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EDITORIAL

Shedding light on the dark side of microscopic colitis

V. Villanacci[1] · E. Antonelli[2] · M. Salemme[1] · G. Bassotti[3]

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Definition

The term microscopic colitis (MC) was coined to describe a clinical and pathological entity characterized by three elements [1]: (a) a clinical history of chronic watery (nonbloody) diarrhea; (b) a normal or almost normal endoscopic appearance of the colon; and c) a peculiar histological pattern [2–7]. It is important to keep in mind that the term MC was in effect a clinical and endoscopic definition, i.e., an "umbrella term" that included two pathological entities called lymphocytic colitis (LC) and collagenous colitis (CC) [8]; for this reason, the term MC has little or no significance from a histopathological point of view.

Epidemiology

Epidemiological studies have shown that the actual incidence and prevalence of MC are higher than initially thought and still show a rising incidence, although this rise is far less pronounced than in the past [9]. A population-based cohort study conducted from 1985 to 2001 in Olmsted County, Minnesota, showed that the incidence of CC was 3.1 per 100,000 and that of LC was 5.5 per 100,000 [5, 10]. Poisson's regression analysis demonstrated that the incidence of MC increased over time, and the incidence of MC by the end of 2001 was 19.6 per 100,000 [5]. The incidence of MC increases substantially with advancing age [11]; LC affects similar numbers of men and women, while CC is up to 20 times more frequent in women than in men [9, 12].

Clinical and therapeutic aspects

The mean age at diagnosis is 60–70 years [11]. The typical clinical presentation features chronic (either recurrent or intermittent) relapsing watery, nonbloody diarrhea. Symptoms may have been present for several months to 2–3 years before medical attention is sought and a diagnosis is made. Less frequent complaints include abdominal cramping, fecal incontinence, and weight loss, although the latter may be seen in 40 % or more of patients with CC [9, 13]. The natural history of MC is variable. Many cases are self-limiting, with symptoms lasting a few weeks or months and resolution of diarrhea in up to 50 % of patients receiving steroid treatment. Others may be symptomatic for years in a relapsing or continuous pattern. About 30 % of patients continue to experience persistent diarrhea, even 10 years after diagnosis [9, 11, 14]. There are rare case reports on spontaneous colon perforation and perforation during colonoscopy in patients with MC [9, 15, 16]. The treatment of these conditions is based on both anti-diarrheal and anti-inflammatory drugs. Oral budesonide can induce remission in both CC and LC and long-term maintenance in CC, although relapse is common when the drug is stopped [11].

✉ V. Villanacci
villanacci@spedalicivili.brescia.it

[1] Istituto di Anatomia Patologica, Spedali Civili di Brescia, Piazza Spedali Civili 1, 25100 Brescia, Italy

[2] Division of Gastroenterology, Perugia General Hospital, Perugia, Italy

[3] Division of Gastroenterology and Hepatology, Department of Clinical and Experimental Medicine, University of Perugia, Perugia, Italy

Diagnostic aspects: histopathology

The diagnosis of CC on hematoxylin- and eosin-stained sections is based on the presence of a thick amorphous hyaline eosinophilic band immediately beneath the superficial epithelium of the mucosa. This layer has an irregular, jagged lower edge, with a thickness of >10 mm, and the number of inflammatory cells in the epithelium and lamina propria is increased. The composition of the infiltrate displays some interesting features: Eosinophils may be markedly increased and are sometimes seen infiltrating crypts and surface epithelium together with T lymphocytes, the number of mast cells may also be increased, and neutrophils are often present and may induce crypt abscesses [12, 17–20]. The diagnosis of LC is based upon a diffuse increase (>20 per 100 epithelial cells) of intraepithelial lymphocytes (IELs) in the superficial epithelium and, in some cases, also within the crypts, without associated thickening of the subepithelial collagen band accompanied by an increase of lamina propria inflammatory cells. These findings are similar to those found in the duodenum of patients with celiac disease; in some cases, LC (and rarely CC) may be associated with this condition [21, 22].

Although the above definitions characterize the histopathological features of the two entities, in recent years several publications appeared in the literature reporting the appearance of different forms of MC under separate names. These were considered as variant of LC (cryptal LC, LC with giant cells, etc.) or CC (CC with giant cells, pseudomembranous CC, etc.), with a clinical presentation usually similar to the classic form. In addition, terms such as incomplete microscopic colitis (IMC) have been used when patients have clear clinical symptoms of MC, but the classic histological criteria for the diagnosis of LC and CC are only partially fulfilled. In particular, an increased number of IELs <20 × 100 epithelial cells in superficial epithelium (incomplete LC) and abnormal thickening of the subepithelial collagen band <10 μm (incomplete CC) together with an increased inflammatory infiltrate in the lamina propria have been reported. Other definitions for these conditions can be found in the literature, such as borderline LC, minimal CC, MC not otherwise specified, and paucicellular LC. To further muddy the waters, the term "undefined MC" (UMC) was recently introduced with the following definition: "if no information for further subtyping was available, cases were classified as UMC. This term was chosen to avoid any confusion with the term IMC which is used for patients with typical MC symptoms not fulfilling the strict histologic criteria for either CC or LC" [23–27].

The terminology used to describe forms of MC can be confusing for pathologists. We feel that, apart from the two main well-defined conditions, LC and CC, there is a "dark side" of MC similar to the term "indeterminate colitis" used for IBD, a container of different conditions that reflects a lack of knowledge or an incomplete histological evaluation. Therefore, to avoid confusion in the histological diagnosis of MC, we propose the following approach to provide more precise definition of this condition.

1. It is of paramount importance to obtain precise and complete clinical information regarding the drugs that may cause symptoms of diarrhea or cause inflammatory changes, since several drugs (e.g., proton-pump inhibitors, nonsteroidal anti-inflammatory drugs) may cause histological features of MC, and both the clinical and histological pictures may reverse following drug withdrawal.
2. Sampling of the colonic mucosa, with at the very least two biopsies from any segment of the colon including the terminal ileum, and correctly oriented samples (on acetate cellulose filters if possible) is needed for a correct histological evaluation, to avoid sampling bias due to too few biopsies and distortion of the fixed samples that may impair a precise evaluation by the pathologist.
3. From an histological point of view, we suggest considering only CC and LC, diagnosed on the basis of strict histological criteria. Thus, it is important to use CD3 to count IELs in the superficial epithelium for LC and the trichrome stain to evaluate the collagen band for CC. It is worth noting that this band may be intermittently present in the colon; therefore, multiple biopsy sampling in different sites is mandatory.
4. Apart from the "variant" forms displaying precise morphological characteristics, such as pseudomembranous collagen colitis and cryptic lymphocytic colitis, we suggest avoiding terms such as IMC and UMC in daily practice, because these terms are misleading and contradictory, with the result that other conditions such as infective, ischemic, pseudomembranous colitis, segmental colitis related to diverticular disease, and inflammatory bowel diseases may be underdiagnosed.

Our purpose is to limit confusion among clinicians by using definitions, such as "probable" or "possible," and to avoid further subcategorizations and subclassifications, to direct the clinician toward the correct treatment which in many cases of LC or CC, once the previous use of drugs is excluded [28], may be started as soon as possible with good results. We are persuaded that simplification is the better way to face actual problems, especially in a complex field such as that of endoscopic histological diagnosis, in order to avoid delays or errors in diagnosis and frequent, often unsuccessful revisions of the biopsy samples.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethical approval was not required by the ethical committee, since this was a reciew paper.

Informed consent Informed Consent was not required, since no patient was investigated in this article.

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