Case report

Tamoxifen induced non-alcoholic steatohepatitis (NASH) – a case report and its clinical implications

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Introduction

Tamoxifen is universally used in the treatment of breast cancer. It is usually well tolerated drug but could rarely cause serious irreversible liver damage which is easily missed, unless one is aware of this, implying regular monitoring of liver functions. Identification of such pathologies will essentially result in withdrawal of tamoxifen leading to alternative therapies. The following case report highlights causation of non-alcoholic steatohepatitis in a tamoxifen treated female.

Case report

A 45 years old female who was on tamoxifen therapy for carcinoma of breast, was referred for further investigation following clinical and ultra sound detection of an asymptomatic hepatomegaly with elevated liver transaminases, and alkaline phosphatases. All the routine investigations including hepatitis screen were normal. The liver histology confirmed presence of non alcoholic steatohepatitis.

Discussion

In 1980 Ludwig and collegues[1] described patients who lacked a history of substantial alcohol consumption, but had findings on liver biopsy that could not be distinguished from those of patients with alcoholic hepatitis. Characterized by two main diagnostic criteria (evidence of fatty changes with lobular hepatitis and absence of alcoholism) the term "non-alcoholic steatohepatitis" NASH, was coined. Although the prevalence of NASH is not well defined, it is reported worldwide and is detected 1.2% to 9% of patients who have had liver biopsy. The pathogenesis of NASH is unclear, but various theories have implicated fatty acids.

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Factors associated with NASH –

Metabolic factors

Obesity, diabetes and hyperglycaemia, hyperlipidaemia, rapid weight loss, acute starvation, intravenous glucose therapy in the week before death, total parenteral nutrition.

Surgical procedures

Jejunal bypass, gastroplasty for morbid obesity Biliopancreatic diversion, extensive small bowel resection.

Drug treatment

Amiodarone, Perhexiline maleate, glucocorticoids, synthetic oestrogens, tamoxifen.

Miscellaneous factors

Jejunal diverticulosis with bacterial over growth, partial lipodystrophy, abetalipoprotainaemia, Weber-Christian disease.

The relation between steatosis, steatohepatitis and fibrogenesis has not been elucidated. Hepatic peroxidation of lipids may result in the generation of potentially toxic intermediates that can induce an inflammatory response in the liver[2,3]. However isolated fatty liver without hepatitis occurs more frequently than does steatohepatitis. Finally, the underlying mechanisms of liver injury in NASH and in alcoholic hepatitis may be similar, as suggested by, similar ratios of mitochondrial AST to total AST[4].

Histology

Various histological features have been described. In many studies[5,6] NASH has been diagnosed by the presence of fatty degeneration (steatosis) and lobular inflammation (hepatitis) only: hepatocyte degeneration, necrosis, fibrosis, cirrhosis and Mallory hyaline bodies may not be present. Other studies[7,8] have used a stricter definition for the histologic diagnosis of NASH, including steatohepatitis and hepatocyte ballooning or degeneration or hepatic fibrosis.

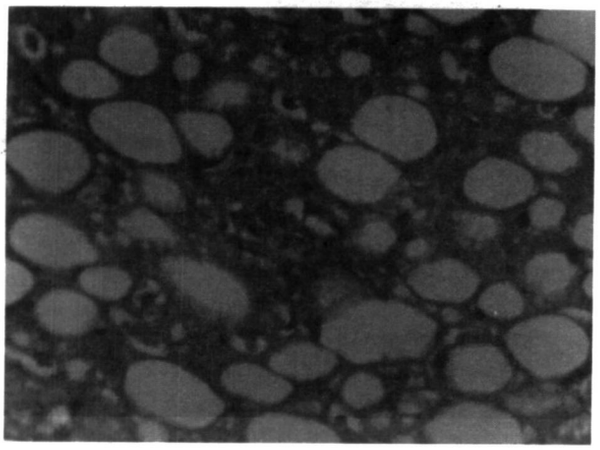

Figure 1. Swollen cells with fatty changes and mild inflammation – high power view.

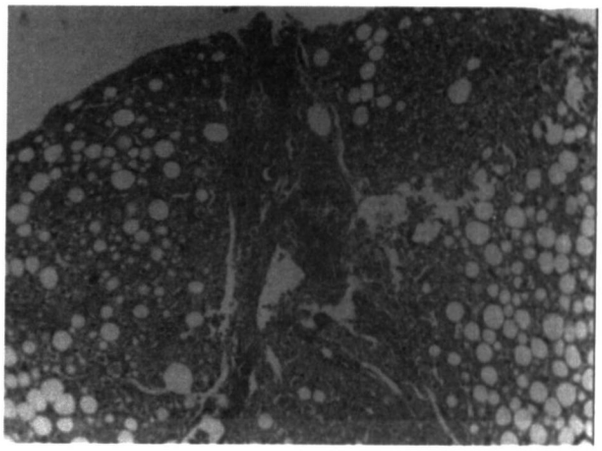

Figure 2. Portal fibrosis-Vangiesen stain. Fibrotic tissue- stained in red- low power view.

Fibrosis in association with NASH ranges from absent to severe and may be perisinusoidal, centrilobular or septate. The prevalence of mild to moderate fibrosis in patients with NASH varies from 76% – 100%[1,8,9,10,11] that of severe fibrosis ranges from 15-50%[1,5,6,8,10]. Cirrhosis, however occurs less frequently in adults (7-6%)[1,5,6,8] and is absent in children[12].

Clinical course

Although patients with NASH generally have an indolent course, nearly 50% develop progressive fibrosis and as many as one sixth develop cirrhosis. No clinical laboratory on histology features can predict progression or distinguish patients with or without worsening liver disease. Approximately 8-17% of patients with NASH[5,8] compared with 38%-50% of patients with alcoholic hepatitis[13,14] progress to cirrhosis after a similar period of follow up.

Management

No proven therapy for NASH exists. If it is caused by a drug, that drug should be withheld. Only urso-deoxycholic acid had been found to result in a significant improvement in both biochemistry and histology in NASH[15,16] which may be due to its direct cytoprotective effects[17] in our patient hepatic transaminases became normal after 3 months treatment with urso-deoxycholic acid 150mg twice daily following withdrawal of tamoxifen. We hope to repeat the liver biopsy at 6 month and 12 month intervals, while on therapy.

Conclusions

- Nonalcoholic steatohepatitis is a rare complication of tamoxifen therapy which could lead to cirrhosis of the liver in some susceptible individuals.
- All users of tamoxifen should be aware of this potential liver damage and therefore, should regularly monitor the tansaminases in every treated patient.
- Urso-deoxy cholic acid is the only known therapeutic option with some benefits, which should therefore be offered to affected patients following withdrawal of tamoxifen.
- Liver biopsy is mandatory in patients on tamoxifen, who show abnormal liver functions to diagnose this potentially serious complication.
- We suggest that multi-centre studies should be carried out to estimate the true incidence of tamoxifen induced NASH.

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