Introduction

We report a case of drug-induced liver injury occurring in a patient prescribed clozapine. The patient, a 49-year-old female with a history of paranoid schizophrenia, had been treated with clozapine for over 4 years without significant adverse events. Following the prescription of clozapine, the patient experienced a transient and benign increase in liver enzymes, which resolved after cessation of the drug. The patient's clinical course and biochemical profiles are consistent with existing literature on clozapine-induced hepatitis, supporting the need for LFT monitoring during treatment.

Case Report

**Patient Presentation**

MsA, a 49-year-old female, presented with a history of paranoid schizophrenia treated with clozapine for over 4 years. She had no history of alcohol or illicit drug abuse. There was no history of alcohol or illicit drug abuse. On examination, her mental state was characterized by negative symptoms and behavioral disturbance.

**Clinical Course**

The patient was prescribed clozapine at a dose of 25 mg/day for treatment of her schizophrenia. Over the next 4 weeks, the patient experienced a transient and benign increase in liver enzymes, with values of bilirubin 86 umol/L, ALP 406 U/L, AST 707 U/L, ALT 569 U/L, GGT 173 U/L, and ALT 338 U/L (normal range: AST 4-32, ALT 12-58 U/L). The patient's C-reactive protein (CRP) was 9.5 mg/L, and serum paracetamol levels were measured at less than 0.1 mmol/L. Magnetic resonance imaging (MRI) and abdominal ultrasound were normal, while levels of serum immunoglobulins and autoantibodies [(antinuclear antibodies (ANA), anti-smooth muscle antibodies (AMA))] were within reference ranges. Hepatitis A, B, C, and E serology were negative, as were CMV and EBV serology. Levels of serum immunoglobulins were normal, and hepatitis was ruled out.

**Treatment and Outcome**

Clozapine was discontinued after 40 days, and symptoms resolved within 56 days. The patient's liver enzymes returned to normal, with values of bilirubin 23 umol/L (normal range: 0-17), ALT 86 U/L (normal range: 0-40), AST 12 U/L (normal range: 0-40), GGT 28 U/L (normal range: 0-50), and ALT 14 U/L (normal range: 0-40). The patient's eosinophil count was 2.39×10^9/L, and her C-reactive protein was 0.7 mg/L.

**Discussion and Conclusions**

The case described above is well recognized in the period following clozapine initiation, with concern arising that the agents were both toxic and associated with pleural effusion. Our case is comparable with other reported cases of liver toxicity with associated pleural effusion. In this case study, we present a case of clozapine-induced hepatitis and bilateral pleural effusion, together with hematuria and proteinuria. The patient's mental state improved over this period, with improvement in MsA's mental state noted within six weeks. All evidence of pleural effusion had disappeared from chest x-ray within two days of clozapine cessation.

**Abbreviations**

- ANA: Anti-nuclear antibodies
- AMA: Anti-smooth muscle antibodies
- ALT: Alanine transaminase
- AST: Aspartate transaminase
- ALP: Alkaline phosphatase
- CRP: C-reactive protein
- MRI: Magnetic resonance imaging
- LFT: Liver function tests
- CMV: Cytomegalovirus
- EBV: Epstein-Barr virus

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**Contributions**

The authors contributed equally.

**Key words**

paranoid schizophrenia, clozapine, drug-induced liver injury, pleural effusion.
city in onset of symptoms (4-5 weeks following clozapine initiation), clozapine dose (300-500 mg daily) and duration before normalization of laboratory results (4-6 weeks), although the LFT figures reported in Ms. A's case surpass those described in existing literature. It should be noted that in many of these cases, clinical symptoms were non-specific, as in Ms. A's case, or absent altogether.

The authors fully acknowledge that the patient's pleural effusion may have occurred due to other etiologies, an assertion that may have been supported by investigations declined by Ms. A. We do, however, believe that the close correlation of clinical symptoms with laboratory tests and the rapid resolution of effusion in the absence of antibiotic therapy support an association with hepatotoxicity. It is also noted that clozapine-induced pleural effusion is not unprecedented in the literature. Whilst both the unsuccessful and successful re-challenges with clozapine therapy following adverse reactions are documented in existing reports, re-challenge was considered inappropriate in Ms. A's case, given the extent of LFT derangement and clinical symptoms.

This case supports existing literature in advocating a high index of suspicion, particularly in the 4-5 weeks following clozapine initiation, when considering clinical symptoms and signs commonly associated with other pathologies. Whilst the documented prevalence of transient LFT elevation should urge caution in the premature cessation of clozapine therapy, clinicians should maintain a low threshold for monitoring such parameters following the emergence of innocuous symptoms and signs.

References