Case Report

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Eosinophilic Myocarditis in Long Term Use of Antipsychotics: Case Series and Review of the Literature

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ABSTRACT:

Eosinophilic myocarditis in long term use of antipsychotics: case series and review of the literature

Long term use of antipsychotics, is encountered in many psychiatric disorders, especially in schizophrenia. Eosinophilic myocarditis is a rare form of myocarditis characterized by myocardial inflamation composed of mostly eosinophils. It is known that it may develop at a rate of 0.2-3 % in long term therapies, especially with clozapine use. Standart treatment can not be established because of rarity of disease and difficulties in the determination of the etiology. In this article, three cases, who have been receiving long term drug treatment for schizoaffective disorder and faced sudden death, were presented. Their autopsies were performed in our institution. When myocardial sections were examinated with light microscope, common findings with three cases were, myocyte damage accompanied with patchy distribution of perivascular and interstitial inflamatory infiltrate rich in eosinophils. When the light microscopic findings evaluated with detailed medical history, autopsy findings and toxicological analysis results, we considered these entities may have developed as a result of hypersensitivity reaction due to long term antipsychotic drug use. Eosinophilic myocarditis is encountered as a rare clinical entity and probably it is a subtype of myocarditis that is overlooked. Failure in the clinical diagnosis and delay in treatment may lead to irreversible myocardial damage and death. Endomyocardial biopsy is still the gold standard in the diagnosis of eosinophilic myocarditis. Here, we present these cases since the drug use is the most frequently accused cause, it is rarely seen in acute deaths and the diagnosis can be reached by histopathological examination.

Keywords: myocarditis, eosinophil, autopsy, antipsychotic treatment

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INTRODUCTION

Long-term use of antipsychotics, is encountered in many psychiatric disorders, especially schizophrenia. As the age of patients progresses, many non-psychiatric drugs are added to psychiatric treatments. In addition to well known side effects of long term use of antipsychotics, there are also adverse effects that can be fatal like eosinophilic myocarditis that are relatively less frequent or clinically overlooked, and usually definitive diagnosis is obtained after the autopsy result. Eosinophilic myocarditis is a rarely seen form of myocarditis[1]. Pathologically it is characterized by diffuse or focal myocardial inflamation composed of mostly eosinophils. Frequently hypereosinophilia is detected in blood. As a result of infiltration of the heart muscle, degranulation of several proteolytic enzymes released by eosinophils may lead to myocyte damage[2]. Eosinophilic myocarditis follows three phases. Phase 1 is known as acute necrotic phase;

it develops as a result of interleukin 5 elevation and extracellular eosinophilic deposits and eosinophilic infiltration. Phase 2 is known as thrombotic phase; it develops with the activation of eosinophilic tissue factors and characterized by endocardial damage and thrombus. Phase 3 is known as fibrotic phase and is characterized by myocardial fibrosis[3]. As a result of endomyocardial fibrosis, restrictive cardiomyopathy may develop with clinical findings such as cardiomegaly, valvular insufficiencies, and cardiac failure in the foreground[1].

Clozapine is an atypical antipsychotic drug that belogs to tricyclic dibenzodiazepine group. It is an important option in treatment-resistant schizoaffective disorders. Its advantages are, low rate of extrapyramidal side effects and decreased tendency of suicide in schizophrenic patients. Besides agranulocytosis and neutropenia can be seen in the follow-up protocols, there also cardiac side effects such as myocarditis which is uncontrollable and can be fatal[4]. Studies in the literature show that there is a strong association between hypersensitivity myocarditis and clozapine[5,6].

However, for this conclusion a certain number of studies are required and the number of cases confirmed by autopsy is not sufficient.

We presented these cases in order to draw attention to eosinophilic myocarditis that may develop due to multiple drug use administered in psychiatric treatment and drugs such as clozapine and this diagnosis is usually made by postmortem histopathological examination.

CASE 1

First case is a 34-years-old woman, who have been treated for psychiatric disorders for approximately 20 years. She died of cardiac arrest at the hospital. She was re-admitted because of deterioration of general health status on the day of discharge from the hospital. According to gross examination at the autopsy the heart weighted as 335 grams. Heart lids and chambers were found to be normal. Coronary arteries were observed as

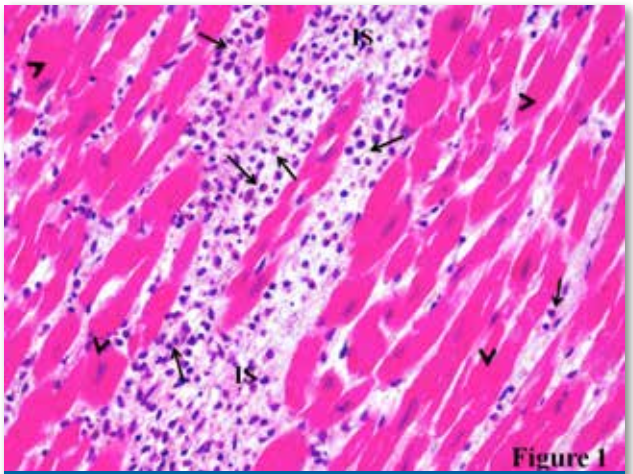

Figure 1: Myocyte damage in perivascular and interstitial spaces, inflammatory infiltrate containing eosinophils (H&E x200) Arrowheads: Myocytes, Arrow: Eosinophils IS: İnterstitial spaces

patent. Pale areas and milimetric pearly appearing areas were noted on the myocardial serial sections. 50 ml of serous fluid was detected in the pericardial space. With ligth microscopic examination, inflammatory infiltrate composed of mostly eosinophils were observed in perivascular and large interstitial spaces causing myocyte damage in patchy fashion (Figure 1). We observed that the inflamatory infiltrate extended to pericardial adipose tissue and visceral pericardium. In the postmortem toxicological analysis, the active ingredients and/ or metabolites of propranolol, haloperidol, valproic acid, clozapin, chlorpheniramin and flurbiprofen were detected in blood and/ or urine.

CASE 2

Second case was a 35-years-old woman who have been treated with a diagnosis of schizoaffective disorder for approximately 20 years. She was reported to be found dead in bed. At the autopsy the heart weighted as 344 grams. On gross examination heart lids and chambers were normal. Atheroma plaques narrowing the lumina of coronary arteries were observed. No macroscopic pathology was noted on the myocardial serial sections. 10 ml of serous fluid was detected in the pericardial space. With the light microscopic

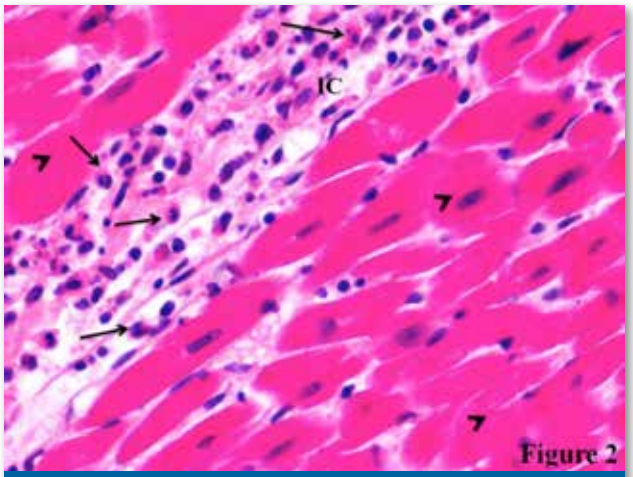

Figure 2: Myocyte damage in perivascular and interstitial spaces, inflammatory infiltrate of mixed character accompanied by eosinophils (H&E x400) Arrowheads: Myocytes, Arrow: Eosinophils, IS: İnterstitial spaces

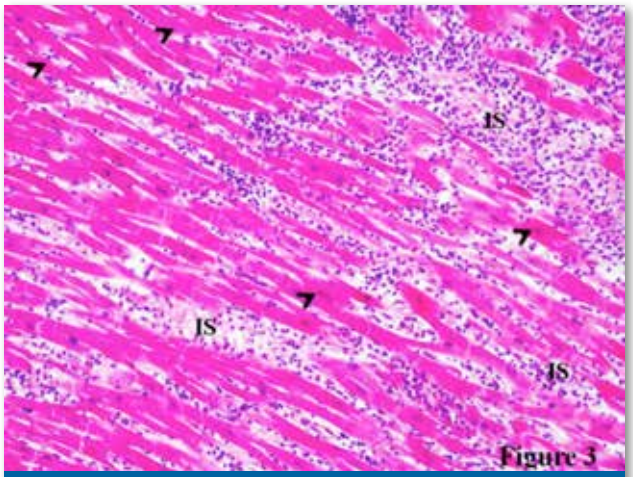

Figure 3: Myocyte damage in perivascular and interstitial spaces, inflammatory infiltrate of accompanied by eosinophils, lymphocytes and macrophages (H&E x100) Arrowheads: Myocytes, IS: İnterstitial spaces

examination, inflammatory infiltrate accompanied by eosinophils, lymphocytes and macrophages was observed in the perivascular and interstitial spaces causing myocyte damage in patchy fashion (Figure 2). With postmortem toxicological analysis, the active ingredients and/or metabolites of chlorpormazine, clonazepam, propranolol, methylphenidate, aripiprazole and biperiden were detected in blood and/or urine.

CASE 3

The third case was a 45-years-old man who have been treated with a diagnosis of schizophrenia for approximately 20 years. He was reported to be found dead in bed. At the autopsy the heart weighted as 432 g. On gross examination heart lids and chambers were normal. Calcified atheroma plaques narrowing the lumina of coronary arteries were observed. No macroscopic pathology was noted on the myocardial serial sections. 120 ml of serous fluid was found in the pericardial space. With the light microscopic examination, we observed inflamatory cell infiltration of mixed character accompanied by mild to moderate degree of eosinophilic infiltration, extending to interstitium and degrading myocardial fibers in a few areas (Figure 3). With postmortem toxicological analysis, the active ingredients and/or metabolites of ephedrine/pseudoephedrine, amisulpride, amninoclonazepam, biperiden and fluoxetine were detected in blood and/or urine

With all these findings, the cases were evaluated as eosinophilic myocarditis.

DISCUSSION

Eosinophilic myocarditis is a rare form of myocarditis[1]. On light microskopic examination, It is characterized by focal or diffuse inflammatory infiltrate containing varying degrees of eosinophils[7]. The inflamatory infiltrate may be focal, multifocal or diffuse. The inflammatory infiltrate may contain lymphocytes, histiocytes, and plasma cells in some cases. Some cases may be accompanied by myocyte necrosis, fibrosis, granuloma formation and collagen fibrinoid necrosis. The inflamatory infiltration may be perivascular or interstitial. Pericardium and endocardium may be involved to some extent[1]. It is reported that myocyte necrosis is more frequently associated with hypereosinophilic syndrome. The process, which results endocardial scar formation and restrictive cardiomyoptahy is associated with heavy eosinophilic infiltration. In some cases atrial inolvement may be more prominent than ventricular involvement[7].

There is no relationship between clinical

findings and the intensity of eosinophilic infiltrate. Cases which are left untreated, this entity may be fatal[1,7]. Decrease in blood potassium levels due to long term and multiple antipsychotic use, stress conditions that may lead to sudden rises in catecholamine levels and increases in plasma cortisol levels may upgrade myocardial cells sensitivity and may cause sudden deaths[8]. There is data supporting that clozapine is the most effective antipsychotic drug. It is considered as gold standard in treatment resistant cases in which typical and antitypical antipsychotic drugs have been failed[9]. However, many studies suggest that myocarditis, pericarditis, and cardiomyopathy may develop in association with clozapine. Although the cardiovascular side effects are observed highly in the first month after initiation of the treatment, myocarditis cases developing a few years later have also been reported in the literature. Myocarditis rate due to clozapine use has been reported to be about 1%. If myocarditis is not identified and treated, it may result to death[10-13].

Myocarditis is rarely recognized clinically. It is usually detected at postmortem examination. It is reported that eosinophilic myocarditis is seen in 0.5% of autopsy series. This rate is observed as 20% in heart transplant patients. In these cases, hypersensitivity due to medication use is reported to be the most common cause[5]. Studies show that eosinophilic myocarditis occurs in 60% of hypereosinophilic syndrome cases[3].

Although the cause of eosinophilic myocarditis could not be detected, several different etiologies have been described. Eosinophilic myocarditis may arise acutely or chronically as a result of connective tissue diseases, hypereosinophilic syndrome, eosinophilic leukemia, infections or drugs. Connective tissue diseases (systemic lupus erythematosus and polymyositis) may be associated with myocarditis and pericarditis but the myocarditis findings are generllay mild[9,14]. The clinical presentation in eosinophilic myocarditis cases is generally nonspecific. Besides noncardiac findings such as fever, skin rashes, cardiac findings such as sinus tachycardia, conduction disorders, and ST-T wave abnormalities may be seen[1]. Endomyocardial biopsy is a valuable tool for confirming diagnosis. However, it is not a very sensitive technique since the myocardial infiltration is usually focal. The diagnosis in majority of cases is based on autopsy findings[15,16]. Eosinophilic myocarditis consists of three phases. Phase 1 lasts about 2-3 weeks. In phase 2 serebral thromboembolism is very common and anticoagulant therapy may not be protective all the time. Favorable prognosis may be mentioned if there is hypereosinophilia controllable with steroid therapy, elevated serum IgE level and absence of leukemic changes[2,7]. In phase 3, as a result of endomyocardial fibrosis, restrictive cardiomyopathy may develop with clinical findings such as cardiomegaly, valvular insufficiencies, cardiac failure in the foreground[2].

Many drugs are implicated in the etiology of eosinophilic myocarditis[1,16,17]. French and Weller first reported a case of eosinophilic myocarditis due to sulfonamide use[18]. It is said that drugs cause myocardial damage leading to allergic hypersensitivity reaction and not by direct toxic effect[7]. Eosinphilic myocarditis may develop independent of the drug dose. It is reported that cases demonstrate typical allergic reaction signs such as fever, skin rashes, eosinophilia in blood[1,7].

Literature and case series in this subject are very limited. The present cases were mostly associated with clozapine treatment. In our case series multiple drug use was present and in only one case clozapine use was available. In other cases there was multiple drug use with first and second generation antipsychotics.

Withdrawal of the etiologic drug is the first action in treatment. In cases with strong suspicion of eosinophilic myocarditis, a dramatic improvement with high dose steroid therapy could be provided without awaiting the confirmation of the definitive diagnosis[2].

In conclusion, early diagnosis in eosinophilic myocarditis is very important in treatment and survival. Therefore, cases receiving long term antipsychotic therapy should absolutely consulted with cardiology and findings that may develop in

electrocardiographic and echocardiographic studies and biochemical analyses should be followed carefully. Whatever the underlying cuase, fatal outcomes can be prevented with systemic corticosteroid treatment. In addition to these, with the diagnosis and treatment of the underlying cause and eosinophilic myocarditis it will be possible to improve long-term outcomes.

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