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Abstract

Natural history of gastric carcinoma development

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Carcinomas of the stomach are very heterogeneous from the morphologic standpoint. This heterogeneity is amply reflected in the diversity of histopathologic classifications on record which are based on different approaches: histologic profile, degree of differentiation, pattern of growth and histogenesis. The classification of Laurén is one of the most widely used, recognizing two major types of gastric cancer: “intestinal” carcinoma and “diffuse” carcinoma, which display different clinicopathologic profiles and occur in distinct epidemiologic settings.

The large majority of gastric cancers are sporadic. However, familial aggregation of gastric cancer, both of the diffuse and the intestinal type, suggest the importance of genetic predispositin in these settings. Presently, it is calculated that about 1% of gastric cancers are hereditary, the majority corresponding to “Hereditary Diffuse Gastric Cancer” (HDGC), caused by germline mutations of E-cadherin gene (*CDH1*).

Risk factors for the development of sporadic gastric cancer encompass environmental factors (diet, *Helicobacter pylori* infection, etc) and host factors. Both *Helicobacter pylori* genotype (regarding *vacA* and *cagA* genes) and host genotype (pro-inflammatory host genetic polymorphisms in the *IL1B, IL1RN* and *TNFA* genes) influence the risk of gastric cancer development.

In sporadic gastric cancer, the available evidence supports the existence of two main histogenetic pathways of carcinogenesis: one leading to ”intestinal carcinoma” *via* chronic

atrophic gastritis, incomplete intestinal metaplasia, namely type III and adenomatous dysplasia, and the other leading to diffuse carcinoma, either *de novo* or *via* hyperplastic changes. Both pathways appear to develop on the background of *Helicobacter pylori* associated gastritis.

Current knowledge on the natural history of HDGC stems essentially from detailed studies performed in prophylactic gastrectomy specimens performed in asymptomatic carriers of *CDH1* inactivating germline mutations. *Foci* of early diffuse gastric cancer were observed in 100% of prophylactic gastrectomy specimens submitted to a detailed reseach protocol. The neoplastic cells in the early invasive cancers displayed the features of signet ring cells. As precursor lesions of the invasive cancers, two distinct types of lesions were identified: i*n situ* signet ring cell carcinoma and pagetoid spread of signet ring cells below the preserved epithelium of glands/foveolae. On the basis of these findings a model of development of hereditary diffuse gastric cancer was recently proposed.

Curriculum Vitae

Fátima Carneiro, M.D., Ph.D.

Born in Angola, Fátima Carneiro received her M.D. from the University of Porto. Her Doctoral Thesis at the Faculty of Medicine of Porto in 1993 dealt with “Pathways of gastric carcinogenesis”. At present, Fátima Carneiro is Full Professor of Anatomic Pathology (Medical Faculty of Porto), Head of Department of Anatomic Pathology (Hospital S. João, Porto) and Senior Researcher at IPATIMUP. She is a member of the following Committees: Scientific Committee of the Working Group on Digestive Diseases of the European Society of Pathology and Tutorial Board of the European Course in Cellular Pathology (EUROCELLPATH).

Fátima Carneiro has a long lasting interest in gastric carcinogenesis, reflected in about 140 peer reviewed papers mainly on cancer and precursor lesions of the stomach and in chapters of books issued by WHO ("Pathology & Genetics of Tumours of the Digestive Tract", 2000) and UICC (Handbook on "Comprehensive Tumour Terminology", 2001). Her research activities are also developed in the frame of international networks: International Gastric Cancer Linkage Consortium; Intervention Study on "Intestinal Metaplasia" (European Organization for Cancer Prevention); European Project on "Environmental factors, *Helicobacter pylori*, genetic susceptibility and gastric cancer risk in the european population" (European Union -FP5).

Her research is directed towards understanding of *i*) etiopathogenesis of gastric cancer, with emphasis on the study of the interplay between *Helicobacter pylori* virulence factors and host

genetic variability in gastric carcinogenesis; *ii*) molecular basis of gastric carcinoma development, with an emphasis on Hereditary Diffuse Gastric Carcinoma (HDGC).

Major contributions in the field of HDGC (obtained in the frame IGCLC research activities) encompass the description of Early gastric cancer in asymptomatic carriers of germline E-cadherin mutations (New Engl J Med, 2001 – paper distinguished with the Benjamin Castleman Award by USCAP) and the proposal of a “Model of early development of diffuse gastric cancer in E-cadherin mutation carriers” (J Pathol, 2004).