

Clozapine-Induced Agranulocytosis Revealing a Hemophagocytic Lymphohistiocytosis: A Case Report

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Submitted: 03 Mar 2018; Accepted: 03 Mar 2018; Published: 25 May 2018

Abstract

Context: The aim of this report is to illustrate a case of hemophagocytic lymphohistiocytosis (HLH) that was revealed in the context of treatment-resistant first-episode psychosis. The incidence of this life-threatening condition is increasing in adults. Prompt diagnosis and treatment are important for an optimal patient outcome.

Case Report: The patient was a 20-year old female who had been admitted to the inpatient unit of a Psychiatric Hospital for disorganized behavior with psychotic features. Clozapine had been introduced as the clinical picture did not evolve despite several trials of antipsychotics. As severe agranulocytosis developed, the patient was transferred to a general hospital. A diagnosis of HLH was suggested. Patient responded well to treatment, and remission of psychotic symptoms was observed.

Conclusion: This case demonstrates the occurrence of HLH in a complicated clinical scenario involving psychotic experiences and the use of clozapine. Further studies are necessary to understand the potential environmental and pathological factors related to HLH.

Keywords: Hemophagocytic lymphohistiocytosis, Psychotic disorders, Clozapine.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome of excessive immune activation usually featuring fever, splenomegaly, cytopenias, elevated ferritin, and/or bone marrow hemophagocytosis. The first reported case was described in 1952 by Farquhar and Claireaux [1]. Typical age of onset is in childhood, with adult-onset occurring less frequently. Primary HLH is caused by genetic factors; there are at least eight different genetic mutations associated with primary HLH, all of which occur on genes related to cytotoxic functions of the immune system [2]. Secondary HLH is generally acquired and refers to cases that develop following severe infections, malignancies, or rheumatologic disorders. Cases of acute HLH episodes can be triggered by infections (immune activation) or immune deficiency (alteration in immune homeostasis). When infectious, pathogens are usually viral, although bacteria, parasites, or fungi are possible [3, 4]. HLH, as a clinical syndrome, presents itself as a severe uncontrolled hyper inflammatory reaction, which can occur in all age groups. We present here a case of a first-episode psychosis patient who developed HLH following the occurrence of clozapine-induced agranulocytosis. Clozapine is an effective atypical antipsychotic reserved for patients with treatment-resistant

schizophrenia. Agranulocytosis is the most concerning side effect with a cumulative risk of 0.8 to 1.5% at one year, and with most cases occurring within the first three months [5].

Case Presentation

Ms. A is a 21-year-old Caucasian woman. Her past medical history includes: recurrent otitis media, developmental delay at age 3, language disorder at age 5 and attention deficit disorder at age 8. She responded to methylphenidate at 36mg/day. Past psychiatric history includes recurrent suicide attempts at age 20. Family history is positive for polysubstance use disorder, schizophrenia and schizoaffective disorder in both parents.

Upon entry into a specialized early intervention service for first-episode psychosis patients, Ms. A had auditory hallucinations and displayed aggressive and disorganized behavior. She presented delusions of persecution, erotomania and control including thought broadcasting and was diagnosed with first-episode psychosis. During her hospitalization, Ms. A did not respond to multiple trials of oral antipsychotics: Aripiprazole, Paliperidone, Fluphenazine, Risperidone, and long-acting antipsychotics which included: Paliperidone, Haloperidol Decanoate, Aripiprazole, and Fluphenazine Decanoate. Clozapine was initiated, and subsequently, her paranoid delusions and anxiety diminished although mild auditory hallucinations persisted.

Ms. A was transferred to a rehabilitation unit on Clozapine 300 mg/day and Haloperidol Decanoate 125 mg IM every 21 days. Within one week, Ms. A developed agranulocytosis, complete blood count showed WBC counts of $0.7 \times 10^3/\text{mL}$ and ANC of $0.2 \times 10^3/\text{mL}$. Clozapine was stopped. Ms. A complained of fatigue and headaches and subsequently developed febrile neutropenia, anemia (Hb of 99), WBC and ANC counts were at $0.8 \times 10^3/\text{mL}$ and $0.0 \times 10^3/\text{mL}$ respectively. Meropenem, Vancomycin, and Filgrastim were initiated, but without improvement. On additional workup, head CT showed calcification of basal ganglia. Ms. A developed a productive cough. Chest CT showed findings suggestive of Aspergillosis. Voriconazole was initiated. There was no evidence of malignancy on the imaging investigations completed. Bone marrow biopsy confirmed the diagnosis of HLH. Genetic markers were consistent with a mutation of the UNC13D gene, one of the four genes linked to HLH. She was successfully treated with high-dose dexamethasone and IV immunoglobulin.

Ms. A remained in remission of positive symptoms despite not being on antipsychotics. She was subsequently maintained on low-dose Lurasidone 60mg/day to prevent relapse, and she remained in complete remission for several months following discharge. She returned to live with her family and was able to go back to work on a part-time basis.

Discussion

HLH is a very rare and fatal condition due to genetic mutations and/or immune activation in the context of infection. It is yet uncertain whether Ms. A became symptomatic of HLH due to underlying genetic factors following immune suppression (clozapine-induced agranulocytosis) or immune activation (aspergillosis). Hence, this case raises a number of speculations. Considering the genetic profile of the case, it is of note that the patient has not developed any symptom of HLH during childhood despite the recurrent episodes of otitis media. Furthermore, the severe psychotic syndrome that resisted both typical and atypical antipsychotic medication, including clozapine; and the complete and sustained remission of psychosis observed after treatment with corticoids raises the possibility that the mutation in the UNC13D gene might have caused a very rare and resistant form of schizophrenia. Under this scenario, it is possible that the treatment with clozapine might have elicited an agranulocytosis, which in turn resulted in severe infection and a HLH reaction. An important aspect of the present case study is that the patient's psychopathological presentation improved dramatically with the HLH treatment. Considering the severity of the initial presentation, this remarkable recovery has shown that favorable outcomes are possible for patients with HLH without any delay in treatment.

Interestingly, the UNC13D gene encodes a protein involved in vesicle maturation and trafficking in neutrophils⁷; which can also raise the possibility that this mutation may increase the risk for agranulocytosis induced by clozapine. Yet, the conjunction of all these unfortunate and rare events might have occurred by chance in this atypical adult case of late-onset Familial Hemophagocytic Lymphohistiocytosis (FHL). Long-term follow-up and genetic investigation in other family members could help differentiate these different hypotheses. Neurologic and psychogenic symptoms among patients presenting with FHL have been reported in the literature. The features of the case presented here add to the broader spectrum of clinical phenotypes observed among adults with HLH. Our case is the first HLH reported with a particular form of psychosis.

Remission of psychosis had coincided with the response to HLH treatment, which suggests that the presenting psychosis may have been of organic origin. With increased awareness about HLH and the call for an international registry of adults with HLH, additional studies are required to promptly address diagnostic and treatment methods [5-9].

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