CASE REPORT

Monocytopenia in clozapine-induced agranulocytosis: insights into pathophysiology and treatment

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SUMMARY

A 26-year-old man with history of schizophrenia was admitted for neutropaenia. He was started on clozapine 3 months prior to admission. As a result he had weekly monitoring of his blood counts and on day of admission was noted to have an absolute neutrophil count (ANC) of 450 cells/ μ L. He was admitted for clozapine-induced agranulocytosis. Clozapine was held and the patient was started on granulocyte colony-stimulating factor (G-CSF) filgrastim and received two doses without any signs of ANC recovery. On further review, it was noted that the absolute monocyte count (AMC) was also low and tracked with the trend of ANC. We then theorised that the impact of clozapine was on a haematopoietic precursor (colony-forming unit granulocyte-macrophage, CFU-GM) which gives rise to both monocytic and myeloid lineages. Therefore, sargramostim GM-CSF was started. After two doses, the ANC and AMC started trending up and by the third dose, both counts had fully recovered. He was discharged from the hospital and there are no plans to rechallenge with clozapine. Thus, we demonstrate a case of monocytopenia accompanying clozapine-induced agranulocytosis with successful use of GM-CSF. At least in this case, the target of the clozapine injury appears to be the CFU-GM, explaining the rapid and full response to GM-CSF after lack of response to G-CSF.

BACKGROUND

Clozapine is a tricyclic dibenzodiazepine derivative commonly classified as an atypical or a second-generation antipsychotic. It is primarily indicated in patients with schizophrenia or schizoaffective disorder whose symptoms are partially or fully resistant to treatment with other antipsychotic drugs or accompanied by persistent suicidal or self-injurious behaviour.¹ Clozapine has a low propensity to cause extrapyramidal side effects and is therefore indicated in patients who are sensitive to extrapyramidal side effects or in patients who develop tardive dyskinesia.² Recent studies have also shown that clozapine is superior compared with other antipsychotic drugs in terms of efficacy and it has been shown to reduce mortality through reduction in suicide.³

Haematological side effects of clozapine including neutropaenia, eosinophilia and leucocytosis have been described and frequently appear to be transient and harmless.⁴ However, clozapine's unique side effect profile, which includes potentially life-threatening agranulocytosis, has

resulted in numerous considerations in prescribing, monitoring and management of side effects when using this drug. The US Food and Drug Administration requires regular monitoring of neutrophil count through the Risk Evaluation and Mitigation Strategy programme, according to which a minimum absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$ is required when initiating clozapine.⁵ Routine neutrophil monitoring is to be performed weekly during the first 6 months, then every other week for the next 6 months, then every 4 weeks after 1 year for the duration of treatment. For mild neutropaenia (ANC: $1.0\text{--}1.5 \times 10^9/L$), the recommendation is to continue treatment but to monitor ANC three times a week. For moderate neutropaenia (ANC: $0.50\text{--}1.0 \times 10^9/L$), clozapine is to be held and ANC is monitored daily until it is greater than $1.0 \times 10^9/L$ at which point clozapine can be restarted. In severe neutropaenia or agranulocytosis, which is defined as $ANC \leq 0.5 \times 10^9/L$, clozapine should be discontinued.⁵

The cumulative incidence of clozapine-induced neutropaenia, defined as $ANC < 1.5 \times 10^9/L$, is 2.7% during the first year of use. The cumulative incidence of clozapine-induced agranulocytosis (CIA) (ANC count $< 0.5 \times 10^9/L$) is 0.8% at 1 year and 0.91% at 18 months. The highest incidence of agranulocytosis is noted at 6–18 weeks after initiating clozapine. Reports from the clozapine national registry, which included 99 502 patients from 1990 to 1994 showed 382 cases of CIA (0.38%) of which 12 patients died from complications of agranulocytosis.⁶

Despite much research, the exact cause of CIA remains unclear. A direct toxic effect is supported by the fact that serum from patients with CIA has been shown to suppress neutrophil oxidative function and also to suppress haematopoietic precursor development in marrow culture assays.⁷ More recent theories include an immune-mediated response against haptenised neutrophils or a toxic effect of clozapine metabolites, especially the highly reactive nitrenium ion.⁸ An immune-mediated aetiology is suggested by the late onset and an association of Human Leukocyte Antigen (HLA) haplotypes B38, DR4 and DQW3 with CIA in Ashkenazic Jews.⁹

Management of CIA mandates immediate discontinuation of the drug. Administration of antibiotics for febrile neutropaenia is instituted to prevent morbidity and mortality from infection. Colony-stimulating factors (CSFs) are also often used. Both granulocyte CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF) have been used to

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Figure 1 AMCs and ANCs over time. Initial parallel drop of monocyte and neutrophil counts, lack of response to G-CSF and response to GM-CSF. G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

treat CIA. A retrospective review of multiple published studies reveal a consistent reduction in the duration of neutropaenia, and a survival benefit in some but not all studies.¹⁰

We report a case of CIA where we identified severe monocytopenia accompanying neutropaenia. To our knowledge, this has not been previously reported. We then discuss how this finding may offer insight into the pathophysiology of CIA, and further discuss how this insight led to our decision to administer successful salvage GM-CSF therapy when G-CSF had no effect.

CASE PRESENTATION

A 26-year-old white man with history of treatment resistant schizophrenia requiring multiple hospitalisations with partial responses to risperidone, aripiprazole and olanzapine had persistent delusions of being persecuted by the Federal Bureau of Investigation (FBI). He was admitted to psychiatric unit in March 2017 for psychosis and auditory hallucinations. He was dishevelled, making poor eye contact, becoming increasingly disorganised and had stopped talking and showering.

Given the severe and persistent nature of his psychosis and significant impairment of his activities of daily living (ADLs), a trial of clozapine was initiated in May 2017 and titrated to 350mg orally at bedtime. He had a dramatic response on this regimen with improvement in his ADLs, displaying more organised thought process and eventually began to deny hallucinations and paranoid delusions. He was discharged home on 6 July 2017 with an ANC of $2.970 \times 10^9/L$. He continued clozapine 350mg daily, had weekly monitoring of blood counts and last dose of clozapine was on the night of 3 August 2017.

On 4 August 2017, he was admitted to the hospital after he was noted to have an ANC of $0.45 \times 10^9/L$ on his outpatient blood work. He had no symptoms and was afebrile. The diagnosis of CIA was made. Clozapine was discontinued and he was placed on neutropenic precautions. The planned therapeutic approach was to start G-CSF 480 μg subcutaneously daily and to monitor the daily ANC. The patient and family were initially hesitant to initiate G-CSF despite understanding the infection risk associated with prolonged neutropaenia, and opted for a conservative approach with monitoring of daily blood counts and to start

antibiotics if he developed a fever. Severe neutropaenia persisted for 5 days. After multiple discussions with the patient and his family, they agreed to initiate G-CSF. Daily laboratories were drawn at 06:00 hours and G-CSF 480 μg was administered daily at 08:00 hours on 9 August 2017 and 10 August 2017 without any improvement in the ANC (figure 1, table 1).

On further review of the differential count, it was noted that the absolute monocyte count (AMC) was also markedly low at $0.040 \times 10^9/L$ (normal range $0.5\text{--}0.8 \times 10^9/L$) and had trended downward in parallel with the ANC (figure 1, table 1). We then hypothesised that CIA, by whatever mechanism, involved an immature haematopoietic precursor common to the neutrophil and monocyte lineages, called the colony-forming unit-GM (CFU-GM).

Table 1 ANCs and AMCs over time

Date	ANC (K/ μ L)	AMC (K/ μ L)
27 July	2.09	0.25
31 July	1.2	0.11
3 August	0.57	0.04
4 August	0.45	0.04
5 August	0.27	0.04
6 August	0.15	0.04
7 August	0.11	0.03
8 August	0.06	0.02
9 August	0.05	0.02
10 August	0.04	0.03
11-August	0.05	0.04
12 August	0.05	0.11
13 August	0.37	0.41
14 August	3	0.91
15 August	5.61	1.01

Initial parallel drop of monocyte and neutrophil counts, lack of response to G-CSF and response to GM-CSF.

AMC, absolute neutrophil count; ANC, absolute monocyte count; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

The granulocyte lineage consists of the maturation sequence of myeloblast, promyelocyte, metamyelocyte, band neutrophil and mature neutrophil; the monocyte lineage consists of monoblast, promonocyte and mature monocyte. Inhibition of the CFU-GM would thus result in marked reduction in these downstream progenitors, explaining the severe monocytopenia and neutropaenia seen in our patient. GM-CSF, not G-CSF, promotes proliferation of the CFU-GM and its ability to differentiate towards granulocytic and monocyte macrophage lineages.¹¹ On the other hand, the major targets of G-CSF are more committed progenitors such as myeloblasts and promyelocytes.¹² Thus, G-CSF would not accelerate marrow recovery in the absence of a sufficient number of myeloblasts or promyelocytes, the likely rationale for the lack of response in our patient.

Accordingly, GM-CSF 500 µg subcutaneous daily was started at 8:00 hours on 11 August 2017. The next day, the AMC improved from 0.04 to $0.11 \times 10^9/L$ and trended upwards. The ANC remained at 50 cells/µL. On 13 August 2017 (after two doses of GM-CSF), the ANC began recovering as well. As expected, the rise in AMC preceded the rise in ANC, since, as outlined above, monocyte maturation in the marrow has fewer stages than the neutrophil; thus monocytes emerge earlier into the peripheral blood. By 14 August 2017, there was complete recovery of the ANC and AMC.

OUTCOME AND FOLLOW-UP

The patient received his last dose of GM-CSF at 8:00 hours on 15 August 2017 and was discharged from the hospital with an ANC of $5.6 \times 10^9/L$ and AMC of $1.01 \times 10^9/L$. There are no plans to rechallenge with clozapine.

DISCUSSION

We demonstrate a case of CIA with concurrent severe monocytopenia. Severe monocytopenia in this entity has not, to our knowledge, been previously reported.

Monocytopenia might not be easily appreciated because of the narrow subnormal range ($0.0\text{--}0.3 \times 10^9/L$). Monocytopenia, in this case, was an integral part of CIA evidenced by the decline of the monocyte count in parallel with the neutrophil count, implying a common pathogenesis. As discussed above, we hypothesise that clozapine induced severe monocytopenia and neutropaenia by impacting the CFU-GM. The marrow in CIA typically shows complete depletion of granulocyte precursors.^{13 14} We were unable to get consent for a bone marrow biopsy in our patient, however, would expect similar findings with depletion of granulocyte precursors. Of note, depletion of monocytes in particular has not been reported in such cases.¹⁵

G-CSF in the setting of early marrow recovery would not be immediately effective, as it is a later differentiation factor. On the other hand, GM-CSF successfully and rapidly treated our patient's cytopenias, presumably by a direct stimulatory effect on the CFU-GM. Our CFU-GM inhibition hypothesis is supported by the literature. Pisciotto *et al*, using marrow culture experiments, showed that serum from patients with agranulocytosis inhibited the CFU-GM, to the point of complete inhibition.⁷ Sperner-Unterwieser *et al* also found inhibition of the CFU-GM in serum of patient's with schizophrenia on clozapine as opposed to healthy controls, but these were not patients with agranulocytosis and thus the relevance of this finding less clear.¹⁶ Gerson and Meltzer found that the metabolite N-desmethylozapine was toxic to the CFU-GM with an IC_{50} only 3–5 times that of its typical serum concentration.¹⁷

Oren *et al* described a similar case of CIA treated with GM-CSF with recovery of total white blood count (WBC) in 4 days. In their case, ANC recovery lagged behind WBC recovery indicating presence of another cell line, which contributed to the total WBC.¹³ They did not report the monocyte count, however, likely explanation for this finding is monocyte recovery followed by neutrophil recovery as seen in our case. Duration to ANC recovery with GM-CSF has been variable. Hurtado *et al* reported four cases of drug-induced agranulocytosis treated with GM-CSF in which two patients had sudden ANC recovery after 4 days of treatment and the other two achieved ANC recovery after 10 days.¹⁴ Rosein *et al* reported a case of methimazole-induced agranulocytosis with ANC recovery after 5 days of GM-CSF treatment.¹⁸ None of the above mentioned reports included monocyte count and therefore correlation of AMC and ANC recovery in these cases remains unclear. Our patient had normal ANC after 3 days of treatment and ANC recovery was followed by AMC recovery.

Of note, Hummer *et al* described blood counts in patients who are on clozapine therapy and note that monocyte counts are for the most part normal in these patients.⁴ However, these are not patients who have developed agranulocytosis, and thus, this observation has no bearings on the possible role of monocytopenia in CIA.

Going forward, we encourage careful analyses of monocyte counts by those taking care of patients with CIA. If a patient has severe monocytopenia as well as neutropaenia, implying significant CFU-GM injury, GM-CSF would expedite marrow recovery faster than G-CSF, which could be life-saving in the face of severe infection.

Learning points

- Severe monocytopenia accompanied the neutropaenia in our case of clozapine-induced agranulocytosis (CIA) and in fact may be an intrinsic element of CIA.
- Presence of concurrent monocytopenia likely indicates an injury to an immature haematopoietic precursor common to the neutrophil and monocyte lineages, called the colony-forming unit granulocyte-macrophage (CFU-GM).
- GM-colony-stimulating factor (CSF), not G-CSF, promotes proliferation of the CFU-GM and its ability to differentiate towards granulocytic and monocyte macrophage lineages.
- Thus, we recommend preferential use of GM-CSF over G-CSF if both severe neutropaenia and monocytopenia is seen in a case of CIA, especially when rapid marrow recovery is required, such as in the case of severe infection.

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