

Further Studies on Serrated Neoplasias of the Cardia: A Review and Case Report

CARLOS A. RUBIO¹, FREDRIK PETERSSON¹, ANDERS HÖÖG¹, JÓN G. JÓNASSON²,
GABRIELLA NESI³, EVANGELOS CHANDANOS⁴ and MATS LINDBLAD⁴

¹Departments of Pathology and ⁴Gastrointestinal Surgery, Karolinska Institute and University Hospital, Stockholm, Sweden;

²Landspítalinn University Hospital, Faculty of Medicine, University of Iceland, Reykjavík, Iceland;

³Università Degli Studi di Firenze, Florence, Italy

Abstract. We have previously recorded 6 cases of serrated adenoma in the cardia. Here we report a case, which differed cytologically from the 6 preceding cases in as much as the adenomatous cells had clear, micro-vacuolated cytoplasm and secreted neutral mucins. Similar cellular features found in gastric carcinomas were classified by Mulligan as of pylorocardiac gland cell type. Six of the 7 cases (including the one reported here) showed areas of invasive carcinoma. Because of its location, histological and histochemical features, the reported neoplasia was called serrated adenoma malignum of the cardia (Mulligan type). Serrated adenomas of the cardia seem to have a particular proclivity to evolve into invasive carcinomas.

In 1923 Konjetzny (1) reported the presence of polypoid changes in the gastric mucosa; three years later, Borrmann (2) described different types of gastric polyps. In 1929 Stewart (3) found among 11,000 autopsies, 47 gastric polypoid lesions with cellular aberrations, that he called adenomas. Since then, many researchers had focused on gastric adenomas (4-20), due to their propensity to evolve into invasive carcinoma.

Gastric adenomas are classified histologically into tubular, villous, tubulo-villous (4-20), and papillary (16-20), and are usually localized in the antrum or in the body, and less frequently in the cardia. In this respect, Kozuka (16) found that of the 155 gastric adenomas examined only 2% were located in the cardia. Single cases of adenomas of the cardia have recently been reported (21-23).

Six years ago, we described a structurally different type of adenoma in the cardia characterized by serrated dysplastic fronds (24). Given that its histological features were similar to those of serrated adenomas in the duodenum (25), the appendix (26), the colon (27, 28), and the pancreatic duct (29), that adenoma was called serrated adenoma of the cardia. In a subsequent communication, we reported 5 additional cases of serrated adenomas of the cardia (30). Remarkably, an invasive carcinoma was found in 5 of the 6 cases.

A new case of serrated adenoma of the cardia, also showing invasive carcinoma is reported.

Case Report

The patient was an 80 year-old female who 20 years previously was subjected to hysterectomy and post-operative irradiation for an endometroid adenocarcinoma of the corpus uteri. Ten years later she fractured the right femur. Because of arteriosclerosis an iliaco-femoral by-pass was performed. The patient also had osteoporosis, hypertension, angina pectoris, and glaucoma, and treated with Waran and Nitromex. No family history of either gastric cancer or gastric ulcer was recorded.

The patient had a profuse hematemesis and tarry. She was admitted to the ward where repeated hematemesis occurred. Despite several transfusions, the hemoglobin remained low (76 g/l). Gastroscopy showed an exophytic bleeding tumor on the lesser curvature of the stomach, at the level of the cardia region. Despite the patient's poor condition, she underwent a total gastrectomy with esophagus-jejunostomy, ad modum Roux-en-Y. The patient had an uneventful post-operative recovery and was doing well two years after surgery.

Pathology. The gastrectomy specimen measured 14 cm along the lesser curvature. An exophytic tumor measuring 4x4 cm was found near the proximal resection margin. Following

Correspondence to: C.A. Rubio, MD, Ph.D., Gastrointestinal and Liver Pathology Research Laboratory, Department of Pathology, Building P1/03/057, Karolinska Institute and University Hospital, 17176 Stockholm, Sweden. Tel: +46 08 51774527, Fax:+46 8 51774524, e-mail: Carlos.Rubio@ki.se

Key Words: Gastric, neoplasia, serrated, pylorocardiac type.

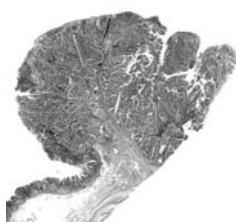


Figure 1. Large section showing protruding, gastric neoplasia (H&E, natural size, 1x).

fixation in 4% neutral formalin, 4 µm thick sections were cut and stained with hematoxylin and eosin (Figure 1). The histological examination revealed a partly eroded protruding adenoma showing elongated folded fronds with lateral crenate, saw-tooth-like notches due to scalloped epithelial indentations (Figure 2). The serrated glands were covered either by a single row of cells or by stratified epithelium of up to three rows of moderately pleomorphic cells with clear cytoplasm having micro-vacuoles (Figure 3). Their nuclei were vesicular with irregular chromatin distribution. Few mitotic figures were found. The adenomatous component showed high-grade dysplasia. Areas with focal submucosal invasion were also present (Figures 1 and 4). The invasive carcinoma component retained the serrated configuration and the cytological features of the adenoma (Figure 4). No metastases were detected in any of the 13 harvested lymph nodes.

Special staining procedures included Periodic Acid Schiff's-Glycogen (PAS), Periodic Acid Schiff's-Diastase (PAS-D), polyclonal antibody NCL-Ki67p, clone MIB-1, Dako Cytomation, Glostrup, Denmark), p53, the transcription factor that regulates the cell cycle (DO-1/sc-126, Santa Cruz Biotechnology, Santa Cruz, CA, USA) and small intestine mucinous antigen (clone SIMA-4D3, Lab Vision, Westinghouse, CA, USA).

The neoplastic cells in the serrated fronds showed PAS positive-diastase resistant cytoplasmic content (Figure 3). Lakes of intensely stained PAS-positive, diastase-resistant secretions were found interspersed between the serrated fronds in both the adenomatous (Figure 3) and in the invasive components (Figure 4). SIMA was neither expressed in neither the microvacuolated cytoplasm nor in the secretion found interspersed between the serrated fronds. Thus, the PAS positive-SIMA negative findings indicated that the secreted material was a neutral mucin and not a sialomucin. SIMA-positive intestinal metaplastic cells were found, however, in areas distal to the tumor.

Fifty per cent of the neoplastic cells in both the serrated adenomatous and in the invasive components were proliferating (Figure 5). The p53 protein was not expressed. The non-neoplastic gastric mucosa showed a few areas with intestinal metaplasia, but no inflammation or dysplasia.



Figure 2. High power view of the adenomatous component of the serrated neoplasia showing elongated fronds with lateral crenate, saw-tooth-like notches due to scalloped epithelial indentations (H&E, 40x).

Discussion

Serrated adenomas of the cardia appear to be very rare since no similar case was recorded in a survey of 113 gastric adenomas removed in Japanese and Icelandic patients (31-33), or in large series of gastric adenomas in the literature (16, 18-20).

Gastric adenomas in general may evolve into invasive carcinoma (16,19,20). The proportion of invasive growth found in gastric adenomas has varied in different series from 6% to 76% (4-20). We have found invasive carcinoma in 6 of 7 cases of serrated adenomas of the cardia (including the one reported here). The cause behind the particular proclivity of these lesions to evolve into invasive carcinomas remains elusive.

Carcinomas of the cardia of pylorocardiac gland cell type are also rare. Although Mulligan (34) reported 13 such cases, no single case was found among 854 carcinomas of the cardia (563 in Japanese (35) and 291 in American (36) patients), or in large series of gastric carcinomas the literature (4-20).

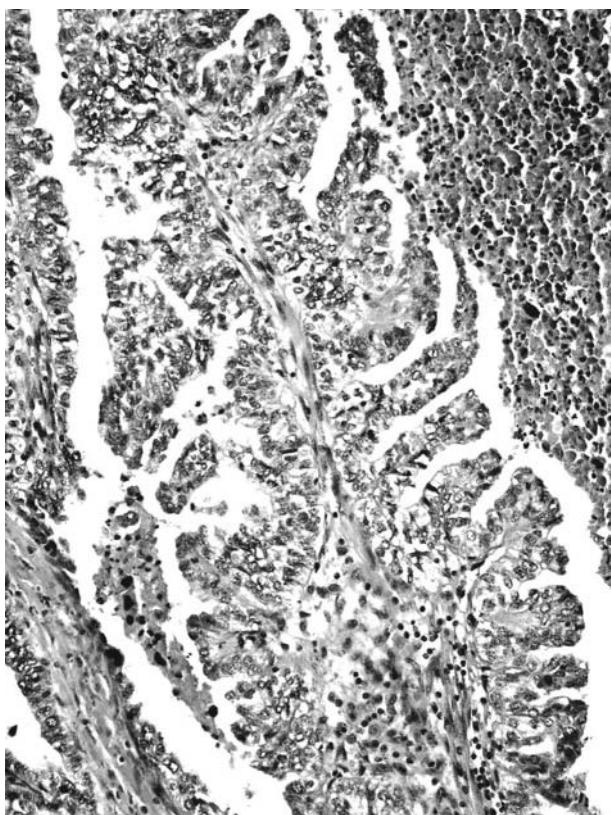


Figure 3. Another view, of the adenomatous component of the serrated neoplasia. Note the Periodic Acid Schiff's-Diastase (PAS-D)-positive secretion accumulated between the fronds (20x).

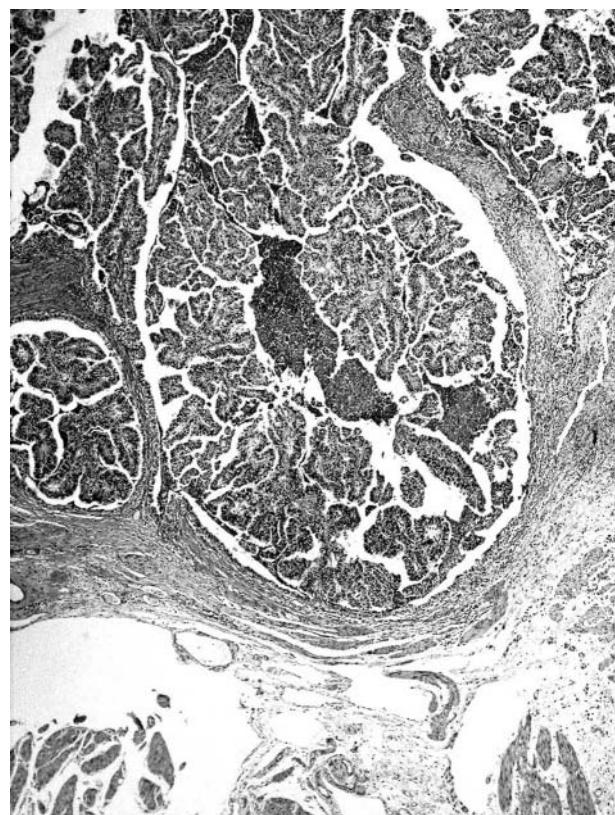


Figure 4. Invasive component of the serrated neoplasia. Note serrated configurations as well as the Periodic Acid Schiff's-Diastase (PAS-D)-positive secretion between the fronds (4x).

The neoplastic cell-secretions in the present case stained with PAS and PAS-D, but not with SIMA-4D3 immunostain, indicating that the neoplastic cells secreted neutral mucins and not sialomucins.

Rationally, the pyloro-cardiac gland neoplasia of the cardia reported here, evolved from mucin-secreting glands present in the cardia region, before the tumor ensued. It should be pointed out that some authors deny the existence of naturally occurring mucin-secreting glands in the cardia, claiming that the presence of such glands in the area is the result of a metaplastic change conveyed by a gastric-esophageal reflux (37). Whether the neoplasia developed from naturally occurring cardia glands or from metaplastic glands could not be determined from the material examined.

The 7th serrated neoplasia reported here differed from the 6 cases reported elsewhere (30) in as much as the saw-tooth like scalloped epithelial indentation was furnished with cells having clear, micro-vacuolated cytoplasm, secreting mucopolysaccharides. Mulligan (34) previously described these features for invasive gastric carcinomas that he called pylorocardiac gland cell type carcinoma. Due to the location and cellular attributes (including

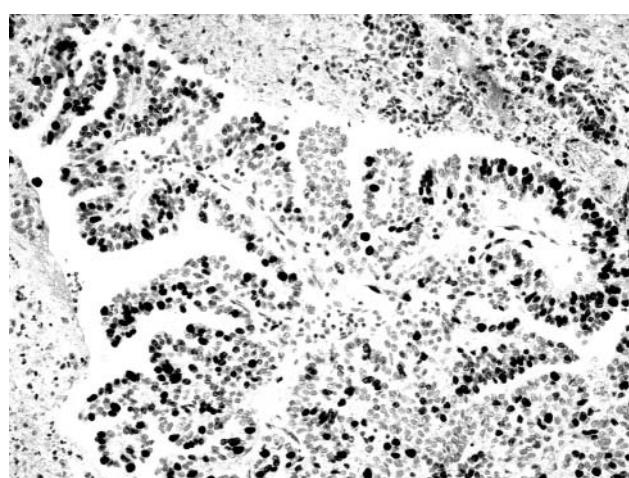


Figure 5. Adenomatous component, showing cell proliferation in the serrated fronds (Ki67, clone MIB-1, 20x).

secretion of neutral mucins), the neoplasm here reported was called serrated adenoma malignum of the cardia (Mulligan type).

Since serrated adenomas of the cardia are aggressive mucosal lesions, all polypoid changes of the cardia having serrated adenomatous configurations in endoscopic biopsies, should be completely excised.

Paradoxically, the 7 cases of serrated adenoma of the cardia in the literature have been reported from one single department. The increased awareness of the existence of these aggressive adenomas of the cardia (including serrated adenoma malignum-Mulligan type) may result in similar cases being reported in the future.

Acknowledgements

The Karolinska Institute supported this study.

References

- Konjetzny GE: Die entzündliche Grundlage der typischen Geschwurbildungen im Magen und Duodenum. Zieglers Beitr 20: 321-345, 1923.
- Borrman R: Geschwärze des Magens. Henke-Lubersch, Handbuch d spez pathol Anatome u Histologie. Berlin 4: 768-933, 1928.
- Stewart MJ: Brit Med J; ii: 567-572, 1929 (cited by Hurst AF: Precursors of carcinoma of the stomach. Lancet 217: 1023-1028, 1929).
- Appelman HD: Pathology of the Esophagus, Stomach and Duodenum. London; Churchill Livingstone pp. 94-100, 1984.
- Bone GE and McClelland RN: Management of gastric polyps. Surg Gynec Obst 142: 933-998, 1976.
- Day DW and Dixon MF: Biopsy pathology of the Oesophagus, Stomach and Duodenum. London. Chapman and Hall Medical. Second Edition, pp. 171-179, 1995.
- Fucuchi S, Hiyama M and Machizuki T: Endoscopical diagnosis of IIa-like borderline lesions (IIa subtype) of stomach. Stomach Intestine 10: 1487-1494, 1975.
- Ito H, Hata J, Yokozaki H, Nakatani H, Oda N and Tahara E: Tubular adenoma of the stomach. Cancer 58: 2264-2272, 1986.
- Johansen A: Elevated early gastric carcinoma. Differential diagnosis as regards adenomatous polyps. Path Res Pract 164: 316-330, 1979.
- Kato Y, Yanagisawa A and Sugano H: Biopsy interpretation in diagnosis of gastric carcinoma In: Gastric Cancer. Nishi M, Ichikawa H, Nakajima T, Maruyama K and Tahara E (ed). Tokyo, Springer Verlag, pp. 133-150, 1993.
- Nakamura T: Patohistologische Einteilung der Magenpolypen mit spezifischer Betrachtung ihrer Entartung. Chirurg 41: 122-130, 1979.
- Rotterdam H and Enterline H: Pathology of the stomach and duodenum. New York; Springer Verlag pp. 117-138, 1989.
- Rubio CA and Kato Y: DNA profiles in mitotic cells from gastri adenomas. Am J Pathol 41: 485-488, 1988.
- Rubio CA and May I: A method for quantitating the nuclear area of gastric polyps using image analysis. Analyt Quant Cytol Histol 12: 117-121, 1990.
- Kamiya T, Morishita T and Asakura H: Long term follow-up study of gastric adenoma and its relation to gastric protruded carcinoma. Cancer 50: 2496-2503, 1982.
- Kozuka S: Gastric polyps. In: Gastric Carcinoma. Filipe M, Jass J (eds.). Edinburgh. Churchill Livingstone, pp. 132-151, 1986.
- Laxén F, Sipponen P, Ihamäki T, Hakkiuoto A and Dortscheva Z: Gastric polyps:their morphological and endoscopical characteristics and relation to gastric carcinoma. Acta Pathol Immunol Scand A 90: 221-228, 1982.
- Ming SC and Goldman H: Gastric polyps. A histogenetic classification and its relation to carcinoma. Cancer 18: 721-726, 1965.
- Tomasulo J: Gastric polyps. Histologic types and their relationship to carcinoma of the stomach. Cancer 27: 1346-1355, 1971.
- Elster: Histologic classification of gastric polyps. In: Current Topics in Pathology. Morson B (ed.). Springer-Verlag, Berlin-Heidelberg-New York 63: 77-93, 1976.
- Yamamoto J, Ohshima K, Kohno S, Ichimiya H, Nakagaki M, Yao T, Iwasaki H and Ikeda S: Extremely well differentiated adenocarcinoma of the stomach diagnosed preoperatively as esophageal achalasia: report of a case. Surg Today 35: 488-492, 2005.
- Lee WA: Gastric extremely well differentiated adenocarcinoma of gastric phenotype: as a gastric counterpart of adenoma malignum of the uterine cervix. World J Surg Oncol 23: 3-28, 2005.
- Nokubi M, Kawanowa K, Kawata H, Hanatsuka K and Hosoya Y: Extremely well-differentiated adenocarcinoma of the gastric cardia: a unique case with columnar cells and laminated stones. Pathol Int 54: 854-860, 2004.
- Rubio CA: Serrated neoplasia of the stomach: a new entity. J Clin Pathol 54: 849-853, 2001.
- Rubio CA: Serrated adenoma of the duodenum. J Clin Pathol 57: 1219-1221, 2004.
- Rubio CA: Serrated adenomas of the appendix. J Clin Pathol 57: 946-949, 2004.
- Rubio CA and Rodensjo M: Flat serrated adenomas and flat tubular adenomas of the colorectal mucosa: differences in the pattern of cell proliferation. Jpn J Cancer Res 86: 756-760, 1995.
- Rubio CA, Nesi G, Messerini L and Zampi GC: Serrated and microtubular colorectal adenomas in Italian patients. A 5-year survey. Anticancer Res 25: 1353-1359, 2005.
- Rubio CA, Grimalius L, Von Sivers K and Hoog A: Intraductal serrated adenoma of the pancreas. A case report. Anticancer Res 25: 3099-3102, 2005.
- Rubio CA and Lagergren J: Serrated adenomas of the cardia. Anticancer Res 24: 2113-2116, 2004.
- Rubio CA, Kato Y and Jonasson JG: Protruding and non-protruding adenomas of the stomach. Anticancer Res 21: 3037-3040, 2001.
- Rubio CA and May I: A method for quantitating the nuclear area of gastric polyps using image analysis. Anal Quant Cytol Histol 12: 117-121, 1990.
- Rubio CA and Kato Y: DNA profiles in mitotic cells from gastric adenomas. Am J Pathol 130: 485-488, 1988.
- Mulligan RM: Histogenesis and biologic behavior of gastric carcinoma. Pathol Annu 7: 349-415, 1972.
- Rubio CA, Kato Y, Yanagisawa A, Ninomiya Y and Mandai K: Cardia carcinomas of intestinal type are associated with histologic changes in the gastric mucosa. Gastric Cancer 2: 215-220, 1999.
- Rubio CA, Jonasson JG, Filipe I, Cabanne AM, Hojman R, Kogan Z, Nesi G, Amorosi A, Zampi G and Klimstra D: Gastric carcinomas of intestinal type concur with distant changes in the gastric mucosa. A multicenter study in the Atlantic basin. Anticancer Res 21: 813-818, 2001.
- Chandrasoma P, Makarewicz K, Wickramasinghe K, Ma Y and Demeester T: A proposal for a new validated histological definition of the gastroesophageal junction. Hum Pathol 37: 40-47, 2006.

Received July 25, 2007

Revised September 28, 2007

Accepted