Case Report

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Sudden Death Associated with Hypersensitivity Myocarditis Induced by Clozapine: An Autopsy Case

Huseyin Es[1], Ipek Esen Melez[2], Ayse Ozgun[3], Deniz Oguzhan Melez[4], Cisem Kertmen[5], Mehmet Cavlak[6]

ABSTRACT:

Sudden death associated with hypersensitivity myocarditis induced by clozapine: An autopsy case

Eosinophilic myocarditis is a rare cause of sudden unexpected death and characterized by eosinophilic infiltration in the myocardium. Clozapine is among the agents that can cause eosinophilic myocarditis. Our case is a 48 year-old female patient who was hospitalized in psychiatry inpatient unit and died unexpectedly on the 35th day of her hospitalization while on clozapine treatment. Even though the autopsy revealed an increased heart weight, fatty streaks on aorta, and thickening of epicardial fat tissue macroscopically, no pathological macroscopic features were noted in the myocardial cross sections. Eosinophilic myocarditis findings were found in the histopathological evaluation. Toxicological assessment revealed presence of clozapine in the blood (735ng/ml clozapine and its metabolite) and the bile. In the lights of these findings, it was concluded that the patient died from clozapine-induced eosinophilic hypersensitivity myocarditis. Drug-induced eosinophilic hypersensitivity myocarditis should be considered in the sudden death cases with a history of clozapine use and/or in presence of clozapine in the toxicological analysis.

Keywords: clozapine, hypersensitivity, eosinophilic myocarditis, autopsy, sudden death

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[1]M.D., Bingol Branch of Council of Forensic Medicine, Bingol - Turkey
[2]Assist. Prof., Bezmialem Vakif University School of Medicine, Department of Forensic Medicine, Istanbul - Turkey
[3]M.D., Council of Forensic Medicine, Department of Pathology, Istanbul - Turkey
[4]M.D., Council of Forensic Medicine, Istanbul - Turkey
[5]M.D., Duzce Brach of Council of Forensic Medicine, Duzce - Turkey
[6]M.D., Ankara Brach of Council of Forensic Medicine, Ankara - Turkey

Corresponding author:
Dr. Hüseyin Eş
Bingöl Adli Tıp Şube Müdürlüğü,
Adliye Sarayı, Bingöl - Türkiye

E-mail address:
drhuseyines55@gmail.com

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INTRODUCTION

Myocarditis is one of the causes of sudden unexpected deaths. The most common form is lymphocytic myocarditis associated with viral infections[1]. Eosinophilic myocarditis is a rare form of myocarditis, characterized by eosinophilic infiltration of the myocardium[2]. Eosinophilic myocarditis can be seen in the course of some systemic diseases such as allergic disorders, parasitic infections, cancer, Churg-Strauss syndrome and hypereosinophilic syndrome[3,4]. Clozapine is among the drugs considered responsible for drug-induced myocarditis[5,6]. This case report presents a sudden death incident due to clozapine-induced eosinophilic hypersensitivity myocarditis (CIEHM), which is rarely seen in the literature and is the first one reported in Turkey.

CASE

A 48 year-old female patient presented to the hospital with complaints of insomnia, self-talking, trouble with the neighbors, and aggression towards her family. She was diagnosed with schizophrenia ten years ago and hospitalized from time to time during this period. Her last hospitalization was for acute psychotic exacerbation of treatment-resistant schizophrenia. She was hospitalized and treated with clozapine, haloperidol, and biperiden in the psychiatry service. On the first day of hospitalization, 25 mg clozapine was administered. Haloperidol and biperiden were included to the treatment on the fourth day. Due to no change in the clinical status, 6 mg risperidon was added and the dosage of clozapine was also increased to 100 mg. After that, clozapine dosage was gradually raised up to 350 mg during 30-day hospitalization.

It was reported that electroconvulsive therapy was planned because of homicidal and suicidal thoughts, however she suddenly died on the 35th day of hospitalization prior to this therapy. No traumatic lesion was noted in external examination during the autopsy. Her body mass index was 42.73 kg/m^2 [104/(1.562)]. In the internal examination, 300ml in each thoracic cavity and 250 ml serous fluid in the pericardium was demonstrated. The heart weight was 564 gr, and was considered as hypertrophic ([4.45x(body weight)]+85.4=548.2 gr) based on Hangartner formula[7]. Increased epicardial fat tissue and fatty streaks of aorta were also noted. Thickness of ventricular wall was 1.5 cm in the left and 0.4 cm in the right ventricular wall. No coronary artery obstruction was found. Also, no macroscopic pathologies were noted in the myocardial cross sections. Both lungs had edematous appearance. Macroscopic pathological evaluation of other organs and microbiological screening was unremarkable.

Histopathological examination demonstrated mononuclear inflammatory cell infiltration, rich in eosinophilic leukocytes in the perivascular areas of myocardium and interstitium (Figure 1-2), sparse hypertrophic muscle fibers and hyperemia. These findings were considered as consistent with the diagnosis of eosinophilic myocarditis. Acute swelling areas, hyperemia, edema, and mild anthracosis were noted in the lungs. Other organs also had hyperemic appearance.

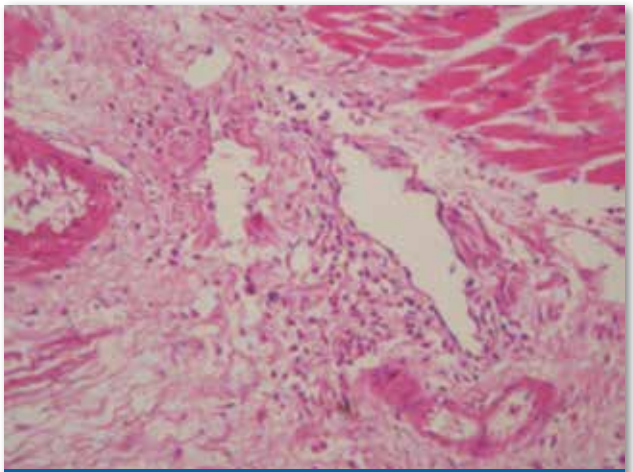

Figure 1: Eosinophilic leukocytes in the perivascular areas of myocardium (HEx20)

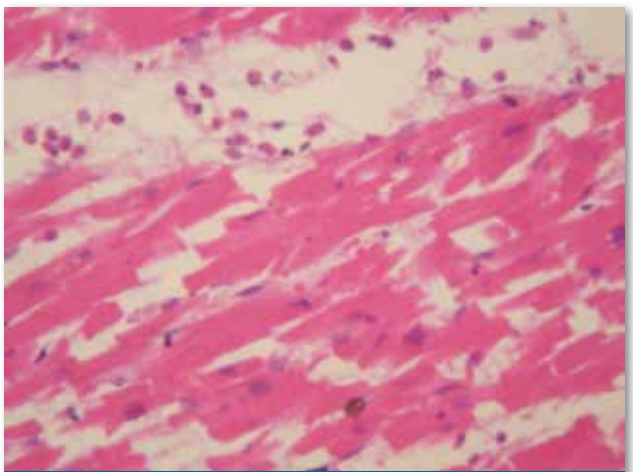

Figure 2: Eosinophilic leukocytes in the interstitium of myocardium (HEx40)

Toxicological examination revealed that clozapine was at the therapeutic level (0.735mg/L) [therapeutic= 0.1-0.6(0.8) mg/L, (seizures= >0.5 mg/L); toxic= 0.8-1.3 mg/L; lethal= 3 mg/L][8], clozapine metabolite, biperiden and risperidon levels were below the calibration interval in the blood and no haloperidol was detected either in blood or in bile. Clozapine and its metabolite were also found in the bile.

In the lights of these findings, no pathological

observations were found except eosinophylic hypersensitivity myocarditis to determine the death cause; furthermore neither the patient's medical files during her hospitalization, nor the postmortem microbiological and histopathological investigations did provide any evidence regarding the cause of eosinophylic hypersensitivity myocarditis. On the other hand, since clozapine was found besides other medications in the toxicological examination, and previously reported as a possible cause of eosinophilic hypersensitivity myocarditis, the cause of death was determined as CIEHM.

DISCUSSION

Because the findings of drug-induced myocarditis are frequently nonspecific, it is rarely diagnosed in antemortem period. Postmortem examination can reveal cardiac enlargement, myocardial paleness, pericardial effusion or completely normal findings[9]. Interstitial and perivascular eosinophilic infiltration and less commonly lymphocyte and histiocyte infiltration are noted in histopathological examination. Even though myocyte necrosis can be seen, it is not widespread[5]. Eosinophilic infiltration can be mild or disseminated[10].

Eosinophylic myocarditis occurs in relation to drug-induced allergic hypersensitivity disorders, often hydrochlorothiazide, methyldopa, penicillin, ampicillin, sulfadiazine, and sulfisoxazole[10,11]. However drug-induced eosinophylic myocarditis is considered to happen in dose-independent manner[10,12]. Besides that, it may also be seen in parasitic infections (Trypanosoma cruzi, Toxoplasma gondii, Trichinella spiralis, Entamoeba fragilis, Isospora belli, Strongyloidiosis, Toxocara canis, Echinococcus, and Schistosomiosis)[13,14], cancer (lymphoma)[3,4,10], endomyocardial fibrosis (also known as Davies' disease), Loeffler myocarditis[15], systemic diseases such as Churg-Strauss and hypereosinophylic syndrome[3,4], and transplant rejection[16]. No previously mentioned causative factor was demonstrated in the medical records or antecessent of our case. Autopsy also did not indicate any diseases causing eosinophylic myocarditis such as parasitic infection, cancer or systemic disorders. The facts that administration and gradual increase of clozapine treatment starting from the first day of hospitalization, additional administration of haloperidol, biperiden, and risperidone, unexpected death of the patient on the 35th day of treatment and medications in postmortem toxicological investigation led to the drug-induced hypersensitivity myocarditis.

Furthermore, the fact that clozapine was the most commonly reported psychiatric drug associated with eosinophylic myocarditis, also supported our conclusion[5,6,17-22]. Drugs including biperiden and risperidone, found in postmortem toxicological investigation, were used as secondary agents during clozapine treatment, and to the best of our knowledge, no previous studies claiming that they could be responsible for eosinophylic myocarditis[23-25]. The study of Ronaldson et al. also reported that secondary drugs used during clozapine treatment were not associated with myocarditis risk except for sodium valproate[25]. When all these factors were considered and other possible diagnoses were ruled out, we concluded that the death occurred as a result of CIEHM.

Clozapine is an antipsychotic agent, usually preferred if other drugs are ineffective, and causes less extrapyramidal side effects. However, it has some life threatening side effects such as agranulocytosis, myocarditis, and cardiomyopathy[26,27]. The risk of developing myocarditis in the patients receiving clozapine treatment was found as 0.187% in the study from Australia, 0.080% in England, and 0.029% in a study conducted by 30 psychiatry clinics from Sweden and Germany[17,28,29]. Again myocarditis incidence was reported between 0.7 and 1.2 in a study from Australia conducted in 2007[21]. Moreover, it was reported that the actual rato could be higher because of under diagnosed cases[30,20]. Death ratio was previously reported as up to 50% in CIEHM cases[17,31,32]. Similarly, death ratio was reported approximately 10% by Haas et al., and 8% by Hill and Woolrych[21,22].

CIEHM is most commonly seen in the third and fourth decades[21]. Even though clinical findings such as ECG abnormalities, fever, tachycardia, high troponin level, chest pain, increased C-reactive protein level can be seen, it can also cause death without any warning signs and symptoms[21,18]. Heart failure, arrhythmias, myocardial infarction and pericarditis-like symptoms can be noted[28]. It is demonstrated that approximately 75% of CIEHM develops in the first 3–4 weeks; more than 85% of the cases diagnosed in the first two months of the treatment[32]. Hass et al. reported that the first four weeks is the danger period[21]. In the study of Killian et al., all of the myocarditis cases were seen in the first 3 weeks of the treatment[17]. The study of Ronaldson et al., which evaluated the factors affecting the development of myocarditis in the patients on clozapine, demonstrated that risk of myocarditis increases with aging, rapid dosing, and additional use of sodium valproate[25]. Obesity was shown to increase the risk of mortality in myocarditis, and coronary pathologies were not usually found along with myocarditis in death cases[19]. Our case was a 48 year-old female patient with a BMI value of 42.73 who died suddenly on the 35th day of clozapine use. Due to clinical features, the patient was in the risk group for sudden death caused by clozapine-induced myocarditis.

Acute hypersensitivity reaction (type 1, IgE-mediated) is usually the responsible mechanism in CIEHM. Besides that, type 3 allergic reaction and direct toxicity of the medication can also lead to myocarditis[17,22]. However, both generalized histopathological findings in other organs and use of lethal dose should be present in the cases resulting from direct toxicity of clozapine[17,33]. There are also some studies claiming that genetic tendency has a role in development of myocarditis[17,22,25]. Toxicological examination of our case revealed that clozapine and its metabolite were within the therapeutic blood level. Furthermore, histopathological examination demonstrated eosinophilic myocarditis findings. No other drug-induced pathologies were revealed in any of the tissues except for the heart.

In forensic medicine examinations, as long as supporting histopathological findings are present, drug-induced eosinophilic hypersensitivity myocarditis should be considered in sudden death cases with the history of clozapine use and/or the presence of clozapine in toxicological analysis. Besides, in psychiatric examinations being careful when prescribing clozapine to middle aged patients in very early weeks of the treatment and following up them appropriately while keeping in mind the cardiac side effects of clozapine as well are of crucial importance.

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