E-cadherin molecular expression in the diffuse and intestinal types of gastric adenocarcinoma. A report from Lima, Peru

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ABSTRACT

Objective: signet ring carcinoma of the stomach is well known to be more aggressive and infiltrating than adenocarcinoma, different studies have proposed that signet ring cell carcinoma would be more infiltrating because of the lost of E-cadherin expression, this cadherin is a class of protein cell membrane protein which plays an important role in cell-adhesion.

Methods: we carried out a transversal comparative study, in order to measure the E-cadherin expression in 10 cases of signet ring cell and in 10 cases of adenocarcinoma, with help of immunohistochemistry.

Results: we found a bigger expression of E-cadherin in adenocarcinomas (100%) than signet ring cell carcinoma (40%), this difference was significative using Fisher test (p = 0,011). The lost of E-cadherine would explain the bigger infiltrating capacity in comparison to adenocarcinoma.

Key words: Gastric signet ring cell carcinoma. Gastric adenocarcinoma. E-cadherine.

INTRODUCTION

Since Lauren (1) described two types of gastric adenocarcinoma (intestinal and diffuse) with different biological characteristics and prognoses back in 1965, much information has been gathered regarding their morphological, clinical, and epidemiological behavior.
From a morphological standpoint, intestinal-type adenocarcinoma is formed by very cohesive glands, and includes WHO classification’s tubular and papilipherous types, while diffuse adenocarcinoma is marked by the presence of individual disperse cells corresponding to the signet ring-cell type of adenocarcinoma.

Clinically and epidemiologically there is much information showing that signet ring-cell carcinoma is more common in females and young patients, usually located in the upper stomach, and frequently invasive. On the other hand, intestinal carcinoma is more common in males and older patients, and is exophytic and located more distally in the stomach (2-4).

*Helicobacter* has been associated with intestinal-type carcinoma not as much as with diffuse gastric cancer (5,6).

In spite of these differences, all of them well established little is known about differences at molecular levels. Some studies have pointed out that intestinal-type carcinoma expresses more epidermal growth receptors Erb B2 and Erb B3 (7), as well as apoptosis-regulating proteins BCL-2 and BAX, findings that are consistent with the replicative but not the invasive power of cancer. In 1994 Becker et al. showed that signet ring-cell carcinoma has more frequent mutations in the E-cadherin gene when compared to the other types of gastric carcinoma (8). Since this publication, several studies have been conducted with sometimes contradictory results. There is no such study in Peru.

Our study analyzes the histological and clinical characteristics of signet ring-cell carcinomas diagnosed between 2000 and 2005, and measures the expression of E-cadherin in diffuse gastric carcinoma versus intestinal-type adenocarcinoma.

**MATERIAL AND METHODS**

This is a comparative cross-sectional study. We identified all cases diagnosed as gastric intestinal and diffuse adenocarcinoma during the period 2000-2005. A case was defined as diffuse or signet ring-cell carcinoma if more than 50% of its cell population was constituted by “signet ring cells” as suggested by WHO (9).

To study E-cadherin, a random sample was obtained from all cases of gastric carcinoma, and 10 cases were analyzed in each group. For E-cadherin detection we used monoclonal antibodies (Zymed Laboratories), and samples were processed using the immunoperoxidase technique. We considered a cell positive to E-cadherin when a gold staining of the cell membrane developed and a case positive to E-cadherin when more than 60% of its cells were positive to E-cadherin. All data were processed using SPSS 13.0, and the statistical analysis was done using the Chi-squared and Fisher’s tests when appropriate.

**RESULTS**

During the study period we identified 90 cases of signet ring-cell carcinoma (mean age 55.9 years, male preponderance 62.5%), and 382 cases of intestinal adenocarcinoma (mean age 64.2 years, male predominance 64.9%). All intestinal-type adenocarcinomas expressed positivity for E-cadherin, whereas only 40% of signet ring-cell carcinomas did so.

We made a contingency table with our data and, using a Chi-squared test and Fisher’s correction, we found a significant difference in the frequency of E-cadherin between intestinal and diffuse adenocarcinomas (p = 0.011).

**DISCUSSION**

When a tumor is invasive this is partly due to the fact that adhesion between cells has been lost. One of the most important proteins for this adhesion between epithelial cells is E-cadherin, a member of the so-called adherens junction zone, which plays an important role in epithelial integrity. E-cadherin is an intercellular adhesion glycoprotein of 120 Kd (10). It is localized on the surface of epithelial cells, preferably on contact surfaces. E-cadherin has a small intracytoplasmatic domain that interacts with actin through a series of molecules called alpha-, beta-, and gamma-catenins (11). Thanks to these catenins, it participates in epithelial adhesion and cohesion.

An absence of these proteins reduces adhesion in both normal and neoplastic tissues, and explains why some tumors are more invasive. Diffuse adenocarcinoma is classically known for its being more aggressive and infiltrating than the intestinal type, and therefore we may assume that diffuse-type adenocarcinoma has a lower expression of this adhesion molecule. In 2002, in Korea, E-cadherin was studied in colon carcinoma. All signet ring-cell carcinomas were negative for this molecule, and only 23% of adenocarcinomas were negative (12).
In gastric cancer results have been contradictory. Chu et al. in 2002, reported a 57% positivity for E-cadherin and cytokeratin in signet ring-cell gastric carcinomas (13). Zhang et al. reported no differences in the expression of E-cadherin between different types of gastric carcinomas (14). Chen HC et al. found a significant difference in cadherine expression between gastric adenocarcinomas of the intestinal and diffuse types (15). Our study shows that signet ring-cell carcinomas have a lower expression of E-cadherin than other types of gastric adenocarcinomas.

Apparent differences between other author’s results and our own results may be explained by the fact that immunohistochemistry positivity or negativity is based on previously agreed criteria. We considered a case as negative if it had more than 40% of its cell population negative to E-cadherin. So there is a point in common among different authors, that there may be a minimal E-cadherin expression even in diffuse-type adenocarcinomas. On the other hand, in intestinal-type carcinomas small zones of epithelial cells lacking E-cadherin expression may be found.

Yong et al., in China, found an inverse relation between grade of tumoral differentiation and expression of E-cadherin, with 18% of altered E-cadherin expression in intestinal carcinomas, and 100% in diffuse types (16). In view of these results we believe that absence of E-cadherin expression would result in loss of
this molecule during tumor growth. In other words, this phenomenon would happen in diffuse-type carcinomas but also in the less well-differentiated intestinal ones. It may also be considered that a genetic factor plays an important role, as happens in familiar cases of gastric adenocarcinomas. In those patients a mutation in E-cadherin genes has been pointed out; in 1998, in New Zealand (17), a mutation in some exons in the E-cadherin gene was demonstrated in a family with signet ring-cell gastric carcinomas. Gayther (18) showed that same year similar mutations in this gene in European families with a family history of gastric cancer, and a few years later in Mexico (19). These mutations were only found in those with diffuse-type carcinomas.

Some authors have reported loss of E-cadherin expression in pre-neoplastic lesions, and in early-stage gastric carcinomas. This could be a reflection of E-cadherin being replaced by Li-cadherin, a molecule usually absent in gastric tissue, but that has been found in gastric intestinal metaplasia and in some intestinal-type gastric carcinomas (20). The replacement of E-cadherin by Li-cadherin may explain why some intestinal-type carcinomas lack E-cadherin but still keep a cohesive tissue.

Zhou et al. found a relation between E-cadherin and tumor size, but not infiltration extent or metastasis. Similar findings have been reported in Chile (21). We must then understand that E-cadherin is not solely responsible for tissue adhesion. Other catenins may also be involved. A non-functional E-cadherin must also be taken in account, so we can explain why some very undifferentiated invasive carcinomas may express E-cadherin positivity, but with a non-functioning molecule. This issue was suggested by Becker (22), who using a monoclonal antibody called “E-cad delta 9-1”, designed to identify a mutant cadherin, showed that this protein is present in 13% of signet ring-cell carcinomas that are positive for E-cadherin. Thus it is implied that signet ring cells positive for E-cadherin express a mutant form of cadherin, and this would be a non-functioning mutant protein.

An adenocarcinoma’s capacity to invade and metastasize depends on its losing the whole complex of adhesion molecules (including E-cadherin), and as Guzmán (23) points out, it also is affected by immune response. In this study we could not evaluate wall invasion extent, as mucosal biopsies were used; however, such an assessment would be of interest (23,24).

In conclusion, our findings show that intestinal type gastric carcinomas express E-cadherin with a frequency significantly higher than that of diffuse carcinomas.

REFERENCES
