BRIEF COMMUNICATION
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Mast Cell Density in Cardio-Esophageal Mucosa

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ABSTRACT

Mast cells are related to certain gastrointestinal complaints. Mast cell density has not been studied in cardio-esophageal region to the best of our knowledge. In this study we wanted to obtain an estimate of mast cell density in this region and compare it with mast cell density in antrum.

From April 2007 till March 2010, we chose children (<14 years old) who underwent upper endoscopy and from whom the taken biopsy was stated to be from lower third of esophagus, but in microscopic examination either cardio- esophageal mucosa or only cardiac mucosa was seen. Mast cells were counted by Giemsa stain at ×1000 magnification in 10 fields. 71 children (<14 years old) were included in this study of which, 63.4% (n=45) were female and 36.6% (n=26) were male. The mean age of patients was 7.20±4.21 years (range: 0.2 -14 years). The most common clinical manifestations were recurrent abdominal pain (64.8%) and vomiting (23.9%) followed by symptoms of gastro-esophageal reflux disorder, poor weight gain, hematemesis and dysphagia.

The mean mast cell density in the cardiac mucosa was 33.41±32.75 in 0.25 mm^2 (range: 0-155), which was two times of that in antral mucosa. We found a significant but weak positive correlation at the 0.05 level between mast cell density of cardiac mucosa and the antrum.

Higher mast cell counts were seen in cardiac mucosa in this study. Significant positive correlation between mast cell density of cardiac mucosa and the antrum could hint to a single underlying etiology for the inflammatory process in gastro- esophageal junction and gastric mucosa.

Keywords: Density; Esophagogastric junction mucosa; Gastroesophageal reflux; Mast cells; Pediatric

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INTRODUCTION

The esophagus is a tubular structure connecting the pharynx to the stomach covered by squamous epithelium. Normally, it passes through the diaphragmatic hiatus to enter the stomach. Most pathologists have accepted that there is a 10 to 20 millimeter-long mucus-secreting glandular mucosa between the acid-secreting oxyntic mucosa of the stomach and the squamous epithelium of the esophagus called junctional or cardiac mucosa that prevents digestion of squamous epithelium by the acid secreting oxyntic mucosa of the stomach.[1] Recently, the presence of cardiac mucosa as a normal finding has been under question since some studies suggest that cardiac mucosa represents an early histological manifestation of gastroesophageal reflux disorder.[2,3]

The understanding of pathologic changes at the Esophagogastric junction is limited because till now, an accurate description of the normal histology of this region is not assigned. Twenty-four-hour pH-monitoring studies show that reflux of gastric contents into the lower esophagus occurs in almost everyone, so, the study of normal histology in this region is also complicated by the difficulty in identifying a control population.[4]

The exact role of specific inflammatory cells in the pathogenesis of esophagitis is still under investigation. Eosinophilic and lymphocytic esophagitis are now two different patterns of esophagitis in which these inflammatory cells play the key role.[5,6]

Immunohistochemical studies have revealed that mast cells (MCs) are involved in chronic gastritis and they increase in number as the disease worsens and progresses.[7]

Sulik et al studied mast cell involvement in chronic gastritis in children and demonstrated that mast cell density was significantly greater in children with chronic gastritis with or without Helicobacter pylori (H. pylori) infection when compared to the controls. They also noted that mast cell through its numerous mediators may play a key role in chronic gastritis especially when H. pylori infection is present.[8]

We previously investigated the relationship between mast cell density, histological severity of gastritis, and presence of H. pylori in the antral mucosa of pediatric patients and we didn't found any correlation between mast cell density and presence and degree of inflammation, activity, presence and score of H. pylori in the antrum and concluded that there may be some other ways for contribution of mast cells in pathologic processes involving gastrointestinal tract in children.[9] In another study, by reviewing gastric biopsy specimens of children with gastric complaints (mainly abdominal pain) we found out a group with normal endoscopic and pathologic findings except for increase in mast cell density and we proposed mast cell gastritis as a new entity.[10]

We frequently encounter biopsies said to be sent from lower third esophagus in pediatric patients suffering from different complaints such as heartburn, abdominal pain and vomiting. Microscopic examination in these cases reveals cardio-esophageal mucosa or only cardiac type of mucosa. We routinely perform Giemsa stain in these cases in search of H. pylori. We then decided to count mast cells in these biopsies. Mast cell count varied between cases and in some, the count was very elevated. So we proposed that at least in some cases, mast cells maybe the dominant inflammatory cells in this area and as we reported in our previous article of the role of mast cells in chronic gastritis, there may be some causal role between mast cell infiltration and clinical complaints in these cases.

To the best of our knowledge, no studies have been performed on mast cell density in the cardiac mucosa and are mostly focused on mast cell density in the antrum and the corpus, also pediatric age group is reviewed in only few studies, so we decided to investigate mast cell density in the cardia and antrum of children with or without H. pylori infection in a referral hospital.

MATERIALS AND METHODS

All patients included in this study, underwent upper gastrointestinal endoscopy at Children Medical Center (children hospital affiliated to Tehran University of Medical Sciences) from April 2007 till March 2010, in order to evaluate gastrointestinal complaints, mainly abdominal pain. Of these, we chose children (<14 years old) from whom biopsy was stated to be sent from lower third of esophagus, but in microscopic examination either cardio- esophageal mucosa or only cardiac mucosa was seen. The specimens were fixed in 10% buffered formalin, processed, embedded in paraffin and cut in sequential 3 micrometer sections. Superficial and deep sections were stained by Hematoxylin-eosin (two slides) and one slide was

stained by Giemsa stain. Mast cells were counted by Giemsa stain at ×1000 magnification in 10 fields with a Zeiss standard 20 light microscope and the sum was calculated for each case (measuring 0.25 mm^2). Biopsy specimens of the antrum of these children were also evaluated. All the mast cell counts and histological evaluation were performed by a single observer (F. Mahjoub). A questionnaire was filled for each patient including clinical, endoscopic and pathologic findings.

The statistical analysis was performed using SPSS, version 17 (SPSS Inc, Chicago, IL, USA).

RESULTS

71 children (<14 years old) were included in this study of which, 63.4% (n=45) were female and 36.6% (n=26) were male. The mean age of patients was 7.20 ± 4.21 years (range: 0.2 -14 years). As shown in table1, most common clinical manifestations were recurrent abdominal pain (64.8%) and vomiting (23.9%) followed by symptoms of gastro-esophageal reflux disorder, poor weight gain, hematemesis and dysphagia.

The mean mast cell density in the cardiac mucosa was 33.41±32.75 in 0.25 mm^2 (range: 0-155). Mast cell density was divided in six categories: 0-29, 30-49, 50-69, 70-89, 90-109, >110. 53.5% (n=38) had 0 to 29, 16.9% (n=12) had 30 to 49, 16.9% (n=12) had 50 to 69, 8.5% (n=6) had 70 to 89, 1.4% (n=1) had 90 to 109 and 2.8% (n=2) had more than 110 mast cells/0.25 mm^2 (Figure 1).

We found no significant relationship between mast cell density in the cardiac area and sex of the patients.

Endoscopic and pathologic findings are summarized in table 2 and 3, respectively. Of 71 patients, H. pylori was present in cardiac mucosa of only 3 persons (4.2%). In all of them, H. pylori was also present in the antrum.

Table 1. Frequency of clinical manifestations

Clinical manifestations	Frequency	% in Studing Cases
Recurrent abdominal pain	46	64.8
Nausea and vomiting	17	23.9
Gastro- esophageal reflux disorder	9	12.7
Poor weight gain	9	12.7
Hematemesis	7	9.9
Dysphagia	3	4.2
Total	71	100

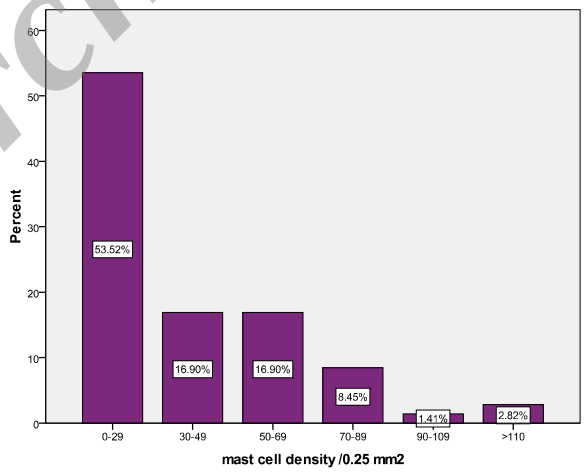

Figure 1. Distribution of mast cell density in cardiac mucosa.

Table 2. Upper endoscopic findings

Esophageal endoscopy	Frequency	Percent
Normal	10	14.1
Mild erythema	33	46.5
Moderate	9	12.7
Severe	9	12.7
Erosive esophagitis	7	9.9
ETC (trachealization, barret's esophagus)	3	4.2
Total	71	100.0

Table 3. Cardiac pathology and mast cell density in cardiac mucosa.

Cardiac pathology	Mast cell density in cardiac mucosa						Total
	0-29	30-49	50-69	70-89	90-109	>110	
Normal	1	2	0	0	0	0	3
Mild inflammation	15	5	5	2	0	0	27
Moderate inflammation	13	3	1	1	1	2	21
Severe inflammation	1	0	0	0	0	0	1
Barret's esophagus	3	2	1	0	0	0	6
Follicular aggregation	5	0	3	3	0	0	11
buried cardiac glands	0	0	2	0	0	0	2
Total	38	12	12	6	1	2	71

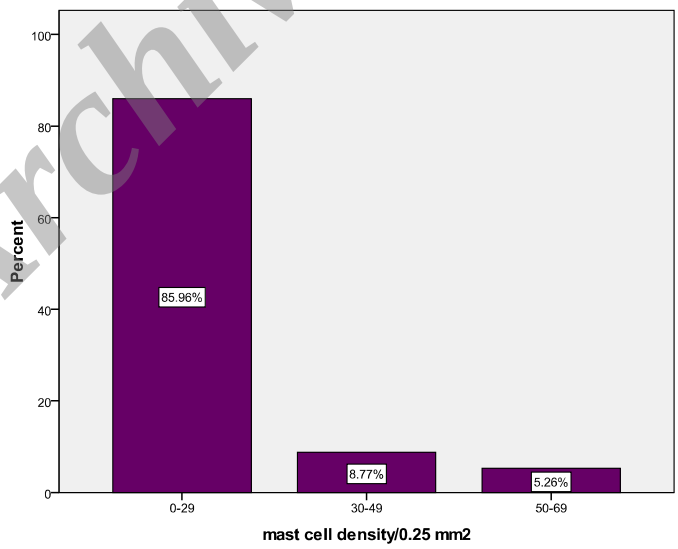

Figure 2. Distribution of mast cell density in antral mucosa.

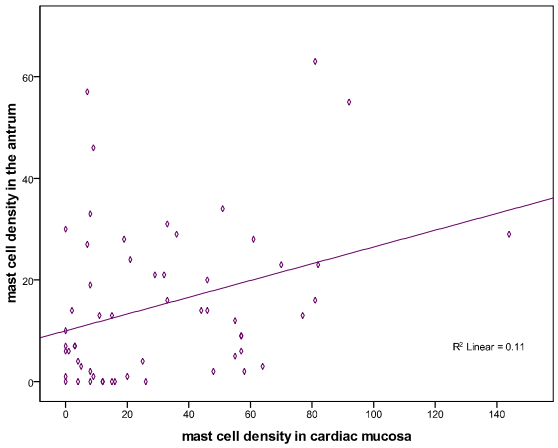

Figure 3. Scatter plot of mast cell density in cardiac and antral mucosa.

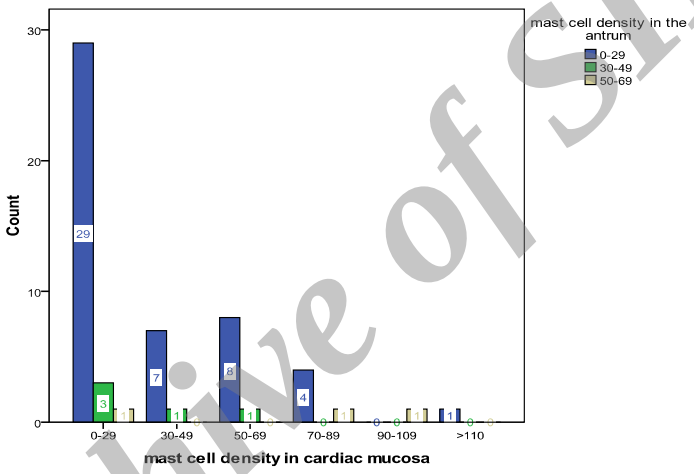

Figure 4. Cluster bar chart of mast cell density in cardiac and antral mucosa.

Antral biopsy has been performed in 57 cases. The mean mast cell density in the antral mucosa was 15.11±15.28 in 0.25 mm^2 (range: 0-63). Mast cell density was divided in three categories: 0-29, 30-49, 50-69. 86 % (n=49) had 0 to 29, 8.7% (n=5) had 30 to 49, 5.3% (n=3) had 50 to 69 mast cells/0.25 mm^2 (Figures 3 and 4).

We found no significant relationship between mast cell density in the antrum and sex of the patients.

Of 57 patients, H. pylori was present in antral mucosa of only 5 persons (8.7%).

We found a significant positive correlation at the 0.05 level between mast cell density of cardiac mucosa and the antrum (spearman's correlation coefficient: +0.308, p=0.02). This correlation seems to be weak (R^2 Linear= 0.11) but generally it means that the higher the count of mast cells in the antrum, we expect to have a higher count of mast cells in cardia.

We did not find any significant relationship between mast cell density in cardiac mucosa and presence of H. pylori, as well as mast cell density in the antrum and presence of H. pylori.

There was no significant difference between the age and sex of H. pylori positive patients and non-infected subjects.

DISCUSSION

Studies performed on the role of mast cells in the inflammatory process of gastritis are highly suggestive of its important effect especially in H. pylori-associated peptic ulcer,[7] although mast cells may also be increased in non-infected subjects[9] and also it may be the sole type of

inflammatory cell to be increased in antral biopsies in subjects mainly presenting with chronic abdominal pain.[10] However, the role of mast cells in pathologic processes in the end of esophagus and cardiac mucosa is not investigated as yet.

This study is performed on biopsy specimens obtained from lower third of esophagus in pediatric patients in a referral children's hospital in which about 2000 gastric endoscopies are performed annually.

It is for the first time that mast cell density is evaluated in the cardio- esophageal junction mucosa. Recent data indicate that the only normal epithelia in the esophagus and proximal stomach are squamous epithelium and the cardiac mucosa and gastric oxyntic mucosa are pathologic findings that could probably represent the presence of gastro- esophageal reflux disorder.[3] It is also acknowledged that it is difficult to establish a true control population for these kinds of studies. In the absence of asymptomatic volunteers, it is unlikely we will ever know what the normal mast cell density of this region is. The fact that the mast cell count is higher in the cardia as compared to the antrum could be 1) a normal finding, 2) a manifestation of GEJ pathology 3) could be a secondary manifestation of vomiting, not its underlying cause.

In our previous article we proposed a new term as "Mast Cell Gastritis" in patients with mast cell counts more than 30/0.25 mm^2. This number was chosen arbitrarily. In this study, 46.5% (n= 33) of cases had more than 30 mast cells/0.25 mm^2. This could be an indicator for the active role of mast cells in the pathogenesis of esophagitis.

Although higher counts were seen more in cardiac mucosa in this study, (mean density of mast cells in cardiac mucosa was two times that in the antrum, also it was higher than the mean in antrum in our previous study which was 12 per 0.25 mm^2), we found a significant correlation between mast cell density of cardiac mucosa and the antrum that could hint to a single underlying etiology for the inflammatory process in gastro- esophageal junction and gastric mucosa.

We did not find any significant difference between mast cell density in H. pylori positive patients and H. pylori negative ones. That will be due to few number of H. pylori positive specimens in this study, however it is compatible with our past findings.[9]

While true comparison of cardio- esophageal region should not be with biopsies from the antrum, but mucosa from the proximal saccular stomach, in future studies we can compare these regions. Also better clinicopathological correlation will further clarify the role of these cells in the future.

In conclusion, we believe that mast cells may also have a role in pathology of lower esophagus and they should be counted and reported if they are more than 30 per 0.25 mm^2.

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