

# A Medication Hiccup: Chlorpromazine-Induced Agranulocytosis in a 72-Year-Old Male

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## ABSTRACT

**Introduction:** Agranulocytosis, a severe decrease or absence of neutrophils, is a side effect of several medications, including chlorpromazine. If not promptly recognized, it can lead to overwhelming infection, sepsis, and death.

**Case Presentation:** A 72-year-old man with adenocarcinoma of the lung status-post recent lobectomy was admitted for postsurgical pain and electrolyte derangement. During his admission, he had intractable hiccups and was started on chlorpromazine 25 mg by mouth 3 times a day. Within a week, he developed pneumonia, type 1 respiratory failure, and a progressive neutropenia. Chlorpromazine-induced agranulocytosis was suspected and chlorpromazine was discontinued; however, the patient expired, with postmortem findings of aspergillus bronchopneumonia as cause of death.

**Discussion:** Chlorpromazine is a well-studied cause of agranulocytosis. This case is novel in its rapid time course of less than 1 week; most cases report the resultant agranulocytosis on the order of weeks rather than days.

**Conclusion:** This case highlights an important need to recognize this medication side effect early so the offending agent may be stopped and the patient properly supported, so as to avoid the severe risk of neutropenic infection, sepsis, and death.

## INTRODUCTION

Chlorpromazine has a long history of use in clinical medicine. Originally developed as an antipsychotic, the first reported cases of white blood cell count (WBC) derangements attributed to chlorpromazine administration date back to the 1950s.<sup>1-3</sup> These abnormalities include leukopenia, agranulocytosis, and neu-

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troponia. Given that neutropenia predisposes to an increased risk of infection, this remains a notable side effect among patients receiving chlorpromazine and other related compounds such as fluphenazine, perazine, and thioridazine.

Chlorpromazine-induced leukopenia remains an infrequently documented adverse effect; Flanagan et al cites the risk of chlorpromazine-induced neutropenia at 0.13%.<sup>2,4</sup> As the use of chlorpromazine increased in the United States early case reports and studies established the association between chlorpromazine and agranulocytosis. Subsequent studies also displayed associated anemia and thrombocytopenia.<sup>2,4,5</sup> These reports noted that each of these adverse effects typically occurred weeks to months following exposure to chlorpromazine.<sup>1</sup> Thus, the risk

of agranulocytosis is highest early on in a patient's therapeutic course, with the majority of patients developing agranulocytosis within the first few weeks of exposure and, rarely, beyond 6 months following administration.<sup>2</sup> Rapid onset of neutropenia is very rare, but a report by Burckart et al described the development of neutropenia in the first 45 hours after exposure in a pediatric patient who ingested a large dose of chlorpromazine (estimated 1.503 g).<sup>6</sup> The following is a case of agranulocytosis occurring within days of exposure to chlorpromazine and the impact on the patients' susceptibility to opportunistic infection.

## CASE REPORT

A 72-year-old man with adenocarcinoma of the lung status-post recent left upper lobe lobectomy presented to the emergency

department on postoperative day (POD) 22 with complaint of left arm swelling, surgical site pain, and swelling in his feet. Vital signs at presentation were as follows: blood pressure 115/77 mmHg, pulse 82/minute, respiratory rate 18/minute, temperature 97.8°F, oxygen saturation 99% on room air. Physical exam revealed scant edema in feet, mild left arm swelling, and a well-healing surgical scar over the left upper chest. He was admitted for surgical consultation, evaluation of postoperative pain, and treatment of hypokalemia of 2.3 mmol/L (reference range: 3.5-4.7) thought secondary to malnutrition and use of furosemide 40 mg daily. Surgical evaluation revealed surgical site in appropriate stages of healing. Other laboratory abnormalities included WBC 12,000/ $\mu$ L (absolute neutrophil count [ANC] 11,300), platelets 61,000/L, and hemoglobin of 12 g/dL. Prior to this admission, his baseline platelet values ranged from 80 k/L to 100 k/L. Additional laboratory evaluation included iron studies consistent with anemia of chronic disease (iron 89  $\mu$ g/dL, total iron binding capacity 193  $\mu$ g/dL, ferritin 479 ng/mL), low copper levels (64  $\mu$ g/dL), low haptoglobin (<8 mg/dL), low reticulocyte index (0.98), and normal lactate dehydrogenase (193 U/L). Glucose-6-phosphate dehydrogenase and fibrinogen were within normal limits. Haptoglobin normalized without intervention. Given apparent malnutrition, folate and multivitamin supplementation were initiated. Hematology/oncology was consulted for evaluation of the worsening thrombocytopenia; microangiopathic hemolytic anemia was ruled out with an absence of schistocytes on peripheral smear, and heparin-induced thrombocytopenia was thought unlikely due to negative platelet factor IV antibody. Given these results, the thrombocytopenia was attributed to acute chronic idiopathic thrombocytopenia purpura (ITP) and malnutrition.

On hospital day 7 (POD 29), the patient endorsed intractable hiccups and was subsequently started on chlorpromazine 25 mg by mouth 3 times a day. The following day, he experienced worsening cough and right-sided chest pain and was noted to have transient sinus tachycardia and mild hypoxia to 89%-91% on room air. Computerized tomography (CT) with pulmonary embolism protocol did not reveal a pulmonary embolus but was significant for nonspecific bilateral perihilar consolidations most prominent in the right upper lobe, concerning for edema or infection. Laboratory values at this time revealed WBC 1.6 k/ $\mu$ L with ANC 1400, hemoglobin 9.8 g/dL, and platelets 29 k/L. On hospital day, 9 his clinical status worsened. His vital signs were as follows: temperature 97.4°F, pulse 123/minute, blood pressure 91/65, respiratory rate 39, oxygen saturation 90% on 10 liters via non-rebreather mask. The chest x-ray obtained at that time was consistent with findings of pneumonia. He was treated with piperazillin-tazobactam and vancomycin and was transferred to the medical intensive care unit (ICU) where he was subsequently intubated in the setting of type 1 respiratory failure.

Given downtrending ANC, chlorpromazine-induced agranu-

**Table.** Selected Patient Laboratory Values by Date Following Admission

Hospital Day	Hemoglobin (g/dL)	WBC k/ $\mu$ L	Platelet Count (k/L)	ANC (/mm <sup>3</sup> )
0	12.5	12.3	61	11,300
1	11.0	9.6	48	
2	10.7	8.4	46	
3	10.8	8.4	45	
4	11.1	8.4	44	
5	10.7	7.4	38	
6	10.0	5.5	36	
7	10.2	4.9	34	
8	10.2	2.9, 2.3	35	
9	9.8	1.6	29	1,400
10	10.2	1.0, 0.8	28, 23, 21	
11	9.7	1.0	53 <sup>a</sup>	700

Abbreviations: WBC, white blood cell count; ANC, absolute neutrophil count.

Patient began chlorpromazine (25 mg by mouth 3 times a day) on hospital day 7 and received filgrastim (5 mcg/kg) on hospital day 11.

<sup>a</sup>Patient received platelet transfusion prior to value.

locytosis was suspected, leading to discontinuation of chlorpromazine on hospital day 10. On hospital day 11, ANC was 700 and peripheral blood smear revealed toxic granulation and Döhle bodies without blasts. Filgrastim (5 mcg/kg) was subsequently administered. On hospital day 12, he developed multiorgan failure and expired. Sputum cultures obtained on medical ICU transfer returned positive for *Aspergillus fumigatus* and final postmortem autopsy findings were significant for aspergillus bronchopneumonia involving right lung lobes and left lower lobe.

## DISCUSSION

Chlorpromazine-induced leukopenia remains an infrequently documented adverse effect that usually has a time course of weeks to months<sup>1,2,4</sup> but has very rarely been reported to occur within days.<sup>6</sup> In this case, the patient developed neutropenia in the setting of chlorpromazine exposure within 4 days. Importantly, he received 25 mg by mouth 3 times a day, which is consistent with dosages previously reported among adult patients who subsequently developed agranulocytosis.<sup>1</sup> Given the patient's documented ANC > 11,000 on admission followed by rapid decline in ANC within days of exposure to chlorpromazine, administration of this medication is the most likely contributing factor leading to neutropenia and death in the setting of aspergillus bronchopneumonia (Table).

Despite close correlation between chlorpromazine administration and development of neutropenia, other mechanisms of neutropenia must be considered. Sepsis may lead to neutropenia through proinflammatory-mediated bone marrow suppression.<sup>7,8</sup> This effect is well-studied in the setting of gram-negative sepsis leading to lipopolysaccharide-mediated bone marrow suppression. Given the patient's symptoms of increased cough, tachycardia, and shortness of breath that prompted further workup

with CT, aspergillus bronchopneumonia was likely present prior to the development of agranulocytosis. While fungal infections are often accompanied by neutropenia, this association is poorly studied in comparison to gram negative infections. Alternatively, vitamin deficiencies, such as folate and copper deficiency, have been associated with the development of anemia, neutropenia, and thrombocytopenia.<sup>9-12</sup> Documented reports of copper deficiency-induced pancytopenia have noted severe deficits, typically as low as <20 µg/dL.<sup>9-11</sup> The patient's copper was just below the normal range at 64 µg/dL and, thus, less likely to be the cause of the observed rapid change in ANC.

The mechanism of chlorpromazine-induced bone marrow suppression is not well understood. Proposed theories include peripheral cytotoxicity, cell division-mediated bone marrow suppression, and immunologic mechanisms.<sup>2,13,14</sup> Importantly, the patient displayed very few signs of infection prior to the administration of chlorpromazine. While neutropenia may mask signs of sepsis, such as fever, the patient's WBC was within normal limits prior to chlorpromazine administration. Of note, he did not receive any other medications with documented adverse effect of agranulocytosis.

While previous evidence for rapid development of agranulocytosis is limited, this case contributes to evidence that agranulocytosis may occur rapidly, within days. Thus, it is important to be aware of medications that may have significant adverse effects, even if they are rare. While the paucity of examples argues against aggressive routine monitoring, consistent consideration of medications as the etiology of patient changes and discussions of these changes with pharmacists should be undertaken. This case further highlights the importance of earlier use of blood count differentials to detect laboratory changes and trends. This enables prompt recognition of agranulocytosis and, with importance placed on medication review, such surveillance will predispose to early discontinuation of causative medications. As mentioned previously, the patient's laboratory workup was notable for mild anemia and thrombocytopenia. While anemia and thrombocytopenia are noted risks of chlorpromazine, the patient displayed mild anemia consistent with anemia of chronic disease and a down-trending platelet count prior to exposure to chlorpromazine. Following consultation with hematology/oncology during his inpatient stay, the patient's thrombocytopenia was attributed to an alternative process, most likely ITP.

## CONCLUSIONS

Agranulocytosis is a dangerous adverse effect with a high risk of morbidity and mortality. As previously noted, this patient developed invasive aspergillosis with rapid deterioration leading to death. While he may have had underlying aspergillosis infection, the agranulocytosis likely allowed for this infection to become overwhelming. Thus, it is important to understand the typical time course for patients who survive past the initial stages of

agranulocytosis, an important period of serious vulnerability to infection.

Previous studies report a typical recovery period from agranulocytosis (time to recovery of neutrophil count) on the order of 1 to 2 weeks.<sup>1,13,14</sup> For this reason, it is imperative to note medications that preclude an increased risk of this dangerous side effect, such as chlorpromazine. This case further contributes to evidence that while chlorpromazine-induced thrombocytopenia, neutropenia, and agranulocytosis typically occur over a period of weeks to months after continued drug exposure, this adverse effect may occur rapidly and with dire consequences. Prompt recognition through monitoring of ANC, immediate discontinuation of offending agent, and treatment are critical to decreasing morbidity and mortality.

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