

# A case of recurrent agranulocytosis due to levamisole

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## ABSTRACT

Agranulocytosis is a rare complication of levamisole. We report a 22-year-old female who developed agranulocytosis due to levamisole. The patient initially presented with salmonellosis and agranulocytosis, and then she recovered with treatment. However, 2 months after discharge, she again presented with tonsillitis and agranulocytosis. This time the family revealed that she had been taking levamisole. Though *Salmonella* infection is a recognized cause of agranulocytosis, any patient presenting with repeated agranulocytosis after an initial recovery should make the clinician suspect another cause, especially drug-induced. A case of *Salmonella* infection where levamisole was an unsuspecting cause of agranulocytosis has not been described in indexed literature. Recurrent agranulocytosis due to repeated exposure to levamisole has also not been described.

**KEY WORDS:** Agranulocytosis, levamisole, salmonellosis

## Introduction

Levamisole is a drug that is rarely used in clinical practice. Agranulocytosis is a rare complication of levamisole.<sup>[1]</sup> Salmonellosis is also known to cause agranulocytosis.<sup>[2]</sup> A 22-year-old female with a history of food intake from outside was diagnosed to have salmonellosis with agranulocytosis. Salmonellosis was suspected to be the cause of agranulocytosis. The patient recovered with treatment. However, 2 months after discharge, she again presented with agranulocytosis; this time with tonsillitis. This time the family revealed that she had been taking levamisole. The information was withheld initially as they considered the drug to be “insignificant.” We report this case because levamisole-induced agranulocytosis is extremely rare and also because of the co-existing and confounding factor of salmonellosis.

## Case Report

A 22-year-old female was admitted with fever and diarrhea. Clinical evaluation was unremarkable except for fever and mild dehydration. Her initial evaluation revealed the presence of marked agranulocytosis (total leukocyte count: 460/cumm; differential leukocyte count: N 0%, L 24%, M 1% - out of 25 cells). The rest of the counts were normal

(hemoglobin [Hb]: 12.6 g/dl, platelets: 204,000/cumm). Stool culture yielded *Salmonella* species. Exact species could not be ascertained as the isolate was nonreacting to the available antisera, including typhi and para typhi. The patient had been taking food from outside. Other cultures were negative. She was started on broad spectrum antibiotics. Antifungals were also initiated empirically in the view of the severe neutropenia. Simultaneously, granulocyte-colony stimulating factor (G-CSF) was also started. There was a steady improvement in her counts, which was normalized by the 5<sup>th</sup> day of initiating G-CSF and the patient was soon discharged thereafter. Among her other investigations, peripheral smear was reported as “marked leukopenia and neutropenia,” other cell lines being normal. Bone marrow study was also done prior to the administration of G-CSF, which came as “hypoplastic.” Subsequent peripheral smear study after the normalization of white blood cell count was normal. The patient had denied intake of any drugs from outside. Other investigations, including B<sub>12</sub> assay, serum uric acid, lactate dehydrogenase levels, HIV, hepatitis B surface antigen, hepatitis C virus, and rheumatoid arthritis (RA) factor, were essentially normal. Only anti-nuclear antibody (ANA) was reported as positive. However, anti-double stranded DNA was in insignificant titers. The patient was followed up as an outpatient for one more month without any incident.

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Two months after discharge, the patient again presented with fever. This time she had tonsillitis. Clinical examination did not reveal anything else. Again, she was found to have marked agranulocytosis (total leukocyte count: 800/cumm; differential leukocyte count: N 1%, L 22%, E 1%, M 1% - out of 25 cells). The rest of the counts were normal (Hb: 14 g/dl, platelets: 220,000/cumm). Peripheral smear and bone marrow study was again repeated; the results were also the same. Cultures including throat swab cultures were also negative. Again, the intake of any drugs from outside was denied. The patient was started on broad spectrum antibiotics and G-CSF. Antifungals were added empirically as before. Clinical response and counts mirrored the earlier admission; by the 5<sup>th</sup> day of initiating G-CSF her counts normalized. Six days into the treatment, the patient's father brought a tablet strip which was prescribed to her by a local GP for some "illness" causing hair fall; the details of which were unclear. The drug was identified as levamisole. She had taken one tablet (50 mg) 15 days prior to her first admission and again 15 days prior to her second admission. This information was not revealed by the family since they considered the drug to be "insignificant." The patient was followed up as an outpatient for another 3 months and continued to be normal.

## Discussion

Levamisole is a potent anti-helminthic agent that was first introduced in 1966.<sup>[3]</sup> This synthetic imidazothiazole derivative has also been used for its immunomodulatory properties: It has been used for the treatment of RA as a disease-modifying anti-rheumatic agent and with 5-fluorouracil for the treatment of Dukes' stage C colon cancer. It has also been used as a steroid-sparing agent in childhood steroid-dependent nephrotic syndrome. However, later it was withdrawn from some countries because of the reports of agranulocytosis. Other toxicities of levamisole include nausea, vomiting, stomatitis, and thrombocytopenia.<sup>[4]</sup> Currently, it is primarily used as an anti-helminthic medication in veterinary medicine.<sup>[5]</sup>

The illegal use of levamisole, however, continues, as an adulterant with cocaine.<sup>[1]</sup> Levamisole increases endogenous opioids and dopamine concentration in the cerebral reward pathway. It is also partially metabolized into an amphetamine-like compound. Illicit users of cocaine are unaware of this deadly cocktail and end up with levamisole toxicity.<sup>[1]</sup>

*Salmonella* is a recognized cause of agranulocytosis.<sup>[2]</sup> Drug-induced agranulocytosis has also been described in *Salmonella* infection.<sup>[6]</sup> However, a case of *Salmonella* infection where levamisole was an unsuspecting cause of agranulocytosis has not been described. Causality assessment with Naranjo adverse drug reaction probability scale,<sup>[7]</sup> suggests that agranulocytosis was probably related to the use of this drug (score 7). Recurrent agranulocytosis due to repeated exposure to levamisole has also not been described in the literature.

Though *Salmonella* infection is a recognized cause of agranulocytosis, any patient presenting with repeated agranulocytosis after an initial recovery should raise the suspicion of an alternative cause, especially drug-induced. In our country where rules regarding prescription drugs are rather lax and this combined with poor knowledge and lack of awareness on the part of the consumer about the medicines they take; the timely and right diagnosis of the cause of an adverse event and its management will remain a challenge for the prescriber.

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## Conflicts of Interest

There are no conflicts of interest.

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