CLINICAL VIGNETTE

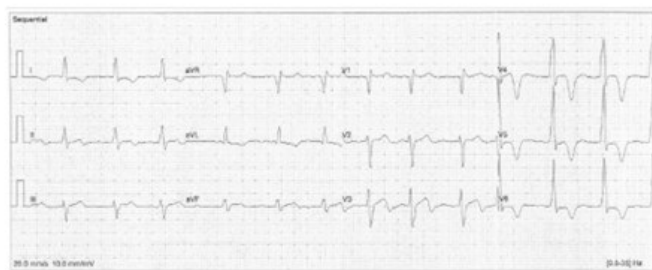# A Case of Yamaguchi Syndrome – A Rare Variant of Hypertrophic Cardiomyopathy

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Case Study

An 85-year-old Japanese-American male with a history of permanent atrial fibrillation on warfarin, coronary artery disease s/p distant stent, heart failure with preserved ejection fraction, and chronic bilateral lower extremity edema presented to the emergency department for chest pain. He described the pain as a mild, left-sided pressure with onset while at rest. It was associated with mildly increased lower extremity edema, but no other symptoms of heart failure. He noted blood pressure 180/110 at home, which prompted him to seek medical attention.

Upon admission, vital signs were unremarkable aside from blood pressure of 160/90s and irregular heart rate on exam he had bilateral 2+ LE edema. Labs included negative serial troponins and BNP 720 (prior 600). Chest x-ray showed evidence of mild fluid overload. EKG most notable for T wave inversions in leads I and V3-V6, most pronounced in V4 and V5 with depth of approximately 10mm in V4 (Figure 1).

Figure 1. EKG in Emergency Department.

Nuclear medicine stress test revealed a fixed defect in left circumflex territory, but no evidence of ischemia. Echo showed ejection fraction 65-70% and severe apical left ventricular hypertrophy. Cardiac MRI confirmed diagnosis of hypertrophic cardiomyopathy apical variant with associated 2.3cm apical aneurysm.

Discussion

Apical hypertrophic cardiomyopathy (apical HCM), also known as Yamaguchi Syndrome, is a rare subtype of hypertrophic cardiomyopathy in which the left ventricle of the heart is hypertrophied predominantly at its apex. There is further distinction between "pure" or "mixed" forms depending if hypertrophy is limited to or extends beyond the apical segments of the left ventricle. Diagnosis is typically made by echocardiography, but the most sensitive modality is cardiac MRI. According to one study, 91% of cases were diagnosed by echo, with the remaining cases subsequently diagnosed with cardiac MRI.[1]

Apical HCM was first described in Japan by Sakamoto in 1976 and in more detail by Yamaguchi in 1978. Yamaguchi studied patients selected on EKG findings significant for "giant T waves" (T wave inversion ≥10mm in leads V4 or V5 which correspond to apex) and high QRS voltage without history of hypertension or coronary artery disease.[2] Ventriculograms showed these patients had "spade-like" apical cavity at end-diastole.[2] Echocardiogram showed significantly greater apical thickness, compared normal controls and other forms of obstructive and non-obstructive hypertrophic cardiomyopathy. This distinguished apical HCM as a distinct type of hypertrophic cardiomyopathy with characteristic features of "giant T waves" and "spade-like" left ventricular cavity at end-diastole.[2]

In Japan, apical HCM is fairly common and represents 13-41% of the HCM population. In non-Asian populations, apical HCM is much rarer, reported between 3-11% of HCM patients.[1,3-4] It also has significantly higher incidence in men, with mean age of presentation between 40s-60s.[1-4] Incidentally, the characteristic "giant T waves" were also more typical in the Japanese population with one study showing this finding in 64% of Japanese patients, but only 30% of American patients.[3]

Presentation of apical HCM is variable and many patients are asymptomatic at time of diagnosis. In a study of 105 Canadian patients, 46% were asymptomatic at presentation with the symptomatic patients, presenting with chest pain (anginal 16%, atypical 14%), palpitations (10%), dyspnea (6%), and presyncope/syncope (6%).[1]

While the clinical course in apical hypertrophic cardiomyopathy was previously thought to be largely "benign", there is increasing appreciation of life-threatening events which warrant close monitoring of apical HCM patients. In the Canadian study, survival was similar to age- and gender-matched controls with only 1.9% cardiovascular deaths from myocardial infarction and congestive heart failure; and no cases of sudden cardiac death. At the time of final follow up 44% were asymptomatic. However, 38% had significant morbid cardiovascular events including atrial fibrillation (12%), myocardial infarction (10%), congestive heart failure (5%),

transient ischemic attack or stroke (7%), ventricular tachycardia or fibrillation (4%).[1] Interestingly, of the 11 patients who developed myocardial infarction, 10 underwent catheterization, and 9 showed clean coronaries.[1] Another study of 454 Korean patients reported 5% cardiovascular mortality including sudden cardiac death (1%), stroke (2%), and congestive heart failure (2%); and 25% major adverse cardiovascular event including heart failure requiring hospitalization, cardiovascular mortality, or stroke.[4] Risk factors for adverse clinical outcomes include advanced age, hypertension, diabetes and echo findings suggestive of impaired myocardial contractility (i.e. reduced systolic mitral annular velocity) or increased left ventricular filling pressures (i.e. left atrial enlargement, greater E/Ea ratio).[4] Finally, a Mayo Clinic study of 210 patients, found overall survival was significantly worse than expected, approaching that of other phenotypes of HCM. They found significantly higher mortality rates in women, while men, had overall survival similar to age-and gender-matched controls. This suggests female gender could be a risk factor for adverse clinical outcomes.[5]

Other, studies reported approximately 2-5% of HCM patients (all subtypes, not just apical) have identified left ventricular apical aneurysms.[6-7] In a study of 93 HCM patients, those with LV apical aneurysm represented a high-risk subgroup with 25% of patients either dying or having significant disease related complications; (ICD placement for ventricular tachycardia/fibrillation, resuscitated cardiac arrest, progressive heart failure requiring transplant, or thromboembolic events). These occured three times greater than their HCM controls without aneurysms.[6] Another study of 28 HCM patient with apical aneurysms reported 43% with adverse events with risks increasing with aneurysm size. This study reported echocardiography identified 54% of LV apical aneurysm, with cardiac MRI identifying the remainder.[7]

Treatment of apical HCM, separate from other types of HCM, has not been reported. The 2011 ACC/AHA guidelines for treatment of HCM do not specify any particular treatments for apical HCM; rather the guidelines discuss general HCM management including medications for symptoms and heart failure (i.e. beta blockers, verapamil, diuretics, ACE inhibitors) and consideration of ICD placement.[8] While the benefit for ICD placement for secondary prevention is well established, there is less certainty for ICD placement for primary prevention. In a retrospective study of 135 patients that underwent ICD placement at Northwestern for HCM (all subtypes, not just apical), the primary prevention cohort had an appropriate therapy rate of 2.6%/year. This was compared to a 4.3%/year that received inappropriate shocks and 10% that experienced significant complications from ICD implantation.[9] Therefore the risks and benefits of ICD implantation for primary prevention in HCM requires more thorough investigation. The current ACC/AHA guidelines recommend ICD placement for secondary prevention and consideration of ICD for patients at higher risk of SCD. These include family history of SCD in first degree relative, LV wall thickness >= 30mm, and unexplained syncope. Presence of LV apical aneurysm is considered one of the "Other Potential SCD Risk Modifiers".[8]

This 85-year-old Japanese male with a history of atrial fibrillation, CAD and HFpEF was diagnosed with apical variant hypertrophic cardiomyopathy with apical LV aneurysm after presenting with chest pain and mild heart failure exacerbation. He presented with many classical features of apical hypertrophic cardiomyopathy, including Japanese ethnicity and deep inverted T waves on EKG. Cardiac MRI was confirmatory. His apical HCM may have contributed to his atrial fibrillation, heart failure, and atypical chest pain. He was continued on metoprolol, warfarin, and furosemide. Given the patient's advanced age, absence of documented ventricular tachycardia, and no prior history of syncope, EP determined there was no indication for ICD at this time.

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