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Letter to the Editor

Recurrence of eosinophilic pneumonia after clozapine treatment

Dear Editor

Clozapine remains the best therapeutic option for refractory schizophrenia despite its association with a wide range of adverse effects. Clozapine is known to cause multiple hematological abnormalities, most serious agranulocytosis, but also notable eosinophilia. Among the unfortunate outcome during clozapine treatment, pneumonia, as well as cardiovascular events, is the common reason for discontinuing (Taylor et al., 2009). Possible mechanisms of clozapine predisposition to infection, particularly aspiration pneumonia, include sialorrhea and impairment of swallowing. However, less is known about whether clozapine has more direct pro-inflammatory effects. Here, we present a case of eosinophilic pneumonia (EP) after initiation of clozapine. Written informed consent was obtained from the patient for publication.

1. Case presentation

A 26-year-old male patient with a treatment-resistant schizophrenia for 6 years and a past history of bronchial asthma was presented to our hospital. Soon after, he received electroconvulsive therapy twelve times, which resulted in ineffectiveness. So, we introduced clozapine treatment (start with 12.5 mg/day, dosing up at 12.5 or 25 mg/day in every 6 to 7 days) with concomitant use of Lithium carbonate 400 mg/day. He showed significant improvement in psychotic symptoms such as auditory hallucinations and suicidal thoughts. When clozapine dose reached 25 mg on day 5, he developed a fever (38.9°C) and mild non-productive cough. Physical examination showed no abnormal findings; laboratory tests revealed leukocytosis (24,900 cells/mm^3; reference, 3300–8600 cells/mm^3), 92% neutrophils (reference, 37%–74%), 0% eosinophils (reference, 0%–6.0%). A high-resolution chest computed tomography (HRCT) showed ground glass opacities (GGO) in the left lower pulmonary lobe (Fig.1-a). Although he showed little sialorrhea, we suspected aspiration pneumonia and administered ampicillin-sodium/sulbactam-sodium for injection (9 g, 3 times daily) on days 6 to 12. Over the next 3 weeks, clozapine was slowly titrated up to 125 mg/day, with eosinophilic count ranging from 7 to 10% of total leukocyte count. However, on day 33, he was febrile (38.7°C), with leukocyte count increased to 18,500 cells/mm^3 (95% neutrophils and 0% eosinophils) and new GGO were detected in the right pulmonary lobes on HRCT, though the lesions detected previously improved (Fig.1-b). Extensive screening tests for various respiratory infection agents were undertaken without any pathogen identified. Therefore, we suspected drug-induced pneumonia and lowered the clozapine dosage to 100 mg/day from day 36. A follow-up HRCT on day 46 showed unremarkable (Fig.1-c), however, a relative eosinophilia persisted at most 9% and finally he got a fever (38.2°C) on day 80. Repeated HRCT revealed another GGO in the right pulmonary lobe (Fig.1-d). Before deciding whether to continue the treatment, he and his family agreed with us to hold clozapine dosage 50 mg/day, because of his failure in other medications in the past and good response to clozapine.

2. Discussion

The temporal relationship between the clozapine treatment and the dramatic changes of radiographic and hematologic findings supported our suspicion that clozapine, due to immunological action, contributed to the recurrence of EP.

Clozapine needs extensive monitoring more than any drug in psychiatry. Eosinophilia, believed to be a non-dose-dependent, has been reported from 0.2 to 62% and mostly occurs during the initial 4 weeks of clozapine-treated patients. It is considered as an allergic reaction with a transient course and spontaneous remission, however, in some cases, it may predict subsequent neutropenia, myocarditis, eosinophilic colitis, pancreatitis, toxic hepatitis, and DRESS syndrome (Hassine et al., 2017; Nielsen et al., 2013).

The diagnosis of EP requires characteristic clinical and radiological features, and the demonstration of alveolar and/or peripheral blood eosinophilia. Our subject showed bilateral, non-segmented pulmonary lesions on HRCT that were transient and migratory. Broncho-alveolar lavage is useful to verify the eosinophil infiltration in the lung, however, we could not perform it because of lacking informed consent.

The pathophysiology of clozapine-induced eosinophilia is unclear. Some investigators have hypothesized that clozapine may stimulate T-lymphocytes, with a subsequent increase in interleukin-5, which promotes the production of eosinophils (Schuepbach et al., 1998). Afterwards, it has been demonstrated that serotonin-2A has an eosinophil chemoattractant profile, regulates cytokine release in airway epithelial cells, and acts as a smooth muscle constrictor in lungs (Boehme et al., 2004). A case of risperidone-induced EP was reported probably due to its strong affinity for serotonin-2A receptor that is equivalent to clozapine (Rizos et al., 2013). In our patient, EP might occurred, through the serotoninergic action of clozapine at low doses. Moreover, recent reports indicated that inflammation or eosinopenia lead to a rise of toxic levels in serum clozapine and its metabolites (Compagni et al., 2019). This is likely to be mediated by cytokine suppression of cytochrome P450 1A2 (CYP1A2) involved in clozapine metabolism (Haack et al., 2013). This enhances further potentials for clozapine toxicity.

In summary, when faced clozapine-induced eosinophilia and/or pneumonia, the risks and benefits must be fully taken into consideration and close monitoring should be done during clozapine treatment.

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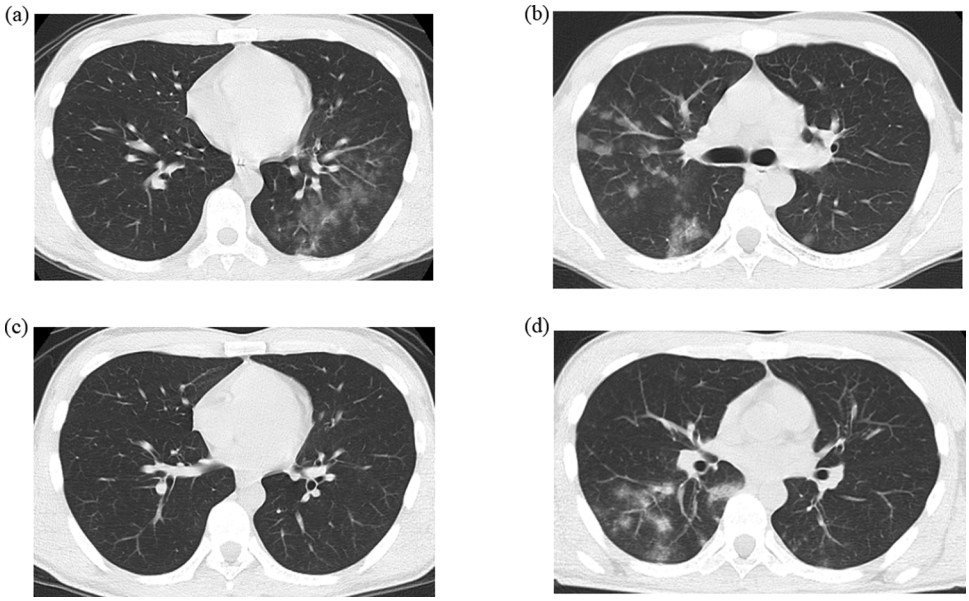

Fig. 1. (a) Axial computed tomography (CT) image showed numerous ground glass opacities (GGO) in the left lower pulmonary lobe on day 6. (b) Axial CT image showed patchy GGO in the right pulmonary lobes on day 33. (c) Axial CT image showed no particular findings in both lungs on day 46. (d) Axial CT image showed another patchy GGO in the right lower pulmonary lobe on day 80.

Disclosure statement

The authors declare no conflicts of interest.

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