CASE REPORT

Role of Rituximab in miraculous cessation of ventricular tachycardia in Granulomatosis with polyangiitis: A case report

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Abstract

Granulomatosis with polyangiitis (GPA) is a rare systemic disorder of unknown aetiology. The histological findings comprise necrotising granulomatous inflammation of small arteries, arterioles, and the capillaries mainly of upper and lower respiratory tract and the kidneys. However, the disease rarely involves the cardiovascular system but may manifest as pericarditis, myocarditis, coronary arteritis, valvular lesions, and severe conduction disorders. We present an interesting, unusual, and complex case of a middle-aged man who initially presented with symptoms suggestive of Wagener's granulomatosis but two years later developed malignant ventricular arrhythmias. A diagnosis of exclusive involvement of the cardiac conduction system, without overt myocarditis, was made only after ruling it out by cardiac MRI, cardiac enzymes, echo, and normal serological markers. Evidence was paired with the cessation of monomorphic ventricular tachycardia due to induction therapy with Rituximab. In this case report, we highlight one of the rarest manifestations of GPA, i.e. Ventricular tachycardia without myocarditis.

Keywords: Granulamatosis with polyangiitis, ventricular tachycardia, myocarditis, Rituximab.

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Introduction

Granulomatosis with polyangiitis (GPA) is a rare systemic disorder of unknown aetiology with histological findings comprising necrotising granulomatous inflammation of small arteries, arterioles, and the capillaries of mainly the upper and lower respiratory tract and the kidneys.[1,2] However, other organ systems are not spared by the pathological process.[3,4] About 90% of the patients actively suffering from the disease have elevated levels of cytoplasmic ANCA (c-ANCA) titres which are directed towards proteinase-3 and myeloperoxidase.[3] Tissue biopsy of the affected organ and positive c-ANCA is used as a diagnostic tool to differentiate it from other diseases with similar manifestations.[1] Granulomatosis with polyangiitis rarely has cardiovascular involvement but, if present, it may manifest as pericarditis, myocarditis, coronary arteritis, valvular lesions, and severe conduction disorders.[3]

Although GPA does not commonly cause clinically significant cardiac involvement, it could still be a cause of cardiac symptoms and adjunctive immunosupression may be required for this subset of patients. Furthermore, it is essential to determine the nature of the cardiac manifestation, to ensure appropriately targeted treatment. Even though Prednisone combined with Cyclophosphamide induces remission and prolongs survival in these diseases, this regimen is toxic and does not prevent relapse. Biologic agents are currently under experiment in new trials as a possible therapy with better efficacy and lesser adverse effects.

We are presenting this case to highlight an important but rare complication of GPA, so that we as clinicians are aware that it can present as arrhythmia and discuss how condition responded to treatment.

Case Report

This report presents the case of a 42-year-old male patient, who was diagnosed with Granulomatosis with polyangiitis in September 2016 at Shifa International Hospital, Islamabad. The condition was characterised by the involvement of the upper and lower respiratory tracts, a positive antineutrophil cytoplasmic antibody (c-ANCA), chronic unspecific inflammation, and no renal involvement. Although his baseline CRP levels always remained moderately elevated, showing some disease activity, overall, his symptoms were controlled on 20 mg Methotrexate/week and maintenance dose of steroids.

In July 2018, he presented to the ER with complaints of central chest pain, apprehension, nausea, and profuse sweating. On arrival, his pulse and blood pressure were unrecordable. Initial ECG showed ventricular tachycardia which was reverted to sinus rhythm by DC cardioversion using 100J of energy. Initial workup, including chest x-ray, cardiac enzymes, serum electrolytes including potassium, calcium, magnesium phosphorus, which were all normal; however, he had a neutrophil count of 13,700 (Table). Echo revealed an ejection fraction of 55%, without any wall

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Tabele: Lab Values; CKMB- Creatine Kinase MB, WBC-White Blood Cell, HB-Haemoglobin, PLT-Platelets, CRP-C-Reactive Protein, ESR-Erythrocyte Sedimentation Rate.

Investigation	First Admission	Second Admission	Third Admission
CK-MB(ng/mL)	2	3	2.5
Trop I(pg/mL)	15	18	16
WBC/mm^3	13700	16400	13000
Hb(g/dL)	14	15	14
Plt/mm^3	474000	520000	388000
CRP(mg/L)	13	10	-
ESR(mm/hr)	15	-	-
Sodium(mEq/L)	135	141	138
Potassium(mmol/L)	4.4	4.5	4.4
Calcium(mg/dL)	9.8	9.7	9.6
Magnesium(mEq/L)	2.2	2.1	2.2
Phosphorus (mg/dL)	2.1	-	-
Creatinine(mg/dL)	0.9	1.2	0.9
Urea(mg/dL)	24	25	19

Normal Range: CK-MB(up to 7.2 in males) , Trop I (upto 34.3), WBC (4500-11000), Hb(12-16), Plt(150000-450000), CRP(0.3-10), ESR(1-15), Sodium(135-145), Potassium(3.5-5), Calcium(8.6-10.3), Magnesium (1.6-2.6), Phosphorus(2.5-4.5), Creatinine(0.75-1.25), Urea(16.6-48.5).

motion abnormality. A CT aortogram revealed slightly thickened aortic valve leaflets with no evidence of coronary artery disease, aortic dissection or aneurysm. He was later admitted to the cardiac care unit. Because of his history of Wegener's granulomatosis, rheumatology team was also involved, which readjusted his prior regimen. He had an uneventful hospital stay and was discharged in stable condition on steroids, Methotrexate, Metoprolol and Ramipril.

One week after discharge from the hospital, he again presented to the emergency department with similar complaints of apprehension and feeling of impending doom. His BP was 90/60 mmHg and was sweating profusely. Once again ECG was done which showed ventricular tachycardia (VT). He was given intravenous Amiodarone and Lidocaine, but the VT was refractory to these medicines. The VT was successfully treated with synchronised direct current cardioversion, Sinus Rhythm was achieved and he was subsequently transferred to the cardiac care unit. During the hospital stay, he had multiple episodes of ventricular tachycardia which only responded to DC cardioversion. As a part of extensive work-up, coronary angiography was performed which was unremarkable. Cardiac MRI was performed on suspicion of myocarditis but it did not show any early or late gadolinium contrast enhancement or motion abnormalities (Figure). Electrophysiology studies confirmed ventricular tachycardia but no specific underlying cause was identified. Pulse steroid therapy was advised by the rheumatology team and the patient was discharged after optimisation, on Azathioprine, Amiodarone and tapering dose of steroids.

He presented again the subsequent month with

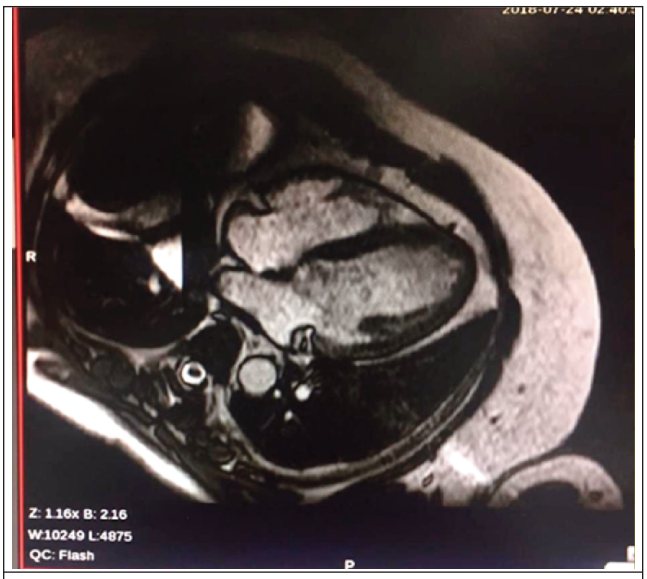

Figure: Cardiac MRI showing no evidence of myocarditis.

palpitations, chest heaviness and one episode of vomiting. However, on arrival, he was stable and this time had sinus rhythm. Considering the recent history of life-threatening VT, he was again admitted to the CCU and initial laboratory tests were done, which were all normal. For this mysterious case, after ruling out all other possible causes of ventricular tachycardia, Wegener's granulomatosis was suspected. The decision regarding cardiac biopsy vs Biologic trial was discussed with the patient and the multi-disciplinary team, and the joint decision of Rituximab administration was made. The initial dose of Rituximab was 375mg/m^2 weekly for four weeks. He was administered the first dose during the same admission, after which he remained stable for the rest of the inpatient course and did not develop any episodes of ventricular tachycardia. He was discharged on a maintenance dose of Rituximab 500 mg six-monthly and has not developed ventricular tachycardia ever again. He is on maintenance therapy for nearly two years; his ESR and CRP are in the normal range and he is clinically fit and stable.

Discussion

This report describes a case of GPA without clinically overt cardiac involvement. Although the existence of a strong causal relationship has not been proven yet, the close temporal association between the diagnosis of GPA and onset of cardiac arrhythmia in a healthy patient without any findings of structural heart disease, ventricular dysfunction, drugs or electrolyte disturbances, GPA with cardiac conduction system involvement was determined to be the most likely cause.

Ventricular arrhythmias are uncommon in hearts with no structural damage, and this is what makes our patient

different.[5] Although unexplained, sustained ventricular tachycardia associated with myocardial dysfunction should be promptly evaluated with an endomyocardial biopsy, a normal MRI, CKMB, Troponin-I, and echocardiogram enabled us to avoid cardiac biopsy. After administration of Rituximab, a miraculous recession of ventricular tachycardia was observed, and remission was achieved, with a maintenance dose of Rituximab.

Despite adequate treatment with steroids and immunosuppressant drugs this patient's ESR always remained high, probably due to ongoing disease activity. Recurrent arrhythmias were, hence, attributed to active GPA, especially in the absence of any other obvious cause. We believe that Rituximab reduced the disease activity and that led to improvement in arrhythmias as evident from a normal ESR. Extensive literature review did not reveal any therapeutic benefit of Rituximab as an antiarrythmic drug.

Two previous studies from North America and France have reported clinically overt cardiac involvement in 3.3% and 13% of the patients, respectively, presenting with GPA.[4,6] Pericarditis is present in majority of the patients but signs and symptoms of coronary artery disease, structural and conduction system abnormalities may also be seen.[7] However, arrhythmias without overt myocarditis are an exceptionally rare association, as seen in our patient.

Cardiac involvement has been associated with increased morbidity, treatment resistance, higher chances of relapse and greater mortality.[8,9]

The global outcomes of patients with GPA have improved over the past decades, especially after the introduction of Biologics. Combination therapy with cyclophosphamide/ methotrexate and corticosteroids is used to induce remission. If it is not effective, biologic treatment (Rituximab) should be considered. Prevention of cardiovascular complications thus constitutes a major therapeutic challenge in the setting of several systemic inflammatory immune disorders like GPA.

Conclusion

This was a challenging case as patient presented with a rather uncommon presentation of GPA. This lead to initial diagnostic uncertainty, however once the diagnosis was made, the response to Rituximab was very favourable.

Disclaimer: Consent was obtained from the patient before writing this manuscript.

Conflict of interest: Dr Zafar Ullah signed the ethical review statement. He is also a co-author of this manuscript.

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