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CLOZAPINE-ASSOCIATED DRESS-LIKE PHENOMENON ACCOMPANIED BY NON-SPECIFIC SEVERE DIARRHEA

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INTRODUCTION

Superior efficacy of clozapine, the criterion-standard antipsychotic in treatment-resistant schizophrenia, compared to other antipsychotics has already been acclaimed, though it remains underutilized because of the concern of its ample spectrum of side effects which are experienced by up to three-quarters of patients under clozapine treatment (Mouaffak et al. 2009). Common acute and prolonged adverse effects include drowsiness, hypersalivation, obesity; however, the patients taking clozapine required to be closely monitored for rare but life-threatening adverse reactions (Marcelino & Dantas 2013). Clozapine is also associated with gastrointestinal side effects ranging from constipation to fatal paralytic ileus, which are attributed to anticholinergic properties (Cohen 2017, Linsley & Williams 2012). Diarrhea, an unexpected side effect of clozapine, was reported in clozapine-treated patients, albeit linked with colitis preceded by intestinal hypomotility (Linsley & Williams 2012, Rask et al. 2020). Among blood dyscrasias, less attention has been paid to eosinophilia, which typically emerges four weeks after clozapine initiation (Ho & Lin 2017, Rehimini et al. 2021), and is mainly attributed to Drug Reaction with Eosinophilia and Systemic Symp (DRESS) syndrome, a life-threatening, drug-induced condition characterized by multiple systemic complications (de Filippis et al. 2020). Furthermore, clozapine-related eosinophilic tissue infiltration with end-organ damage, including colitis, was mainly focused in relevant literature (Linsley & Williams 2012, Marchel et al. 2017, Rask et al. 2020). However, diarrhea without documented colitis accompanied by eosinophilia in the absence of full-blown DRESS syndrome has never been reported as clozapine's adverse reaction. Here we describe a patient with a rapid eosinophilic response to clozapine accompanied by diarrhea without other signs of colitis, dramatically resolved following the cessation of the drug.

CASE PRESENTATION

Mr. K., a 48-year-old male patient, was diagnosed with delusional disorder a year previously and was being treated for the past four months at our forensic psychiatry inpatient unit with a compulsory treatment order, which is ruled by the court for the first-degree murder of his wife under the influence of infidelity delusions. On admission, the score of the Scale for the Assessment of Positive Symptoms (SAPS) was 10/65, markedly dominated by persistent infidelity delusions. Risperidone p.o. was started at 1 mg/day and increased up to 4 mg/day during the admission; however, in the fourth month, he was still found to preoccupied with the same delusions with a SAPS score of 9/65. Following an increase of oral risperidone to 5 mg/day, acute extrapyramidal symptoms (EPS) emerged including tremor, slurred speech, akathisia, dystonia, which did not respond to oral lorazepam or biperiden administration. His EPS were improved after tapering off and ceasing risperidone. Considering his refractory delusions and sensitivity to developing EPS, clozapine was given at an initial dose of 12.5 mg/day p.o. following a detailed pre-treatment monitoring including hemogram, blood lipids, liver functions, blood glucose, electrocardiogram and vital signs, all of which were within the normal range. Clozapine was titrated up to 100 mg on day 10. On day 11, the patient abruptly presented with severe diarrhea without blood or mucus in faeces and without abdominal pain. The patient reported the absence of any history of inflammatory bowel disease or familial gastrointestinal illness. Other service users or staff in the unit did not suffer from any concomitant gastrointestinal symptoms, which guided us not to consider an inpatient setting gastroenteritis outbreak. Immediate blood screenings included hemogram, liver, thyroid and renal functions, C-reactive protein, procalcitonin and serum electrolytes; all outcomes were normal except increased blood eosinophils ($1.85x10^3/\mu L$), with a normal total white blood cell count ($9.93x10^3/\mu L$). Fever was not detected and other vital signs were normal. Analysis of peripheral blood smear identified an increased number of eosinophils without any morphological changes. The abdominal examination did not reveal any diffuse or localized pain, guarding, tenderness, rigidity, and rebound tenderness, while increased bowel sounds were auscultated. Lymphadenopathy was not detected while serology for viral markers was

negative. Skin lesions including rashes that may indicate an infectious disease or allergic reaction were not observed. The microscopic examination of stool specimen was negative for red and white blood cells, parasites, Charcot–Leyden crystals, and stool fat. Abdominal computerized tomography scanning was non-significant. Intravenous rehydration was provided because he had more than four loose, watery stools per day for two days. Following the exclusion of possible etiology for diarrhea and eosinophilia, those symptoms were considered as an adverse reaction related to clozapine and a score of 8 on the Naranjo Adverse Drug Reactions Probability Scale confirmed a probable relationship between the symptoms and clozapine (Kose et al. 2017). Therefore, clozapine was discontinued and switched to aripiprazole 5mg/day. Three days after the cessation of clozapine, the patient showed marginal improvement of diarrhea and a follow-up hemogram revealed a significant decrease in eosinophil count. A week after, diarrhea fully disappeared, eosinophil counts reached the normal range ($0.3x10^3$ /μL), while he did not develop any EPS under 10 mg/day aripiprazole p.o. treatment.

DISCUSSION

According to the literature, clozapine-associated eosinophilia is transient and benign in nature and not necessarily recommended discontinuation of the drug (Rehimini et al. 2021), however, concomitant persistent diarrhea which led to dehydration was associated with clozapine use, therefore, we decided to cease the drug. Eosinophilia and diarrhea remitted shortly upon discontinuation of clozapine. The mechanism of clozapine-associated eosinophilia has yet to be fully understood. It has been suggested that drug-induced eosinophilia may be explained either with involvement of type I hypersensitivity reaction supported by elevation of immunoglobulin E levels (Roberts et al. 2011), or with T cell-mediated type IV hypersensitivity reaction associated with accumulated drug metabolites, namely DRESS syndrome (Schrijvers et al. 2015). Cardinal features of DRESS invariably captures skin lesions, fever, lymphadenopathy, blood count abnormalities including eosinophilia, atypical lymphocytes and involvement of at least one internal organ; a minimum of three of which are required for the diagnosis of DRESS (Kardaun et al. 2007). In our case, isolated diarrhea was not regarded as an internal organ involvement due to the absence of colitis findings; therefore, a quintessential DRESS syndrome was not considered due to unmet diagnostic criteria despite eosinophilia presented, and DRESS syndrome is expected to resolve within several weeks rather than days (de Filippis et al. 2020), and typically characterized by a longer latency between drug exposure and disease onset (Rask et al. 2020), which is only eleven days in the index patient.

In light of current knowledge, we may consider several mechanisms to explain concurrent eosinophilia and isolated persistent diarrhea. An elegant series of in-vitro studies have consistently reported that IgE-mediated immune reactions induce eosinophilotactic and eosinophil-stimulating factors (Kaplan 2001). Furthermore, specific gastrointestinal disorders characterized by eosinophilia are suggested to be associated with the IgE-mediated allergic sensitization process (Rothenberg 2004). In such a process, an increased count of circulating eosinophilia is driven by allergen- or culprit drug-activated type 2 T-helper lymphocytes, which release large amounts of allergy-regulating cytokines including interleukin-5 that stimulates eosinophil differentiation, activation, and survival (Sanderson 1992). Increased eosinophils have cognate and indirect interactions with multiple immune processes, therefore may contribute to a mild local inflammation leading to subtle alterations of the villous architecture of intestinal mucosa (Hawe & Bolton 2008), which may trigger diarrhea. Moreover, in vivo studies have suggested that eosinophilic gastrointestinal disorders and oral allergen-induced diarrhea have been linked to the involvement of mast cells, which have a critical role in IgE-mediated allergic sensitization (Brandt et al. 2003, Jaffe et al. 1994).

CONCLUSION

Our case adds convincingly to the relevant literature that eosinophilia and gastrointestinal symptoms of clozapine not only restricted to full manifestation of colitis and typical DRESS syndrome but also rare subthreshold manifestations could be encountered. Taken together, our report suggests that clozapine, and maybe its metabolites, are a potential etiologic agent in the development of hypereosinophilia and diarrhea led by unique pathophysiological mechanisms. Although these adverse reactions are likely being uncommon, when eosinophilia emerges with accompanying non-specific symptoms, clinical awareness is warranted to monitor clozapine-treated patients in case of any specific organ pathology.

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Contribution of individual authors:

Yasin Hasan Balcioglu: first and final draft, case follow-up.

Besim Burcu Dudakli: data collection, literature review, first draft.

Simge Seren Kirlioglu: data collection, literature review.

Ahmet Turkcan: supervision.

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