Correspondence

Are Syndromic Fundic Gland Polyps True Neoplasms?

To the Editor-in-Chief:

We read with great interest the article by Abraham et al,¹ which recently appeared in your Journal. In their seminal article, the authors have elegantly demonstrated the frequent occurrence of somatic *APC* gene mutations in fundic gland polyps (FGPs) associated with familial adenomatous polyposis (FAP).

FGPs were originally described in two different clinical settings. Sporadic FGPs are prevalent in middle-aged women without any other pathological association.^{2,3} On the other hand, FGPs with identical histology were described in association with FAP and attenuated variants (AFAP),^{4,5} with both sexes equally affected at an earlier age.

Both sporadic and syndromic FGPs were initially considered harmless, until Wu et al⁶ demonstrated a high percentage of dysplastic change in syndromic FGPs compared to sporadic ones (20% versus 1%). Moreover, some case reports of development of gastric adenocarcinoma from FGPs in FAP patients have been reported in the literature.^{7,8}

It is against this background that the paper by Abraham et al really has shed new light on the pathology of syndromic FGPs. They have found the occurrence of somatic *APC* gene mutation in the FGPs of 12 of 17 FAP-AFAP patients. No somatic *APC* mutation of the normal control mucosa from each patient was demonstrated. Only 1 of 13 patients with sporadic FGPs showed an *APC* gene mutation.

Moreover, the somatic *APC* gene mutations were not correlated with the development of dysplasia. Therefore, FGPs in FAP-AFAP patients represent a unique example of gastrointestinal polyps with somatic *APC* gene mutation without adenomatous morphology.

We would like to comment on two points. The first one is related to the significance of the term "neoplastic." If we interpret neoplastic (benign or malignant) in a strict histological sense, we could not consider syndromic FGPs as neoplastic until the overt development of dysplasia (FGP plus adenomatous change). On the other hand, if one considers the term in a biological sense, we can agree with the authors that mutated yet histologically "benign" FGPs are neoplasms.

The second point concerns the kind citation by Abraham et al of one of our papers.⁹ We would like to point out that we reported only about the proliferative rate of a case series of sporadic FGPs, so our interpretation of FGPs as hyperplastic lesions was not by any means extended to syndromic polyps.

In conclusion, we feel that the paper by Abraham et al¹ has really shed light on the understanding of the biology of these lesions: syndromic FGPs, histologically identical to sporadic ones, show somatic *APC* gene mutations. This finding not only may warrant close endoscopic surveillance of the upper GI tract in FAP patients, but in our opinion every new patient with FGPs should have a thorough clinicopathological study to exclude the possible association with FAP-AFAP.

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Authors' Reply:

We are pleased to have the opportunity to respond to the correspondence by Declich et al regarding our study of the frequent presence of somatic *APC* gene alterations in syndromic fundic gland polyps,¹ and hopefully to shed some light on the molecular pathogenesis of sporadic FGPs as well.² As detailed by Declich et al, FGPs associated with familial adenomatous polyposis or attenuated FAP present a fascinating conundrum, because while the majority of such polyps appear histologically benign, a subset (approximately 25%) demonstrate epithelial dysplasia,³ and rare cases of gastric adenocarcinoma arising in a background of fundic gland polyposis have been reported. The results of our study indicate that: 1) somatic *APC* gene alterations are frequent events in FAP-associated FGPs, and 2) these *APC* mutations are not related to the presence of epithelial dysplasia and are commonly found in non-dysplastic FGPs. To clarify (or complicate) matters further, we have recently shown that the vast majority (>90%) of sporadic FGPs arise through activating mutations of the β -catenin oncogene, despite the fact that such polyps only rarely demonstrate epithelial dysplasia.²

We therefore believe that, taken together, these results indicate that FGPs in general arise through alterations of the *APC*/ β -catenin pathway, as do most other lesions (or neoplasms) that are increased in incidence in patients with FAP. Apropos the terminologic issue of whether FGPs represent "neoplasms," we prefer to regard FGPs biologically as neoplastic growths, because they contain mutations in the *APC* tumor suppressor gene and β -catenin oncogene. Despite their (usually) small size, (usually) non-dysplastic histology, and (usually) benign course, the molecular pathogenesis of FGPs is similar to that of colorectal adenomatous polyps. Whether the less aggressive behavior of FGPs in comparison to adenomatous colorectal polyps is the result of an intrinsic biological difference, or whether their different location in the gastrointestinal tract and possibly lower exposure of the hyperproliferative epithelium to bacterial and pancreatobiliary toxins might play a role, is an issue that is unknown and requires further study. However, it is tantalizing in this regard to note that while both FAP-associated gastric adenomas and peri-ampullary adenomas also show similar somatic *APC* mutations (and epithelial dysplasia), the risk of peri-ampullary carcinoma is markedly increased in FAP patients, while gastric carcinoma arising from gastric adenomas is rare in Western FAP patients.⁴

Finally, we would like to comment on the suggestion by Declich et al that all patients with an FGP require a thorough work-up to exclude FAP or attenuated FAP. It is clear that although FGPs are increased among patients with FAP, most FGPs are sporadic events not associated with underlying FAP. Additionally, in the sporadic setting, no case of gastric adenocarcinoma associated with fundic gland polyposis has yet been reported. FGPs are now common findings among patients receiving proton pump inhibitor therapy. However, we agree that patients with unusual manifestations (e.g., FGPs in young patients, numerous and/or large FGPs, or FGPs with epithelial

dysplasia) should have FAP or attenuated FAP carefully excluded.

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Plexiform Lesion in Severe Pulmonary Hypertension: Association with Glomeruloid Lesion

To the Editor-in-Chief:

Sundberg et al¹ have recently described the formation of glomeruloid bodies in ears of athymic mice injected with a nonreplicating adenovirus engineered to express the 164-amino-acid form of the vascular permeability factor/vascular endothelial growth factor (VPF/VEGF). This important work contributes significantly to our current understanding of the vascular proliferation associated with malignancies such as glioblastoma multiforme, in that it demonstrates that VPF/VEGF expression suffices to induce these lesions.

To the list of pathological processes associated with the glomeruloid lesion, we wish to add the plexiform lesion present in severe pulmonary hypertension. Severe pulmonary hypertension, a condition associated with marked elevation of pulmonary artery pressures, heart failure, and high mortality, may present with the formation of plexiform lesions in medium sized pulmonary arteries. We had previously demonstrated that plexiform lesions are composed of proliferated endothelial cells.^{2,3} We have proposed that the endothelial cell proliferation in plexiform lesions occurs via a process of disordered angiogenesis since the endothelial cells express VPF/VEGF, VEGF receptor II or KDR, HIF- α and HIF1- β (aryl receptor hydrocarbon translocator (ARNT)).⁴ The partnership of HIF1- α and HIF1- β , leading to the formation of the hypoxia inducible factor (HIF) transcription factor may activate the expression of VEGF, among numerous genes that are induced by hypoxia.