Morphometric distinction of signet-ring cell adenocarcinoma cells from foamy macrophages in gastric endoscopic biopsies

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Aims: To distinguish signet-ring cancer cells from foamy macrophages in the small gastric endoscopic biopsies using objective morphometric measurements of nuclei.
Material and methods: Using computerized image analysis, the mean nuclear area, length, breadth, perimeter and roundness were analyzed in histological sections of ten gastric endoscopic biopsies with signet-ring cell adenocarcinoma and four benign lesions with numerous foamy macrophages.
Results: Nuclei of signet-ring cell adenocarcinoma were significantly bigger than nuclei of foamy macrophages. Mean nuclear area (34.25 μm^2 for carcinoma cells vs. 25.41 μm^2 for macrophages) and mean nuclear breadth (5.82 μm vs. 4.99 μm, respectively) differed significantly ($P < 0.05$), whereas the remaining parameters did not.
Conclusion: Nuclear morphometry can distinguish foamy macrophages from signet-ring cell adenocarcinoma cells in endoscopic gastric biopsies.

Key words: stomach cancer, signet-ring cell adenocarcinoma, macrophages, morphometry, gastric biopsy.

Introduction

Among histologic types of gastric carcinoma, signet-ring cell adenocarcinoma shows peculiar morphology [1]. It is composed of small dispersed cells or small clusters of cells containing intracytoplasmic mucous vacuoles. These cells tend to infiltrate diffusely the wall of the stomach and may be accompanied by marked fibrosis. In small endoscopic biopsies, tumour cells of signet-ring cell adenocarcinoma can be confused with foamy macrophages infiltrating the mucosa and differential diagnosis can sometimes be difficult. Immunohistochemistry for epithelial and histiocytic markers may be useful in difficult cases since signet-ring cell adenocarcinoma cells are cytokeratin positive and CD68 negative, whereas macrophages are negative for cytokeratin and positive for CD68. However, quite often the results of immunohistochemical staining may be inconclusive.

The purpose of this study was to examine whether signet-ring cell adenocarcinoma cells can be distinguished from foamy macrophages in the small endoscopic biopsies by objective analysis of morphometric features of their nuclei with the use of computerized image analysis.

Material and methods

Tissue samples

Ten haematoxylin and eosin stained endoscopic biopsies with signet-ring cell adenocarcinoma and four benign lesions with infiltration of the stomach mucosa by foamy macrophages were retrieved from the archives of our institution. Histological diagnosis of signet-ring cell adenocarcinoma was established according to the WHO criteria and confirmed by positive immunohis-

tochemical staining for cytokeratin MNF116 (DAKO, Denmark, dilution 1 : 50) and negative staining for CD68 (DAKO, Denmark, dilution 1 : 50). Foamy macrophages were identified by opposite immunoreactivity. Histostain-SP kit (Zymed Laboratory, USA) was used for immunostaining.

Morphometry

Up to 300 nuclei were selected and measured in each case using computerized image analyzer Quantimet 600S (Leica, UK). Morphometric nuclear features such as area, length, breadth, perimeter and roundness were assessed under 400 × magnification.

Statistical analysis

The Mann-Whitney nonparametric test was used. A P-value of < 0.05 was considered to be statistically significant.

Results

Foamy macrophages (Fig. 1 A) may be difficult to distinguish from signet-ring cell adenocarcinoma cells (Fig. 1 B) in haematoxylin and eosin stained paraffin sections, however, we found that signet-ring cell adenocarcinoma cells had bigger nuclear area, length, breadth and nuclear perimeter than nuclei of

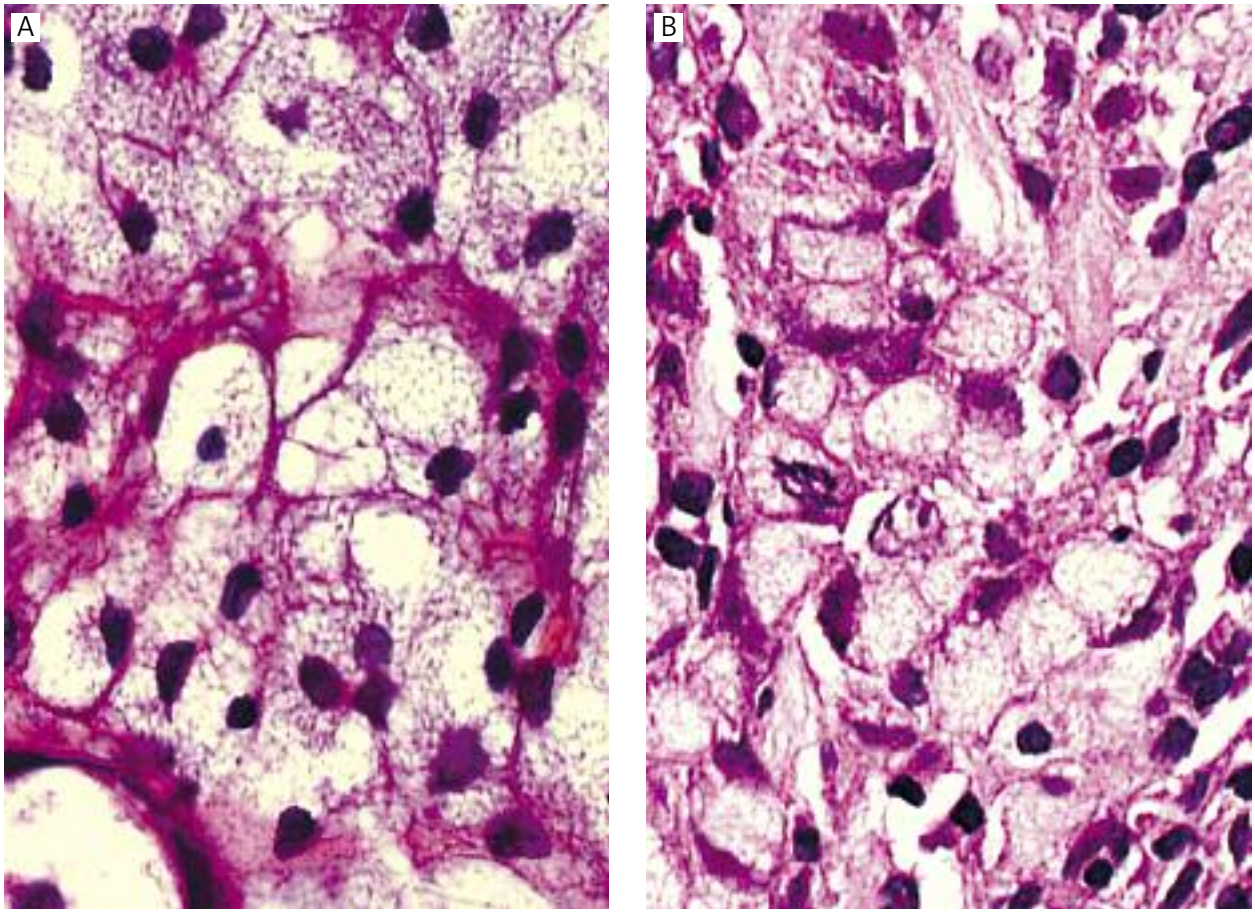

Fig. 1. Foamy macrophages (A) and signet-ring adenocarcinoma cells (B) infiltrating gastric mucosa. Haematoxylin-eosin stain

Table I. Nuclear morphometric characteristics of signet-ring cell adenocarcinoma and foamy macrophages in small endoscopic gastric biopsies (Mean ± SD, *P < 0.05)

Cell type	Area (μm²)	Length (μm)	Breadth (μm)	Perimeter (μm)	Roundness
Carcinoma cells	34.25 ±3.29	8.95 ±0.40	5.82 ±0.31	28.65 ±1.40	1.86 ±0.21
Macrophages	25.41 ±0.28*	7.90 ±0.96	4.99 ±0.13*	25.64 ±4.13	2.27 ±0.77

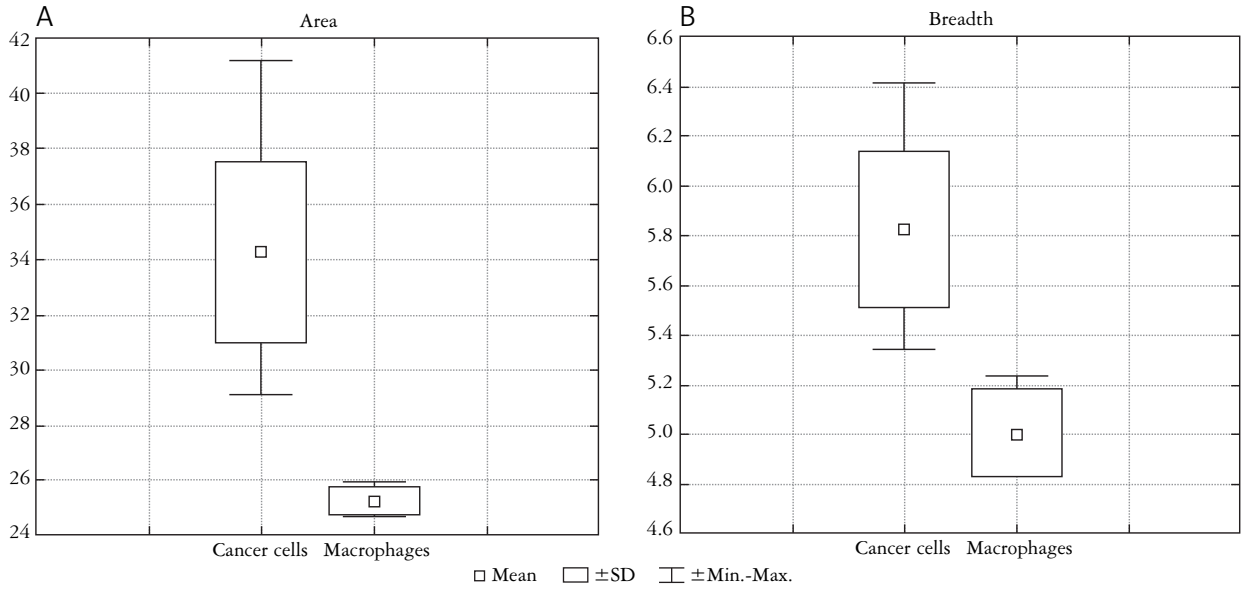

Fig. 2. Area and breadth of nuclei of signet-ring adenocarcinoma cells vs. foamy macrophages

macrophages (Table I). Out of all morphological parameters studied only two, i.e. mean nuclear area (34.25 μm^2 for carcinoma cells vs. 25.41 μm^2 for macrophages) and mean nuclear breadth (5.82 μm vs. 4.99 μm, respectively) differed significantly ($P < 0.05$) (Table I, Fig. 2). The nuclear area value of 25 μm^2 constituted the cut-off level between signet-ring cell adenocarcinoma cells and foamy macrophages.

Discussion

The presence of foamy macrophages in gastric mucosa has been known as a diagnostic pitfall in the differential diagnosis with gastric signet-ring adenocarcinoma [2-4] especially when they infiltrate lamina propria [3]. Signet-ring carcinoma cells are usually described as cells with a large, mucous-containing cytoplasmic vacuole, pushing the nucleus to the side or as "cells with central nuclei resembling histiocytes" [1]. Macrophages are characterized by foamy cytoplasm, studded with minute vacuoles and usually with peripheral nuclei. The differential diagnosis between signet-ring cancer cells and foamy macrophages is especially important nowadays since pathologists have to face an increasing number of small gastric endoscopic biopsies and the foamy macrophages of lamina propria may be mistaken for signet-ring cells of superficial cancer [4]. Despite immunohistochemical differences that exist between these two types of cells, it has been stressed that the differential diagnosis of signet-ring cells and undifferentiated carcinoma cells from foamy macrophages within the lamina propria can be best achieved by careful assessment of the nuclear morphology of the cells [3] because nuclei of signet-ring carcinoma cells are larger, more hyperchromatic and pleomorphic in comparison with the nuclei of macrophages. Our results provide the objective evidence that careful assessment of nuclear features with the use of computerized image analysis separates foamy macrophages from signet-ring carcinoma cells in the stomach mucosa and that the best discriminator is the mean nuclear area. To our knowledge, this is the first description of morphometric characteristics of nuclei of signet-ring cell adenocarcinoma cells and foamy macrophages in the gastric endoscopic biopsies.

We conclude that in small gastric endoscopic biopsies when microscopic, histochemical and immunohistochemical evidence is inconclusive, objective morphometric measurement of nuclei may help to distinguish tumour cells of signet-ring cell adenocarcinoma from foamy macrophages.

References

1. Fenoglio-Preiser C, Carneiro F, Correa P, et al. Gastric carcinoma. In: Pathology and Genetics. Tumours of the Digestive System. Hamilton SR, Aaltonen LA (eds.). IARCPress, Lyon 2000; 39-52.
2. Laforga JB. Foamy macrophages in pylorocardiac gastric carcinoma: a source of confusion with signet ring cell carcinoma. Histopathology 2003; 43: 98-100.
3. Fletcher CD. Diagnostic histopathology of tumors. Vol. l. 3rd ed.; Churchill Livingstone Elsevier, Philadelphia 2007; 350-351.
4. Drude RB Jr., Balart LA, Herrington JP, et al. Gastric xanthoma: histologic similarity to signet ring cell carcinoma. J Clin Gastroenterol 1982; 4: 217-221.

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