International Journal of Clinical and Experimental Medicine Research, 2022, 6(2), 187-196
https: //www.hillpublisher.com/journals/ijcemr/
ISSN Online: 2575-7970
ISSN Print: 2575-7989

Nitofurantoin Induced Dress—Rarely Seen and MIMICKS HfPEF

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How to cite this paper: Parveen Malhotra, Naveen Malhotra, Vani Malhotra, Rakhee Malhotra, Naman Malhotra, Navya Malhotra, Pranav Malhotra. (2022) Nitofurantoin Induced Dress—Rarely Seen and MIMICKS HfPEF. *International Journal of Clinical and Experimental Medicine Research*, 6(2), 187-196.
DOI: 10.26855/ijcemr.2022.04.012

Received: February 27, 2022
Accepted: March 24, 2022
Published: April 22, 2022

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Abstract

Case report: A seventy five year old female was on regular treatment for hypertension and hypothyroidism for last 30 years. She was treated over a period of six months for recurrent urinary tract infection (U.T.I). During this period, she had multiple episodes of pulmonary edema which were diagnosed to be due to heart failure with preserved ejection fraction (HfPEF) and was thoroughly investigated but for no relief. Ultimately, diagnosis of non cardiogenic pulmonary edema due to Nitrofurantoin toxicity was proved and on retrospective and minute analysis, all the varied clinical manifestations and complications like recurrent fever, hyponatremia, lymphadenopathy, alopecia which were thought to be disease related, turned out to be as side effects of Nitrofurantoin therapy. **Conclusion:** One should first rule out common diagnosis and then try to look for other uncommon differential diagnosis, on basis of unexplained biochemical or radiological investigation. It is duty and responsibility of treating doctors to be fully aware of all the side effects, even rare, of medicines being prescribed by them.

Keywords

Nitrofurantoin, Urinary Tract Infection, Non cardiogenic Pulmonary Edema, Rash, Lymphadenopathy, Hyponatremia, Alopecia, Heart Failure with Preserved ejection Fraction

1. Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug-induced hypersensitivity syndrome (DIHS), and DIDMOHS (drug-induced delayed multi organ hypersensitivity syndrome) [1], is a delayed potentially fatal multi-organ systemic idiosyncratic drug reaction [2, 3]. The prevalence of DHS ranges between 1 in 1,000 and 1 in 10,000 exposures. It occurs more frequently in females [2-4]. Symptoms typically develop after 2 to 6 weeks of medication use. Re-exposure to the same drug may cause symptoms even within twenty four hours. The symptoms may last for weeks or even months after the medication discontinuation [5]. DRESS induces by Th2-lymphocytes and CD8+ cells. Th2 cells probably induce type IVb hypersensitivity response affecting the skin, while CD8+ T cells cause damage to internal organs [6]. The toxic metabolite acts as a hapten, initiating an immune response. Nitrofurantoin is very commonly used for treating Urinary tract infection (UTI), especially related to lower urinary tract and has been reported to cause various side effects including DRESS. Urinary tract infections (UTI) often caused by bacteria, are resistant to antibiotics and are major health issue, especially in adults. The major worry regarding urinary tract infections is partial or improper treatment leading to renal involvement. UTI is one

of the major experienced problems in urological clinics [7]. Escherichia coli (E.Coli) are the predominant cause of UTI, followed by Staphylococcus saprophyticus, Kleibsiella species, Enterobacter, Proteus and Enterococcus species [8]. Nitrofurantoin has bactericidal action and is frequently used to treat uncomplicated urinary tract infection. It is a synthetic chemotherapeutic agent belonging to nitro furan family and was first discovered in 1940s. It was first initiated into health care practice in 1952 [9]. It is reduced by the action of bacterial flavoproteins to reactive intermediate compounds that non-specifically inactivate ribosomal proteins resulting in inhibition of protein synthesis. It exhibits high quality success against most bacteria anticipated in urinary tract infection. Nitrofurantoin has been recommended for prophylaxis in the treatment of reinfection in case of recurrent uncomplicated genitourinary tract infections [10] and is one of the treatment options for urinary tract infection due to extended spectrum beta lactamase producing Escherichia coli. It is normally well tolerated and common side effects include nausea and headache. The uncommon side effects are aplastic anemia, peripheral neuropathy, liver toxicity, pulmonary toxicity, and Stevens - Johnson syndrome [11]. Nitrofurantoin may generate many pulmonary signs and symptoms like chronic or acute interstitial pneumonia, pulmonary hemorrhage, bronchospasm, anaphylaxis and pleural effusion [12].

2. Case Report

A seventy five year old female was on regular treatment for hypertension and hypothyroidism for last 30 years. Her hypertension was under control on daily once dose of Amlodipine & Atenolol combination (5 mg +50 mg) and Eltroxin 75 microgram. She underwent open reduction for fracture in right tibia and fibula with rod placement nine years back and Bilateral Total Knee replacement seven years back. After some time, she developed bilateral pedal edema but more on right side which was attributed to post surgery and hypothyroidism. The need of antihypertensive gradually increased over last one year, to Telmesartan + Hydrochlorothiazide combination (40 + 12.5 mg) twice daily and Amlodipine & Atenolol combination (2.5 mg +25 mg) daily once. She intermittently gave history of dyspnea on exertion. She was on tablet gabapentin 300 mg daily once and sulfaslalazine 500 mg twice daily, Tramadol & Crocin combination and Pantaprazole daily once for last one year for suspected Right Hip arthritis. She had COVID-19 infection in October, 2020 and remained in home isolation, never required oxygen therapy, was treated with oral antiviral and low dose steroids. She became COVID negative within two weeks and later on received two doses of COVID vaccine in April & May, 2021. She had symptoms of gastro esophageal reflux disease since January, 2021 which leads to decreased total calorie intake of 1,000 Kilo calories/day. She developed enteric fever in March, 2021 which remained for one week and was symptomatically treated with oral antibiotics.

On 3rd July, 2021, she developed high grade fever with rigor & chills with increased need of antihypertensive. Initially, oral ant malarial were given but for no relief. She had leucocytosis with predominant neutrophilia, raised erythrocyte sedimentation rate (ESR), increased thyroid stimulating hormone (TSH) levels, urine complete examination, blood culture, Dengue serology & viral screen were negative but widal test was positive. Hence oral antibiotics were started but high grade fever persisted, requiring regular antipyretics and use of intravenous broad-spectrum antibiotics in form of Ceftriaxone and Metrogyl for one week. The neutrophilic leucocytosis and ESR showed upward trend for ten days and later on decline was noticed. After total duration of seventeen days, leukocyte count normalized but ESR remained on higher side. At this stage, for ruling out any other source of infection, computed tomography scan (CT) chest and abdomen was done which revealed sub centimeter sized mediastinal, paraaortic, aortacaval, bilateral iliac group lymph nodes. In lungs, there was mild intralobular septal thickening with interstitial fibrotic strands and early reticular pattern in bilateral basal segments in sub pleural location-likely minimal post COVID fibrosis (see Figure 3). The CT scan bilateral knee joint and right lower limb done for ruling out any infection at implant/rod site was found to be normal. The urine culture grew E.Coli and as per culture & sensitivity, tablet Nitrofurantoin was started. One day suddenly she developed transient features of proximal myopathy & confusion and was diagnosed to be having hyponatremia along with features of congestive heart failure (CHF), in form of increased pedal edema and increased dyspnea on exertion. The hyponatremia was thought to be secondary to CHF, both of them were gradually corrected over period of one week and fever also subsided.

After few days, she again started having fever with rigor & Chills and investigations again revealed leucocytosis with predominant neutrophilia, widal test was negative, urine complete examination showed pus cells, urine culture grew E.Coli species with intermediate sensitivity to Nitrofurantoin and ultrasound abdomen was suggestive of renal concretions. Hence she was again treated with Nitrofurantoin at night time. She developed unexplained tacypnoea with respiratory rate of 24-30/minute and tachycardia with pulse rate of 95-105/minute, which used to rise even higher during episode of fever with rigor and chills. She was persistently having nausea which was taken as in-

creased severity of previous GERD, in view of antibiotics and UTI related.

On night of 25th July, 2021, after going to toilet, she suddenly developed difficulty in breathing associated with cough, wheeze, tachycardia (Pulse rate-120/mt), tacypnoea (Respiratory rate-24/mt), hypertensive readings (176/100 mm of Hg), hypoxia (oxygen saturation of 90% on room air), followed after half an hour by high grade fever (102 degrees Fahrenheit), back pain and examination revealed features of pulmonary edema, i.e., bilateral basal crept. She was given single shot of intravenous diuretic & steroid, along with antipyretic and settled within one hour and slept. Next day, her leukocyte count, serum electrolytes, urine complete were normal but D-dimer, C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) was significantly raised and Hemoglobin (Hb) was on lower side which was thought to due to Urosepsis. The Cardiology consultation was taken, her Electrocardiogram was normal, Echocardiography revealed Mid Mitral (MR) ,Tricuspid regurgitation (TR), Aortic Regurgitation (AR), Grade-1 Diastolic dysfunction with mild left ventricular hypertrophy which was thought to be age & hypertension related but ejection fraction was normal i.e. 55% (see Figure 2). The colour Doppler for bilateral lower limbs and abdomen done for ruling out any possibility of pulmonary thromboembolism revealed bilateral lower limbs subcutaneous edema, bilateral inguinal lymphadenopathy but was negative for deep vein or inferior venacava thrombosis (see Figure 1). At this point of time, she was diagnosed to be having heart failure with preserved ejection fraction (HfPEF) which was being precipitated by Urosepsis in background of old age obese women with long standing hypertension. Hence, regular oral diuretics, beta blocker, angiotensin receptor blockers (ARB) and oral antibiotics were started. After a gap of three days, there was jump in neutrophilic leucocytosis, with raised serum potassium levels (>6), decreased serum calcium levels (6.40), high ESR (76) and hemoglobin showed downward trend (8.9 gm/dl) which was again thought to be sepsis related. Her D-dimer repeated within gap of twelve hours fell to half, i.e. from 8986 I.U. to 4904 I.U but were still high. The TSH level got further deranged and increased to 13.2 for which dose of Eltroxin was increased to 87.5 microgram per day. She was treated with high ceiling loop diuretics and potassium deficient diet. Surprisingly, serum potassium level became normal within forty eight hours. Oral calcium and iron tablets, along with injectable iron were started for low serum calcium and hemoglobin levels. The dose of antihypertensive decreased over time and majority of time only oral diuretics were required for controlling blood pressure. It was thought to be due to decrease in sympathetic drive. The patient intermittently became febrile over next two weeks, despite being on oral cephalosporin. The leukocyte count touched normal after two weeks and urine culture also became sterile.

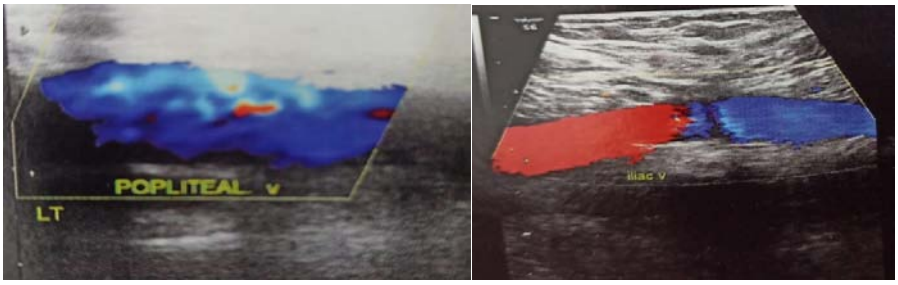

Figure 1. **Showing Normal Popliteal and Iliac Veins on Color Doppler.**

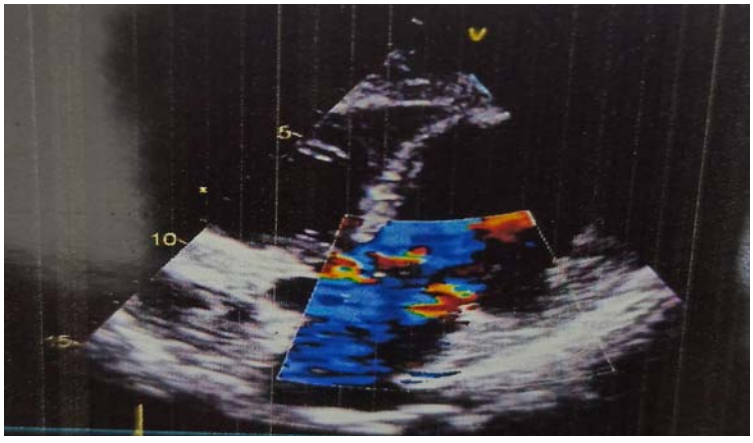

Figure 2. Echocardiography Showing Mild MR,TR and AR.

After a gap of one week, again in midnight, next episode of left heart failure occurred with same symptoms but with more severity, thus for maintaining oxygen saturation, supplemental oxygen was needed for 3 hours. The treatment protocol was same with use of single shot of steroid, intravenous diuretics and broad spectrum antibiotics but need of intravenous diuretics this time remained for five days. Her blood picture revealed same neutrophilia predominant leucocytosis, raised ESR but for the first time there was significant Eosinophilia. There was transient rise in levels of serum potassium, serum creatinine, blood urea level with hyponatremia. The serum potassium and blood urea returned to normal within two days but serum sodium levels took next two weeks for normalizing. The Anti nuclear antibody (ANA) level and Quantiferon test for tuberculosis and Polymerase chain reaction (PCR) test of urine for tuberculosis were normal. The complete urinary examination and widal test were normal but TSH level was still on higher side. The urine culture again showed E.Coli with intermediate sensitivity to Fosfomycin and patient was treated with the same. The neutrophilic predominant leucocytosis and raised ESR persisted for next two weeks but Eosinophilia settled within one week. The urine culture twice in these two weeks, now revealed Kleibsiella and was treated for five days with intravenous antibiotic meropenem, as per culture and sensitivity report. Later on she became afebrile and again was put on increased dose of oral diuretics, oral antibiotics and antihypertensive as per need.

Later on, patient used to get intermittent fever with occasional pus cells seen in urine but urine culture remained sterile. The leukocyte count used to marginally increase but Eosinophilia reappeared and serum ferritin level were markedly raised (>1,000) which were attributed to injectable iron therapy which was given to improve hemoglobin. At this stage, for ruling out any other source of fever like occult abscess or malignancy, CT scan chest and abdomen were repeated which revealed same previous findings. The Angiotensin converting enzyme (ACE) levels done for ruling out sarcoidosis were normal. The pulmonary angiography done to rule out remote chance of pulmonary thromboembolism was found to be normal.

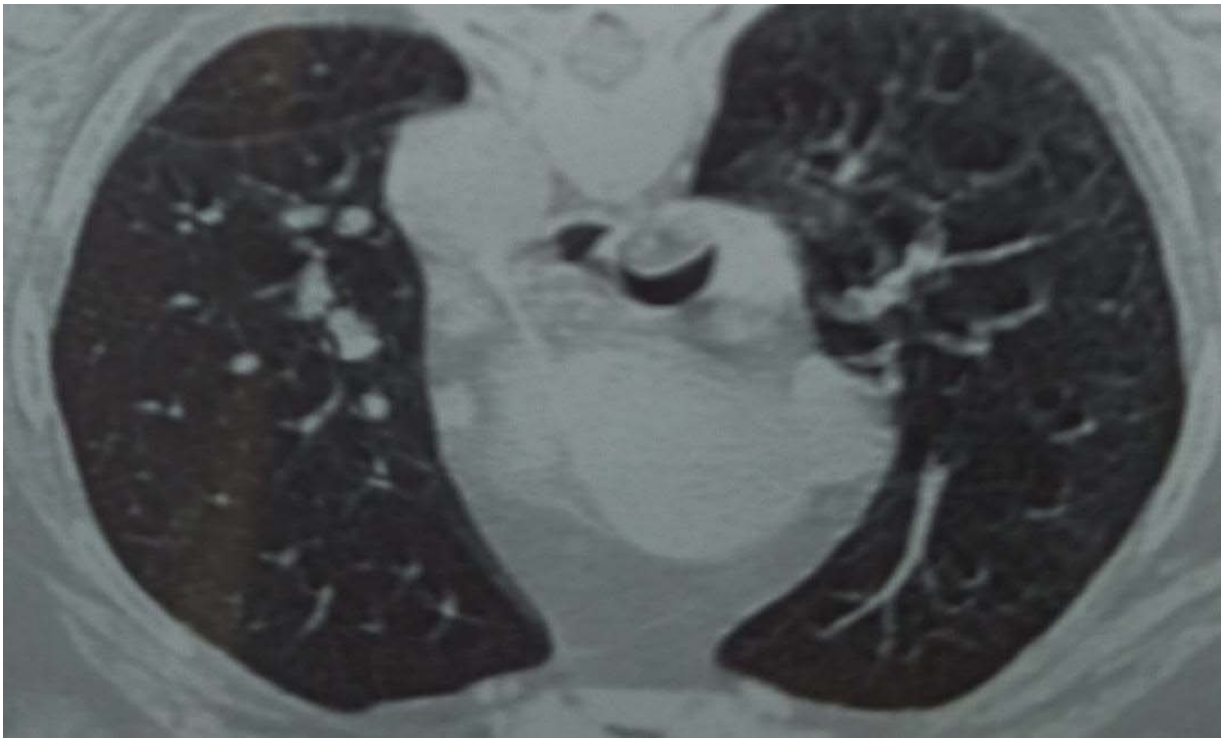

Figure 3. Showing On CECT Chest Interstitial Reticular Pattern with Fibrotic Bands.

One day, she suddenly developed urinary retention for which urinary catheterization was done and Cystoscopy performed by urologist revealed chronic cystitis changes and Diverticulum without any mechanical obstruction, most likely due to age related bladder neck muscle dysynergia (see Figure 4). Thus, alpha-2 blocker were started which showed improvement in symptoms of urinary hesitancy, urgency and dribbling of urine, after removal of urinary catheter. At this point of time, patient revealed that she intermittently use to strain during passing urine for last six months and had increased nocturnal frequency for last two months. After ten days, she suddenly developed urticarial, itchy, red colored rash on buttocks, abdomen, back and extensor surface of bilateral arm and forearm (see

Figure 5). The dermatologist diagnosed it to be drug or infection related and it got relieved within two weeks with antihistaminic and local oil application. The urine culture remained sterile for next one month.

After, few days, again in midnight, next episode of left heart failure occurred with increased severity of symptoms. She remained drowsy for next twelve hours, required immediate oxygen support due to hypoxia and developed hypotension, oliguria after twelve hours of attack, for which small dose ionotropic support, intravenous fluids with diuretics were given. The oxygen therapy and ionotropic support was required for twelve hours, after which heamodynamically stability with adequate urinary output was achieved. Fever this time remained only for one day. The injectable steroid was not used, thinking pulmonary edema of cardiac origin, thus intravenous diuretics and broad spectrum antibiotics were given. The blood picture again revealed same neutrophilia predominant leucocytosis with raised ESR, D-dimer, C-reactive protein, pro-calcitonin and pro-BNP levels but blood culture and urine culture were sterile. Her urine complete examination revealed mild hematuria and proteinuria her repeat ECHO confirmed the same previous findings and same diagnosis of HfPEF was made. After receiving five days of intravenous diuretics and antibiotics, she was switched back to oral therapy. She received prophylactically oral anticoagulants for a period of one month. The TSH level still remained high and was attributed to drug interaction, hence oral gabapentin, proton pump inhibitors, iron and calcium were stopped.

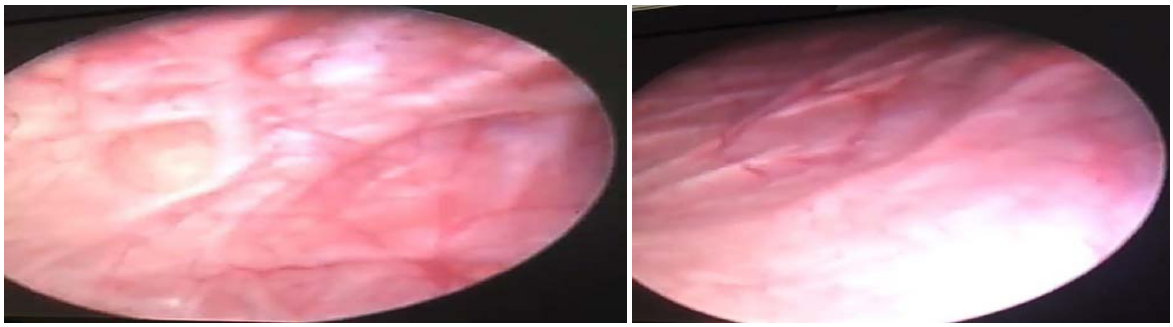

Figure 4. Showing on Cystoscopy Diverticulum and Atrophic Mucosa of Chronic Cystitis.

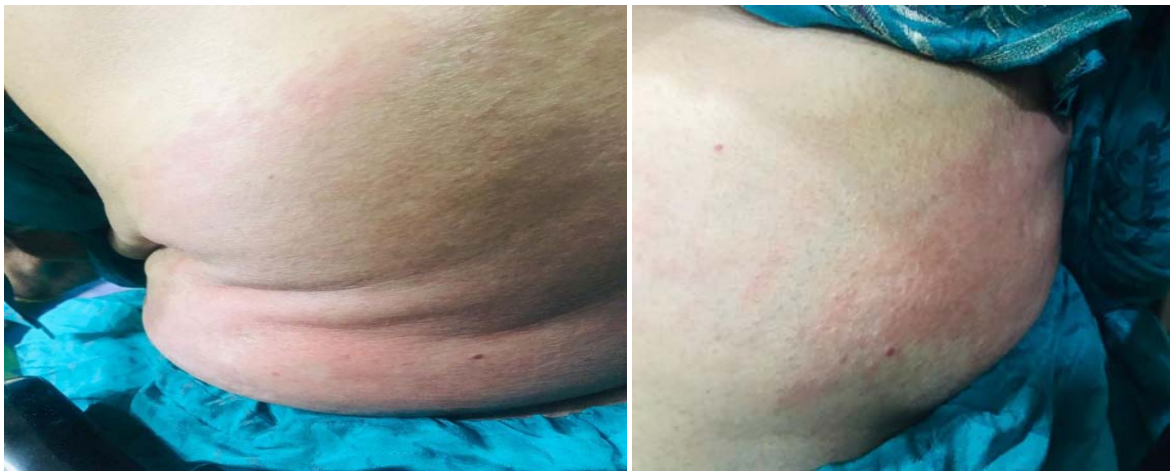

Figure 5. Showing Red, Itchy Uricarial Rash on Back and Abdomen.

In view of repeated attacks, unconfirmed diagnosis, for ruling out infective endocarditis and localizing any other hidden abscess or malignancy, Positron Emission Tomography (PET) scan was done which revealed hyper metabolic multiple discrete small sized lymph nodes, both supra & infra diaphragmatic (see Figure 6) and Magnetic resonance imaging (MRI) abdomen revealed mild cystitis changes. For determining etiology of lymphadenopathy, fine needle aspiration cytology (FNAC) was done from right inguinal lymph node in which lymphoid cells showed bimodal population of mainly medium sized lymphocytes with paucity of small mature lymphocytes with plasma cell infiltration-suggestive of lymphoproliferative or reactive. Thus for ruling out lymphoproliferative disorder, excisional inguinal lymph node biopsy was done which revealed chronic reactive lymphadenitis and was negative for malignancy on immuno-histochemical stains (IHC). The two independent teams of pathologist have the same opinion on lymph node biopsy. The patient developed lymphorrhea at the biopsy site for which negative suction drain was needed for four weeks.

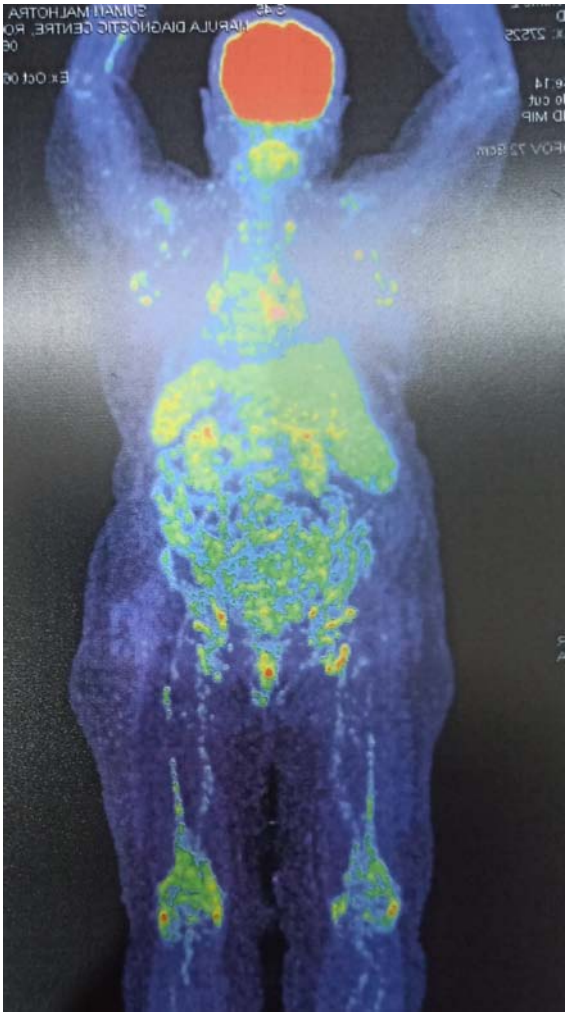

Figure 6. Showing on PET Scan Diffuse Lymphadenopathy.

After two weeks, there was next episode of left heart failure, wheeze, dyspnea, tacypnoea, tachycardia, hypertension, rigors &chills, followed by high grade fever. But this time again she became drowsy, required immediate oxygen support due to hypoxia and developed hypotension ,oliguria after twelve hours, for which small dose ionotropic support, intravenous fluids with diuretics were given but steroids were not used. The oxygen therapy and ionotropic support was not needed after twelve hours, as she became heamodynamically stable with adequate urinary output. The fever this time also remained only for one day. Her blood picture again revealed same neutrophilia predominant leucocytosis with Eosinophilia, raised ESR, D-dimer and increased thyroid stimulating hormone (TSH) levels for which dose of Eltroxin was increased to 100 microgram. The urine complete examination revealed red blood cells and mild proteinuria. Her repeat ECHO revealed the same previous findings of mild MR, TR, AR, Left ventricular hypertrophy (LVH) with good ejection fraction (55%). The fever again this time remained only for one day. After receiving five days of intravenous diuretics and antibiotics, she was switched back to oral therapy. During this episode of left heart failure, two distinct things were observed—first leg stockings were worn by patient for twelve hours in daytime which led to substantial decrease in pedal edema and second was restart of tablet Nitrofurantoin, two hours before the episode of left heart failure. It was presumed that may be excessive fluid movement from bilateral lower limbs into circulation may have precipitated the left heart failure.

In the next three weeks patient remained asymptomatic but her urine complete intermittently showed pus cells and sometimes urine culture was suggestive of Kleibsiella or E.Coli, thus again patient was given five days intravenous antibiotics followed by oral antibiotics but surprisingly during these three weeks, fever was non-significant, leukocyte count remained normal, ESR and Eosinophilia had declining trend. She was on regular antibiotics, on advice of Cardiologist and Urologist, for preventing HfPEF due to Urosepsis. The auto immune profile, serum and urinary tests for ruling out any adrenal pathology, as differentials for causing flash pulmonary edema were

non-contributory but 24 hour urine revealed proteinuria. The Coronary angiography done for ruling out any ischemic cause of left heart failure, revealed only less than 50% blockage in left circumflex artery, rest of coronaries were normal and conservative management with lipid lowering agents was started. The bilateral renal color Doppler/CT renal angiography was also planned for ruling out renal artery stenosis causing flash pulmonary edema.

Once again when oral antibiotics Nitrofurantoin was reintroduced at night time, within two hours she developed next episode of acute left heart failure with dyspnea, wheeze, tachycardia, tacypnoea, hypertension, followed by high grade fever, immediate hypoxia, development of early hypotension i.e. within three hours, oliguria and this time it was associated with severe itching for few hours after the acute attack. Again she required oxygen support for twelve hours but ionotropic support was needed for 24 hours. This time also diuretics were given without the use of steroids. Fever, this time also remained for one day only. Her biochemical parameters revealed mild neutrophilic predominant leucocytosis, prominent Eosinophilia and raised ESR.

Sometimes God sends signal and one day, patient himself enquired from the treating team whether she is having any kind of drug allergy which may be responsible for her illness and she has never felt good after taking Nitrofurantoin. Now, at this point of time, it was analyzed that during two episodes there was documented history of developing pulmonary edema after two hours of Nitrofurantoin and when all the dates and records were re-looked, it was confirmed that all the five episodes of acute pulmonary edema were related to therapy with Nitrofurantoin which was immediately stopped. The total serum IgE levels were found to be very high (>1,000). The patient was put on oral steroids, antiallergics, diuretics, antihypertensive and showed good recovery within two weeks. The leukocyte count, Eosinophilia, ESR, D-dimer, Serum Ferritin CRP, total IgE and TSH normalized.

3. Discussion

The majority of patients who present with pulmonary reactions to Nitrofurantoin are women due to their greater susceptibility to recurrent urinary tract infections, thus exposing to long-term Nitrofurantoin more often than men [13, 14]. The median age among those presenting with the acute or chronic forms of the illness is approximately 60 and 70 years, respectively [14, 15]. A cohort study in adults aged 65 and older found an increased risk of lung injury with chronic, compared with acute, use of Nitrofurantoin [16]. The acute form of the illness is the most common pulmonary reaction to Nitrofurantoin, occurring in approximately 1 in 5,000 patients after first exposure [17, 18]. In one study, among 66 patients with pulmonary reactions, 80 percent had an acute presentation and 20 percent had a sub acute or chronic presentation [15]. Respiratory impairment severe enough to require hospitalization occurs in approximately 1 of 750 long-term users [19].

Nitrofurantoin reaction with Eosinophilia produces systemic symptom and rarely may be life threatening [11, 20]. Long established acute pulmonary response develops within hours to weeks after the consumption of the same. This reaction syndrome is distinguished by sudden onset of fever, chills, cough, myalgia, and dyspnea [21]. Sub acute pulmonary reactions due to it normally appear after one month of drug intake. This reaction is marked by persevering and progressive cough, dyspnea, orthopnoea and fever [21]. Chronic Nitrofurantoin pulmonary event is another form of reaction, associated with indirect production of nonproductive cough and dyspnea [22]. Adverse reactions, mostly related to chronic utilization of Nitrofurantoin, includes gastrointestinal problems, hepatotoxicity, peripheral neuropathy, hematologic disorders, skin eruptions, neurological defects, pulmonary problems and other malformations [21, 23]. During Nitrofurantoin therapy, acute hemolytic anemia is the major hematological adverse effect associated with deficiency of glucose-6-phosphate dehydrogenase [24]. Pulmonary fibrosis and hepatotoxicity problems have been seen in patients receiving Nitrofurantoin as prophylaxis for several months or years [25]. Acute pulmonary syndrome, a rare but severe adverse reaction linked to Nitrofurantoin therapy. This syndrome is seldom observed at the moment of presentation, which potentially subjects patients to unnecessary treatment and result in discontinuation of therapy [26]. Chronic drug induced lung disease due to Nitrofurantoin after long term use is noticed frequently in aged women presenting with respiratory problems [27].

Our case clearly depicts the need of strict vigil on all the side effects of any drug, may be rare, being used for the patient. There is no doubt patient had recurrent urinary tract infection, as repeatedly evidenced by significant number of pus cells in urine and positive culture reports. The introduction of Nitrofurantoin complicated the picture by development of its side effects like Non cardiogenic pulmonary edema, fever, rash, hyponatremia, hyperkalemia, deranged renal function tests, hematuria, proteinuria, alopecia, lymphadenopathy, anemia, worsening of hypothyroidism, nausea. It led to overtreatment with antibiotics, thinking later episodes of drug fever as recurrent U.T.I and unnecessary treatment with anticoagulants for rare possibility of pulmonary thromboembolism. Moreover, patient was over investigated, in view of prolonged course of illness with varied complications, forcing to think for other

differential diagnosis. The unwarranted tests to which patient was subjected to included repeated ECHO, Angiography, repeated ultrasound abdomen, CECT scan abdomen & chest, PET scan, Pulmonary angiography, multiple times biochemical parameters evaluation, including for adrenal pathology, FNAC and excisional inguinal lymph node biopsy leading to lymphorrhea, requiring drainage for one month.

Three cases of Nitrofurantoin induced DRESS are reported with liver, kidney, and lung involvements (1.18% out of 254 reported antibiotic-induced DRESS cases). These reactions occurred shortly after Nitrofurantoin use and completely resolved by routine measures. DRESS reaction characterized by a generalized exanthematous morbilliform rash, fever, enlarged lymph nodes, internal organ involvement (usually the liver and kidneys), and hematologic findings including leucocytosis with hypereosinophilia [2,3]. Skin presentations can be as exfoliative erythroderma, follicular, or non follicular pustules, purpuric lesions or blisters, and tense bullae induced by dermal edema. Typically involved sites are the face, upper trunk, and extremities [5]. Additionally, encephalitis, aseptic meningitis, myositis, bleeding, thyroiditis, respiratory distress syndrome, pericarditis, myocarditis, pneumonitis, colitis, pancreatitis, hypotension, interstitial nephritis, arthritis, arthralgia, and orchitis have been reported as organ involvements which typically occurs 1-2 weeks after skin eruption [5]. The pulmonary manifestation of DRESS presents in a wide spectrum from mild cough or dyspnea with nonspecific interstitial changes on chest imaging to acute respiratory distress syndrome (ARDS) with life threatening hypoxic respiratory failure [28]. The mortality rate due to DRESS is reported between 10 and 30% [29]. Fulminant hepatitis is the main cause of death associated with this syndrome, occurring in 5 to 10% of cases [29]. Myocarditis and respiratory failure are other main causes of death [28]. There have been isolated case reports describing systemic inflammatory response syndrome (SIRS) after nitrofurantoin administration with associated abrupt onset of fever, malaise, leucocytosis, and occasionally pleuritis [30-33]. Back and colleagues also discussed a similar clinical syndrome like in our patient. In this study, 18 patients who received nitrofurantoin developed hypersensitivity including fever, cough, malaise, pleuritis, leucocytosis, and occasionally eosinophilia. This study concluded that there seems to be an association between high IgG antibody titers and nitrofurantoin sensitivity [34].

Nitrofurantoin is known to cause all the above listed side effects which occurred in our patient which actually was spectrum of DRESS and was seen at different point of course of illness and treatment. The side effects of Nitrofurantoin can mimic symptoms of other diseases leading to delayed diagnosis. Normally, Nitrofurantoin does not show immediate side effects but lead to priming of human body in first one week and later on when it is used, can cause varied manifestations including life threatening episodes of Non cardiogenic pulmonary edema.

In present case, first side effect of Nitrofurantoin was development of anemia which was confused as to be due to infection. The next side effect was hyponatremia which was thought to be due to congestive heart failure but that also developed due to Nitrofurantoin only. The Lymphadenopathy (LAP), a side effect of Nitrofurantoin was thought to be sepsis related or due to some lymphoproliferative disorder. The increased rate of loss of hairs (alopecia) was explained as illness or decreased nutritional intake related. The side effect of repeated attacks of drug fever associated with predominant neutrophilic leucocytosis mimicked severe bacterial infections which was attributed to recurrent U.T.I. The persistently raised inflammatory markers like ESR,CRP,D-dimer were confused to be as sepsis or hypercoaguable state due to Post-COVID infection and vaccination. The multiple attacks of Non cardiogenic pulmonary edema due to Nitrofurantoin anaphylaxis was thought to be as pulmonary edema due to HfPEF and led to its detailed evaluation and treatment. The transient episodes during acute attacks of Nitrofurantoin anaphylaxis of hyperkalemia, Eosinophilia, hypocalcaemia and deranged TSH were confused to be as sepsis related. The presence of hematuria and proteinuria which was most likely due to Nitrofurantoin induced interstitial nephritis was taken as Urosepsis related.

The clinching points which were overlooked included clinical presentation of acute pulmonary edema which came and went like a storm for twenty four hours and development of fever after half an hour of starting of acute attack of pulmonary edema. In HfPEF, it should be reverse, there should be gradually rising fever leading to precipitation of pulmonary edema. The initial two attacks were less severe because in both of them injectable steroid were given at the onset which countered anaphylactic reaction, thus hypotension, oliguria or drowsiness never developed. There was perceptible change in fever pattern, in last three episodes of pulmonary edema, when fever remained only for one day, unlike in previous episodes of U.T.I in which it was hectic type and used to remain for five to seven days. Moreover, hypotension and hypoxia remained for few hours only after the episodes of Non cardiogenic pulmonary edema due to Nitrofurantoin, in contrast to cardiogenic pulmonary edema which takes few days to settle down and patient are usually not drowsy. During attack of Non cardiogenic pulmonary edema, there was transient rise of Eosinophils, ESR and serum potassium, despite being regularly on loop diuretics which cause hypokalemia. The skin rash during the course of treatment was not attributed to Nitrofurantoin but instead thought

to be infection related. There was sudden jump in the leucocytes after acute attack but use to fall in very short period. The patient was never toxic during whole course of treatment. In sepsis, with sudden rise of leucocytes like in ruptured abscess or peritonitis, patient is usually toxic and leukocyte count take few days to decline but in our case there was significant fall even within twelve hours which cannot occur due to rapid response of antibiotics but was due to Nitrofurantoin. The patient was seen by three different teams of Cardiologist and underwent ECHO for five times and every time inference was mild MR, TR and LVH with good ejection fraction. No doubt, all of them could not explain the recurrent episodes of pulmonary edema on these minor findings of ECHO which could have been just age related and made diagnosis of HfPEF by excluding other differential diagnosis but Non cardiogenic pulmonary edema due to Nitrofurantoin was missed. Over six months of illness, three separate Urologist, Endocrinologist, Dermatologist, Critical Care specialist and Physician treated this patient, but none suspected the varied clinical presentation as side effects of Nitrofurantoin, including Non cardiogenic pulmonary edema.

4. Conclusion

In management of patient, both indoor & outdoor, there should be written documentation of every drug dosage & side effects, vital parameters, biochemical and radiological investigations which helps in better analysis of course of illness. As a thumb rule, always first think of common diagnosis and then try to rule out other uncommon differential diagnosis, on basis of unexplained biochemical or radiological investigation. It is duty and responsibility of treating doctors to remain vigil for all the side effects, even rare, of medicines being prescribed by them, so as to save patient from overtreatment, life threatening conditions, mental agony and financial loss.

References

[1] Fahim, S., Jain, V., Victor, G., Pierscianowski, T. (2006). Piperacillin tazobactam–induced drug hypersensitivity syndrome. Cutis, 2006, 77: 353-357.

[2] Cacoub, P., Musette, P., Descamps, V., Meyer, O., Speirs, C., Finzi, L., et al. (2001). The DRESS syndrome: a literature review. Am J Med., 2001, 124(7): 588-597.

[3] Cabanas, R., Calderon, O., Ramirez, E., Fiandor, A., Prior, N., Caballero, T., et al. (2014). Piperacillin-induced DRESS: distinguishing features observed in a clinical and allergy study of 8 patients. J Investig Allergol Clin Immunol., 2014, 24(6): 425-430.

[4] Girelli, F., Bernardi, S., Gardelli, L., Bassi, B., Parente, G., Dubini, A., et al. (2013). A new case of DRESS syndrome induced by sulfaslalazine and triggered by amoxicillin. Case Rep Rheumatol, 2013: 409152.

[5] Sharpe, A., Mourad, B. M., Hardwick, J., Reilly, T., Dweck, E., Bondarsky, E. (2019). Oxacillin-induced drug reaction with eosinophilia and systemic symptoms (DRESS). Am J Case Rep., 2019, 20: 345-348.

[6] Artuković, M., Kuštelega, J., Lugović-Mihić, L. (2010). DRESS syndrome with mild manifestations as a diagnostic and therapeutic problem: case report. Acta Clin Croatica, 49(4): 479-484.

[7] Jhang, J. F., Kuo, H. C. (2017). Recent advances in recurrent urinary tract infection from pathogenesis and biomarkers to prevention. Ci Ji Yi Xue Za Zhi, 2017, 29(3): 131-7.

[8] Ronald, A. (2003). The etiology of urinary tract infection: traditional and emerging pathogens. Dis Mon, 2003, 49(2): 71-82.

[9] Cunha, B. A. (1989). Nitrofurantoin: an update. Obstet Gynecol Surv., 1989, 44(5): 399-406.

[10] Guay, D. R. (2001). An update on the role of nitrofurans in the management of urinary tract infections. Drugs, 2001, 61(3): 353-64.

[11] Leao, R. N., Barreto, P., Leao, R. R., et al. (2013). Nitrofurantoin: Cause of dress syndrome. BMJ Case Rep., 2013; 2013. pii: bcr2013008991.

[12] Travis, W. D., Colby, T. V., Koss, M. N., et al. (2002). Non-neoplastic disorders of the lower respiratory tract. Atlas of nontumor pathology. Washington, The American Registry of Pathology, 2002, 2: 327.

[13] Mendez, J. L., Nadrous, H. F., Hartman, T. E., Ryu, J. H. (2005). Chronic Nitrofurantoin-induced lung disease. Mayo Clin Proc, 2005, 80: 1298.

[14] Holmberg, L., Boman, G. (1981). Pulmonary reactions to Nitrofurantoin. 447 cases reported to the Swedish Adverse Drug Reaction Committee 1966-1976. Eur J Respir Dis., 1981, 62: 180.

[15] Sovijärvi, A. R., Lemola, M., Stenius, B., Idänpään-Heikkilä, J. (1977). Nitrofurantoin-induced acute, sub acute and chronic pulmonary reactions. Scand J Respir Dis., 1977, 58: 41.

[16] Santos, J. M., Batech, M., Pelter, M. A., Deamer, R. L. (2016). Evaluation of the Risk of Nitrofurantoin Lung Injury and Its

Efficacy in Diminished Kidney Function in Older Adults in a Large Integrated Healthcare System: A Matched Cohort Study. J Am Geriatr Soc., 2016, 64: 798.

[17] Kabbara, W. K., Kordahi, M. C. (2015). Nitrofurantoin-induced pulmonary toxicity: A case report and review of the literature. J Infect Public Health, 2015, 8: 309.

[18] Huttner, A., Verhaegh, E. M., Harbarth, S., et al. (2015). Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. J Antimicrob Chemother, 2015, 70: 2456.

[19] Jick, S. S., Jick, H., Walker, A. M., Hunter, J. R. (1989). Hospitalizations for pulmonary reactions following Nitrofurantoin use. Chest, 1989, 96: 512.

[20] Velema, M. S., Voerman, H. J. (2009). Dress syndrome caused by Nitrofurantoin. Neth J Med., 2009, 67(4): 147-9.

[21] Munoz-Davila, M. J. (2014). Role of old antibiotics in the era of antibiotic resistance. Highlighted Nitrofurantoin for the treatment of lower urinary tract infections. Antibiotics, 2014, 3(1): 39-48.

[22] Marshall, A. D., Dempsey, O. J. (2013). Is "Nitrofurantoin lung" on the increase? Br Med J., 2013, 346: f3897.

[23] Brumfitt, W., Hamilton-Miller, J. M. (1998). Efficacy and safety profile of long-term Nitrofurantoin in urinary infections: 18 years' experience. J Antimicrob Chemother, 1998, 42(3): 363-71.

[24] Holmberg, L., Boman, G., Bottiger, L. E., et al. (1980). Adverse reactions to Nitrofurantoin. An analysis of 921 reports. Am J Med., 1980, 69(5): 733-8.

[25] Huttner, A., Verhaegh, E. M., Harbarth, S., et al. (2015). Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. J Antimicrob Chemother, 2015, 70(9): 2456-64.

[26] Broes, M. J., Roelofs, B. F., Mudde, A. H., et al. (2012). Pulmonary toxicity resulting from the use of Nitrofurantoin. Ned Tisdschr Geneeskd, 2012, 156(44): A4990.

[27] Mendez, J. L., Nadrous, H. F., Hartman, T. E., et al. (2005). Chronic Nitrofurantoin-induced lung disease. Mayo Clin Proc, 2005, 80(10): 1298-302.

[28] Taweesedt, P. T., Nordstrom, C. W., Stoeckel J., Dumic. (2019). Pulmonary manifestations of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a systematic review. Biomed Res Int., 2019, 5: 1-10

[29] Díaz-Mancebo, R., Costero-Fernandez, O., Vega-Cabrera, C., OleaTejero, T., Yebenes, L., Picazo, M. L., et al. (2012). Dress syndrome and acute tubulo interstitial nephritis after treatment with vancomycin and beta-lactams. Case report and literature review. Nefrología (English Edition), 2012, 32(5): 685-687.

[30] Forster, C. J., Cohee, B. M., Wood-Morris, R. N., Hartzell, J. D. (2009). Nitrofurantoin-induced systemic inflammatory response syndrome. Am J Med Sci., 2009, 338: 338-340.

[31] Gandotra, S. D., Smotrys, M. A., Patel, D. B., Chadha, A. (2017). Systemic inflammatory response syndrome (SIRS) and a left bundle branch block (LBBB) due to nitrofurantoin. BMJ Case Rep., 2017, 2017: bcr2016218127.

[32] Gohar, A., Abdallah, M., Elsayed, S., Pierobon, J. (2020). Systemic inflammatory response syndrome due to nitrofurantoin use. Am J Ther. Published online January 13, 2020. doi:10.1097/ MJT.0000000000001110.

[33] Smith, A. A., LeDoux, E. (2011). A convincing case of nitrofurantoin induced systemic inflammation response syndrome. J Gen Int Med., 2011, 26: S376.

[34] Bäck, O., Liden, S., Ahlstedt, S. (1977). Adverse reactions to nitrofurantoin in relation to cellular and humoral immune responses. Clin Exp Immunol., 1977, 28: 400-406.