Original Research Paper

Volume - 11 | Issue - 06 | June - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Neurology

ACUTE CORONARY SYNDROME FOLLOWING INTRAVENOUS IMMUNOGLOBULIN THERAPY : A HIDDEN RISK

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ABSTRACT Intravenous immunoglobulin (IVIG) is one of the main line modalities of therapy for chronic inflammatory demyelinating polyneuropathy (CIDP). We hereby, report an incidence of acute myocardial infarction probably induced by IVIG during the treatment of CIDP. A 76 year old female with no history suggestive of cardiovascular disease, developed an acute Non ST Segment Elevation Myocardial Infarction (NSTEMI) and severe left ventricular dysfunction after receiving three doses of IVIG. Since hypercoagulability is a concern with IVIG therapy, it was discontinued. Hence, we highlight the importance of cardiac evaluation before initiation and during the course of IVIG therapy in elderly patients as well as in patients with known risk factors for cardiovascular disease and thrombotic events.

KEYWORDS : Intravenous immunoglobulin, NSTEMI, Hypercoagulability

INTRODUCTION

Intravenous immunoglobulin (IVIG) - a highly purified preparation derived from the pooled plasma of healthy donors is used in the treatment of a wide array of disorders, including primary and secondary immune deficiency states and also in a variety of autoimmune and inflammatory disorders. IVIG has been considered a safe mode of therapy, with minor adverse effects that are transient. The majority of the adverse effects are mild, self limiting and usually correlates to the speed of infusion and almost never necessitate the discontinuation of therapy. ST elevation myocardial infarction, Non ST elevation myocardial infarction and thromboembolic events have been reported with IVIG administration, but a definitive association between IVIG administration and occurrence of myocardial infarction has not been established yet and the pathophysiology of IVIG induced thrombosis is not well recognized.[1-3]

CASE DESCRIPTION

A 76 year old female with an ideal body weight of 75 kg was admitted to the ward with complaints of quadriparesis, inability to swallow liquids and solids, occasional change in voice with nasal regurgitation for three days. She presented a history of progressive weakness of all four limbs over a period of two months. She is a known case of Diabetes Mellitus for the past 20 years on Inj. Human Mixtard 30/70 15U-0-10U and Systemic Hypertension for the past 27 years on Tab. Amlodipine 2.5mg twice daily. Neither had she any addictions nor any history of neurological diseases. Initially, she developed numbness and weakness of toes, which later progressed to bilateral lower limbs. The symptoms aggravated with time and ascended to involve bilateral upper limbs, which led to difficulty in performing daily activities and eventually confined her to bed.

On admission, patient was conscious and alert. She had symmetric areflexic quadriparesis (motor power in upper limbs and lower limbs : 1/5, Overall Neuropathy Limitation Scale [ONLS] - 12). She was initiated on nasogastric tube feeds and Enoxaparin therapy for prophylaxis of deep vein thrombosis. Electrocardiogram (ECG), Echocardiogram (ECHO), complete blood count, glycosylated hemoglobin level, renal and liver function profiles, urine analysis, serum electrolytes and sugar levels were all found to be normal. She was negative for evaluation of Paraneoplastic antibodies, Anti Ach E receptor antibodies and Anti Musk antibodies. Cerebrospinal fluid analysis showed elevated protein levels without pleocytosis. Video laryngoscopy was performed and normal movement of vocal cords was observed. Magnetic resonance imaging showed age related cerebral atrophy with chronic ischemic changes of vessels in bilateral periventricular white matter. Nerve conduction study (NCS) was done on day 2 of hospitalization, which was suggestive of CIDP. It revealed partial block and reduction of velocity in motor conduction and prolongation of F wave latency.

On day 3 of hospitalization, she developed breathlessness of sudden onset and had acute desaturation in the ward. The patient eventually had type 2 respiratory failure and was shifted to the medical intensive care unit, where she was intubated. Considering the findings revealed by the investigations which where pointing to a probable diagnosis of CIDP with respiratory failure, she was started on intravenous Immunoglobulin (IVIG) at the dose of 0.4g/kg/day (30g/day), pertaining to her ideal body weight which was 75 kg. She received three doses of IVIG and on day 5 (2 hours after the third dose of IVIG), she developed hypotension of a sudden onset along with chest pain and profuse sweating. Noradrenaline infusion was initiated to maintain blood pressure. On evaluation, ECG [Figure 1] showed non ST elevation myocardial infarction (NSTEMI) and ECHO [Figure 2] revealed global hypokinesia with moderate left ventricular (LV) dysfunction (LV Ejection fraction – 35%). Serial evaluation of serum Troponin T levels were positive (474 and 989 respectively). IVIG was withheld and she was started on therapeutic anticoagulation, dual antiplatelets and low dose statin. Coronary angiography was planned to be performed once the patient's condition becomes stable. Noradrenaline infusion was tapered gradually and stopped after 9 hours.

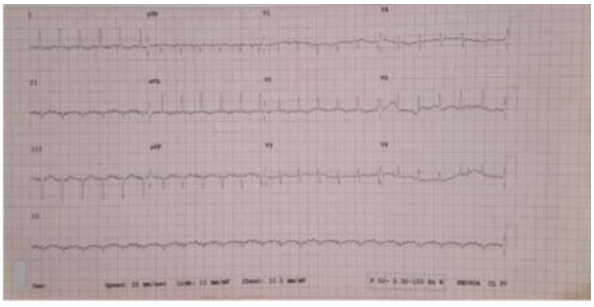

Figure 1 : ECG showing NSTEMI

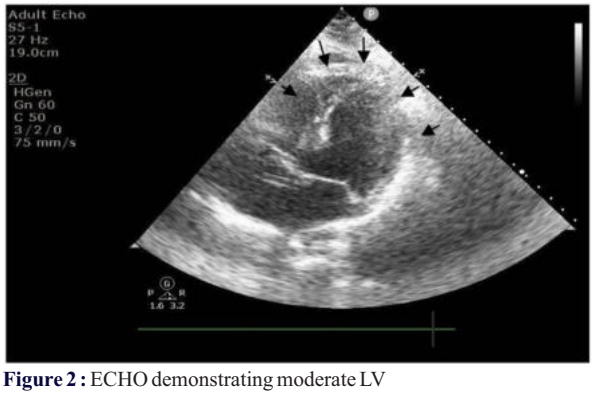

Figure 2 : ECHO demonstrating moderate LV (A4CW view – arrow depicting global hypokinesia of left ventricle)

Patient was gradually weaned to spontaneous mode of mechanical ventilation. ECHO was repeated on day 8 and showed improvement in LV function (Ejection fraction – 50%). Patient was extubated on day 9 and bridge therapy with non invasive ventilation was provided. On day 12, She was shifted back to the ward and was started on a low dose of oral steroid. Physiotherapy and speech therapy were provided in

addition to medical management. After nearly a month of stay in the hospital, she was able to walk with support and was discharged. One week after discharge, patient underwent coronary angiography and the coronary arteries appear normal.

DISCUSSION

Chronic inflammatory demyelinating polyneuropathy is an acquired, immune-mediated neuropathy affecting peripheral nerves and nerve roots. It is characterized by a relapsing-remitting or progressive course. It is responsive to glucocorticoids and exhibits electrodiagnostic or pathologic features suggestive of demyelination.[4,5] The mainline modalities of therapy for CIDP are IVIG, glucocorticoids and plasma exchange. For treatment-naive patients with CIDP who are suffering from the active phase of the disease and related disability, initial immune-modulating treatment using either IVIG or glucocorticoids or plasma exchange are recommended. The initial choice among these equally effective therapies is influenced by the severity of the disease, presence of concurrent illnesses, availability of venous access, side effects associated with the treatment, availability of drugs and cost.[6]

The dose of IVIG is 2 g/kg infused over a period of two to five days (usually 0.4 g/kg per day for five days). The recommended rate of infusion to initiate therapy is 0.5ml/kg/hr for a 5% IVIG solution and may be titrated as tolerated by the patient. The common adverse effects of IVIG are usually mild, self limiting and is often in association with the speed of infusion. Although several case reports describing IVIG induced myocardial infarction (MI) have been published, generally it is not considered as a definitive adverse effect of IVIG. The association between IVIG administration and MI has not been well established so far. Literature regarding the same, suggests that elderly individuals or those with pre existing heart disease are potentially at a risk for cardiac ischemia with IVIG administration.[1,2,3,7]

Infusion of IVIG may affect the cardiovascular system by two different mechanisms, which may operate synergistically: it may lead to expansion of plasma volume with consequent hypertensive reactions, increased oxygen demand and cardiac decompensation on one end[8], and increase in plasma and blood viscosity on the other end.[9,10] The pathophysiology of IVIG induced thrombosis is not well recognized. The proposed mechanisms suggest that it may be due to platelet or endothelial cell activation and increased blood viscosity. Viscosity of blood is an important determinant of subendocardial oxygen delivery.[11] Increased blood viscosity may induce myocardial ischemia via rouleaux formation, cross linking of fibrin and eventually resulting in thrombosis.[12]

CONCLUSION

Administration of IVIG at a lower rate of infusion may be advisable for patients with increased age, renal impairment and underlying cardiac disease. Symptoms of angina around the time of infusion should trigger prompt discontinuation of IVIG therapy and the patient should be further investigated for cardiac events in light of the published incidents.

The true incidence of MI and other thrombotic complications associated with IVIG therapy are not well known. However cardiovascular evaluation should be performed before initiation and during the course of IVIG therapy in elderly patients as well as in patients with known risk factors for cardiovascular disease and thrombotic events.

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