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● *Original Contribution*

DIFFERENTIATION OF INFLAMMATORY FROM FIBROTIC ILEAL STRICTURES AMONG PATIENTS WITH CROHN'S DISEASE BASED ON VISUAL ANALYSIS: FEASIBILITY STUDY COMBINING CONVENTIONAL B-MODE ULTRASOUND, CONTRAST-ENHANCED ULTRASOUND AND STRAIN ELASTOGRAPHY

Emilio Quaia,* Antonio Giulio Gennari,† Maria Assunta Cova,† and Edwin J.R. van Beek*

* Edinburgh Imaging Facility, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, Scotland, United Kingdom; and † Department of Radiology, Cattinara Hospital, University of Trieste, Trieste, Italy

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Abstract—The aim of this pilot study was to assess prospectively the feasibility of conventional B-mode ultrasound (US) and contrast-enhanced ultrasound (CEUS) combined with real-time strain elastography (SE) in the differentiation of inflammatory from fibrotic ileal strictures among patients with Crohn's disease (CD) based on visual analysis. Twenty non-consecutive patients (15 male and 5 female; mean age ± standard deviation, 40.2 ± 10.22 y) with CD and stricture of the terminal ileal loop were scanned by conventional B-mode US and CEUS and, subsequently, by real-time SE. Two independent readers visually classified each bowel stricture as fibrotic or inflammatory based on conventional B-mode US, CEUS, SE, individually and then for all techniques combined. All techniques combined had a higher ($p < 0.05$) sensitivity (reader 1, 9/20 [45%]; reader 2, 7/20 [35%]), specificity (reader 1, 5/20 [25%]; reader 2, 8/20 [40%]) and diagnostic accuracy (reader 1, 14/20 [70%]; reader 2, 15/20 [75%]) and higher ($p < 0.05$) area under the receiver operating characteristic curve (reader 1, 0.953; reader 2, 0.921) than individual techniques. Inter-reader agreement was fair for conventional B-mode US ($k = 0.46$) and CEUS ($k = 0.39$), moderate for SE ($k = 0.6$) and fair for all techniques combined ($k = 0.38$). Conventional B-mode US and CEUS, in combination with SE, may improve differentiation of inflammatory from fibrotic ileal strictures among patients with CD based on visual analysis. (E-mail: equaia@exseed.ed.ac.uk)

Key Words: **Crohn's disease, Ultrasound, Microbubbles, Elastography, Stricture, Fibrosis.**

INTRODUCTION

Patients with ileal Crohn's disease (CD) develop bowel lumen strictures in approximately 40% of cases (Cosnes et al. 2011), which are often characterized by inflammation, fibrosis and/or muscular hypertrophy at the same time. The differentiation of predominantly inflammatory from predominantly fibrotic bowel strictures is crucial because pharmacologic anti-inflammatory treatment is indicated in the presence of inflammatory changes, whereas endoscopic dilation or surgical resection is required in the presence of fibrosis (Bettenworth et al. 2016).

Although all imaging techniques are capable of visualizing bowel wall inflammation based on mural enhancement after contrast administration (Cheng et al. 1994), the detection of the coexisting bowel wall fibrosis is much more challenging. Computed tomography (CT) and magnetic resonance (MR) enterography have moderate accuracy in differentiating mural fibrosis from inflammation (Prassopoulos et al. 2001) and require administration of large amounts of enteric contrast material often requiring nasointestinal tube insertion with consequent significant patient discomfort. Moreover, CT exposes patients to high radiation doses, especially if repeated during a strict follow-up schedule, as in patients with CD. Recently, even more advanced imaging techniques, including positron emission tomography (PET)/CT and PET/MR enterography (Catalano et al. 2016; Lenze et al. 2012) were shown to differentiate purely fibrotic ileal strictures from mixed or inflammatory strictures in patients with CD.

Address correspondence to: Emilio Quaia, Edinburgh Imaging Facility, Queen's Medical Research Institute, University of Edinburgh, 47 Little France Crescent, Edinburgh, EH16 4 TJ, Scotland, United Kingdom. E-mail: equaia@exseed.ed.ac.uk

Quantitative analysis of contrast-enhanced ultrasound (CEUS) cine clips was reported to improve the differentiation of fibrotic from inflammatory ileal strictures (Quaia et al. 2012, 2016, 2017; Ripollés et al. 2009, 2013), although there is overlap between the two entities in the peak enhancement (Quaia et al. 2012, 2016, 2017; Ripollés et al. 2009, 2013). Quantitative analysis is not clinical routine because of the time constraints and complexities, including US signal variables, such as signal gain, focalization depth, power and dynamic range. Consequently, the routine use of visual analysis would be more feasible provided that high levels of diagnostic accuracy and confidence are maintained.

Ultrasound elastography represents another imaging modality that could be applied to characterize fibrotic ileal strictures in patients with CD based on the stiffness of the mural wall (Baumgart et al. 2015; Dillman et al. 2013, 2014; Havre et al. 2014; Lu et al. 2017; Sconfienza et al. 2016; Stidham et al. 2011). Shear wave elastography generates a US force that propagates a shear wave through tissue to assess quantitatively the elastic properties of tissues (Lu et al. 2017) whereas real-time strain elastography (SE) uses autocorrelation of the position of image lines under repeated stress by applying slight mechanical compression with the transducer to calculate the displacement of tissue and creates a color-coded representation of the relative elasticity of tissues superimposed on the B-mode image (Mulabecirovic et al. 2016). Even though secondary analysis of real-time elastograms is required to obtain semiquantitative data, SE has the advantage of not necessarily requiring the use of quantitative analysis; instead, it could simply employ image visual analysis.

The aim was to assess prospectively the feasibility of conventional B-mode ultrasound (US) and CEUS combined with real-time SE in the differentiation of inflammatory from fibrotic ileal strictures among patients with CD based on visual analysis.

METHODS

Patients

This prospective pilot study was approved by the ethics committee of our institute, and written informed consent was obtained from all patients.

During a 24-mo period (from June 1, 2014 to June 1, 2016), we recruited all patients with a biopsy-proven diagnosis of CD who underwent conventional B-mode US, CEUS and SE. Inclusion criteria were (i) CD with stricture of the terminal ileal loop as visualized by cross-sectional imaging (CT or MR enterography), defined as lumen narrowing with proximal lumen dilation, or endoscopy, defined as persistent severe luminal narrowing by inability to pass the scope, within 1 mo from US examination; (ii) thickness of the terminal ileal loop >3 mm as measured on conventional B mode US; (iii) available histologic reference assessment for intestinal inflammation and fibrosis including endoscopy with serial deep mucosal biopsies or analysis of the gross surgical specimen of the terminal ileal tract no more than 1 mo after US examination; (iv) availability of the inflammatory histologic score or mural fibrosis diagnosis based on the analysis of mucosal biopsies or gross surgical specimens.

Table 1. Patient characteristics

Age, y	40.2 ± 10.22 (15–65)*
Sex, male/female	15/5
Body mass index, mean (range)	24.67 (15.59–42.72)*
Duration of disease, y	6 (1–10)*
Location of disease	
Ileum	18
Ileum and colon	2
Pharmacologic therapy	
Corticosteroids	4
Biologic drug + corticosteroids	10
Adalimumab	2
Infliximab	4

* Mean (range).

Forty patients were initially included in this study. Twenty of these patients were finally excluded because of unfeasible intubation of the distal ileum at ileum colonoscopy (n = 2) or involvement of ileal tracts other than the terminal tract (n = 18). Therefore, 20 non-consecutive patients (15 male and 5 female; mean age ± SD, 40.2 ± 10.22 y) with a diagnosis of CD with a history of CD of 1–10 y (mean, 6 y) were finally included (Table 1). At the time of examination, these patients were undergoing specific anti-inflammatory treatment based on biological drug (n = 6 patients; infliximab, n = 4; adalimumab, n = 2), biological drug and corticosteroids (n = 10; infliximab, n = 8 patients; adalimumab, n = 2 patient) or corticosteroids only (n = 4 patients).

US examination

Each patient underwent an US examination of the terminal ileal loop to make the scanning consistent between different patients. US examination was conducted with an iU22 xMATRIX Ultrasound System (Philips Healthcare, Bothell, WA, USA) using a broadband 256-element linear-array transducer (L12-5, 5–12 MHz, 50 × 10 mm). After a fast of at least 6 h, the terminal ileal loop was scanned by a diagnostic radiologist with 10 y of experience in US of the abdomen who was not blinded to pathologic results.

On conventional B-mode US, the terminal ileal loop wall thickness (mm) was measured at the level of the anterior wall; the depth of the ileal loop was measured from the leading serosal edge of the anterior bowel wall up to the skin surface (cm); and the absolute extension of the ileal tract involved was measured from the beginning up to the end of the ileal tract involved by the thickening of