
Note
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Re: Helicobacter pylori and Atrophic Gastritis: Importance of the cagA Status

We read with great interest and fully concur with the findings reported by Kuipers et al. (1) in a recent issue of the Journal; most importantly, they concluded that infection by Helicobacter pylori (H. pylori) of the cagA (cytotoxin-associated gene A) strain is of importance in defining gastric cancer risk.

Three years ago, we started a research network on gastric cancer and precursor lesions, which we named MHEPHISTO (Metaplasia Helicobacter pylori Histology). Within this program, we follow prospectively patients with gastric cancer who are under our care at our hospitals in Turin, Italy.

The patients were given a 13C-urea breath test for the detection of H. pylori infection according to the European standard (2) and blood samples were taken and analyzed for antibodies against H. pylori. Total immunoglobulins against H. pylori were tested by use of a commercial enzyme-linked immunosorbent assay, while anti-cagA antibodies were identified by use of an enzyme-linked immunosorbent assay designed to detect serum immunoglobulins directed against the cagA protein (3,4). The antigen used in the test was from A. Covacci (IRIS Biocine, Siena, Italy).

Of the 51 patients operated on for gastric cancer and in whom we tested for antibodies to the cagA protein, 49 (96%) were found to be positive. Hence, we defined them as being infected by the cagA-positive strain of the bacterium. We estimate that the general population of Turin carries an 18% positivity for anti-cagA antibodies as determined by testing 555 consecutive individuals admitted to the Emergency Care Unit of our hospital during August 16-31, 1994 (5). The risk of dying from gastric cancer in Turin is 2.3% (cumulative risk based on individuals aged 0-74 years) (6). Thus, it is probable that one of every eight anti-cagA-positive individuals in our city will die of gastric cancer before reaching 74 years of age.

We are unaware if other populations are similarly at risk, but Dr. Kuipers' report seems to signal that this may be so in the Dutch population as well. Considering the findings of Kuipers et al. (1) and our own, we believe that in defining gastric cancer risk, we should not overzealously suspect H. pylori unless it has been shown to have the cagA gene. Instead, we recommend that people aged 45 years and older in Turin be tested for anti-cagA antibodies. Those individuals testing positive should then be offered upper gastrointestinal tract endoscopy with multiple biopsies to identify diffuse atrophic gastritis and intestinal metaplasia, two conditions placing these patients at an increased risk of cancer.

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References

Note
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Response
We appreciate the reaction of Ponzetto et al. to our report concerning the presence of cagA (cytotoxin-associated gene A) serum antibodies and the risk of the development of atrophic gastritis. The observations communicated in their letter are potentially very valuable and further support the hypothesis that infection with a cagA-positive H. pylori strain imposes a greater risk for the development of atrophic gastritis and gastric cancer than does infection with a cagA-negative strain. This association has now been reported to exist in three different populations around the world: inhabitants of Italy and The Netherlands and Japanese-American men from
In our recently published cohort study (1), we observed the presence of atrophic gastritis in 62% of 24 cagA-positive patients, compared with 32% of 34 cagA-negative patients, corresponding with an odds ratio (OR) of 3.48 (95% confidence interval [CI] = 1.02-12.2). In a previous, prospective, nested case-control study (2), we observed the development of gastric cancer in 109 subjects who had had a phlebotomy 13 ± 5 years (mean ± standard deviation) earlier. On the basis of serologic testing, 103 (94%) of these subjects had been infected with H. pylori at the time of bleeding. In an extension of this study, it appeared that 90 (87%) of these 103 patients with gastric cancer had been infected with cagA-positive strains (3). This proportion was 78% in 103 matched H. pylori-infected control subjects who did not develop gastric cancer during follow-up, corresponding with an OR of 1.9 (95% CI = 0.9-4.0) (3). The association between infection with a cagA-positive H. pylori strain and gastric cancer was strongest for intestinal-type carcinomas of the distal stomach (OR = 2.3; 95% CI = 1.0-5.2) (3). Ponzetto et al. found cagA antibodies in 96% (95% CI = 87-100) of 51 patients with gastric cancer. This percentage is in agreement with our previous findings, but is remarkably high considering that the specimens were from patients who already were diagnosed as having cancer. During the process of the development of atrophy and cancer, signs of a pre-existing H. pylori infection may disappear (4). The 18% prevalence of cagA antibodies in the control subjects, on the other hand, seems rather low when compared with other studies. It is not clear whether or not all of the 555 consecutive individuals tested were H. pylori positive.

In total, the findings of Ponzetto et al. are very provocative. They would be best served by a fuller exposition of the data, including formal information on the accuracy of the diagnostic tools used, rates of infection with cagA-positive strains in appropriate controls, location and histologic type of the tumors, and H. pylori status of patients and controls. We look forward to this more extensive publication.

References


Re: How Does the MRP/GS-X Pump Export Doxorubicin?

A recent correspondence to the Journal (1) addressed the role of the MRP gene-encoded multidrug resistance protein (MRP) (2) in cytotactic drug resistance. It has been shown that transfection of the MRP gene induces transport of the cytotactic drug doxorubicin (3) as well as adenosine triphosphate (ATP)-dependent transport of glutathione S-conjugates (GS-X) (4), the organic anion calcine (5), and the heavy metal ion arsenite (6). The discussion in the above-cited correspondence addressed the question of how one protein might mediate the active transport of anions (dinitrophenyl-S-glutathione and calcine) as well as neutral (etoposide) and cationic (doxorubicin, daunorubicin, vincristine, and rhodamine 123) lipophilic drugs.

In our contribution to this discussion, we wish to summarize some related evidence that has not been adequately considered. Ishikawa et al. (1) tried to find explanations for the fact that doxorubicin efflux from cells is not remarkably enhanced by transfection with the MRP gene alone. Their hypothesis is that doxorubicin must first be conjugated to glutathione in a series of chemical reactions in order to be recognized as a substrate for MRP.

To our knowledge, convincing data excluding the possibility that nonconjugated doxorubicin is actively transported from MRP gene-transfected cells have not been published. Demonstration of such doxorubicin transport requires a sensitive, carefully controlled experimental setup because of extensive binding of this drug to plastics and proteins. In addition, the ratio of active to passive transport that determines the accumulation deficit caused by P-glycoprotein or MRP is not as favorable for doxorubicin as it is for other substrates (e.g., rhodamine 123 or calcein-AM for P-glycoprotein). Therefore, since available MRP gene-transfected cells do not exhibit very high MRP overexpression, active doxorubicin transport might easily be missed. The apparent absence of ATP-dependent transport of doxorubicin in MRP overexpressing inside-out vesicles (1) is not definitive evidence of the absence of such transport.

On the other hand, some data on MRP-mediated transport are consistent with the transport of unmodified drug molecules. First, a much more rapid efflux rate has been shown for daunorubicin and etoposide with MRP-overexpressing cells than with drug-sensitive cells (7). This efflux rate is comparable to efflux rates in cells highly overexpressing Pgp (8). However, it has not been found that glutathione conjugates of doxorubicin are formed in tumor cells in amounts appreciable enough to account for this rapid efflux (6). In addition, if labile glutathione conjugates were pumped into the culture medium by MRP, then an increase in glutathione efflux should have been found at maximal pump rates for daunorubicin. This was not the case (9).

References