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CASE REPORT

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Sudden cardiac death due to hypersensitivity myocarditis during clozapine treatment

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Abstract The case concerns the sudden death of a 29-year-old male during clozapine therapy started 2 weeks before. He had a history of treatment-resistant chronic schizophrenia. A complete immunohistochemical study was performed on heart specimens. Histologically, the heart presented diffuse eosinophilic infiltrates located around perivascular structures and focal myocyte necrosis with numerous interstitial eosinophils admixed with histiocytes. The diagnosis of acute myocarditis with an eosinophilic infiltrate was established as the cause of death. The autopsy findings and a detailed medical history supported the conclusion that clozapine-induced hypersensitivity myocarditis was the most likely cause of death.

Keywords Hypersensitivity · Myocarditis · Sudden death · Clozapine treatment

Introduction

With the increasing use of medications, iatrogenic causes of hypersensitivity myocarditis from drugs need to be understood and considered. The medical literature suggests a strong association between clozapine and cardiomyopathy and hypersensitivity myocarditis, however few cases have been sufficiently studied and confirmed by autopsy [1, 2].

Clozapine is a dibenzodiazepine antipsychotic with a strong affinity for D4-dopaminergic receptors and potent serotonergic noradrenergic, histamine and cholinergic M2 receptor blocking ability [3]. It is a valuable drug in treating 30% of the patients with schizophrenia who do not respond to conventional therapy. Myocarditis has been associated with the use of clozapine, and other cardiac effects such as heart failure, cardiomyopathy, and electrocardiographic abnormalities have been described [4, 5].

Our report concerns the sudden death of a young psychiatric patient undergoing clozapine therapy due to eosinophilic myocarditis, which was undiagnosed after a first forensic examination.

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Case history

A 29-year-old man was admitted as a voluntary patient to the Hospital psychiatric unit with a history of treatment-resistant chronic schizophrenia. During the hospitalisation the therapy was modified with the introduction of clozapine (400 mg/die). Within 1 week the patient presented fever, asthenia, lack of appetite and diarrhoea. Baseline blood tests were unremarkable except for peripheral eosinophilia (5.2%), but 1 week later the patient lost consciousness in bed. Cardio-pulmonaryresuscitation was unsuccessful. A complete autopsy was performed 48 h after death.

Autopsy findings

The body was that of a young man, height 180 cm, weight 75 kg. Examination revealed widespread acute haemostasis and a heart with normal shape, dimensions (10×9×5 cm) and weight (390 g). The coronary vessels were normal at the origin and during the course with the coronary circulation predominantly right-sided. The other organs did not show specific alterations except for an intense vascular congestion.

A total of 16 myocardial samples were processed for histologic examination and sections were stained by haematoxylin and eosin or by specific stains (e.g. Mallory, Weigert elastic, Movat pentachrome, Afog), when needed.

In addition, an immunohistochemical study was conducted with a panel of antibodies directed against the common lymphocyte antigen (CLA), T-lymphocytes (UCHL-l, CD3, CD4, CD8, CD45RO), B-lymphocytes

(CD20), macrophages (MAC387, CD68) and eosinophils (EG2). Additional tests were carried out in order to identify possible pathogenic agents through immunohistochemical studies with a panel of antibodies directed against antigens of the respiratory syncytial virus, Herpes virus type 1 and type 2, *Varicella zoster*, and *Toxoplasma gondii*.

The heart presented diffuse eosinophilic infiltrates located around perivascular structures and focal myocyte necrosis with numerous interstitial eosinophils admixed with histiocytes (Fig. 1). Numerous inflammatory cells, present throughout the interstitium and in perivascular regions, stained with the antibody against CLA (CD45), while the cardiac myocytes did not (Fig. 2). Immunohistochemistry showed a majority of CD68 (Fig. 3) and EG2 in the interstitium.

Histological investigations showed haemostasis of all organs and mild cerebral and pulmonary oedema.

The immunohistochemical tests for the pathogenic agents were negative for all of the antigens tested (RSV, HSV1, HSV2, VZV, *Toxoplasma Gondii*).

Toxicological tests revealed a therapeutic clozapine concentration in the blood from the femoral vein.

The diagnosis of acute myocarditis with an eosinophilic infiltrate was established as the cause of death [6].

Discussion

In the present case, clozapine-induced fatal hypersensitivity myocarditis was recorded as the cause of death. Since there are, to date, few reports of similar deaths in psychiatric patients, our report provides useful information on the present experience with this myocardial damage.

Hypersensitivity myocarditis is the most common form of acute drug-related myocardial injury. Clinically, the criteria for diagnosis of hypersensitivity to drugs are well established. They consist of a prior assumption of the drug with no reaction, absence of a relationship between a hypersensitive reaction and the drug dose; the reaction is neither a pharmacological nor toxic effect of the drug itself and is characterised by the classic symptoms that accompany allergies. An immunological test and persistence of the symptoms until the drug is suspended are also necessary as criteria for a correct diagnosis [7]. The histopathologic features of hypersensitivity myocarditis include temporally uniform lesions distributed in the subendocardial, perivascular, and interstitial tissues. The predominant inflammatory cells are eosinophils, but variable numbers of histiocytes and lymphocytes are also found. Myocyte necrosis is absent or focal and limited [8]. Necrotising vasculitis is not found, but infiltration of vessel walls by inflammatory cells is common [9].

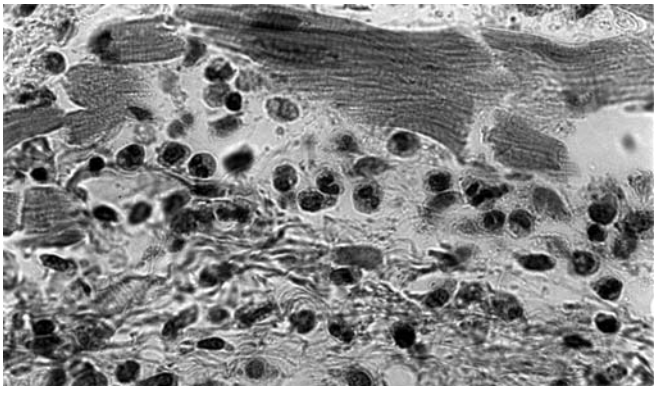

Fig. 1 Diffuse eosinophilic infiltrates admixed with histiocyte located in the interstitium (H&E ×400)

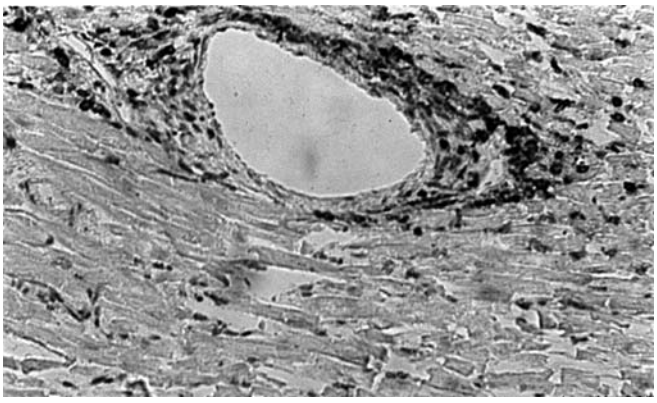

Fig. 2 Numerous inflammatory cells present in perivascular region stained with CD45 (CLA) (×200)

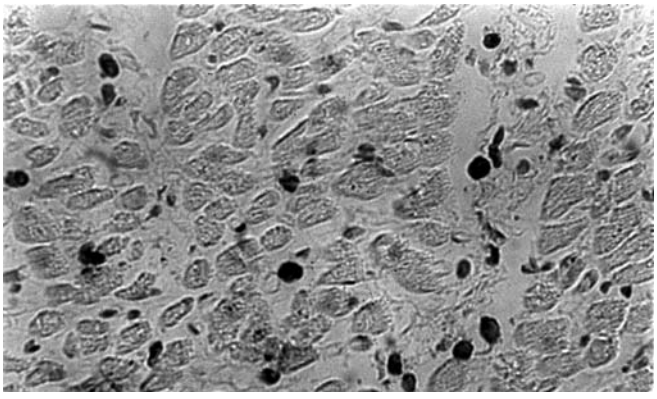

Fig. 3 $CD68^{+}$ histiocytes (×400)

Post-marketing surveillance data from four countries that employed haematological monitoring of clozapine-treated patients revealed: 30 reports of myocarditis with 17 fatalities in 205,493 U.S. patients (August 2001), 7 reports of myocarditis with 1 fatality in 15,600 Canadian patients (August 2001), 30 reports of myocarditis with 8 fatalities in 24,108 U.K. patients (August 2001), and 15 reports of myocarditis with 5 fatalities in 8,000 Australian patients (March 1999). These reports represent an incidence of myocarditis of 5.0, 16.3, 43.2, and 96.6 cases/100,000 patient-years, respectively. The incidence of death was 2.8, 2.3, 11.5, and 32.2 cases/100,000 patient-years, respectively (Novartis, Dear Health Care Provider, February 2002).

Similarly, in Sweden 12 fatal cases of myocarditis were described in the psychiatric population between 1983 and 1999 [4]. Before, only occasional case reports described

the recurrence of fatal cases due to myocarditis during the therapeutic assumption of clozapine [10, 11, 12, 13].

The mechanism by which clozapine causes myocardial toxicity is unclear. One hypothesis is that myocardial toxicity is an immunoglobulin E-mediated hypersensitivity (type I allergic) reaction. This is unlikely as other type I reactions (i.e. urticaria and anaphylaxis) rarely occur during clozapine therapy. Another theory postulates that this reaction is due to a hypereosinophilic syndrome induced by clozapine. This explanation is more plausible as eosinophilia has been associated with clozapine myocarditis. Finally, it has been suggested that clozapine has a direct toxic effect on myocardial tissue [14].

A reported case of clozapine-induced acute interstitial nephritis, however, suggests that other internal organs may be involved in reactions to this drug [15].

In our fatal case, the clozapine therapy was initiated 2 weeks before exitus and the drug was prescribed and administered at a dosage of 400 mg/die, corresponding with the daily recommended dose (200–500 mg/die). Exitus was preceded by unspecific symptoms (i.e. fever, asthenia) which worsened quickly and unexpectedly. The microscopic cardiac examination, including immunohistochemical analyses, led us to diagnose a hypersensitivity myocarditis, characterised by a great number of eosinophils admixed with macrophages. We concluded that clozapine-induced myocarditis was the most likely cause of death.

Drug induced myocardial dysfunction remains a significant diagnostic problem and the list of drugs implicated continues to grow [9]. Postmortem examination [16, 17], using a complete immunohistochemical panel [18, 19], is warrant for the diagnosis of the disease, having a high index of diagnostic suspicion in patients who died during clozapine treatment associated with peripheral eosinophilia [20].

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