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The relation of *Helicobacter pylori* with intestinal metaplasia, gastric atrophy and BCL-2

Helikobakter pylori'nin intestinal metaplazi, atrofik gastritis ve BCL-2 ile ilişkisi

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Background!aims: *It is assumed that the sequence of events in gastric cancer is as follows: chronic gastritis, atrophy, intestinal metaplasia (IM), dysplasia, and carcinoma. It isalso known that Helicobacter pylori (Hp) can be involved in the chain of these chronic phenomena. Therefore, we studied the relation of Hp with chronic inflammation, atrophy, activity level, IM and bcl-2. Methods:The number ofpatients included in this study was 52; 35 (67.3%) were female and 17 (32.7%) were male. The average ages of women and men were determined as 44.5 and 41.5 years, respectively. Hp was determined in 53.8% ofall cases and chronic inflammation was found in all cases. No dysplasia or gastric cancer was found in our cases. A statistically significant positive correlation was found between the Hp intensity and the degrees of chronic inflammation, atrophy and activity.* ***Results:*** *Bcl-2 was found positive in 7.1% of the patients with Hp, and in 4.1% of the Hp-negative patients. However, bcl-2 was positive in 2 (8.7%) of 23 Hp-positive patients with chronic atrophic gastritis and in 1 (11.1%) of 9 Hp-negative patients with chronic atrophic gastritis. In other words, bcl-2 was found more in Hp-negative chronic atrophic gastritis than in Hp-positive chronic atrophic gastritis. Also, atrophy and IM were present together in 2 bcl-2-positive patients in whom Hp was positive. Bcl-2 was found positive more in IM than atrophy, proportionally. According to these data, although bcl-2 was found positive more often in Hp (+) cases proportionally, it was not statistically significant. Nevertheless, no significant difference was found between bcl-2 positivity and atrophy according to the statistical data. The data regarding the relation between IM and bcl-2 were statistically significant, and a positive correlation was found between them.* ***Conclusions:*** *We concluded that Hp infections result in chronic gastritis, have a role in the development of atrophy and IM, and that Hp infection has a significant relation with neutrophile activation. The more Hp intensity increases, the greater the degrees of chronic gastritis, activity and atrophy. We also found that Hp, which is known to increase apoptosis, increases the expression of bcl-2, an anti-apoptotic gene, not directly but rather by causing atrophy development. We observed more bcl-2 positivity in IM than in atrophy. Further studies with an extensive series of cases, including patients with dysplasia and gastric cancer, are needed to clarify statistical rates and to support the suggestion that bcl-2 expression increases with the progression to gastric cancer.*

Keywords: *Helicobacter pylori,* intestinal metaplasia, gastric atrophy, bcl-2

Amaç: *Gastrik kanserdeki olaylar dizisinin; kronik gastritis, atrofi, intestinal metaplazi, displazi ve karsinoma şeklinde olduğu kabul edilmektedir. Hp'nin bu kronik olaylar zincirinin başında yer aldığı bilinmektedir. Bu nedenle; Hp'nin kronik inflamasyon, atrofi, aktivite derecesi, intestinal metaplazi ve antiapoptotik bir gen olan bcl-2 ile ilişkisini araştırdık.* ***Yöntem:*** *Çalışmaya, endoskopilerinde antrum ağırlıklı kronik gastritis saptanan toplam 52 alındı. 35'i kadın (% 67.3), 17'si erkek (% 32.7) hastadan oluşup, kadınların yaş ortalaması 44.5; erkeklerin yaş ortalaması ise 41.5 olarak tespit edildi. Tüm vakalarda % 53.8 oranında Hp saptandı ve tüm vakalarda kronik inflamasyon bulundu. Hp yoğunluğu ile kronik inflamasyon derecesi, atrofi derecesi ve aktivite derecesi arasında istatistiksel olarak anlamlı olmak üzere (+) korelasyon görüldü.* ***Bulgular:*** *Hp saptanan hastaların % 7.1'inde bcl-2 (+) bulunurken, Hp (-) hastaların % 4.1'inde bcl-2 (+) bulundu. Ancak, Hp (+) kronik atrofik gastritisli 23 hastanın 2'sinde (% 8.7) bcl-2 (+) iken, Hp(-) kronik atrofik gastritisli 9 hastanın 1'inde (% 11.1) bcl-2 (+) bulundu. Yani Hp (-) kronik atrofik gastritisde, Hp (+) kronik atrofik gastritise göre daha fazla bcl-2 (+)'liği görüldü. Hp(+) saptanan bcl-2 (+) 2 vakada da atrofi ve İM birlikteliği görüldü. İM'de atrofiye göre oransal olarak daha fazla bcl-2 (+)'liği görüldü. Bu verilere göre, oransal olarak bcl-2 (+)'liği Hp (+)'lerde daha fazla bulunmasına rağmen, istatistiki olarak anlamlı bulunamadı. Yine, bcl-2 (+)'liği ile atrofi arasında istatiksel verilere göre anlamlı bir ilişki bulunamadı. Bu durum vaka sayısının fazla olmamasına bağlandı. İM ile bcl-2 arasında ise istatistiki olarak veriler anlamlı bulunmuş olup, aralarında (+) korelasyon saptanmıştır.* ***Sonuç:*** *Bu verilerden Hp infeksiyonunun kronik gastritis gelişiminden sonra atrofi, İM gelişiminde önemli bir rol oynadığı, nötrofil aktivasyonu ile anlamlı bir ilişkisi olduğu ve yine Hp yoğunluğu arttıkça kronik gastritis derecesi, aktivite derecesi ve atrofi derecesinin arttığı sonuçlarını çıkarabiliriz. Apoptozisi arttırdığı bilinen Hp'nin, direkt olarak değil de, indirekt olarak atrofi ve İM oluşumuna yol açarak antiapoptotik bir gen olan bcl-2 expresyonunu arttırdığını gördük. İM'de atrofiye göre daha fazla bcl-2 (+)'liği gördük. İstatistiksel oranların anlam kazanması ve gastrik kansere doğru ilerledikçe bcl-2 ekspresyonunun arttığını desteklemek için, displazik ve gastrik Cali hastaları da kapsayacak şekilde geniş vaka serili çalışmalara ihtiyaç vardır.*

Anahtar kelimeler: *Helikobakter pylori,* gastrik atrofi, intestinal metaplazi, bcl-2

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INTRODUCTION

Helicobacter pylori *(Hp)* infection is the most common bacterial infection worldwide (1). *Hp* is an important bacterium that has a role in the etiology of duodenal and gastric ulcer, gastric cancer, and MALT-lymphoma. The disease is present in 20% of the patients who are *Hp* infected, and the remaining 80% are asymptomatic (2). The ones who are infected with this bacterium have histopathological gastritis whether or not they have any complaint.

Although the infection always causes chronic gastritis, the later clinical manifestations are variable. Since the risk for gastric cancer increases in people with *Hp* infection compared to those who are not *HP*-infected, and because the incidence of gastric cancer would be high over time in individuals with *Hp* infection, the relation between *Hp* infection and gastric cancer has been investigated. In addition, in some studies, other factors, such as genetic and nutritional, have been suggested as explanations for why gastric cancer develops in only a small proportion of those infected with Hp. The sequence of events in gastric cancer is assumed to follow as chronic gastritis, atrophy, intestinal metaplasia (IM), dysplasia, and carcinoma. It is known that *Hp* can be involved in the chain of these chronic phenomena. Therefore, the aim of this study was to investigate the relation of *Hp* with chronic atrophic gastritis, IM, and bcl-2.

MATERIALS AND METHODS

This study was a prospective study performed by the Departments of Gastroenterology and Pathology. Fifty-two patients who applied to the polyclinic of Gastroenterology from January to July 2002, having dyspeptic complaints and not treated with eradication therapy for *Hp,* and also in whom antral predominant gastritis was found on endoscopy were included in this study. Six to eight biopsies were taken from each patient under sterile conditions, with at least three of them from the antrum. The biopsy samples were fixated with formalin 10% and examined in the Department of Pathology. The tissues were embedded in paraffin after being subjected to routine procedures. Cross-sections, 4 micron in thickness, taken from paraffin blocks underwent deparaffinization, and were then stained with hematoxylin-eosin and evaluated under light microscope. Giemsa stain was applied to determine the presence of *Hp,* or its intensity in certain cases when necessary. The histopathologic examination was performed according to the updated System of Sydney (3).

The avidin-biotin-peroxidase method was used for the immunohistochemistry examination. Hence, one cross-section 4 micron in thickness was taken from each block with polylysined microslides. The microslides were dried at + 4°C overnight, and were then deparaffinized in xylol and rehydrated in 95% ethyl alcohol. The rehydrated sections were placed in a plastic container with PBS (phosphate buffered saline), and this container was placed in a sterilizer at 121°C for 50 minutes. Hydrogen peroxide (3%) was used to block the endogen peroxide. It was placed in a microwave oven for 20 minutes to reveal the antigen. After the process done with block solution, bcl-2 antibody (Doke, mouse, anti-bcl-2, Carpinteria, CA) was dropped on the sections and these tissues were placed in a moist atmosphere for one hour. The sections were washed with PBS, and then incubated for 20 minutes with the anti-mouse secondary antibody with biotin and for 20 minutes with the conjugate of streptavidin. The substrate of AEC (3 amino-9-ethyl carbazole) was used as chromogen. Contrast staining was applied with hematoxylin of Mayer; it was dehydrated, clarified and closed with glycerin gel. Samples of palatine tonsils, known to stain positive with bcl-2, were used for positive controls. For the negative controls, PBS was used instead of primary antibody and the remaining steps were applied in the same manner. Bcl-2 was examined in lymphoid aggregates.

Table 1. Updated Sydney system

Histologic properties	Definition	Grade Mild	Moderate	Severe
Chronic inflemmation	Lymphosit and plasma cell propria	+	++	+++
Neutrophil activation	Neutrophil infiltration in lamia propria or superficial epithelium	<l/3	1/3-2/3	>2/3
Glandular atrophy	Loss of corpus and antral glands	+	++	+++
IM	IM in mucosal epithelium	<l/3	1/3-2/3	>2/3
Hp	Hp intensity in epithelium	+	++	+++

All of the cases were evaluated according to the classification of Sydney, and the relation of *Hp* with chronic inflammation, atrophy, IM, activity and bcl-2 was investigated. The statistical data were obtained from SPSS v7.5 computer program. Chi-square test was used for analysis of data. A value of $p<0.05$ was accepted as significant. Spearman's correlation test was used to determine the relation between the data.

RESULTS

The number of the patients included in this study was 52; 35 (67.3%) were female and 17 (32.7%) male. The average ages of women and men were determined as 44.5±14.9 and 41.5±13.8 years, respectively (t=-0.687, p=0.495).

The relation of Hp with inflammation:

Hp was found in 28 (53.8%) of 52 patients; the remaining 24 (46.2%) were *Hp*-negative.

Among the 16 *Hp* (+) patients, mild and moderate chronic inflammation was found in 14 (87.5%) and 2 (12.5%) patients, respectively.

Among the 8 *Hp* (++) patients, mild, moderate and severe chronic inflammation was found in 4 (50%), 3 (37.5%) and 1 (12.5%) patients, respectively.

Among the 4 *Hp* (+++) patients, moderate and severe chronic inflammation was found in 3 (75%) and 1 (25%) patients, respectively.

Among the 24 *Hp* (-) patients, mild and moderate chronic inflammation was found in 22 (91.7%) and 2 (8.3%) patients, respectively.

The statistical analysis done with chi-square test suggested a statistically significant relationship between intensity of *Hp* and the degree of chronic inflammation (p: 0.001), and a positive correlation (rho: 0.596) was determined between them.

The relation of Hp with atrophy:

While no atrophy was found in 15 (62.5%) of 24 *Hp* (-) patients, mild atrophy was seen in 9 (37.5%) of these patients. No moderate or severe atrophy was observed in the *Hp* (-) patients.

While 23 (82.1%) of 28 ^-positive patients had atrophy, the remaining 5 (17.9%) patients did not.

There was no atrophy in 4 (25%) of 16 *Hp* (+) patients; mild and moderate atrophy was found in 8 (50%) and 4 (25%) patients, respectively.

There was no atrophy in 1 (12.5%) *oîSHp* (++) patients; mild, moderate and severe atrophy was found in 3 (37.5%), 3 (37.5%) and 1 (12.5%) patients, respectively.

Among the 4 *Hp* (+++) patients, moderate and severe atrophy was found in 3 (75%) and 1 (25%) patients, respectively.

The statistical analysis done with chi-square test suggested a statistically significant relation between the intensity of *Hp* and the degree of atrophy (p: 0.0001), and a positive correlation (rho: 0.67) was determined between them.

Table 2. The relation of Hp intensity with degree of chronic inflammation (x^2=22.208, p=0.001)

	Hp(-)	Hp(+)	Hp (++)	Hp (+++)	Total
Mild inflammation	22	14	4	-	40
Moderate inflammation	2	2	3	3	10
Severe inflammation	-	-	1	1	2
Total	24	16	8	4	52

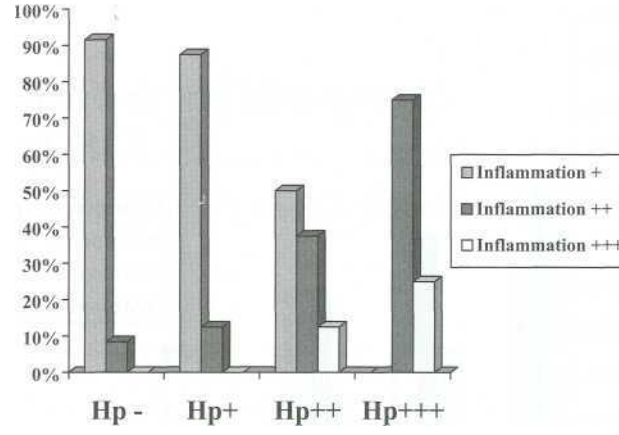

Figure 1. The proportional relation between *Hp* intensity and degree of chronic inflammation (rho= 0.596, p= 0.00012)

The relation of Hp with intestinal metaplasia:

Intestinal metaplasia was found in 9 (17.4%) of all cases: in 7 (25%) of 28 *Hp*- positive patients and in 2 (8.3%) of 24 *Hp* (-) patients. All of the 9 cases were seen in chronic atrophic gastritis (28.1%); no IM was present in chronic non-atrophic gastritis.

There was no statistically significant relation between the intensity of *Hp* and the degree of IM (p>0.05); a relation at the limit (p: 0.05) was found between IM and atrophy.

Activity was present in 25 (89.3%) of 28 ffp-positive cases.

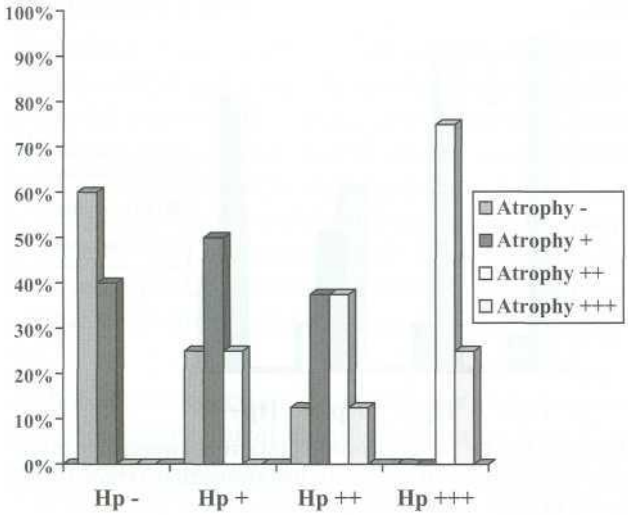

Figure 2. Proportional relation between *Hp* intensity and degree of atrophy (rho= 0.672, p= 0.000048)

Table 3. Relation of *Hp* intensity with degree of atrophy (x^2= 29.900, p= 0.00045)

	Hp (-)	Hp (+)	Hp(++)	Hp (+++)	Total
No atrophy	15	4	1	-	20
Mild atrophy	9	8	3	-	20
Moderate atrophy	-	4	3	3	10
Severe atrophy		-	1	1	2
Total	24	16	8	4	52

Table 4. Relation of *Hp* with atrophy (x^2=10.882, p=0.001)

	Hp (+)	Hp(-)	Total
Chronic atrophic gastritis	23	9	32
Chronic non-atrophic gastritis	5	15	20
Total	28	24	52

Table 5. Relation between *Hp,* chronic atrophic gastritis and intestinal metaplasia (x^2 Fisher's exact test p=0.501) (rho= 0.082, p= 0.655)

	Hp(+) chronic atrophic gastritis	Hp(-) chronic atrophic gastritis	Total
IM (+)	7	2	9
IM (-)	16	7	23
Total	23	9	32

Table 6. Relation of *Hp* intensity with degree of activity

	Hp(-)	Hp(+)	Hp(++)	Hp(+++)	Total
No activity	21	3	-	-	24
Mild activity	2	12	5	-	19
Moderate activity	1	1	3	3	8
Severe activity	-	-	-	1	1
Total	24	16	8	4	52

While no activity was found in 3 (18.7%) of 16 *Hp* (+) patients, mild and moderate activity was determined in 12 (75%) and 1 (6.3%) patients, respectively.

Among the 8 *Hp* (++) patients, mild and moderate activation was found in 5 (62.5%) and 3 (37.5%) patients, respectively.

Among the 4 *Hp* (+++) patients, moderate and severe activation was found in 3 (75%) and 1 (25%) patients, respectively.

While there was no activity in 21 (87.5%) of 24 *Hp* (-) patients, mild and moderate activity was found in 2 (8.3%) and 1 (4.2%) patients, respectively.

The statistical analysis done with chi-square test between the intensity of *Hp* and the degree of activity was suggested to be statistically significant (p: 0.000028), and a positive correlation (rho: 0.794) was determined between them.

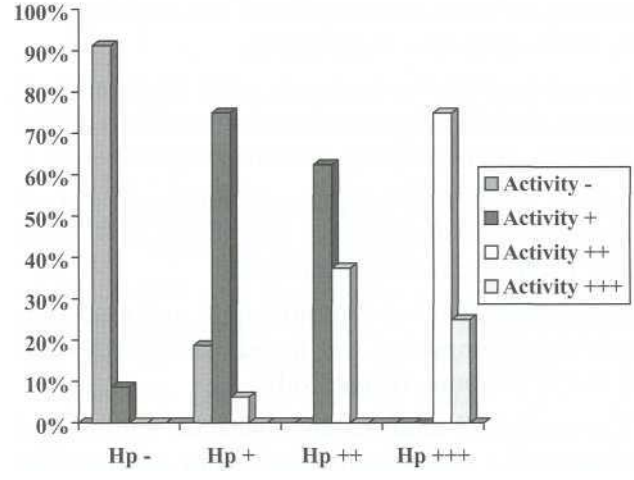

Figure 3. Proportional relation between *Hp* intensity and degree of activity (rho= 0.794, p= 0.00003)

The relation of Hp with bcl-2:

Bcl-2 was found positive in 2 (7.1%) of 28 Hp-positive patients. Bcl-2 was also found positive in 1 (4.1%) of 24 *Hp* (-) cases. Bcl-2 was found positive in 3 (9.3 %) of 32 patients with chronic atrophic gastritis. There was no bcl-2 positivity in cases with chronic non-atrophic gastritis.

While bcl-2 was positive in 2 (7.8%) of the 23 *Hp*-positive patients with chronic atrophic gastritis, bcl-2 was also positive in 1 (11.1%) of the 9 *Hp* (-) patients with chronic atrophic gastritis. Positive staining with bcl-2 was observed in 2 (22.2%) of

Table 7. Relation of Hp with bcl-2 (x^2 Fisher's exact test p= 0.559) (rho= 0.064, p= 0.654)

	Hp (+)	Hp (-)	Total
Bcl-2(+)	2	1	3
Bcl-2(-)	26	23	49
Total	28	24	52

the 9 patients with IM. Both of these cases were *Hp*-positive and had chronic atrophic gastritis.

No significant difference was found in the statistical analysis done with chi-square test (Fisher's exact test) between *Hp* and bcl-2 (p>0.05). All three cases with positive bcl-2 were found to have atrophic gastritis; nevertheless, no statistically significant difference was found between bcl-2 positivity and atrophy.

DISCUSSION

Hp incidence is variable among countries and even among different regions in one country. *Hp* incidence is known to be connected with low socioeconomic status. It is still not clearly known how *Hp* infects humans. To date, no reservoir for this bacterium other than humans has been determined. *Hp* is believed to transmit from person to person by oral-oral, gastric-oral or fecal-oral routes.

While antral gastritis, gastric and duodenal ulcers, gastric cancer and MALT lymphoma are included in the group of diseases in which *Hp* is definitively effective, *Hp* has also been cited in some studies as playing a possible role in non-ulcer dyspepsia, development retardation of children, coronary heart disease and Menetrier's disease. *Hp* infection always exists with inflammation in the stomach and always leads to chronic gastritis. Therefore, there is mild and moderate chronic gastritis, primarily on the antrum, together with neutrophile infiltration in almost all *Hp*-infected individuals.

It is assumed that the sequence of events in gastric cancer is as follows: chronic gastritis, atrophy, IM, dysplasia, and carcinoma. It is known that *Hp* is involved in the chain of these chronic phenomena. Therefore, we intended to study the relation of *Hp* with chronic atrophic gastritis, IM, and bcl-2.

Kenji et al. (4) studied the relation of *Hp* infection with atrophy, IM and the degree of gastritis. They found that there is a direct relation between *Hp* infection and the degree of gastritis, and that atrophy and IM are the results *of Hp* infection. Sipponen et al. (5) detected a positive correlation between the degree of *Hp* colonization and the degree of inflammation. Furthermore, Asaka et al. (6) studied the relation of *Hp* with atrophic gastritis and IM. They found the rate of atrophic gastritis as 82.9% in the *Hp*-infected group and as 9.8% in the non-infected group. Similarly, the rates of IM were 43.1% and 6.2% in infected and non-infected groups, respectively. As a result, atrophy and IM rates were found to be higher in *Hp* (+) patients than in *Hp* (-) patients.

Sasa et al. (7) suggested a positive correlation between the degree of gastric activity and the degree of *Hp* colonization, but a negative correlation between the degree of *Hp* colonization and atrophy and IM frequency. Heng Jun et al. (8) examined the relation of *Hp* with atrophy, IM, dysplasia, gastric cancer and bcl-2, and found that bcl-2 expression increases from atrophy to gastric cancer.

Maor-Kendler et al. (9) found that bcl-2, which blocks apoptosis, increases in atrophic gastritis; however, they could not find a direct relation of *Hp* in this situation, and reported that bcl-2 positivity arises from atrophy. Jorge et al. (10) performed antral biopsy in 57 patients with chronic gastritis, studied the relation of *Hp* with bcl-2 and found that *Hp* positivity directly increases the bcl-2 expression. II Ju Choi et al. (11) reported that *Hp* directly increases the expression of anti-apoptotic bcl-2, as well as causes apoptosis. Yang et al. (12) found that *Hp* causes apoptosis by decreasing the expression of bcl-2.

In our study, it was shown that the greater the intensity of .Hp, the greater the degree of chronic inflammation, and a statistically significant, positive correlation was defined between them. These results were found concordant to two different studies performed by Kenji et al. (4) and Sipponen et al. (5).

According to our data, a statistically significant and positive correlation was found between the intensity of *Hp* and the degree of atrophy. These results were found concordant with two different studies performed by Kenji et al. (4) and Asaka et al. (6). Nevertheless, these results were not concordant with the study of Sasa et al. (7), who found a negative correlation between atrophy frequency and the degree of *Hp* colonization. It could be concluded that *Hp* causes atrophy but does not colonize in atrophic areas. Likewise, *Hp* colonization was not seen in the glands with atrophy in our study, but *Hp* colonization balanced with the deg-

ree of atrophy was observed in the other areas where atrophic glands were not found. This may explain the study of Sasa et al. (7).

No statistically significant relation was found between the intensity of *Hp* and IM in our study; however, IM was more frequent in *Hp* (+) than in *Hp* (-) cases, proportionally. The reason for not finding a statistically significant result was related to the smallness of the number of cases. These results were found concordant with two different studies performed by Kenji et al. (4) and Asaka et al. (6). Nevertheless, they were not concordant with the study of Sasa et al. (7), who found a negative correlation between the frequency of IM and the degree *of Hp* colonization. As well as in atrophy, *Hp* causes IM but cannot be colonized in IM areas. *Hp* can be colonized only by adhering to gastric epithelium. Likewise, no *Hp* colonization was found in the areas with IM; however, *Hp* colonization was observed in the sections of the same biopsies without IM.

All of the nine cases were seen in chronic atrophic gastritis (28.1%), and no IM was present in chronic non-atrophic gastritis. According to these data, a relation statistically at limit was found between IM and atrophy; therefore, it can be concluded that *Hp* existence is an important factor for the development of atrophy and that atrophy can cause IM.

It was shown in our study that the greater the intensity *of Hp,* the greater the activity, and a statistically significant and positive correlation was defined between them. These results were found concordant with the study of Sasa et al. (7).

Bcl-2 was found positive in a total of three cases, in 2 (7.1%) of 28 ii/p-positive patients and in 1 (4.1%) of 24 *Hp* (-) cases. According to these data, although bcl-2 positivity was higher in Hp-positive cases proportionally, it was not found statistically significant. Although atrophy was found in all three bcl-2 positive cases, there was no statistically significant difference between bcl-2 positivity and atrophy. This was related to the smallness of the number of cases. In our study, bcl-2 was positive in 2 (7.8%) of the 23 *Hp* (+) patients with chronic atrophic gastritis, and in 1 (11.1%) of the 9 *Hp* (-) patients with chronic atrophic gastritis. That is, bcl-2 was found positive significantly more in *Hp* (-) patients with chronic atrophic gastritis than in *Hp* (+) patients with chronic atrophic gastritis. This result illustrates that *Hp* increases bcl-2 by causing atrophy. Thus, bcl-2 is related indirectly to *Hp* and directly to atrophy. This result supports the suggestion of Maor-Kendler et al. (9) that increased bcl-2 expression is related to atrophy but not associated directly with *Hp.* Nevertheless, it does not support the studies of Jorge et al. (10) and II Ju Choi et al. (11), who suggested that *Hp* increases bcl-2 directly, nor of Yang et al. (12) who suggested that *Hp* decreases the expression of bcl-2.

IM was present in both of the cases who were *Hp* and bcl-2 positive. Bcl-2 positive staining was seen in 2 (22.2%) of nine patients with IM, and bcl-2 positivity was found in 1 (2.3%) of 43 IM (-) patients. The greater bcl-2 expression in IM compared to atrophy may support the study of Heng Jun et al. (8) and may suggest that bcl-2 expression increases while advancing to gastric cancer.

We concluded from these data that *Hp* infection results in gastritis, it has a role in development of atrophy and IM, and that it has a significant relation with neutrophile activity. We found that the greater the intensity *of Hp,* the greater the degrees of activity and atrophy. We determined that *Hp,* which is known to increase apoptosis, increases the expression of bcl-2, an anti-apoptotic gene, by causing development of atrophy. We observed more bcl-2 positivity in IM compared to atrophy. Further studies with an extensive series of cases, including patients with dysplasia and gastric cancer, are needed to clarify statistical proportions and to support the suggestion that the expression of bcl-2 increases along with advancement to gastric cancer.

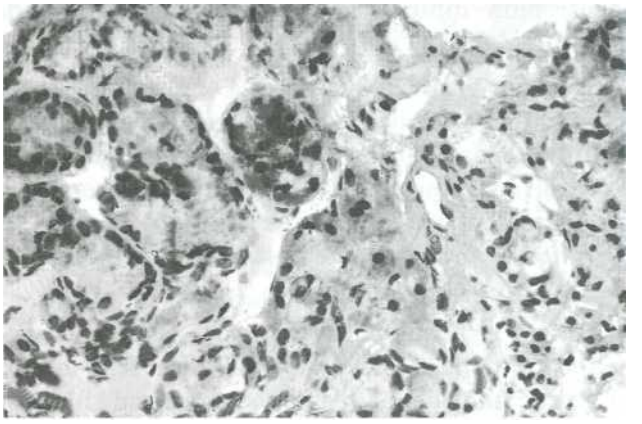

Figure 4. Bcl-2 was found positive in patients with chronic atrophic gastritis

REFERENCES

1. Brown LM. Helicobacter pylori epidemiology and routes of transmission. Epidemiol Rev 2000; 22(2): 283-97.
2. Nguyen TN, Barkun AN, Fallone CA. Host determinants of H. pylori infection and its clinical outcome. Helicobacter 1999; 4(3): 185-97.
3. Dixon MF, Genta RM, Harley JH, et al. Classification and grading of gastritis. The updated Sydney system. Am J Surg Pathol 1996; 20(10): 1161-81.
4. Kenji O, Mitsuo O, Hiroshi M, et al. Association of Helicobacter pylori infection with atrophic gastritis and intestinal metaplasia. J Gastroenterol Hepatol 2000; 15(10): 1105.
5. Sipponen P, Stolte M. Clinical impact of routine biopsies of the gastric antrum and body. Endoscopy 1997; 29: 671-8.
6. Asaka M, Sugiyama T, Nobuta A, et al. Atrophic gastritis and intestinal metaplasia in Japan: results of a large multicenter study. Helicobacter 2001; 6: 294-9.
7. Sasa G, Milosav S, Vuka K. The relationship between the density of Helicobacter pylori colonisation and the degree of gastritis severity. Gastroenterolhepatol 2002; 21: 3- 4.
8. Heng Jun G, Lian Z, Jian Feng B, et al. Multiple genetic alterations and behavior of cellular biology in gastric cancer and other gastric mucosal lesions: H. pylori infection, histological types and staging. World J Gastroenterol 2000; 6(6): 848-54.
9. Maor-Kendler Y, Gabay G, Bernheim J, et al. Expression of bcl-2 in autoimmune and Helicobacter pylori-associated atrophic gastritis. Dig Dis Sci 1999; 44 (4): 680-5.
10. Jorge O, Cuello Carrion FD, Jorge A, Ciocca DR. Helicobacter pylori infection affects the expression of PCNA, p53, c-erbB-2 and Bcl-2 in the human gastric mucosa. Rev Esp Enferm Dig 2003; 95(2): 97-104, 89-96.
11. II Ju Choi, Joo Sung K, Jung Mogg K, et al. Effect of inhibition of extracellular signal-regulated kinase 1 and 2 pathway on apoptosis and bcl-2 expression in Helicobacter pylori-infected AGS cells. Infection and Immunity 2003; 71(2): 830-7.
12. Yang Y, Deng CS, Peng JZ, et al. Effect of Helicobacter pylori on apoptosis and apoptosis related genes in gastric cancer cells. Mol Pathol 2003; 56(1): 19-24.W