Crohn's Disease

Giovanni Maconi

Contents

Abstract

Intestinal ultrasound has been proven to be a useful as a screening tool in patients with clinically suspected Crohn's disease as well as in the follow-up of patients already diagnosed with Crohn's disease. In these patients, it is possible to assess the site and extent of the lesions and ensure early detection of intra-abdominal complications, in particular abscesses and strictures. Intestinal ultrasound may be also used for monitoring Crohn's disease following surgery, revealing early recurrence of the disease and suggesting the clinical and endoscopic outcome. Despite several attempts to correlate the ultrasonographic findings with Crohn's disease activity, to date, only ultrasonographic assessment of endoscopic activity is convincing.

1 Introduction

Abdominal ultrasound (US) thanks to its accuracy, good repeatability and noninvasiveness is currently employed in many chronic inflammatory conditions, not only for purely diagnostic purposes, but also for management of the disease. In Crohn's disease (CD) patients, US has become the first-line imaging procedure for early diagnosis of the disease (Parente et al. 2004a), and more frequently for the follow-up, to detect intra-abdominal complications (strictures, fistulae and abscesses), to assess activity and monitor the course of disease, as a prognostic index of recurrence (Table 1).

2 Pathological Features

Crohn's disease is a chronic granulomatous inflammatory condition of the alimentary tract of unknown origin. Although there are no pathognomonic features of the disease, it is characterised by a segmental and transmural

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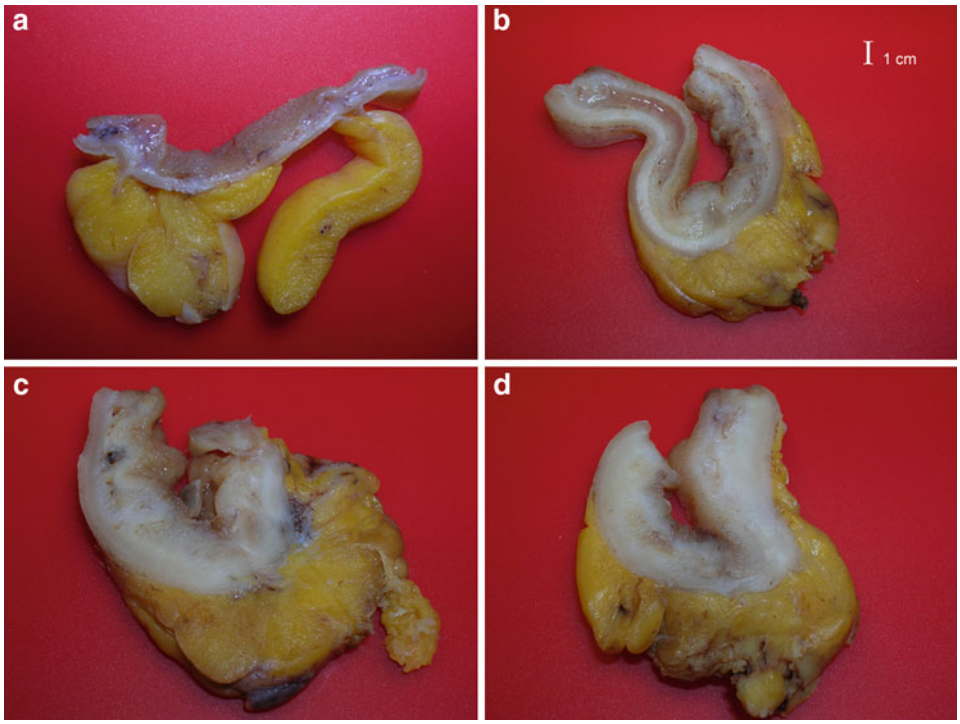


Fig. 1 Opened transverse sections of a normal ileal wall (**a**); thickened bowel wall in a CD patient with loose (*left side*) and markedly inflamed (*right side*) submucosa (**b**); markedly thickened bowel wall with fibrosis and loss of stratification (**c**,**d**). (Courtesy by dr. Paolo Fociani, Department of Pathology, 'L. Sacco' University Hospital, Milan)

Table 1 Indications for bowel US in CD

Early evaluation of patients with suspected CD
Evaluation of site and extension of CD
Differential diagnosis between chronic inflammatory colitis
Diagnosis of CD abdominal complications
Stenosis and intestinal occlusion
Internal and external fistulae
Intra-abdominal abscesses
Perforation and toxic megacolon
Assessment of CD activity
Post-operative follow-up and prediction of CD recurrence

inflammation of the intestinal wall, particularly ileum (30 %), colon (20 %) or both the large and small bowel (50 %). Macroscopically, the bowel wall often appears greatly thickened, and hypo-elastic or stiff with luminal narrowing (Fig. 1).

Mucosal abnormalities consist of longitudinal and aphtous ulcerations, which, in advanced disease, may penetrate into the submucosa and muscularis leading the serosa and outside, creating fissures and fistulas. These may invade the adjacent loops, organs, skin or end blindly in the mesentery, sometimes resulting in intra-abdominal or retroperitoneal abscesses. The mesentery is often thickened and fatty, surrounding the thickened walls and containing enlarged lymph nodes.

3 Ultrasonographic Features of Bowel Walls

The abnormalities of bowel wall include bowel wall thickening, alterations of bowel wall echopattern, hyperemia, loss of elasticity and peristalsis, creeping fat and mesenteric lymph nodes. Intra-abdominal complications of CD typically include stenoses and obstruction, fissures and fistulae, inflammatory masses (phlegmon or abscesses).

3.1 Bowel Wall Thickening

US examination in CD patients frequently reveals stiff and thickened bowel walls, usually >4 mm (which is considered the limit of normal bowel wall for the ileum and colon) up to 15 mm. The wall thickness of a diseased segment is measured in a transverse section from the central hyperechoic line of the lumen (representing interface between content of the lumen and the mucosa) to the outer hyperechoic margin of the wall (representing the serosa) (Fig. 2). Literature usually considers the maximum bowel wall thickness, that can be reproduced along the bowel wall for at least 2–4 cm.

The abnormal thickening of bowel walls is the most widely and commonly US finding reported in the literature

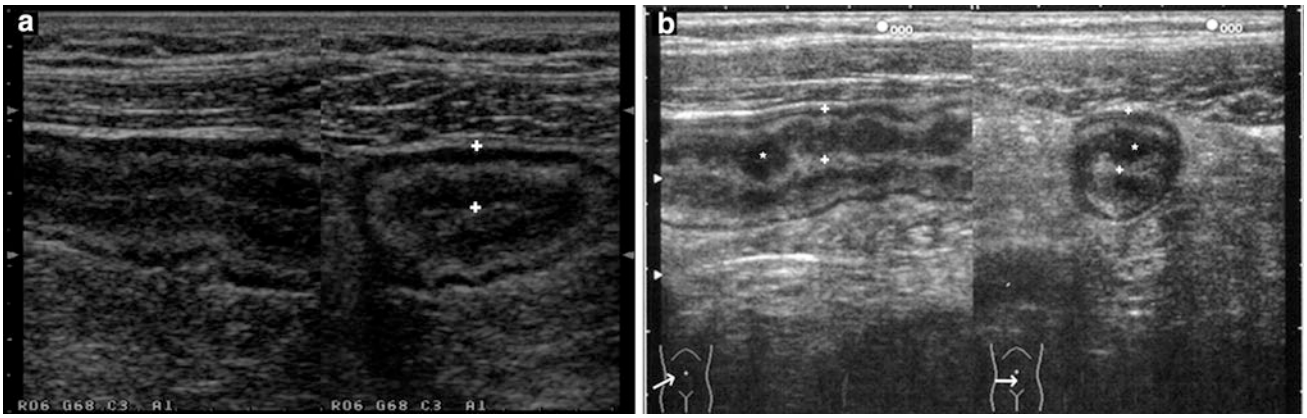


Fig. 2 **a**, **b** Longitudinal (*left*) and transverse (*right*) sections of a thickened bowel wall characterised by stratified echopattern showing the markers (+) on the inner hyperechoic line (lumen) and outer hyperechoic margin (serosa) of the thickened wall. (* = gross nodularity of the mucosa)

to diagnose CD. In a meta analysis aiming at evaluating the impact of different cut-off values of bowel wall thickening (3 vs 4 mm) in determining the presence of CD, it has been shown that when a >3-mm cut-off level was observed for abnormality, sensitivity and specificity were 88 and 93 %, respectively, whilst when a cut-off level of >4 mm was used sensitivity was 75 % and specificity 97 % (Fraquelli et al. 2005). The accuracy of US in detecting CD has been also compared with that of other cross-sectional imaging techniques, in a systematic review. This study showed that US has high accuracy for evaluation of suspected CD (overall per-patient sensitivity and specificity: 85 and 98 %, respectively), comparable to that of magnetic resonance imaging (MRI) (overall per-patient sensitivity and specificity: 78 and 85 %, respectively) (Panes et al. 2011).

However, these remarkable data also show that intestinal US, even in expert hands, may result in false-negative and false-positive findings. False-negative findings may be in obese patients or when CD is characterised by only superficial lesions, such as rare aphtous ulcers or mucosal erosions (Maconi et al. 1996a). False-positive findings rely on the fact that thickening of the bowel walls is not specific for CD, being present also in infectious, neoplastic and other inflammatory diseases (Truong et al. 1998). Therefore, when US is used as a first imaging diagnostic procedure, the diagnosis of CD is suggested when wall thickening involves the terminal ileum, is circumferential and segmental. However, the definitive diagnosis—when possible, and always for colonic lesions—should rely on endoscopic and histological examinations of pathological tissues. US may represent a useful tool, prior to other invasive or expensive diagnostic investigations, which can be postponed in the case of negative US findings.

In CD patients, US can be usefully employed in localising CD lesions within the bowel (particularly ileal lesions, which can be detected in more than 90 %) and in assessing the length of small bowel involvement (Brignola et al. 1993; Maconi et al. 1996a; Parente et al. 2003, 2004a, 2011).

The clinical significance of the degree of thickening of diseased bowel wall in CD is controversial. Several studies attempted to establish a relationship between maximum bowel wall thickness and clinical severity (Crohn's disease activity index, CDAI) and biochemical activity (Erythrocyte Sedimentation Rate, C Reactive Protein) of CD. However, almost all the results of these studies produced weak correlations, although somewhat significant (Maconi et al. 1996a; Futagami et al. 1999; Mayer et al. 2000; Bru et al. 2001; Haber et al. 2000, 2002; Parente et al. 2003). On the contrary, the thickening of bowel wall significantly correlates with endoscopic activity of CD. It has been shown that US thickening of bowel wall has an overall high sensitivity and specificity (85 and 91 %, respectively) for the detection of endoscopic active CD (Panes et al. 2011).

Likewise, the US assessment of bowel wall thickening is useful to identify postoperative recurrences following resection, to assess the efficacy of conservative surgical treatment, and to obtain predictive data on the risk of recurrences in these patients. Postoperative endoscopic recurrences of CD may be correctly identified using bowel US in more than 80 % of patients (Di Candio et al. 1986; Andreoli et al. 1998). Moreover, US offers the possibility to assess the behaviour of diseased bowel walls following conservative surgery (namely strictureplasty and minire-section), in CD patients. In fact, in patients showing an improvement or return to normality of the bowel wall thickening 6 months after conservative surgery, the clinical and surgical recurrence rate have being significantly lower than in those maintaining the same level of bowel wall thickening (Maconi et al. 2001). Likewise, it has been shown that a high bowel wall thickness (>7 mm) at US is a major risk factor for intestinal resection (Rigazio et al. 2009; Castiglione et al. 2004).

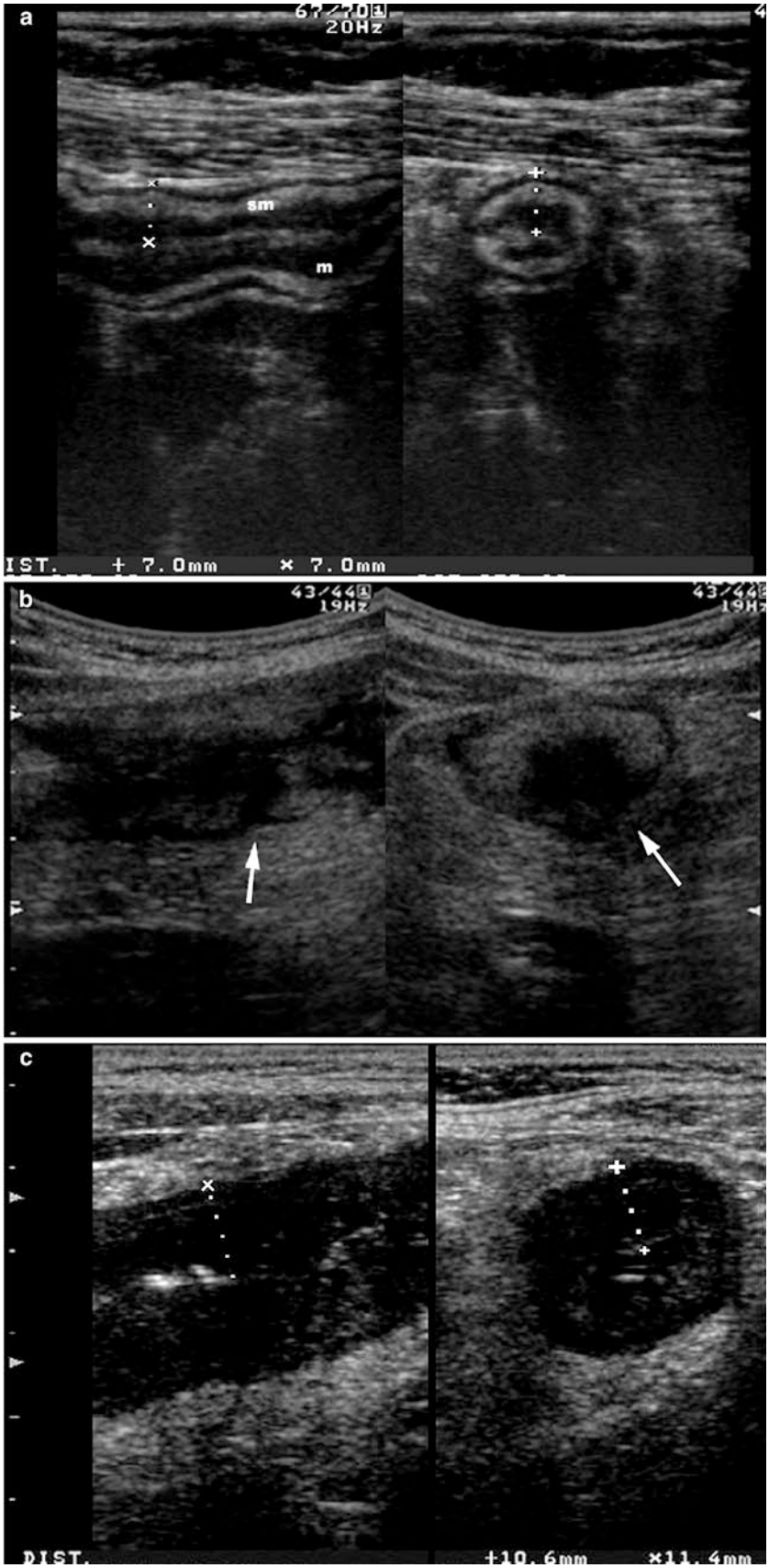


Fig. 3 Echopattern of thickened bowel walls. **a** Longitudinal (*left*) and transverse (*right*) sections of thickened bowel walls characterised by stratified echopattern with thickening of mucosal (*m*) and submucosal (*sm*) layers. **b** Longitudinal (*left*) and transverse (*right*) sections of thickened bowel walls characterised by stratified echopattern interrupted at the mesenteric side by hypoechoic areas (*arrows*), suggesting the presence of deep ulcers. **c** Longitudinal (*left*) and transverse (*right*) sections of thickened bowel walls characterised by hypoechoic echopattern with disappearance of wall stratification

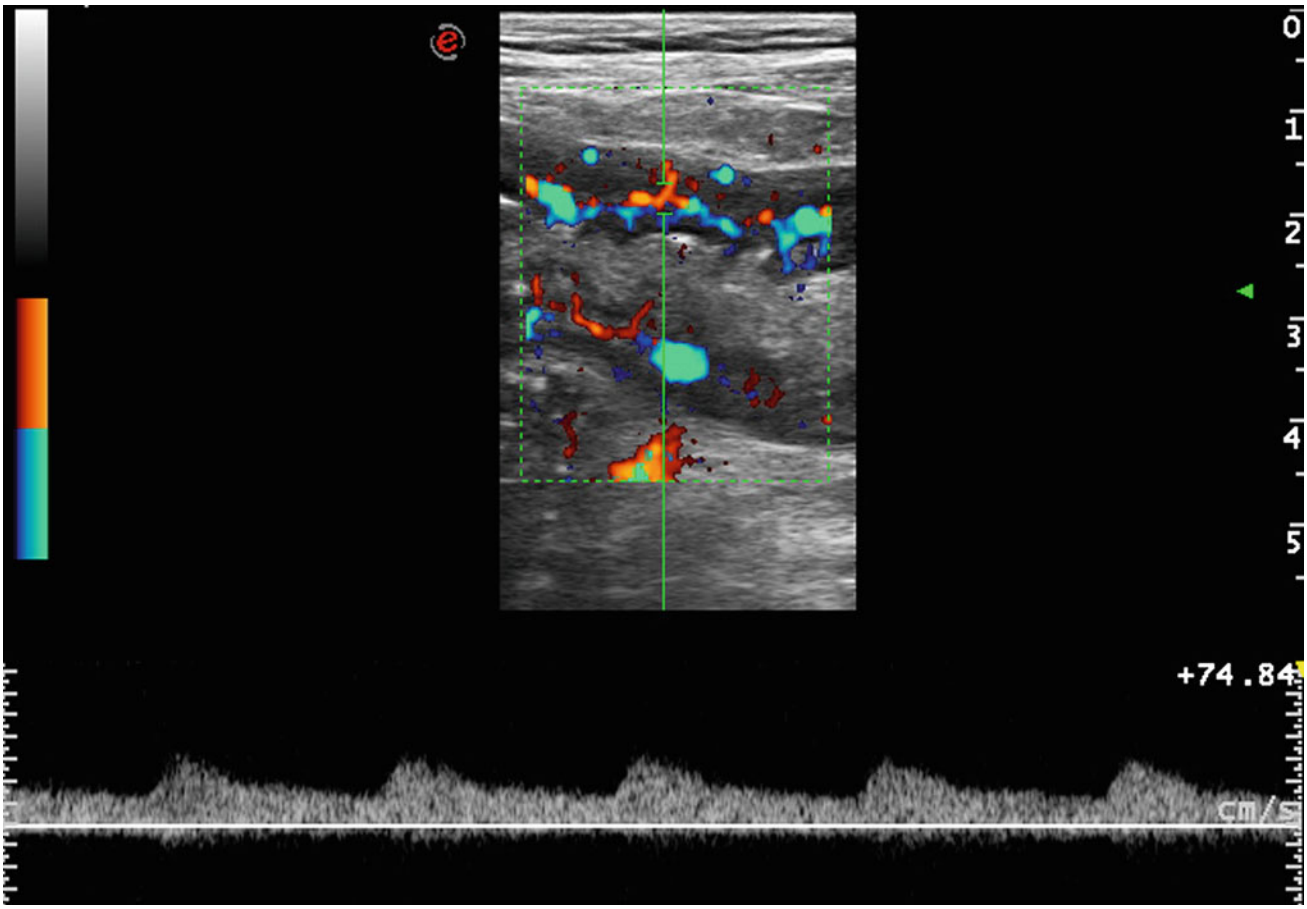


Fig. 4 Increased vascularity within the bowel wall showed by color Doppler ultrasound. Pulsed Doppler at this level detects the presence of low resistance arterial blood flow (*bottom side*)

Therefore, bowel US offers a useful alternative to invasive procedures in the postsurgical follow-up of CD patients, in particular for those CD patients who have undergone conservative surgery in whom endoscopy is not suitable to identify CD patients at high risk of clinical and surgical relapse, thus offering the opportunity to tailor the appropriate postoperative medical treatment.

3.2 Bowel Wall Echopattern

The thickened bowel wall in CD may show different echopattern. It may maintain the regular stratification (Fig. 2) or may be characterised by a partial or complete loss of layering. Sometimes, bowel segments with alternate persistence and loss of stratification, may be observed.

In stratified echopattern, the thickened walls display a variable enlargement of the mucosal, submucosal or muscular layers. Often the layer corresponding to the submucosa is thicker than others (Fig. 3a). The echo-stratification may be interrupted by hypoechoic areas (some with hyperechoic spots) corresponding to deep ulcers (Fig. 3b), or may completely disappear (Fig. 3c). The disappearance of echo-stratification indicates the presence of large, deep longitudinal ulcers associated with intense inflammation and neovascularisation (Kunihiro et al. 2004).

The clinical and pathological significance of bowel echopattern and, in particular, its importance in defining CD activity has been investigated in two studies, one of which in patients with stenosis. In vitro studies, that compared US images with the in vitro histopathological findings of related resected specimens, showed that the loss of stratification (hypoechoic echopattern) correlated with the severity of inflammation and that persistence of stratification in bowel wall of strictures suggested a high degree of fibrosis within the submucosa and *muscularis mucosae* (Hata et al. 1994; Maconi et al. 2003a). A recent study showed that fibrosis is correlated with an increase of echogenicity in the muscularis propria and a decrease of echogenicity in the submucosa (Nylund et al. 2008).

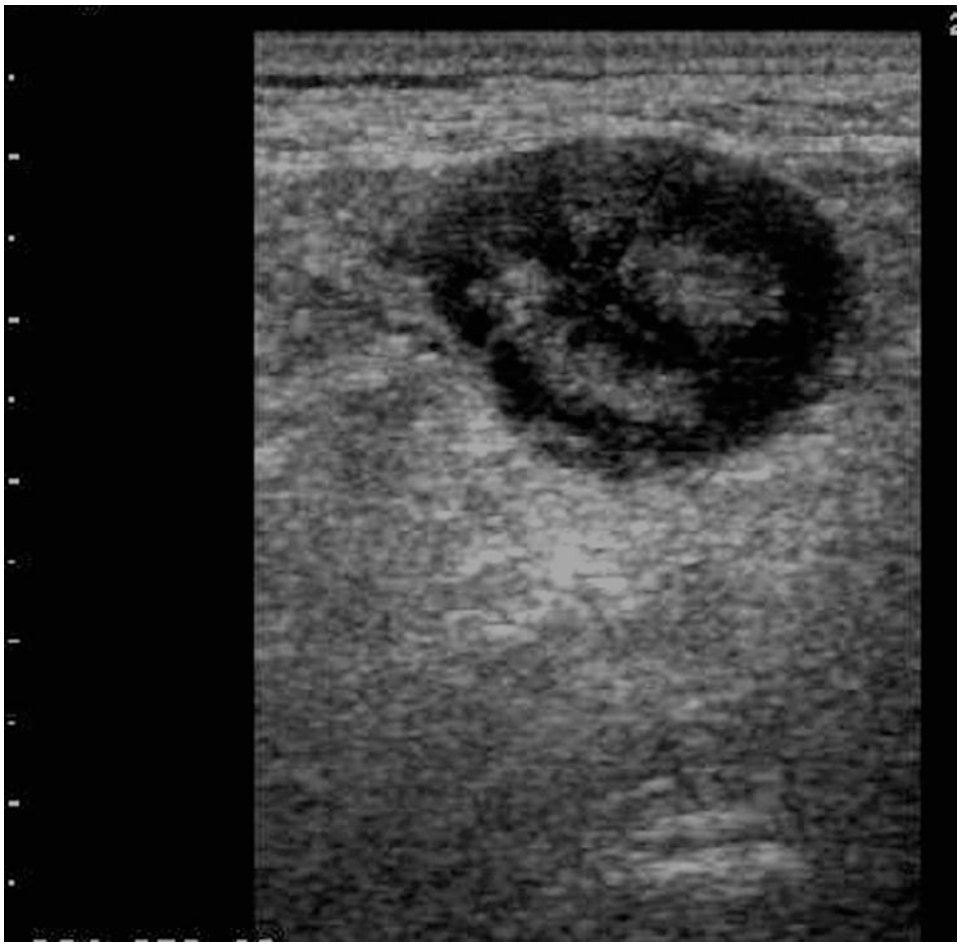


Fig. 5 Mesenteric hypertrophy, appearing at US as hyperechoic, sometimes inhomogeneous area surrounding thickened bowel walls

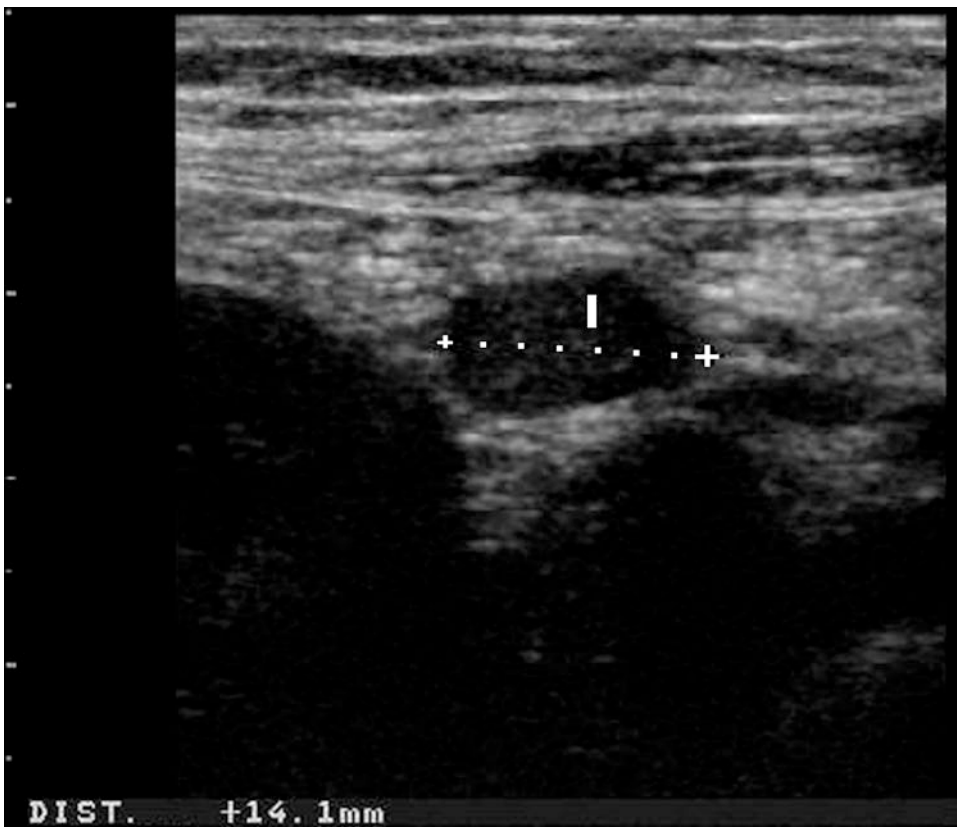


Fig. 6 Enlarged mesenteric lymph node (*l*) appearing at US as oval, homogeneous hypoechoic nodules with regular margins

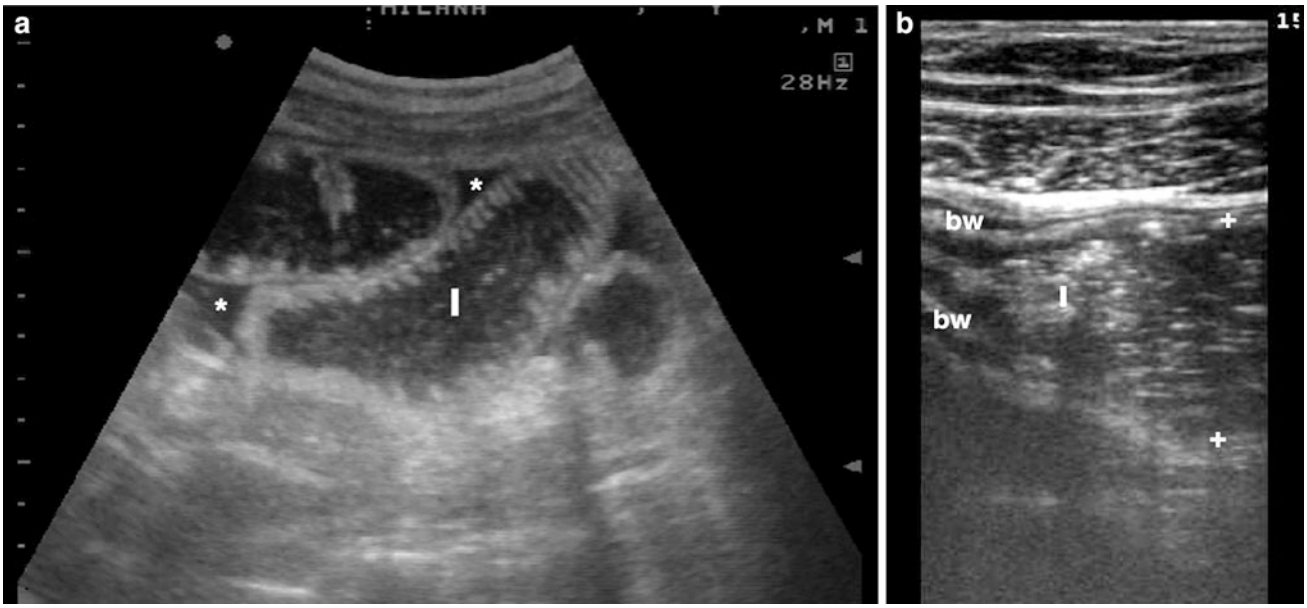


Fig. 7 Stenosis at US presented as thickened bowel wall, with narrowing of lumen associated with pre-stenotic dilatation >3 cm in diameter, and often associated with liquid content and air in the lumen. **a** Acute obstruction associated with a variable amount of liquid within the lumen (*l*) of the proximal loop, increased peristalsis and small amount of free peritoneal fluid (*asterisks*). **b** Chronic stenosis characterised by stratified bowel wall echopattern, showing an amount of gas within the proximal loop and weak peristalsis (*bw*, bowel wall; *l*, lumen)

Table 2 Sensitivity and specificity of Ultrasound, Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) in detecting stenosis, fistulae and abscesses complicating CD (modified form Panes et al. 2011)

	Ultrasound % (IC95 %)	MRI % (IC95 %)	CT % (IC95 %)
Stenosis			
Sensitivity	79 (71–84)	89 (84–92)	89 (83–94)
Specificity	92 (87–96)	94 (90–96)	99 (95–100)
Fistulae			
Sensitivity	74 (67–79)	76 (71–82)	70 (64–76)
Specificity	95 (91–97)	96 (92–98)	97 (94–99)
Abscesses			
Sensitivity	84 (79–88)	86 (79–91)	84 (78–90)
Specificity	93 (89–95)	93 (88–79)	97 (94–99)

3.3 Bowel Wall Vascularity

The increased vascularity is often observed in bowel wall with decreased echogenicity. This is likely due to hyperaemia and neovascularisation related to the increased inflammatory response (Maconi et al. 2003a; Di Sabatino et al. 2004). Therefore, vascularity within the thickened bowel walls, assessed by power-color Doppler US, has been used as an index of CD activity (Fig. 4).

Vascularity has been evaluated using a simple scoring system according to the semi-quantitative (and subjective) intensity of colour signals and/or by analysis of Doppler curves (measurement of resistive index) obtained from vessels detected within the bowel walls. However, neither of these parameters correlated well with clinical or biochemical activity in most studies, whereas often a significant correlation was often found between vascularity and endoscopical/radiological activity (Spalinger et al. 2000; Esteban et al. 2001; Haber et al. 2002; Heyne et al. 2002; Scholbach et al. 2004; Neye et al. 2004; Yekeler et al. 2005).

The vascularity of diseased bowel walls in CD has been recently assessed by US i.v. contrast agents. This issue will be widely discussed elsewhere (see "Intravenous contrast-enhanced bowel ultrasound").

3.4 Elasticity and Peristalsis

Thickened bowel walls in CD may be associated with reduction or absence of peristalsis in the small bowel and loss of haustra coli in the colon (Sarrazin and Wilson 1996; Di Mizio et al. 2004). Although this manifestation is quite subjective and difficult to quantitatively assess, it has been regarded as relevant sign in most US studies, probably because associated with intestinal stenosis. Waiting for the

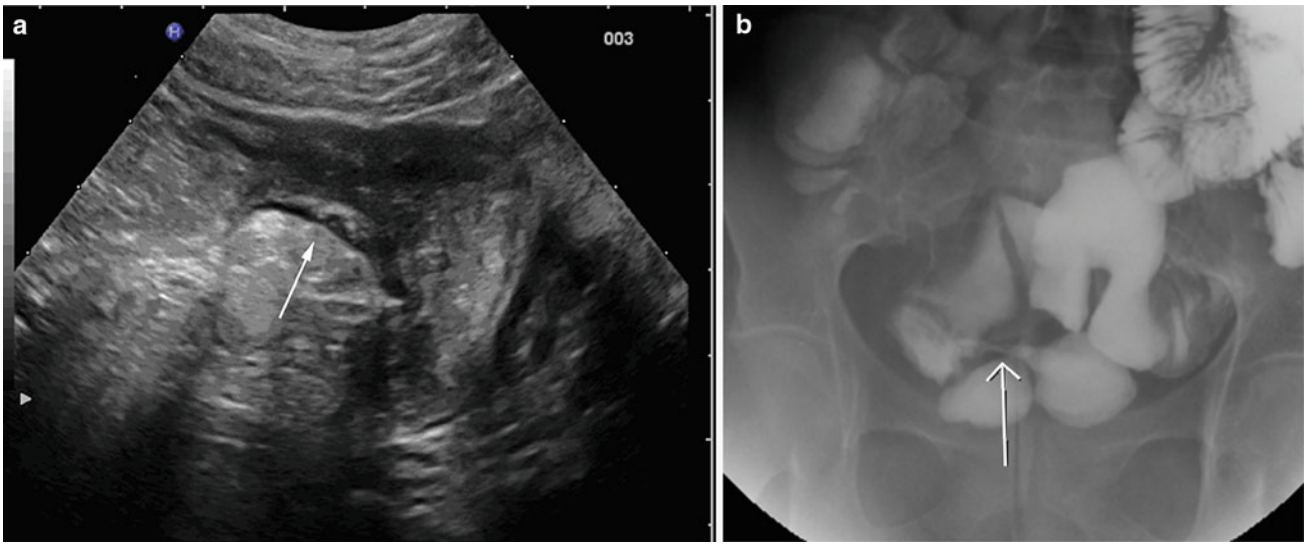


Fig. 8 **a** Longitudinal section of the bowel wall showing mixed (hypoechoic and stratified) echopattern at level of a short stenosis (*arrow*). **b** Correspondent radiographic imaging of the same stricture (*arrow*) given small bowel enteroclysis

results of US elastography (see "Imaging of Tissue Elasticity in Gastrointestinal Disorders"), oral contrast agents may be used for a more accurate US assessment of this feature (Parente et al. 2004b).

3.5 Mesenteric Hypertrophy and Mesenteric Lymph Nodes

Mesenteric hypertrophy (also named mesenteric fibrofatty proliferation or creeping fat) appears at US as hyperechoic, sometimes inhomogeneous area surrounding thickened bowel walls (Fig. 5). It is found in up to 50 % of CD patients (Goldberg et al. 1983; Maconi et al. 2008) and is correlated with biochemical and clinical activity of CD and with internal fistulas and increase bowel wall thickness (Maconi et al. 2008).

Enlarged mesenteric lymph nodes appear at US as oval, homogeneous hypoechoic nodules with regular margins (Fig. 6). This is a frequent finding in CD patients, in particular in young CD patients, in an earlier phase of CD and in patients with septic complications such as internal fistulas and abscesses. Its prevalence and clinical significance is discussed elsewhere in this book (see "Mesenteric Lymphadenopathy").

4 Crohn's Disease Abdominal Complications

The clinical course of CD is often characterised by abdominal complications such as stenosis, fistulae or abscesses and rarely by free perforation.

4.1 Stenosis and Intestinal Occlusion

Stenosis develops in 21 % of patients with ileal CD and in 8 % of those with ileocolic disease (Fenoglio-Preiser et al. 1989; Simpkins and Gore 1994). It is the most frequent cause of surgery. The diagnostic gold standard of this complication is contrast radiography that reveals all the occluded sites, the degree of intestinal narrowing and the length of the stenotic segments.

Bowel stenosis can be revealed by US as thickened bowel walls, associated with narrowed lumen and increased diameter of the proximal loop >2.5–3 cm. Acute stenoses are often associated with a variable amount of liquid and gas within the lumen of the proximal loop and with increased peristalsis (Fig. 7a) (Ko et al. 1993). In chronic, non-occlusive, stenoses the amount of air within the proximal loop prevails, and peristalsis is usually weak (Fig. 7b).

Using this definition, US correctly diagnoses stenosis in 70–79 % of unselected CD patients and in >90 % of patients with severe intestinal stenoses needing surgery, with false-positive diagnoses limited to 7 % (Maconi et al. 1996b; Gasche et al. 1999; Parente et al. 2002, 2004b). Results may be even better using an oral contrast agent (see "Intravenous Contrast-Enhanced Bowel Ultrasound") and are comparable to those of MRI and computed tomography (Table 2; Panes et al. 2011).

US assessment of the echopattern of the bowel wall of the strictures may also offer an insight into the histological features, discriminating between fibrotic and inflammatory strictures (Maconi et al. 2003a). Loss of stratification of the bowel wall at the level of the stricture suggests its inflammatory nature with a low degree of fibrosis, whilst the

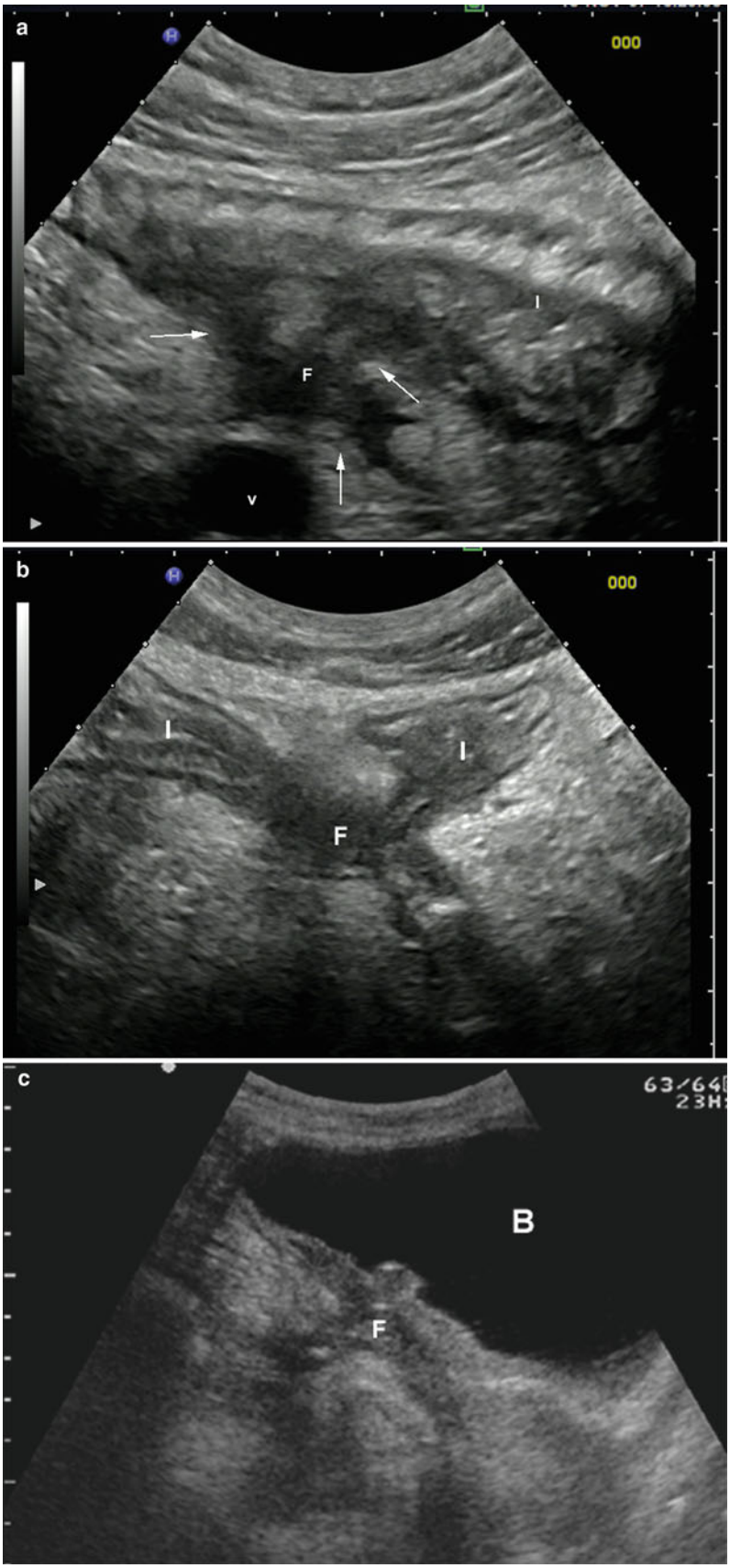
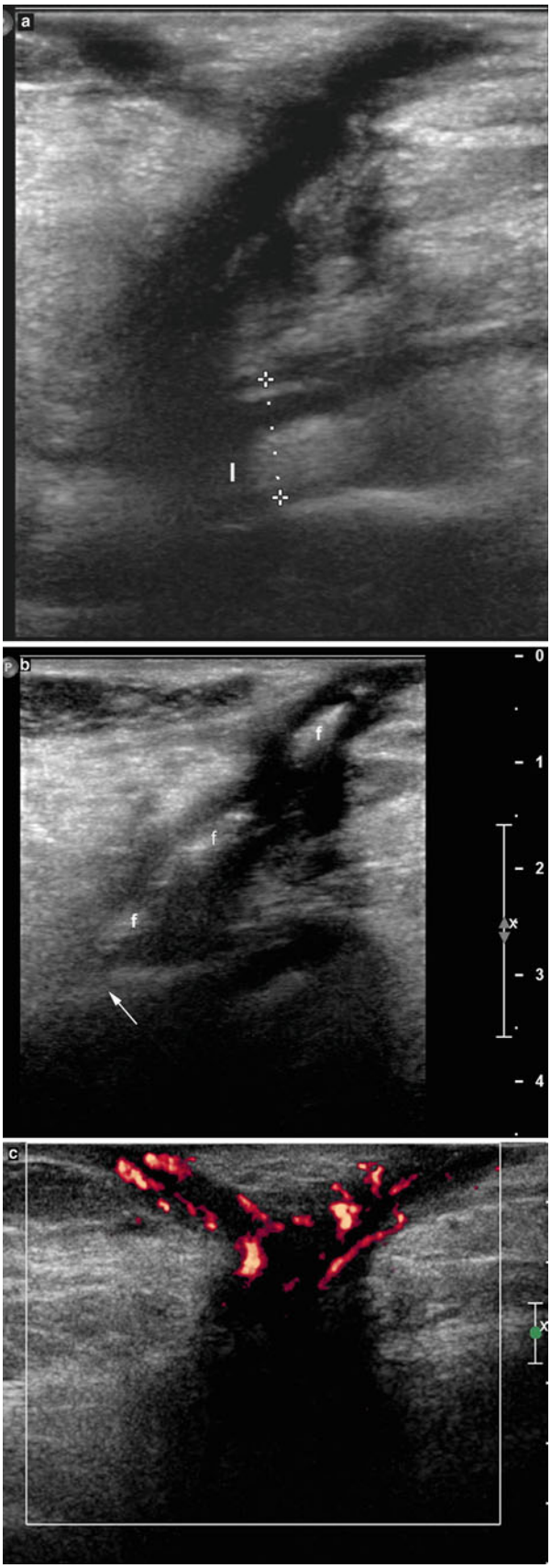


Fig. 9 Ultrasonographic appearance of internal fistulae. Entero-mesenteric (**a**), entero-enteric (**b**) and entero-vescical (**c**) fistulae (*F*) revealed at US as hypoechoic area deforming the margins of bowel wall (*arrows*), as hypoechoic ducts between the intestinal loops (*l*) and as hypoechoic areas between intestinal loops and bladder (*B*), respectively. *v*: iliac vein



◀ **Fig. 10** Assessment of enterocutaneous fistula by US fistulography. **a** US assessment of the enetrocutaneous fistula and **b** evaluation of the same lesion by the injection of contrast agent within the fistula (*f*) that reveals its openness (*arrow*) previously not clear and defines the extension and the configuration of the lesion. **c** The presence of blood flow detected within the fistula wall can also suggest the activity of the fistula, despite the absence of conspicuous drainage. (*f*, Fistula; *l*, Intestinal loop)

presence of stratification suggests a higher degree of fibrosis of the stenosis (Fig. 8a, b).

4.2 Sinus Tracks and Fistulae

Fistulae occur in 17–82 % of CD patients. They are a transmural extension of the disease, often resulting from intestinal stenosis (Oberhuber et al. 2000), which ends blindly in the surrounding mesentery or connects intestinal loops or adjacent organs. Depending on their site and extension, abdominal fistulae are commonly subdivided into external or internal (enteroenteric, enteromesenteric).

Fistulae may appear on US as hypoechoic ducts or hypoechoic areas between intestinal loops or between loops and other structures such as the bladder (enterovescical fistula) or the skin (enterocutaneous fistulae) (Fig. 9a, b, c). Sometimes, fistulae display internal echoic spots due to the presence of air, debris or intestinal material (Maconi et al. 1996b; Gasche et al. 1999).

At present, there is no reliable technique for the diagnosis of this complication. Using surgical findings as reference standard, we showed that the accuracy of US and X-ray studies in detecting internal fistulae was comparable, with a sensitivity of 71.4 % for US and 69.6 % for X-ray studies, and a specificity of 95.8 % for both. We also showed that the combination of these two techniques significantly improved preoperative diagnostic performance (sensitivity 97.4 % and specificity 90 %) and that in selected severe cases of CD, with clinical suspicion of septic complications (i.e. abdominal mass or fever), sensitivity of US is even higher (88.5 %), thus confirming the high sensitivity of a previous US study (Gasche et al. 1999; Maconi et al. 2003b).

Noteworthy, US, MRI and CT have comparable sensitivity and specificity in detecting internal fistulae in CD (Panes et al. 2011). Since fistula wall is characterised by granulation tissue and neoangiogenesis, it may be easily recognised at US by detecting intra-mural blood flow using power-Doppler or i.v. contrast-enhanced US (Maconi et al. 2002).

US may also be usefully employed to define the features of external fistulae, particularly if US is combined with the injection of echoic contrast medium composed of hydrogen

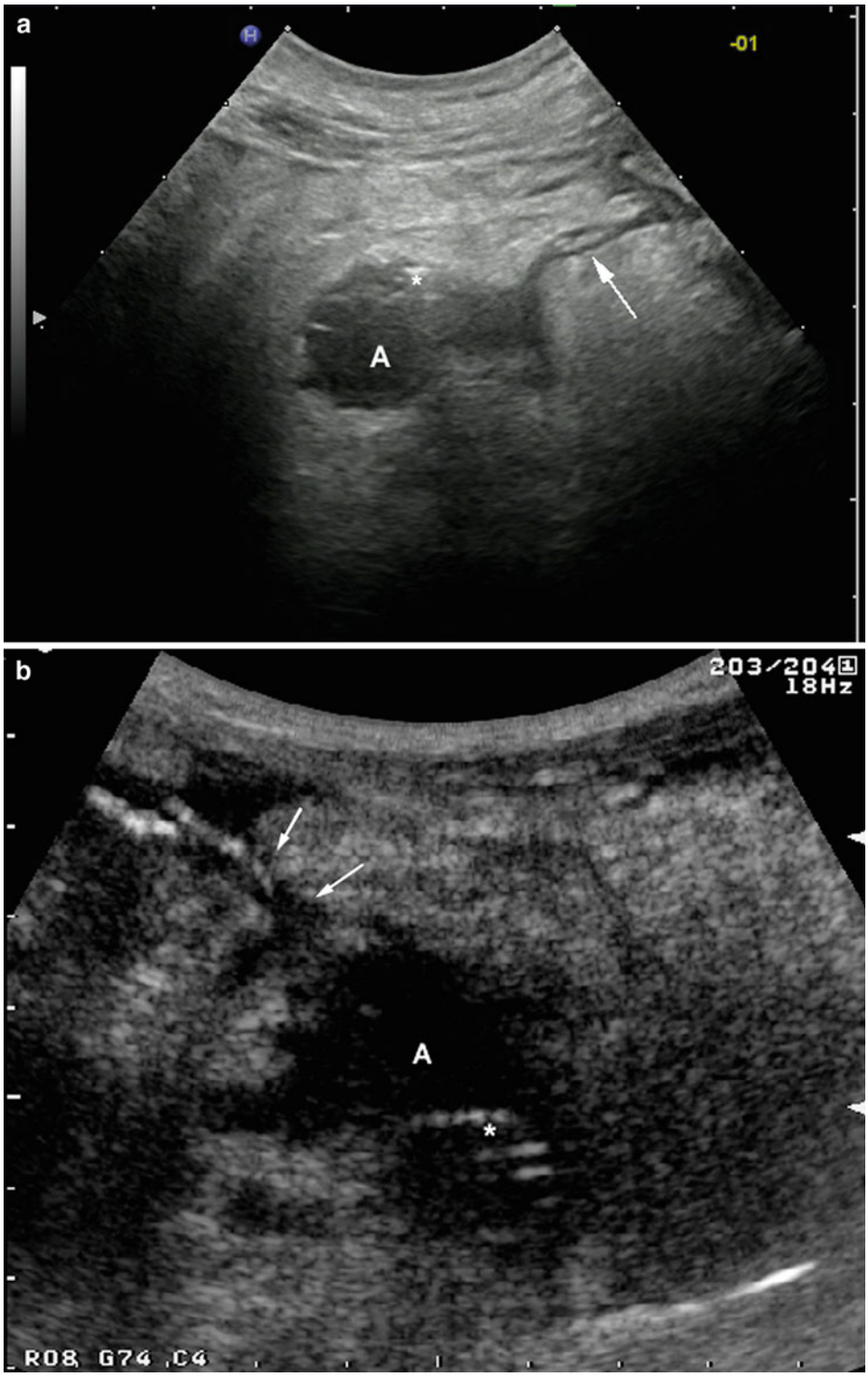


Fig. 11 **a**, **b** Intra-abdominal abscesses (*A*) appearing as hypo-anechoic lesions, often originating form a fistula (*arrow*), with irregular wall, with internal echoes due to presence of debris or air (*asterisk*), and characterised by posterior echo-enhancement

peroxide and povidone iodine into the fistula. This sort of US fistulography defines the extension and the configuration (linear or with ramifications) of the enterocutaneous fistulae (Fig. 10) is well tolerated and does not expose the patient to the risk of septic dissemination during the injection of the contrast medium (Maconi et al. 1999).

4.3 Intra-Abdominal Abscesses and Inflammatory Masses

Intra-abdominal abscesses occur in 12–30 % of CD patients, usually as a consequence of fistulising disease or as a postoperative complication (Steinberg et al. 1973;

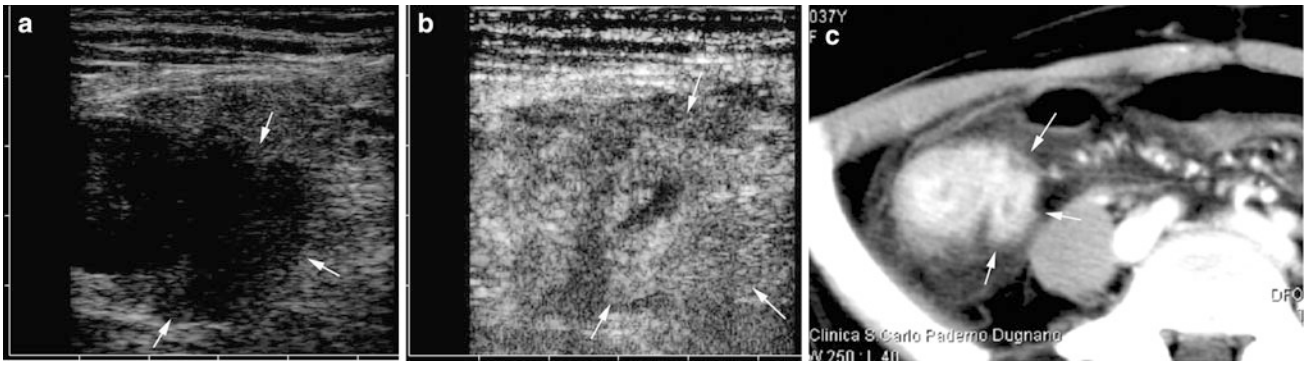


Fig. 12 Inflammatory mass detected by US (**a**) and characterised by i.v. contrast agent (**b**) that shows the absence of fluid within the mass. **c** Correspondent i.v. contrast CT imaging of the same lesion

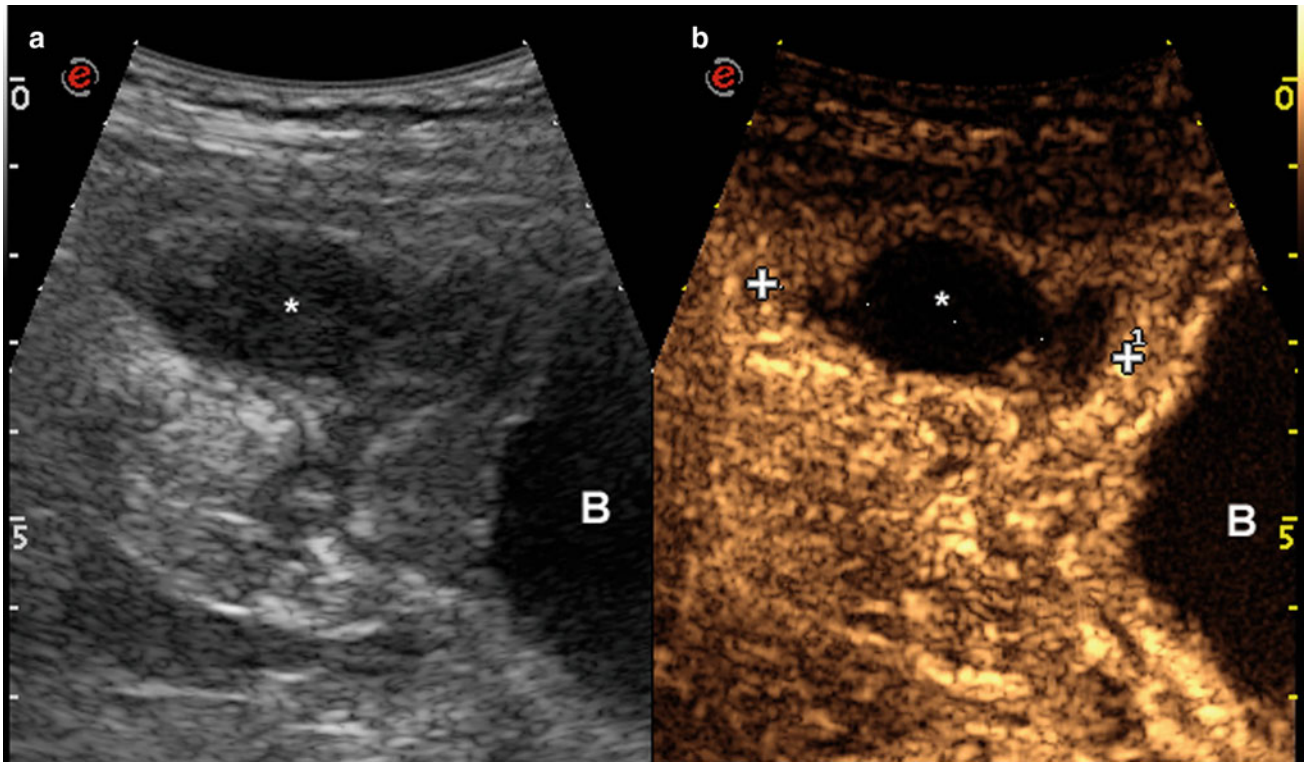


Fig. 13 Intra-abdominal abscess (*asterisks*) detected by b-mode US (**a**) and characterised by i.v. contrast agent (**b**) that shows the absence of vascularity within the mass. *B* bladder

Nagler et al. 1979). At US, abscesses appear as hypoanechoic lesions with fluid collection and irregular thickened walls, sometimes containing internal echoes due to the presence of debris or air, and characterised by a posterior echo enhancement (Fig. 11). Hypoechoic masses, especially those of small size and located close to the intestine, may be missed or mistaken for large sinus track, hypoechoic lymph nodes or phlegmon. Conventionally, these lesions are diagnosed when characterised by irregular borders, no identifiable wall or liquefaction. Inflammatory masses, phlegmons and intra-abdominal abscesses, identified or suspected at US, may be confirmed and distinguished detecting vascular signals by color-power Doppler US or, better, by i.v. contrast-enhanced US, around and/or within the lesions. Phlegmon and inflammatory masses, in fact, show increased colour signals within (Fig. 12), whilst abscesses present fluid collections with a peripheral flow (Fig. 13) (Tarjan et al. 2000; Maconi et al. 2002).

US detection of intra-abdominal abscesses shows a mean sensitivity and specificity of 84 and 93 %, respectively, quite similar to those of MRI and CT (Table 2; Panes et al. 2011). In particular, US shows a higher sensitivity in the detection of superficial intra-peritoneal abscesses, while the diagnosis of deep pelvic or retroperitoneal abscesses is more difficult due to the presence of overlying bowel gas and the difficulty in differentiating an abscess from an intestinal loop with stagnating fluid.

4.4 Perforation

Perforation is a potentially lethal complication of CD. It occurs in 1–2 % of the patients as a consequence of deep fissures in the intestinal wall. Free perforation should be suspected when US shows the presence of intra-peritoneal liquid and air, indicative of purulent peritonitis or the presence of free air under the diaphragm.

Focal perforations are more frequent than free perforations and may be diagnosed by US as areas of asymmetric and focal thickening of the wall associated with small peripariental collections of liquid and air.

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