

# Histological Features of Gastric Cardia in Adults: an Autopsy Study

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## Abstract

**Background & Aims.** The existence, histology and origin of gastric cardiac mucosa are controversial. The aim of the present study was to determine the existence, histological characteristics and length of cardiac mucosa and to correlate these features with the patients' age and the presence of inflammation in the gastric cardia and/or esophagus. **Methods.** The cardiac mucosa within the whole esophagogastric junction was histologically analyzed in 38 consecutive autopsy specimens and measured in 24 cases. **Results.** The cardiac mucosa was identified in all specimens from all cases, with a mean length of 6.7 mm, range 0.927-19.5 mm. In the majority of cases, the length of cardiac mucosa was less than 10 mm (87.5%) and greater than 5 mm (71%). Cardiac mucosa was composed of a combination of pure mucous glands and mucous glands with parietal cells in 74% of cases, and only of mucous glands with parietal cells in 26% of cases. Carditis was recorded in 23.7% cases and reflux esophagitis in 15.8%. The length of cardiac mucosa was not significantly different between cases with and without carditis ( $p>0.05$ ), between those with and without esophagitis ( $p>0.05$ ), and between age groups older and younger than 60 years ( $p>0.05$ ). **Conclusion.** In the adult population, a short histological segment of gastric cardia was consistently present as a normal histological structure. The type, length and circumferential presence of cardiac mucosa were not significantly associated with carditis, esophagitis or age.

## Key words

Cardiac mucosa – gastric cardia – esophagogastric junction – histology.

Received: 08.12.2010 Accepted: 17.02.2011

J Gastrointest Liver Dis

March 2011 Vol. 20 No 1, 13-18

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## Introduction

During the last decades there has been an increasing incidence of esophageal and gastric cardia adenocarcinomas [1] and subsequently, the histopathology of gastric cardia has become the focus of intense investigation.

Traditionally, gastric cardia has mostly been defined anatomically, as an ill-defined proximal part of the stomach which lies around the orifice of the tubular esophagus and extends for 10 to 30 mm distal to the esophagogastric junction (EGJ) [2-5]. Also, gastric cardia has been histologically described as a narrow circular area at the transition between the esophageal squamous mucosa and the oxyntic, acid-producing gastric mucosa [3, 6, 7]. Differences in definition and usage of the terms "cardia," "cardiac mucosa," and "gastric cardia" have contributed to the confusion that exists in this area of histology and pathology [8]. Most authors agree that there is variability in the extent and composition of the gastric cardia; some references describe only pure mucus glands inherent to the cardiac mucosa [3, 7-9], whereas others include oxyntocardiac mucosa as well [4-6, 10, 11]. Some view the cardia as a normal structure that is present at birth [6, 7, 9, 12-14], whereas others suggest that cardiac mucosa is abnormal and develops in the distal esophagus as a metaplastic mucosa due to gastroesophageal reflux disease (GERD) [8, 15-19]. According to the latter view, there is a normal direct continuity between the esophageal squamous- and gastric oxyntic mucosa.

Thus, the nature, location, extent, and even the existence of cardiac mucosa are controversial. The ideal approach to define the histological characteristics and the length of the gastric cardia is to perform the microscopic examination of the whole EGJ in a random sample of the general population. The histology of the gastric mucosa within the whole EGJ circumference has been investigated mostly in fetal/neonatal/pediatric autopsy-based studies [6, 7, 9, 12, 18]. In the adult population, cardiac mucosa of the whole circumference has been histologically analysed in three series only: one was an autopsy-based study [8], and the other two series were founded on operation specimens [10, 20].

The aim of the present study was to investigate the

presence, composition and length of gastric cardiac mucosa in autopsy samples of the whole EGJ in adults.

## Material and methods

We used tissue samples obtained from 44 consecutive adult autopsies performed at the Institute of Pathology and Institute of Forensic Medicine, Medical School, University of Belgrade. At autopsy, the distal esophagus and stomach were excised in one piece. Specimens were opened longitudinally, stretched and pinned on a cork before fixation. In every case the anatomic EGJ coincided histologically with the squamocolumnar junction (SCJ). The former was anatomically defined by the incisura between the esophagus and the stomach, and the mucosal SCJ line always matched the line connecting the two points of the incisura. No evidence for Barrett's esophagus was present on gross examination. Peptic ulcer disease of the duodenum was found in two cases and Crohn's disease of the ileum in one case.

For histological orientation of the EGJ, we used black ink to mark esophageal squamous mucosa up to its transition to gastric mucosa. The specimens were fixed in 10% formalin and the entire EGJ was sectioned longitudinally so most of the section (approximately 3.5 cm) was composed of gastric mucosa with only about 0.5 cm of esophageal mucosa [12]. Six cases in which autolysis prevented adequate estimation of mucosal characteristics were excluded; therefore, the histological analysis was performed in 38 cases. The number of blocks from EGJ varied between 5 and 13 (average: 9) per sample. Only one level per block was analysed.

Slides from all paraffin blocks were stained with hematoxylin and eosin. For the purpose of this study, the "true" gastric cardia was labeled as transitional zone (TZ) and defined as the area of columnar mucosa located distally to the SCJ and proximally to the portion of stomach (corpus) that was composed entirely of oxyntic glands [6, 20]. Inflammation of this histologically defined cardia was referred to as "carditis" [8]. In this study no attempt was made to identify *Helicobacter pylori* (*H. pylori*) as the cause of carditis because the autopsy material was unreliable for accurate diagnosis.

The types of mucosa of the transitional zone were classified into three groups: 1. pure cardiac-type mucosa (CM), 2. oxyntocardiac-type mucosa (OCM), and 3. oxyntic-type mucosa (OX) [6-8, 12]. Pure cardiac mucosa is composed of mucous glands containing only mucus-secreting cells. Oxyntocardiac-type mucosa consists of mucous glands with occasional parietal cells but without any chief cell. Oxyntic-type mucosa (i.e., fundic-type mucosa) is characterized by glands that contain specialized chief and parietal cells.

The type and extent of any glandular mucosa between squamous epithelium and pure oxyntic mucosa (i.e., TZ) of each case and of the whole series were recorded by histologic examination and measurement. Measurements were performed by two of the authors (S.R. and S.M.) on all microscopic slides with a calibrated ocular micrometer

using an Olympus microscope. For each case, the minimal and the maximal length of CM, OCM, and total TZ mucosa were recorded.

Carditis was graded into the categories positive or negative. Inflammation was considered to be positive when marked inflammatory infiltrate dissociated glandular lobules in addition to the presence of reactive lymphoid follicles. The presence of reflux esophagitis/carditis was determined according to standard criteria [11]. The results were analyzed by means of descriptive statistics, chi-square test, t-test and Fisher exact test. A p-value <0.05 was accepted as statistically significant.

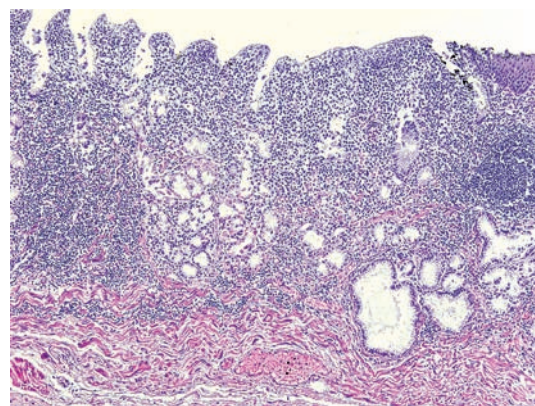
## Results

Patients age ranged from 21 to 84 years (mean 59 years) and 21 patients were male. Distances were measured in 24/38 cases – in the remaining 14 cases, twisting of tissue specimens during processing and/or embedding did not allow reliable measurements.

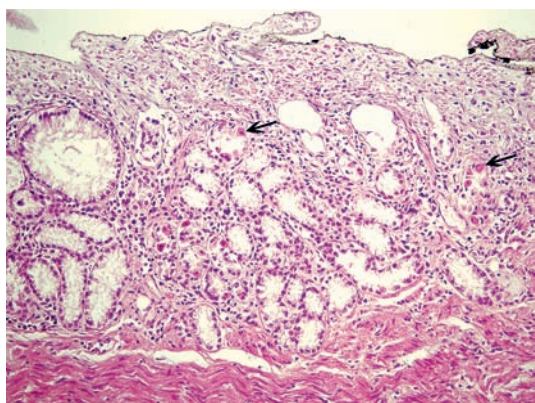
Transitional mucosa was circumferentially present in all cases, i.e. the esophageal squamous epithelium bordered directly to the fundic mucosa of the stomach in none of the slides examined. The type and length of mucosa in TZ varied in different portions of the circumference of the cardia in each patient. The glands of TZ mucosa were not associated with squamous-lined ducts or esophageal glands proper in any specimen confirming that the TZ mucosa was always located at the gastric site of the EGJ, and not in the distal esophagus as metaplastic cardiac-type mucosa.

Transitional mucosa consisted of both CM and OCM in 74% (28/38) of cases (Fig. 1) and only of OCM (Fig. 2) in 26% (10/38) of cases. The combination of CM+OCM mucosa was significantly more frequent in TZ than the sole OCM ( $p < 0.01$ ). With regard to the existence of pure CM (Fig. 3), it was always present in association with OCM, i.e., it was never recorded as the sole constituent of TZ.

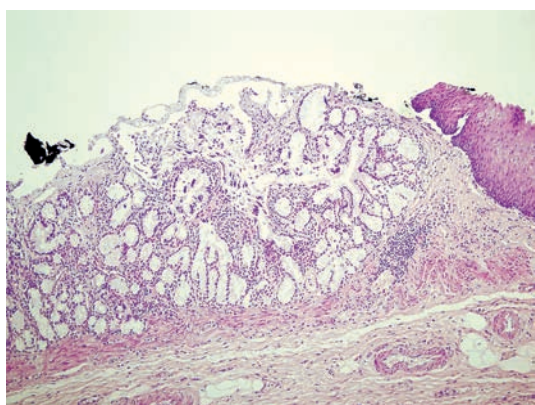
Concerning TZ mucosa that was represented only by the OCM, or the sum of CM and OCM, the mean minimal and



**Fig 1.** Transition zone mucosa, i.e., cardiac mucosa consisting of combination of pure mucous glands (right) and oxyntocardiac glands (left). Carditis is also present with dense inflammatory infiltrate that separates cardiac glands (H&E x100)



**Fig 2.** Oxyntocardiac glands in OCM-type mucosa are characterized by mucous glands containing sporadic parietal cells (arrows) (H&E x200)



**Fig 3.** Pure cardiac mucosa (CM) is composed of mucous glands containing only mucus-secreting cells, devoid of parietal cells (H&E x100).

maximal length per case was 2.244 mm and 14.115 mm, respectively. In the whole series, the length of TZ mucosa ranged between 0.927 and 19.5 mm (mean 6.732 mm, SD=3.076). In 70.8% (17/24) cases the length of TZ mucosa was greater than 5 mm (Table I). In 87.5% cases the mean length of TZ mucosa was less than 10 mm.

**Table I.** Mean length of transitional (TZ) mucosa in adults

Mean length (mm)	No. of cases	%
<5	7	29.2
5-10	14	58.3
>10	3	12.5
Total	24	100

TZ, transition zone

The length of TZ greater than 10 mm was noted in three (12.5%) patients (aged 56, 67, and 83 years) and measured 12.19 mm, 14.11 mm and 13.52 mm, respectively. Both esophagitis and carditis (with corpus and antrum gastritis) were recorded in the case in which TZ was 13.52 mm. In the other two cases with TZ >10 mm, carditis and/or esophagitis were not evidenced.

The length of OCM ranged between 0.53 and 10.229 mm (mean 4.924 mm; SD=2.627). When present, CM ranged in length between 0.325 and 8.125 mm. The mean length of CM was 2.243 mm (SD=1.987). Cardiac mucosa-type glands were present in all age groups and increased in incidence in older patients. Cardiac-type mucosa was noted in three out of four cases (75%) under the age of 30 years, in 11/13 (85%) cases in the middle aged (30-60 years), and in 14/21 (67%) cases older than 60 years. Oxyntocardiac-type mucosa was present in every case of TZ mucosa, irrespective of the presence of CM and of the age (Table II).

**Table II.** Types of transitional (TZ) mucosa in relation with age

Age (yrs)	Type of TZ mucosa		
	CM+OCM (n=28)	sole OCM (n=10)	Total (n=38)
<30	3	1	4
30-60	11	2	13
>60	14	7	21

TZ, transitional zone; CM, pure cardiac-type mucosa; OCM, oxyntocardiac-type mucosa

Regarding the circumferential presence, OCM was noted in all cases within the entire circumference of EGJ. Cardiac-type mucosa was circumferentially located only in 16% (6/38) and partially in 58% (22/38) cases (Table III).

Carditis on the whole was recorded in 23.7% (9/38) cases (Table III, Fig. 1): in 13.2% (5/38) it was isolated, whereas in 10.5% (4/38) it was associated with corpus/antrum gastritis. No statistically significant association between the mucosal type of TZ and carditis was found: carditis was recorded in 25% (7/28) cases of with CM+OCM mucosa, and in 20% (2/10) of cases with only OCM ( $p>0.05$ ). It seemed that there was no association between carditis and the extent of CM within EGJ circumference, but this could not be statistically proved due to the small number of cases: carditis was noted in 1/9 (11%), 2/7 (28.5%), 1/6 (17%), and 3/6 (50%) of cases with CM present in 1/4, 1/2, 3/4, and the whole EGJ circumference, respectively (Table III). Reflux carditis and reflux esophagitis were recorded in 23.7% (9/38) and 15.8% (6/38) of cases, respectively. Cardiac-type mucosa was found in only 55.5% of cases with reflux esophagitis.

The mean length of TZ mucosa with carditis (9 cases)

**Table III.** The extent of cardiac type mucosa (CM) within the circumference of the EGJ in association with carditis

CM in EGJ circumference	No. of cases (%)	Carditis	
		Present, n	Absent, n
Whole circumference	6 (16)	3	3
3/4 circumference	6 (16)	1	5
1/2 circumference	7 (18)	2	5
1/4 circumference	9 (24)	1	8
Absent	10 (26)	2	8
Total	38 (100)	9	29

CM, cardiac-type mucosa; EGJ, esophagogastric junction

was 6.897 mm (range 3.531–9.558 mm; SD=2.344), that was similar to the mean length of 6.676 mm (range 2.244–14.115 mm; SD=3.342) of non-inflamed TZ mucosa. The mean length of TZ mucosa in 6/24 cases with reflux esophagitis (6 cases) was 5.842 mm (range 2.244–13.52 mm; SD=3.992). The mean length of TZ in cases without reflux esophagitis was 7.028 mm (range 3.403–14.115 mm; SD=2.782). The length of CM was not significantly different between cases with and without carditis ( $p>0.05$ ), and between those with and without esophagitis ( $p>0.05$ ). A trend was present suggesting that the length of TZ mucosa increased with age (Table IV): we found greater mean lengths of TZ mucosa in the age group older than 60 years than in the group younger than 60 years, although these differences were not statistically significant ( $p>0.05$ ).

**Table IV.** The mean length of transitional (TZ) mucosa in relation with age

Age (yrs)	No. of cases	Mean length of TZ mucosa (mm)
<30	2	5.591 (SD=1.387)
30-60	11	5.972 (SD=2.929)
>60	11	7.699 (SD=3.326)

TZ, transition zone

## Discussion

From a gross and endoscopic point of view, the stomach begins at the most proximal aspect of the gastric folds, which is currently the accepted definition of the anatomic and endoscopic EGJ [5, 21]. In normal individuals, the anatomic EGJ coincides histologically with the squamocolumnar junction (SCJ), or Z-line [3, 4, 6, 11, 12]. The gastric cardia has long been defined as the region of the stomach that joins the esophagus. Pathologists often define the gastric cardia by its histologic features rather than by its gross anatomic appearance. This area has become the matter of debate since the group of Chandrasoma [8, 22, 23] disputed the traditional view that cardiac mucosa is a normal histological structure, considering it to be an acquired, metaplastic mucosa of esophageal squamous mucosa. Since then, there has been an increased interest regarding the etiology, pathogenesis, and natural history of the pathologic processes that occur in the EGJ area. All investigators recognize that cardiac mucosa exists histologically, but its anatomic position is controversial. According to the group of Chandrasoma [15-17, 22], cardiac mucosa (consisting of CM and OCM) is always an inflamed metaplastic mucosa of the distal esophagus, occurring as a consequence of GERD. The inflammation of cardiac mucosa may also be caused by *H. pylori* which denotes its gastric localization [24, 25]. Some authors support both etiologies for carditis [26, 27]. The paramount importance of carditis is the development of intestinal metaplasia (IM) and dysplasia in the inflamed cardiac mucosa, whether it is localized in the proximal stomach or in the distal esophagus. If IM arises within the metaplastic CM in the distal esophagus, it denotes Barrett's esophagus which is regarded as the precursor of adenocarcinoma via IM – dysplasia sequence.

The same sequence occurs in gastric *H. pylori* carditis. Some studies suggest a lower risk of progression of IM of gastric cardiac mucosa to adenocarcinoma when compared with IM in Barrett's esophagus [28]. Accordingly, it has become important to differentiate gastric cardiac mucosa with IM from Barrett's mucosa.

Many studies, based on biopsies, resections, or autopsies have been performed in an attempt to delineate the normal histology of the true gastric cardia [6-8, 12-14, 18, 20, 23]. These studies have shown variable results due to differences in patient populations (e.g., adults vs. children, GERD vs. non-GERD), methodology, definitions and terminology used to define anatomic and histological features of the gastric cardia. Hence, the length, cell types, and origin of mucosa that constitute the true gastric cardia are still a subject of debate. The most reliable information regarding the existence and histological features of gastric cardia in adults is obtained by biopsy or autopsy. There are very few studies regarding the histology of gastric cardia within the whole EGJ circumference in the adult population: the present study is the second autopsy series that has investigated the histology of the entire EGJ, after the study of Chandrasoma et al [8] and the fourth series addressing this topic [8, 10, 20].

The terms „cardiac mucosa” and „the transitional zone” (TZ) in our study are used as synonyms; we did not use the term „cardiac mucosa” in order to avoid the equation with cardiac-type mucosa, which is a histologic variant of cardiac mucosa glands. We have postulated the normal presence of a transitional zone set in between squamous esophageal and gastric oxyntic mucosa and investigated the type(s) of mucosa present within.

The main result of our study was that TZ (cardiac mucosa) existed in all specimens from all cases, i.e., gastric oxyntic mucosa was always separated from the squamous esophageal mucosa by gastric cardiac mucosa. In the literature, this histological structure was reported to be completely absent in a subset of population only in two series: in Chandrasoma's [8] and Park's [18] autopsy studies on adult and fetal/pediatric patients, cardiac mucosa was not recorded in 56% and 22% cases, respectively. Our findings are in agreement with two other studies performed in the adult population [10, 20] and with the autopsy-based pediatric series [6, 7, 9, 12] which confirmed the presence of cardiac mucosa within the whole EGJ circumference at the gastric site.

The most reliable endoscopic-anatomic landmarks for the level of the EGJ are the level of the proximal margin of the gastric folds and the level of the normally located SCJ; the latter is best recognized by the distinct difference in color between normal gray-colored squamous epithelium and red-colored columnar epithelium [21]. We defined the EGJ by the incisura between the esophagus and the stomach, and not by the proximal limits of the gastric folds which were not always clearly discernible in the autopsy material. We are aware of the possible existence of a millimetric difference between the SCJ and the top of the gastric folds, i.e. the EGJ, in autopsy material that cannot be discerned

macroscopically with certainty. However, we believe that the cardiac mucosa in the specimens of our series was from the gastric side of the EGJ because the mean length of TZ mucosa of 6.732 mm exceeded this millimetric difference between SCJ and EGJ.

Recent studies have unveiled that the extent of the cardiac epithelium is shorter than it was traditionally considered. In fetal/neonatal/pediatric population the length of cardiac mucosa ranges from 0.1 mm to 4 mm [7, 9, 12, 18]. The mean length of cardiac mucosa in adults was recorded as follows: 8 mm [10], 11 mm [20] and less than 5 mm in 94% of cases [8]. In our specimens, cardiac mucosa measured 6.7 mm.

Cardiac mucosa was composed of a mixture of CM and OCM, or only of OCM, similar to the other studies [6, 8, 12, 18, 20]. The 100% presence of OCM within cardiac mucosa was also noted in the other series [8, 18, 20]. Cardiac mucosa-type was traditionally believed to be the unique normal glandular mucosa of the gastric cardia [3] and it was universally present in two pediatric autopsy studies [7, 9]. In our series, CM was never the sole mucosal type of the cardiac mucosa, and when present, it was recorded in only 16% cases within the entire cardiac circumference. This uneven distribution may explain why CM is completely absent in endoscopic biopsies of a substantial percentage of adults [20]. Cardiac mucosa-type was present in all age groups and increased in incidence in elderly people. We assume that the increased incidence of CM in the elderly was merely the reflection of the predominance of older patients in our autopsy study.

Our findings could not confirm the relationship between the existence, length and the type of cardiac mucosa and inflammation (carditis and/or esophagitis). Inflammation of cardiac mucosa was seen in only 23.7% cases, unlike in the Chandrasoma et al [8] series where it was always inflamed. This feature and the lack of universal presence of cardiac mucosa led these authors to conclude that cardiac mucosa was not a normal structure. Although the length of cardiac mucosa was not significantly dependent on the presence of carditis and esophagitis in our series, the small number of cases and the inability to correlate with clinical history were limitations for a reliable conclusion regarding the relationship between the cardiac mucosa length and GERD. Similarly, it is difficult to compare the results of our study with the biopsy-based studies on the cardia which are supplied with clinical data.

However, we may conclude that the cardiac mucosa in our study was not a metaplastic esophageal mucosa related to GERD, as it was not associated with esophageal structures, i.e. esophageal glands and their ducts in any specimen.

We noted only a trend for cardiac mucosa to increase in length with age, similarly to the findings of Chandrasoma et al [8]. However, this increase in length of cardiac mucosa (of any type) due to aging was not statistically significant in our series, just as it was also insignificant in the aforementioned series [8].

**In conclusion**, our study showed that the cardiac mucosa was a normal histological structure, present in all specimens

on the gastric side of the entire EGJ circumference. It was a narrow area with a mean length of 6.7 mm; it was usually shorter than 10 mm and it extended very rarely to 20 mm. Cardiac mucosa consisted of pure mucus glands and/or mucous glands with dispersed parietal cells. The type and length of the epithelium in the gastric cardia varied in different parts of the circumference of the cardia in individuals.

## Conflict of interest

We declare that we have no conflict of interest.

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