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A RARE CASE OF NITROFURANTIOIN INDUCED AUTOIMMUNE LIKE HEPATITIS

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Abstract:

The class of nitro furan antibiotics includes Nitrofurantoin, an agent primarily used to treat urinary tract infections. It is efficacious as it can attain therapeutic concentration in urine and elicit both bactericidal and bacteriostatic activity against both gram positive and gram-negative organisms. Hence proving its efficacy in treating lower urinary tract infections. It also shows very less resistance and although widely used it also has its side effects like rashes, loss of appetite, dizziness, fever, diarrhoea,,. It can also cause adverse reactions like pulmonary toxicity, hepatic toxicity, haemolytic anaemia but the incidence of such events is rare. Even though the occurrence of hepatotoxicity is rare, to overlook monitoring for possible liver injury may prove fatal. As nitrofurantoin is one of the most common drugs behind drug induced liver injury checking for any possible liver injury becomes crucial. The drug is also capable of presenting autoimmune features like presence of auto antibodies and may trigger autoimmune hepatitis and if not discontinued in time can lead to complications like cirrhosis or liver failure. Occurrence of drug induced autoimmune hepatitis is unusual and can considered as a phenotype of the drug. Differentiating between a drug induced mimicry of autoimmune features and idiopathic autoimmune hepatitis is very difficult. But if it is drug induced liver injury mimicking autoimmune hepatitis, discontinuation of the drug can help resolve the event.

Here we present a case of a 56-year-old woman who was on a long-term treatment with nitrofurantoin against recurrent urinary tract infection for over a period of about 1 year. She was admitted with complains of yellowish discoloration of eyes and skin, dark coloured urine, abdominal pain, vomiting, edema on both legs and history of weight loss. She also had highly elevated liver enzymes. She also showed presence of autoantibody. However, her symptoms resolved on discontinuation of nitrofurantoin, liver enzymes reduced to a normal range and the patient showed response to treatment with corticosteroids and with no relapse on follow up.

KEY WORDS: NITROFURANTOIN, AUTOIMMUNE HEPATITIS, DRUG INDUCED AUTOIMMUNE LIKE HEPATITIS, URINARY TRACT INFECTION, AUTOANTIBODIES

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INTRODUCTION:

A nitro furan antibiotic called Nitrofurantoin was licensed by the US FDA in 1954. It is extensively used in treating urinary tract infection as a first line therapy and also as a prophylactic agent for the same. (1). Nitrofurantoin has proved to be beneficial in treating UTIs as it can attain therapeutic concentration in urine while preserving a low serum concentration and it has a low incidence of resistance. (2) It is effective in UTIs and as most uropathogens can be either gram negative or gram positive, they will come under the coverage of drug. Nitrofurantoin is also capable of both bacteriostatic and bactericidal activity the latter mostly in higher concentration (2)(3). Thus, Nitrofurantoin becomes a very favourable choice in treatment of UTIs.

Though the exact mechanism behind action of the drug is still unclear it is suggested that Nitrofurantoin acts in multiple ways, it acts by inhibiting bacterial enzymes responsible for the synthesis of carbohydrates DNA and RNA at varying concentration. It also gets transformed into reactive electrophilic intermediates due to the presence of nitro reductase in bacteria. This reactive intermediate is responsible for inhibition of protein synthesis (4)(5) Nitrofurantoin is a relatively safe drug, but as all drugs it also has some adverse effects and is capable of toxicity like haemolytic anaemia, pulmonary toxicity and hepatoxicity though the incidence of such events is very rare. (5)

Here we focus of Nitrofurantoin induced liver damage .The pathway behind Nitrofurantoin induce liver injury is still not very evident .In some animal studies conducted on isolated hepatocytes to find the structure toxicity relationship it was found that Nitrofurantoin can deplete glutathione which is a sign of oxidative stress as glutathione provides protection against oxidative stress (6-7)Studies have shown that Nitrofurantoin is able to produce reactive oxygen species (ROS)and free radicals thus generating oxidative stress and cytotoxicity .ROS have been found to act as mediators for inflammatory liver conditions .Also oxidative stress can also lead to the generation of novel auto antigens and thus exacerbation of the autoimmune response (8)(9)
The formation of a bond between drug or the drug metabolite and hepatocyte might appear as a novel antigen to the immune system and thus it may elicit response against the perceived threat by producing antibodies against it. (9) Thus an autoimmune like hepatitis presentation can be observed. Female gender, age, renal impairment, chronic alcohol, history of hepatitis are some of the factors that can result in higher chances for Nitrofurantoin induced liver damage (10)

With the emergence of growing resistance, older antibiotics like Nitrofurantoin has got a newfound purpose .But sometimes there could be occurrence of adverse events if not monitored .Drug induced Autoimmune like hepatitis can also overlap with features of classical autoimmune hepatitis making the diagnosing complicated, especially if one is not aware of the possibility of such an event occurring. Detecting drug induced liver injury can help in remission and provide prevention from other fatal consequences like liver failure (11)

Here is a case of 56 year old women with recurrent UTI chronic use Nitrofurantoin who developed an autoimmune like drug induced hepatitis.

CASE REPORT:

A 56-year-old female patient presented with complaints of lower abdominal pain since past 1 week and had recent episodes vomiting (1 episode each for 2 days) with loss of appetite for the past 2 days. Patient showed yellowish discoloration of sclera, face and skin, presence of dark coloured urine and edema on both lower limbs She also had history of mild weight loss. On admission she had no h/o fever, loose stools and melena

Patient is a known case of Kyphoscoliosis and has a H/o right pyelonephritis with pyelitis diagnosed a year ago. She also has H/o multiple level spine degenerative changes with neurogenic bladder with recurrent UTI. Medication reconciliation was done for both native and allopathic drugs. She was found to be taking T. Nitrofurantoin 100 mg HS for 1 year as treatment for recurrent UTI. No other potential offending agents were found No obvious causes of hepatitis or jaundice was found. Patient also had no history of any such event or history of jaundice or any liver injury.

On admission the initial blood workup showed a highly deranged levels in liver function test with SGOT (314) , SGPT(349) and ALP (193). Patient also had an INR (1.48), CRP (17.9), creatinine (0.53) and other parameters as shown below (Table 1,2 and 3) The serological testing showed negative for ASMA, LK-M1 as shown in 9Table D1). Test for hepatitis A, B and C were all non-reactive ruling out viral causes. The test for Scrub typhus and Leptospira were also negative. But ANA was positive+2 as seen below (Table 4). Ultrasound of liver showed presence of no

focal lesions, periportal echogenicity – mildly distended gall bladder with wall edema.

The patient was started on oral steroids Prednisolone 30 mg once daily. Patient was also put on a foleys catheter and fluid intake was restricted to 1.5-2 L/day. Steroids had to be withheld as the patient developed fever but once the fever subsided steroid was restarted. Patient was initially treated with antibiotic injection ceftriaxone but the culture sensitivity report isolated with klebsiella pneumonia showed intermediate sensitivity to this antibiotic. It was then escalated to injection meropenem. Later it was de-escalated to tablet cephalexin375 mg twice a day

Over the course of her stay Liver enzyme gradually began to decrease after discontinuation of nitrofurantoin Patient showed response to treatment with corticosteroids. The liver enzymes also started to show a decreasing trends. On discharge patient was stable and her liver enzymes had reached normal levels. Steroid was tapered slowly on follow up and stopped. Patient showed no relapse after withdrawal of steroids.

Table 1: Liver Function Test

PARAMETERS	ON ADMISSION	ON DISCHARGE	ON FOLLOW UP -1	ON FOLLOW UP -2
TOTAL BILIRUBIN	8.39	5.26	1.22	0.89
DIRECT BILIRUBIN	5.26	2.76	0.51	0.27
INDIRECT BILIRUBIN	3.13	2.50	0.71	0.62
SGOT	314	78	30	35
SGPT	349	128	21	19
ALP	193	155	109	110
S. GLOBULIN	2.7	2.6	2.7	2.9
S.ALBUMIN	3.59	3.27	3.46	3.74
INR	1.41	1.16	0.98	1.08

Table 2 : CBC

PARAMETERS	ON ADMISSION	ON DISCHARGE	ON FOLLOW UP	ON FOLLOW UP -2
TOTAL COUNTS	6910	9100	7680	5900
DC (P//E/L/M)	69/1/25/5	62/2/33/3	50/3/41/5	52/3/39/5
PCV	32.7	33.9	34.8	/31.7
MCV	85.4	90.1	89.2	83.6
MCH	28.7	30.2	29.5	28.1
MCHC	33.6	33.5	33	33.6
Hb	11	11.4	11.5	10.6
RBC	3.82	3.76	3.90	3.8
PLT	2.81	3.01	2.57	2.96
RETICULOCYTE COUNT	3.85	1.83	1.53	0.59

Table:3

OTHER PARAMETERS	RESULT
FERRITIN	638.52
GAMMA GLUTAMYL TRANSFERASE	269.80

Table: 4 Serological Parameters

PARAMETERS	RESULT
HEPATITS A	NON REACTIVE
HEPATITS B	NON REACTIVE
HEPATITIS C	NON REACTIVE
ANA	POSITIVE
ASMA	NEGATIVE
LKM I	NEGATIVE
SCRUB TYPHUS	NEGATIVE
LEPTOSPIRA	NEGATIVE

DSCUSSION:

Nitrofurantoin has proved to be efficacious in the treatment of urinary tract infection. But it is also capable of causing certain toxicities as mentioned above like pulmonary or hepatotoxicity though incidence of such events are uncommon. When it comes to Nitrofurantoin as few as 1 in 10,000 to 100,000 people have been documented to experience drug-induced liver damage. (12) In a study conducted on 3400 individuals above the age of 65 on Nitrofurantoin, only 3.9 % were found to have an adverse reaction due to Nitrofurantoin. Out of these only one was Nitrofurantoin induced hepatotoxicity with chronic use (13). When it comes to Nitrofurantoin induced autoimmune like hepatitis it is even more unusual. In another study conducted with 261 patients diagnosed with Autoimmune Hepatitis (AIH) about 9 % of AIH patients was found to be drug induced autoimmune hepatitis DIAH and two main drugs behind this event were minocycline and Nitrofurantoin .(14) Although it's a rare to have Nitrofurantoin induced autoimmune like hepatitis it is significant enough be considered because one it is easily resolvable by discontinuing the drug and if the event is drug induced then drug needs to be identified and stopped before it causes serious damage like cirrhosis or trigger AIH. But the literature provides only a few case reports and series for nitrofurantoin induced autoimmune like hepatitis.

The main issues with DIAH is that it can overlap with classical AIH and distinguishing between them can be quite difficult. To differentiate between them we must know their basics features When it comes to Autoimmune Hepatitis there are two types to it AIH 1 which is marked by the presence of antibodies ANA or ASMA or both peaking at age of 45-70 more in female gender. Whereas type 2 shows predominance of anti LKM1 majorly seen in a young population and also seen more in females (15).But If we are considering the drug to be the offending agent for liver injury then there are 3 types of drug induced liver injury (DILI)to be considered. 1). Direct is due to an inherent property of the drug to cause damage it is predictable dose and frequency related. 2) Idiosyncratic is neither dose nor frequency dependent with variable latency, marked elevation of liver enzymes and bilirubin and often accompanied with presence of auto antibodies. 3) Indirect is neither related to intrinsic property nor idiosyncratic action but depend on the action of the drug. (16)

Our case here is resembles the features of Type 1 like AIH with an idiosyncratic liver injury .In terms of onset of the event it can be either acute or chronic depending upon the duration of exposure , it can be insidious or sudden , presence of auto antibodies generally takes more than 2 months (12) Our patient had an exposure . 6 months and had presence of auto antibody ANA all this pointing to a chronic form of liver injury.

In this case patient shows signs of liver injury as her AST /ALT are more than x 5 times elevated, ALP only modestly about its normal upper limit value . It is similar to a hepatocellular pattern of liver injury which has highly elevated AST and ALT but only slight increase less than 3 times the upper limit in ALP and

this commonly seen in viral or drug induced causes. Hys law for DILI also shows highly elevated ALT/AST /bilirubin and mild ALP elevation (17)(18) The R-value was found to be > 5 (5.4)confirming a hepatocellular pattern of liver injury also found in AIH .Nitrofurantoin can cause a hepatocellular liver injury, as shown in a study in which 86 % of the cases had hepatocellular injury caused by the drug and 22 % of them were found to be DIAH (19)Other than that the patient had elevated Gamma Glutamyl Transferase levels an obvious sign of liver damage an elevated INR level(1.41)and CRP (17.9) showing inflammation There is also elevated ferritin autoimmune hepatitis s often times may show elevated blood ferritin levels.(20)

Clinical picture of nitrofurantoin induced liver injury can also show autoimmune features like presence of auto antibodies ANA, ASMA, LK M1 viral markers and such. On one hand Presence of auto antibodies gives an implication of autoimmune involvement but on other hands drugs can also be responsible to shown presence of autoantibodies as a mimicry of autoimmune reaction. In this case we have ANA positive (+2) with a high titre All viral markers are negative therefore ruling out an viral causes.

But is it simply a phenotype of drug or autoimmune hepatitis is still stands as a challenge. Another way to determine is considerable improvement on discontinuation of drug, making it more evident that the offending agent behind this adverse event was the drug. Also the transition of liver enzymes to normal level after discontinuation of the drug further confirms the cause to be drug induced. In case of AIH the treatment is done with help of steroids but in 85 % cases relapse is observed and no relapse with response to corticosteroid therapy on follow up is characteristic to DIAH. (21). In one study all the patients with DIAH (14 out of 14) had no relapses after treatment with corticosteroids but 65% of AIH patients suffered relapse after corticosteroid intervention (14) In AIH chronic immunosuppression is needed to treat the condition as relapse are fairly common unlike in DIAH .Our patient here not only showed transition of liver enzymes to a normal level but also complete response to corticosteroid therapy even after 2 months on follow up but the ANA remained positive (+3)

Though histopathology was not done as patient didn't give consent for biopsy it could have helped better identify typical features of AIH such as interface hepatitis , regenerative rosettes etc. but drugs can also mimic the same changes but with slightly different intensity (22-23) There were other factors pointing towards DIAH such as female gender , hepatocellular injury , high titre ANA , long term exposure of drug , transition of liver enzyme to normal levels on discontinuation and no relapse with corticosteroid therapy The Naranjo score for ADR came out to be 7 showing a probable ADR while the AIH score was only showing a low likely possibility of AIH without considering the histopathological factors .Thus pointing more towards a possibility of Nitrofurantoin induced autoimmune like hepatitis

Even if it's not much reported drug induced autoimmune like hepatitis exist and can be confused with autoimmune hepatitis. When prescribing nitrofurantoin for a long period of time monitoring liver function test is essential to help early detect any possible liver injury. It could also be helpful to check for autoantibodies like a simple ANA test once if the treatment period exceeds more than 6 months and or liver enzymes appear deranged and the event can easily be managed if drug is the reason behind the event.

CONCLUSION:

One must keep in mind that drugs are also able to mimic autoimmune features and a thorough investigation should be done to confirm that the reaction is indeed a autoimmune hepatitis or not. The benefit with DIAH is complete resolution is possible if the offending drug is discontinued but if it remains undented it can trigger AIH and cause fatal consequences.

ABBRIVIATIONS	FULL FORM
UTI	URINARY TRACT INFECTION
ROS	REACTIVE OXYGEN SPECIES
AIH	AUTOIMMUNE HEPATITIS
ALP	ALKALINE PHOSPHATASE
ANA	ANTI NUCLEAR ANTI BODIES
DIAH	DRUG INDUCED AUTOIMMUNE HEPATITIS
DILI	DRUG INDUCED LIVER INJURY
ASMA	ANTI-SMOOTH MUSCLE ANTIBODY
CRP	C-REACTIVE PROTEIN
LK-M1	LIVER KIDNEY MICROSOMAL TYPE 1 ANTIBODIES
SGPT	SERUM GLUTAMIC PYRUVIC TRANSAMINASE
SGOT	SERUM GLUTAMIC-OXALOACETIC TRANSAMINASE.
INR	INTERNATIONAL NORMALIZED RATIO

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