Conclusion that autoimmune gastritis does not predispose to gastric cancer is unproven

I read with great interest the paper by Rugge *et al*[1] with the commentary by Goldenring[2] challenging an old, established fact that autoimmune gastritis (AIG) (pernicious anaemia) predisposes to gastric adenocarcinoma.[3] The idea behind the study by authors from three different countries was that AIG induces gastric adenocarcinoma only in those having had an initial, but transient *Helicobacter pylori* infection not detectable at the time of cancer diagnosis. They studied patients with presumed AIG (gastritis restricted to the oxyntic mucosa and negative for *H. pylori*) by endoscopy with biopsies two times with a mean of 7.5 years between the initial and follow-up endoscopy.[1] Atrophy was evaluated by histology.[4] Curiously, they did not do any serological assessment of oxyntic atrophy like pepsinogen I, vitamin B12 or gastrin. The quantification of oxyntic atrophy by histology based on a few biopsies is naturally inferior to the serological methods which reflect the function of the total area of oxyntic mucosa. At the second and final endoscopy, 109 of 211 subjects had no oxyntic atrophy and the remaining 109 only mild atrophy.[1] It is thus not surprising that they did not detect any adenocarcinomas or intraepithelial precancer lesions.[1] In a German study where one of the authors of the present study was the last author, 4.9% of the gastric cancer patients had AIG and many of them had pernicious anaemia as an important clinical sign.[5] The mean age of the patients with AIG and gastric cancer was 67 years[5] compared with the age of 55.7 years in the Rugge *et al* study.[1] Reduced vitamin B12 as well as pernicious anaemia seem not to be associated to *H. pylori* gastritis.[6] Pernicious anaemia was also recognised as a late manifestation of AIG in an AGA Clinical Practice Update on Atrophic Gastritis recently published.[7] Determination of B12 could accordingly be used in the discrimination between oxyntic atrophic gastritis caused by *H. pylori* and autoimmunity.

Achlorhydria has previously been accepted as a condition predisposing for gastric cancer.[8] Unfortunately. The study by Rugge *et al*[1] was not designed to allow for such an evaluation. The authors describe enterochromaffin-like (ECL) cell hyperplasia in a proportion of the patients indirectly indicating hypergastrinaemia. At follow-up, the degree of ECL cell abnormalities had slightly increased indicating a process under evolution. It is strange that the authors do not discuss the role of the ECL cell in carcinogenesis in patients with AIG taking into consideration that gastric carcinomas in patients with pernicious anaemia showed ECL cell/neuroendocrine differentiation when examined with the most sensitive methods.[9] Among the authors, there are specialists of pathology,[1] and it would have been natural to comment on the publications of ECL cell differentiation in adenocarcinomas in general.

Finally, have the authors any explanation of the mechanism for the postulated early loss of *H. pylori* in those with AIG who later develop gastric cancer? Taking into consideration that patients with antral *H. pylori* gastritis leading to duodenal ulcer are saved from gastric cancer does not support that *H. pylori* is such a potent and direct carcinogen? Is *H. pylori* a direct carcinogen, or does *H. pylori* gastritis induce gastric cancers indirectly by inducing oxyntic atrophy?

If Rugge *et al*[1] had examined patients with *H. pylori* at a relatively early phase, for instance 10 years after infection, they would not have found any increase in gastric cancer and accordingly concluded that *H. pylori* does not cause this malignancy. Interestingly, and in contrast to the postulated transient *H. pylori* infection,[1] a recent study described increased risk of gastric neoplastic lesions in patients with AIG treated with proton pump inhibitors before diagnosis.[10] In conclusion, the postulated *H. pylori* infection as the cause of gastric cancer in AIG is pure speculation.

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