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Myocarditis Associated with Clozapine Studied by Cardiovascular Magnetic Resonance

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INTRODUCTION

Clozapine is a neuroleptic agent which has been classified as atypical due to its peculiar pharmacological characteristics; many clinical trials have proved its efficacy in schizophrenic patients which are refractory to typical neuroleptics (1,2). Unfortunately, clozapine administration may be associated with severe cardiac side effects, in particular cardiomyopathy and myocarditis (2-8).

Myocarditis is an inflammatory disease of the myocardium which is most frequently caused by infectious agents, but may also be associated with various pharmacological therapies (9-12).

We report the first case of clozapine-induced myocarditis documented by late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR).

CASE REPORT

A 32-year-old man was admitted to the Department of Psychiatry of our hospital for a relapse of schizophrenia and started on a clozapine therapy (400 mg/day per os). After one week from the clozapine initiation, the patient developed atypical chest pain, fever, diarrhea and vomiting.

Laboratory evaluation revealed elevation of myocardial necrosis enzymes (troponin I = 3.4 ng/mL and creatine kinase-MB = 13 μg/L) and of inflammatory markers (C-reactive protein = 86 mg/L and erythrosedimentation velocity = 15 mm/h); leukocytosis was also observed (13×10^9/L) with hypereosinophilia (10%). The viruses studies were all negative (HIV, HCV, HBV, HSV, Parvovirus, EBV, Echovirus, CMV, Coxsackievirus A and B, Adenovirus in the serum).

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An ECG evaluation revealed the presence of Q waves in DIII and aVF derivations. Echocardiography showed inferior-posterior mid-basal left ventricle (LV) wall hypokinesia and moderate mitral valve insufficiency.

The patient had been subsequently submitted to LGE-CMR study.

CMR was peformed on a 1.5 T scanner (Gyroscan Intera Master; Philips Medical Systems, Best, The Nederlands) using a 30 mT/m gradients system and the five-element Synergy cardiac coil with the Vectorcardiogram option (Philips Medical Systems). Morphologic images in the cardiac short-axis, 4 chambers long-axis and 2 chambers long-axis planes were acquired by using a T2-weighted black blood (T2W/BB) sequence. T2W/BB images were obtained without and with fat suppression.

In the same planes, cine-CMR was performed by using a breath-hold balanced fast field-echo sequence. The cine-CMR short-axis images encompassed the entire LV from the base to the apex (stack of 10 contiguous short-axis slices; thickness = 8 mm, gap = 2 mm) in order to obtain a volumetric evaluation in a three-dimensional fashion.

Late gadolinium enhancement CMR was performed 10–15 minutes after the intravenous administration of Gadolinium-DTPA (Shering AG, Berlin, Germany) (0.2 mmol/kg) using a 3D T1-weighted TFE-Segmented Inversion Recovery sequence. Also the LGE images were obtained in the cardiac short-axis, vertical long-axis and horizontal long-axis planes. Two consecutive stacks, each one composed of 10 contiguous slices (20 slices; thickness = 5mm, gap = 0 mm) were acquired in the short-axis plane to encompass the entire left ventricle.

The images analysis revealed that LV was minimally enlarged, with end-diastolic volume (EDV) of 158 mL and end-diastolic mid-ventricular diameter of 56 mm; wall thickening was preserved, with a mild hypokinesia located on the anterior mid-ventricular wall; however, global LV contractility was normal, with an ejection fraction (EF) of 61%.

The morphologic T2W/BB images with fat suppression revealed a signal hyperintensity located in the inferior mid-basal wall, which could be attributed to the presence of myocardial oedema due to the known water-sensitive characteristic of this technique (Fig. 1). Subepicardial striae of LGE were present in the same LV wall area, suggesting the presence of

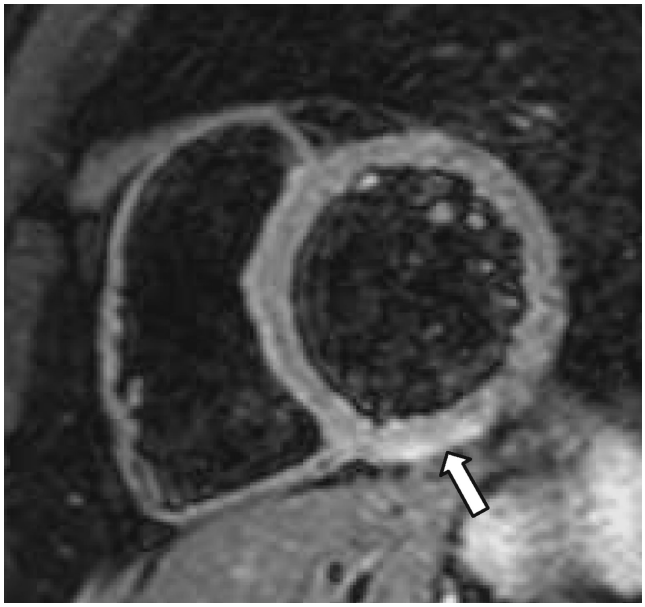


Figure 1. T2W-BB image in the cardiac short-axis plane showing signal hyperintensity located in the subepicardial side of the inferior mid-basal LV wall, suggesting the presence of myocardial oedema. In the same location, LGE was detected (see Fig. 2a).

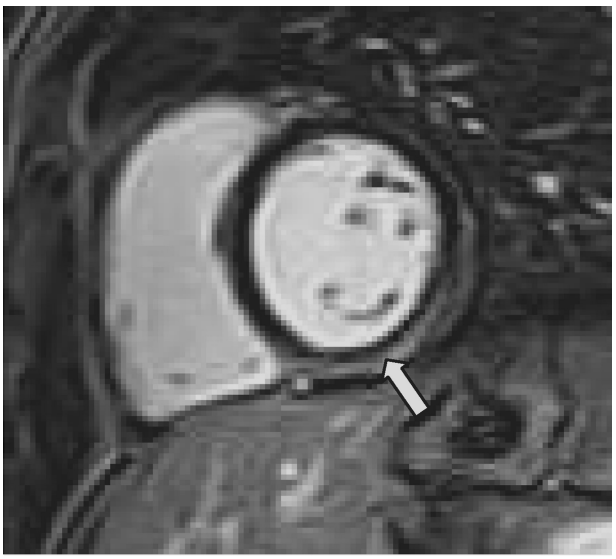
myocyte damage concomitant to myocardial oedema (Figs. 2a and 2b).

On the basis of the patient's history and of the LGE-CMR informations, the clinical suspicion of clozapine-induced myocarditis was posed; the gradual resolution of the symptoms (atypical chest pain, fever, diarrhea and vomiting) and of the ECG (Q waves in DIII and aVF derivations) and echocardiographic signs (inferior-posterior mid-basal LV wall hypokinesia and moderate mitral valve insufficiency) with normalization of laboratory testing (troponin I = 1.2 ng/mL, creatine kinase-MB = 5.5 μg/L, C-reactive protein = 12 mg/L, erythrosedimentation velocity = 6 mm/h, leukocytes = 6×10^9/L with eosinophils = 3%), that were observed in a follow-up medical examination 5 weeks after the clozapine theraphy withdrawal, supported with stronger evidence the diagnosis of clozapine-induced myocarditis.

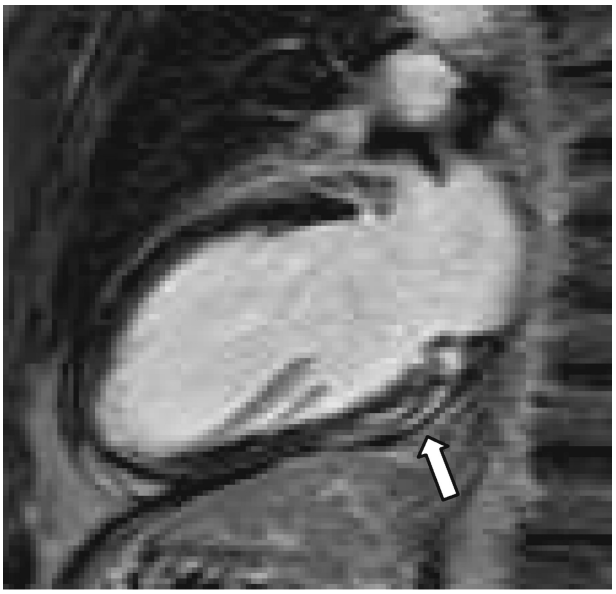
DISCUSSION AND CONCLUSION

Clozapine, a tricyclic benzodiazepine, is an atypical neuroleptic agent which is considered the treatment of choice in schizophrenic patients who do not respond to or are unable to tolerate standard antipsychotic medications (13). The use of clozapine is restricted to this category of patients because of the drug's most feared adverse effect, agranulocytosis, which requires strict hematologic monitoring (14); in addition, other important side effects have been observed recently: myocarditis and cardiomyopathy.

Myocarditis is an inflammatory disease of the myocardium, whose real incidence and prevalence are uncertain. Moreover, clinical manifestations of myocarditis may be extremely various,



(a)



(b)

Figure 2. (a) T1W LGE image in the cardiac short-axis plane showing subepicardial striae of enhancement in the inferior mid-basal LV wall, which is the same location where hyperintensity in the morphologic image was found (see Fig. 1). (b) T1W LGE image in the cardiac 2 chambers-long axis plane showing subepicardial striae of enhancement in the inferior mid-basal wall.

ranging from the asymptomatic state to fulminant acute heart failure and cardiogenic shock. The myocardial inflammatory process may be associated with conduction disturbances, with ventricular tachyarrhythmias (15), or mimic an acute myocardial infarction (16).

Even if spontaneous recovery from myocarditis is common, the disease can progress to dilated cardiomyopathy or fatal arrhytmias, with sudden death: therefore, the availability of

accurate diagnostic tools and the administration of an adequate therapy are fundamental (17).

The association between clozapine and myocarditis have been extensively studied only in recent years, when a lot of reports appeared in literature concerning myocarditis cases in clozapine users in the western countries (3-7). In these papers (3-7) and in the following review article by Merrill et al (2), the data analysis revealed that Schizophrenic patients treated with clozapine have an absolute myocarditis risk between 0.015% and 0.188%, many times greater than in the genaral population, as estimated by the manufacturer (18).

Various theories have been suggested regarding the possible pathogenetic origin of clozapine-associated myocarditis; the most interesting of them is probably the one from Kilian et al who have hypothesized that clozapine use can induce acute hypersensitivity (type I, IgE-mediated) myocarditis, characterized by serum hypereosinophilia and myocardial eosinophilic infiltrates (4, 12, 19). Other pathogenetic theories take into consideration a type III allergic reaction (4), with formation and precipitation of immuno-complexes, a direct clozapine toxic effect on the heart (4), and a hypereosinophilic syndrome induced by the drug (7), but these hypotheses have still to be proven.

To date, in literature there are no reports concerning CE-CMR study of clozapine-related myocarditis. For this reason, we believe that our case report may be interesting in the diagnostic challenge that clozapine-induced myocarditis represents: as recent studies (20, 21) have demonstrated that CE-CMR may be useful in noninvasive recognition of myocardial inflammation in the settings of acute myocarditis, and as we had the clinical suspicion of acute myocarditis in the patient, CE-CMR was performed.

In this particular case, CE-CMR provided the possibility of an important morphological and functional evaluation of the patient's heart, together with the even more interesting LGE imaging study, which allowed us to identify myocardial damage with the typical distribution and location of myocarditis.

We are aware that the distinction between viral and clozapine-induced myocarditis is not possible with CE-CMR, yet the negativity of the virological studies, the hypereosinophilia and the gradual resolution of the patient's signs and symptoms with clozapine withdrawal were relevant evidences that supported the clinical diagnosis.

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