Case report

A fatal case of levamisole induced bone marrow failure

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SUMMARY

A 20-year-old college student presented with high grade, intermittent fever for 10 days associated with blood stained loose stools after taking tablet levamisole for 17 days for vitiligo vulgaris. He was febrile, had a toxic appearance and appeared pale. Investigations showed neutropaenia with thrombocytopenia. Blood cultures were sterile and stool cultures did not grow any enteric pathogens. His bone marrow examination was suggestive of an aplastic anaemia. He was administered empirical antibiotics, granulocyte colony stimulating factor and platelet transfusions. However, his fever and blood stained stools persisted. A repeat bone marrow examination after 2 weeks still revealed a hypoplastic marrow. Hence, a diagnosis of a levamisole induced bone marrow failure was made. While being worked up for an allogeneic stem cell transplantation, he developed neutropenic enterocolitis and refractory septic shock with carbapenem resistant *Klebsiella pneumoniae* and succumbed to his illness.

BACKGROUND

Levamisole (Lm) is an antihelminthic agent which was introduced in 1968. It was being used for a variety of diseases for its immunomodulatory properties.^{1–3} However, its use was banned in USA in 1999 after reports of agranulocytosis surfaced.^{3,4} Since then sporadic cases of Lm toxicity in the developed countries have been seen among people using cocaine adulterated with Lm.^{3,5} It is however, frequently used in developing countries like India for dermatological conditions.⁶

CASE PRESENTATION

A 20-year-old college student presented with high grade, intermittent fever for 10 days associated with blood stained loose stools. He had taken oral antibiotics for 5 days after which he had relief of symptoms. However, his symptoms recurred after 5 days. Twenty days prior to the development of his symptoms, he was diagnosed with a skin disorder for which he started taking tablet Lm 150 mg once daily along with tablet methoxsalen 10 mg two times per day for 17 days. He did not have similar illnesses in the past and there was no history of family members requiring recurrent blood transfusions. He did not have any known drug allergies. He was not taking any other regular medications and had never used homeopathic or naturopathic medications.

On examination he was febrile, had a toxic appearance and was pale. No evidence of dehydration was present. He had depigmented patches over his lips, shins and forearms. There was no lymphadenopathy or hepatosplenomegaly. Respiratory and cardiovascular system examination was normal.

INVESTIGATIONS

He had a clinical syndrome of an acute dysenteric illness which was thought to be due to enteric fever, shigellosis, entero-invasive *Escherichia coli* (*E. coli*) gastroenteritis, amoebic dysentery or an acute presentation of inflammatory bowel disease. Investigations showed a bicytopenia with neutropaenia: haemoglobin of 140 g/L, total white cell count of $0.5 \times 10^9/L$ with an absolute neutrophil count of 0 and platelet counts of $81 \times 10^9/L$. Coagulation parameters were normal. His laboratory investigations are summarised in table 1. Three blood cultures were sterile and stool cultures did not show any enteric pathogens.

His serologies for HIV, hepatitis B virus and hepatitis C virus were negative. His Liver and renal function tests were normal. A bone marrow (BM) trephine biopsy (figure 1A) showed a cellular marrow with erythroid prominence, markedly reduced myeloids, mild lymphoplasmacytosis and absent megakaryocytes, with no evidence of granulomas or malignancies. Connective tissue tests for systemic lupus erythematosus (SLE) and vasculitis were normal. Brucella antigen was not detected in his blood. His serum vitamin B₁₂ and folate levels were normal.

DIFFERENTIAL DIAGNOSIS

He had a clinical syndrome of an acute dysenteric illness which was thought to be due to enteric fever, shigellosis, entero-invasive *E. coli* gastroenteritis, amoebic dysentery or an acute presentation of inflammatory bowel disease. However, as his investigations revealed agranulocytosis with thrombocytopenia, haematological malignancies like leukaemias or a lymphoma with BM involvement were considered. Other systemic disorders including infections like disseminated tuberculosis, brucellosis, severe sepsis and HIV infection; inflammatory disorders like sarcoidosis, SLE and other vasculitic disorders; nutritional disorders like vitamin B₁₂ or folate deficiency and Lm drug toxicity were considered.

TREATMENT

In view of neutropenic fever he was started on Intravenous antibiotics - injection meropenem

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Table 1 Relevant laboratory investigations

Test	Result	Normal range
Complete blood count		
White cell count	$0.5 \times 10^9/\text{L}$	$4.4\text{--}12 \times 10^9/\text{L}$
Neutrophils	0%	40%–70%
Lymphocytes	90%	20%–40%
Monocytes	10%	2%–6%
Eosinophils	0%	1%–6%
Basophils	0%	1%–2%
Haemoglobin	140 g/L	120–150 g/L
Platelets	$81 \times 10^9/\text{L}$	$150\text{--}450 \times 10^9/\text{L}$
Prothrombin time (s)	11.2	9.8–11.2
INR	1.02	
APTT (s)	31.6	26.5–35.3
Urea (mg/dL)	12	10–40
Creatinine (mg/dL)	0.49	0.7–1.4
Liver function tests		
Total bilirubin (mg/dL)	1.24	0.5–1.0
Direct bilirubin (mg/dL)	0.78	
Total protein (g/dL)	6.9	6.0–8.5
Albumin (g/dL)	3.7	3.5–5.0
AST (U/L)	26	8–40
ALT (U/L)	27	5–35
Alkaline phosphatase (U/L)	66	40–125
LDH (U/L)	300	225–460
Vitamin B ₁₂ (pg/ml)	390	200–950
Folic acid (ng/ml)	9.7	4.5–45

ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; INR, International normalized ratio; LDH, lactate dehydrogenase.

followed by injection vancomycin and injection amphotericin which were added sequentially in view of persistent febrile episodes. He was also given granulocyte colony stimulating factors and platelet transfusions. However, his fever persisted and there was no improvement in his white cell counts or platelet counts, and his haemoglobin levels also started to drop. He also complained of persistent lower abdominal pain with blood stained stools with no abdominal tenderness on examination. Repeat stool cultures were negative and *Clostridium difficile* toxin was not detected in stools. Blood cultures done repeatedly remained sterile. A CT abdomen (figure 2) was done which showed features of pancolitis with a contained perforation in the right iliac fossa, which was thought to be

Figure 1 (A) Bone marrow trephine biopsy showing cellular marrow with erythroid prominence, markedly reduced myeloids, mild lymphoplasmacytosis and absent megakaryocytes. (B) Repeat bone marrow trephine biopsy done after 2 weeks showing hypocellular marrow with markedly reduced erythroids and myeloids, and occasional megakaryocytes.

Figure 2 Contrast enhanced CT abdomen showing pancolitis with a contained perforation and a thin walled collection in the right iliac fossa (marked with white arrow).

a neutropaenic enterocolitis. He was given bowel rest; intravenous metronidazole to cover *Bacteroides* species and was continued on other antibiotics. As his agranulocytosis was thought to be secondary to Lm toxicity, a repeat BM examination (figure 1B) was performed after 2 weeks which now showed a hypocellular marrow with markedly reduced erythroids and myeloids and occasional megakaryocytes. This was in keeping with an Lm induced BM failure. He was seen by a team from haematology and he was worked up for an allogeneic stem cell transplantation.

OUTCOME AND FOLLOW-UP

He developed refractory septic shock and at this time, his blood cultures grew carbapenem resistant *Klebsiella pneumoniae*. He was started on injection colistin and meropenem, however his condition continued to deteriorate, and he succumbed to his illness.

DISCUSSION

Lm is used as an antihelminthic agent in veterinary medicine and was used in various conditions like rheumatoid arthritis, colon cancer, steroid resistant nephrotic syndrome and in dermatological conditions for its immunomodulatory effects.^{1–3} However, after reports of agranulocytosis had surfaced, its use was banned in USA in 1999.^{3,4} There is now a re-emergence of various side effects of Lm as it is being increasingly used as an adulterant in cocaine.^{3,5} However, in developing low and middle income countries like India, it continues to be used for various purposes and it is used not infrequently by dermatologists.⁶

Lm increases T-cell activation, proliferation and induces a T helper cell 1 cytokine response. It also augments neutrophil mobility, adherence, chemotaxis and enhances the function of macrophages. It can hence induce inflammatory responses at a certain location.^{13,7} Lm also acts as a hapten, increasing the formation of antibodies to various antigens and triggering an immune response involving the opsonization and destruction of leucocytes.^{5,8,9} The predominant adverse effects observed with it are haematological: agranulocytosis, leucopenia^{15,9–12}; immunological: cutaneous vasculopathy, vasculitis and pseudovasculitis^{2,5,7,13,14}; and neurological: multifocal inflammatory leucoencephalopathy.^{5,9,15,16} Other adverse effects that have been described are thrombocytopaenia,^{10,17–19} aplastic anaemia,⁴ pulmonary hypertension,⁴ renal failure,^{15,20,21} acute coronary syndrome,²² headaches and arthralgias.⁵ Among these, agranulocytosis is the most common adverse effect noted, followed by vasculopathy.²³ Agranulocytosis is seen in 2.5%–13% of the patients using Lm as an immunomodulator.¹ Lm has also rarely been reported to cause thrombocytopaenia.^{10,17–19}

The precise mechanism by which Lm induces agranulocytosis has not been elucidated. Lm dependent serum leucoagglutinins have been demonstrated in high titres during periods of neutropaenia in a few studies.^{19 24} Also autoimmune and non-agglutinating granulocytotoxins have been demonstrated in patients with severe neutropaenia receiving Lm.^{1 24} It has also been proposed that Lm may act as a hapten on the leucocyte membrane, provoking an immune response leading to their destruction.⁸ Wolford *et al*²⁵ have proposed that the metabolic activation of Lm to protein reactive metabolites by myeloperoxidase or other oxidative enzymes may be capable of inducing immune mediated blood dyscrasias. The thiourea metabolites of Lm are thought to be the prime suspects in this process.

BM biopsies in these patients have shown hypercellular BM with a relative myeloid hypoplasia, with or without megakaryocyte hyperplasia.^{5 23} Patients with rheumatoid arthritis, women, patients with Human Leucocyte Antigen (HLA) B27 antigen and patients taking high doses of Lm are at an increased risk of developing agranulocytosis. Similar mechanisms have been proposed for thrombocytopenia which is seen with Lm usage.⁹

There are no guidelines for the management of agranulocytosis seen with Lm usage. However, most of the studies report spontaneous neutrophil recovery in 5–14 days.^{5 9}

There are recent studies which have shown that Lm in combination with cyclosporine may be effective in patients with low risk myelodysplastic syndrome²⁶ and moderate aplastic anaemia.²⁷ This may be explained by the various immunomodulatory effects of Lm and its complementary and synergistic effects with cyclosporine.²⁷

Our patient developed BM failure with a strong temporal relationship with Lm use. A thorough search for other aetiologies yielded no results. Hence by exclusion a diagnosis of Lm induced BM failure was made. A thorough literature search showed neither reports of drug interactions between Lm and methoxsalen nor reports of the latter's BM toxicity. The sustained BM failure 2 weeks after stopping Lm probably represents an idiosyncratic reaction to Lm in this patient. It can also be argued that our patient had an underlying constitutional BM disease like Fanconi anaemia and Lm could have led to a 'second hit' culminating in a severe BM failure. Though we wished to perform tests for constitutional aplastic anaemias, like Fanconi anaemia and telomere diseases in the patient, we were unable to do so as he developed neutropaenic enterocolitis with carbapenem resistant *K. pneumoniae* with septicaemia and succumbed to his illness before we could perform them.

Learning points

- ▶ Levamisole is commonly used as an adulterant with cocaine.
- ▶ Levamisole use is not uncommon in low and middle-income countries especially for dermatological conditions.
- ▶ Levamisole should be used cautiously and sparingly due to its serious adverse effects like agranulocytosis and cutaneous vasculopathy.
- ▶ Patients receiving levamisole should be followed up closely for early detection of its various adverse effects.

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AMJ were involved in reviewing existing literature and revising the report. ES was involved in providing the final histopathological diagnosis and revising the report. JTG is a guarantor.

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