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Case Report

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Nitrofurantoin-Induced Pulmonary Eosinophilia

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Abstract

Nitrofurantoin is an antibiotic used in the treatment and prevention of urinary tract infections (UTIs). However, one serious and rare adverse effect is nitrofurantoin-induced pulmonary eosinophilia (NIPE) - a disease caused by abnormal accumulation of certain white blood cells and Immunoglobulin E (IgE) in the lungs that results in cough, shortness of breath, chest tightness and tiredness. This case report presents a patient who starts experiencing cough, dyspnea, and fatigue after taking nitrofurantoin for a urinary tract infection. This case underlines the possibility of serious adverse drug reactions of nitrofurantoin-induced pulmonary eosinophilia even with such common dosage and treatment duration. The existing complexity in the patient's history (DM type 2, CKD stage 4, COPD) may have predisposed them to develop NIPE. It highlights the need for close follow-up for adverse effects, especially for patients with multiple comorbidities and those prescribed with polypharmacy. While NIPE is a known adverse effect of nitrofurantoin, this case report adds to the current literature by 1) Presenting a case in a patient with multiple comorbidities; 2) Highlighting how careful medication reconciliation and potential drug interactions should be considered; and 3) Stressing the continued alertness in monitoring for adverse drug reactions, even with commonly used medications. Major clinical findings were high levels of IgE in urine, increased absolute eosinophil count, and a diagnosis of NIPE on clinical scenario, laboratory tests, and timing to nitrofurantoin use. The diagnoses henceforth made was NIPE, DM type 2, CKD stage 4, COPD, and UTI. Measures in such cases included withdrawal of nitrofurantoin, bronchodilators, corticosteroids; management of underlying disorders such as diabetes, CKD; and supportive therapy refer to patient response to treatment (e.g., improvement in respiratory symptoms, resolution of eosinophilia) and the long-term impact of NIPE on the patient's pulmonary function, where available.

Keywords: Nitrofurantoin, Antibiotic, Urinary Tract Infections, Nitrofurantoin Induced, Pulmonary Eosinophilia, Upper Respiratory Tract Infection, Diabetes Mellitus Type 2, Chronic Kidney Disease, Chronic Obstructive Pulmonary Disease, Adverse Effect, Pulmonary Eosinophilia, Drug Induced Lung Disease

Abbreviations

NTF- Nitrofurantoin Antibiotic
UTIS- Urinary Tract Infections
NIPE- Nitrofurantoin Induced Pulmonary Eosinophilia
URIT- Upper Respiratory Tract Infection
DM TYPE 2- Diabetes Mellitus Type 2
CKD- Chronic Kidney Disease
COPD- Chronic Obstructive Pulmonary Disease
ADE- Adverse Effect
PE- Pulmonary Eosinophilia
DILD- Drug Induced Lung Disease

1. Introduction

Pulmonary eosinophilia (PE) is a lung disorder characterized by an abnormal accumulation of eosinophils in the respiratory tract. Eosinophils that are normally involved in the immune response against allergens and parasites in PE, however, the aberrant accumulation of eosinophils within the airways and alveolar spaces triggers an inflammatory cascade leading to tissue damage and dysfunction [1].

PE can be broadly classified into two main categories (1) Primary Eosinophilia -a group of idiopathic disorders where the underlying cause of the increased eosinophils remains unknown, and the pathogenesis is thought to involve an autoimmune process. Ex: Idiopathic Hyper-eosinophilic Syndrome (HES). (2) Secondary Pulmonary Eosinophilia - It is caused by an identifiable underlying condition, such as: drugs, environmental exposures, other clinical conditions [2].

The diagnosis of PE is based upon the combination of clinical presentation, chest imaging findings, peripheral blood eosinophilia, and bronchoalveolar lavage (BAL) with a characteristic eosinophilic infiltrate (usually > 3% of the total differential cell count) [3]. The mainstay of treatment for PE depends on the etiology. For primary eosinophilia corticosteroids are the main drug of choice and in secondary eosinophilia discontinuation of the offending drug and allergen avoidance or specific medications for allergic causes helps in better patient care. This case report describes an old male patient who developed NIPE following treatment with nitrofurantoin [4,5].

While generally well-tolerated, nitrofurantoin can cause a variety of pulmonary complications. One rare but serious adverse effect is nitrofurantoin-induced pulmonary eosinophilia. It is usually given in doses from 25mg, 50mg,100mg IV and 100mg PO on discharge and usually prescribed for not >7 days.

Measures in such cases included withdrawal of nitrofurantoin, bronchodilators, corticosteroids; management of underlying disorders such as diabetes, CKD; and supportive therapy refer to patient response to treatment (e.g., improvement in respiratory symptoms, resolution of eosinophilia) and the prolonged impact of NIPE on the patient's pulmonary function, where available.

2. Pathophysiology of Developing NIPE

Nitrofurantoin is well-absorbed orally, primarily metabolized in the liver, and excreted mainly through the kidneys. Its mechanism of action involves interfering with bacterial cell wall and protein synthesis.

After metabolism of the drug in liver to form reactive metabolites. Whether the parent drug itself or the metabolites acts as haptens (small molecules that binds to proteins in the body) and forms antigenic complexes which triggers an immune response. In susceptible patient, after administration it activates the immune system, particularly T lymphocytes that releases cytokines and chemokines, recruiting inflammatory cells to the lungs. Eosinophils that are involved in allergic reactions are recruited to lungs in response to inflammatory signals where they migrate from bloodstream to lung tissue further releasing various mediators such as chemokines, cytokines causing tissue damage and inflammation.

Adverse effects include gastrointestinal symptoms, rare hematologic abnormalities, pulmonary toxicity, neuropathy, and hepatotoxicity. It's generally safe in pregnancy but excreted in breast milk. Dosage adjustments are needed in renal impairment. Drug interactions and monitoring parameters, like renal function and hematologic parameters, should be considered [6-8].

3. Case Report

3.1 Patient Details

A 60-year-old male patient presented with symptoms of fever, chills, rigors, vomiting, headache and anorexia in the past 5 days. He had a medical record of DM TYPE 2 and recently diagnosed with typhoid 15 days back. His medication history includes Tab. Voglibose (0.2mg) +Metformin (500mg) +Glimepiride (2mg) for DM TYPE 2 and for typhoid he was on 5days treatment with Tab. Azithromycin (250mg) + Omeprazole (20mg) and again for 10 days he was on Tab. Cefuroxime (250mg) + Tab. Omeprazole + Domperidone (40mg/10mg). His social and occupational history shows that he is a farmer who works part-time at a mill and consumes both vegetarian and non-vegetarian foods, with alcohol consumption occurring once every six months.

On admission he was provisionally diagnosed with Dengue with Dengue IgG positive in k/c/o DM TYPE 2 and CKD Grade 4 with significant lab reports attached in **Table 2.1.1**

Investigations	**Days**					**Normal Range**
	Day 1	Day 7	Day 8	Day 10	Day 14	
Blood Urea Nitrogen	162	128	76	-	-	10-45mg/dl
Sr. Creatinine	3.54	2.55	1.64	-	-	0.6-1.4mg/dl
Sr. sodium	131	136	-	-	-	135-145mEq/l
Sr. chlorine	107	111	109	-	-	96-106 mEq/l
Random blood sugar	254	-	-	-	-	80-140mg/dl
C reactive protein	27.58	28.69	-	-	-	<5mg/L
Hemoglobin	11.3	11.1	10.1	10.2	9.4	13.5-17g%
Mean corpuscle volume	71.3	72	73.1	73.6	74.2	80-95 fl
Pack cell volume	37.4	37.1	34.7	34.3	32.1	40-54%
Mean Corpuscular Haemoglobin	21.5	21.5	21.7	21.8	21.7	27-31pg

Mean Corpuscular Haemoglobin Concentration	30.1	29.9	29.7	29.6	29.3	32-36%
Red cell width	18.2	18.1	18.1	18	17.5	10-15%
Abs. neutrophils	7104	-	-	7660	-	2000-7000u/L
Diff. lymphocytes	16	-	19	16	-	20-40%
Diff. neutrophils	74	-	-	71	-	55-70%
Sr. calcium	-	8.35	-	-	-	8.5-11mg/dl
Total RBC	-	-	-	-	4.32	4.6-6.2mili/cm2
Procalcitonin	-	-	-	3.78	4.48	1.08-2.82mEq/L
Abs. eosinophils	-	-	-	-	647	20-500 u/L
IgE antibodies						
(urine culture)	-	-	-	-	1611	</= 165 U/ml

Table 1: Lab Investigations

a. Green color highlights increased count and red color highlights decreased count
b. Other relevant results not reported were within normal limits

The patient was prescribed with dosage regimen mentioned below in **Table 2.1.2**

Dosage Form	Indication	Drug name	Dose	Freq .	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Injection	Antibiotic	Cefaperazone + Sulbactam	1.5 g	BD	+	+	+	+	+	+	-	-	-	-
Injection	Antacid	Rabeprazole	20 mg	BD	+	+	+	+	+	+	-	-	-	-
Injection	Antiemetic	Ondansetron	4 mg	TDS	+	+	+	+	+	+	-	-	-	-
Injection	Antipyretic	Mefenamic acid + Paracetamol	1 g	TDS	+	+	+	+	+	+	-	-	-	-
Injection	Diabetes mellitus 2	Human insulin	8 units each	BD	+	+	+	+	+	+	+	+	+	+
Tablet	Hypertension	Nifedipine	20 mg	BD	+	+	+	+	+	+	+	+	+	+
Tablet	UTI antibiotic	Nitrofurantoin	100 mg	BD	+	+	+	+	+	+	+	+	+	+
Tablet	Urine alkalization	Sodium Bicarbonate	500 mg	TID	+	+	+	+	+	+	+	+	+	+
Tablet	Vitamins	Calcium + Vitamin D3	500 mg	OD	-	+	+	+	+	+	-	-	-	-
Tablet	Abdominal Pain	Drotaverine	40 mg	BD	-	+	+	+	+	+	-	-	-	-
Tablet	Runny nose, sneezing	Levocetirizine + Montelukast	5mg + 10 mg	HS	-	-	-	+	+	+	+	+	+	+

Syrup	Allergic Rhinitis	Chlorpheniramine Maleate + Dextromethorphan Hydrobromide	4mg + 10mg	2 tbsp TDS	-	-	-	+	+	+	+	+	+	+
Tablet	Vitamin D Prophylaxis	Calcitriol	0.25mg	OD	-	-	-	+	+	+	+	+	+	+
Injection	Asthma + COPD	Theophylline + Etophylline	84.7mg+ 25.3 mg	TDS	-	-	-	-	-	-	+	+	+	+
Injection	Prophylaxis	Magnesium Sulphate	1g	OD	-	-	-	-	-	-	+	+	+	+
Capsules	GERD	Domperidone and Pantoprazole	30mg + 40mg	OD	-	-	-	-	-	-	+	+	+	+
Nebulizer	wheezing and shortness of breath	Budesonide	8 hourly	TDS	-	-	-	-	-	-	+	+	+	+

Table 2: Treatment Chart

USG abdomen showed fatty liver grade 1 with early changes of renal parenchymal tissue. His eGFR calculated was 29ml/min/1.73m2 indicating CKD stage 4 (severe kidney damage). Urinalysis showed presence of bacteria, pus cells, RBCs and epithelial cells confirming urinary tract infection for which he was treated with Tab. Nitrofurantoin 100mg B.D for 10 days. His final diagnosis upon discharge from the hospital following a 15-day stay was iron deficiency anaemia, diabetic nephropathy, non-alcoholic fatty liver grade 1, COPD, UTI, CKD stage 2, and asthma in k/c/o DM type 2.

4. Clinical Evidence

PFE due to nitrofurantoin is a very rare occurrence. NTF-induced pulmonary toxicity typically appears as fever, cough, pleuritis, dyspnea, and diffuse parenchymal opacities, with isolated pleural effusion being unusual. On 10th day of the treatment with nitrofurantoin, the patient experienced symptoms of cough, cold and chest tightness confirming ADE of NTF through lab investigation showing increased IgE antibodies in urine and increased Abs. eosinophil counts. Current Infectious Disease Society of America guidelines recommend nitrofurantoin monohydrate/macrocrystals as a first-line antibiotic for uncomplicated urinary tract infections and the prescribed days for nitrofurantoin are only 7 days or a week, although the patient was prescribed nitrofurantoin 100mg B.D. for more than 7 days i.e.10 days.

5. Discussion

The patient's clinical symptoms were suggestive for drug related event. As the laboratory reports and objective evidence showcased only after treatment with Nitrofurantoin more than prescribed days there was a suspected adverse drug reaction [9]. His symptoms improved upon with appropriate treatment for eosinophilic pneumonia. Nitrofurantoin-induced pulmonary eosinophilia, though uncommon, can mimic other respiratory illnesses. Elevated blood eosinophil levels supported the diagnosis of NIPE.

The ADR was neither predictable nor preventable due to its rarity. No De-challenge nor Re-challenge was performed WHO- Causality Assessment Scale gave probable causality term as the event had a reasonable laboratory investigations abnormality and time relationship with drug intake and was unlikely attributed to other drugs or disease. The Naranjo Scale (Table 3.1) gave a score of 6 i.e. Probable.

Questions	Yes	No	Do not know	Score
Are there previous conclusive reports of this reaction?	+1	0	0	+1
Did the adverse event appear after the drug was given?	+2	-1	0	+2
Did the adverse reaction improve when the drug was stopped or a specific antagonist was given?	+1	0	0	0
Did the adverse reaction reappear upon re-administration of the drug?	+2	-1	0	0
Were there alternative causes (other than the drug) that could have caused the reaction?	-1	+2	0	+2
Did the reaction reappear when a placebo was given?	-1	+1	0	0
Was the drug detected in the blood (or other fluids) at concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
Total Score				6

Table 3: 1 Naranjo Scale

This case presentation aligns with previously reported cases with similar symptoms like cough, dyspnea, and chest infiltrates are consistent. While nitrofurantoin is widely used, some reports emphasize the rarity of pulmonary eosinophilia, making this case and awareness of this potential complication even more important [10-18].

5. Conclusion

Pinning down the exact prevalence of nitrofurantoin-induced pulmonary eosinophilia (NIPE) is a formidable task NIPE as a side effect itself makes accumulating large-scale data challenging. Additionally, NIPE symptoms can be mistaken for other lung conditions, potentially leading to underdiagnosis and inaccurate prevalence figures. PE is a rare but serious complication associated with nitrofurantoin. Studies suggest that older age, pre-existing lung issues, and prolonged nitrofurantoin use might increase the risk of NIPE, offering clues for further investigation. This report discusses a case of interstitial lung illness linked to the usage of Nitrofurantoin and the potential pathways of lung harm. Clinicians should be mindful of the plausible side effects of Nitrofurantoin when administering it to patients over time. DIILDs may be caused by a variety of medicines and substances. Medication reconciliation and medication history have a crucial role in determining the main cause of interstitial lung disease. The first step in managing DIILD is to identify the causative medicine and discontinue it promptly. Patients on Nitrofurantoin should be regularly examined for potential lung damage.

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