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Is the prevalence of intestinal metaplasia at the squamocolumnar junction different in patients with progressive sytemic sclerosis?

Progresif sistemik sklerozlu olgularda squamokolumnar bileşkede intestinal metaplazi sıklığı farklı mı?

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Background/aims: *Gastroesophageal reflux disease is seen frequently in patients with progressive systemic sclerosis. The aim of the present study was to determine the prevalence of intestinal metaplasia-squamocolumnar junction in patients with progressive systemic sclerosis and to investigate the association with gastroesophageal reflux disease.* ***Methods:*** *Thirty-one patients with progressive systemic sclerosis (Group A), 58 patients with gastroesophageal reflux disease -without progressive systemic sclerosis (Group B) and 36 patients without progressive systemic sclerosis or gastroesophageal reflux disease (Group C) were prospectively enrolled into this study. Biopsies were taken from the antrum, body, squamocolumnar junction (Z-line), and from the esophagus (3 cm above the Z-line). All biopsies were independently evaluated by two pathologists who were unaware of the diagnosis.* ***Results:*** *We found that grade C-D esophagitis, esophageal stricture and Barrett's esophagus were statistically significantly higher in Group A ($p<0.05$). Intestinal metaplasia at squamocolumnar junction was detected in 31% of Group A, in 32% of Group B and in 29% of Group C patients ($p>0.05$), and prevalence of Helicobacter pylori was 61%, 67% and 38% in Groups A, B and C, respectively. Prevalence of Helicobacter pylori was similar in Group B and Group A, and significantly higher in Group B than Group C. Within each group, no significant relationship was detected between intestinal metaplasia at squamocolumnar junction and gender, age, smoking, alcohol consumption, body mass index, gastric atrophy, and prevalence of Helicobacter pylori.* ***Conclusions:*** *Patients with progressive systemic sclerosis have a higher tendency to the more severe forms and complications of gastroesophageal reflux disease including Barrett's esophagus than in those without progressive systemic sclerosis. However, there was no difference in the prevalence of intestinal metaplasia at squamocolumnar junction between groups, and it can be pointed out that intestinal metaplasia at squamocolumnar junction might not be related with gastroesophageal reflux disease.*

Key words: Progressive systemic sclerosis, squamocolumnar junction, intestinal metaplasia

Amaç: *Gastroözofageal reflü hastalığı progresif sistemik sklerozlu olgularda sıktır. Çalışmanın amacı, progresif sistemik sklerozlu olgulardaki squamokolumnar bileşkede intestinal metaplazi sıklığını tanımlamak ve bunun gastroözofageal reflü hastalığı ile ilişkisini araştırmaktır.* ***Yöntem:*** *Progresif sistemik skleroz tanısı alan 31 olgu (grup A), progresif sistemik sklerozu olmayan- gastroözofageal reflü hastalığı olan 58 olgu (grup B) ile progresif sistemik sklerozu ve gastroözofageal reflü hastalığı olmayan 36 olgu (grup C) prospektif olarak araştırıldı. Antrum, korpus, squamokolumnar bileşke (Z-çizgisi) ve özofagustan (Z-çizgisi 3 cm proksimalinden) alınan biyopsiler tanı bilinmeden, bağımsız 2 ayrı patolog tarafından değerlendirildi.* ***Bulgular:*** *Grup A'da grade C-D özofajit, özofageal sitriktür ve Barrett özofagusu anlamlı daha sık olarak saptandı ($p<0.05$). Squamokolumnar bileşkede intestinal metaplazi, grup A'da %31, grup B'de %32 ve grup C'de %29 olarak bulundu ($p>0.05$). Helikobakter pilori sıklığı grup A'da %61 (19/31, grup B'de %67 (39/58), grup C %38 (14/36) idi. Grup B'de Helikobakter pilori sıklığı grup A ile benzerdi ve grup B'de anlamlı olacak şekilde grup C'den yüksekti. Gruplar arasında, squamokolumnar bileşkede intestinal metaplazi ve cinsiyet, yaş, sigara içme, alkol kullanımı, vücud-kitle indeksi, gastrik atrofi ve Helikobakter pilori prevalansı arasında anlamlı ilişki saptanmadı.* ***Sonuç:*** *Progresif sistemik sklerozlu olgularda Barrett özofagusu da dahil gastroözofageal reflü hastalığının komplikasyonları progresif sistemik sklerozlu olmayanlara gore daha sık ve daha şiddetli seyretmektedir. Bununla birlikte squamokolumnar bileşkede intestinal metaplazi sıklığı açısından gruplar arasında fark saptanmamıştır ve squamokolumnar bileşkede intestinal metaplazi ile gastroözofageal reflü hastalığı arasında ilişki olmayabileceği belirtilebilir.*

Anahtar kelimeler: Progresif sistemik skleroz, squamokolumnar bileşke, intestinal metaplazi

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INTRODUCTION

Progressive systemic sclerosis (PSS) is a connective tissue disorder with a high frequency of gastrointestinal (GI) involvement. GI involvement consists of a variety of symptoms and conditions that include nausea and vomiting, difficulty in swallowing, constipation, diarrhea, gastroesophageal reflux disease (GERD), dyspepsia, and gastroparesis. Although any part of the GI tract can be involved, esophageal disease occurs in nearly all patients with PSS as a clinical consequence of esophageal dysmotility. Motility abnormalities and GERD, Barrett's esophagus (BE), adenocarcinoma, infectious esophagitis, and drug-induced esophagitis were reported as the common esophageal manifestations in PSS (1). Smooth muscle atrophy and fibrosis of the distal two-thirds of the esophagus accompany the disease. Motility studies show peristaltic contractions with reduced amplitude or no peristaltic contractions in this region. Lower esophageal sphincter pressure was in normal range or mildly decreased. All of these changes and reduced gastric transition contribute to the prevalence of GERD and its complications in this population (2-5).

The high prevalence of intestinal metaplasia at squamocolumnar junction (IM-SCJ) was first described by Spechler et al. (6) It is not yet known whether this finding is meaningful in clinical settings. It is also presently not clear what causes IM-SCJ. The pathogenesis of IM-SCJ might be related with two factors: GERD and *Helicobacter pylori (HP)*.

This may underlie the rising frequency of cancer of the gastroesophageal junction (GEJ) in the United States and Europe (7, 8). As a developing country with high *HP* prevalence, contrary to the status in developed countries, distal gastric adenocarcinomas remain more frequent than proximal gastric adenocarcinomas (9). Turkey is particularly important for the evaluation of GERD for several reasons. First, prevalence of both GERD (22.8%) and *HP* (75-82%) is high; however, prevalences of BE (0.02%) and other complications of GERD are very low compared to westernized countries in Turkey (10, 11). It is not known why the ratio of distal versus proximal gastric adenocarcinomas has not changed in our country. However, prevalence of IM-SCJ in patients referred for upper GI endoscopy is as common as in developed countries (12). Since PSS predisposes patients for development of GERD and its complications, it might be important to determine the prevalence, related factors and pathogenesis of IM-SCJ in these patients.

We aimed to evaluate the prevalence of IM-SCJ in patients with PSS and to compare to GERD patients without PSS and patients without PSS or GERD who were referred for upper GI endoscopy because of the presence of dyspeptic symptoms. The relationship between IM-SCJ and alcohol consumption and cigarette smoking, medications, GERD, *HP* status, carditis, and IM in other regions of the stomach were evaluated in these three groups.

MATERIALS AND METHODS

This prospective study included 31 consecutive patients with PSS (Group A), 58 patients with GERD-without PSS (Group B) and 36 patients without PSS or GERD (Group C) as controls who were referred for upper GI endoscopy for dyspepsia. Upper GI endoscopy was performed in all patients after completing a validated questionnaire in Turkish for symptoms of GERD (13). Questions were employed that related to the presence of the following: major (heartburn, regurgitation, dyspepsia) and related (dysphagia, odynophagia, chest pain) symptoms, triggering factors of these symptoms, associated medical conditions, medical history, family history, and demographic and soci oeconomic data. GERD indicates that a major symptom (heartburn and/or regurgitation) occurs at le ast once a week or commonly (http://www.acg.gi.org/).

Exclusion criteria were all malignancies, achalasia, esophageal varices, history of esophageal therapeutic approach, diseases with accompanying coagulopathy, and gastric outlet obstruction.

Upper endoscopy was performed in all subjects by two authors. Endoscopic findings were classified according to LA grading system for esophagitis and Prague classification for BE. A total of 13 biopsies were taken from each patient: three from antrum, two from the body of the stomach (corpus), four from Z-line, and two biopsies 3 cm above the Z-line. Additionally, one biopsy from the antrum and one from the body were taken for rapid urease tests. Fixation of all biopsies was performed in 10% formalin solution, and after tissue process, sections were stained with hematoxylin and eosin in all tissues. In order to increase the possibility of detection of goblet cell, Alcian blue (pH 2.5) stain were applied to all Z-line and stomach biopsies. All sections were evaluated by two

independently blinded pathologists. Statistical evaluation was performed by one-way analysis of variance (ANOVA), Student T test, Fisher's exact test, and logistic regression.

RESULTS

Mean age was significantly lower in Group A compared to Groups B and C [46±9 (21-62), 51±14 (23-79) and 56±15 (24-83) respectively; $p<0.05$]. Female gender was also significantly more prevalent in Group A versus Groups B and C (Table 1). Dysphagia was statistically more frequent in Group A than in Groups B and C, while abdominal pain and bloating were less in Group A than in Groups B and C. The ratios of odynophagia and anorexia were similar in all groups. As expected, regurgitation and heartburn were more prevalent in Group B than in Groups A and C ($p<0.05$) (Table 1). The length of availability of disease change between 12-360 months and mean value of the presence of disease in the PSS group was 140 months. There was no significant correlation between age of disease and severity of GERD.

We found that grade C-D esophagitis, stricture and BE were significantly higher in patients with PSS (Group A) ($p<0.05$) (Table 2). However, IM-SCJ was detected in 31% in Group A (6/19), 32% in Group B (15/46) and 29% in Group C (9/31) ($p>0.05$ for all comparisons) (Table 3, Figure 1). Prevalence of *HP* was found in 61% (19/31) in Group A, 67% (39/58) in Group B and 38% (14/36) in Group C. Prevalence of *HP* was significantly higher in Group B than Group C; however, no difference was observed between Group A and Group B. No significant relationship was detected between IM-SCJ and gender, age, smoking, alcohol consumption, body mass index, gastric atrophy, and prevalence of *HP* between groups. IM-SCJ was determined more frequently in the patients with carditis than in those without carditis in all three groups ($p<0.05$). There were no correlation between IM at the antrum and *HP* in any of the groups, and similarly, no correlation between IM-SCJ and *HP*. Epithelial dysplasia was not detected in any of the patients with IM-SCJ.

Table 1. Patients' general characteristics

Characteristics	Group A n=31 (%)	Group B n=58 (%)	Group C n=36 (%)
Male/Female	5/26 (16/84)[a]	23/35 (40/60)	14/22 (39/61)
Heartburn	9 (29)	41 (71)[b]	0 (0)
Regurgitation	11 (35)	54 (86)[b]	0 (0)
Dysphagia	15 (48)[a]	12 (21)	4 (11)
Odynophagia	4 (13)	4 (6.8)	2 (5.5)
Abdominal pain	7 (23)[a]	27 (46)	21 (58)
Bloating	2 (6.4)[a]	43 (74)	20 (55)
Belching	13 (42)	35 (60)	12 (33)[c]
Vomiting	3 (10)	25 (43)[b]	8 (22)
Chest pain	9 (29)	12 (21)	3 (8.3)[d]
Anorexia	10 (32)	11 (19)	8 (22)

([a]Group A vs Group B, C $p<0.05$)
([b]Group C vs Group B $p<0.05$)
([c]Group B vs Group A, C $p<0.05$)
([d]Group C vs Group A $p<0.05$)

Table 2. Findings of upper gastrointestinal endoscopy

Findings	Group A n=31 (%)	Group n=58 (%)	Group C n=36 (%)
Normal	10 (32)[a]	38 (65)	30 (83)
Mild esophagitis (A-B)	6 (19)	18 (31)[b]	2 (5)
Severe esophagitis (C-D)	7 (22)[a]	0 (0)	1 (3)
Esophageal stricture	3 (10)[a]	0 (0)	0 (0)
Columnar epithelium in esophagus			
<3cm	6 (19)	9 (15)	4 (11)
>3cm	6 (19)[a]	3 (5)	1 (3)

([a]Group A vs Group B, C $p<0.05$)
([b]Group B vs Group A, C $p<0.05$)

Table 3. Comparative findings of endoscopic investigation and pathologic examination

Findings	Group A n=31 (%)	Group B n=58 (%)	Group C n=36 (%)
Normal	13 (32)	31 (53)	22 (61)
Intestinal metaplasia at SCJ	6 (31)	15 (32)	9 (29)
Columnar epithelium in esophagus (CEE)	6 (19)	10 (17)	3 (8)
Barrett's (short and long)	6 (19)[a]	2 (3)	2 (5)

([a]Group A vs. Group B $p<0.05$)

DISCUSSION

This study was designed to evaluate the prevalence of IM at a normal in appearance SCJ in patients with PSS, GERD and controls. The study area has different characteristics compared to the published data from westernized countries in terms of GERD, such as low (nearly diminished) prevalence of BE, severe erosive esophagitis (11) dominance of distal gastric adenocarcinomas, and high *HP* rate. The prevalence of *HP* was 75-82% in two recent countrywide studies (14, 15). Given the different characteristics of our previous data, we wanted to evaluate whether the prevalence of IM at the SQJ was different than in the published literature. Because patients with PSS have a higher tendency for BE, we wondered whether these patients have a higher

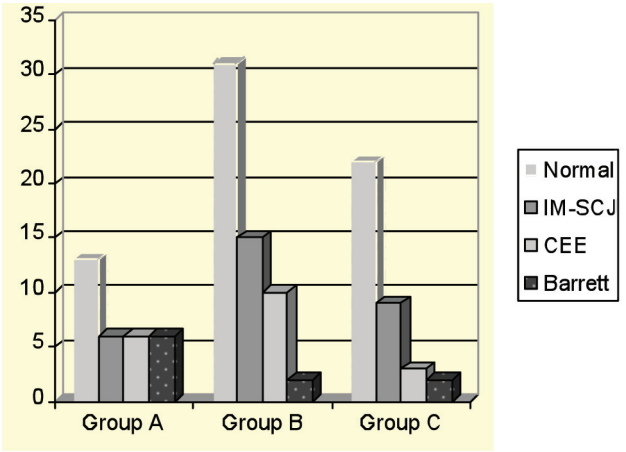

Figure 1. Distribution of endoscopic and pathologic findings in the three groups.
CEE: Columnar epithelium in esophagus.

rate of IM-SQJ. We found that the prevalence of IM-SQJ was similar in patients with GERD, PSS and those referred for endoscopy for any reason other than GERD/PSS, mainly dyspepsia. However, BE rate was significantly higher in patients with PSS compared to Group B and Group C patients (19% vs. 3% and 5%, respectively). These figures might indicate that there was no strong relationship between BE and IM-SQJ.

No statistically significant relationship was seen between the prevalence of IM localized at the antrum and body and presence of *HP* and IM-SQJ. Furthermore, no relationship was detected between IM-SQJ and gender, age, smoking, alcohol consumption, body mass index, and gastric atrophy.

Esophageal and gastric involvement is frequently seen in patients with PSS. GERD has been found in 71% of patients (16). Impaired peristalsis, with a delayed clearance of acid, and low pressure of lower esophageal sphincter are responsible for esophageal mucosal damage. On the other hand, symptoms of GER are not a reliable predictor of erosive esophagitis. As expected in patients with PSS, we found that severe esophagitis was more frequent, but heartburn and regurgitation were not as frequent as in the GERD without PSS group, which means that even patients with PSS without major GERD symptoms had erosive esophagitis. This might be a reflection of nerve end damage related with the collagen specific amino acids (hydroxyproline and hydroxylysine) deposition in the esophageal mucosa in the disease (17).

It has been shown in a number of studies from developed countries that IM is as common as 7-25% in a normal in appearance Z-line (IM-SCJ) in patients referred for upper GI endoscopy (6, 18-22). This wide range might be related with different patient selection criteria, staining techniques or the characteristics of study areas, such as low prevalence of *HP*, high income and obesity, etc. The clinical importance and consequences of this common condition are not clearly known. Two major factors have been cited as responsible for the presence of IM-SQJ in a normal Z-line: 1) GERD (as a reflection of BE, called ultra-short segment Barrett's [SSBE]) and 2) *HP* (result of *HP*-related carditis). Data on the roles of GERD and *HP* infection in the pathogenesis of IM at the GEJ are confusing and sometimes contradictory. Hackelsberger et al. (22) suggested that the pathogenesis of IM at the SCJ is not uniform. They found that IM-SQJ is a sequela of *HP* gastritis, but endoscopic features BE are associated with GERD. Goldblum et al. (23) also found that the prevalence of cardia IM was also significantly lower in patients with either GERD or BE than in control patients. It was suggested that in patients with IM at the GEJ, the condition may be a manifestation of a diffuse *HP* gastritis (i.e., there is *HP*-induced IM of the gastric cardia without esophageal disease). For others, GERD may cause IM in segments of the esophagus that are so short that the condition can not be distinguished endoscopically from the normal Z-line (18, 20). Pereira et al. (24) suggested that SSBE and IM-SCJ were two different entities. Reflux symptom and male gender were seen more frequently in patients with SSBE, while females were more commonly affected in the IM-SCJ group. The majority of the studies concluded that there was no relationship between the presence of IM-SCJ and GERD or *HP* and they suggested that IM-SQJ does not have any clinical implication and further, that due to these results, biopsies from a normal Z-line should not be obtained routinely. However, one of the most notable changes in the epidemiology of gastric and esophageal cancer is the increasing incidence of adenocarcinoma of the esophagus and esophagogastric junction in the United States and Western countries over the past two decades (7, 8, 25-27). Whether this change is a result of IM-SCJ is not exactly known. We showed in our countrywide study that Turkey, a developing country with high *HP* prevalence, represents a different profile than that of the developed countries, as manifested by

the dominance of distal adenocarcinomas (9). Contrary to the state in the developed countries, the ratio of distal vs. proximal gastric adenocarcinomas did not change within the last 11 years. The prevalence of BE and severe forms of erosive esophagitis was found low in a prospective countrywide multicenter study on 1783 cases in our GERD population compared to the Western countries (13). We might conclude that BE is not an important health problem for the Turkish population in accordance with the low rate of proximal gastric cancer. We wondered whether IM-SCJ is important in our population. While data from developed countries indicate a high prevalence of IM-SCJ, published data is lacking as to whether a similar tendency exists in the developing or under-developed countries.

Esophageal involvement is frequent in patients with PSS. This disease is related with a high prevalence of BE (5) and erosive esophagitis. However, it is not known whether this increase is accompanied by an increase in IM-SQJ. We showed that prevalence of IM-SQJ in patients with PSS was not higher than in patients with GERD or patients with dyspepsia. In view of these results, it may be suggested that there is no relationship between IM-SQJ and GERD and no effect on the development of BE. This is the first study related with PSS and IM-SCJ in the English literature. More studies should be performed in order to supply more powerful evidence related to these findings and to determine the differences in countries with different socioeconomic status.

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