

***In vivo* detection of mucosal healing-involved histiocytes by confocal laser endomicroscopy**

Gheorghe Hundorfean, Abbas Agaimy, Mircea T Chiriac, Walter Geißdörfer, Jochen Wacker, Markus F Neurath, Jonas Mudter

Gheorghe Hundorfean, Mircea T Chiriac, Markus F Neurath, Jonas Mudter, Medical Clinic I, University of Erlangen-Nuremberg, 91054 Erlangen, Germany

Abbas Agaimy, Institute of Pathology, University of Erlangen-Nuremberg, 91054 Erlangen, Germany

Walter Geißdörfer, Microbiology Institute-Clinical Microbiology, Immunology and Hygiene, University of Erlangen-Nuremberg, 91054 Erlangen, Germany

Jochen Wacker, Medical Clinic III, University of Erlangen-Nuremberg, 91054 Erlangen, Germany

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Correspondence to: Gheorghe Hundorfean, MD, Medical Clinic I, University of Erlangen-Nuremberg, Ulmenweg 18, 91054 Erlangen, Germany. gheorghe.hundorfean@uk-erlangen.de
Telephone: +49-9131-8545034 Fax: +49-9131-8535102

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Abstract

Histiocytes have a pivotal role in wound repair and intestinal epithelial recovery - the most important goal to sustain gut functionality. Yet, an *in vivo* description of colonic histiocytes by confocal laser endomicroscopy (CLE) is missing. Here, we report the case of a 45-years-old male patient who was referred to our clinic with

weight loss and a history of two consecutive *Clostridium difficile* colitis episodes, the latter cured 3 wk before present admission. Stool microbiology was negative. Conventional colonoscopy showed atrophy and a light mucosal oedema in the distal colon. During on-going endoscopy, we performed a fluorescein-aided CLE which revealed large polygonal (histiocytes-like) cells with copious cytoplasm and large nuclei in the lamina propria of the sigmoid colon as well as regenerative epithelial changes. Histopathological assessment of biopsies from the same areas confirmed the endomicroscopical findings: Periodic acid-Schiff- and CD68-positive foamy histiocytes in the colonic lamina propria and an advanced epithelial recovery. Since stool microbiology was repeatedly negative and polymerase chain reaction-analysis from colonic biopsies could not detect any mRNA for *Thropheryma whipplei* and common pathogens, we interpreted this particular setting as a mucosal healing process after consecutive *Clostridium difficile* infections. In conclusion, by describing these colonic histiocytes, we highlight the clinical usefulness of CLE in describing the entity of histiocytes *in vivo* and in real-time during the process of post-infectious mucosal healing in the colon.

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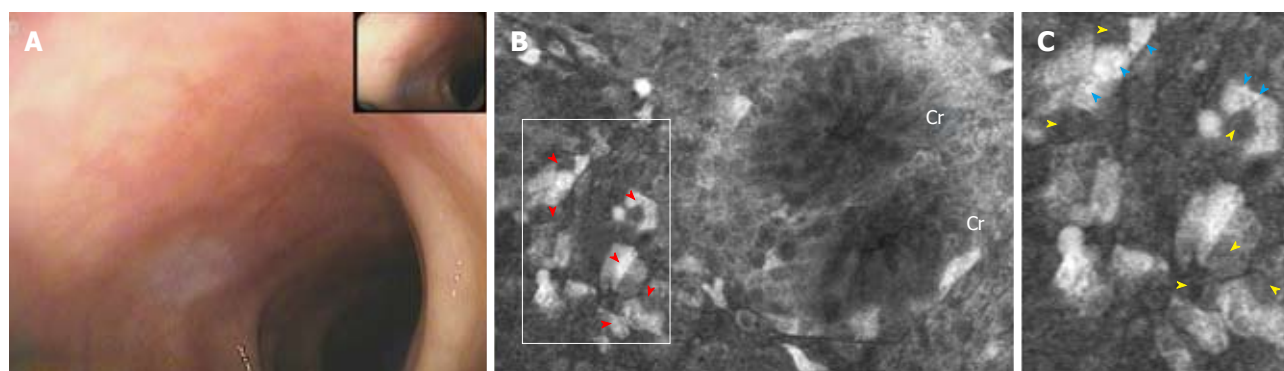


Figure 1 Endoscopic and endomicroscopic characterization of the sigmoid colon in the context of a post-infectious mucosal healing process. A: White light colonoscopy shows mild atrophy and reduced vascular pattern in the sigmoid colon; B: Fluorescence-guided confocal laser endomicroscopy reveals large polyclonal cells (red arrowheads) with copious cytoplasm in the lamina propria - near two crypts (Cr) - corresponding morphologically to foamy histiocytes; C: In an enlarged manner the aggregated histiocytes with large fluorescence-negative nuclei (yellow arrowheads) and foamy cytoplasm (blue arrowheads) defining their appearance and nomenclature.

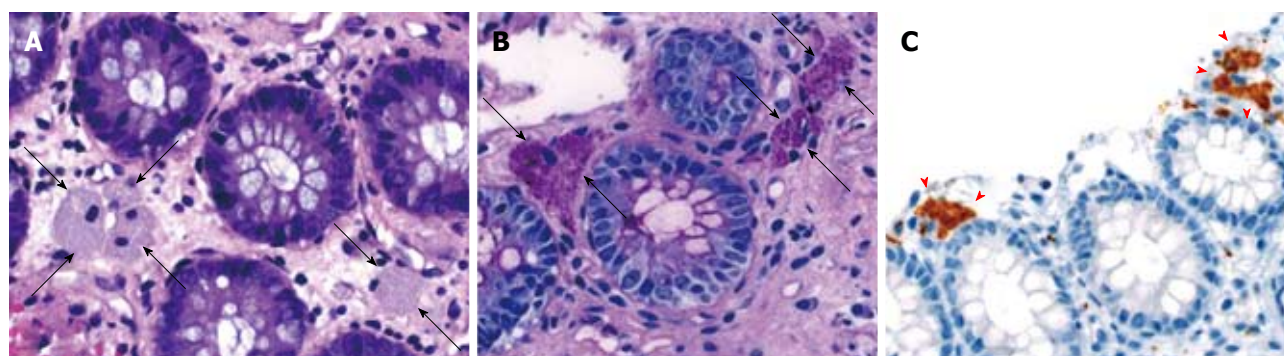


Figure 2 Histopathologic confirmation of the endomicroscopic findings. A-C: Large polyclonal histiocytes between mucosal crypts (arrows) are highlighted in the hematoxylin-eosin stain (A) as well as in Periodic acid-Schiff stain after diastase predigestion (B) and image (C) (CD68 immunostaining) with a CD68-positive cytosol, overall confirming the endomicroscopical findings.

INTRODUCTION

A subset of macrophages differentiating to histiocytes were proved to have a pivotal role in wound repair processes^[1] and intestinal epithelial recovery. This is the most important goal to sustain functionality of the gut and it was also defined as therapeutic goal in order to achieve mucosal healing in chronic inflammatory bowel disease^[2]. So far, two reports have described histiocytes in the duodenum^[3,4] using confocal laser endomicroscopy (CLE)^[5]. Yet, the *in vivo* description of histiocytes within the colon by confocal endomicroscopy has not been published so far.

CASE REPORT

Here, we report the case of a 45-year-old male patient who was referred to our endoscopy unit with anaemia and weight loss. In the last three months he had a history of 2 consecutive *Clostridium difficile* (*C. difficile*) colitis episodes, the latter resolved completely after appropriate treatment 3 wk before the present admission. Microbiological analysis of stool samples was repeatedly negative for *C. difficile* and other intestinal pathogens (Salmonella, Shigella, Yers-

inia, Campylobacter). White light colonoscopy showed signs of atrophy, mild mucosal oedema and reduced vasculature pattern in the distal colon (Figure 1A). During on-going endoscopy, we performed a fluorescein-aided confocal endomicroscopy of the colonic mucosa which revealed large polygonal (histiocytes-like) cells with copious cytoplasm and large nuclei in the lamina propria of the sigmoid colon (Figure 1B, C). By taking biopsies from the areas analysed by confocal imaging, we were able to correlate and verify the endomicroscopical findings with histopathology. These were Periodic acid-Schiff-positive and CD68-positive foamy histiocytes in the colonic lamina propria between basal mucosal crypts (Figure 2A-C).

DISCUSSION

Since stool microbiology was repeatedly negative and PCR-analysis could not detect any intestinal pathogens (incl. *Tropheryma whippelii* that causes Whipple's disease), we interpreted this particular setting as a mucosal healing process after two consecutive *C. difficile* infections^[6].

In conclusion, by describing these colonic histiocytes *in vivo* and real-time, we highlight the clinical usefulness of confocal laser endomicroscopy in characterizing the

cell entity of colonic histiocytes and the context of a post-infectious mucosal healing process in the colon, for the first time. Confocal laser endomicroscopy was used previously for the detection of architectural changes, vascularity changes like leakage but not for the differentiation of a specific cell entity. Our report provides the morphological criteria and exemplifies the differentiation and characterization of a particular cell entity, namely the foamy histiocytes, involved in the post-infectious mucosal healing.

In this histopathological and clinical setting, our report is also the first non-invasive and real-time description of human foamy histiocytes in the colon.

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