

## LETTER TO EDITOR (VIEWERS CHOICE)

# LEVAMISOLE INDUCED AGRANULOCYTOSIS

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### KEYWORDS

Agranulocytosis, levamisole, Neutropenia

### ARTICLE HISTORY

Received 26 May 2021

Accepted 5 June 2021

A previously healthy 16 year old girl presented with fever for the past 9 days. There were no other symptoms or signs to localize the etiology. She had received intravenous (IV) antibiotics (ceftriaxone and amikacin) for 3 days and was referred to our hospital on day 7 of illness. At admission, her temperature was 100°F and vital parameters were within normal limits. On examination, she had a wart present over the right forearm. Other systems were normal. Investigations revealed anemia, leucopenia with severe neutropenia with elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (table 1). Infectious disease workup in form of Widal test for typhoid, rapid antigen test for malaria, HIV Elisa, Hepatitis B surface antigen (HBsAg) were negative. Cytomegalovirus IgM, Epstein-Barr virus IgM and scrub typhus IgM were also negative and blood culture did not grow any organism. She was empirically started on IV cefaperazone-sulbactam with amikacin in view of severe neutropenia. Anti- nuclear antigen and anti-ds DNA were negative. In view of bicytopenia with unexplained fever, bone marrow biopsy was done which appeared hypoplastic with marked myeloid suppression and maturation arrest of granulopoiesis, with no evidence of malignancy. On further enquiry, it was found that she is on oral levamisole (150 mg once a day) for the cutaneous warts for past 1 month. Provisional diagnosis of levamisole induced agranulocytosis was made, as other etiologies

of neutropenia has been reasonably ruled out. The drug was withheld from day 3 of hospitalization. Her blood counts started showing a rise in trend from day 12 of illness and it was completely normalized by day 14 (Table 1). She became afebrile from the day 15 of illness. On follow up, she remained clinically stable with normal blood counts.

Levamisole is a synthetic imidazothiazole derivative, which was initially introduced as an anthelmintic agent.<sup>1</sup> Later, it found widespread use as an immunomodulating agent for the treatment of various systemic disorders.<sup>1</sup> The adverse effects of levamisole are generally mild and transient and rarely warrant its discontinuation. There are reports of agranulocytosis, multifocal leukoencephalopathy, ataxia, psychosis, fixed drug eruptions, necrotizing vasculitis and retiform purpura with levamisole.<sup>2,3,4</sup> Agranulocytosis (less than 20% neutrophils) due to levamisole occurs most frequently in patients with rheumatic diseases, in women, and in HLA B27 genotypes.<sup>3</sup> The pathogenesis behind neutropenia caused by levamisole is not fully understood. Levamisole is thought to form antigen-antibody complexes that deposit on the surface of neutrophils causing complement fixation, activation and cytolysis. It increases T-cell activation and proliferation and increases neutrophil mobility, adherence, and chemotaxis. Also, levamisole acts as a hapten increasing the formation of antibodies to granulocyte

**Table 1.** Serial blood counts.

Day of Illness	Reference range	Day 7	Day 9	Day 14
Hemoglobin (g/dl)	12.5-16	10	9.5	9.8
White cell count (cells/cumm)	4,000-10,500	1,200	1,180	5,430
Neutrophils (%)	54-62	5	5	55
Platelet (cells/cumm)	1,50,000-4,00,000	2,54,000	3,76,000	4,86,000
Absolute neutrophil count (cells/cumm)		60	60	2,985
ESR (mm at end of 1 hour)		110		20
CRP (mg/dl)		106		negative

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antigens and triggering an immune response resulting in destruction of leukocytes.<sup>5</sup> Another explanation is that it could serve as a substrate for myeloperoxidase to form reactive metabolites that might stimulate autoimmunity.<sup>5</sup> Neutropenia is spontaneously reversible after 5-10 days of cessation of levamisole.<sup>6</sup> Supportive

care during the period of agranulocytosis and having a low threshold in initiating antimicrobials is of high importance and can prevent life-threatening opportunistic infections.

We conclude that it is essential to take a comprehensive drug history for all children who present with severe neutropenia, thereby reducing the need for extensive investigation and health care cost.

#### **Compliance with Ethical Standards**

Funding: None

Conflict of Interest: None

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