



# Clozapine Associated Troponin Elevation. Not Always Myocarditis!

Rawan Alhau M.D., Yassir Mahgoub, M.D.

Department of Psychiatry and Behavioral Health, Penn State Health Milton S. Hershey Medical Center

## Background

- Clozapine is associated with potentially lethal side effects, such as myocarditis, which often requires immediate discontinuation and discourages future rechallenge.
- Accurate diagnosis of clozapine-associated myocarditis (CAM) is challenging due to nonspecific symptoms and overlapping laboratory findings with other conditions.
- Pneumonia is very frequent among patients receiving clozapine, and distinguishing between myocarditis and pneumonia can be challenging due to the overlap in clinical symptoms, lack of specificity, and the results of most used diagnostic tests.
- Pneumonia in patients with clozapine necessitates temporary dose reduction, without discontinuation, due to the inhibition of cytochrome P450 1A2 (CYP1A2), which impairs clozapine metabolism and increases the risk of toxicity.

## Case Summary

- A 47-year-old female with a history of schizoaffective disorder was admitted for worsening psychosis and initially treated with risperidone 6 mg daily. She subsequently developed catatonia by day 24, prompting risperidone discontinuation and a trial of lorazepam, reaching a dose of 8 mg. However, lorazepam was ineffective and resulted in a worsening of sedation.
- ECT was not considered due to the problems obtaining IV and the concern about poor self-care with a central line.
- Clozapine was initiated and titrated to 50 mg in the morning and 75 mg in the evening, leading to significant improvement in both psychosis and catatonia. However, on day 42, the patient developed fever, fatigue, and tachycardia. EKG revealed nonspecific ST changes; troponin levels increased from 111 to 137 ng/L over 24 hours.
- Chest X-ray suggested right lung pneumonia. Clozapine was suspended, and the patient was treated with azithromycin and cefepime. The cardiology team was consulted, and echocardiography showed no evidence suggesting myocarditis. Following the resolution of pneumonia, clozapine was safely resumed, and the patient remained stable for two years.

## Discussion

- Clozapine-associated myocarditis presentation can range from subclinical to acute heart failure.
- Pneumonia occurs frequently among patients with clozapine and shares overlapping clinical presentation and diagnostic findings.
- Ronaldson et al. proposed using biomarkers such as C-reactive protein and troponin as diagnostic markers without needing histology. While these biomarkers are sensitive, they are not specific, and troponin can be elevated in myocardial infarctions, sepsis, heart failure, pulmonary embolism, and renal failure.
- Cardiac biopsy and MRI can be used for diagnosis. However, they are either invasive or not easily accessible.
- Consulting a cardiologist to interpret clinical presentations and diagnostic tests might be required to diagnose or exclude myocarditis.

Overlapping features	Clozapine-associated myocarditis	Clozapine-associated pneumonia
Clinical symptoms of fever, tachycardia, dizziness, fatigue, shortness of breath	Very common	Very common
Rate	Estimated between 0.06% -3.88%	Estimated between 19%-34%
Elevated Troponins	Sensitivity 34% and specificity 89%	It can be elevated in about 65% of patients
Elevated CRP	Sensitivity 52% and specificity 81%	It can be elevated in about 75% of patients
EKG changes	22% of patients can show a normal EKG	It can occur and usually non-specific
Chest X-ray changes		Can possibly miss pneumonia in 35-50% of cases

## Conclusion

- Myocarditis can overlap with other conditions like pneumonia and share several clinical presentations and results of biomarkers
- The overlap between clozapine-associated myocarditis and pneumonia can lead to over-diagnosis or poor recognition of pneumonia, highlighting the need for caution and a comprehensive understanding of these markers.
- A multidisciplinary approach is essential to ensuring patient safety while maintaining clozapine's therapeutic benefits, emphasizing the value of collaboration in the medical field.

## References

1. Meltzer HY, et al. Clozapine for suicidality: InterSePT. *Arch Gen Psychiatry*. 2003;60:82-91.
2. Kilian JG, et al. Myocarditis with clozapine. *Lancet*. 1999;354:1841-5.
3. Ronaldson KJ, et al. Clozapine-induced myocarditis protocol. *Aust NZ J Psychiatry*. 2011;45:458-65.
4. Putot A, et al. Troponin in pneumonia. *J Clin Med*. 2020;9:3623.
5. De Leon J, et al. Pneumonia in clozapine-treated patients. *Schizophr Bull*. 2020;46:1-3.