

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.

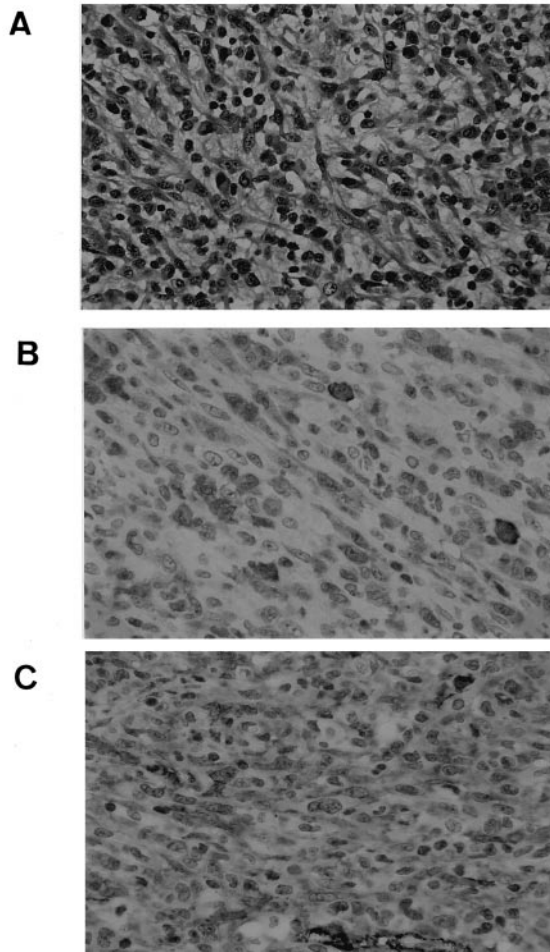


Figure 1. Lymph node biopsies of the patient. **A:** Diffuse infiltration of spindle-shaped tumor cells show a storiform pattern (hematoxylin and eosin staining, original magnification $\times 250$). **B** and **C:** The lymphoma cells are positive for cytoplasmic ALK (**B**, original magnification $\times 375$) and α -smooth muscle actin (**C**, original magnification $\times 375$).

Plexiform lesions form ubiquitously as a growth of endothelial cells within the lumen of small precapillary pulmonary arteries, and early clusters of endothelial cells in these lesions strikingly resemble the early stages of formation of the glomeruloid lesion as shown in Figure 1B by Sundberg et al. However, in contrast to the fact that the expression of VPF/VEGF is in cells outside the glomeruloid lesions described by Sundberg et al and in malignant glioblastoma cells surrounding the glomeruloid endothelial cell hyperplasia,⁵ the endothelial plexiform lesions appear to express both VPF/VEGF and its receptor II. Such a pattern of gene expression, suggestive of an autocrine action of VEGF on its receptor II, has been characteristically described in neoplastic endothelial cell processes.

The resemblance of the endothelial cell proliferation in plexiform lesion to neoplasia is further supported by the fact that endothelial cells in idiopathic forms of severe pulmonary hypertension, also called primary or idiopathic pulmonary hypertension, are monoclonal whereas the morphologically identical plexiform lesions in severe pulmonary hypertension associated with congenital heart malforma-

tions are polyclonal.⁶ In line with the finding that the endothelial cells in primary pulmonary hypertension are monoclonal, we have recently reported microsatellite instability and mutations in microsatellite sites of the endothelial cell growth regulatory genes transforming growth factor- β receptor II and Bax.⁷ Impaired transforming growth factor- β signaling likely impairs apoptosis in the plexiform lesions' endothelial cells and could permit increased VEGF gene expression. An animal model of the glomeruloid lesions such as the one described by Sundberg et al¹ may aid in the elucidation not only of similar lesions in cancer but also in the pathogenesis of plexiform lesions in severe pulmonary hypertension.

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Sarcomatoid Variant of Anaplastic Large Cell Lymphoma with Cytoplasmic ALK and α -Smooth Muscle Actin Expression: A Mimic of Inflammatory Myofibroblastic Tumor

To the Editor-in-Chief:

In a recent issue of *The American Journal of Pathology*, Lawrence et al¹ reported their immunohistochemical studies on ALK in inflammatory myofibroblastic tumors