

## Nitrofurantoin: Is a Rare Cause of Autoimmune Hepatitis

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Rec date: Nov 13, 2015, Acc date: Dec 24, 2015, Pub date: Jan 2, 2016

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### Abstract

Auto-immune hepatitis is of unknown origin. The detection of non-organ and liver-related autoantibodies in the absence of viral, toxic, metabolic and genetic causes constitutes the hallmark for the diagnosis.

**Keywords:** Nitrofurantoin; Autoimmune hepatitis

### Introduction

Auto-immune hepatitis is of unknown origin. The detection of non-organ and liver-related autoantibodies in the absence of viral, toxic, metabolic and genetic causes constitutes the hallmark for the diagnosis [1,2].

Drug-induced immune-mediated liver injury is an adverse immune response against proteins within the liver that can lead to a syndrome of autoimmune hepatitis (AIH). Reactive metabolites created through hepatic metabolism of some drugs have been shown to bind to cellular proteins such as cytochrome P450. These can then be recognized by the immune system as neoantigens. Many drugs were described to induce AIH but only 2 were well documented. Nitrofurantoin has been available for the treatment of urinary tract infections (UTIs) since 1953. It is being used for the treatment of uncomplicated and for prophylaxis in people prone to recurrent UTIs. Many adverse effects have been described, among them auto-immune hepatitis.

### Clinical Case

This is the case of a 61 years old female patient presenting for loss of appetite, tiredness associated with diffuse myalgia and polyarthralgia of all her distal articulations. She is known to have rheumatoid arthritis treated with Methotrexate, recurrent urinary tract infections taking nitrofurantoin from one year. The patient did not have any history of liver disease, blood transfusions, alcohol consumption or acetaminophen intake. Liver enzymes were normal one year ago. At the admission, physical exam was unremarkable with no arthritis, no icterus, and no fever. Initial laboratory results were normal except for elevated transaminases, ALT 555 U/L, AST 346 U/L, alkaline phosphatase 176 U/L, lactate LDH 294 U/L and a normal bilirubin level. Serology was negative for hepatitis A, B and C. Anti-nuclear antibody (ANA) done by indirect immunofluorescence method was positive 1/1200 with a positive anti mitochondrial antibody (AMA) done by western blot method. We had a polyclonal gamma globulin of 3.3 g/dl. Abdominal ultrasound was normal. A liver biopsy was refused by the patient. Nitrofurantoin was stopped. One month later, liver enzymes were normal. The ANA and AMA were normal after 6 months.

### Discussion

Drug induced autoimmune hepatitis is similar to idiopathic autoimmune hepatitis. The difference is that drug induced autoimmune hepatitis typically resolves completely once the medication is withdrawn, although recovery may be slow and lead to a limited course of corticosteroid therapy.

The early clinical manifestations are typically insidious. Sometimes the extra hepatic manifestations such as rash or joint pains precede symptoms due to hepatic injury like fatigue, nausea, anorexia. Jaundice appears later, and may follow several months the nonspecific symptoms.

Medications that typically cause autoimmune hepatitis include minocycline, nitrofurantoin, hydralazine, methyldopa, statins, fenofibrate, alpha and beta interferon, infliximab and etanercept. Nonsteroidal antiinflammatory agents, azathioprine, and some herbals treatment can induce autoimmune hepatitis-like syndrome. In addition, isoniazid, procainamide some can induce autoantibodies even in the absence of hepatic injury [1].

Most cases of drug induced autoimmune hepatitis described in the literature, begun at least six months, but can be up to several years after initiation of the therapy. Rarely, with using minocycline, nitrofurantoin, methyldopa, hydralazine, and pathology is more rapid and can cause an acute viral hepatitis-like syndrome. The clinic resembles to acute hepatitis, but the appearance of auto antibodies may take more than 2 months.

Most cases of nitrofurantoin induced auto-immune hepatitis occurred in female patients due to higher risk of urinary tract infection and most of them are in their fifties years. Majority of cases described in the literature begun at least six weeks after the consumption the medicament, and 85% of patients after 6 months [3,4].

In case of autoimmune hepatitis due to drugs, biology is manifested by moderate serum aminotransferase elevations and minimal increase in alkaline phosphatase levels. Antinuclear (ANA), smooth muscle antibody (SMA) or antibody to liver-kidney microsomes (LKM) is usually present. Anti-mitochondrial antibody (AMA) may be found in up to 20% of AIH individuals [5]. AMA occur in about 5% of AIH patients in the absence of other biliary features [6,7]. They are usually lower in titre (1:40 or less) and, in some, represent false positives. The

presence of AMA should not necessarily be interpreted as an AIH-primary biliary cirrhosis overlap.

The liver biopsy is showing features of chronic hepatitis. The presence of interface hepatitis and prominence of plasma cells is characteristic [3,6,8,9].

The important differential diagnosis for drug induced autoimmune hepatitis is idiopathic autoimmune hepatitis a disease that can have spontaneous remissions and relapses but that is typically severe and progressive without adequate immunosuppressive therapy.

The pathogenesis of autoimmune hepatitis due to medications is not clear. Liver injury from nitrofurantoin is also not known. It has been speculated, however, that it is an immunoallergic rather than a metabolic reaction [10]. Supporting an immunoallergic reaction are the presence of (ANA), smooth muscle antibody (SMA), antibody to liver-kidney microsomes (LKM), anti-mitochondrial antibody (AMA), hypergammaglobulinemia and the presence of chronic active hepatitis on liver histology [11,12].

Genetic predisposition may also contribute to AIH. HLA types (HLA3, Dr3, Dr03) in Caucasian and northern Europeans with autoimmune hepatitis were implicated but it has not been well defined in DIAIH. Cases have been described of nitrofurantoin induced chronic active hepatitis found to have HLA B8, a possible marker for enhanced immunoresponsiveness and a risk factor for developing auto-immune hepatitis [6,7,13]. Nowadays, there are not enough data to establish an association between HLA antigens and susceptibility to DIAH.

No established diagnostic criteria for drug induced autoimmune hepatitis [9,10]; however based upon the similarity with autoimmune hepatitis, the same criteria are being used with the addition of the necessity of the presence of an agent that is typically associated with drug induced autoimmune hepatitis with the time to onset of the disease is 2 months. Discontinuation of the drug led to clinical and biochemical improvement in most cases [14]. Some patient needs steroids treatment if no beneficial effect after withdrawing nitrofurantoin [15]. In other cases, the result was fatal despite the addition of steroids [14] for patients with continued exposure to the drug.

In our case, and despite the presence of rheumatoid arthritis and methotrexate treatment that may also give hepatic impairment, the improvement of liver enzymes, the normalization of ANA and AMA tests after stopping nitrofurantoin treatment, shows the role of drugs in the genesis of the disease.

## Conclusion

Exposure to nitrofurantoin may be the cause of chronic active hepatitis. This adverse reaction shares a number of features with

autoimmune hepatitis, including histopathology and immune markers and possibly the response to glucocorticoids.

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