Dysplasia in inflammatory bowel diseases

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Mauro Frego - *Guest Editor*

This Editorial Symposium is dedicated to the two surgeons who have been example of life and surgical style for me. Professor Andrea Tropea, who first in our group addressed his studies and professional interest to inflammatory bowel diseases, dedicating his life to patients suffering of these, at times wasting, diseases and who was personally involved in until his premature death. Professor Davide F. D'Amico, master and teacher of surgery, who continuously stimulated our interest in the fascinating world of surgery, always reminding us that surgical skill cannot be deprived of scientific culture.

The *Editorial Symposium* highlights on the complex problem of dysplasia in patients chronically affected by inflammatory bowel diseases (IBD) and is based on the experience accumulated at the School of Professor D'Amico at Padua University, consisting of more than 500 patients operated on for Ulcerative Colitis (UC) and Crohn's Disease (CD) during a 30-year period. The clinical course of IBD usually requires most of these patients be followed up for many years, both by surgeon and gastroenterologist. At least 10% of them will develop some form of dysplasia, sooner or later in the natural history of the disease, and this situation should be interpreted on clinical ground facing important therapeutic decisions such as to continue observation or to proceed to surgery. Unluckily, some patients will directly present with an overt cancer, despite surveillance. The following papers deeply analyse the problem considering the most updated knowledge about the steps of carcinogenesis mediated by colonic inflammation and the new techniques of endoscopic, pathological and molecular diagnosis.

Dysplasia has been defined as unequivocal neoplasm of the epithelium confined to the basement membrane, without invasion into the lamina propria. A standardized classification system introduced by Riddell in 1983 divided dysplasia into categories, including indefinite dysplasia, low grade dysplasia, high grade dysplasia and cancer [1]. In 2000 the Vienna new classification of epithelial neoplasia of the gastrointestinal tract substantially confirmed the original frame and recognized five graduations from negative, to indefinite for neoplasia/dysplasia, to non-invasive low grade and high grade neoplasia (high grade adenoma/dysplasia, non-invasive carcinoma and suspicion of invasive carcinoma), and to invasive neoplasia (intramucosal carcinoma, submucosal carcinoma or beyond) [2]. It has been by now accepted that in IBD dysplasia can develop both on a raised polypoid lesion and in an area of flat mucosa based on its gross endoscopic appearance; hence the problem of how to recognize flat dysplasia at normal endoscopy and the need to develop new diagnostic tools [3].

The problem of the progressive degeneration of chronically inflamed mucosa towards cancer refers either to Crohn's disease (CD) or to ulcerative colitis (UC), but from a practical point the papers that compose this symposium are mainly focused on patients with UC. In fact, regular clinical surveillance by endoscopy and biopsies is restricted to large bowel and no other clinical and/or serum marker of dysplasia can be found out of pathological examination. Also for this reason dysplasia arising in CD is much less extensively known. In patients with CD the skip lesion pattern and the most often ileal involvement make much more difficult to detect and to study dysplasia. It is recognized that CD is associated with an increased risk to develop intestinal cancer compared to the general population [4] but the dysplasia rate in CD is still unknown. In CD, although several studies reported a 2 to 20-fold increase for large bowel can-

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cer [5] and an increased rate of small bowel cancer [6], discussion about cancer risk still remains controversial. A recent meta-analysis, based on population-based studies only, confirmed an overall increased risk of both small and large bowel cancer among patients with CD [7]. Nevertheless, risk factors associated with the development of carcinoma in CD are not well defined and only long disease duration and more extensive colon involvement have been indicated to contribute to the development of cancer in CD , similarly to UC [8,9].

The following papers deeply analyse the problem considering the most updated knowledge about the steps of carcinogenesis mediated by colonic inflammation and the new techniques of endoscopic, pathological and molecular diagnosis.

The *first review* summarizes the various problems encountered when dealing with patients with chronic IBD, also referring to the 35-year experience gained at our Institute. Particularly, the various risk factors have been considered, and the different surveillance protocols mainly based on endoscopy. Indications to surgery and surgical policy are debated in the light of early and late results, without omitting to consider the quality of life.

The *second review* focus on the pathological aspect of dysplasia in UC, whose definition does not show the real difficulties in the proper identification of the problem in a heavily inflamed colonic mucosa. In fact, although several classifications were created in the last decades, several acknowledged limitations remain, including poor inter-observer agreement and intra-observer reliability, even among expert gastrointestinal pathologists [10]. This review will show the most upgraded knowledge on this hot topic.

The *third review* takes in consideration that patients with UC are exposed to repeated episodes of inflammation that predispose to various tumorigenic events. The sequence of these events are different from those that contribute to develop a sporadic colorectal cancer. In fact, in UC the early events are represented by DNA methylation that produce an inhibition of onco-suppressor genes, mutation of p53, aneuploidy and microsatellite instability. Hypermethylation of tumor suppressor and DNA MMR gene promoter regions, is an epigenetic mechanism of gene silencing that contributes to tumorigenesis and may represent the first step in inflammatory carcinogenesis. P53 is frequently mutated in the early stages of UC-associated cancer; 33–67% in dysplasia and 83–95% in UC related cancer. Aneuploidy is an independent risk factor for forthcoming carcinogenesis in UC.

The *fourth review* analyses the clinical diagnostic issues of dysplasia in UC. The current approach to surveillance is based on the fact that dysplasia is a premalignant lesion and its identification and elimination could prevent or minimize complications associate with an invasive colonic cancer. The standard surveillance management includes a first colonoscopy performed after 8-10 years from the onset of the disease. However, results of a recent authoritative Dutch study showed that the diagnosis of colorectal cancer is delayed or missed in a substantial number of patients (17-28%) when conducting surveillance strictly according to these formal guidelines [11]. Therefore, the debate is still open and this review illustrates the different point of view about endoscopic dysplasia management, particularly considering new technologies.

The *fifth review* deals with the surgical treatment of patients who develop any form of dysplasia in the setting of UC. It mainly focus on two problems: is the presence of dysplasia an absolute indication to surgery? and should the dysplasia modify the surgical strategy and technique? Particularly, should surgery be the same as in uncomplicated disease or be more similar to patients with overt large bowel cancer? and should the degree and location of dysplasia influence the technical choice? There are no comparative studies on this specific field and answer can't be unique, therefore the final choice seems mainly to depend on personal experience rather than specific protocols.

Diagnosis and treatment of complications of UC, such dysplasia of different degree and cancer, require high level of attention and expertise. Due to the variety of this unique, fascinating problem management of these patients should be performed by a dedicated multidisciplinary team.

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