Gastric eosinophilia – clinical and morphological correlations

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Abstract
Eosinophils of the gastrointestinal tract are involved in the host immune response that occurs in the presence of the pathogens in the digestive lumen, taking part in maintaining the homeostasis of the gastrointestinal epithelium. Their involvement in inflammatory processes of chronic gastritis is less known. In our study, we identified the presence of eosinophils in chorion gastric mucosa (lamina propria) in over 34% of chronic gastritis. Eosinophils were more numerous in atrophic gastritis with intestinal metaplasia. More than 65% of chronic gastritis associated with Helicobacter pylori also had eosinophils in the gastric mucosa.

Keywords: eosinophilia, immune response, allergic reactions, intestinal parasitosis.

Introduction
Eosinophils are granulocytary white blood cells found in the blood and connective tissues. These cells arise in the hematogenous bone marrow (red bone marrow) stem cells pluripotent. The structural and functional maturation processes happen at the same site. After maturation, they are present in the blood stream from 12 hours to several days, then passing into the connective tissue, where they participate in the immuno-allergic reaction, being the immune cells that belong to the innate cell immunity. Eosinophil differentiation of myeloid progenitor cells takes place under the influence of inflammatory cytokines such as interleukin-3 (IL-3), interleukin-5 (IL-5) and granulocyte-monocyte colony-forming stimulating factor (GM-CSF) [1–3]. The name derives from their property of staining with acid dyes (Eosin). Cells are about 12–17 μm in diameter, often with a two-lobed nucleus and cytoplasm rich in intensely eosinophilic granules spread relatively evenly, with a diameter between 0.8 and 1 μm.

Eosinophilia is defined as an increase in the number of eosinophils in the peripheral blood above 3% or the presence of more than 500 eosinophils per μL of blood. This condition can be observed in people with parasitic infestation, allergic diseases (allergic rhinitis, asthma), collagen diseases (rheumatoid arthritis, asthma), collagen diseases (Hodgkin’s disease), viral infections and so on.

Within tissues, activate eosinophils release several mediators, such as: cationic proteins [4, 5], eicosanoids and prostaglandins [6], reactive oxygen species [7], cytokines [8], growth factors [9], enzymes, etc. These cells are involved within the gastrointestinal tract in the immune response of the host towards pathogen agents found in the digestive lumen, taking part in the preservation of the homeostasis of the gastrointestinal epithelium [10]. Relatively new data suggests that tissue eosinophils play other parts as well, such as reparatory and tissue remodeling processes, graft rejection, help macrophages with the phagocytosis processes and so on [11].

In the present study, we aim to quantify the eosinophilic reaction at the level of the gastric mucosa in patients diagnosed both clinically and by upper endoscopy with chronic gastritis.

Materials and Methods
In our study, we included a total of 207 adult patients aged 26 to 72 years who presented to the Office of Gastroenterology at the “Renaissance” Medical Centre in Craiova, Romania, between January and December 2010 for various dyspeptic subjective complaints: heartburn, postprandial distension, eructation, gastroesophageal reflux, weight loss, loss of appetite. After clinical examination and after obtaining informed consent from all patients, we performed a gastroscopy to highlight the morphological changes and functional disorders present in the esophagus, stomach and duodenum and establish a correct therapeutic behavior. During the examination, we took biopsies from five regions of the gastric mucosa, according to the updated Sydney Protocol. Hence, we selected two fragments from the gastric antrum (one from the small curvature and one from the large curvature) two centimeters from the pylorus, the third biopsy from
the gastric angle, a fourth from the small curvature of the vertical portion of the stomach, half the distance between the cardia and the gastric angle, while the fifth biopsy was taken from the large curvature – the vertical mid portion of the stomach. For the identification of Helicobacter pylori (H. pylori), we used the urease rapid test based on the ability of the bacterium H. pylori to secrete urease enzyme that catalyzes the conversion of urea into ammonia and bicarbonate.

For the histopathological study of the gastric mucosa, we fixed the fragments in 10% neutral formalin and embedded in paraffin. We performed the demonstration and quantification of eosinophils by using classic HE (Hematoxylin–Eosin) staining.

Results

In our study, the distribution of cases of chronic gastritis varied greatly depending on age. Grouping cases by age decades has enabled us to observe the following distribution:

- Between 25–34 years, we found 22 patients accounting for 10.63%;
- Between 35–44 years, we found 47 patients representing 22.70%;
- Between 45–54 years, we registered 55 patients representing 26.57%;
- Between 55–64 years: 64 patients, representing 30.92%;
- Over 65 years: 19 patients, representing 9.18%.

Judging by the endoscopic appearance of the most common forms of gastritis we found atrophic gastritis of the stomach (67 cases, representing approximately 32.37%), followed by erosive gastritis (43 cases – cca. 20.77%), erythematous-exudative gastritis (38 cases – approximately 18.37%), bile reflux gastritis (35 cases – cca. 16.90%) and papulopustular erosive gastritis (24 cases – approx. 11.59%).

Regarding H. pylori infection in our study, the urease reaction was positive in 112 (54.1%) patients, which indicates that more than half of our group were patients infected with this bacterium.

We performed the histopathological study of eosinophils on all fragments of gastric mucosa taken by endoscopic biopsy in all patients included the study. Eosinophils were identified relatively easily on histological cups based on the intense acidophilic and homogeneous appearance of the cytoplasm. They appeared as oval cells with a diameter of 10–17 μm, uninculeate, with normochromic nucleus, often two-lobed, arranged eccentrically with numerous acidophilic granules in the cytoplasm. We identified eosinophils in only 71 (34.3%) patients of the 207 included in the study. The arrangement of eosinophils in the chorion gastric mucosa appeared uniform in all areas and in all patients. We encountered the lowest eosinophil counts in fragments of gastric mucosa taken from the upper half of the stomach – the small and large curvature of the vertical portion. The richest regions in eosinophils appeared to be biopsies taken from antral areas. The number of eosinophils varied from 14 to 370/mm² of gastric mucosa. Correlated with the form of gastritis, the most numerous eosinophils were identified in atrophic gastritis with intestinal metaplasia and the poorest in bile reflux gastritis.

The location of the cells in the thickness of the stomach’ chorion was non-uniform; however, in chronic erosive gastritis eosinophils were mainly disposed at the surface of the gastric mucosa (Figures 1 and 2), while in chronic gastritis with intestinal metaplasia we found uniform eosinophils distributed throughout the stomach chorion (Figures 3 and 4). Regarding the relationship between the presence of eosinophils and H. pylori infection, in our study we found 112 cases of HP gastritis and identified eosinophils in the inflammatory infiltrate of the chorion in 73 (65.17%) patients.

The number of eosinophils did not always correlate with the intensity of the inflammatory infiltrate of the gastric chorion. Some gastritis showed a strongly infiltrated chorion with lymphocytes and plasma cells, but eosinophils were absent or reduced in number, while in other cases the inflammatory infiltrate was moderate but rich in eosinophils.

In some cases of erosive gastritis, we observed the process of eosinophilic cell degranulation (Figure 5).

Discussion

Chronic gastritis represent the long-term development of an inflammation of the gastric mucosa, characterized by the extension of the inflammatory process both on the surface and in depth, with the destruction of the glandular epithelium or some of the gastric wall components. According to other authors [12], chronic gastritis has a high incidence in the adult population and its incidence increases with age. In our study, the highest number of chronic gastritis occurred in people between 45 and 64 years. They totaled 119 cases, accounting for 57.48% of patients with chronic gastritis, which confirms many of the observations so far.

Chronic gastritis is one of the most important pre-cancerous lesions, particularly chronic atrophic gastritis. In our study, we found chronic atrophic gastritis in 32.37% of patients with chronic gastritis. In addition, a significant percentage of chronic gastritis associated with infection were HP positive, which increases the risk of gastric carcinogenesis. Therefore, we believe that patients with chronic gastritis should be treated very carefully and evaluated clinically and endoscopically to prevent malignant degeneration of the gastric mucosa.

Currently, it is believed that infection with H. pylori is the largest pandemic in the world. According to some authors [13], more than half the world’s population is infected with this bacterium. Colonization of gastric mucosa by H. pylori occurs most often in childhood and causes an inflammatory response, predominantly of the lymphocyte type. Initial acute gastritis is followed by active chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia and gastric cancer [14]. Like any chronic inflammatory lesion, gastritis is characterized by a chronic inflammatory cell infiltrate predominantly located in the chorion of the gastric mucosa and submucosa but sometimes consisting mainly of lymphocytes and plasma cells and rare neutrophils and eosinophils. Although gastritis were considered the normal path of development of the gastric mucosa due to aging, exposure to various attacks throughout life, it is now clear that the most common causes of gastritis is the inflammatory process that occurs at this level due to infection with H. pylori [15].
The role of eosinophils in etiopathology of digestive disorders is still unclear [16]. Most studies claim that these cells have a significant role in the host immune response to the action of pathogens in the digestive tract lumen. Relatively recent data indicate that the presence of eosinophils in the lining of the digestive tract is induced by the presence of pathogenic agents. Mishra A et al. [17] showed that the migration of eosinophils in the
gastrointestinal tract of mammals is present antepartum, prior to bacterial colonization of the gastrointestinal tract. Moreover, it appears that there are significant differences between circulating eosinophils and those located in the gastrointestinal tract. Straumann A et al. [18] showed that unlike circulating eosinophils, those found in the gastrointestinal tract are strongly activated, even within the non-inflamed lining, being ready for immediate immune response to luminal bacterial action in the case of lost epithelial integrity.

In a healthy person, eosinophils may be present in small numbers in the lamina propria (chorion) of the gastric and intestinal mucosa. The numbers increase both in the blood and in the gastrointestinal tract helminthic infestations [19]. However, eosinophilia can occur in a variety of conditions, sometimes with no identifiable cause. Recently, “primary eosinophilic gastrointestinal disorders” have been accepted as a clinical identifiable cause. Recently, “primary eosinophilic gastro-intestinal disorders” have been accepted as a clinical entity that includes eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis [10].

Defining eosinophilic gastritis is more subjective, being characterized by the presence of an increased number of eosinophils in the gastric mucosa chorion. If the definition of eosinophilic esophagitis has been suggested to be a minimum number of eosinophils more than 15 cells per microscope field examined through a 40× [20, 21], for eosinophilic gastritis, there is until now no cut-off value.

We believe that defining the eosinophilia after the number of cells per microscopic field is not a proper method, because the dispersion of eosinophils in the gastrointestinal mucosa chorion is completely inhomogeneous. Therefore, we propose that the number of eosinophils should be reported per unit area (square millimeter), after reading at least 10 adjacent fields through a 20× objective. Furthermore, assessment of gastrointestinal eosinophilia through endoscopic biopsy may be inappropriate when the biopsy is superficial. For an accurate assessment of eosinophils consider biopsy must reach the muscularis mucosa.

In our study, the number of eosinophils varied from 14 to 370/mm² of gastric mucosa, being more numerous in atrophic gastritis with intestinal metaplasia. The presence of eosinophils was observed in a number of chronic gastritis associated with H. pylori infection. We believe that H. pylori, through the inflammatory process that it induces, is a factor that attracts eosinophils in gastric mucosa, having strong antibacterial properties. It is known that cationic protein and eosinophil peroxidase are both toxic to both Gram-positive and Gram-negative bacteria and contributes to the bactericidal activity of these cells [22]. The exact role of HP is not known to date in gastric mucosal eosinophilic infiltration.

Regarding the age of the patients with gastric eosinophilia we could not determine any correlation, eosinophilia occurring in all age decades.

The presence of an increased number of eosinophils in the gastric mucosa may be encountered in food allergies [23], which clinically mimic chronic gastritis.

Therefore, we believe that at present the role of eosinophils in gastric pathology is not well defined. We believe that accurate knowledge of the role of these cells in gastric pathology will open new therapeutic possibilities.

Conclusions

Eosinophils were present in a third of patients with chronic gastritis, the most common being chronic atrophic gastritis and in patients infected with HP. The number of gastric chorion cells varied greatly, from 14 to 360 cells per mm² of gastric mucosa. The roles of these cells in immune defense, especially in gastric mucosal inflammatory processes are not well known. In the absence of clear morphological boundaries between normal infiltration of the gastric mucosa and gastric pathology eosinophilia cannot be ascertained.

Contribution Note

All authors had equal contributions to preparing this manuscript.

References

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