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Activin A in Carcinoid Heart Disease: A Possible Role in Diagnosis and Pathogenesis

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Background: Carcinoid heart disease (CHD), a complication of NETs, is characterized by right heart fibrotic lesions. In addition to serotonin, cytokines and growth factors with fibrogenic properties may play a role. We sought to examine the relationship between plasma levels of fibrogenic cytokines and growth factors and CHD, to provide further insight into possible biomarkers of CHD and into the pathogenesis of CHD.

Methods: Plasma samples from 71 NET patients and 18 controls were analyzed using enzyme immunoassays. All patients underwent echocardiography. Tumor biopsies and a CHD lesion were analyzed via IHC.

Results: 15 patients had CHD. CHD patients were older (p=0.01), had larger (p=0.007) and more numerous liver metastases (p=0.04), and had elevated U-5HIAA (p=0.03) and serum chromogranin A levels (p=0.02). CHD patients had higher plasma levels of C-reactive protein (p=0.03), osteoprotegerin (p=0.005) and activin A (p=0.005) than patients without CHD. A direct correlation between activin A and U-5HIAA levels was observed in the total patient group (r=0.30, p=0.02). Activin A ≥0.34 ng/ml (OR 5.35 [1.01;28.17]) and age ≥69.5 (OR 6.10 [1.60;23.24]) were independent predictors of CHD. Activin A ≥0.34 ng/ml

detected CHD with 87% sensitivity and 57% specificity. Tumor tissue and a CHD lesion showed positive staining for activin A.

Conclusion: Elevated plasma activin A levels are associated with the presence of CHD. Activin A is expressed in tumor tissue and in CHD lesions.