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CASE REPORT

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Identifying causative medications for agranulocytosis: A case report of an older adult with cerebral infarction

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Key Clinical Message

Most drugs that cause adverse events are difficult to identify in critically ill patients undergoing polypharmacy. We share our experience in identifying the causative drug among four suspect drugs administered during emergency treatment.

Abstract

We present the case of a 93-year-old man who was admitted for the treatment of cerebrovascular events. The patient was initially prescribed dual antiplatelet therapy with aspirin and clopidogrel along with lansoprazole, Hange-koboku-toh, and elobixibat. On day 36 after admission, the patient was found to have developed agranulocytosis. To improve his cerebrovascular prognosis, we first discontinued medications other than the anticoagulant medicines and initiated filgrastim. We discontinued clopidogrel 9 days after the discontinuation of the other medicines considering his low white blood cell count. One day after the discontinuation of clopidogrel, the agranulocytosis was alleviated. Considering the time course, clopidogrel, lansoprazole, Hange-koboku-toh, and elobixibat were suspected as the culprit medicines. This case highlights the considerable challenges encountered in clinical practice when attempting to identify the drugs responsible for agranulocytosis, particularly in patients on intensive medication therapy.

KEYWORDS

agranulocytosis, clopidogrel, elobixibat, Hange-Koboku-Toh, lansoprazole, multiple drug use

1 | INTRODUCTION

Drug-induced agranulocytosis is a severe and potentially life-threatening adverse effect. Predicting its occurrence is challenging for medical professionals owing to its association with individual allergic reactions. Identifying and addressing agranulocytosis is relatively straightforward in patients receiving monotherapy for non-life-threatening conditions. However, identifying the responsible drug is extremely challenging in patients under intensive care who are receiving multiple medications for severe diseases since discontinuing medication is not a straightforward option in these patients. In this report, we present a challenging case in which we identified the causative drug for agranulocytosis in an older adult patient on intensive medication therapy for cerebrovascular infarction.

2 | CASE PRESENTATION

A 93-year-old man with a history of cerebrovascular bleeding (15 years ago) and benign prostatic hyperplasia was admitted to Showa University Koto Toyosu Hospital as an emergency case owing to atherothrombotic cerebral infarction. On admission, dual antiplatelet therapy consisting of 200 mg/day aspirin and 75 mg/day clopidogrel was started along with 15 mg/day lansoprazole and 2.5 mg/day rosuvastatin. On day 10, the patient developed dysarthria and right lower limb weakness, which were determined to be caused by left caudate hemorrhage based on magnetic resonance imaging and computed tomography assessments. Due to cerebral hemorrhage, dual antiplatelet therapy was discontinued for both drugs, and nicardipine was initiated at a dosage of 48 mg/day. On day 15, only clopidogrel was reintroduced at a reduced dosage of 50 mg/day since bleeding did not worsen.

However, on day 17, the patient developed aspiration pneumonia and was subsequently started on intravenous sulbactam/ampicillin at a dosage of 6 g/day for 9 days and Hange-koboku-toh at a dosage of 5 g/day starting from day 21. On day 26, we started elobixibat for constipation. On day 36, the patient's white blood cell (WBC) count decreased to 2270/μL (45% of which were neutrophils). By day 38, the WBC count had further declined to 1150/μL (4% neutrophils). Considering the possibility of drug-induced agranulocytosis, the patient was transferred to an isolated room, and lansoprazole, Hange-koboku-toh, and elobixibat were discontinued. Decreased neutrophil count might lead to infection. Therefore, to increase the number of neutrophils, filgrastim and cefepime were started at dosages of 75 μg/day and 2 g/day, respectively.

Day 39 onwards, filgrastim was administered at a dosage of 150 μg/day. Owing to the lack of improvement in the patient's WBC count after starting filgrastim, clopidogrel was discontinued on day 47. On day 48, a slight increase was observed in the WBC count, reaching 1220/μL (23% neutrophils). On day 51, filgrastim and cefepime were discontinued because the patient's WBC count had returned to a normal level (9850/μL, 72.5% neutrophils). In addition, we started taking 100 mg/day of oral cilostazol instead of clopidogrel. Day 55 onwards, cilostazol was administered at a dosage of 200 mg/day, and the patient was able to manage without developing cerebral hemorrhage or stroke and was discharged from our hospital and admitted to a rehabilitation facility.

3 | DISCUSSION

This case report describes a case in which challenges were encountered in identifying the drug responsible for agranulocytosis in an older adult undergoing intensive medication therapy for cerebrovascular disease.

Clopidogrel, lansoprazole, Hange-koboku-toh, and elobixibat were initially administered based on the interval between the initiation of these drugs and the onset of agranulocytosis. Typically, agranulocytosis manifests within 1 week to 10 days of starting the suspected drugs, primarily owing to allergic reactions. However, if patients have been previously exposed to the culprit drug, symptoms may develop within approximately 1 h to 1 day. In cases involving other mechanisms of agranulocytosis, it takes several weeks for direct toxic effects to occur in the bone marrow hematopoietic stem cells. Considering these mechanisms of action, Hange-koboku-toh and elobixibat were initiated approximately 1–2 weeks before the onset of agranulocytosis, whereas clopidogrel and lansoprazole were initiated approximately 5–6 weeks before. The reported incidences of agranulocytosis for these drugs were as follows: Hange-koboku-toh, unknown; lansoprazole, 0.14%; clopidogrel, 0.04%–0.1%; and elobixibat, unknown. The Naranjo scale was used to give scores to each of the potential causative drugs (clopidogrel, lansoprazole, Hange-koboku-toh, and elobixibat). The scores for each were as follows: Clopidogrel, 4 points; lansoprazole, 4 points; Hange-koboku-toh, 4 points; and elobixibat, 3 points.

Based on the Naranjo scale, clopidogrel, lansoprazole, and Hange-koboku-toh were considered equal suspects to be causing adverse effects.

In this case, we believe that agranulocytosis was believed to result from a complex interplay between (1) bone marrow hematopoietic toxicity and (2) allergic reactions. Several studies have reported clopidogrel-induced agranulocytosis.[1–3] Additionally, stem cell activity is elevated after cerebrovascular events.[4,5] Wu et al.[2] proposed a possible mechanism for clopidogrel-induced agranulocytosis, suggesting a toxic reaction that impairs the growth of myeloid colonies. In our case, the patient's WBC count improved 1 day after discontinuing clopidogrel, and agranulocytosis caused by clopidogrel has been reported to resolve within 3–8 days after discontinuation.[2] Given the timing and frequency of agranulocytosis onset, lansoprazole appears to be implicated in bone marrow hematopoietic toxicity, and clopidogrel is the likely culprit for causing agranulocytosis in this patient (Figure 1).

Kampo medicine has been frequently reported to be associated with agranulocytosis, but the mechanisms by which it induces agranulocytosis remain unclear.[6–12]

However, in our case, the timing between the onset of agranulocytosis and the initiation of Hange-koboku-toh suggests an allergic mechanism.

This case report highlights the complexity involved in determining the culprit drugs for agranulocytosis in older adults with cerebrovascular disease.

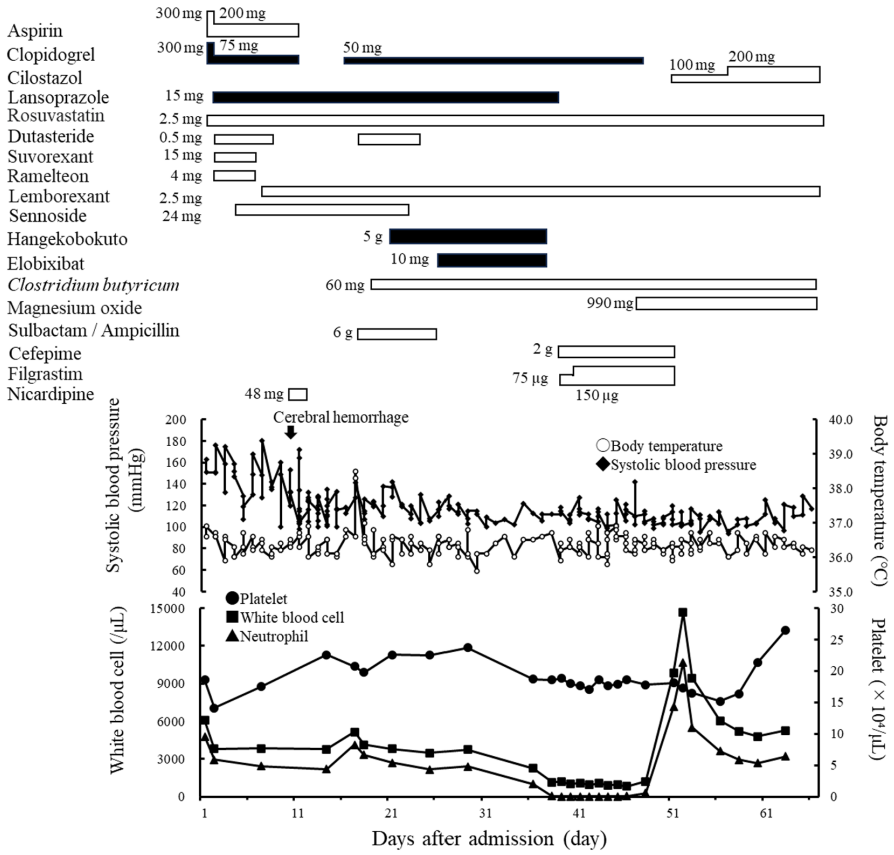

FIGURE 1 Clinical course of the present case.

Patients under intensive care receive multiple medications, making it challenging to discontinue any particular drug. Especially in older adults, multiple drug use is considered a predisposing factor for drug-induced agranulocytosis.[13]

In conclusion, sharing knowledge regarding the complexities surrounding drug-induced agranulocytosis and clinical practices to identify suspected drugs is crucial for educational purposes. Based on our experience, agranulocytosis varies among individuals, and careful consideration of the susceptibility to drugs, time course, and order of medication therapy is essential.

AUTHOR CONTRIBUTIONS

Yuuri Kurokawa: Investigation; writing – original draft. **Ayako Watanabe:** Conceptualization; funding acquisition; investigation; methodology; writing – original draft. **Yuka Kashiwabara:** Supervision. **Saori Fukuda:** Investigation; validation. **Shohei Nomoto:** Investigation; validation. **Ayako Kuriki:** Investigation; supervision; visualization. **Kenji Momo:** Project administration; supervision; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

The Department of Hospital Pharmaceutics, School of Pharmacy, Showa University received funds from Ono for a contract research project, according to a collaborative research agreement. KM received honorarium fees for presentations from AbbVie, Nippon Kayaku, Sawai, and Eisai and travel fees from AbbVie for a conference. YK received an honorarium fee for the presentation at Daiichi Sankyo and Chugai. The Department of Hospital Pharmaceutics received research grants from Nippon Kayaku, Ono, Shionogi, Bayer, Daiichi Sankyo, Eisai, Mochida, and Taiho. The other authors declare no conflicts of interest associated with this work.

DATA AVAILABILITY STATEMENT

All information pertaining to this case is included in this case report.

ETHICS STATEMENT

We obtained approval from the ethics committee to present the case (CR2023016-A).

CONSENT

We obtained written informed consent from the patient's family for the publication of this report.

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