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Prevalence of cardiac arrhythmias in a mouse model of carcinoid disease

Sofia Penrose, BS[1], Sydney Kuehn, BS[1], Rodney F. Pommier, MD[2], Belinda H. McCully, PhD[3].

[1]Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific- Northwest, Western University of Health Sciences, Lebanon, OR; [2]Division of Surgical Oncology, Department of Surgery, Oregon Health & Science University, Portland, OR; [3]Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific- Northwest, Western University of Health Sciences, Lebanon, OR.

BACKGROUND

Neuroendocrine tumors that release prostaglandins and biogenic amines that can impact cardiac function. In consequence, patients with carcinoid liver metastases are at risk for carcinoid heart disease. This is primarily characterized by fibrosis in the heart that leads to plaques on the valvular cusps, leaflets and walls of the atrium and ventricles leading to a thickened right heart with regurgitation. Interestingly, 50-80% of patients with carcinoid heart disease also have irregular electrocardiogram (ECG) tracings, with common abnormal findings of non-specific ST segment changes and sinus tachycardia. What is not known is when the onset of these arrythmias occur relative to metastatic disease progression. Therefore, the purpose of our study was to longitudinally assess the occurrence of cardiac arrythmias during the course of tumor development in a mouse model of carcinoid disease.

METHODS

Anesthetized (3-5% isoflurane in 100% O2), J:Nu nude mice (25-30g) received intrasplenic injection of 1x107BON1 neuroendocrine tumor cells (BON1, n=12) or vehicle (VEH, n=5). Mice were monitored for 8 weeks to allow the development of liver carcinoid metastases. During this period, stable 10-minute ECG tracings were recorded in anesthetized mice every two weeks. Tracings were assessed for ECG irregularities and heart rate. ECG irregularities were identified as abnormal tracings that deviated from a normal sinus rhythm. Livers were assessed for metastases by gross examination and hematoxylin-eosin (H&E) staining.

RESULTS

Over the duration of the study, VEH mice did not present with abnormal ECG tracings at any time point. In contrast, abnormal ECG tracings were present in 83% (10/12) of BON1 mice during at least one time point during weeks 2-8 (p=0.029 versus VEH). Abnormal rhythms were predominantly characterized by irregularly irregular rhythms, and biphasic P-wave and QRS complexes. The highest presence of abnormal rhythms occurred during week 4, which were present in 58% (7/12) BON1 mice (p=0.044 versus VEH). Heart rate did not change over time in either VEH (p=0.888) or BON1 (p=.390) mice. Upon tissue collection, gross dissection and H&E staining verified evidence of metastatic tumor growth in BON1 mice, and its absence in VEH mice.

CONCLUSIONS

Our findings identify the time course of when cardiac arrythmias can develop in a mouse model of carcinoid disease. We specifically show an early presence of varied abnormal ECG rhythms, which primarily occur at four weeks following BON1 cell injection. Future studies are needed to determine the etiology of arrythmia development in this mouse model, and how it may impact cardiac function.

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