Introduction

Myasthenia gravis (MG) is a rare disorder with specific autoantibodies directed against the nicotinic acetylcholine receptor (AChR) in the neuromuscular junction [1]. Despite the absence of AChR in the cardiac myocytes, cardiac involvement in MG ranging from asymptomatic ECG changes to fatal tachyarrhythmias, myocarditis, conduction blocks, heart failure and sudden cardiac death has been documented in a few case reports [2]. In this case series, we report two cases of myasthenia gravis in crisis presenting with deep diffuse persistent T wave inversions as a marker for possible MG-related cardiac disease.

The Cases

Case 1

A 68 year old Filipina diagnosed case of Myasthenia Gravis since 2012 consulted at our emergency room for dysnea. The patient underwent thymectomy and radiotherapy for malignant thymoma in 2013. She has been maintained on Pyridostigmine 60 mg/tab 1 tablet BID and Prednisone 10 mg/tab 1 tablet BID since then. She's been diagnosed with Hypertension Stage I for 5 years prior to admission, with good compliance and blood pressure control on Losartan 50 mg/tab 1 tab OD. She had fair functional capacity, independent in all activities of daily living and denied heart failure and angina symptoms. She denied smoking, alcoholic beverage intake and use of illicit drug use. The patient was admitted last September 2014 for 4-week history of progressive motor weakness, dysphagia and dyspnea, with a 3-day history of high grade fever and productive cough with yellowish sputum. She complained of pleuritic chest pain but denied orthopnea, paroxysmal nocturnal dyspnea or bipedal edema. The patient was admitted tachycardic, tachypneic, normotensive and afebrile. She had bilateral ptosis. No pallor, jaundice, neck vein engorgement or anterior neck mass. She had coarse crackles on left lung base. On chest examination, there was adynamic precordium, distinct heart sounds, no murmurs nor edema. Neurologic examination was essentially normal except for symmetric motor weakness (grade 3/5) on all extremities. There was positive drift after repetitive movements for 30 seconds. Deep tendon reflexes are normal.

She was managed as a case of Myasthenia Gravis in crisis, possible malignant thymoma recurrence, Community Acquired Pneumonia, High Risk, Acute Respiratory Failure from hypoventilation and aspiration pneumonia, Hypertension Stage I, controlled. She was intubated and committed to full mechanical ventilatory support. Hydration and intravenous antibiotics (Piperacillin Tazobactam) were started. Pyridostigmine dose was uptitrated. High dose steroids (1 mg/kg/day) was started as well.

Work up revealed a baseline ECG showed regular sinus rhythm, normal axis, low voltage complexes on limb leads, poor R wave progression, prolonged QT interval, diffuse T wave Inversion on all leads.

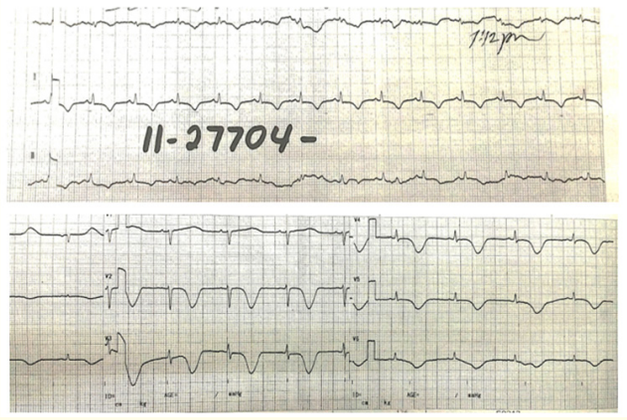

Figure 1: Baseline Electrocardiogram.

Due to multiple cardiac risk factors present in the patient, work up for myocardial ischemia was performed. Troponin I quantitative was borderline elevated (2x the upper normal limit) while CK MB was normal. Serial monitoring of cardiac enzymes was not consistent with myocardial infarction. Chest x-ray revealed left ventricular hypertrophy and a radiopaque density on the right cardiac border forming a double density sign. 2D echocardiogram showed concentric left ventricular hypertrophy with good wall motion and contractility and preserved systolic ejection fraction (EF 65% by Teicholz method). No evidence of pericardial thickening and effusion.

Serial monitoring of ECG showed deepening diffuse symmetric T wave inversion (deepest is 11 mm deep).

This was interpreted as probably non-ischemic in nature and maybe secondary to the autoimmune pathology of MG in crisis. Patient underwent therapy with IV antibiotics, high dose pyridostigmine, prednisone and subsequently had 6 cycles of plasmapheresis. Patient was hemodynamically stable and chest pain free through out the hospital stay. Repeat ECG taken a month post plasmapheresis showed normalization of previously documented T wave inversion.

Case 2

A 29 year old female, with Myasthenia Gravis (MG) was admitted at our institution for difficulty of breathing. She was diagnosed with this condition 2 years ago when she presented with charac-

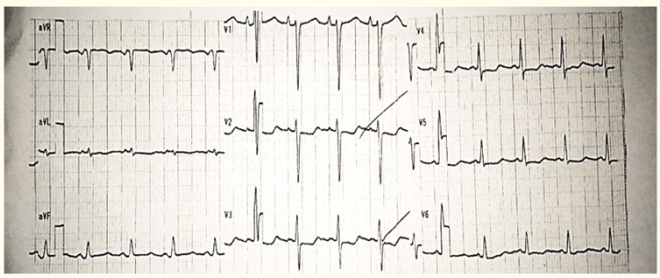

Figure 2: Repeat Electrocardiogram taken 1 month after treatment.

teristic weakness and was maintained on Pyridostigmine 60 mg QID and Prednisone 5 mg/tab OD but with poor compliance and follow up. She had no vices and other known comorbid conditions. Family history was negative for premature coronary artery disease, cardiomyopathy or sudden cardiac death. There was no other member in the family with a similar condition.

Current history started 4 days prior to admission when she had productive cough with purulent sputum and shortness of breath with note of progressive severe generalized weakness. On the day of admission when she had severe difficulty of breathing prompting admission at our emergency room. She was received awake but in severe respiratory distress. Immediate endotracheal intubation was done to support the airway. Cardiac examination was normal with undisplaced apex beat, distinct S1 and no S3 nor S4. There were crackles on both bibasal lung fields.

The arterial blood gas revealed severe hypoxia with pO2 of 55.4 mmHg. The initial working impression was acute respiratory failure secondary to MG in crisis, community acquired pneumonia, high risk with aspiration component. Chest X-ray revealed infiltrates on the right lung field. Complete blood count showed leukocytosis with neutrophilic predominance. Endotracheal aspirate culture was positive for heavy growth of *Klebsiella pneumonia* and antibiotics were adjusted according to the culture sensitivity results.

The patient was extubated on her 8th hospital day but still had intermittent episodes of difficulty of breathing, retractions and desaturation and so on the 5th day of extubation, she was re-intubated and hooked back to the mechanical ventilator. From then on, patient had hypotensive episodes, managed with aggressive hydration and antibiotic regimen. A repeat ECG at this point revealed regular sinus rhythm, normal axis, 2 mm ST segment elevation at leads V2-V3 with 3mm T wave inversion on leads V4-V6, in contradistinction to the initial ECG done early on admission which showed: sinus tachycardia, normal axis, normal QT interval of 0.40ms, with upright T waves in all leads.

Repeat ECG 10 hours later showed deeper T wave inversion on leads V2 to V6. Though the patient lacked conventional risk factors for coronary atherosclerosis, an acute coronary event was considered as one of the differentials for the dynamic T wave inversions and hypotension. The qualitative Troponin I was positive, while the CKMB and CK total were within the normal reference limits. 2D echocardiogram revealed a normal-sized left ventricle with good wall motion and contractility, and preserved systolic function at 82%. An acute coronary syndrome was deemed unlikely. The serum electrolytes were within normal limits and the patient's neurologic status was stable. Daily ECG done revealed persistent T wave inversion on the anterolateral leads, with deepest at 14 mm in lead V4 the next day. The last ECG done prior to discharge still showed T wave inversion on leads V3-V6, with deepest at 7mm on lead V4.

The dynamic ECG changes were attributed to possible cardiac involvement in MG, possibly immunologic myocarditis, as few case reports have been published in the past of MG in crisis presenting with deep T wave inversions. The rest of the patient's hospital stay was relatively unremarkable. She eventually underwent tracheostomy and completed the course of antibiotics. She was discharged improved and stable.

Discussion

Myasthenia gravis is a rare autoimmune neuromuscular disorder characterized by the presence of autoantibodies against the neuromuscular junction that clinically manifests as muscle weakness and fatigue [1]. The cardiac involvement in MG is thought to be caused by some auto-antibodies have been shown to react with cardiac muscle, thus being termed skeletal and heart reactive autoantibodies or "striational antibodies" [1]. Some studies have implicated the antibodies against a) titin, b) ryanodine receptor (RyR) found in the sarcoplasmic reticulum, c) A myosin, α-actin and actinin. The existence of all these antibodies offers possible theoretical mechanisms for direct cardiac involvement in MG by interfering with cardiac contractility, conduction, autonomous regulation or by an immunological attack on the myocardium, involving complement activation, infiltrates of inflammatory cells and with consequent necrosis [3]. Unfortunately, there are no studies at present directly correlating the presence of these cardiac auto-antibodies with the development of clinical cardiac disease.

On the other hand, MG has indirect effects to the heart as well. The respiratory impairment and low muscle tone seen in patients with MG in crisis lead to reduce venous return thus altering cardiac hemodynamics. The altered metabolic mileu caused by hypoxia, hypercapnia, acidosis and associated respiratory infections in myasthenic crisis could give rise to persisting myocardial changes [4].

Cardiac involvement in myasthenia gravis has been documented by several case reports. It may take several forms, from asymptomatic ECG changes to fatal tachyarrhythmias, myocarditis, conduction system disorders manifesting as blocks, heart failure and sudden cardiac death [2]. In one study of 108 patients, 16% of the patients had cardiac involvement manifesting as arrhythmia, asystole and sudden cardiac death. These abnormalities were attributed to myocarditis from an autoimmune process. Electrocardiogram abnormalities may be present in 16-88% of patients with MG. Changes in cardiac function as registered by changes in the ECG have been taken as a marker for MG-related cardiac disease however, there are no distinct features of the ECG that can be assigned to MG alone [1]. Most of these changes include non-specific ST T wave changes, abnormal T waves, prolonged QT interval, sinus tachycardia, sinus arrhythmia [5].

Among the ECG changes seen in our patients are diffuse persistent T wave inversion. Ashok in 1983 found that 4 of 10 MG-patients had flat to inverted T- waves, ST-depression and poor progression of R-waves in three precordial leads. All these abnormalities reverting to normal following oral neostigmine [6]. As shown in the first case, the patient also developed diffuse, deep T wave inversions, ST depression and poor R wave progression similar to the pattern reported by Ashok. These changes resolved 1 month after plasmapheresis.

A case report of a 69 year-old male with MG crisis presenting as respiratory failure has earlier been reported. The ECG showed deep T wave inversion, deepest inversion at 17mm in V4. Because of the patient's age and concentric hypertrophy on the echocardiogram, there was a need to rule out coronary artery disease. Coronary angiogram was eventually done which revealed normal epicardial coronary arteries. The ECG changes reverted back to normal only after three months.

Similar to this case, our patients presented with deep T wave inversions. An acute coronary syndrome was ruled out for the first case and was not highly considered for the second case given the patient's age and lack of other cardiac risk factors. The normal echocardiogram in both cases likewise made this consideration unlikely. The other differentials that had to be ruled out included the following: central nervous system disorders, pericarditis, myocarditis and metabolic abnormalities. The neurologic status of both patients was stable, and the electrolytes were all within normal levels in both cases. The possibility of an autoimmune myocarditis was thus the primary impression considered for both cases.

Conclusion

We report these interesting cases of patients with myasthenia gravis in crisis, presenting with dynamic electrocardiographic changes. The mechanism of myocardial involvement in myasthenia gravis up to the present still remains largely unknown. Serial monitoring of the electrocardiogram as well as the cardiac status of this patient is warranted. The dynamic ECG changes were attributed to possible cardiac involvement in MG, possibly immunologic myocarditis, as few international case reports have been published in the past of MG in crisis presenting with deep T wave inversions. The importance of this ECG case report highlights that neurologists, internists and cardiologists should be aware that MG can present with this typical ECG feature, albeit seemingly alarming, usually follows a benign course and resolves with the resolution of MG crisis. Caution should be made in interpreting T wave inversion as myocardial ischemia in the context of MG crisis and it should be correlated with the conglomeration of atherosclerotic risk factors to prevent unnecessary costly work up for acute coronary syndrome.

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