Letter to the Editor

Helicobacter pylori infection and colorectal carcinoma: pathologic aspects

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To the Editor,

Fleming *et al.* (1), by reviewing the pathologic aspects of colorectal neoplasms, summarized the pathogenesis and molecular classification of colorectal carcinoma (CRC) including mainly molecular pathways and environmental factors. However, they did not mention the potential pathologic aspects of environmental factors involved in colorectal oncogenesis, particularly in sporadic CRC.

More than 95% of colorectal cancers are sporadic, also mentioned by the authors (1), without a significant hereditary risk. Geographic variation in the incidence of CRC is substantial with a higher incidence observed in the West. Environmental factors contribute considerably to this variation (2); the majority of the sporadic cancer is believed to be due to modification of mutation risk by other genetic and/or environmental factors. Dietary factors may influence the oncogenic process by modifying intestinal transit time, altering the flow and recycling of bile, or changing the intestinal bacterial flora composition. Numerous studies support a role for the gut microbiota in colorectal oncogenesis and the colonic microbiota drives the progression towards colorectal malignancy including generation of reactive metabolites and carcinogens, alterations in host carbohydrate expression and induction of chronic mucosal inflammation (3); long-term colonization of the colon by rogue commensal bacteria capable of inducing chronic DNA damage could contribute to sporadic CRC developement, thereby suggesting sporadic CRC as an infectious disease (4).

In this regard, *Helicobacter pylori* (*Hp*), a curved spiral gram-negative bacterium found in the gastric mucosa of a large proportion of humans worldwide (>50%), has been evaluated as a possible etiologic agent for CRC and recent data indicate that there is a serological association between *Hp* infection (*Hp*-I) and the risk of CRC, especially for left-sided and early-stage cancers (5). Moreover, *Hp* seropositive subjects are associated with a modest increase in the risk for colorectal adenoma, and since *Hp*-I can increase the risk especially of advanced adenomas, the medical community should take into account that a preventive strategy is needed, and, furthermore, elucidating the pathophysiological role of *Hp* in the development of CRC is highly warranted (6). However, as mentioned by the authors (5,6), the serologic measurement of infection status is less than perfect, thereby representing a specific limitation of their studies. Indeed, the serological test does not discriminate between current and past infections and, apart from past infection that may even be more relevant for oncogenesis, such a distinction is essential because only current *Hp*-I induces humoral and cellular immune responses that produce or perpetuate chronic inflammatory processes in gastrointestinal tract with potential oncogenic sequelae; many neoplasms including colorectal adenomas and cancers arise at the sites of chronic inflammation and infection (7-10).

Based on histology, the practical gold standard for *Hp*-I diagnosis, our own preliminary studies indicated *Hp* presence in malignant tissue in 34 of 41 (82.9%) patients with CRC (23 men, mean age 73.6±7.9 years) (11). Extending these preliminary data we currently included 50 patients (28 men, mean age 71.3±9.7 years) with CRC and 25 patients (13 men, mean age 72.8±10.1 years) with colonic polyps with the following results: *Hp* presence in malignant and polyp tissues of patients were observed in 84% and 64%, respectively, confirming our preliminary data (12). It is important to note that, apart from Cresyl fast violet staining mainly used to detect *Hp*, its presence was also documented by immunohistochemical method (using polyclonal rabbit anti-*Hp* antibody (dilution 1:50, DAKO, Athens, Greece) in adenoma and malignant colonic tissues. Specifically, in accordance with Hong *et al.* (6),

Hp progressive increased presence was observed in our patients with adenomas associated with mild (50%) and moderate/high-grade (80%) dysplasia; the latter lesions are frequently described as advanced adenomas. However, contrary to the authors' considerations (6), our series showed an increased *Hp* presence in left-sided (79%) than in the proximal colon (21%) adenomas; left-sided cancers were also observed in 70.7% of our patients, a finding also noticed by Zhang *et al.* (5), thereby suggesting that *Hp*-I might be associated with a rather relevant risk increase in the left CRC.

The multistep model of gastric cancer postulates that there is initially an inflammation, caused mainly by *Hp*-I, which can lead to the development of chronic active gastritis. In a subset of these patients, this inflammatory process leads to the development of atrophic gastritis, followed by intestinal metaplasia, dysplasia, and, ultimately, early and advanced gastric cancer (13). It is considered that all stages prior to the development of high-grade dysplasia are potentially reversible, although this is still controversial (13). Because, *Hp* also induces inflammatory changes in colonic mucosa (14), it would be reasonable to further speculate, in view of our data, that chronic inflammatory process induced by *Hp*-I in colonic mucosa may lead to adenoma - mild-moderate/high grade dysplasia - CRC development sequence. These findings may emphasize the need for *Hp* eradication to prevent the development of both colon and gastric cancer (13).

In addition, we found that presence of *Hp* in malignant colonic tissue was associated with Ki-67 oncogene increased expression in all tumor specimens and low expression in all adjacent tissue specimens (15). Moreover, p53 increased and low expression was observed in 72.5% and 100% of tumor and adjacent tissues specimens, respectively. Likewise, antiapoptotic Bcl-2 protein was observed in 60% and 9% of tissue specimens, respectively, whereas proapoptotic Bax protein was observed in 9% and 100% of tissue specimens, respectively (15). Therefore, *Hp* colonizing colonic neoplasm tissue seems to be associated with an increased cell proliferation and impaired apoptotic process in malignant tissue compared with normal adjacent colonic mucosa, thereby possibly contributing to colon normal mucosa-adenoma-cancer sequence (15). In this regard, *Hp*-induced gastrin as an oncogenic growth factor, shows antiapoptotic activity through the Bcl-2 upregulation and contributes to gastric and colon carcinogenesis through stimulation of mutagenic and tumorigenic cyclooxygenase-2 expression (16). Animal models suggested the mitogenic action of gastrin to be limited to the left colon, elevated gastrin levels are more pronounced in their associations with rectal than with colon cancer, and the relation between hypergastrinemia and colorectal adenomas confers an increased risk only for distal colon adenomas. These findings are consistent with and may explain our findings and Zhang *et al.* (5) findings of selective risk increase with respect to left-sided CRC and adenomas.

Experimental data indicate that *Hp*-I leads to development of chronic inflammation, hyperplasia, metaplasia, dysplasia and recruitment and accumulation of bone marrow-derived cells (BMDCs) which may contribute to tumor formation in animal models with *Hp*-induced chronic gastric inflammatory process (9,13). Because *Hp* similarly induces the mentioned inflammatory changes in colonic mucosa (14), it would be reasonable to further speculate that chronic *Hp*-I in humans also induces repopulation of the colon with BMDCs that might facilitate colon adenoma and cancer development and progression (9,13). In this regard, our own preliminary studies indicated increased expression of CD44 [a marker of human hematopoietic stem and progenitor cells and cancer stem cells (CSCs)] in malignant colonic tissue in 75.6% patients with CRC (11). Extending these preliminary data, increased expression of CD44 was observed in 78% and 16% of patients with cancers and polyps, respectively (12). We also obtained comparable data with gastric cancer (9,13). Therefore, these findings suggest the possible BMDCs and/or CSCs involvement in *Hp*-associated gastric cancer development and colon adenoma and cancer growth and/or progression (9,13).

However, larger-scale future studies are warranted to show that the BMDCs move into areas of the upper and lower gastrointestinal tract and/or CSCs might be induced in the context of *Hp* chronic injury or inflammation with potential long-term colon adenoma malignant consequences in *Hp*-positive subjects. Finally, it is important to know if the authors (1) considered relative pathologic aspects in their studies.

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