Autoimmune hepatitis induced by nitrofurantoin. The importance of the autoantibodies for an early diagnosis of immune disease

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Abstract

Nitrofurantoin has been in use since 1953 as an effective agent for the prevention of recurrent urinary tract infection. It is associated with a wide range of adverse drug reactions. Chronic active hepatitis has increasingly been observed and many cases have been reported with case fatalities. We present a case of nitrofurantoin induced chronic active hepatitis and briefly review the serology and clinicopathological features of 57 similar cases reported in English literature. The consistent presence of antinuclear antibody, anti smooth muscle antibody, elevated immunoglobulin and pathological feature suggests an immunologic mechanism. Complete recovery is possible in most cases if medication is discontinued in time. Steroids may play a role in management if no improvement occurs despite discontinuation of medication. We suggest all patients who are on prolonged nitrofurantoin therapy be followed up with anti nuclear antibody, anti smooth muscle antibody, serum immunoglobulin and hepatic panel every three months.

Introduction

Nitrofurantoin is an effective agent for the treatment and an appropriate prophylactic antibiotic choice for recurrent urinary tract infections. Adverse reactions to nitrofurantoin after short term and long term use are well documented which include: Lupus like syndrome, arthralgias, leucopenia, hemolysis, pneumonitis, neuropathy, nephritis, pulmonary fibrosis and variety of hepatic injuries.1-4 Chronic active hepatitis is the most common hepatic pathology with long term use. Diagnosis is made by clinical history and exclusion of other causes of chronic active hepatitis. The serological markers as well as histological features closely resemble an autoimmune hepatitis. We recently encountered a case of nitrofurantoin induced chronic active hepatitis, which met the simplified criteria for the diagnosis of autoimmune hepatitis (score 7).6 We briefly reviewed the literature to explore whether there is any consistent association of anti nuclear antibody (ANA), anti smooth muscle antibody (SMA), and an increase in immunoglobulin levels which could be used as a predictor of clinical hepatitis. We briefly reviewed all the 57 cases of chronic active hepatitis reported in English literature since 1974.

Case Report

A 62-year-old woman was referred by her primary care physician to a gastroenterologist for progressive loss of appetite, tiredness, feeling weak and passing dark colored urine for two weeks. A lab tests revealed deranged liver enzymes and admitted for further evaluation. This patient did not have any history of liver disease; hepatitis or prior blood transfusions could be used as a predictor of clinical hepatitis. Marked portal inflammation was noted with chronic active interface hepatitis involving (1.81 g/dL). Computed tomography of the abdomen did not show any focal lesions in the liver. Liver biopsy revealed nearly normal parenchymal architecture with moderate portal fibrosis and focal band, bridging and septal fibrosis. Marked portal inflammation was noted with chronic active interface hepatitis involving many plasma cells (Figures 1 and 2). Bile ductules were moderately proliferated with some cholestasis. Iron stain was negative. Reticulum stain showed normal lobular architecture. Trichrome stain confirmed portal fibrosis and incomplete bridging fibrosis. Liver biopsy findings were consistent with autoimmune chronic active hepatitis. Nitrofurantoin was held and she was treated with short course of steroid. Clinical and biochemical improvement were dra

Figure 1. Moderate chronic inflammatory cell infiltration was seen in mildly expanded portal tracts with interface inflammation. Inflammation (accentuated periportally) also seen in lobules with point necrosis and hepatocyte dropout.

Figure 2. High magnification demonstrates many plasma cells (red arrows) among infiltrating inflammatory cells.
Table 1. Clinico pathological features of 57 reported cases of chronic active hepatitis.

| Year | Pt | Age/gender | Exposure | Nitrofurantoin dose (mg/dL) | Total bilirubin (mg/dL) | SGOT (IU/L) | SGPT (IU/L) | ANA | Anti SMA | Increased in immunoglobulin | Albumin (mg/dL) | Liver biopsy | Immuno-suppression used | Outcome |
|------|----|------------|----------|-----------------------------|------------------------|-------------|-------------|-----|----------|-----------------------------|----------------|-------------|--------------------------|---------|
| 19741 | 1  | NA/F       | 2 years  | 100-200 mg/day              | NA                     | Elevated    | Elevated    | + ve | + ve     | + ve                        | NA             | NA          | No                        | Good    |
| 19741 | 2  | NA/F       | 2 years  | 100-200 mg/day              | NA                     | Elevated    | Elevated    | + ve | + ve     | + ve                        | NA             | NA          | No                        | Good    |
| 19741 | 3  | 76/F       | 38 months| 150 mg/day                  | Normal                | 142         | 76          | + ve | + ve     | Yes                         | NA             | Yes CAH     | No                        | Good    |
| 19754 | 4  | 82/F       | 18 months| 100 mg/day                  | Normal                | 116         | 161         | - ve | - ve     | Yes                         | Low            | Yes CAH     | No                        | Good    |
| 19754 | 5  | 60/F       | 14 months| 100 mg/day                  | Normal                | 67          | 93          | - ve | - ve     | Yes                         | Low            | Yes CAH     | No                        | Good    |
| 19754 | 6  | 85/F       | 14 weeks | 100 mg/day                  | Normal                | 125         | 69          | - ve | - ve     | Yes                         | Low            | Yes CAH     | No                        | Good    |
| 19754 | 7  | 74/F       | 9 months | 100 mg/day                  | Normal                | 482         | 466         | - ve | - ve     | Yes                         | Low            | Yes CAH     | No                        | Good    |
| 19754 | 8  | 59/F       | 3 years  | 200 mg/day                  | 18.8                   | 570         | NA          | - ve | NA      | Yes Normal                  | Yes CAH+ Cirrhosis No | Good       |
| 19754 | 9  | 36/F       | 12 months| 200 mg/day                  | 9                      | 290         | NA          | + ve | - ve     | Yes                         | Normal         | Yes CAH     | Good                      |
| 19754 | 10 | 78/F       | 14 months| 150 mg/day                  | 8                      | 920         | 410         | + ve | + ve     | Yes                         | 2.1            | Yes CAH     | No                        | Good    |
| 19766 | 11 | 54/F       | 2 months | NA                          | 15                     | 600         | Elevated    | + ve | + ve     | Yes                         | 2.7            | Yes CAH     | Yes                       |
| 19766 | 12 | 65/F       | 2 years  | NA                          | 11                     | 590         | Elevated    | + ve | + ve     | Yes                         | 3.2            | Yes CAH     | No                        | Good    |
| 19766 | 13 | 59/F       | 2 years  | NA                          | 10                     | 1500        | Elevated    | + ve | + ve     | Yes                         | 2.6            | Yes CAH     | No                        | Good    |
| 19766 | 14 | 53/F       | 4 years  | 100 mg/day                  | 2.4                    | 605         | 254         | + ve | + ve     | Yes                         | NA             | Yes CAH     | No                        | Good    |
| 19766 | 15 | 45/F       | 6 years  | 200 mg/day                  | Elevated              | NA          | Elevated    | + ve | NA      | Yes                         | 4.5            | Yes CAH     | Yes                       |
| 19766 | 16 | 56/F       | 5 years  | 50-100 mg/day               | Elevated              | NA          | Elevated    | + ve | NA      | Yes                         | 3.2            | Yes CAH     | Yes Recovered |
| 19766 | 17 | 59/F       | 3 years  | 200 mg/day                  | Elevated              | NA          | Elevated    | + ve | NA      | Yes                         | 4.2            | Yes CAH     | Yes                       |
| 19766 | 18 | 62/F       | 1 year   | 50 mg/day                   | Elevated              | NA          | Elevated    | + ve | NA      | Yes                         | 3.7            | Yes CAH+Cirrhosis No | Died      |
| 19766 | 19 | 64/F       | 6 years  | 100-200 mg/day              | Elevated              | NA          | Elevated    | + ve | NA      | Yes                         | 3.9            | Yes CAH     | Yes                       |
| 19766 | 20 | 22/F       | 6 years  | 150 mg/day                  | Normal                | 400         | NA          | - ve | + ve     | Yes Normal                  | Yes CAH         | Yes CAH     | Yes                       |
| 19801 | 21 | 52/F       | 12 months| NA                          | 6.6                    | 435         | NA          | + ve | + ve     | No Low                      | Yes CAH         | Yes         | Good                      |
| 19801 | 22 | 60/F       | Few years| NA                          | 10                     | 1000        | NA          | NA      | NA      | NA                         | Yes CAH         | No Recovered |
| 19801 | 23 | 50/F       | 12 months| 200 mg/day                  | 34                     | 750         | NA          | NA      | NA      | NA                         | Low            | Yes CAH     | Yes           |
| 19801 | 24 | 72/F       | 2 years  | 100 mg/day                  | 5.9                    | 520         | NA          | - ve | + ve     | Yes                         | 2.7            | Yes CAH     | Yes Recovered |
| 19801 | 25 | 47/F       | 24 months| 100 mg/day                  | 3.5                    | 904         | 525         | + ve | + ve     | Yes                         | 2              | Yes         | Good                      |
| 19801 | 26 | 48/F       | 18 months| 100 mg/day                  | 1.3                    | 375         | 209         | + ve | + ve     | Yes                         | NA             | Yes CAH     | No                        | Good    |
| 19801 | 27 | 59/F       | 2 years  | 100 mg/day                  | 4.2                    | 1250        | 1328        | + ve | + ve     | Yes                         | NA             | Biopsy declined by the pt No | Good    |
| 19821 | 28 | 65/M       | 12 months| 100 mg/day                  | 55                     | Elevated    | Elevated    | + ve | + ve     | Yes                         | 2.8            | Yes CAH     | Yes Good       |
| 19841 | 29 | 66/F       | 6 years  | 40 mg/day                   | 0.8                    | 138         | 190         | + ve | + ve     | Yes                         | NA             | Yes CAH     | No                        | Good    |
| 19851 | 30 | 71/F       | 2 years  | 100 mg/day                  | 16                     | 1828        | NA          | + ve | + ve     | Yes                         | NA             | Yes CAH+Cirrhosis Yes | Good     |
| 19851 | 31 | 61/F       | 5 years  | 100-200 mg/day              | 10.5                   | 1200        | NA          | + ve | NA      | No                         | 3.4            | Yes CAH     | NA Good       |
| 19821 | 32 | 33/F       | 4 years  | 200 mg/day                  | Elevated              | 1186        | NA          | + ve | + ve     | Yes                         | 3.0            | Yes CAH+Cirrhosis Yes | Good     |
| 19821 | 33 | 56/F       | 4 years  | 50 mg/day                   | Elevated              | 839         | NA          | + ve | - Ve     | No                         | 2.7            | Yes CAH     | No Died       |
| 19821 | 34 | 67/F       | 2 years  | 100 mg/day                  | 7.6                    | 1124        | 1184        | + ve | + ve     | NA                         | NA             | Yes CAH     | No Good       |
Table 1. Continued from previous page.

| Year | Pt | Age/gender | Exposure | Nitrofurantoin dose (mg/dL) | Total bilirubin (mg/dL) | SGOT (IU/L) | SGPT (IU/L) | ANA | Anti SMA | Increased in immunoglobulin | Albumin (mg/dL) | Liver biopsy | Immuno-suppression used | Outcome |
|------|----|------------|----------|----------------------------|-------------------------|-------------|-------------|-----|---------|-----------------------------|----------------|-------------|---------------------------|---------|
| 1994 | 35 | 51/F      | 12 years | 100 mg/day | 3.8                      | 492         | 470         | -ve | NA      | Yes                         | 3.1             | Yes         | CAH+Cirrhosis             | Good    |
| 1999 | 36 | 60/F      | 3 years  | 100 mg/day | 13.2                     | 904         | 467         | +ve | +ve     | No                          | 3.5             | Yes         | CAH+Cirrhosis             | Died    |
| 2001 | 37 | 73/F      | 14 months| 400 mg/day | 14.5                     | 1160        | 884         | +ve | -ve     | No                          | 3.1             | Yes         | CAH+Cirrhosis             | Died    |
| 2002 | 38 | 64/F      | 5 years  | 100 mg/day | Elevated                | 300         | 1700        | +ve | -ve     | NA                          | 2.9             | Yes         | CAH+Cirrhosis             | Died    |
| 2002 | 39 | 72/F      | 1 year   | NA          | Elevated                | 960         | 515         | -ve | +ve     | NA                          | 2.5             | Yes         | CAH+Cirrhosis             | Good    |
| 2002 | 40 | 76/F      | 2 years  | NA          | Elevated                | 830         | 850         | +ve | -ve     | NA                          | 3.3             | Yes         | CAH+Cirrhosis             | Good    |
| 2004 | 41 | 67/F      | 6 months | NA          | 9.7                      | 690         | 206         | +ve | -ve     | Yes                         | 1.5             | Yes         | Fulminant hepatitis        | Died    |
| 2007 | 42 | 72/F      | 11 months| 100-300 mg/day | Elevated | 631         | 825         | +ve | +ve     | Yes                         | 3.7             | Yes         | CAH+Cirrhosis             | Good    |
| 2010 | 43 | 78/F      | 2 years  | 100 mg/day | 11                       | 1511        | 1201        | +ve | -ve     | Yes                         | 2.9             | Yes         | CAH+Cirrhosis             | Died    |
| 2010 | 44 | 55/F      | 27 months| NA          | 2.7                      | 282         | 336         | -ve | +ve     | NA                          | NA              | Yes         | CAH+Cirrhosis             | Good    |
| 2010 | 45 | 55/F      | 36 months| NA          | 37.1                     | 2069        | 1479        | -ve | +ve     | NA                          | NA              | Yes         | CAH+Cirrhosis             | Good    |
| 2010 | 46 | 58/F      | 6 months | NA          | 1.8                      | 827         | 1059        | +ve | +ve     | Yes                         | NA              | Yes         | CAH+Cirrhosis             | Good    |
| 2010 | 47 | 64/F      | 7 months | NA          | 1.1                      | 436         | 188         | -ve | +ve     | Yes                         | NA              | Yes         | CAH+Cirrhosis             | Good    |
| 2010 | 48 | 55/F      | 4 months | NA          | 7.8                      | 918         | 1165        | +ve | -ve     | Yes                         | NA              | Yes         | CAH+Cirrhosis             | Good    |
| 2010 | 49 | 75/F      | 60 months| NA          | 20.6                     | 1725        | 1141        | +ve | +ve     | Yes                         | NA              | Yes         | CAH+Cirrhosis             | Good    |
| 2010 | 50 | 52/F      | 36 months| NA          | 4.5                      | 814         | 778         | +ve | +ve     | Yes                         | NA              | Yes         | CAH+Cirrhosis             | Good    |
| 2010 | 51 | 67/F      | 36 months| NA          | 30.9                     | 1538        | 1652        | +ve | +ve     | Yes                         | NA              | Yes         | CAH+Cirrhosis             | Good    |
| 2010 | 52 | 66/F      | 36 months| NA          | 0.9                      | 300         | 450         | +ve | +ve     | Yes                         | NA              | Yes         | CAH+Cirrhosis             | Good    |
| 2010 | 53 | 66/F      | 36 months| NA          | 0.9                      | 300         | 450         | +ve | +ve     | Yes                         | NA              | Yes         | CAH+Cirrhosis             | Good    |
| 2010 | 54 | 64/F      | 24 months| NA          | 3.5                      | 757         | 448         | +ve | +ve     | Yes                         | NA              | Yes         | CAH+Cirrhosis             | Good    |
| 2010 | 55 | 65/F      | 72 months| 50 mg/day   | 37.9                     | 1322        | 227         | +ve | +ve     | Yes                         | 2.8             | Yes         | CAH+Cirrhosis             | Good    |
| 2010 | 56 | 42/F      | 24 months| 50 mg/day   | NA                       | NA          | 469         | +ve | +ve     | Yes                         | NA              | Yes         | CAH+Cirrhosis             | Good    |
| 2010 | 57 | 74/F      | 24 months| 100 mg/day  | 23.0                     | NA          | 1423        | +ve | -ve     | Yes                         | 1.6             | Yes         | CAH+Cirrhosis             | Good    |
| 2012 | 58 | 55/F      | 6 months  | 200 mg/day  | 8.12                     | 466         | 430         | +ve | +ve     | Yes                         | 2.9             | Yes         | CAH+Cirrhosis             | Good    |

Pt, patients; ANA, anti nuclear antibody; Anti SMA, anti smooth muscle antibody; SGOT, alanine aminotransferase; SGPT, aspartate aminotransferase; NA, not available; +ve, positive; -ve, negative; CAH, chronic active hepatitis.
matic. Three weeks after cessation of Nitrofurantoin, her AST, ALT, ALP, and total bilirubin trended down to 46 IU/L, 35 IU/L, 101 IU/L, and 1.6 mg/dL, respectively. Review after two months revealed normal liver functions.

**Discussion**

Almost all of the patients were females (55 out of 57). One male patient was on nitrofurantoin for recurrent UTI and the other one was for chronic prostatitis (Table 1). The youngest patient was 22 years and the eldest one was 85 years old. The daily dose of nitrofurantoin ranged from 50 mg to 400 mg. The duration of continuous drug exposure was as short as two months to 12 years observed in one patient. However, vast majority (93%) of patients symptoms appeared after six months of drug exposure and only four patients out of 57 presented before six months. ANA titer was positive in 78% of patients (43 out of 55) and in two patients ANA titer was not available. Anti SMA antibody was positive in 72% of cases (34 out of 47). In ten patients anti SMA test was not available. Many of the patients reported in the early eighties did not have anti smooth muscle antibody performed. It is possible that the percentage of positive Anti SMA would have been even higher if those cases had this test performed. However, considering both tests together, 88% of reported cases were positive for either any one of them. There was also a high incidence of hypergammaglobulinemia (79%) observed in these patients. In almost all cases hepatitis serology was done and was negative. With the exception of four patients, all had histological proven chronic active hepatitis with varying grades of inflammation and stages of fibrosis. One patient declined biopsy and in the other patient post mortem examination revealed acute massive hepatocellular necrosis with nodular regeneration. The first two cases reported did not have the liver biopsy done but all of these four cases had clinical and biochemical features consistent with chronic active hepatitis. Development of cirrhosis was noted in eight patients. Histologic pattern observed by Ramachandran and Kakar in their study showed significant fibrosis and cirrhosis with minocycline use than with nitrofurantoin. Contrary to that our review indicates that significant number of cases with nitrofurantoin use also end up with cirrhosis. Steroids were used in 65% of patients either in the form of prednisone or intravenous methylprednisone. Two patients did not improve after a trial of withdrawing the medication and in turn had to be put on steroids, this resulted in complete resolution of symptoms. Moreover in almost all patients, clinical and biochemical improvement was noted immediately after stopping the medication. Liver enzymes along with serologic markers normalized by two months after stopping the medication to up to three years in some cases. Simultaneous pulmonary involvement was recorded in 18% of the patients.

Eight patients (14%) out of 57, died despite withdrawal of offending medication. Elevated liver enzymes were noted early in two patients however nitrofurantoin was continued and both patients developed progressive liver failure causing death. Another patient was left to continue with the nitrofurantoin and later presented with fulminant liver failure and underwent orthotopic liver transplant and survived. Nitrofurantoin has been associated with wide spectrum of hepatotoxic reactions. The estimated frequency of hepatotoxic reactions to nitrofurantoin ranges from 0.3 in 100,000 to 35 in 100,000 treated patients. Acute form of liver injury is more common than the chronic type. In a review of 921 reports of nitrofurantoin toxicity, pulmonary and acute allergic reactions comprised 43 and 43% of reports respectively and chronic interstitial pneumonitis (5%), liver damage (6%), blood dyscrasias (2%) comprised the remainder. Review of 52 cases of hepatic injury associated with use of nitrofurantoin reported to the Netherlands center for monitoring of adverse drug reactions since 1963, most patients with acute hepatic injury had symptoms appearing within six weeks and they recovered well except for few patients with the case fatality rate of 12%.

Nitrofurantoin, minocycline, methyldopa and clometacin are commonly implicated in drug induced autoimmune hepatitis. Concerns have been raised recently on increasing use of minocycline for acne and rheumatoid arthritis and development of autoimmune hepatitis. All these medications can cause chronic hepatitis that is serologically and morphologically indistinguishable from de novo autoimmune hepatitis. Generally chronic hepatitis is a necroinflammatory disease of the liver lasting more than six months. Chronic active hepatitis is the most common liver abnormality observed with long term nitrofurantoin use and has been reported with as short as after six weeks to twelve years of chronic exposure. Most reports came from Scandinavia, the Netherlands and Israel, but Klemola et al. first reported it in 1975. Although the similar case was reported in 1974 by Beck and colleagues, there was no histology available to confirm it.

Both acute and chronic hepatic injury is more frequent in females. This preponderance of female sex is likely due to the fact that more women are treated for UTI than men. Most patients are above the age of 50; again explained by higher incidence of urinary tract infection in this age group. Underlying mechanism behind nitrofurantoin induced liver injury is not fully understood. Although few studies have demonstrated dose related direct toxic injury to cultured mouse cells, it seems that immune mediated response to toxic metabolites of nitrofurantoin are required to cause hepatotoxicity. There is no consistent correlation of the drug with the dose or duration of therapy but continued presence of drug is necessary for the pathogenesis. The presence of ANA and anti SMA, hypergammaglobulinemia and the histology resembles the findings of autoimmune hepatitis. Autoantibodies were present in both the acute and chronic types of hepatic injury although much more frequent in the later. Autoantibodies such as albumin-immunoglobulin G complexes (tailing albumin) have been associated with nitrofurantoin use supporting the autoimmune theory of pathogenesis. Presence of Lupus like syndrome and long-term hepatic memory for hypersensitivity to nitrofurantoin favors this mechanism as well. Recurrent hypersensitivity reaction occurred in patients even after seven years from the last exposure. We find a consistent relationship with presence of both ANA and ASMA in these patients. Our findings correlates with the data presented by Sharp et al. in their review of cases of chronic hepatitis until 1980. In their review, the incidence of ANA was 71%, anti SMA 91%, hypergammaglobulinemia 82% and hypoalbuminemia was noted in 87% of cases studied. In a review of nitrofurantoin induced chronic active hepatitis cases reported to the Netherlands center for monitoring of adverse reactions, anti SMA was positive in 73%, ANA positive in 82%, hypoalbuminemia 67% and hypergammaglobulinemia was found in 100% of cases (Table 2). With the immune mediated response the autoantibodies

**Table 2. The Netherlands center for monitoring of adverse reactions: serology of 13 patients with chronic active hepatitis.**

| Age (years) | Percentage |
|------------|------------|
| 20         | 0%         |
| 21-40      | 0%         |
| 41-60      | 15%        |
| 61-80      | 85%        |

| Gender (female/male) | Percentage |
|----------------------|------------|
| 12/1                 |            |

| Immunology+proteins  | Percentage |
|----------------------|------------|
| Antinuclear factor   | 82% (n=11) |
| Antismooth muscle antibodies | 73% (n=11) |
| Lupus erythematosus cells | 50% (n=6) |
| Hypoalbuminemia      | 67% (n=12) |
| Hypergammaglobulin   | 100% (n=12) |

| Onset of symptoms: time interval | Percentage |
|---------------------------------|------------|
| ≤1 week                         | 0%         |
| 1-6 weeks                       | 0%         |
| 6 weeks - 6 months              | 15%        |
| >6 months                       | 85%        |

| Undetermined                   | 0%         |

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should appear first before the development of active liver injury and clinical manifestations. The time gap between the appearance of these autoantibodies and development of hepatic injury and clinical manifestations are not clear. There was no documentation of last normal liver functions in any reported cases. In our case liver enzymes six month prior to the admission was normal. It took at least six months in most cases to present with symptoms after commencing on nitrofurantoin. With these observations we believe that these autoantibodies appear before the clinical symptoms develop and may take at least three months before presenting clinically as chronic active hepatitis. We propose that these patients should be monitored with ANA, anti SMA and immunoglobulin levels at least once in three months. Should any of this be abnormal, discontinuation of medication is indicated and progressive liver injury can be halted to some extent if not prevented completely. Although autoantibodies play a major role in the pathogenesis of chronic active hepatitis, four of the reported patients did not show positivity for either ANA or anti SMA prompting on some other mechanism, which played a role in minority of patients. Titters of ANA and ASM antibody fall spontaneously and may persist for long time even 2-3 years after liver functions return to normal.4,11

Cases have been reported of nitrofurantoin induced chronic active hepatitis found to have HLA B8, a possible marker for enhanced immunoresponsiveness and a risk factor for developing autoimmune hepatitis.6,9,10,11 Little data exists in literature to support this theory. Johnson Lindbergh and colleagues studied the frequency of human leukocyte antigens in 46 chronic active hepatitis patients which included 13 drug induced hepatitis and they did not differ significantly from control group.4 The same conclusion was inferred by Alain Berson after studying 73 cases and in their study HLA phenotype did not contribute significantly to idiosyncratic drug induced hepatitis.12 Another association noted was the concurrent involvement of lung along with hepatitis. Nitrofurantoin induced chronic lung toxicity can occur in approximately 10% of patients.8,19 We found 18% of them with simultaneous pulmonary involvement favoring combined mechanism for the pathogenesis and presence of any one should prompt searching for the other. In almost all cases reviewed, histology showed findings of chronic active hepatitis with varying grades of inflammation and stages of fibrosis and some progression to cirrhosis. There is no definitive way of establishing the diagnosis of nitrofurantoin-induced hepatitis. In the absence of specific immunologic markers for drug induced chronic active hepatitis, the diagnosis is by exclusion of other causes, assessment of temporal relationship between drug exposure and the development of clinical symptoms. Clinical and biochemical improvement after stopping the nitrofurantoin is the most reliable factor supporting the nitrofurantoin-induced hepatitis. Treatment is withdrawal of offending agent. Steroids have been used in addition to discontinuing the nitrofurantoin, however there is no substantial evidence to support their use and generally not indicated in view of the spontaneous recovery observed in most cases.1,4,10,11,13,15,16 It has been observed that no improvement in symptoms occurred with steroids while patient was on nitrofurantoin emphasizing the fact that ongoing drug is the main factor.22 Also important to note that auto immune hepatitis relapses if steroids discontinued differentiating drug induced liver injury from autoimmune hepatitis.11 Minocycline has been increasingly used for acne and rheumatoid arthritis as a second line agent, which can also cause similar autoimmune hepatitis. In one of the review of relevant publications from the American and European literature with 30 cases of minocycline induced autoimmune hepatitis showed positive ANA in 89% of patients.16 Similar principles can be applied to monitor these patients for liver injuries. Drug toxicity can cause significant morbidity and mortality and may be fatal. Timely identification may result in complete recovery. Consideration should be given for alternative agents before prescribing nitrofurantoin for long-term use. Alternatively, regular use of cranberries, topical vaginal estriol cream especially in postmenopausal women, have been shown to be effective in preventing recurrent UTT.22 Self initiated intermittent treatment with short course of antibiotic would be more acceptable alternative to minimize the adverse reaction to long term use of drugs.22

Conclusions

In conclusion, it seems clear that the immune mechanism is very likely for the development of chronic active hepatitis. We propose continuous monitoring of patients on long-term nitrofurantoin with ANA, anti SMA, immunoglobulin levels and hepatic panel at least once in three months.

Educational points

- Drug induced hepatotoxicity is believed to be underreported. Although its use has come down recently, nitrofurantoin is still one of the common antibiotics prescribed for the long-term prophylaxis of chronic urinary tract infection;
- nitrofurantoin can cause both acute and chronic immune mediated hepatocellular injury and autoimmune hepatitis. Steroids may play an important role if no improvement occurs despite discontinuing the medication;
- consistent presence of ANA and anti SMA in cases of nirofurantoin-induced hepatitis suggests an immunological mechanism and may help in identifying the patients developing hepatic syndrome in early stage;
- a systematic approach should be taken to review the full drug history, determine the cause of hepatotoxicity and remove the offending agent. Complete recovery is possible if the medication is discontinued in time.

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