Nitrofurantoin-Induced Neutropenia: A Case Report

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ABSTRACT

This case study describes the clinical course of a 60-year-old woman who presented to the general medicine department with a fever, body aches and a headache. Initial examination revealed fever, slightly elevated blood pressure and abnormal hematological parameters suggestive of dengue fever and Urinary Tract Infection (UTI). The patient tested positive for dengue NS1 antigen and exhibited urinary abnormalities consistent with UTI. Treatment comprised a regimen including nitrofurantoin for UTI, among other medications. Despite the intended treatment for UTI, the patient experienced adverse effects, notably neutropenia, as evidenced by a significant decline in neutrophil count. This adverse reaction underscores the importance of vigilant monitoring of patients on nitrofurantoin therapy to detect and manage potential complications promptly. Adjustments to the treatment plan may be necessary to mitigate risks and optimize patient care. This case highlights the critical need for clinicians to remain vigilant for adverse reactions, particularly in patients with comorbid conditions or complex medical histories. Effective management of adverse drug reactions is paramount to ensuring patient safety and therapeutic efficacy.

Keywords: Dengue fever, Urinary Tract Infection (UTI), Nitrofurantoin, Adverse drug reaction, Neutropenia, NS1 antigen, Hematological parameters, Patient safety, Therapeutic efficacy, Blood count monitoring, Treatment adjustment, Clinical management.

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INTRODUCTION

Neutrophils are the most common type of white blood cell in the bloodstream and play a vital role in immune defense, as people with congenital neutrophil deficiencies are prone to life-threatening infections.[1] The body's defense mechanisms against bacterial infections and the acute inflammatory response depend on neutrophils.[2] In healthy individuals, neutrophils in the bloodstream remain in a resting state to avoid the accidental release of their toxic contents, which could harm the body's tissues. Neutrophil activation occurs in 2 distinct phases. First, neutrophils are "primed" and then directed to the site of infection or inflammation, where they respond to specific signals that trigger bacterial killing. Various factors, including bacterial components, cytokines and chemokines such as TNF-α, GM-CSF, IL-8 and IFN-γ, are known to prime resting neutrophils.[3] Neutropenia, characterized by a decrease in the absolute count of neutrophils present in the bloodstream.[4] It raises the risk of infection, especially from microbes that often live on body surfaces.[2] Nitrofurantoin is a distinctive antibiotic characterized by a nitro-substituted furanyl side chain linked to a hydantoin ring. It is effective against both gram-positive and gram-negative bacteria, including *Staphylococci, Streptococci, E. coli, Klebsiella* and *Citrobacter* species. Unlike many other antibiotic classes, nitrofurantoin demonstrates minimal resistance and lacks cross-resistance. It is commonly prescribed for treating uncomplicated urinary tract infections.[5] Nitrofurantoin has been linked to hematological adverse effects, although only a few cases of agranulocytosis have been reported globally.[6]

CASE DESCRIPTION

Mrs. R, a 60-year-old woman, was admitted to the general medicine department with complaints of fever, body aches and headache. She had no prior medical or medication history. Upon physical examination, she was found to be conscious, oriented and febrile. Vitals show slightly elevated blood pressure and elevated body temperature (Table 1) and her hematological report shows decreased RBC, Hb, PCV, RDW, WBC, Neutrophil, platelets and increased lymphocytes, monocytes (Table 2). The urine analysis showed yellow color with slight haziness and tested positive for urine albumin and blood, with increased pus, epithelial cells and red blood cells. Her dengue profile report shows dengue Ns1 antigen positive. The patient was ultimately diagnosed with dengue fever and a urinary tract infection. On the 2nd day of admission, she reported experiencing epigastric pain.

She was treated with the following medications over a period of six days, Infusion normal saline 100 mL/hr, inj. Acetaminophen 1 mg TID, inj. Pantoprazole 40 mg BD, inj. Ondansetron 4 mg BD, T. Nitrofurantoin 100 mg BD, T. Chloroquine phosphate 500 mg OD and Syp. Ranitidine 10 mL TID.

DISCUSSION

Mrs. R, a 60-year-old woman, was diagnosed with dengue fever and a Urinary Tract Infection (UTI) based on her clinical symptoms and laboratory findings. Dengue fever, a mosquito-borne viral illness caused by the dengue virus, can present with a spectrum of clinical symptoms ranging from mild febrile episodes to severe conditions like dengue hemorrhagic fever or dengue shock syndrome. Her hematological profile revealed reductions in Red Blood Cells (RBC), Hemoglobin (Hb), Packed Cell Volume (PCV), Red cell Distribution Width (RDW), White Blood Cells (WBC), neutrophils and platelets, along with an increase in lymphocytes and monocytes-findings typical of the Hematological alterations associated with dengue fever.

CLINICAL PRESENTATION

Fever, Body Pain and Headache: These are typical symptoms of dengue fever and often present in the initial stages of the disease.

Epigastric Pain: This symptom, which emerged on the second day of admission, could be attributed to gastritis, which is common in dengue due to the use of NSAIDs or even due to the disease itself. It could also be related to the accompanying UTI.

Vital Signs

The patient's vitals initially showed elevated blood pressure (150/60) and temperature (100.2ºF), which gradually improved over the course of treatment. Blood pressure trends from day 1 (150/60) to day 6 (110/60) show a decrease, likely due to the resolution of the acute phase of the disease and the rehydration with normal saline. The pulse and respiratory rates remained stable throughout the hospitalization, which suggests that there were no significant cardiovascular or respiratory complications.

Hematological Findings

Thrombocytopenia (Low Platelets): This is a hallmark of dengue fever and is due to the virus's effects on bone marrow suppression and platelet destruction. The patient's platelet count was critically low, reaching a nadir of 0.54×10^9/L on day 5, but started to recover by day 6 (0.96×10^9/L).

Leukopenia (Low WBCs): The WBC count was also low, which is common in dengue due to bone marrow suppression. However, there was a slight improvement by day 6 (3180/µL).

Neutropenia and Lymphocytosis: The decrease in neutrophils and the relative increase in lymphocytes are consistent with a viral infection, such as dengue.

Anemia and Decreased RBCs, Hemoglobin and PCV: While mild, these findings could be due to the viral effect on bone marrow or hemoconcentration commonly seen in dengue fever.

Urinalysis

The presence of yellow, slightly hazy urine, positive albumin and blood with increased pus cells, epithelial cells and RBCs indicate a urinary tract infection. UTIs can occur in patients with dengue due to dehydration and immunosuppression.

Management

The patient was treated for both dengue fever and UTI with a combination of symptomatic and supportive therapies:

Infusion of Normal Saline: Adequate hydration is crucial in dengue management to prevent hemoconcentration and reduce the risk of dengue shock syndrome.

Inj. Acetaminophen: Used to control fever, it is preferred over NSAIDs in dengue to avoid the risk of bleeding complications.

Inj. Pantoprazole and Syp. Ranitidine: These were used to manage the epigastric pain, likely due to gastritis or stress-related mucosal damage.

Inj. Ondansetron: To control nausea, which is a common symptom in dengue.

T. Chloroquine Phosphate: Although chloroquine is primarily an anti-malarial, it may have been prescribed based on a local protocol or as a precautionary measure in an endemic region, though it is not standard for dengue fever.

T. Nitrofurantoin: an antibiotic commonly prescribed for Urinary Tract Infections (UTIs), can lead to a decrease in neutrophil count, a condition known as neutropenia. This occurs because nitrofurantoin generates reactive intermediates during its metabolism, particularly through reduction by bacterial

Table 1: Baseline data.

Parameters	D1	D2	D3	D4	D5	D6
Blood pressure	150/60	120/80	90 /60	80/60	110/80	110/60
Pulse rate	72	85	62	68	80	80
Temperature	100.2	100.4	98.9	97.2	97.6	97.5
Respiratory rate	20	23	21	21	22	20

Table 2: Haematological data.

CBC Parameters	D1	D2	D3	D4	D5	D6
RBC	4.23 ↓	3.72 ↓	4.25 ↓	4.24↓	4.30↓	4.51
Hb	12.6 ↓	11.0 ↓	12.7↓	12.5↓	12.7↓	13.5
PCV	37.7 ↓	32.8↓	37.5 ↓	37.4↓	37.7↓	39.9 ↓
Eosinophils	0.1 ↓	0.5 ↓	0.4↓	0.9↓	1.8	1.9
Basophils	0.6↓	1.1	1.1	1.4	1.1	1.3
Platelets	0.87 ↓	0.78↓	0.81 ↓	0.72↓	0.54↓	0.96 ↓
RDW	11.4↓	11.3 ↓	11.5 ↓	11.3 ↓	11.4 ↓	11.3 ↓
Neutrophil	79	62.3	60.8	38.6↓	31.8↓	27.2 ↓
WBC	3780↓	2850↓	2170↓	2330↓	3200↓	3180↓

Table 3: Naranjo scale (The adverse drug reaction probability scale).[7]

Naranjo Adverse Drug Reaction Probability Scale				
Question	Yes	No	Do Not Know	Score in our case
1. Are their previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	0
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
TOTAL SCORE:				6

enzymes such as flavoproteins. These reactive intermediates can damage essential macromolecules within cells, including DNA, RNA, proteins and cell walls, thereby impairing cell function and survival. Neutrophils, a type of white blood cell vital for combating infections, can be particularly affected. When the body experiences neutropenia, it has a reduced ability to fight off infections and even normally benign bacteria can become pathogenic, posing a significant risk to health.[6]

Definite: ≥9; Probable: 5-8; Possible: 1-4; Doubtful: ≤0.

The causality assessment using the WHO-Naranjo adverse reaction probability scale yielded a score of 6 , shown in Table 3, suggesting a probable adverse reaction in terms of severity.

CONCLUSION

In this case, the patient was prescribed nitrofurantoin for UTI treatment. However, it led to adverse effects, including neutropenia. This highlights the importance of closely monitoring patients on nitrofurantoin therapy for potential adverse reactions, such as neutropenia to ensure effective management of their condition and minimize harm. Adjustments to the treatment plan may be necessary to mitigate these risks and optimize patient care.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

RBC: Red Blood Cells; **Hb:** Hemoglobin; **PCV:** Packed Cell Volume; **RDW:** Red Cell Distribution Width; **WBC:** White Blood Cells; **TNF-α:** Tumor Necrosis Factor Alpha; **GM-CSF:** Granulocyte-Macrophage Colony-Stimulating Factor; **IL-8:** Interleukin-8; **IFN-γ:** Interferon Gamma; **UTI:** Urinary Tract Infection; **NSAIDs:** Non-Steroidal Anti-Inflammatory Drugs; **BD:** Twice Daily; **TID:** Three Times Daily; **OD:** Once Daily; **NS1:** Non-Structural Protein 1; **DNA:** Deoxyribonucleic Acid; **RNA:** Ribonucleic Acid.

REFERENCES

1. Amulic B, Cazalet C, Hayes GL, Metzler KD, Zychlinsky A. Neutrophil function: from mechanisms to disease. Annual review of immunology. 2012;30(1):459-89.

2. Boxer L, Dale DC. Neutropenia: causes and consequences. InSeminars in hematology 2002;39(2):75-81. WB Saunders.

3. Wright HL, Moots RJ, Bucknall RC, Edwards SW. Neutrophil function in inflammation and inflammatory diseases. Rheumatology. 2010;49(9):1618-31.

4. Boxer LA. How to approach neutropenia. Hematology 2010, the American Society of Hematology Education Program Book. 2012;2012(1):174-82.

5. Mahdizade Ari M, Dashtbin S, Ghasemi F, Shahroodian S, Kiani P, Bafandeh E, *et al.* Nitrofurantoin: properties and potential in treatment of urinary tract infection: a narrative review. Frontiers in cellular and infection microbiology. 2023;13:1148603.

6. Lopes V, Ramos J, Dias P, Santos A. Nitrofurantoin-induced agranulocytosis. BMJ Case Reports CP. 2021;14(11):e246788.

7. National Institutes of Health. Adverse Drug Reaction Probability Scale (Naranjo) in Drug Induced Liver Injury. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. 2019.