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Review

Magnetic resonance enterography (MRE) and ultrasonography (US) in the study of the small bowel in Crohn's disease: state of the art and review of the literature

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Summary. Crohn's disease (CD) is a chronic idiopathic disease and its diagnosis is based on a combination of clinical symptoms, laboratory tests and imaging data. There isn't a diagnostic gold standard: the ileocolonoscopy with mucosal biopsies represents the standard for luminal disease, while cross-sectional imaging such as Ultrasound (US), Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) can show transmural alterations and extraintestinal manifestations. CD is usually diagnosed in the young age and after baseline diagnosis, the patients have to undergo to variable follow-up depending on remission or active disease. The aim of our review is to compare Magnetic Resonance Enterography (MRE) to Ultrasonography (US) in the follow-up of CD. (www.actabiomedica.it)

Key words: MR enterography, Crohn's disease, IBD, CEUS

Introduction

Crohn's disease (CD) is a chronic idiopathic disease that is commonly characterized by recurrent gastrointestinal tract inflammation. Patients affected by CD are mainly at reproductive ages and they need frequent follow-up (1)

The disease involves the whole gastrointestinal tract, in particular the small bowel (70%) in the tract of terminal ileum and colon (2); it is a pathology with multifactorial etiology and is more common in Europe and North America (3). It has an incidence in the U.K. of 83 per million people. Symptomatic manifestations may be unspecific. Danese et al. (4) have constructed the Red Flags index to individuate early symptoms and have established a value of 8 as highly predictive of CD diagnosis: chronic diarrhea (>3 bowel movements and >4-week duration); chronic abdominal pain (>3 months); rectal bleeding; extra-intestinal manifestations. There is a poor correlation between symptomatology and disease severity (5). Frequent complications are intestinal strictures (40% of cases) but also abscesses, phlegmons and fistulas (6). Diagnosis and staging of CD require different diagnostic exams: serological testing (C-reactive protein and fecal calprotectin), clinical and endoscopical evaluation (7, 8), video-capsule endoscopy for proximal small bowel. Endoscopy consists in ileocolonoscopy with biopsies from the terminal ileum and colon in order to confirm the diagnosis (9); esophagogastroduodenoscopy is used for suspected upper tract disease (10). The ileocolonoscopy represents the standard for luminal disease (11). Cross-sectional imaging (MRI, CT and US) techniques, gained large application in

gastrointestinal radiology (12-48); in the setting of inflammatory bowel diseases, they are is advised as first line techniques in the diagnosis, staging and follow-up (49, 50). An expert consensus committee from the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) and European Society of Paediatric Radiology (ESPR) has established guidelines for performing these diagnostic techniques, including patient preparation, technical recommendations and scan protocol (51). Radiological examinations can evaluate accurately severity; they are non-invasive and not limited to the colon and terminal ileum (52) but can demonstrate complications of CD and extraintestinal manifestations. Aim of this review is to compare Magnetic Resonance Enterography (MRE) with Ultrasonography (US) as non-invasive, radiation-free and appropriate techniques for follow-up in patients affected by CD. In particular, dynamic imaging techniques can assess the degree of disease activity and the efficacy of treatment .

Magnetic resonance enterography

Magnetic resonance imaging is one of the most largely used imaging tool in many diagnostic (53-57) and interventional settings (58, 59) thanks to its intrinsic excellent soft tissue contrast and the absence of ionizing radiation compared to CT (55, 60-87). Magnetic resonance enterography (MRE) plays an important role in supporting the diagnosis, and in establishing severity and presence of penetrating or extra-intestinal disease. To date, MRE is the most employed technique to assess the response to medical or surgical treatment . Common complications of Crohn's disease are intestinal strictures that may be of fibrotic, inflammatory and mixed types (88). The distinction is important in treatment planning; therefore, an appropriate diagnosis of inflammatory stenosis is required. The inflammatory stenosis responds to medical therapy while the fibrotic one requires endoscopic approach or intestinal resection. The exact distinction is sometimes difficult to be determined (89, 90). In a recent review of 2016, Westerland et al (90) analyze advantages and appropriate sequences that allow evaluation of the intestinal wall and distinction between inflammatory or fibrotic component. MRE is a panoramic technique that shows intestinal wall layers, presence of penetrating disease and extraluminal complications such as fistulas or abscesses. Important factors during MRE are: optimal distension of the small bowel, obtained with biphasic agent (mannitol or polyethylene glycol); antiperistatical agent to minimize bowel peristalsis (91, 92). Conventional sequences, used to evaluate typical pathological alterations, are True-FISP or FIESTA (true fast imaging with steady-state free-precession), T2-weighted and T1- weighted fat-saturated sequences. FIESTA sequences are less sensible to motion artifact and show good contrast between the bowel wall, lumen and mesenteric fat. It is useful for a morphological evaluation of the bowel loops (93) (Fig. 1). T2-weighted sequences have a high sensitivity (83%-91%) and specificity (86%-100%) to detect inflamed bowel with a mural thickness greater than 3mm and T2-signal increased for the presence of mural and mesenteric edema. Other features of acute disease are: mesenteric vascular prominence (comb sign), hyperenhancing and enlarged lymph nodes (short axis up to 8 mm) (Fig. 2). In T1- weighted fat-saturated sequences acquired after contrast media, the active inflammatory appears with a stratified pattern of enhancement (hyper- intense mucosa and serosa and hypointense/edema submucosa) (Fig. 3). The chronic inflammation is characterized by T2 hypointense mural signal without adjacent mesenteric inflammation and homogeneous transmural enhancement on T1-weighted fat-saturated sequences (92) (Fig. 4). The distinction between inflammatory and fibrostenotic disease is facilitated by the peculiar tissue contrast obtained in MR images . Recently, Diffusion Weighted Imaging (DWI) has been added to conventional sequences and many studies (94) show that there is a restricted diffusion in active inflammation: the presence of a cellular inflammatory response in the bowel wall prevents the movement of water molecules, showing mucosal hyperintensity on DWI and corresponding low signal on the Apparent Diffusion Coefficient (ADC) map. A quantitative evaluation (for example through ADC) helps to determine the severity of the disease and to monitor treatment response: Rimola et al. (95, 96) have elaborated the MR index of activity (MaRIA), considering MR parameters such as wall thickness, relative contrast enhancement, presence

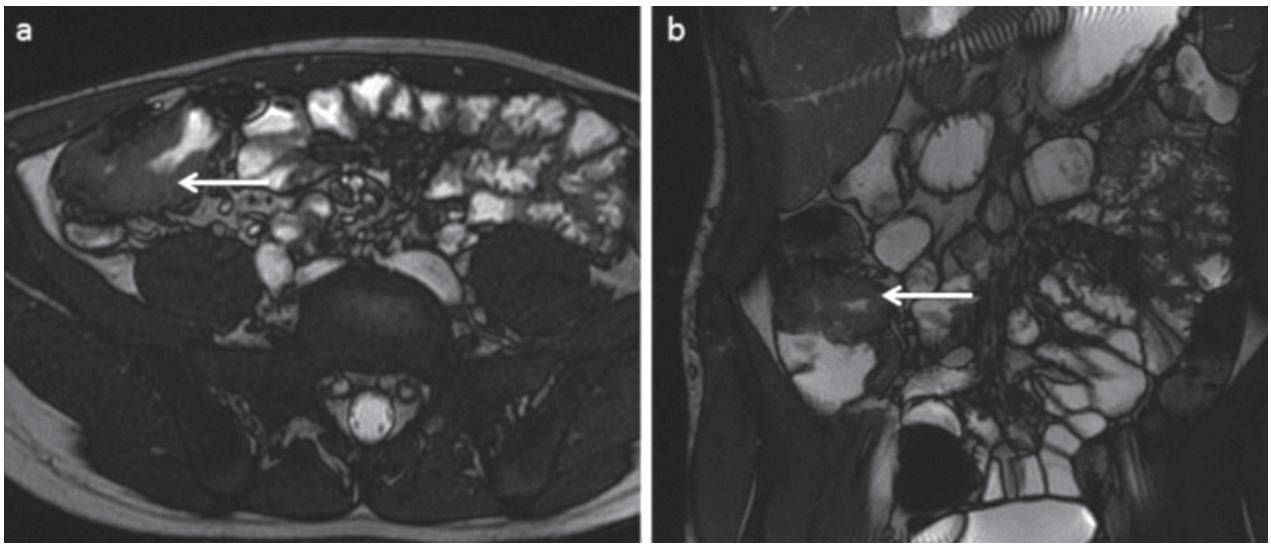

Figure 1. 14-year-old patient with abdominal pain, diarrhoea and elevated inflammatory biomarkers levels. Axial (a) and coronal (b) FIESTA sequences show active inflammation with increased wall thickness of the terminal ileum (arrows)

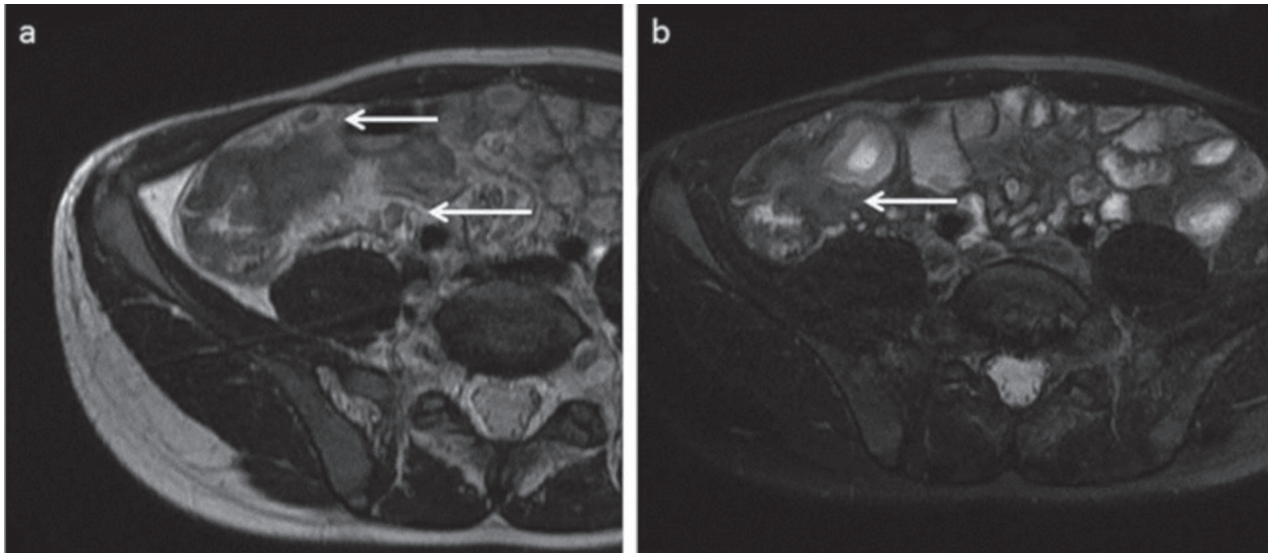

Figure 2. T2-weighted sequences show enlarged lymph nodes (a) and mural edema (b)

of edema, ulcers, pseudopolyps and enlarged lymph nodes. This index has a significant correlation with the endoscopic findings and, though being frequently quoted, it is not diffusely accepted in the clinical practice. In a study carried out in 2017, Kim et al (97) demonstrated that modified MaRIA scoring is quite accurate, because DWI, enteric and portal phase scans can improve reproducibility of the scoring system.

Ultrasonography

Ultrasonography (US) is the least invasive imaging examination, well tolerated by patients. This technique does not employ ionizing radiations, is repeatable with high diagnostic accuracy and is widely used in the diagnostic setting and as guidance in many interventional radiology procedures (61, 63, 98-105).

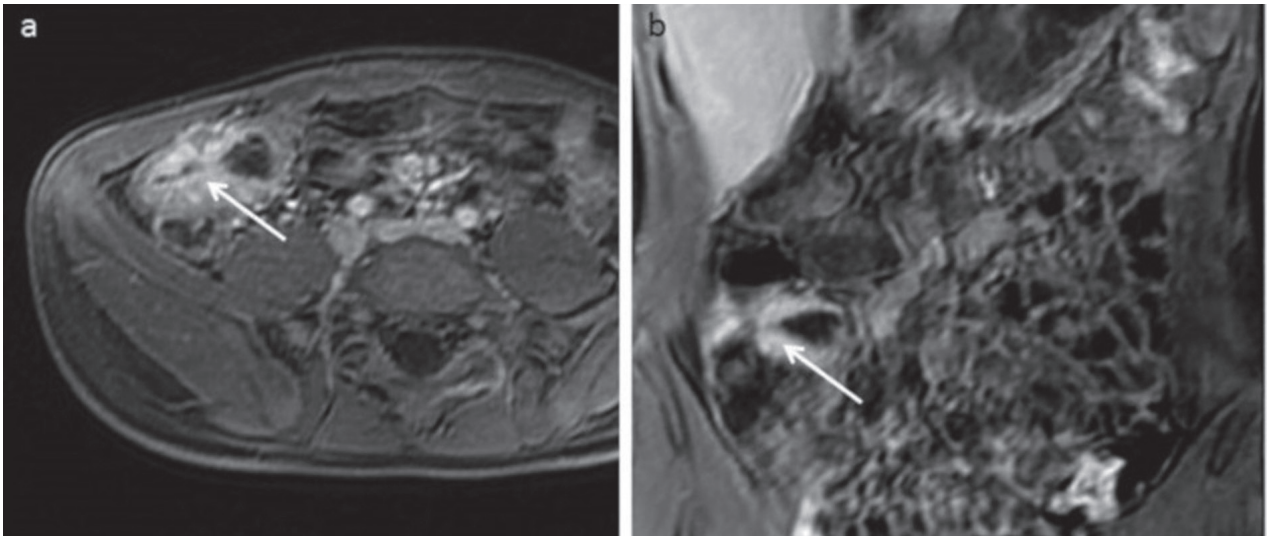

Figure 3. T1-w fat saturated images in axial (a) and coronal (b) planes, after contrast injection, show hyperintense mucosa (arrows) during the arterial phase

US can identify morphological features of bowel wall drawing the layer pattern and wall thickness (>3 mm in CD) (106) (Fig. 5). For this reasons, US is useful during active CD to show inflammatory processes of angiogenesis and hypervascularization into the intestinal wall (107); computed tomography (CT) and MR are unsuitable for repeated follow-up due to radiation exposure (CT) and high cost and complexity (MR) (108, 109). US can evaluate parietal vascularization using Color or Power Doppler: active disease is characterized by the increased number and caliber of vessels (110). Contrast-enhanced US is more accurate (111). The introduction of oral contrast solution (water and polyethylene glycol) to distend the bowel can improve the image quality and diagnostic accuracy in the evaluation of mild intestinal damage (112); the use of intravenous contrast media in US (CEUS) can emphasize the presence of an increased bowel wall vascularization that it is typical in the active form of CD. US with oral contrast agent (SICUS), as reported by Mocci et al. (113) in a review of 2017, has a sensitivity ranging from 96 to 100% if compared to that of conventional US (from 57 to 96%). Furthermore, it has been demonstrated that SICUS has high accuracy to identify complications and post-operative recurrence (114). An Italian group (115) has compiled a SICUS quantitative sonographic lesion index (SLIC) to study the evolution of the transmural bowel damage in CD patients in medical therapy. The index includes wall thickness, length of damaged intestinal tract, dilation and strictures. It identifies five classes of severity ranging from the lower (class A) to the higher score (class E). CEUS uses an intravenous contrast (Sonovue, at the recommended dose of 2.4-4.8 ml) and has a good ability to distinguish hypo- or hypervascularized intestinal strictures, identifying inflammation from fibrostenotic lesions (116) (Fig. 6). Active inflammation characteristics include rapid wash-in, when the microbubbles appear <20 second after infusion in bolus, and slow wash-out, when the microbubbles wash out in <80s (117). Some authors have shown that CEUS can be correlated with CD clinical activity (118). A quantitative method is proposed to evaluate vascularization of the intestinal wall in association with disease activity (the CD activity index, CDAI). Migaleddu et al. (119) have demonstrated that CEUS has the highest performance: 93.5% sensitivity, 93.7% specificity and 93.6% accuracy. In post-surgical recurrences, the values are 97%, 91%, 96%, respectively (120). The distinction between inflammatory and fibrotic lesions, as already mentioned, is very important for the therapeutic approach but some studies are controversial about this distinction: increased echogenicity of the submucosal layer results in inflammation while a clear visibility of all intestinal layers suggests fibrosis with reduced blood volume and flow (121, 122). The introduction of

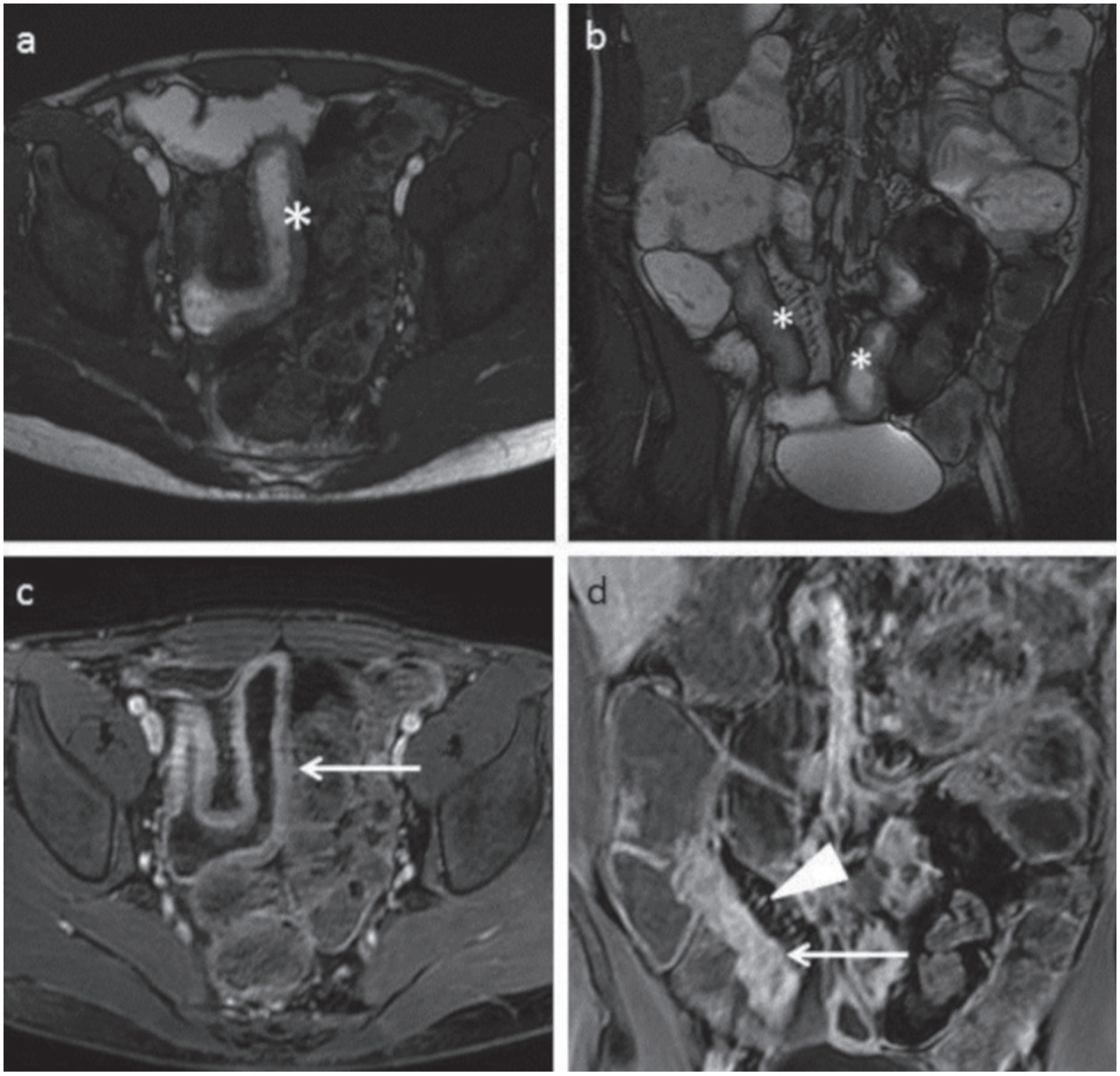

Figure 4. Follow-up at 5-years surgical treatment in 23-year-old patient. Images show, near ileum-ileal anastomosis, an inflamed loop, with increased thickness (*), vascular prominence (arrowhead), fibro-fatty proliferation and progressive transmural hyperenhancement (arrows). Early enhancement is showed in axial plane (a) and transmural enhancement in late venous phase (b)

a dedicated US software, the QLAB (Philips, Koninklijke, Belgium) and the Qontrast (Bracco, Milan, Italy) has allowed a quantitative and semi-quantitative analysis of contrast enhancement of the inflamed area. These data are derived from a selected "region of interest" (ROI) in which median values of the image intensity and a perfusion analysis are calculated to generate a time-intensity curve and obtain a good correlation between CD inflammatory activity and bowel wall vascularization (123, 124). In a recent study, Quaia (125) shows a positive correlation between contrast enhancement in affected tracts of small bowel and laboratory data in CD, so that the quantitative CEUS can define responder from non-responder patients affected by active disease and treated with immunosuppressive and biological therapies. The strain elastography (SE)

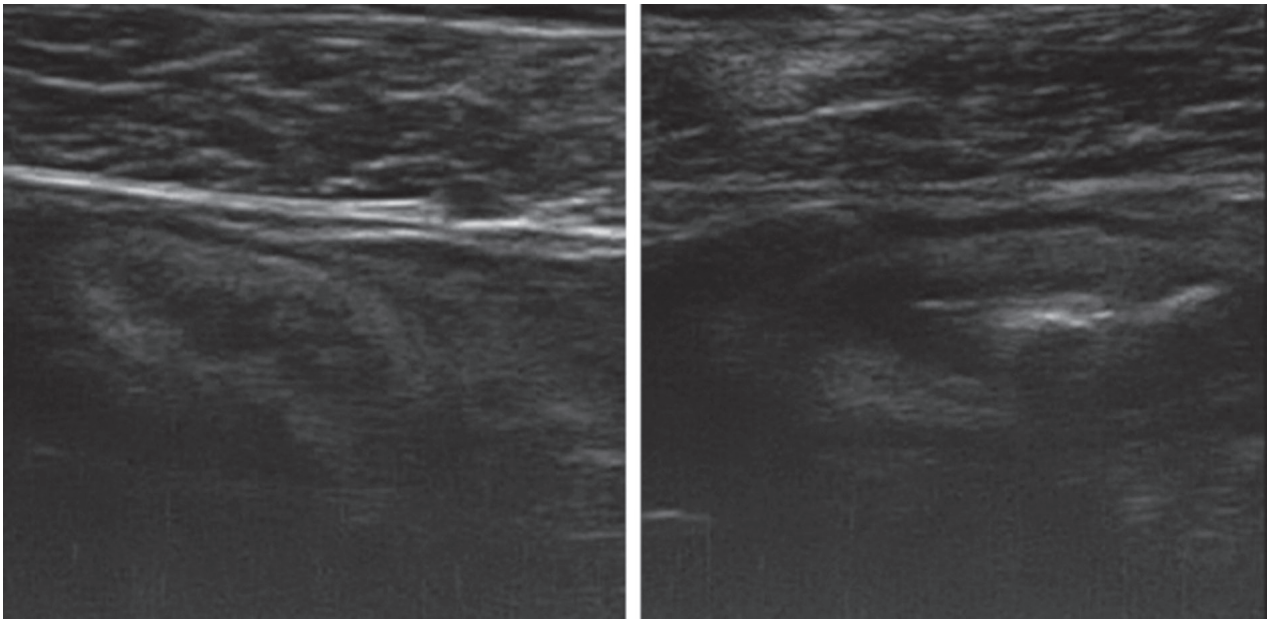

Figure 5. B-mode US with linear probe shows loop affected by CD and with increased mural thickness

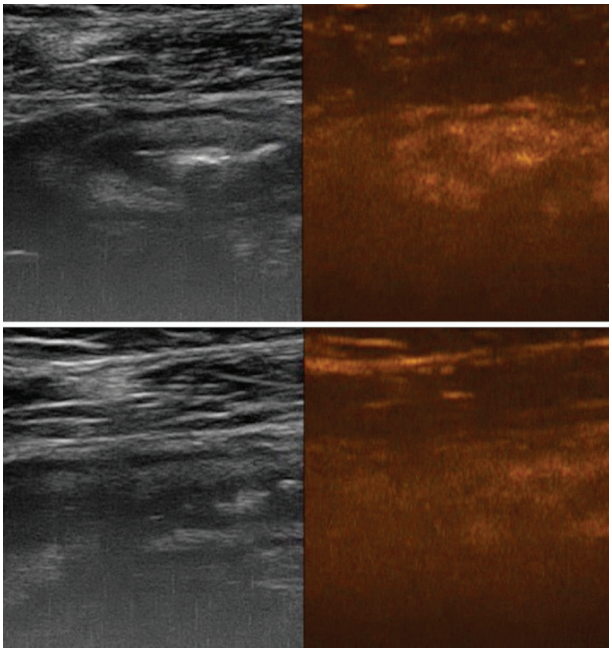

Figure 6. US after second-generation microbubble contrast shows slight enhancement, without signs of significant inflammation

is another diagnostic method useful but not routinely used for clinical management of inflammatory bowel diseases. It is a technique to evaluate the elasticity of the tissues as demonstrated in a case of ileum Crohn stricture by Giannetti (126) and confirmed by macroscopic and microscopic examination: the terminal ileum wall appears with abnormal elasticity and higher percentage of "blue" areas, suggesting stiffness.

Advantages and disadvatages of US

US has many advantages (127). It is widely used, low-cost, repeatable, noninvasive and radiation-free, all reasons that make of this technique one of the most tolerated by the patients. An experienced sonographer can find mural and extramural complications visualizing a good part of the small intestine and colon, in particular as the first approach in urgent assessment of complications. US is accurate in investigating stenosis, abscesses and fistulas; intraluminal oral contrast may improve image quality, but MR can show complicated fistulas better than US. Moreover, the use of intravenous contrast is necessary to distinguish CD strictures with predominantly inflammatory or fibrotic component especially when the stenosis is impassable with the endoscope. CEUS has an important role in revealing the presence and activity of CD in terminal ileum in particular in the follow-up of patients with known ileal localization of disease (128). Unfortunately, US

has some limitations: it is operator-dependent and the comparison or revision of images during the follow-up is not easy. Large body size, intestinal meteorism (in some cases it can be reduced by intraluminal solution) or depth of the region of interest can limit the exam. US cannot explore abdominal regions (retroperitoneum area) and intestinal tracts such as stomach, duodenum, jejunum, transverse colon, deep intrapelvic loops and rectum (129).

Advantages and disadvatages of MRE

MRE is another radiation-free diagnostic technique and represents the first choice in the pelvic localization of CD (11). It has high diagnostic accuracy and ability to investigate the complete bowel tract; it has multiplanar reconstructions, good visualization of soft tissues and easy detection of complications (strictures, abscess and fistulas) (Fig. 7) thus playing an important

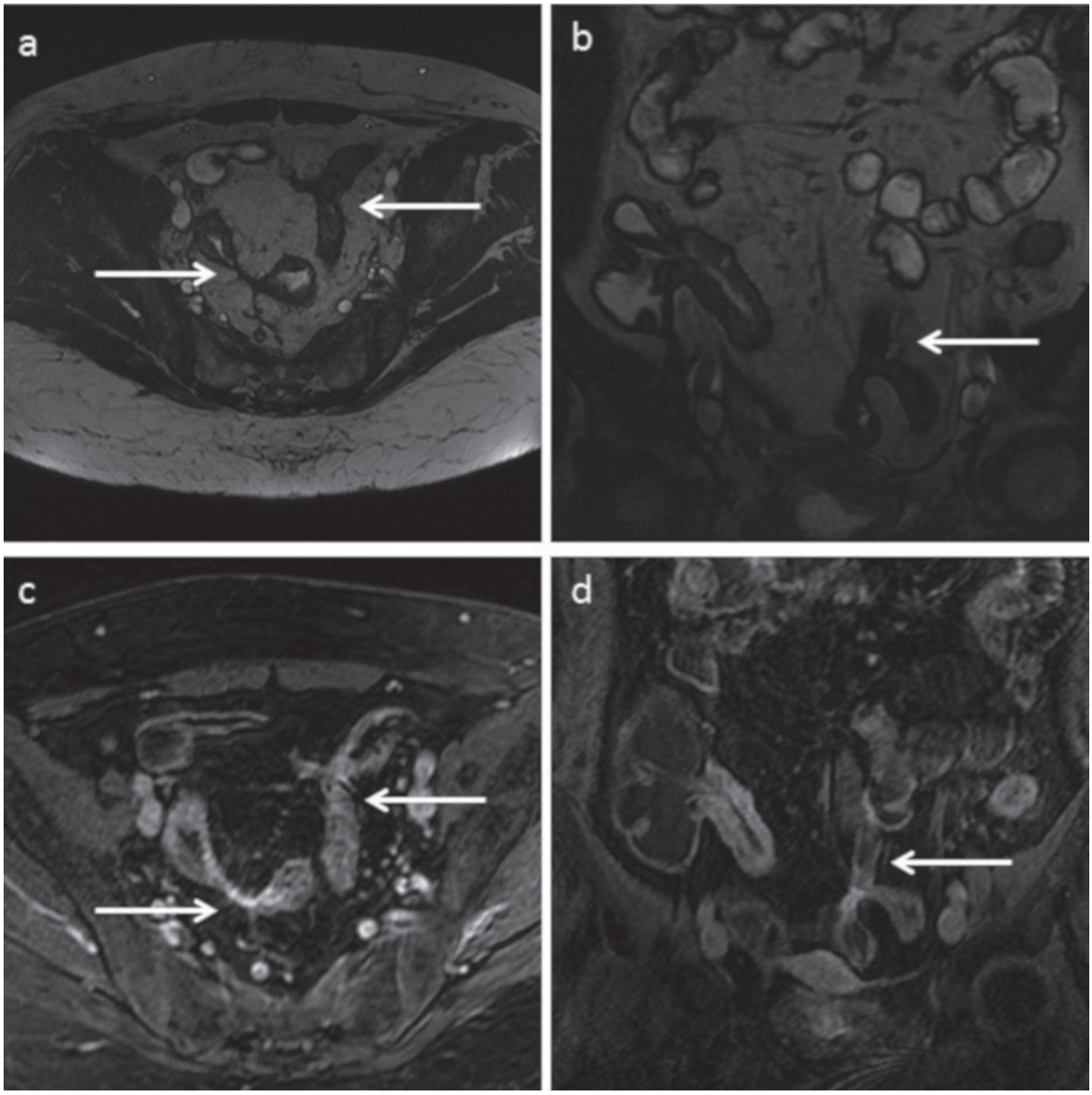

Figure 7. Example of enterocolic fistula formations (arrows) in a patient with CD for about 10 years. FIESTA images show «star sign» in axial (a) and coronal(b) planes and transmural enhancement appears in axial (c) and coronal (d) T1-weighted fat-saturated images

role in surgical planning (127). It provides a panoramic view of the entire abdominal region, mesenteric tissue and retroperitoneum area, allowing a good visualization also in patients in whom US is limited (e.g., overweight patients). Unfortunately, MRE is less used in clinical practice, because it is expensive, needs specific radiological competences and is time consuming (130). Other limitations include presence of metal devices, claustrophobia or sensitivity to MR contrast agents (131, 132).

CEUS vs MRE

A study by Malagò et al. (133) shows a good correlation between MRE and CEUS activity, with a Spearman's coefficient (rho) = 0.791 and a statistically significant p value (<0.0001). In particular, a high correlation was found in the study of the small bowel to evaluate wall thickness, lymph nodes and vasa recta (rho=0.926; p<0.0001); accurate correlation was obtained to assess layered wall appearance, disease extension and fibro adipose proliferation (rho=0.716; p<0.001). An excellent correlation between imaging and clinical laboratory data was achieved. MRE and CEUS are non-invasive techniques used in the diagnosis of CD, and in monitoring its activity. The affected loop and the main signs of the disease can be determined by both imaging modalities, despite different accuracy rates. In active disease, CEUS offers the possibility of recognizing all the characteristic signs, using intravenous contrast agent (gas microbubbles) that remains inside the microcirculation throughout the procedure, breaks up in the vascular system and is not retained in the fibrous tissue. This technique better shows the bowel-wall enhancement and the increased vascularization of the affected bowel loop (133). Conversely, MRI contrast agent has an initial vascular phase, tends to migrate and to accumulate in the interstitium. Therefore, gadolinium can detect also chronic lesions. Quaia et al. (134-137) demonstrated the accuracy of both techniques, with a quantitative analysis of enhancement patterns. Time intensity curves in CEUS and MRE are adequate for assessing intestinal-wall vascularity and for a more objective evaluation of the parietal enhancement compared with observer experience. In chronic lesions (133), which are fibrous scar tissue, MRE shows moderate enhancement in the venous phase with a pattern restricted to the mucosa, layered or homogeneous, while CEUS does not reveal any vascular enhancement.

Conclusions

An accurate diagnosis of CD is important to plan therapy and follow-up. The diagnosis is accomplished also by means of a bioptic extraction from the mucosal alteration performed during colonoscopy. In clinical practice, MRE is used as a first imaging exam to determine intestinal localization, extension and extra-intestinal complications. It can distinguish between inflamed and fibrotic component and helps in the therapeutic decision-making: medical therapy or surgical treatment. CEUS is useful in the explorable intestinal tracts, already visualized by previous MRI exams, and it is used in the follow-up after medical or surgical treatment or as fist-line exam in patients unsuitable to MR. Besides, CEUS can be helpful in emergency conditions as first approach examination in case of acute complications and recurrence. In conclusion, both techniques are useful and complementary in the study of CD evolution.

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

Conflict of interest: None to declare

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