Research and Science Today
WWW.RSTJOURNAL.COM

DOI: 10.38173/RST.2021.22.2.13:131-137

Title:	*THE PERI-APPENDICEAL RED PATCH: A TRADEMARK SKIP LESION IN ULCERATIVE COLITIS*
Authors:	Monica COJOCARU Cristian GHEORGHE Gabriel BECHEANU

Section: MEDICINE

Issue: 2(22)/2021

Received: 27 September 2021	**Revised:** -
Accepted: 2 November 2021	**Available Online:** 15 November 2021

Paper available online HERE

RST Research and Science Today
WWW.RSTJOURNAL.COM
AUTUMN 2021
No. 2(22)/2021
ISSN-P: 2247-4455 / ISSN-E: 2285-9632

Medicine

THE PERI-APPENDICEAL RED PATCH: A TRADEMARK SKIP LESION IN ULCERATIVE COLITIS

Monica COJOCARU[1]
Cristian GHEORGHE[2]
Gabriel BECHEANU[3]

ABSTRACT:
CONVENTIONALLY, UC IS RECOGNIZED AS A DISEASE WITH CONTINUOUS MUCOSAL INFLAMMATION THAT EXTENDS FROM THE RECTUM TO THE PROXIMAL PART OF THE COLON, BUT DURING THE LAST DECADE, A PARTICULAR PATTERN OF COLITIS THAT INVOLVES THE DISTAL COLON WITH A NORMAL APPEARANCE MUCOSA INTERPOSED AND A WELL DEFINED AREA OF INFLAMMATION AROUND THE APPENDIX HAS BEEN HIGHLIGHTED. WE USED A TERTIARY CARE CENTER EVIDENCES TO ANALYZE THE CHARACTERISTICS OF UC PATIENTS WITH PARP. WE EVALUATED 76 PATIENTS WHO WENT TO OUR CLINIC FOR INVESTIGATING CHRONIC DIARRHEA SYNDROME BETWEEN JANUARY 2018-DECEMBER 2020 AND FOR WHOM A DIAGNOSIS OF ULCERATIVE COLITIS WAS ESTABLISHED . ONLY 7 PATIENTS HAD ENDOSCOPICALLY ASPECT OF PARP (THIS HAPPENED DURING FOLLOW-UP ENDOSCOPY), ASPECT SUPPORTED ALSO BY THE HISTOLOGICAL DESCRIPTION (NANCY INDEX SCORE). DURING FOLLOW-UP, MOST PATIENTS WITH PARP KEPT THE SAME EXTENT OF LESIONS.
***CONCLUSIONS**: WE CONFIRM THE PRESENCE OF PARP AS A "SKIP LESION" IN DISTAL UC, DIAGNOSTIC SUPPORTED ALSO BY THE HISTOPATHOLOGIST, AND EVEN THOUGH WE ARE CONFIDENT IN THE DIAGNOSIS OF ULCERATIVE COLITIS, ONE PATIENT HAD A CROHN'S DISEASE PHENOTYPE SWITCH DURING THE EVOLUTION. NONETHELESS, WE CANNOT CONCLUDE THAT PARP HAS A ROLE IN THE EXTENSION OF LESIONS, REMISSION OR RELAPSE OF DISEASE, GIVEN THE FACT THAT WE DO NOT HAVE A SUFFICIENT GROUP OF ELIGIBLE PATIENTS, FOR WHICH REASON DETAILED STUDIES ARE NEEDED.*

KEYWORDS: CECAL PATCH; PERI-APPENDICEAL RED PATCH (PARP); APPENDICEAL ORIFICE INFLAMMATION (AOI); ULCERATIVE COLITIS (UC).

[1] Fundeni Clinical Institute, Gastroenterology and Hepatology Department, Bucharest, Romania; monicaluciacojocaru@yahoo.com
[2] Fundeni Clinical Institute, Gastroenterology and Hepatology Department, Bucharest, Romania; Carol Davila University and Pharmacy, Bucharest, Romania
[3] Fundeni Clinical Institute, Gastroenterology and Hepatology Department, Bucharest, Romania; Fundeni Clinical Institute, Pathology Department, Bucharest, Romania

INTRODUCTION

Over the last few years, the display of inflammation near the appendix in patients presenting with proctitis/ left-sided ulcerative colitis (UC) has been underlined. Anyway, the practical importance of appendiceal orifice inflammation (AOI)/ peri-appendiceal red patch (PARP)/ cecal patch as a skip lesion in UC is not very clearly established.

UC is one of the two subtypes of inflammatory bowel diseases, most often affecting young adults, with an increasing incidence and prevalence in developed countries. The current manifesto of UC pathogenesis basically implies a constellation of genetic, environment and microbiota modifications, along with an altered response and a damage of the epithelial barrier.

Differentiation between UC, Crohn's disease and other pathologies (such as infectious colitis, ischemic or radiation colitis, segmental colitis associated with diverticulosis) is of critical importance for a tailored management, because each pathology demands particular therapeutic approach and it has a distinct prognosis.

UC produces lesions that spread in a continuous manner, starting from the rectum to the proximal parts of the colon, the ileum being rarely affected (except for "backwash ileitis", when the ileal mucosa is exposed to cecal bacteria).The typical lesions detected, differ on the severity of the disease, and accepted and validated endoscopic scores are helpful. Therefore, depending on the disease activity, the following lesions can be described as follows: erythema, erosions, blurring of the normal vascular pattern, oedema, friability of the mucosa or the presence of pseudopolpys/mucopurulent exudates. There are a few exceptions from the already known rule and this is when the rectum is of normal macroscopic appearance, as in: pediatric population, fulminant colitis, the use of topical 5-aminosalicylate (5-ASA) or in association with sclerosing cholangitis[4]. This topic is receiving emerging attention, giving the fact that in recent years studies that demonstrated the existence of UC with an atypical distribution of inflammatory lesions were published[5].

This particular lesion (AOI/PARP) was first described in 1958 by Lumb and Protheroe, which reported eight cases of UC with an island of inflammation of the cecum mucosa, opposite to the ileocecal valve[6].

Regarding Crohn's disease, the major endoscopic findings that are suggestive for this diagnosis are: aphtous ulcers, cobblestoning and discontinuous lesions. Basically, a normal appearance rectum directs the diagnosis to Crohn's disease[7].

---

[4] Faubion WA, Jr., Loftus EV, Sandborn WJ, Freese DK, Perrault J. Pediatric "PSC-IBD": A descriptive report of associated inflammatory bowel disease among pediatric patients with psc. J Pediatr Gastroenterol Nutr 2001;33:296-300; Odze R, Antonioli D, Peppercorn M, et al. Effect of topical 5-aminosalicylic acid (5–ASA) therapy on rectal mucosal biopsy morphology in chronic ulcerative colitis. Am J Surg Pathol. 1993;17: 869–875; Jorgensen KK, Grzyb K, Lundin KE, et al. Inflammatory bowel disease in patients with primary sclerosing cholangitis: Clinical characterization in liver transplanted and nontransplanted patients. Inflamm Bowel Dis 2012;18:536-45

[5] Sang Hyoung Park, Suk-Kyun Yang, et al. Atypical distribution of inflammation in newly diagnosed ulcerative colitis is not rare. Can J Gastroenterol Hepatol. 2014 Mar; 28(3): 125–130; S H Kroft, S J Stryker, M S Rao. Appendiceal involvement as a skip lesion in ulcerative colitis. Mod Pathol. . 1994 Dec;7(9):912-4

[6] Pera A, Bellando P, Caldera D, Ponti V, Astegiano M, Barletti C, David E, Arrigoni A, Rocca G, Verme G . Colonoscopy in inflammatory bowel disease. Diagnostic accuracy and proposal of an endoscopic score. Gastroenterology. 1987;92(1):181

[7] Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, D'Haens G, D'Hoore A, Mantzaris G, Novacek G, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis. 2012;**6**:991–1030

The size of the problem, when we refer to establishing a clear diagnosis, is big because medical treatment and type of surgery is vey relevant, in particular when procto-colectomy may be needed.

Studies from the literature show that the clinical evolution of patients with atypical distribution may be slightly different (in a positive way) from that of patients with classical distribution, regarding remission, relapse or the need for colectomy or hospitalization.

It is well known the fact that the cecal inflammation may be part of the normal mucosal state of health, because the cecum consists of a high number of eosinophils, Paneth cells and cellularity in lamina propria (lymphocites and plasma cells). In a study published in 2007 in American Journal of Gastroenterology, regarding "the importance of recognizing increased cecal inflammation in health and avoiding the misdiagnosis of nonspecific colitis'' which involved taking biopsies from the cecum and rectum in 85 people without any digestive symptoms, they found out that there is an increased microscopic inflammation of the cecum in healthy persons and every pathologist and clinician must be aware of these modifications[8].

Some studies published over the years have shown conflicting results between the role of appendectomy and the progression rate of ulcerative colitis: a cohort study from Denmark and Sweden which included 709353 patients with a familial predisposition to inflammatory bowel disease (IBD), appendicitis or mesenteric lymphadenitis during childhood or adolescence had a low risk to develop UC in adulthood[9]. On the other hand, the results published from a study from British which included 3829 patients who suffered an appendectomy and were compared with the same number of controls, did not found a relationship between these two pathologies[10].

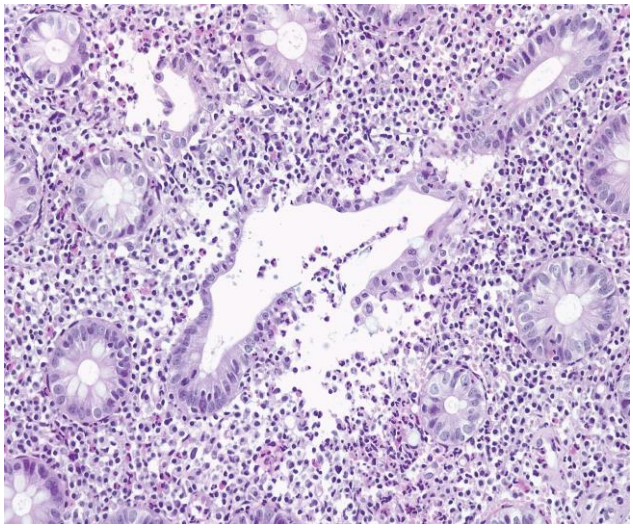

Fig.1 Chronic active inflammation, erosive, non-granulomatous, located peri-appendicular.

[8] Paski, S. C., Wightman, R ., Robert, M.E., & Bernstein, C.N. The importance of reconginizing increased cecal inflammation in health and avoiding the misdiagnosis of nonspecific colitis. The American Journal of Gastroenterology. 2007. 102(10), 2294-299

[9] Morten Frisch, Bo V Pedersen, Rolland E Andersson. Appendicitis, mesenteric lymphadenitis, and subsequent risk of ulcerative colitis: cohort studies in Sweden and Denmark. BMJ. 2009; 338: b716

[10] Carla Felice, Alessandro Armuzzi. Therapeutic Role of Appendectomy in Ulcerative Colitis: A Tangible Perspective? *Journal of Crohn's and Colitis*, Volume 13, Issue 2, February 2019, Pages 142–143

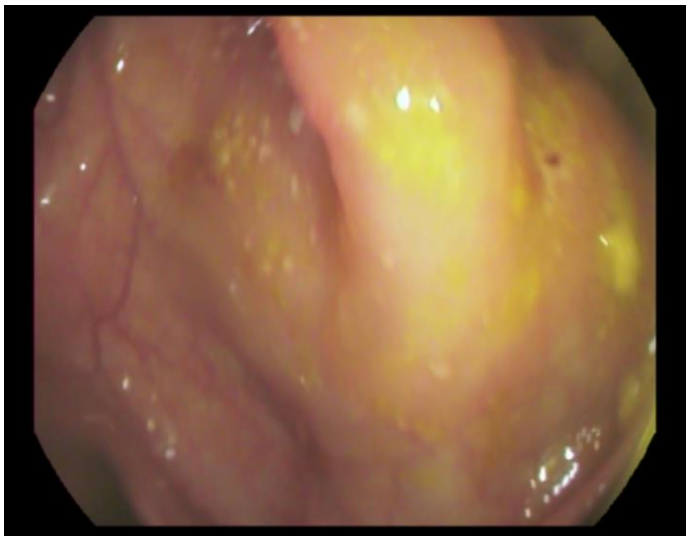

Fig. 2 showing the aspect of AOI

MATERIALS AND METHODS

The aim of this study is to explore the clinical characteristics and course, principally focused on distal extension of UC and AOI.

We searched our hospital database for the files of all patients who presented in our clinic between January 2018- December 2020 for symptoms associated to chronic diarrhea and carried a diagnostic of ulcerative colitis (either new diagnostic or follow up colonoscopy), and the disease activity was mild to moderate. We excluded those patients with indeterminate colitis, incomplete colonoscopy (the impossibility to explore correctly the cecum), or who had lesions proximal the splenic flexure. All the endoscopies were performed by well trained doctors from the same medical clinic.

The endoscopic report had to mention the cecal patch (and the degree of AOI was noted endoscopically as follows: 1- oedema, 2- moderate inflammation, 3- marked inflammation), appendiceal orifice inflammation or peri-appendiceal red patch, in the presence of proctitis or left-sided colitis to meet the eligibility criteria.

Baseline informations regarding demographic datas, family history of IBD, clinical disease activity, extent of the disease, the treatment used during the evolution, the number of colonoscopies performed, the progression of lesions, the necessity of surgery, as well as the histopathologist report were evaluated. Histological inflammation was scored by a pathologist with experience in UC, using Nancy score. The diagnostic of UC was made corroborating clinical symptoms, colonoscopy and histopathological specific features congruent with the disease.

Due to the fact that we had a small group of patients, basic statistics were calculated.

RESULTS

Were identified 98 patients who performed colonoscopy in our medical institution, of which 22 had pancolitis, so they were excluded from our study. Demographic data showed that 31 patients (40.00%) were females and 45 (60.00%) were males, most of them living in urban area (72.00%), and 36 of them (48.00%) were ex-smokers. Only one male patient (1.3%) with UC had a family history of IBD and this patient also met endoscopic criteria to be included in the AOI group. The treatment initated for all the patients, from the beginning, in order to maintain the remmision, included 5 aminosalicylic acid and most of them received

oral preparations and enemas. For 21 (28.00%) patients it was decided that the activity of disease was moderate and corticosteroid therapy was initiated, and some (16 patients) had multiple courses of corticosteroids, during the follow-up period. Of this 21 patients, 3 had also endoscopic (and histologic) diagnostic of AOI. Due to the severity of disease, 21.33% (16) got azathioprine and 11 patients (14.67%) needed anti-TNF therapy during follow-up period; none of them has lost the response for this treatment.

At the first presentation in the clinic, we appreciated that 1 patient (1.33%) had only rectal involvement, 25 (31.97%) had procto-sigmoiditis and 50 (66.67%) had lesions that extend till the splenic flexure, but none was diagnosed with PARP from the first beginning.

In regard to extraintestinal manifestations, 67 patients (87.67%) had none, but 3 of them had ankylosing spondylitis, 1 had hemolytic anemia, 3 had dermatologic disease (vitiligo and eritema nodosum) and 2 had hepatobiliary disease (primary sclerosing cholangitis and gallstones).

The surgeries performed for other pathologies are as follows: renal pathology (urolithiasis) -7 patients, cardiac pathology (coronary artery bypass graft surgery)-1 patient, neurosurgical pathology-1 patient and proctological impairment (anal fissure and hemorrhoids)-2 patients.

The report from the endoscopist showed typical features of UC at the index colonoscopy, with erythema, friability, ulcerations and granularity, without a specific aspect of PARP, but in evolution, this appearance was described in 7 patients, and the degree of macroscopic inflammation was at least moderate.

7 of the 76 eligible patients had PARP reported endoscopically, during their follow-up visits. Of this 7 patients, most of them (5) were non- smoking males, lived in the urban area and there weren't any important distinctions between those with or without PARP, in terms of age or progression of disease, but one woman had a restorative proctocolectomy with ileal pouch-anal anastomosis, because she failed medical therapy and the pathology specimen was used to endorse the already known diagnostic.

The endoscopy performed at the time of PARP diagnosis showed that all 7 patients had continuous lesions till the splenic flexure, meaning that for this group of patients, the lesions remained constant as extension.

There were 191 colonoscopies performed for all patients that had macroscopic and documented histological display of UC and 24 of it were performed for the 7 patient with PARP during the 3 year follow-up (median number of 3 colonoscopies, with a range of 2- 6). Biopsies from the cecum were taken every time a macroscopic apperence of AOI was suggested and out histopathologist noted the presence of basal plasmocitosis, chronic inflammatory infiltrate, the presence of neutrophils in lamina propria or in the epithelium and as well as the presence of erosions or ulcerations, calculating Nancy index in order to assess the histological disease activity. This histological activity resembled the activity shown in distal disease. All 7 patients with PARP obtain a grade 4 of the Nancy score, which is the analogous to severely active disease.

None of these patients had an escalation of treatment, after they were diagnosed with PARP lesions. It is important to mention that one person was found to have Crohn's disease during the natural process, distinguished by the the appearance of complex perianal fistulas. The diagnostic was then supported by histopatology and radiologic findings.

CONCLUSION

Endoscopic and histopathologic classification of inflammatory bowel disease is of critical importance in order to establish a clear diagnostic and implement the correct

medication. Although this specific entity is neglected by endoscopists and not all of them report it, the cecal patch is a signature lesion in ulcerative colitis, about which all those involved in the treatment of such disease should be aware, not to be confused with Crohn's disease. Nonetheless, a "cecal patch" of confined periappendiceal inflammation, probably due to normal immune cell density is a autograph skip lesion, contravening the well-known idea of continuous damage of the colonic mucosa. In our group of patients, the presence of PARP was not significantly correlated with an increased risk of proximal disease extension, so further studies are needed, with a larger group of patients to determine if there is a disparate prognosis in terms of disease severity, extension of the lesions or progress to colorectal cancer. To conclude, these patients should be prudently followed-up with complete colonoscopy and even though our colleagues described this entity, the idea that it was not missed on other occasions cannot be ruled out with certainty.

REFERENCES

1. **Faubion WA, Jr., Loftus EV, Sandborn WJ, Freese DK, Perrault J.** Pediatric "PSC-IBD": A descriptive report of associated inflammatory bowel disease among pediatric patients with psc. J Pediatr Gastroenterol Nutr 2001;33:296-300.
2. **Odze R, Antonioli D, Peppercorn M, et al.** Effect of topical 5-aminosalicylic acid (5–ASA) therapy on rectal mucosal biopsy morphology in chronic ulcerative colitis. Am J Surg Pathol. 1993;17: 869–875.
3. **Jorgensen KK, Grzyb K, Lundin KE, et al.** Inflammatory bowel disease in patients with primary sclerosing cholangitis: Clinical characterization in liver transplanted and nontransplanted patients. Inflamm Bowel Dis 2012;18:536-45
4. **Sang Hyoung Park, Suk-Kyun Yang, et al.** Atypical distribution of inflammation in newly diagnosed ulcerative colitis is not rare. Can J Gastroenterol Hepatol. 2014 Mar; 28(3): 125–130.
5. **S H Kroft, S J Stryker, M S Rao.** Appendiceal involvement as a skip lesion in ulcerative colitis. Mod Pathol. . 1994 Dec;7(9):912-4.
6. **Pera A, Bellando P, Caldera D, Ponti V, Astegiano M, Barletti C, David E, Arrigoni A, Rocca G, Verme G** . Colonoscopy in inflammatory bowel disease. Diagnostic accuracy and proposal of an endoscopic score. Gastroenterology. 1987;92(1):181.
7. **Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, D'Haens G, D'Hoore A, Mantzaris G, Novacek G, et al.** Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis. 2012;**6**:991–1030.
8. **Paski, S. C., Wightman, R ., Robert, M.E., & Bernstein, C.N.** The importance of reconginizing increased cecal inflammation in health and avoiding the misdiagnosis of nonspecific colitis. The American Journal of Gastroenterology. 2007. 102(10), 2294-299
9. **Morten Frisch, Bo V Pedersen, Rolland E Andersson.** Appendicitis, mesenteric lymphadenitis, and subsequent risk of ulcerative colitis: cohort studies in Sweden and Denmark. BMJ. 2009; 338: b716
10. **Carla Felice, Alessandro Armuzzi.** Therapeutic Role of Appendectomy in Ulcerative Colitis: A Tangible Perspective? *Journal of Crohn's and Colitis*, Volume 13, Issue 2, February 2019, Pages 142–143