LETTER TO THE EDITOR

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# Active *Helicobacter pylori* Infection Is a Risk Factor for Colorectal Mucosa: Early and Advanced Colonic Neoplasm Sequence

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*To the Editor:*

Based on serology, Lee *et al*.[1] concluded that *Helicobacter pylori* infection (*Hp*-I) increased the risk of advanced colorectal neoplasm (CRN), particularly when combined with atrophic gastritis (AG), thereby warranting strict colonoscopy screening and surveillance in *Hp*-positive AG patients. Indeed, *Hp*-related chronic gastritis could be involved in an increased risk of CRN that seems to be enhanced by the progression of gastric atrophy and the occurrence of active inflammation.[2]

However, the serological test does not accurately discriminate between current and past infections, also mentioned by the aurhors,[1] and, apart from past infection that might even be more relevant for oncogenesis, such a distinction is crucial because only current *Hp*-I induces humoral and cellular immune responses that induce or perpetuate chronic inflammatory processes in gastrointestinal tract with potential oncogenic sequelae; many neoplasms including colorectal carcinoma (CRC) arise at the sites of chronic inflammation and infection.[3,4]

Based on histology, the practical gold standard for current *Hp*-I diagnosis, our data in 50 CRC patients, 25 patients with colorectal adenomas (CRA) and 10 controls, showed significantly higher presence of *Hp*-I in the CRA (68%) and CRC (84%) groups compared with controls (30%).[5] Regarding the features of histological severity in CRA group, presence of *Hp*-I was observed in 50% of patients with mild and 80% of patients with moderate/severe dysplasia. Likewise, presence of *Hp*-I in the CRC group was observed in 89% of patients with mild and 83% of patients with moderate/severe grade.[5] Noteworthy, Hp presence was documented by immunohistochemical stain in CRA and CRC tissues.[5] In addition, presence of *Hp*-I with accompanying immunohistochemical expression of CD44 (indicator of cancer stem cells [CSCs] and/or bone marrow-derived stem cells [BMDSCs]) in biopsy specimens was found in a high proportion of CRA patients accompanied with moderate/severe dysplasia (88%) and CRC patients with moderate/severe degree of malignancy (91%).[5,6] Comparable pictures were also obtained for proliferation marker Ki-67, anti-apoptotic Bcl-2 and CD45 (assessing mainly T and B lymphocytes locally) immunohistochemical expressions.[5,6]

By introducing univariate analysis, the authors found that metabolic syndrome (MetS) was significantly associated with overall and advanced CRN.[1] In this regard, in a systematic review, we reported an association between *Hp*-I and insulin resistance (IR), the major underlying mechanism responsible for the MetS.[7] Our data further indicate that *Hp*-I might represent one further hit contributing to nonalcoholic fatty liver disease (NAFLD) pathogenesis, representing the hepatic component of MetS;[8] NAFLD closely related to IR is involved in colon oncogenesis. Other studies also suggest that *Hp*-I with concomitant MetS might further increase CRA risk.[9]

Components of MetS are also associated with esophageal adenocarcinoma (EAC) risk and *Hp*-related IR[7] might associated with gastroesophageal reflux disease (GERD), Barrett's esophagus (BE) and EAC.[10] Although epidemiologic studies do not suggest causality with Hp, the interplay between *Hp* and host factors plays an important role in the pathogenesis of GERD and its complications BE and EAC in certain subpopulations.[10]

Therefore, casting further light in the uncertain pathophysiological mechanisms underlying *Hp* and CRN association, apart from gastrin mitogenic action mentioned by the aurhors,[1] our results indicate that *Hp*-I has an impact on colorectal oncogenesis by: causing a possible chronic inflammatory mucosal damage, comparable to upper gastrointestinal tract (UGT); stimulating CSCs or recruiting BMDSCs, similar to UGT *Hp*-I-associated

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chronic inflammation, AG, hyperplasia, metaplasia, dysplasia and BMDSCs recruitment that may facilitate tumor formation and progression in animal models and humans;[5,6] and affecting MetS parameters, oncogenes and immune surveillance processes, that may be involved in the sequence: colon epithelium transformation to CRA–dysplasia–CRC development/progression. Finally, *Hp*-related IR and additional MetS parameters might also contribute to GERD-BE-EAC sequence particularly in certain subpopulations,[10] though further studies are warranted to elucidate the proposed mechanisms involved in *Hp*-induced colorectal and possibly UGT oncogenesis.

Therefore, Hp and MetS-related colon oncogenesis might justify CRN screening and surveillance program in the mentioned by the authors and by others high-risk patients[9] and Hp eradication might inhibit the development or delay progression of CRN and possibly EAC.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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