**Psychiatr. Pol. 2026; 60(3): 445–451**
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/221813

# Aortitis with eosinophilia as a rare complication of clozapine treatment – a case of a patient with paranoid schizophrenia

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**Summary**

Clozapine is an antipsychotic medication used to control the symptoms of schizophrenia. Due to the frequent occurrence of adverse effects, it is reserved for patients meeting the criteria of treatment-resistant schizophrenia. Among the less typical side effects of clozapine are asymptomatic eosinophilia and eosinophilic inflammation of organs such as the myocardium, as well as vasculitis, which most commonly affects small vessels in the skin.

We present the case of a 54-year-old woman with treatment-resistant paranoid schizophrenia, who developed aortitis accompanied by eosinophilia as an adverse reaction to clozapine therapy. Symptoms resolved after discontinuation of the medication. The patient gave written consent for the publication of her medical case and treatment course.

Inflammatory changes in large vessels such as the aorta during clozapine treatment have not been described in the literature. The coexisting eosinophilia suggests an eosinophilic nature of the inflammatory changes within the aortic wall. The presented case aims to raise awareness about possible atypical complications of the treatment and to expedite their diagnosis, which may prevent permanent negative health consequences in patients.

**Key words:** psychiatry, aortitis, clozapine

## Introduction

Clozapine is an antipsychotic drug classified as atypical neuroleptic. It is commonly used in the treatment of schizophrenia in whom previous treatment has been ineffective or poorly tolerated. Due to its frequent side effects, it is reserved for patients meeting the criteria for treatment-resistant schizophrenia and for the treatment of psychosis in the course of Parkinson's disease [1]. It is administered through a gradual dose escala-

tion, followed by maintenance therapy. The most dangerous side effects of clozapine are related to damage to the hematopoietic system. The risk of agranulocytosis, usually in the form of neutropenia, requires regular monitoring of leukocyte counts during therapy. The cumulative incidence of agranulocytosis reported by the UK Clozapine Patient Monitoring Service is 0.78%. Most cases (approximately 70%) occur within the first 18 weeks of treatment [1]. A less common complication is eosinophilia. In most patients, it is reported within the first 4 weeks of starting clozapine, is asymptomatic and usually resolves spontaneously [2].

Vasculitis following clozapine administration is a rare complication. Cases of inflammatory changes in large vessels, such as aorta, are absent in the literature. The only reported type of vasculitis is leukocytoclastic vasculitis, which affects small vessels, primarily in the skin [3].

## Case report

A 54-year-old patient was admitted to the psychiatric ward with her consent, in an emergency mode, after she had committed active aggression towards her brother in the form of a knife attack. The patient had not been treated psychiatrically so far, but the specificity of the symptoms and the time of their occurrence justified the diagnosis of paranoid schizophrenia. According to the family, the patient had been gradually withdrawing from social contacts for 15 years, but had not neglected her professional duties. For 2 years before admission, she had become verbally aggressive and began to display strange behavior, for example, putting out "crumbs for the ghosts" by the door. In the last 3 months preceding hospitalization, she conducted self-talk and reported feeling threatened and observed. On the day of admission, she committed active aggression for the first time.

On admission, the patient was auto – and allopsychologically oriented, slightly maladjusted in behavior. Verbal contact was difficult due to the distracted thinking, laconic answers, paralogies, thought blocking, and cognitive slippage. The patient was suspicious, looked around distrustfully, and her affect was described as flat, she was periodically tense. Psychomotor drive was slightly reduced, and motor stereotypes were present. She presented delusions of control, thought withdrawal and insertion, auditory pseudohallucinations, and visual hallucinations. She strongly denied suicidal thoughts. Physically, the patient's general condition did not show any major abnormalities.

On the 1$^{st}$ day after admission, risperidone was started at a maximum daily dose of 3 mg, the dose was gradually increased to 6 mg per day. Due to persistent delusions, auditory and visual hallucinations, as well as negative symptoms, the drug was discontinued on the 7$^{th}$ day and olanzapine 10 mg in intramuscular injections was started. Due to increased psychotic anxiety, lorazepam was added after two days at a total daily dose of 3 mg. A decrease in anxiety and a slight improvement in well-being were noted, however, due to excessive sleepiness, lorazepam was discontinued the following day. After three days of treatment with olanzapine in the intramuscular form, it was changed to an oral form at a daily dose of 20 mg, but no clinical effect was achieved. Due to the patient's smoking and thus exposure to polycyclic aromatic

hydrocarbons (PAHs) contained in tobacco smoke, which induce the activity of the CYP1A2 isoenzyme – the main metabolic pathway of olanzapine – it was decided to increase the dose of the drug to 25 mg/day. Although this dose exceeds the maximum recommended in the summary of product characteristics (20 mg/day), it was considered clinically justified in order to achieve the appropriate therapeutic concentration [4, 5]. The olanzapine treatment continued for 14 days, however, was still non-effective. The criterion of drug resistance – the lack of adequate clinical improvement despite the use of at least two different antipsychotic drugs, including an atypical antipsychotic drug, in appropriate doses and for an appropriate time – was not fully met, but it was decided to qualify the patient for clozapine treatment.

The drug was used in increasing doses, starting from 12.5 mg to a maximum dose of 200 mg on the 18$^{th}$ day of treatment. The mental state remained unchanged. Along with the increase in the dose of the drug, adverse symptoms appeared: tingling in the fingers of both limbs, increased appetite, salivation, urinary incontinence, constipation, deterioration of well-being, and a drop in blood pressure to 80/60 mmHg in morning measurements. On the 8$^{th}$ day of clozapine treatment, a control blood count was performed, eosinophil count was 0.13 x $10^3$/µl (reference range: 0.05–0.5 $10^3$/µl) – the results corresponded to normal values. However, in subsequent tests eosinophil count increased to 0.96 x $10^3$/µl. In relation to the total leukocyte count, an increase in the proportion of eosinophils was observed from 2% to 14.5%. An increase in CRP (C-reactive protein) concentration to 61 mg/l (reference range: <5 mg/L) was also observed, with normal chest X-ray and general urinalysis. On the 16$^{th}$ day of clozapine treatment, an increase in D-dimers to 1,084 ng/ml (reference range: 0–550 ng/ml) was noted, on the following days an increase to a maximum value of 3,378 ng/ml. Enoxaparin was introduced at a dose of 40 mg/0.4 ml s.c., on the following day it increased to 0.6 ml. On the 21$^{st}$ day from the start of treatment, a decision was made to gradually discontinue clozapine. An internist and rheumatologist consultations were ordered, according to which p-ANCA (perinuclear anti-neutrophil cytoplasmic antibody) and c-ANCA (cytoplasmic anti-neutrophil cytoplasmic antibody) were determined, the results were negative. Computed Tomography Angiography (CTA) of the pulmonary arteries was performed, where embolism was excluded, but inflammatory changes in the aortic arch were found: a slightly thickened wall of the thoracic aortic arch and vessels branching off it, indicating vasculitis or non-calcified atherosclerotic changes. Radiologically, further assessment and a control CTA in a few days were recommended, and after consultation, further cardiological diagnostics were waived. Three days after discontinuing clozapine, a control test showed a further increase in eosinophil concentration at the level of 1.68 x $10^3$/µl, however, in subsequent measurements the above-mentioned laboratory parameters normalized. A control CTA of the aortic arch after a month showed a normal image of the aorta and vessels branching off it.

After the patient's somatic condition was balanced, amisulpride treatment was started, which resulted in an improvement of the patient's mental state, full remission of psychotic symptoms, with stabilization of thought flow and psychomotor drive. However, negative symptoms persisted, such as flat emotional reactions and withdrawal. Due to improvement of the patient's state, she was discharged home in a good general condition.

## Discussion

### Clozapine Safety

Many studies and observations distinguish clozapine from other medications as the most effective treatment for treatment-resistant schizophrenia. It is also proven to reduce suicidal tendencies in patients [6]. On the other hand, it is a neuroleptic drug monitored by the Food and Drug Administration (FDA) for safety and the occurrence of serious adverse events during its use due to their frequent occurrence. The two most serious adverse events are agranulocytosis and myocarditis. According to the VigiBase analysis, the leading causes of death in patients treated with clozapine for treatment-resistant schizophrenia are: pneumonia, sudden cardiac arrest, agranulocytosis, myocarditis, constipation, arrhythmias, seizures, and syncope. It should be noted that some of these deaths are to some extent related to risk factors specific to the disease itself [6]. Clozapine is more likely than other antipsychotics to cause sedation and excessive salivation, which increases the risk of aspiration, potentially leading to pneumonia. Furthermore, cytokines released from inflammation slow down the metabolism of clozapine, leading to increased side effects such as drooling, sedation, aspiration, and arrhythmia, creating a self-reinforcing feedback loop. Sudden cardiac arrest is the least specific of the listed causes of death, and a significant number of deaths likely result from causes other than clozapine [7]. Agranulocytosis is one of the most serious adverse effects of clozapine and can lead to death due to severe infections resulting from neutropenia [8]. The predisposition to agranulocytosis may be multifactorial, with risk factors including advanced age, female gender, and genetic predisposition [9]. Studies indicate that the risk of neutropenia is highest in the first year of therapy, particularly during the first 18 weeks, and then gradually decreases. Based on these data, a simplified monitoring regimen based solely on the absolute neutrophil count (ANC) was proposed: weekly monitoring for the first 18 weeks, then monthly until the end of the first year of treatment. After one year without a neutropenic episode, ANC can be monitored every 12 weeks, and after two years of treatment, annually [10]. Said guidelines on white blood cells monitoring are in force also in Poland [11].

In an overall comparison of clozapine with other antipsychotics, it demonstrated superior efficacy in positive symptoms. It also outperformed other first – and second-generation antipsychotics in the short-term (i.e., 3 months) reduction of negative symptoms. However, it was not more effective in treating negative symptoms in the long term. It is not fully understood why the long-term benefits of clozapine are limited to positive symptoms. Cases with more severe psychosis at baseline predicted better outcomes with clozapine [12].

### Eosinophilia

Many cases of asymptomatic eosinophilia have been described as a side effect of clozapine, which resolved upon discontinuation of the drug. In these cases, this complication usually occurred within the first 4 weeks of starting clozapine, did not

cause symptoms, and most often resolved spontaneously [13]. Accurately determining the frequency of transient eosinophilia is very difficult. Studies monitoring the occurrence of adverse events during clozapine treatment have noted a wide range of 0.2–62% of patients [14].

Two distinct forms of eosinophilia occurring during clozapine treatment can be distinguished: transient benign eosinophilia and eosinophilia leading to organ damage. Some studies have found an association between eosinophilia and myocarditis, pancreatitis, colitis, toxic hepatitis, pleural effusion, or interstitial nephritis [6, 13]. In some patients with myocarditis, eosinophilia has been reported to coexist with pericarditis or pericardial effusion. However, it remains uncertain whether eosinophilia is a reliable prognostic factor for myocarditis [2].

## Pro-inflammatory effects of clozapine

Inflammatory reactions occurring during clozapine therapy can take various forms. They can be transient and isolated, such as fever and eosinophilia, or serious, life-threatening, such as myocarditis. They often appear in the first weeks of treatment, during dose escalation [15]. Many studies have demonstrated the pro-inflammatory effects of clozapine and, therefore, suggested monitoring inflammatory markers during treatment initiation. Clozapine's potential to induce systemic inflammatory and immunological reactions has also been indicated. However, given the mixed results of studies and the lack of routine use of markers such as TNFα (Tumor Necrosis Factor α) and other interleukins in clinical practice, it is not possible to develop specific recommendations for monitoring inflammation as a complication of clozapine treatment [13].

Myocarditis is a well-described adverse effect of clozapine. Studies report that its occurrence correlates with the rate of dose escalation. Several clozapine treatment regimens exist; in Europe, a slow dose escalation mechanism is used, while in Australia, rapid dose escalation is practiced. Based on this, it was noted that myocarditis is very rare in Europe, while in Australia it is seven times more common. The same relationship applies to inflammation of other organs, such as the serosa, lungs, liver, pancreas, intestines, or kidneys. The increasing inflammatory reaction may be accompanied by fever, eosinophilia, and/or increased CRP. Monitoring the risk of inflammation and its escalation in individual patients is a method for monitoring CRP levels and, in the case of myocarditis, troponin levels [6]. It is worth noting that myocarditis during clozapine treatment is a phenomenon regularly described and included in the Summary of Product Characteristics, unlike aortitis, which occurred in the described case.

In the literature describing cases of clozapine-induced vasculitis, the most common type is leukocytoclastic vasculitis, also known as hypersensitivity vasculitis. It typically affects small vessels such as venules, arterioles, and capillaries. The clinical presentation of leukocytoclastic vasculitis can vary depending on the location of the lesions. Small cutaneous vessels are often involved, with purpura being the clinical manifestation. In most cases, skin lesions due to leukocytoclastic vasculitis appear 1 to 3 weeks after initiating the drug and may occur after increasing the dose or after rechallenging [3, 16]. Two cases have also been described where skin lesions associated with vasculitis

appeared after two years of clozapine treatment. Discontinuation of the drug resulted in resolution of symptoms [17, 18].

## Limitations

A limitation of this study derives from its nature – a single case report, which prevents generalization of conclusions. Furthermore, due to the short duration of treatment (3 weeks), the patient did not meet the criteria for drug resistance before clozapine was initiated. In clinical practice, during hospital treatment, maintaining an observation period longer than 6 weeks can be difficult. Another significant limitation is the lack of serum clozapine concentration determination at the time of treatment complications, which prevents assessment of the relationship between drug concentration and observed adverse events. For ethical reasons, no attempt was made to reintroduce clozapine, which limits the possibility of unequivocally confirming a causal relationship.

## Recapitulation

Clozapine, whose superior antipsychotic efficacy has been confirmed in numerous studies, is not usually used as a first-line treatment due to its many known, dangerous side effects. Vasculitis is a rare complication of clozapine therapy. In the described case, the unusual location of inflammation of the aortic arch is noteworthy, as is the temporal coincidence of the aortic changes with the presence of eosinophilia in the patient

To date, no cases of aortitis associated with clozapine therapy have been reported in the literature. This case report aims to highlight the potential for unusual complications of treatment with this drug and emphasize the importance of early diagnosis in preventing long-term health consequences.

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