Ultrasonographic findings in Crohn's disease

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Abstract In recent years transabdominal bowel sonography has become a first-line modality both in the diagnosis and in the follow-up of inflammatory bowel diseases, especially Crohn's disease, reaching values of sensitivity ranging from 84 to 93 %. In particular, its role is very useful in the early diagnosis of complications such as stenosis, phlegmons, abscesses and fistulae. According to the available literature the ability of US to provide information about disease activity is still under debate and further studies are necessary. In this regard, of fundamental importance is the use of additional techniques such as color- and power-Doppler and contrast-enhanced ultrasound. The purpose of this paper is to report the main sonographic intestinal and extraintestinal findings detectable in Crohn's disease.

Keywords Transabdominal bowel sonography · Crohn's disease · Color and power Doppler · CEUS · Disease activity

Riassunto Nel corso degli ultimi anni l'ecografia delle anse intestinali è andata affermandosi come metodica di prima linea nella diagnosi e nel follow-up delle malattie infiammatorie croniche intestinali, soprattutto nella malattia di Crohn, con valori di accuratezza diagnostica dell'84–93 %. In particolare il suo ruolo risulta preminente nella precoce diagnosi delle complicanze, quali stenosi, flemmoni, ascessi e fistole. In accordo con la letteratura disponibile più discussa rimane la capacità di fornire

informazioni circa l'attività di malattia ed ulteriori studi appaiono necessari. A tal proposito è fondamentale l'utilizzo di metodiche quali color e power Doppler e l'ecografia con mezzo di contrasto (CEUS). Scopo del presente lavoro è quello di riportare i principali quadri ecografici intestinali ed extra-intestinali evidenziabili nella malattia di Crohn.

Transabdominal ultrasound

In recent years, thanks to an increasing experience with the use of ultrasound (US) in the assessment of gastrointestinal diseases, transabdominal US has become a first-line, non-invasive, imaging modality in the diagnosis of inflammatory bowel disease (IBD), with a sensitivity ranging from 84 to 93 % [1, 2]. Indeed, transabdominal bowel sonography (TABS) is repeatable, cheap, efficient and virtually hazard free, although quite unspecific; taking this into account its role in primary diagnostics is to detect a pathological feature and guide further investigations. Nevertheless, on the other hand nowadays the most important indication is in the follow-up of patients known to be affected by Crohn's disease (CD). According to this approach this technique provides an early detection of intra-abdominal complications, such as stenosis, fistulae and abscesses; moreover it may be useful both in the treatment approach and in the precocious diagnosis of post-treatment (medical or surgical) recurrence, giving important prognostic information [3].

Patient examination and ultrasound technique

The patient should be examined in the supine position to help the relax of the abdominal muscles and to reduce the

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antero-posterior diameter of the abdomen, at least after 6-h fasting to diminish peristaltic movements and intraluminal air. Gradual compression with the US probe helps to reduce intraluminal air, allowing a better view.

Transabdominal bowel sonography should start with a conventional abdominal scan with a 3.5- to 8-MHz convex probe to avoid overlooking of extraintestinal causes of abdominal discomfort; in addition the use of a convex probe, providing a broad overview, allows to assess the extent of the affected bowel. The following approach consists in using a high-frequency (4–13 MHz) linear array probe with increased resolution of the intestinal wall, which is essential for the assessment of wall thickness and wall layer discrimination.

In agreement with the available literature the use of external and internal landmarks for orientation is essential; in fact almost the entire bowel is freely movable. The most common starting point is the right iliac fossa. In summary, the main points of reference are mesogastrium for the proximal small intestine, right iliac vessels for the terminal ileum, the right side for the ascending colon, epigastrium for the transverse colon, left side for the descending colon, left iliac vessels and bladder dome for the sigma and retroperitoneal or retroprostatic space for the rectum; moreover the small intestine is characterized by the presence of circular folds of Kerckring and active peristalsis, while the large intestine by haustra coli. According to our experience, the ileocecal region and the sigmoid colon are the most easily explorable regions in all patients. The right and left colon can be studied in most of cases. The right and left colonic flexures are more difficult to visualize due to their position and fixation to the diaphragm, especially the left one. The transverse colon can be easily identified, below the gastric antrum in longitudinal scan. On the other hand it is difficult to visualize the rectum and anal region using the transabdominal approach due to their pelvic location.

Ultrasonographic aspects of the normal intestinal wall

Intestinal wall usually present five different layers (Fig. 1): The first layer, which is hyperechoic, corresponds to the interface between the lumen and the superficial mucosa. The second hypoechoic layer is composed by the interface between the deep and superficial mucosa. The third layer, which appears hyperechoic and is the most involved layer in inflammatory bowel disease, is determined by the submucosa and muscularis propria interface. The fourth layer is hypoechoic and corresponds to the muscularis propria. The fifth layer represents the interface of the perivisceral serosa and appears hyperechoic [4, 5].

As described before the small intestine shows the circular folds of Kerckring (Fig. 2 A) and the colon shows the haustra (Fig. 2 B).

Fig. 1 Normal bowel wall showing 5 different layers; they are numbered from the luminal side to the surface. *Layer 1* (hyperechoic): interface echo between the lumen and the mucosa; *layer 2* (hypoechoic): mucosa; *layer 3* (hyperechoic): submucosa; *layer 4* (hypoechoic): proper muscle; *layer 5* (hyperechoic): interface echo between serosa and adjacent structures

Intestinal lumen ranges from a small diameter in the jejunum, ileum and proximal colon to a larger diameter in the sigmoid colon (n.v. ≤ 25 mm.) due to the hypertensive function of this zone [4, 5]. Intestinal wall thickness, which is one of the most important parameters in the diagnosis of IBD, is considered normal when is ≤ 3 mm. Usually we evaluate the anterior wall because of its better definition.

Color- and Power-Doppler examination

The B-mode transabdominal US of the gastrointestinal tract should always be completed with color- or Power-Doppler examination because inflammatory bowel diseases are associated with hyperaemia and neovascularization of the intestinal wall in the affected areas [4]. Color Doppler can depict the parietal vessels and using power Doppler it is possible to improve the resolution of the slow flows. Several studies showed a correlation between among color-Doppler sonographic vascularity, colonoscopy and histology of the terminal ileum and the right colon and they suggest the use of Doppler US in the follow-up of the bowel wall changes during pharmaceutical treatment [6, 7]. However, these measurements are only qualitative. Moreover pulse-wave Doppler, especially of the superior mesenteric artery (SMA), provides several quantifiable parameters; in particular through the peak systolic (PSV) and end diastolic velocity (EDV) it is possible to calculate the resistive index ($RI = [(PSV - EDV)/PSV]$). The estimated mean velocity (V_{mean}) together with the SMA diameter is used to measure the mean blood flow (MBF). It should be said that color Doppler in

Fig. 2 **a** The circular folds of Kerckring in the small intestine—longitudinal US scan; **b** normal large intestine characterized by multiple haustra—longitudinal US scan

combination with pulse-wave Doppler can be used for local RI measurements. An important aspect to emphasize is that these methods may be helpful in differentiating among inflammation and cancer neovascularization; in fact inflammation is characterized by several signals with low resistivity index (RI) while cancer neovascularization is characterized by several signals with a high RI. Pulse-wave Doppler measurements of SMA can be evaluated with a convex probe, while a linear probe (7.5–14 MHz) enables to detect vessels in the GI walls [8].

Contrast-enhanced ultrasound (CEUS)

In recent years, CEUS emerged as one of the most important imaging techniques in the diagnosis and follow-up of patients with CD. It is performed given intravenously a second-generation US contrast agent consisting of phospholipid-stabilized microbubbles filled with sulfur hexafluoride (SonoVue, SV, Bracco, Italy). CEUS is non-invasive and non-ionizing, easily repeatable, well tolerated, with significant diagnostic accuracy. The contrast agent is easy to use and carries no risk of nephrotoxicity. The only absolute contraindication to the use is severe cardiomyopathy [9]. CEUS can characterize bowel wall thickening by differentiating fibrosis, edema and inflammatory neovascularisation and may help to grade disease activity by assessing the presence and distribution of vascular perfusion within the layers of intestinal wall.

Moreover, CEUS can discriminate between abscesses and peri-intestinal inflammatory involvement, such as phlegmons by evidence of peripheral or diffuse vascularity, respectively [10].

In conclusion CEUS can be helpful in monitoring both the clinical outcome and the response to treatment; in fact

it could provide additional findings regarding Crohn's disease activity [11].

Small intestine contrast ultrasonography (SICUS)

In the last few years, abdominal ultrasonography performed after the ingestion of an intraluminal oral contrast has been proposed as a non-invasive technique which enables visualizing the entire small bowel [12, 13], detecting not only established CD lesions but also minor changes of the intestinal wall [14], and has been shown to be comparable to radiology [15], in particular in the detection of strictures.

Table 1 Differential diagnosis between ulcerative colitis and Crohn's disease

US findings	Ulcerative colitis	Crohn's disease
Localization	Rectum/colon	GI tract (mainly terminal ileum)
Extension	Continuous	Discontinuous
Haustra coli	Absent	Absent
Bowel wall thickening	5–7 mm	5–14 mm
Echopattern	Stratified (usually)	Variable
Vascularization	Mucosal side	Transmural
Complications (stenosis, fistulae, abscesses)	Rare	Common
Mesenteric hypertrophy	Rare	Common
Intra-mesenteric lymphadenopathy	Rare	Common
Abdominal free fluid collection	Rare	Common

According to Pallotta et al. [16] SICUS seems appropriate to be indicated as an accurate method for the detection of small intestinal complications in CD; moreover it can play an important role in planning the treatment in patients affected by severe CD of small intestine. However, the diagnostic accuracy of SICUS is not known in the assessment and characterization of internal fistulas,

intra-abdominal abscesses and mesenteric involvement. It may be useful to underline that has been proven that it SICUS has higher diagnostic accuracy than transabdominal ultrasound even in inexperienced examiners [16].

Fig. 3 Marked bowel wall thickening localized at terminal ileum with (a) and without (b, c) stratified echopattern; d bowel wall thickening localized at colon with stratified echopattern and

submucosal hypertrophy; e ileo-colonic anastomosis with marked wall thickening at terminal ileum (caliper 2); colon (caliper 1) characterized by normal echopattern

US aspects in Crohn's disease

Crohn's disease (CD) can involve any part of the intestinal tract with different manifestations including inflammation, stricture or penetration, as described by the Montreal classification [17]. Nevertheless, in 90 % of patients the disease is localized at the terminal ileum and 40–55 % of the patients show an ileum and colonic involvement [5, 18]. Only 15–25 % of the patients show only colonic localization [5]. US can determine the extension of involvement by identifying the affected bowel loops, intestinal wall thickness and the partial or total loss of the multilayer pattern. In particular, the degree of bowel wall thickening and the extent of the intestinal wall involvement have been used as an index of activity in CD [19]. An important feature of Crohn's disease is the discontinuity, and the inhomogeneity of the transmural inflammation [20] is an important feature of differential diagnosis with ulcerative colitis. Limberg et al. [21] showed that sonography made possible the differentiation of colonic Crohn's disease from ulcerative

colitis in 93 % of the cases relying on features of the bowel walls. The definitive diagnosis of Crohn's disease should rely on endoscopic and histological examination of pathological tissues [20]. Table 1 summarizes the main US findings for the differential diagnosis.

We need to underline that most of false-negative results in diagnosis of CD are due to patients with only ano-rectal lesions or superficial mucosal lesions, such as aphthous ulcers or erosions; furthermore in some cases TABS is not very reliable, for example in large obese or in patients with surgical scars.

Ultrasonographic features of the intestinal wall in Crohn's disease

In agreement with the recent literature the bowel is considered to be thickened when the wall is more than 3 mm (Fig. 3).

Fraquelli et al. [22] compared different bowel wall thickness cutoff values in a meta-analysis. A sensitivity and specificity of 88 and 93 % respectively, were observed

Fig. 4 Color-Doppler examination of thickened bowel walls showing different vascular patterns: **a, b** the absence of significant vascularization; **c, d** mild degree of vascularization; **e, f** severe increased

vascular signal; **g** power-Doppler examination that reveals severe increased vascular signal

Fig. 4 continued

when a bowel wall thickness greater than 3 mm was used, and sensitivity and specificity of 75 and 97 % respectively were obtained when a threshold greater than 4 mm was used. Thus, a cutoff of 4 mm can be considered a sensible and specific limit for primary diagnosis, while a threshold greater than 3 mm can be considered a sign of active disease during follow-up [22].

Several studies showed a relation among bowel wall thickness, clinical disease activity and endoscopic findings, using the Crohn's Disease Activity Index (CDAI) at initial diagnosis and during the clinical course of CD [23, 24]. In particular, patients with a wall thickness of more than 7 mm have an increased risk of surgery [25].

Using the transverse scan, a classic sonographic finding is the so called “target sign”, with an hypoechoic rim (thickened bowel) surrounding a central hyperechogenicity due to the gas in the lumen [10].

Active CD is characterized by hypervascularization of affected areas. Color- or power- Doppler imaging of thickened wall segments can reveal an increased mucosal and/or submucosal and/or transparietal vascularization with a degree ranging from mild to severe [26]. Spalinger et al. [27] documented that hypervascularization associated with CD reflects clinical disease activity. Moreover, the authors reported that inflamed intestinal loops have a higher vessel density in comparison with bowel wall during remission.

Fig. 5 a, b After intravenous administration of US contrast agent, rich contrast enhancement (wash-in) is observed within bowel wall (b)

Fig. 6 **a** Bowel stenosis with a markedly thickened wall (up to 8.4 mm) that narrows the lumen; **b–d** different degrees of pre-stenotic dilatation (in **d** lumen diameter greater than 50 mm) with fluid and air in the lumen

Esteban et al. [28] defined three groups with different degree of vascularity using a simple scoring system: the absence of color signal, weak or scattered color signal and multiple color signal (Fig. 4).

CEUS allows an adequate and better evaluation of the increased parietal vascularization (Fig. 5). Di Sabatino et al. [29] showed an increased accuracy of TABS in CD diagnosis and follow up using intravenous Levovist injection.

Serra et al. [11] described four different patterns of enhancement: pattern 1: complete enhancement of the entire wall section, from mucosal to serosal layer; pattern 2: the absence of enhancement in the outer border of the muscularis propria; pattern 3: enhancement only of the intermediate layer; pattern 4: complete absence of enhancement within the entire wall. Migaleddu et al. [30] observed three different types of enhanced perfusion pattern of the diseased intestinal wall: a submucosal prevalent enhancement pattern, a transperietal enhancement starting from the submucosa and a transperietal enhancement pattern starting from extra-visceral vessels and secondary involving the wall of the intestinal loop with an external to internal direction. These patterns are related to the activity of CD as assessed by the CDAI index. Thus, CEUS is

Fig. 7 SICUS shows better detection of bowel's stricture

especially indicated for evaluating inflammatory activity in CD. Patients with active CD and with a thickened enhancing small bowel wall after contrast agent injection have a higher probability of positively responding to medical treatment than patients with active CD and low or absent enhancement, while patients with quiescent CD but thickened enhancing intestinal wall have a higher risk or recurrence [30]. Moreover, CEUS can characterize bowel

wall thickening by differentiating fibrosis, edema and inflammatory neovascularisation. The increase in echogenicity of the third layer of the intestinal wall (submucosal layer) is considered an expression of submucosal hyperemia or edema, while in advanced lesions with increased transperietal fibrosis CEUS shows inward transperietal enhancement starting from the extraparietal vessels [31].

Abdominal complications and extraintestinal features

US also allows the identification of extraintestinal features that may be associated with active CD, such as mesenteric fat hypertrophy, the presence of regional enlarged lymph nodes and intraperitoneal free fluid accumulation [32, 33].

Fig. 8 a–c Inflammatory stenosis characterized by hypoechoic thickened wall with loss of stratification and hypervascularization at color-Doppler study (c); d–f fibrotic stenosis with maintenance of stratified echopattern, submucosal hypertrophy and no significant vascularization (e)

Since US can find both intraluminal and extraintestinal pathological features, it is a valuable tool for the detection of complications such as stenosis, fistulas and abscesses. Most patients with CD will develop intra-abdominal complications during the course of their disease. Intestinal stenosis develops in 21 % of patients with CD and they are the most frequent cause of surgery. They are usually asymptomatic until the lumen is so narrow that it causes obstruction.

A stenotic intestine has a thickened wall, a narrow lumen and reduced or no peristalsis, and is often associated with pre-stenotic dilatation greater than 25 mm in diameter, and with liquid and air in the lumen (Fig. 6).

As described before in recent years the use of the small intestine contrast ultrasonography (SICUS) has become crucial in particular in the detection of strictures (Fig. 7); in fact it has been shown to be comparable to radiology [15].

It is often difficult to differentiate between fibrotic stricture and inflammatory edema as underlying causes. If stratification is retained it suggests a fibrotic stenosis while the loss of stratification is associated with inflammation [34]. According to Maconi et al. [34] the reduced echogenicity in the hypoechoic pattern should be referred to hyperaemia and neovascularization related to the increased inflammatory response rather than oedema. On the other hand the stratified echo pattern is secondary to collagen deposition, especially in the submucosa; this is the reason of the common absolute and/or relative hypertrophy of that tunica. Migaleddu et al. [10] described two different US patterns according to the clinical phase of CD: in the acute one they showed a diffuse inflammatory edema with a loss of stratification or with thickening of the submucosa, while in the chronic phase the layers are visible regardless of the bowel wall thickened. Finally, color- or power-Doppler and US contrast studies may differentiate between the hyper-vascularization of the inflammatory stenosis and the reduced vascularity of the fibrosis (Fig. 8) [35]. These concepts are even more important in relation to the different therapeutic approaches.

Fistulas are a major complication for many patients with CD, occurring in 17–82 % of patients, and are defined as a hypoechoic, duct-like, peri-intestinal lesions with a diameter smaller than 2 cm, with fluid or air content, communicating between two intestinal loops (Fig. 9) or between intestinal loops and other structures, commonly subdivided into perineal, external and internal [33, 36, 37].

Since the fistula wall is characterized by granulation tissue and neoangiogenesis, it may be recognised on US also by detecting an intramural blood flow using power-Doppler or CEUS [38]. Internal fistulas, which are asymptomatic and unrecognized, can form between intestinal loops (enteroenteric) or they end blindly in the mesentery (enteromesenteric). External fistulas, which

Fig. 9 **a** Enteroenteric fistula (caliper 1) revealed as a hypoechoic peri-intestinal duct-like lesion (diameter 3.5 mm) that connects a bowel loop (caliper 2) with wall markedly thickened (up to about 13 mm), hypoechoic and without stratification to a bowel loop with normal sonographic features; **b** color-Doppler study showing severe increased vascular signal

frequently give rise to symptoms and are more easily diagnosed, can form between intestine and the bladder (enterovesical), the vagina (enterovaginal), or the abdominal wall (enterocutaneous).

Intra-abdominal abscesses and phlegmons can occur in CD patients with a prevalence of approximately 4 % [39] usually as a complication of fistulating disease or as a consequence of surgery [40, 41]. Abscesses may be distinguished according to their site as retroperitoneal or intraperitoneal. Intraperitoneal abscesses are more common and can be defined as superficial, when they are adjacent to the abdominal wall, or deep if they are localized between the intestinal loops and the mesentery [42]. US is useful for an initial screening; abscesses appear as hypoechoic or anechoic masses with peripheral blood flow at color Doppler, which is expression of fluid collection, in close relation to a pathological intestinal loop (Fig. 10).

The shape of the cavity walls, the presence of debris, internal echogenicity, and the presence of gas within fluid collections all may suggest infection. On US phlegmons are ill-defined hypoechoic masses without wall and with

Fig. 10 a–d Intra-abdominal abscesses (white arrow) occurring in US as an hypo-anechoic lesion characterized by irregular outlines, internal echoes due to the presence of air or debris, a mild posterior

echo enhancement and no internal vascular signals using color-Doppler examination (c)

internal color signals on color Doppler [43]. CEUS can be used in the differential diagnosis; using CEUS phlegmon shows intralesional enhancement, while abscess shows the absence of enhancement in the hypoechoic mass [44]. However, an absolute diagnosis cannot be made and computed tomography is considered the study of choice for the diagnosis [41]. It is crucial to underline that there are very important implications in differentiating between abscess and phlegmon, in particular in consideration of the different treatments (surgical or medical).

As described before the mesentery that surrounds involved loops is often thickened (Fig. 11) and contains enlarged lymph nodes (Fig. 12). The mesentery consists of fibrofatty tissue, so the normal sonographic appearance consists of fixed thin hyperechoic areas that surround the bowel loops. In case of inflammation it becomes thickened (“hyperechoic halo”), and encloses and separates from each other the involved intestinal loops.

Maconi et al. [45] showed that enlarged mesenteric lymph nodes are found more frequently in young patients ($p < 0.0001$) and with a shorter disease duration; in

particular age, disease’s duration and the presence of internal fistulas or intra-abdominal abscesses have been demonstrated to be the best independent predictive factors linked to the presence of enlarged mesenteric lymph nodes. Although this feature have been thought to be related to increased disease activity, we must emphasize that there are a few studies that show a significant correlation and further are needed. In quiescent CD, mesentery hypertrophy does not seem to be a risk factor of relapse [45].

In the end, another US finding in Crohn’s disease may be the presence of free fluid between bowel loops; usually it assumes a typical triangular appearance (Fig. 13). Nowadays there are no studies about the prevalence and the clinical value of this ultrasonographic feature.

Conclusions

In agreement with the available literature, our large series allows us to assert that transabdominal bowel sonography,

Fig. 11 **a, b** Mesentery surrounding affected bowel loops thickened, hyperechoic and fatty expression of secondary perivisceral inflammation

in addition with color and power Doppler, CEUS and SI-CUS is very useful both in diagnosis and mainly in the follow up of Crohn's disease. In fact in the initial diagnosis, US, although not specific, is sensitive and can quickly direct further investigations; on the other hand in the follow-up it is able to assess site and extension of disease and rapidly detects complications, also extraintestinal. Maconi et al. [3] report that almost all correlations between US findings of the bowel wall and disease severity are weak and of limited value in clinical practice; taking this into account it is interesting to underline that our group suggested an US score (CDUS: Crohn's Disease Ultrasonographic Score) for disease activity and showed a statistically significant correlation with the SES-CD (Simple Endoscopic Score for Crohn's Disease) [46]. In our opinion, further studies are needed to validate this method and to find other useful correlations.

In conclusion, for this reason we emphasize that, although colonoscopy represents the gold standard in CD, ultrasound, such as CT and MRI, can provide information not only concerning the luminal side of the

Fig. 12 **a, b** Multiple intra-mesenteric lymph nodes (calipers); these are hypoechoic, thin, elongated and with hilar vascularity on color Doppler to report to acute inflammatory lymphadenopathy

Fig. 13 Free fluid between intestinal loops (white arrow) that assume a typical triangular appearance; the bowel wall is markedly thickened

bowel but also about the serous one and the peripheral structure; moreover US is repeatable, safety and well-accepted, but unlike CT is radiation-free and unlike MRI is cheap, virtually hazard free for all patients, without contraindications.

Conflict of interest Gabriella Carnevale Maffè, Laura Brunetti, Pietro Formagnana, Gino Roberto Corazza declare that they have no conflict of interest.

Informed consent No patient information was included in this study.

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