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ISSN: 0975-3583

Journal of Cardiovascular Disease Research

An Official Publication of SciBiolMed.Org (A publishing division of Phcog.Net)

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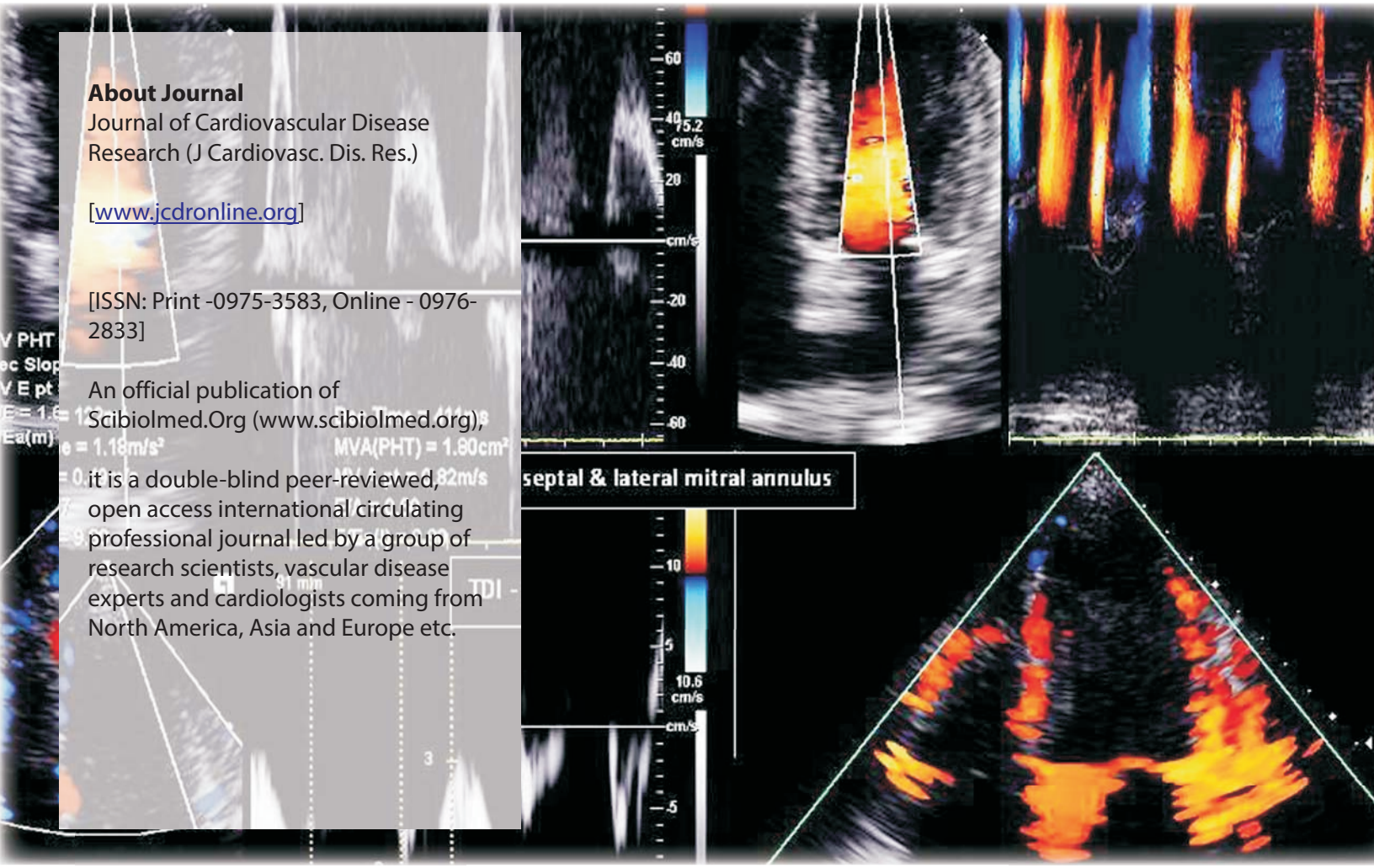
Volume 7, Issue 2, Apr-Jun, 2016



About Journal

Journal of Cardiovascular Disease Research (J Cardiovasc. Dis. Res.)

[www.jcdronline.org]

[ISSN: Print -0975-3583, Online - 0976-2833]

An official publication of Scibiolmed.Org (www.scibiolmed.org),

it is a double-blind peer-reviewed, open access international circulating professional journal led by a group of research scientists, vascular disease experts and cardiologists coming from North America, Asia and Europe etc.

Indexed and Abstracted in : The journal is indexed with Caspur, Chemical Abstracts, CNKI (China National Knowledge Infrastructure), DOAJ, EBSCO Publishing's Electronic Databases, Expanded Academic ASAP, Genamics JournalSeek, Google Scholar, Health & Wellness Research Center, Health Reference Center Academic, Hinari, Index Copernicus, MANTIS, OpenJGate, PrimoCentral, ProQuest, Scimago Journal Ranking, SCOLOAR, SCOPUS, SIIC databases, Summon by Serial Solutions and Ulrich's International Periodical Directory

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J Cardiovasc Disease Res., 2016; 7(2): 93-96
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Case Report

Clozapine-Induced Perimyocarditis

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ABSTRACT

Atypical antipsychotic drugs are widely used in the treatment of schizophrenia due to their higher efficacy and better side-effect profile compared with traditional antipsychotic drugs. However, serious cardiac toxicity of these drugs can occur, and if not recognized early, can be fatal. In this report, we present a case of acute perimyocarditis following the initiation of Clozapine, a frequently used atypical antipsychotic drug, for the treatment of refractory schizophrenia, which completely resolved after the discontinuation of this drug.

Key words: Clozapine, Atypical antipsychotic drug, Perimyocarditis.

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Submission Date: 17-05-2015; **Review completed:** 16-01-2016;

Accepted Date: 28-01-2016.

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DOI: 10.5530/jcdr.2016.2.8

INTRODUCTION

Clozapine is an Atypical antipsychotic drug usually used for the treatment of refractory schizophrenia with high suicidal risk.[1,2] While agranulocytosis, seizures, and hepatitis are commonly encountered adverse effects of Clozapine; cardiac involvement has been increasingly recognized in patients treated with this drug.[3–5] A wide range of clinical manifestations of Colzapine-induced cardiac toxicity have been reported, including acute myocarditis, cardiomyopathy, acute pericarditis, arrhythmia, and sudden cardiac death.[3] In this report, however, we present a 68-year-old male Veteran with acute perimyocarditis following the initiation of Clozapine therapy, which completely resolved after this therapy was discontinued.

Case Presentation

This is a 68-year-old Caucasian maleVeteran who was hospitalized for the evaluation of dysphagia, odynophagia, exertional dyspnea, and chest painfor 3 days. His past medical history was significant for esophageal stricture, which was endoscopically dilated 2 years earlier, hypertension, dyslipidemia, diabetes mellitus, and paranoid schizophrenia. His schizophrenia was refractory to typical anti-psychotic medications, requiring prolonged hospitalization in the mental health unit, and the initiation of Clozapine, which resulted in good symptomatic response.The patient was started on Clozapine 6 weeks prior to his presentation at a dose of 12.5 mg twice daily which was gradually increased to a dose of 150 mg twice daily at the time of his presentation. His medications included, in addition to Clozapine, Aspirin, Divalproex Sodium, Hydrochlorothiazide, Simvastatin, and Terazosin. He had no prior personal or family history of heart disease. He had a 30 pack-year history of tobacco use, quitting 13 years earlier. He consumed 1–2 alcoholic beverages daily for many years, abstaining 2 years earlier. He had no history of elicit drugs use.

On presentation, his physical examination was pertinent for normal blood pressure of 107/66 mmHg and temperature of 98.6 degrees Fahrenheit, tachycardia with heart rate of 116 beats per minute, mild tachypnea with respiratory rate of 22 per minute, and normal cardiopulmonary examination with no additional heart sounds, murmurs, or pericardial rub. Chest radiograph showed mild pulmonary vascular congestion, without cardiomegaly or parenchymal lung disease. Electrocardiogram (ECG) showed sinus tachycardia and diffuse ischemic changes with ST-segment depression in the anterior and inferior leads and ST-segment elevation in leads V1, V2, and aVR. Laboratory data was significant for elevated serum Troponin I level at 26.2 ng/mL, low Sodium level at 129 mg/dl, normal renal function and thyroid function tests, and negative anti-nuclear antibodies screen. Transthoracic echocardiogram (TTE)showed asmall, predominantly posterior and inferior pericardial effusion; mildly reduced left ventricular systolic function with an estimated left ventricular ejection fraction (LVEF) of 40%; an inferior wall akinesis; and moderate mitral regurgitation (Figure 1). An urgent left heart catheterization showed minimal non-obstructive coronary artery disease, mild to moderate left ventricular systolic dysfunction, and elevated left ventricular end-diastolic pressure. For evaluation of dysphagia and odynophagia, and esophagram was performed showing no significant stricture or other pathology. Lastly a cardiac magnetic resonance imaging (CMR)was performed showing focal areas of sub epicardiallate gadolinium enhancement in the mid-to-basal anteroseptal and inferoseptal wall segments, withevidence of pericardial inflammation and small pericardial effusion, consistent with the diagnosis of perimyocarditis (Figure 2). An endomyocardial biopsy was deferred, and pericardiocentesis was considered unsafe due to the small size of the pericardial effusion and its posterior location.

Based on the temporal relationship between the initiation of Clozapine therapy and the onset of symptoms (6 weeks), and the reasonable exclusion of other common etiologies, it was concluded that the patient most likely had Clozapine-induced perimyocarditis. Clozapine was immediately discontinued and substituted with another antipsychotic agent Olanzapine. In addition, the patient was treated with a short course of diuretic therapy, and started on a beta-blocker, an

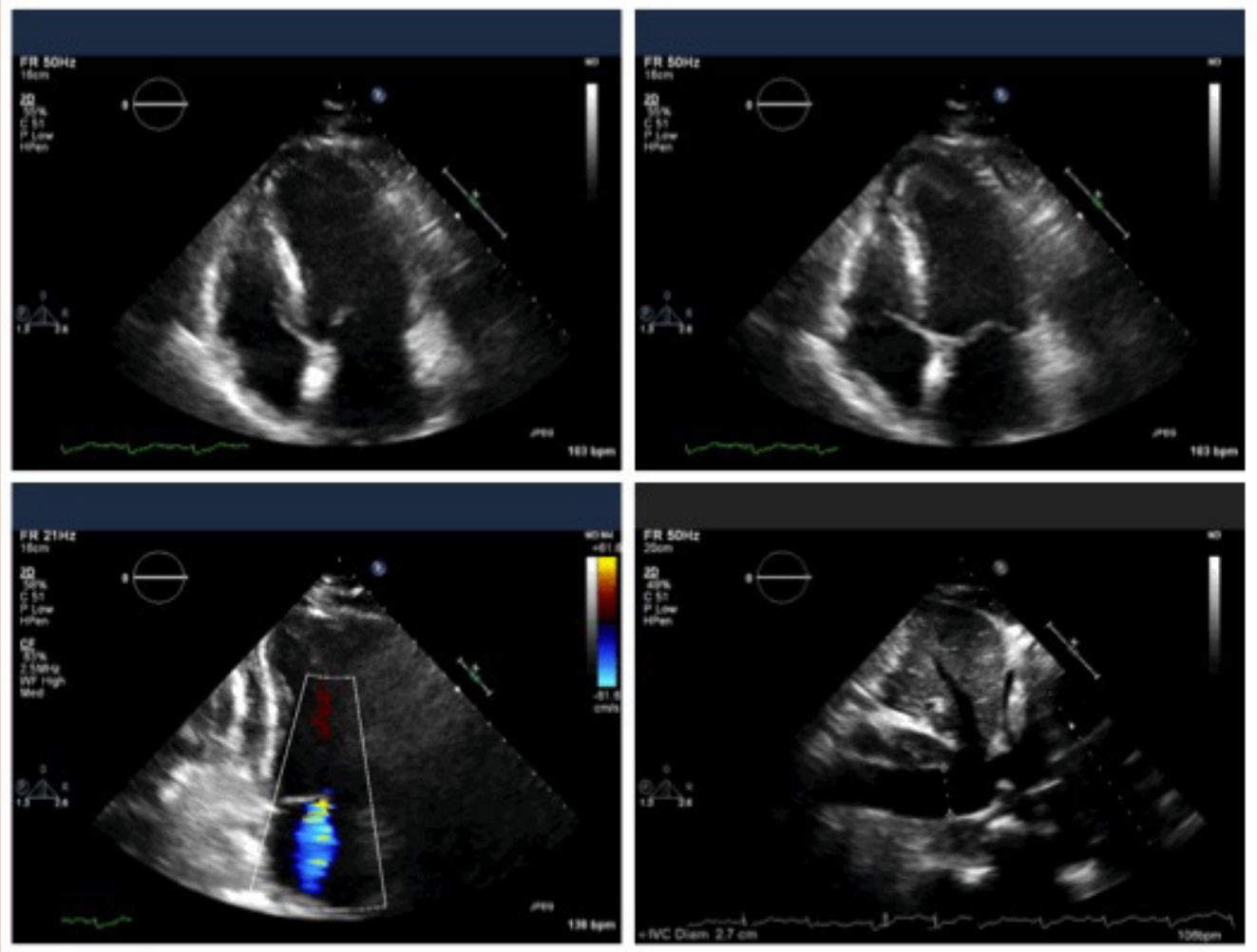

Figure 1: Transthoracic echocardiogram at initial presentation showing asmall, predominantly posterior and inferior pericardial effusion; mildly reduced left ventricular systolic function with an estimated ejection fraction, and a dilated inferior vena cava. End-diastolic apical 4-chmaber view (left upper); End-systolic apical 4-chamber view (right upper); Apical 2-chamber view (left lower); subcostal view of the inferior vena cava (right lower).

angiotensin-converting enzyme inhibitor, and an aldosterone antagonist. For the pericarditis component, non-steroidal anti-inflammatory drugs were not used due to prior history of esophagitis and gastritis, and steroids were not used due to insufficient evidence of benefit and the associated increased risk of recurrence.

Ten days after discontinuation of Clonazipine, the patient had complete resolution of chest pain and dysphagia, and significant improvement of his heart failure symptoms. The patient was discharged 2 weeks later on the following new medications: Olanzapine, Lisinopril, Metoprolol, Spironolactone, and Warfarin. During follow-up clinic visit 8 weeks later, the patient reported no recurrence of dysphagia, dyspnea, or chest pain. Electrocardiogram showed restoration of normal sinus rhythm, and echocardiogramshowed complete resolution of pericardial effusion, wall motion abnormalities, and left ventricular systolic dysfunction, with an LVEF of 55–60%.

DISCUSSION

Clozapine is a tricyclic dibenzodiazepine anti-psychiotic drug that is highly effective in the treatment of refractory schizophrenia and is associated with a remarkably lower incidence of suicide.[1,2] Its high affinity to the dopaminergic receptors D1 and D4, sparing D2 and D3 receptors, results in a much better extra pyramidal side-effect profile[6]. Clozapine, however, has been associated with serious side effects, both non-cardiac (agraneulocytosis, seizures, neuroleptic malignant syndrome, hyperglycemia, pulmonary embolism, and acute hepatitis) and cardiac (acute myocarditis, acute pericarditis, dilated cardiomyopathy, and sudden cardiac death) 3,6. To our knowledge, this is the first case reported to present with both acute myocarditis and pericarditis, and to respond rapidly to the discontinuation of Clozapine.

Clozapine-induced myocarditis was first reported in 1980and it has been increasingly recognized with the widespread use of this drug.[5,7,8] Recent warning from the manufacturer of Clozaril (a trade mark name for Clozapine), Novartis, states that myocarditis should be considered in all patients treated with Clozapine who present with persistent resting tachycardia or other arrhythmia, and/or symptoms of heart failure.[9] The incidence of Clozapine-induced myocarditis is estimated at 0.015% to 1.2% per year.[10]The risk of developing myocarditis is especially high during the first month of treatment, but can occur at any time during therapy and with a wide range of Clozapine daily dosage (from 50 yo

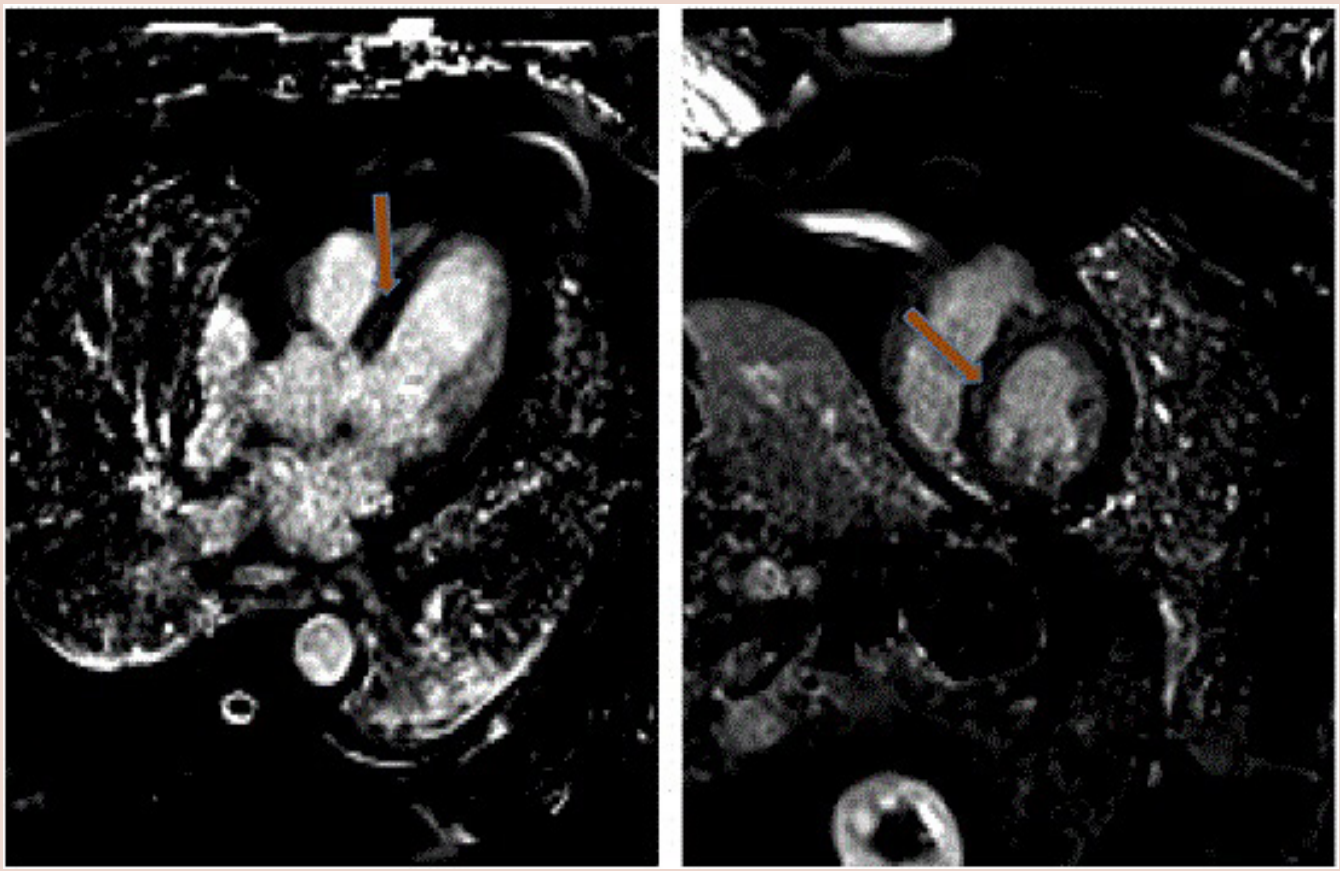

Figure 2: Cardiac Magnetic Resonance Imaging: Showing focal areas of subepicardial late gadolinium enhancement in the mid-to-basal anteroseptal and inferoseptal wall segments.

725 mg).[4] Involvement of the pericardium is rare, and can be isolated or as part of a polyserositis syndrome.[11–13]

Several mechanisms have been proposed for Clozapine-induced myocarditis including immune-mediated and direct toxicity.[3] Type I, IgE mediated, hypersensitivity reaction to the drug has been described and is supported by the occasional presence of peripheral eosinophilia in patients with this condition.[8] Direct myocardial toxicity has also been described and attributed to either Clozapine blocking of M2 cholinergic receptor, or the accumulation of toxic nitrenium metabolites of Clozapine, especially in the setting of Selenium deficiency.[14,15]

Clinical manifestations of Clozapine-induced myocarditis are nonspecific, and diagnosis is often delayed[16]. Patients can present with fever, flu-like illness, fatigue, dyspnea, or chest pain, requiring a high degree of vigilance in order to make the diagnosis.[3] Likewise, clinical manifestations of Clozapine-induced Perimyocarditis are also non-specific, including pleuritic-type chest pain and, rarely, dysphagia and odynophagia due to posterior pericardial involvement as in our case. Patients may have peripheral eosinophilia, elevated cardiac biomarkers, and ECG changes. TTE may reveal segmental or global wall motion abnormalities and, with pericardial involvement and pericardial effusion as in our case. CMRhas evolved as a useful tool to diagnose myocarditis, showing focal edema on T2-weighted imaging and sub-epicardial late gadolinium enhancement.[17] Our patient did not have significant myocardial edema on the T2-weighted imaging, likely due to delayed presentation. Finally, the role of endomyocardial biopsy is limited due to its low diagnostic yield, and is often deferred, unless the etiology of myocarditis remains unclear, or the clinical course is malignant.[18]

Treatment of Clozapine-induced myocarditis and perimyocarditis involve discontinuation of the drug once the diagnosis is suspected, early initiation of guideline-driven drug therapies for left ventricular systolic dysfunction, supportive therapy for pulmonary congestion, and recognition and treatment of potential complications including pericardial effusion, cardiac tamponade, cardiac arrhythmia, and cardiogenic shock.[18] Prompt discontinuation of the drug, while essential, it imposes a major challenge in patients with refractory schizophrenia and who are at high risk of suicide.[16] Therefore, this must be done in a controlled setting and under the supervision of a psychiatrist who will often initial an alternative therapy.

CONCLUSION

While the evidence of cardiac adverse effects of Clozapine is well established in the literature, we report this case for 3 main reasons. First, to enhance the awareness of Clozapine-induced cardiac toxicity as this drug has become widely used due to its high efficacy and favorable side-effect profile. Second, to emphasize the non-specific clinical presentation, and the wide variation in pathophysiology of Clozapine-induced cardiac toxicity. Third, to demonstrate that Clozapine-induced cardiac toxicity can be completely reversed upon discontinuation of the drug. Providers, both cardiologists and non-cardiologist must be aware of

serious cardiac-toxicity associated with the use of Clozapine, and its non-specific clinical manifestation. Studies are needed to determine the usefulness of screening asymptomatic patient who are treated with Clozapine for any cardiac involvement.

ACKNOWLEDGEMENT

We acknowledge the contribution of the staff in cardiovascular imaging department at the VA medical center for providing the Echocardiographic and MRI images.

CONFLICT OF INTEREST

None.

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Cite this article : Murad K, Gezahegn SG, Tamene AM, Li J-M. Clozapine-Induced Perimyocarditis. J Cardiovasc Disease Res. 2016;7(2):93-6.