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Equipe : Cancer digestif associé à l'infection par Helicobacter, cellules souches cancéreuses et stratégies thérapeutiques

Report on the Thesis Dissertation of Malgorzata Osmola

entitled

Biomarkers, Autoantibodies and Micronutrient Deficiencies in Gastric Precancerous Lesions

The thesis dissertation is a document of 106 pages including a summary in English and in Polish (2 pages for each), an introduction to the topic (28 pages), the aims of the thesis (1 page) followed by 4 published articles (44 pages), a summary and conclusion (3 pages), 140 references and the statements of ethics, funding and authorship.

In the Introduction, the author presents nicely the status of gastric cancer, its epidemiology, the different classifications proposed, the risk factors including the rare genetic predisposition in addition to *Helicobacter pylori* infection, Epstein Barr Virus and some environmental factors. Then the treatments used are presented, including the more recent ones with the results of clinical trials. A second part is dedicated to the gastric precancerous lesions describing the peculiarities of *H. pylori* gastritis versus those of the emerging autoimmune gastritis. In the third part, the different non-invasive biomarkers of gastric precancerous lesions are considered, first pepsinogens and the pepsinogen I/II ratio for which the most data are available, then emerging ones: human epididymal protein 4 (HE-4), interleukin 6, adiponectin, Krebs von den Lungen-6 and finally the possible use of combinations of different biomarkers.

After a short part related to gastric precancerous lesions and gastric cancer, the micronutrient deficiencies in gastric precancerous lesions are developed. These deficiencies are not usually correctly explored, especially iron deficiency linked to the stomach hypochlorhydria, notably in the case of autoimmunity, but also when *H. pylori*, which uses iron, is present. Vitamin B12 deficiency occurs later and, for *H. pylori* infection, the mechanism has not been fully explored.

Then the author presents the rationale for the articles, all of which are based on prospective multicenter studies carried out in France, and their aims.

<u>First article</u>

In this article, the detection of pepsinogens and the new markers indicated above was performed by a chemiluminescent enzyme immunoassay using a fully automated apparatus from Fujirebio named Lumipulse. Histology was used as the reference for the gastric precancerous lesions on a cohort of 356 patients previously tested for pepsinogens by ELISA.

Interestingly, a relatively good sensitivity (75%) and specificity (92.6%) were found for moderate to severe corpus atrophy, using the pepsinogen I/II ratio while the sensitivity of IL-6 for moderate to severe antrum atrophy was 72.2%. In addition, the combination of pepsinogen I/II ratio and HE-4 had a sensitivity of 85.2% for detection of moderate to severe atrophy at any location.

This study has the advantage to present receiver operating characteristic (ROC) curves for the different types of atrophic gastritis.

This article was published in the journal *Diagnostics* (IF: 3.6), with M. Osmola as the third author.

Second article

In the second article, the same group of patients was tested but the location of the gastric atrophy was essentially considered, *i.e.* corpus limited atrophy or not. They could show that PGI and PGI/II ratio was significantly lower in the case of autoimmune gastritis, either corpus limited or extensive, compared to non-autoimmune gastritis, antrum limited or extensive.

The difference was also significant when considering chronic atrophic gastritis involving the corpus only in the case of an autoimmune component versus involving the antrum, the limit being the low sample size.

The conclusion is that pepsinogens allow a discrimination between autoimmune gastritis and non-autoimmune gastritis, *i.e. H. pylori* gastritis.

This article was published in *Digestive and Liver Disease* (IF: 5.16) with M. Osmola as the third author.

Third article

This article aimed to investigate the presence of autoantibiodies in patients with chronic atrophic gastritis. The emergence of a possible new type of gastric cancer without *H. pylori* infection for which autoimmunity has been suggested motivates this research.

In the same patient group as before, 19 autoantibiodies were tested by immunoblot, including 12 myositis-specific autoantibodies.

The results show that anti-parietal cell antibodies and anti-intrinsic factor antibodies are more frequent in autoimmune gastritis versus non-autoimmune gastritis or controls while anti-nuclear antibodies were also found in these two categories. Myositis antibodies did not have any interest in this context. In a multivariate analysis, antinuclear antibodies were linked to female gender. So globally speaking, this study did not support an over-representation of common antibodies in patients with chronic atrophic gastritis.

This article was published in the journal *Diagnostics* (IF: 3.6) with M. Osmola as the first author.

Fourth article

In this article the consequence of chronic atrophic gastritis on micronutrient deficiencies are explored.

Serum ferritin was used as an indicator of iron deficiency, taking into account a possible inflammation by adjustment on CRP. Iron deficiency was present twice more often in case of autoimmune gastritis versus non-autoimmune gastritis and controls (33% versus 17%).

Vitamin B12 deficiency was found in 13% of autoimmune gastritis, 1.5% of non-autoimmune gastritis, and 2.8% of controls.

The multivariate analysis indicated only a link between autoimmune gastritis and vitamin B12 deficiency according to what is known.

However, the frequency of iron deficiency indicates that it should be screened in autoimmune gastritis. It was not possible to conclude with regards to the impact of *H. pylori* infection on iron deficiency.

Concomitant iron and vitamin B12 deficiency appears to be a rare event.

This article was published in *Digestive Diseases* (IF: 2.3) with M. Osmola as the first author.

In summary, this thesis has the advantage of considering the different aspects of gastric precancerous lesions and their consequences studied on the same group of patients. It is especially pertinent at a time when the possibility of autoimmune gastritis is rising, especially in a younger population, with its impact on micronutrient deficiencies.

It also introduces a new method for pepsinogen testing with the chemiluminescent enzyme immunoassay which was compared to the standard ELISA and shows the interest to combine pepsinogen I/II ratio with another marker, *i.e.* HE-4 to increase the accuracy of the result.

The detection of a large panel of autoantibodies also has the merit of showing the interest of anti-nucleic antibodies, in autoimmune gastritis, despite its limited sensitivity.

This thesis is an important addition to our knowledge on gastric precancerous lesions with adequate references and the information it offers will help to prevent gastric cancer, given that prevention is the essential measure to be taken.

The doctoral dissertation meets the conditions specified in Art. 187 of the At of July 20, 2018, Law on Higher Education and Science (Journal of Laws of 2018, item 1668).

I strongly support the defense of this thesis by M. Osmola to obtain the title of Doctor of Medical Sciences of the University of Warsaw.

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