Int J Clin Exp Pathol 2014;7(3):1241-1245
www.ijcep.com /ISSN:1936-2625/IJCEP1401082

Case Report

Morules in fundic gland polyposis: a case report

Giovanni De Petris, Longwen Chen

Department of Pathology, Mayo Clinic in Arizona, 13400 E Shea Blvd, Scottsdale AZ, 85259, USA

Received January 22, 2014; Accepted February 18, 2014; Epub February 15, 2014; Published March 1, 2014

Abstract: Morular metaplasia has been exceptionally described in the stomach. We report the formation of morules in a case of sporadic fundic gland polyposis with low grade dysplasia in a 47 year old woman that underwent total gastrectomy. The immunophenotype of the morules was CD10, CDX2, Beta-catenin nuclear positive; p63, Ki67, chromogranin, synaptophysin, Ck20 negative. The presence of morules in a neoplasm know to be associated with the disruption of *wnt*/β-catenin pathway is discussed. The report provides the first description of the immunophenotype of morules in the stomach and hypothesizes the biological similitude of fundic gland polyposis to other tumors characterized by morules formation and *wnt*/β-catenin pathway dysfunction.

Keywords: Fundic gland polyp, morules, beta-catenin

The gastrointestinal tract can give origin to cellular proliferations that can be easily confused with neoplastic processes. Reactive and infiltrative processes, numerous forms of heterotopia, can all be invoked in the genesis of pseudoneoplasms of the gastrointestinal tract [1, 2]. In the present report we focus on morules: a proliferation considered by several authors "metaplastic", associated with both neoplastic and non-neoplastic processes. The biological potential or significance of morules in the stomach remains incompletely understood.

Morules are mulberry-like proliferations that originate from adjacent glands. They are composed of benign appearing round cells, of intermediate to small size, with bland round nuclei, often with empty, round, biotin-rich nuclear inclusions. Mitotic activity is low. The cluster cells are tightly cohesive but never with spinous processes.

While the terms "squamous morules" are sometimes used, it has been repeatedly shown that morules are distinct from squamous metaplasia and the two should not be confused [3, 4].

The lesion may be perplexing when appearing in the unusual setting of a fundic gland polyp (FGP). A single case report of Schlosnagle and Hardin in 1988 [5] described the pathology here presented. What is new here is the description of the immunohistochemical features of morules in a case of sporadic fundic gland polyposis. Also we suggest that morules associated with low grade dysplasia in fundic gland polyposis may join the field of morules-associated tumors with *wnt*/β-catenin pathway disruption: a group of tumors with less aggressive behavior.

Case history

A 47 year old woman affected by dermatomyositis with chronic cough and reflux disease underwent upper gastrointestinal endoscopy that showed carpeting of the fundus by numerous polyps. Genetic counseling elicited no family history of polyposis or malignancies. PTEN gene, MutYH and APC gene germline mutation analysis was negative. Few polyps were removed and were found to be fundic gland polyps, several with low grade dysplasia. A colonoscopy was negative for polyps. A total gastrectomy was performed. Numerous soft and red polyps, varying from 2 cm to few millimeters, were in the fundic portion of the resection. Four years after gastrectomy the patient is alive with no evidence of polyposis or phenotypical changes associated with any polyposis.

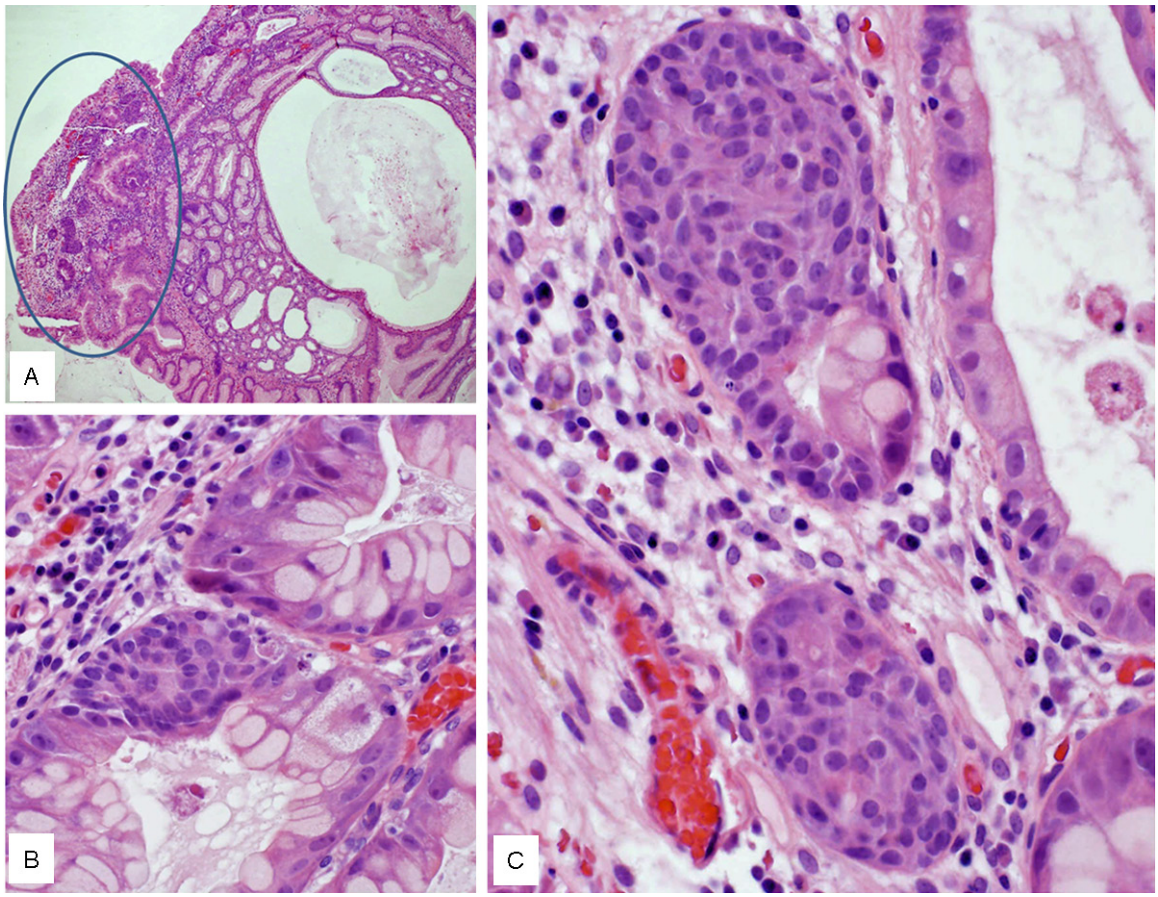

Figure 1. A fundic gland polyp showed low grade dysplasia with morules in the superficial aspect (circled) (A). Morules are shown at higher magnification in (B and C) highlighting their relationship with the adjacent dysplastic glands. Hematoxylin-Eosin stain, 2X magnification in (A), 20X in (B and C).

Histopathology

Several fundic glands polyps showed morules consisting of small round clusters of bland appearing cells, round to oval, with regular nuclei and small nucleoli, budding from the glands toward the stroma or reducing or occluding the glands lumina (**Figure 1**). The morules were all located in the superficial aspect of the polyp. Dysplasia of low grade was present in the glands from which the morules grew (**Figure 1**). There was no infiltrative growth from the morules nor any spindle or squamous differentiation. Only a rare round empty appearing nuclear inclusion was seen. The immunophenotype obtained (antibodies from DAKO, Carpinteria, CA, USA, used according to manufacturer specifications) was as follows: CDX2 and β-catenin produced nuclear positivity (**Figure 2A** and **2B**); positivity for nuclear β-catenin extended into the nuclei of the adjacent glands. CD-10 showed diffuse membranous positivity (**Figure 2C**). p63, chromogranin, synaptophysin, Ki-67 (**Figure 2D**), and CK 20 antibodies were negative.

Discussion

FGPs are classifiable as sporadic or syndromic when in the setting of familial adenomatous polyposis (FAP). They are the most common gastric polyp, found in 5.9% of adults and in up to 84% of FAP patients [6]. Due to the presence of numerous and dysplastic FGPs in our case, FAP and MutYH polyposis were dutifully ruled out to reach the diagnosis of sporadic fundic gland polyposis. It is known that in FAP the FGPs arise via a “second hit” alteration of the APC suppressor gene. In contrast APC gene alterations are unusual in sporadic FGPs. Sporadic FGPs depend on activation of the β-catenin gene (via mutation on or near several

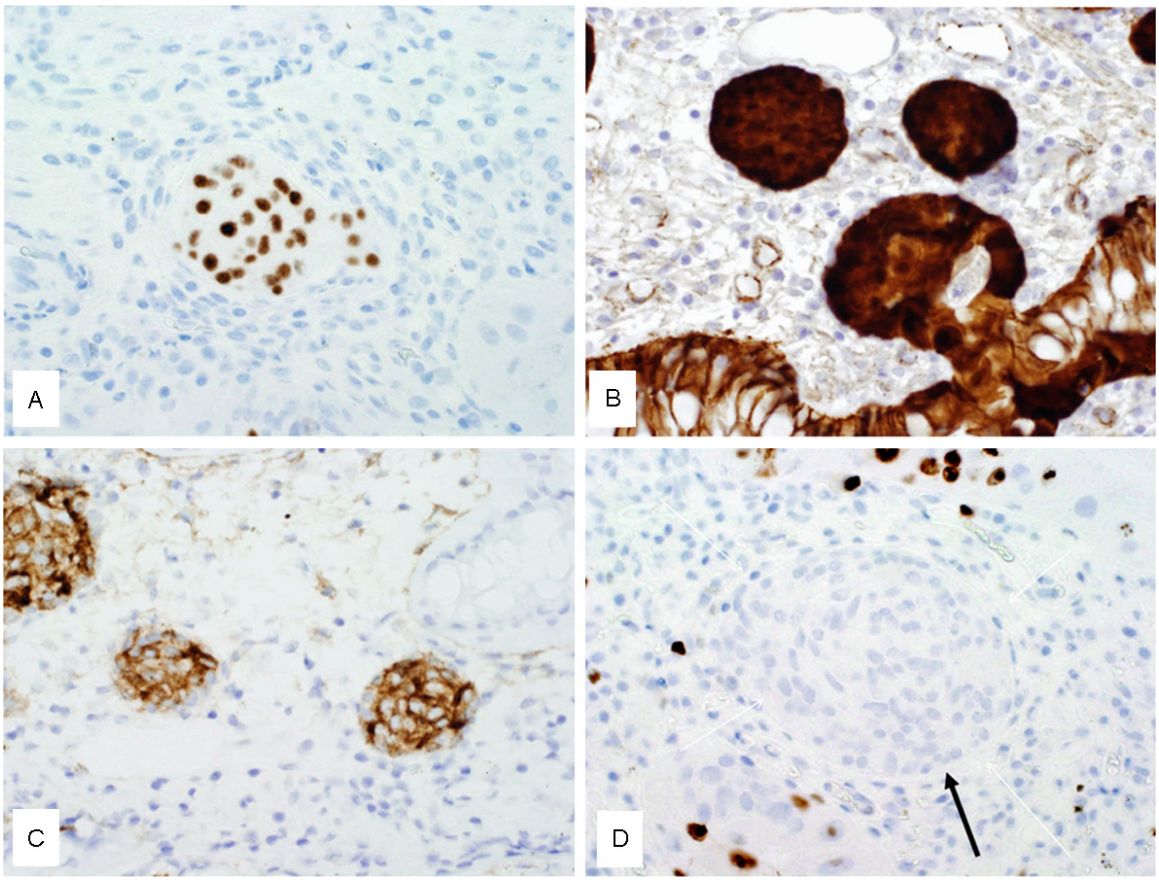

Figure 2. The morules showed nuclear positivity for CDX2 (A) and for β-catenin (B) with positivity extending to nuclei of the adjacent gland; membranous positivity for CD10 (C) highlighted the morules clearly. Ki-67 was negative (D), a morula is indicated by the arrow.

phosphorylation sites in exon 3 of the β-catenin gene) [7]. The mutations cause stabilization of β-catenin protein with accumulation and overexpression in the affected cells.

The findings in this case provide an interesting morphological manifestation of the molecular basis of FGPs in the sporadic setting.

Morules are small quasi-spherical aggregates of round or cuboidal bland cells with faintly eosinophilic cytoplasm and small round, nuclei. The cells lack expression of high molecular weight cytokeratins and of involucrin[3]. Often noted to display nuclear clearing due to biotin, the nuclei of morules from neoplasms of various organs show β-catenin positivity reliably, (e.g. in thyroid, lung, ovary, endometrium, gallbladder and pancreas [1, 4, 8-10]. The morules were also positive for nuclear β-catenin in our case. Alterations of the *wnt*/β-catenin pathway therefore are a possible molecular signature of morules in various organs.

P63 is a marker of mature squamous differentiation: it was negative in the fundic gland polyps; similar results have been obtained in uterine endometrioid adenocarcinoma [11] and further support the concept that morules should be distinct from true squamous differentiation in this case.

CD10 and CDX2 were positive in our morules. Chiarelli et al [12] have shown that CD10 is a useful marker of morules in endometrioid lesions of the female genital tract. The positivity of CD10 was found subsequently in morules of the cribriform-morular variant of papillary thyroid carcinoma, fetal lung type pulmonary adenocarcinoma, pulmonary blastoma and pancreatoblastoma. All tumors that in common have the disruption of the *wnt*/β-catenin signaling pathway (with aberrant nuclear expression of β-catenin, mutations of β-catenin or of APC genes). We here confirmed CD10 morular positivity in another site: fundic gland polyps with

low grade dysplasia. CDX2 positivity in FGPs morules is similar to CDX2 positivity in endometrial lesions where it displayed strong correlation with nuclear β-catenin expression [13]. In the uterus, again, full squamous differentiation differed from morules as it was always negative for CDX-2 [14]. The reasons for CDX-2 expression in morules remain unclear although it may indicate an interaction between β-catenin and CDX-2 pathways.

The observations add to the suggestion that morules develop in a group of neoplasms with: 1) abnormalities of the *wnt*/β-catenin pathway, 2) of glandular type and 3) with low grade biological potential. The latter is suggested, for example, by the known behavior of the majority of cases of cribriform-morular papillary carcinoma of the thyroid, (themselves a manifestation of the APC mutation-led FAP), or of complex endometrial hyperplasia with morules [14]. While β-catenin mutations in FGPs indicate their neoplastic nature, it is known that FGPs have very limited malignant potential. Low grade dysplasia in FAP FGPs reached an incidence of 44% in a study from Italy [15], while sporadic FGPs show low grade dysplasia in less than 1 percent of cases and have very low or no association with progression to gastric cancer [16]. The morules themselves also appear inert due to the very low Ki-67 positivity, an observation reproduced in other organs such as in premalignant endometrial neoplasia [17].

In summary we have described a new case of morules formation in the setting of fundic gland polyps in which we confirmed the similarity of the immunophenotype of the morules with those reported in other organs and its distinction from squamous metaplasia. We suggest that the findings described are compatible with the hypothesized model of low grade aggressiveness in neoplasms with morules and *wnt*/β-catenin pathway disruption because of the known molecular basis for FGPs formation and their low progression potential [18].

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Giovanni De Petris, Department Of Pathology, Mayo Clinic in Arizona, 13400 E Shea Blvd, Scottsdale AZ, 85259, USA. Tel: 480-301-4083; Fax: 480-301-8372; E-mail: depetris.giovanni@mayo.edu

References

[1] De Petris G, Leung ST. Pseudoneoplasms of the gastrointestinal tract. Arch Pathol Lab Med 2010; 134: 378-92.

[2] Dhungel BM, De Petris G. Bizarre stromal cells in the esophagus: report of 2 cases and literature review. Int J Surg Pathol 2013; 21: 368-72.

[3] Chinen K, Kamiyama K, Kinjo T, Arasaki A, Ihama Y, Hamada T, Iwamasa T. Morules in endometrial carcinoma and benign endometrial lesions differ from squamous differentiation tissue and are not infected with human papillomavirus. J Clin Pathol 2004; 57: 918-26.

[4] Houghton O, Connolly LE, McCluggage WG. Morules in endometrioid proliferations of the uterus and ovary consistently express the intestinal transcription factor CDX2. Histopathology 2008; 53: 156-65.

[5] Schlosnagle DC, Hardin RD. Squamous morules in gastric mucosa. J Clin Gastroenterol 1988; 10: 332-4.

[6] Abraham SC. Fundic gland polyps: common and occasionally problematic lesions. Gastroenterol Hepatol (N Y) 2010; 6: 48-51.

[7] Torbenson M, Lee JH, Cruz-Correa M, Ravich W, Rastgar K, Abraham SC, Wu TT. Sporadic fundic gland polyposis: a clinical, histological, and molecular analysis. Mod Pathol 2002; 15: 718-23.

[8] Nakatani Y, Masudo K, Miyagi Y, Inayama Y, Kawano N, Tanaka Y, Kato K, Ito T, Kitamura H, Nagashima Y, Yamanaka S, Nakamura N, Sano J, Ogawa N, Ishiwa N, Notohara K, Resl M, Mark EJ. Aberrant nuclear localization and gene mutation of beta-catenin in low-grade adenocarcinoma of fetal lung type: up-regulation of the Wnt signaling pathway may be a common denominator for the development of tumors that form morules. Mod Pathol 2002; 15: 617-24.

[9] Hirokawa M, Maekawa M, Kuma S, Miyauchi A. Cribriform-morular variant of papillary thyroid carcinoma--cytological and immunocytochemical findings of 18 cases. Diagn Cytopathol 2010; 38: 890-6.

[10] Sekine S, Shibata T, Matsuno Y, Maeshima A, Ishii G, Sakamoto M, Hirohashi S. Beta-catenin mutations in pulmonary blastomas: association with morule formation. J Pathol 2003; 200: 214-21.

[11] Blanco LZ Jr, Heagley DE, Lee JC, Gown AM, Gattuso P, Rotmensch J, Guirguis A, Dewdney S, Bitterman P. Immunohistochemical characterization of squamous differentiation and

morular metaplasia in uterine endometrioid adenocarcinoma. Int J Gynecol Pathol 2013; 32: 283-92.
[12] Chiarelli S, Buritica C, Litta P, Ciani S, Guarch R, Nogales FF. An immunohistochemical study of morules in endometrioid lesions of the female genital tract: CD10 is a characteristic marker of morular metaplasia. Clin Cancer Res 2006; 12: 4251-6.
[13] Wani Y, Notohara K, Saegusa M, Tsukayama C. Aberrant Cdx2 expression in endometrial lesions with squamous differentiation: important role of Cdx2 in squamous morula formation. Hum Pathol 2008; 39: 1072-9.
[14] Brachtel EF, Sanchez-Estevez C, Moreno-Bueno G, Prat J, Palacios J, Oliva E. Distinct molecular alterations in complex endometrial hyperplasia (CEH) with and without immature squamous metaplasia (squamous morules). Am J Surg Pathol 2005; 29: 1322-9.
[15] Bertoni G, Sassatelli R, Nigrisoli E, Pennazio M, Tansini P, Arrigoni A, Rossini FP, Ponz de Leon M, Bedogni G. Dysplastic changes in gastric fundic gland polyps of patients with familial adenomatous polyposis. Ital J Gastroenterol Hepatol 1999; 31: 192-7.
[16] Genta RM, Schuler CM, Robiou CI, Lash RH. No association between gastric fundic gland polyps and gastrointestinal neoplasia in a study of over 100,000 patients. Clin Gastroenterol Hepatol 2009; 7: 849-54.
[17] Lin MC, Lomo L, Baak JP, Eng C, Ince TA, Crum CP, Mutter GL. Squamous morules are functionally inert elements of premalignant endometrial neoplasia. Mod Pathol 2009; 22: 167-74.
[18] Cameselle-Teijeiro J, Alberte-Lista L, Chiarelli S, Buritica C, Goncalves L, Gonzalez-Campora R, Nogales FF. CD10 is a characteristic marker of tumours forming morules with biotin-rich, optically clear nuclei that occur in different organs. Histopathology 2008; 52: 389-92.