Schizophrenia Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Clozapine-induced myocarditis

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ARTICLE INFO

Article history:
Received 2 February 2016
Received in revised form 6 April 2016
Accepted 11 April 2016
Available online xxxx

Keywords:
Clozapine
Myocarditis
Magnetic resonance imaging
Schizophrenia
Drug hypersensitivity reaction

Dear Editors,

Clozapine is considered to be the reference standard in treatment of refractory schizophrenia because of its greater efficacy and lesser tendency to induce extrapyramidal side effects when compared to conventional neuroleptics such as haloperidol (Toren et al., 1998). However, due to several other adverse effects including severe gastrointestinal obstruction, diabetic ketoacidosis and most notably potentially fatal agranulocytosis, its applicability has been limited to last-line therapy (Miller, 2000). Over the past two decades, mandatory registration and closer monitoring of patients started on clozapine have greatly reduced the incidence of these serious complications (Kilian et al., 1999) and allowed for wider clinical use to be advocated (Warnez and Alessi-Severini, 2014).

Other complications arose however, with an increasing number of reports on possible cardiac side effects appearing in literature, such as arrhythmia, (peri-)myocarditis and even dilated cardiomyopathy after prolonged use (Kilian et al., 1999). Among these, myocarditis has been of particular recent interest because of its dose-independent, acute onset that often shortly follows clozapine initiation. Since the first case of clozapine-induced myocarditis was documented in 1994 (Jensen and Gøtzsche, 1994), over 250 cases have been described (Ronaldson et al., 2015a) with increasing incidences over the past two decades of up to 1.2% among patients on clozapine (Haas et al., 2007). Although this increase could partially be attributable to rising awareness, the true incidence (which is expected to be around 3% (Ronaldson et al., 2015a)) probably remains underestimated, as many of the nonspecific symptoms associated with myocarditis such as hypotension, tachycardia and fatigue are still considered to be benign side effects of clozapine dose up-titration (Munshi et al., 2014).

Through the following case and subsequent overview of literature, we've attempted to emphasize the importance and difficulty of the timely diagnosis of clozapine-induced myocarditis, and demonstrate that cardiac magnetic resonance imaging (CMR) can herein be of additional value.

1. Case presentation

A 22-year-old Caucasian male without prior somatic medical history was referred to the coronary care unit (CCU) because of acute-onset pleuritic chest pain. He had been started on clozapine 11 days prior to admission and had experienced a fever (spiking up to 40 °C), hypotension and mild but progressive tachycardia over the past five days. For over a year now, he had intermittently been admitted to our psychiatric unit because of a psychotic disorder not-otherwise-specified (possibly schizophrenia) combined with an autism spectrum disorder. He had previously been treated with high doses of haloperidol, olanzapine and quetiapine consecutively, all of which had to be discontinued due to intolerable adverse effects and little to no improvement in his mental wellbeing.

At clozapine initiation, baseline investigations including vital signs, ECG and laboratory tests had been within normal limits. During the following week, the dose of clozapine had been gradually increased from 25 mg once daily up to 100 mg twice daily, with the last increase having taken place 5 days prior to referral, before the fever arose. Three days prior to admission, the clozapine had already shortly been discontinued because of worsening symptoms, which had resulted in resolution of the fever and alleviation of physical complaints. The next day however, the clozapine had to be reinitiated due to psychiatric deterioration, after which the fever reappeared.

At admission in the CCU, the patient's main complaint was a nagging, sharp, non-radiating pain on the left side of his chest, which was accompanied by malaise, a moderate fever and a tickly cough. Besides slightly lowered blood pressure and tachycardia, the additional history and physical examination were unremarkable; there were no risk factors

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http://dx.doi.org/10.1016/j.schres.2016.04.016

for cardiovascular disease. His concurrent medications included temazepam, lorazepam, biperiden, glycopyrrolate and a low dose of haloperidol. Furthermore, amoxicillin/clavulanate had been added at the first occurrence of fever for suspected upper respiratory tract infection.

The ECG showed a sinus tachycardia of 127 bpm without any repolarization disturbances, and laboratory testing revealed an elevated white blood cell (WBC) count (14.2×10^9/L; normal range 4.5–11×10^9) and elevated blood levels of CRP (54 mg/L; normal range ≤ 10 mg/L) and hsTnT (112 ng/L; normal range ≤ 14 ng/L). CK was within normal limits (59 U/L; normal range 55–170 U/L). Cultures of blood, feces and urine, as well as autoantibody screening and viral serologies were all negative, and extensive examinations including abdominal ultrasound and chest and sinus X-rays revealed no infectious focus.

Transthoracic echocardiography (TTE) in the CCU demonstrated slight global hypokinesia of the left ventricle and 1 cm of circumferential pericardial effusion. Afterwards, using a 1.5 T scanner (Signa HDxt, GE Healthcare, Waukesha, WI) and an 8-channel cardiac coil, CMR was performed, which included cine images, triple-inversion recovery (fat-saturated) T2-weighted images and delayed enhancement sequences obtained 15 min after gadolinium injection (Fig. 1, panels A–C). The cine images likewise showed a slightly decreased left ventricular function (ejection fraction 43%) and an ample amount of pericardial effusion, while the T2-weighted images demonstrated a clearly delineated area of myocardial edema in the basal anteroseptal wall (panel B, arrow). Although the delayed enhancement images were of poor quality, they gave the impression of a thin rim of gadolinium retention in the same area, but this was not clearly distinguishable from the blood pool in the right ventricle (panel C).

The patient was concluded to have clozapine-induced perimyocarditis and the clozapine was ceased, after which his symptoms quickly resolved and the WBC count and CRP and hsTnT levels normalized within 3 days. Repeat TTE showed a slight decrease in pericardial effusion and normalization of left ventricular function, whereupon the patient was returned to the psychiatric facility for assessment of alternative antipsychotic medications. Six months later, repeat CMR revealed a normalized global left ventricular function (ejection fraction 53%), near complete resorption of the pericardial effusion and full resolution of the myocardial edema. Furthermore, mild local hypokinesia and now more clearly delineated delayed enhancement were found in the basal anteroseptal wall (panels D–F).

2. Background

While the exact mechanism underlying clozapine-related myocarditis remains unknown, it is hypothesized that clozapine, a tricyclic dibenzodiazepine derivative, induces an IgE-mediated hypersensitivity reaction that is characterized by myocardial eosinophilic infiltrates, as seen in a biopsy (Kilian et al., 1999). This hypothesis is supported by evidence that the reaction is often accompanied by hypereosinophilia, generally occurs within 2–3 weeks after initiation of clozapine (Ronaldson et al., 2010) and is considered to be dose-independent (Haas et al., 2007). Other (as yet unsupported) theories attribute the cause of myocarditis to toxic clozapine accumulation due to a cytochrome P450 1A2/1A3 deficiency or increased plasma levels of norepinephrine and inflammatory cytokines.

Although a few cases of late clozapine-induced myocarditis have been reported (Lang et al., 2008; Tan et al., 2015), the vast majority manifest in the initial two months of treatment (while the dose is still

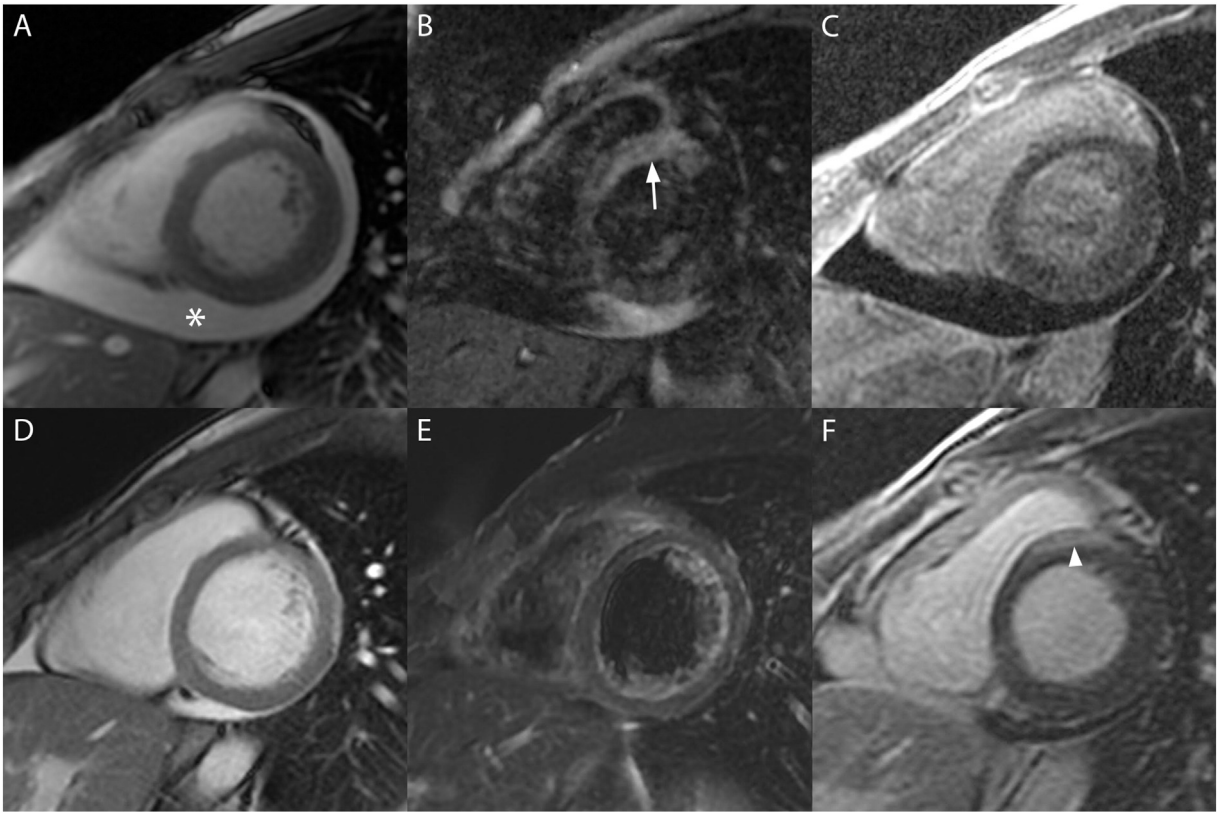

Fig. 1. First (A–C) and second (D–F) CMR scan, acquired clinically during acute myocarditis and in an out-patient setting after 6 months of follow-up respectively. On the first scan, the short-axis cine (A) and triple-inversion recovery T2-weighted (B) CMR images showed circumferential pericardial effusion (asterisk) and myocardial edema in the basal anteroseptal wall (arrow), while the delayed enhancement sequence gave the impression of a thin line of gadolinium retention in the same area (C), that could however not easily be distinguished from the blood pool in the right ventricle. After 6 months, the short-axis cine (D) and double-inversion recovery T2-weighted (E) CMR images showed almost no more pericardial effusion and complete resolution of the myocardial edema, while an area of mid- to epicardial delayed enhancement (F) was now clearly delineated in the same region (arrowhead).

Please cite this article as: Swart, L.E., et al., Clozapine-induced myocarditis, Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2016.04.016