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Histopathological features of mucosa atrophy in atrophic body gastritis

Características histopatológicas da atrofia da mucosa na gastrite atrófica do corpo

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ABSTRACT

Introduction: Gastric mucosa atrophy became a major issue in gastric pathology because of its connection with risk lesions for gastric cancer. Although gastric atrophy is frequently associated with different diseases, it has been included in many studies simply as a generic pathological condition, and different causes of gastric atrophy are omitted. **Objective:** To study the histopathological features of gastric mucosa atrophy in *H. pylori*-negative patients with atrophic body gastritis (ABG). **Material and methods:** Consecutive cases of patients diagnosed with ABG, and presenting normal or just lightly inflamed antral mucosa, were studied. Patients with gastrointestinal cancer and those with history of prior gastrointestinal surgery were excluded. The presence of intestinal metaplasia and pseudoantral (PSA) metaplasia in atrophic body mucosa was assessed. **Results:** During the period of 2004-2006 a total of 7,309 patients underwent gastroesophageal endoscopy with biopsies of the gastric mucosa; 3,556 (48.6%) were males, and 3,753 (51.4%) females. Among them, 105 had the diagnosis of ABG confirmed, with 32 (30.5%) males, and 73 (69.5%) females ($p < 0.001$). Intestinal metaplasia and/or PSA metaplasia were identified in all patients. As isolated lesions, PSA metaplasia was more frequent than intestinal metaplasia, respectively 42 (40%) vs. four (3.8%) cases. In most patients (56.2%) both types of metaplasia occurred simultaneously, and no differences were observed among genders ($p = 0.67$). **Conclusion:** Gastric mucosa atrophy in ABG shows distinctive histopathological features which should be considered in studies on the relationship between gastric mucosa atrophy and gastric cancer.

Key words: gastritis; atrophic gastritis; stomach; stomach diseases.

INTRODUCTION

Gastric mucosa atrophy has now become a major issue in the chapter of gastrointestinal pathology in view of its close connection with risk lesions for gastric cancer[1-6]. The first objective descriptions of this association were reported in the 1970s[1]. This period of time coincided with the advent of endoscopy of the digestive tract under direct vision that has spread rapidly as a method of great value for the diagnosis of gastroduodenal lesions. Endoscopic observation of the gastrointestinal mucosa has become complemented by the histopathologic analysis of mucosal fragments removed during endoscopic procedures. Histological examination of these tissue specimens became a very useful tool for the final completion of the gastrointestinal endoscopy.

The diagnosis of gastric atrophy and intestinal metaplasia, both of them considered risk factors for gastric cancer, has always been a source of concern as a result of the histopathological examination of endoscopic biopsies. As different types of intestinal metaplasia are morphologically well-defined, the histopathological diagnosis of these lesions is made with due precision[7]. However, the same does not occur in relation to histopathological recognition of the different degrees of gastric mucosa atrophy[8-10]. This is true in relation to histopathology as well as in relation to conventional endoscopic evaluation; nevertheless, severe atrophy of the gastric mucosa can be very easily recognized by histology, and with significant frequency by conventional endoscopy[11].

Although the histopathologic diagnosis of the evolutionary subdivisions of gastric atrophy has been reported to be unreliable, most gastric atrophy ratings used in the practice continue to persist with these subdivisions. Since the term "atrophic gastritis" is often used generically, especially in epidemiological studies related to gastric cancer, the link "gastric atrophy-gastric cancer", sometimes conveyed implicitly, cannot always be considered a reliable bond.

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This question becomes more relevant when considering that gastric atrophy may be the result of different diseases which, in turn, may have different degrees of importance as risk factors for gastric cancer[12].

Given these assumptions, this study was aimed at analyzing the morphological characteristics of atrophy of the gastric mucosa restricted to the gastric body, and in absence of *H. pylori* infection. These histopathological characteristics generally constitute the usual pattern expressed in the advanced stages of autoimmune gastritis, and therefore, a different disease from the atrophic gastritis associated with *H. pylori* infection. Towards this end, and in order to improve accuracy in the diagnosis of gastric atrophy, only the cases of atrophic body gastritis (ABG) with severe body mucosal atrophy were considered in this paper.

MATERIAL AND METHODS

For the purpose of evaluating the outcomes of endoscopic examination in patients with a final histopathological diagnosis of ABG, we surveyed all cases of upper gastrointestinal endoscopy with biopsy sampling of gastric antrum and gastric body performed from 2004-2006 at the endoscopy unit of Hospital das Clínicas, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte city, Brazil. A total of 7,309 patients, 3,556 (49%) males and 3,753 (51%) females, underwent gastroesophageal endoscopy with gastric biopsies of antral and body mucosa. The routine gastroscopy service at Instituto Alfa de Gastroenterologia (IAG) recommends obtaining two antral and two corpus biopsies. Almost all patients with the final diagnosis of ABG had at least two tissue samples from the corpus properly examined. When necessary, the corresponding paraffin blocks were retrieved for new histological sections. Giemsa-stained sections were used for *H. pylori* diagnosis. The presence, amount and distribution of intestinal metaplasia and pseudoantral (PSA) metaplasia were examined in the histologic sections of the atrophic body mucosa.

As inclusion criterion, all these selected subjects presented morphologically normal antral mucosa or just mild inflammatory mononuclear infiltrate in *lamina propria*. Patients with gastrointestinal cancer and patients who had undergone prior gastrointestinal surgery were excluded. This work was approved by the institutional ethics committee (ETIC 479/04).

Chi-square test (**Tables 1** and **2**) and Fisher's exact test (**Table 3**) were used to compare the found values. $p < 0.05$ was considered statistically significant.

TABLE 1 – Gender distribution of total patients who underwent esophagogastric endoscopy with biopsy and patients with the final diagnosis of ABG

Gender	Total patients (%)	ABG (%)
Female	3,753 (51.4)	73 (69.5)*
Male	3,556 (48.6)	32 (30.5)*
Total	7,309 (100)	105 (100)

*p < *0,001; ABG: atrophic body gastritis.*

TABLE 2 – Prevalence of intestinal metaplasia and pseudoantral metaplasia in atrophic gastric mucosa of patients (n = 105) with ABG

Subjects	only IM (%)	only PSA (%)	IM + PSA (%)	Total (%)
Female*	2 (2.7)	30 (41.1)	41 (56.2)	73 (100)
Male*	2 (6.3)	12 (37.5)	18 (56.2)	32 (100)
Total	4 (3.8)	42 (40)	59 (56.2)	105 (100)

*p = *0.67; ABG: atrophic body gastritis; IM: intestinal metaplasia; PSA: pseudoantral metaplasia.*

TABLE 3 – Patients (n = 59) with atrophic body gastritis presenting simultaneously intestinal metaplasia and PSA in atrophic gastric mucosa. Comparative amount of metaplastic glands

Subjects	PSA > IM (%)	PSA < IM (%)	PSA ~ IM	Total (%)
Female*	22 (53.7)	8 (19.5)	11(26.8)	41 (100)
Male*	10 (55.6)	6 (33.3)	2 (11.1)	18 (100)
Total	32 (54.2)	14 (23.8)	13 (22)	59 (100)

*p = *0.3; PSA: pseudoantral metaplasia; IM: intestinal metaplasia.*

RESULTS

Severe body atrophy was patent in all histological preparations from the 105 studied patients, with total or subtotal disappearance of oxyntic-peptic glands, which were replaced by metaplastic glands accompanied by different degrees of condensation of the fibrous components of the *lamina propria* (**Figures 1** and **2**).

Among the 105 patients with ABG, the prevalence of women was more than two times higher than that of men, respectively 69.5% vs. 30.5% (Table 1). Intestinal metaplasia and/or PSA metaplasia, regardless of gender, were identified in atrophic body mucosa of all patients. As isolated lesions, PSA metaplasia was more frequently seen than intestinal metaplasia, respectively 42 (40%) vs. four (3.8%) cases. In most patients (59 [56.2%]), intestinal metaplasia and PSA metaplasia in the atrophic mucosa of the gastric body occurred simultaneously. In those 59 cases in which intestinal metaplasia and PSA metaplasia occurred simultaneously, the latter occupied larger areas than the first, regardless of patients' gender. In only 13 (22%) patients, the relative proportions of intestinal metaplasia and PSA were apparently the same (Tables 2 and 3).

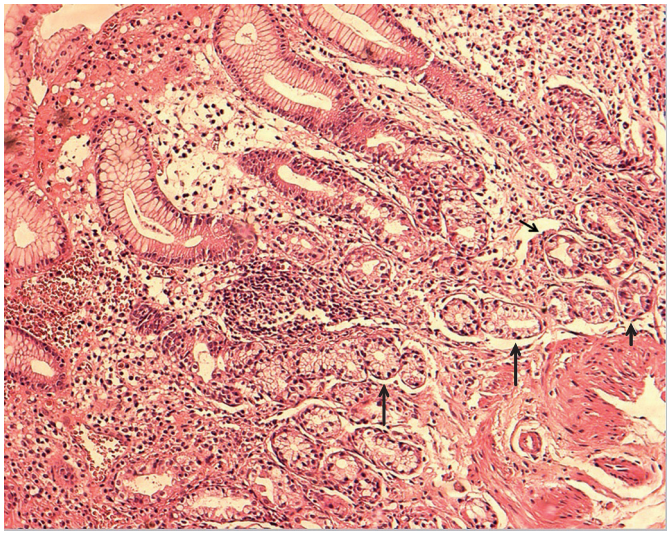

FIGURE 1 – *Severe glandular atrophy of the gastric corpus. Presence of few remaining oxyntic glands presenting regressive changes (short arrows), and numerous mucous secreting glands, named PSA (long arrows). HE, original magnification 100×*

PSA: pseudoantral metaplasia; HE: hematoxylin and eosin.

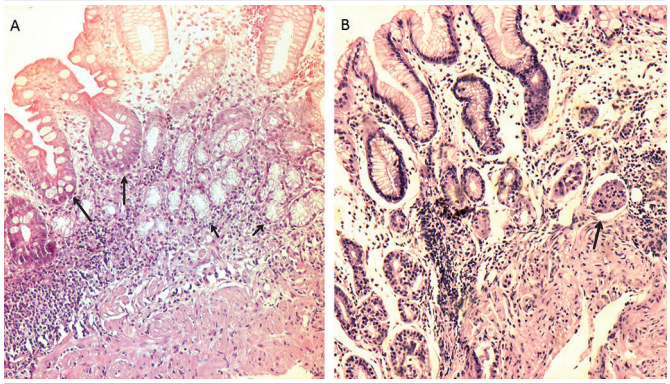

FIGURE 2 – *Severe atrophy of the body mucosa presenting in: A) areas of intestinal metaplasia (long arrows) and of PSA (short arrows); B) endocrine-like nodules immersed in* lamina propria *(arrow). This latter finding is indicative of mucosa atrophy associated with autoimmune disease. HE, original magnification 100×*

PSA: pseudoantral metaplasia; HE: hematoxylin and eosin.

DISCUSSION

The term "gastric mucosa atrophy" has been often used generically, without a precise definition of its meaning and its limits. Moreover, in recent years this gastric mucosa change reached the status of "risk factor" for gastric cancer because of its close association with the intestinal type stomach carcinoma, and also with the so-called "risk lesions" associated with this neoplasia[3, 4, 13-15].

Endoscopy with biopsy of the digestive mucosa has become a routine workup activity, representing an important tool for analysis of the gastric mucosa; however, it has been unable to allow reliable conclusions about the developmental stages of gastric atrophy. Even for the most intense degrees of gastric atrophy, the conventional endoscopy may be flawed[11, 16]. In turn, histology shows good levels of accuracy in the diagnosis of severe gastric atrophy, but it is also not reliable to define the intermediate phases of this injury. Although histological recognition of these evolutionary stages of gastric mucosal atrophy displays a great deal of subjectivity, it is used in almost all histological classifications of chronic gastritis, particularly in those cases associated with *H. pylori*[17]. In addition, it has been used as a common denominator among the risk lesions for gastric cancer, regardless of the different diseases associated with glandular atrophy[2, 3, 18, 19].

In the present assessment of patients with severe atrophy of the gastric body mucosa, and in the absence of *H. pylori* infection, it was not possible to find any case of non-metaplastic atrophy, as it is frequently described in cases of multifocal atrophic gastritis associated with *H. pylori* infection. In advanced stages of *H. pylori* infection, glandular atrophy usually occurs both in antral and body mucosa, with or without intestinal metaplasia; in the latter, only the filling of connective tissue can be found in the areas of missed glands.

Some characteristics linked to ABG, most of them described here, should be highlighted because they differ from those observed in multifocal gastritis: 1) the glandular structures of antral mucosa are completely preserved or nearly completely preserved; 2) frequently, the plentiful cellular endocrine component of the body mucosa does not participate in the severe atrophy of the exocrine glands. On the contrary, these endocrine cells usually present hyperplastic changes, and appear to continue their secretory activity; 3) the high frequency of metaplastic mucous glands in atrophic body mucosa. These glands, usually called "pseudo antral" metaplasia (PSA metaplasia), occurred in 92.2% of our patients, that is, in only four of them (7.8%) this type of metaplasia was not observed in the sampled material. One could assume that a few more endoscopic biopsies from the atrophic body mucosa of these patients could prove the presence of this type of metaplasia in 100% of cases. Interestingly, the PSA metaplasia appeared as an isolated change in 42 (40%) patients, while in 59 (56%) it was associated with intestinal metaplasia. In these cases, PSA metaplasia occupied larger areas than intestinal metaplasia in 54% of patients. This fact demonstrates why endoscopic biopsies of gastric body mucosa, when not properly referenced in the exam request, may lead to misdiagnosis of antral gastritis or multifocal gastritis[11] (Figure 1B). These interpretations can lead to suspicion of the infectious etiology of gastritis, and patients may be asked to undergo further tests to detect *H. pylori*, since this microorganism is not usually present in ABG. Besides, the unexpected higher prevalence of PSA metaplasia over intestinal metaplasia in ABG suggests that the relationship of this condition with gastric cancer

would not be the same as that believed to occur in *H. pylori* atrophic gastritis[20].

Neuroendocrine hyperplasia is known to be a common reaction in atrophic mucosa of the gastric body, what can help distinguish ABG from atrophic gastritis associated with *H. pylori*. Thus, when these nodules are visible in routine staining sections, in between the inflammatory infiltrate, they can be a sign of ABG, and not of multifocal atrophic gastritis (Figure 2B). However, neuroendocrine hyperplasia occurs more frequently without the formation of nodules, and in such cases the suspected endocrine hyperplasia can be confirmed by silver staining or immunohistochemistry using antibodies against neuroendocrine markers.

Among the patients here studied, 70% were women, and 30% were men. Although these patients had originated from a population of 7,309 patients who underwent upper endoscopy, in which gender distribution was nearly equivalent (respectively 51% vs. 49%), in ABG they presented a conspicuous differentiated gender distribution. This fact also indicates that ABG should be treated as a different pathological entity from *H. pylori*-associated gastritis, including the subtypes *H. pylori*-associated corpus gastritis and *H. pylori*-associated fundal gastritis.

In conclusion, the severe gastric mucosa atrophy observed in ABG shows remarkable morphological features that seem to be specific of this pathological condition, and quite different from those described in *H. Pylori*-associated atrophic gastritis. Thus, the generic terminology of "gastric atrophy" should not be considered a common denominator among risk lesions for gastric cancer, because different types of gastric mucosa atrophy may have variable degrees of importance in relation to gastric carcinogenesis.

AUTHORSHIP

Guarantor of the article: Alfredo J. A. Barbosa.

Specific author contributions: Barbosa – Project conception/design; data analysis/interpretation; manuscript drafting and critical revision. Boldt and Rodrigues – Database creation; data analysis/interpretation; critical revision. Silva, Ferreira and Pereira – Database creation.

All authors approved the final version of the manuscript.

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RESUMO

Introdução: *A atrofia da mucosa gástrica tornou-se capítulo importante da patologia gástrica devido ao seu estreito relacionamento com as lesões de risco para o câncer gástrico. Embora a atrofia gástrica possa estar associada a diferentes doenças, ela tem sido abordada como um processo genérico, omitindo-se suas diferentes causas.* ***Objetivo:*** *Estudar as características histopatológicas da atrofia da mucosa gástrica em pacientes com gastrite atrófica do corpo (ABG).* ***Material e métodos:*** *Foram estudados casos consecutivos de pacientes com diagnóstico de ABG que apresentavam mucosa antral normal ou apenas alterações inflamatórias mínimas. Pacientes submetidos a cirurgia gastrointestinal prévia ou portadores de câncer gastrointestinal foram excluídos. Nas preparações histopatológicas, estudou-se a presença de glândulas que exibiam metaplasia intestinal e metaplasia pseudoantral (PSA).* ***Resultados:*** *No período 2004-2006, 7.309 pacientes foram submetidos à endoscopia esofagogástrica com biópsias, sendo 3.556 (48,6%) homens e 3.753 (51,4%) mulheres. Entre eles, 105 pacientes* H. pylori *negativos tiveram o diagnóstico de ABG confirmado, sendo 32 (30,5%) homens e 73 (69,5%) mulheres (*$p < 0,001$*). Glândulas com metaplasia intestinal e/ou metaplasia PSA foram identificadas em todos os pacientes. Isoladamente, a metaplasia PSA foi mais frequente que a metaplasia intestinal, respectivamente 42 (40%)* vs. *quatro (3,8%). Os dois tipos de metaplasia ocorreram simultaneamente na maioria (56,2%) dos pacientes, não se observando diferenças entre os gêneros (*$p = 0.67$*).* ***Conclusão:*** *A atrofia da mucosa gástrica na ABG mostra características histopatológicas próprias que devem ser consideradas nos estudos sobre o relacionamento da atrofia gástrica com o câncer gástrico.*

Unitermos: *gastrite; gastrite atrófica; estômago; gastropatias.*

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