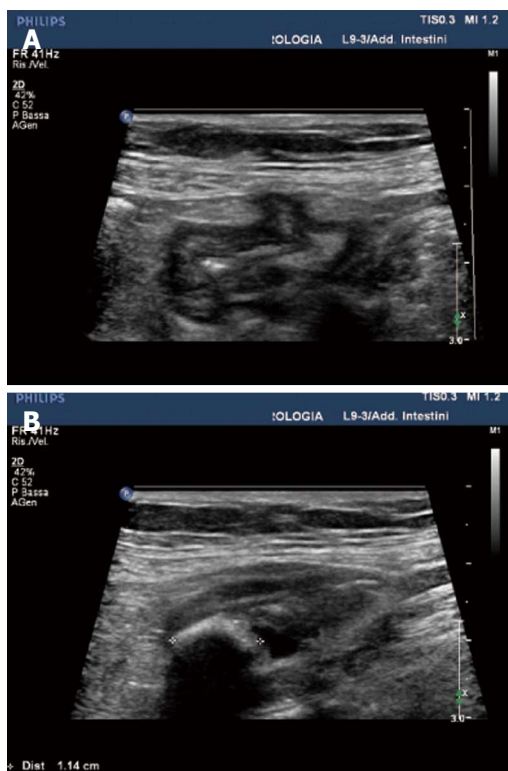
Figure 4 Diverticular disease. A: Reflective outpouchings adjacent to the colonic wall; B: Acoustic shadowing outside the lumen indicating the presence of a coprolith.

small bowel carcinoids appear as hypoechoic, homogenous, predominantly intraluminal masses with smooth intraluminal contours. The tumour is attached to the wall with a broad base, leading to interruption of the submucosa and thickening of the muscularis propria[49].

Pseudomembranous colitis: The sonographic findings of pseudomembranous colitis (PC) have been described in a number of reports. Striking thickening of the colonic wall with a wide inner circle of heterogeneous medium echogenicity surrounded by a narrow hypoechoic muscularis propria is found in all patients, reflecting the submucosal oedema. The lumen of the colon is almost completely effaced by the mural oedema, and 64%-77% of patients have ascites[50,51].

Diverticulitis: The sensitivity of US in the diagnosis of acute colonic diverticulitis ranges from 84% to 100% in different studies and is similar to the sensitivity of CT. US features of diverticulitis are the presence of colonic outpouchings associated with bowel-wall thickening and severe local pain induced by graded compression.

Diverticula are round or oval echogenic foci observed in or next to the gut wall, mostly with internal acoustic shadowing[52-56] (Figure 4).

Colonic carcinoma: There are two possible sonographic appearances of colonic carcinoma. The first is a localised hypoechoic mass up to 10 cm or more with an irregular

shape, lobulated contours and a cluster of high-amplitude echoes (the intramural gas) located eccentrically. The second appearance is a segmental and irregular thickening that could be eccentric or circumferential but is less evident than the first type. The central echo clusters are small because the diseased lumen is usually narrow. This type frequently leads to colonic obstruction. Rectal carcinoma is observed only when the bladder is well-filled[57-60].

Shirahama *et al*[61] described four sonographic findings associated with colonic carcinoma in 90% of patients: localised colonic wall thickening with heterogeneous low echogenicity, irregular contour, lack of movement on real-time scanning, and the absence of the layered appearance of the colonic wall. However, negative findings during sonographic examination do not rule out the diagnosis of colonic carcinoma because small masses and overlying bowel gas can lead to false-negative results. Because of these limitations, abdominal sonography cannot be an effective screening technique in colon cancer[57,62].

Intussusception: Intussusception has a characteristic appearance, and it is usually not mistaken for other bowel abnormalities. Transverse sections reveal a swirled pattern of alternating hyperechogenicity and hypoechogenicity, representing alternating layers of mucosa, muscularis, and serosa: the "doughnut" or "bull's eye" sign[63,64]. On longitudinal sections, alternating loops of bowel and a loop-within-loop have a sandwich-like appearance (pseudokidney sign). The outer hypoechoic ring is formed by the intussuscipiens and the everted returning limb of the intussusceptum with their mucosal surfaces face-to-face. The centre of the intussusception varies with the scan level. At the apex, the centre is hypoechoic because of the entering limb of the intussusceptum. At the base, the entering bowel wall forms a hypoechoic centre that is surrounded by the hyperechoic mesentery[65,66].

Perfusion of the bowel wall: The role of colour-power Doppler and CEUS

Colour and power Doppler techniques may provide additional information about the macrovascularisation of the bowel wall. In particular, colour and power-Doppler may be helpful in differentiating among ischaemia, inflammation and cancer neovascularisation. The differential diagnosis is possible because ischaemia is characterised by few or no signals, inflammation is characterized by several signals with low resistivity index (RI) (< 60) and symmetric thickening, and cancer neovascularization is characterised by several signals with a high RI (> 60) and asymmetric thickening[67].

CEUS has recently gained increasing attention because it clearly improves the visualisation of perfusion in various tissues. The development of second-generation, contrast-enhancing agents used in low-mechanical-index harmonic US has enabled real-time assessment of the microvascular circulation and quantification of bowel vascularity[68-70].

US contrast agents consist of micro-bubbles (1-7

micrometres), often made of a phospholipid shell with a gaseous content that are given intravenously and excreted through the lungs. Obviously, the individual capillaries cannot be discerned, but the micro-bubble content gives rise to a signal "wash" with an intensity that is proportional to the micro-bubble concentration and thus to the blood volume in the portion of the tissue[71]. This technique has led to important new applications for US. The essential tool is the transit or wash-in, wash-out curve, often referred to as a time-intensity curve (TIC), in which the time course of the transit of micro-bubbles is measured, hence the term "dynamic contrast-enhanced US" (DCE-US). Two categories of information are available from these TICs: results, that depend on timing events such as the arrival time and the time to peak enhancement, and results that depend on the amount of enhancement detected such as the peak enhancement and the area under the TIC.

Such micro-bubble studies have been used to assess inflammatory diseases, giving important information about the severity of the inflammation and its response to therapy[72-83].

IBD: CD and ulcerative colitis: IBD is associated with hypervascularity of the bowel wall during active disease.

In patients with CD, CEUS is useful for assessing the pattern of neovascularisation within the intestinal layers, allowing better discrimination between active and inactive disease, between inflammatory and fibrotic strictures, and between inflammatory pseudo-tumours and abscesses[84-89].

In particular, Serra *et al*[84] prospectively evaluated the vascularisation of the thickened terminal ileum in CD patients using CEUS and compared the clinical activity as measured by the CD activity index (CDAI) with the CEUS findings. They used two parameters to assess the vascularisation of the bowel wall: a semi-quantitative method, the pattern of enhancement; and a quantitative method, the E/W ratio, which is the ratio between the major thickness of the enhanced layer (E) and the thickness of the entire wall section (W). The results showed a significant correlation between CDAI and the pattern of enhancement. In particular, the frequency of active patients (CDAI > 150) was significantly related to the enhancement of the entire wall section and the submucosal enhancement. A positive correlation was observed between the E/W ratio and the CDAI values[84].

Migaleddu *et al*[90] demonstrated that DCE-US might help in characterising bowel-wall thickening by differentiating fibrosis, oedema and inflammatory neovascularisation and may help to grade disease activity by assessing the presence, initial site, direction and distribution of enhancement.

De Franco *et al*[91] assessed microvascular activation in the thickened terminal ileal wall in patients with CD using CE-US and evaluated its correlation with a composite index of CD activity (CICDA), the CDAI and the simplified endoscopic score for CD (SES-CD). In this study, unlike the two previously discussed studies, the authors evaluated the mural microvascularity with a quantitative method, analysing software-plotted time-enhancement intensity curves to determine the maximum peak intensity (MPI) and wash-in slop coefficient (β). The MPI and β coefficient were significantly increased in patients with CICDA, CDAI and SES-CD scores indicative of active disease[91].

The introduction of new drugs such as immunomodulators or biological therapies such as monoclonal anti-TNF alpha antibodies in the treatment of CD has led to a need for non-invasive methods to assess the efficacy of pharmacologic treatment. A recent study demonstrated that CEUS could be suitable for evaluating changes in bowel wall vascularisation during anti-inflammatory therapy[92]. In this study, all of the kinetic parameters (slope, time to peak, and area under the curve) developed from TICs showed significant changes after treatment and were correlated with the CDAI score.

Acute appendicitis, acute terminal ileitis, diverticulitis, colitis: In these inflammatory pathologies, especially in the early stages, it is possible to find increased vascularisation with both colour-Doppler and CEUS techniques. The presence of visible hyperaemia or increased flow in the hypoechoic muscular layer of the bowel wall may be a marker of appendicitis, whereas increased flow in the mucosal layer most likely represents enteritis. Increased flow in the fat surrounding the appendix is indicative of transmural extension of the inflammation with mesenteric response. The absence of blood flow indicates gangrenous change or paracolic abscess formation[93].

Ischaemic disease: In chronic ischaemia of the small bowel, stenotic or occlusive lesions in the coeliac and/or mesenteric arteries are found, and patients typically have postprandial epigastric pain and weight loss. In acute ischaemia, during the first hour, little or no signal from colour-Doppler or echo-enhancing contrast US can be observed. If the ischaemia has lasted a few hours, dilated bowel loops and a thickened bowel wall can be observed, but these signs are non-specific, and the examination is often made difficult by increasing amounts of intraluminal air.

However, Doppler scanning is not the method of choice for diagnosing acute ischaemia of the small bowel because it does not permit the evaluation of the compensatory collateral circulation and distal embolisation. Thus, angiography must be performed for a definite diagnosis[94,95].

Neoplastic disease: Colour-Doppler and CEUS are not the techniques of choice for the diagnosis of tumours or to differentiate between benign and malignant neoplasia, but, because the tumours are often highly vascularised, these techniques may be helpful to differentiate between tumours and other benign lesions such as abscesses, cysts, and haematomas.

A finding of arterial enhancement with rapid wash-out on CEUS or arterial signs with an RI > 60 on Doppler are highly indicative of a malignant lesion. DCE US with time-intensity curves has recently been used to evaluate tumour responses to anti-vascular therapy[83].

Extra-intestinal structures: perienteric fatty tissue, mesenteric lymph nodes and adjacent organs

Several intestinal pathologies may involve other structures around the diseased segment such as perienteric fatty tissue, mesenteric lymph nodes, and adjacent or distant organs. The discovery of these findings by US may be helpful for the correct diagnosis.

IBD: Peri-intestinal inflammation leads to the "creeping fat" sign, which appears as a uniform hyperechoic mass typically observed around the ileum and caecum. Mesenteric lymph adenopathy appears as multiple oval hypoechoic masses, usually in the right lower quadrant.

Some of the possible complications of CD are fistula, abscess formation, mechanical bowel obstruction and perforation. Abscesses appear as poorly defined, mostly hypoechoic focal masses that can contain hyperechoic gas. Fistulas are a hallmark of CD and appear in up to one third of patients with advanced disease as hypoechoic tracts with gas inclusion connecting bowel loops or adjacent structures (bladder, abdominal wall, vagina, or the psoas muscle). Detection of gas bubbles in abnormal locations raises the possibility of fistulous communication[96,97].

Appendicitis: The surrounding mesentery is often inflamed, which can appear as a hypoechoic diffuse halo sign around the appendix.

The presence of a generalised adynamic ileus associated with the presence of free fluid should raise suspicion of perforating appendicitis, even if the appendix has not been found to be enlarged.

Abscess formation is the major complication of a perforating appendicitis. Abscesses may extend into the pelvis or into the peritoneal spaces of the upper abdomen. They may appear as a complex inflammatory mass or localised complex fluid collection. This appearance is indistinguishable from perforated bowel neoplasm. Mesenteric lymph adenopathy may be visualised as multiple oval hypoechoic masses, usually in the right lower quadrant[98].

Diverticulitis: The sonographic features of acute colonic diverticulitis include inflammatory changes in the pericolonic fat that appear as ill-defined echogenic masses adjacent to the involved thick-walled colonic segments. The most common complication of acute colonic diverticulitis is perforation with abscess formation: this condition is suggested by the presence of an associated localised complex fluid collection.

It is important to note that although sonography can be used to diagnose uncomplicated diverticulitis with excellent sensitivity and specificity, CT remains the technique of choice for further evaluation of acute colonic diverticulitis, particularly for the assessment of complications such as abscess formation, fistulas, and perforations[52,56,99,100].

Neoplastic disease: Malignant neoplasia, especially at advanced stages, can extend beyond the intestinal wall to involve perienteric tissues such as in peritoneal carcinomatosis.

The presence of regional malignant lymph adenopathy is highly suggestive of malignant disease. Malignant lymph nodes are larger than 1 centimetre and can measure up to several centimetres. They are round but may colliquate to form large irregular masses with necrotic areas and internal calcifications[51].

CONCLUSION

In the last decade many cross-sectional imaging techniques have evolved as superior alternatives to fluoroscopic imaging in the examination of the small and large bowels. In particular, transabdominal US may be regarded as the first imaging procedure in the diagnostic work-up and follow-up of bowel diseases. US has gained acceptance, especially in IBD, because it can provide important information including the extent and activity of the disease and the presence of complications. New sonographic techniques combined with the application of intravenous contrast agents increase the accuracy of Doppler US in evaluating bowel wall vascularisation in a real-time manner. The quantitative assessment of bowel wall vascularity by CEUS could provide a useful and simple method to assess the effectiveness of medical treatment.

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