Azathioprine induced liver cirrhosis: An unusual side effect

Aida Ben Slama Trabelsi1*, Eya Hamami1, Mehdi Ksiaa1, Ahlem Souguir1, Mohamed Ben Mabrouk2, Ahlem Brahem1, Ali Jmaa1, Salem Ajmi1

1Department of Gastroenterology, Sahloul Hospital, Sousse, Tunisia
2Department of Surgery, Sahloul Hospital, Sousse, Tunisia
Email: *aida.benslama@yahoo.fr

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ABSTRACT

In recent years, the hepatotoxic potential of thiopurines, in particular 6-thioguanine (6-TG), has been discussed in literature. However, cirrhosis was exceptionally reported. We report the case of a 56-year-old woman with ileocaecal Crohn’s disease treated with azathioprine. After taking azathioprine (2 mg/kg daily) for four years, she underwent surgical treatment for acute intestinal obstruction. In peroperative, we noticed a cirrhotic liver. A surgical biopsy was performed and the diagnosis of cirrhosis was confirmed. Autoimmune and viral liver diseases were ruled out by laboratory parameters. Therefore, Azathioprine is believed to be the causative factor for inducing liver cirrhosis. Thus, treating inflammatory bowel disease effectively while trying to limit iatrogenic disease is a continuous struggle.

Keywords: Azathioprine; Crohn’s Disease; Hepatotoxicity; Liver Cirrhosis

1. INTRODUCTION

Nowadays, thiopurines (azathioprine (AZA) and mercaptopurine (6 MP)) are the most commonly used immunomodulatory drugs for managing patients with inflammatory bowel disease (IBD) [1]. They are among the pharmacological agents with the greatest potential to cause adverse reactions. The side-effects of thiopurines can be divided into dose independent or “allergic/idiopathic” and dose-dependent events. Hepatic toxicity is believed to be a dose independent side effect of AZA.

In recent years, the hepatotoxic profile of thiopurines has been recognised. Most hepatic lesions described are vascular, such as peliosis hepatis, veno-occlusive disease, perisinusoidal fibrosis, hepatoportal sclerosis, and nodular regenerative hyperplasia.

Even after long term treatment, most series report a rate of hepatic abnormalities of between 1% - 3%, which are usually limited to abnormal liver function tests and minor changes seen on liver biopsy specimens. The occurrence of side-effects, however, is a major drawback in the use of AZA or MP [2]. Cirrhosis is an exceptional complication of thiopurine drugs; only one case was reported in literature [3].

We report a rare case of liver cirrhosis in a Crohn’s disease patient associated with AZA therapy and we try to do a review of the literature regarding this complication.

2. CASE REPORT

A 56-year-old woman was followed, for 20 years, for ileocaecal Crohn disease complicated with stenosis. A corticosteroid pulse therapy was administered to induce remission. In 2000, a surgical treatment consisting of an ileocaecal resection was performed due to an acute intestinal obstruction caused by the terminal ileum stenosis (Figure 1). During surgery, liver was macroscopically normal. In the post-operative, Budesonide therapy was immediately initiated. The disease remained quiescent and regular laboratory controls including serum transaminases were normal.

In 2006, the patient was treated with AZA in doses of 2 mg/kg/j. She remained free of endoscopic and clinical recurrence until 2010 when she underwent reoperation for adhesions bowel obstruction. She had a new resection of the ileum. At laparotomy, the liver was macroscopically normal. In the post-operative, Budesonide therapy was immediately initiated. The disease remained quiescent and regular laboratory controls including serum transaminases were normal.

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Liver function tests were normal. Viral liver diseases...
Figure 1. CT scan: stenosis of terminal ileum.

were ruled out by laboratory parameters. Autoimmune
diseases of the liver are also unlikely in the absence of
autoantibodies. Then, AZA therapy (4 years) was belie-
ved to be the causative factor of cirrhosis.

3. DISCUSSION

The thiopurine drugs such as AZA and 6-MP represent
an effective and widely used immunosuppressant in the
therapeutic armamentarium of IBD. They can induce and
maintain remission of Crohn’s disease and ulcerative
colitis, and have steroid-sparing effects in patients with
steroid-dependent IBD [4,5]. However, their therapeutic
role is disputable because of toxicity. Up to 25% of pa-
tients may be unable to continue the drug due to side
effects. The incidence of hepatotoxicity associated with
thiopurine use is reported between 0% and 32% [6].

Many of the symptoms of hepatotoxicity can be non-
specific and can be confused with a flare-up of inflam-
matory bowel disease. As well, the subtype resulting in
portal hypertension can occur without biochemical ab-
normals.

Thiopurine-induced hepatotoxicity can be grouped in
three syndromes: hypersensitivity, idiosyncratic chole-
static reaction, and endothelial cell injury (with resultant
raised portal pressures, veno-occlusive disease, or pelio-
sis hepatitis, perisinusoidal fibrosis and nodular regenera-
tive hyperplasia) [7].

AZA and 6-MP are metabolized into active and inac-
tive metabolites by the same enzymatic cascade. AZA is
a pro-drug that is converted to 6-MP via a nonenzymatic
metabolic pathway and its imidazole derivative by glutathione in the liver. Then, 6-MP enters cells and is subject
to 3 competing enzymatic pathways [8]. It may be ac-
tivated via a multi-step enzymatic pathway to produce
the active metabolites, the 6-thioguanine nucleotides (6-
TGNs). 6-MP is also metabolized by thiopurine methyl
transferase (TPMT) to 6-methylmercaptopurine (6-MMP)
or by xanthine oxidase to 6-thiouric acid.

Several metabolites have been held responsible for in-
duction of adverse events. Many studies have shown that
hepatotoxicity seems to be related to the accumulation of
methylated metabolites such as 6-MMP [3,9]. The enzy-
me TPMT is the key enzyme in the metabolic pathway: pa-
tients with very high TPMT activity are resistant to
thiopurine drugs due to shunting of 6-MP away from 6
TGN towards over production of 6-MMP [9,10], and at
the risk of hepatotoxicity due to high 6-MMP concen-
trations [11-16].

In our case, high TPMT activity can not be the mecha-
nism of hepatotoxicity. Indeed, azathioprine was effec-
tive in maintaining remission in our patient at a dose of 2
mg/kg/day.

The hypothesis that high 6-TGN levels are hepatotoxic
may provide an explanation why our patient developed
liver cirrhosis. The higher occurrence of histological
liver abnormalities during 6-thioguanine (6-TG) treat-
ment in comparison with AZA or 6-mercaptopurine (6-
MP) may be explained by the significantly higher levels
of 6-TGN reached by 6-TG [3].

This case illustrates the potential toxicity of AZA,
highlights the need to monitor liver function tests in pa-
tients treated with thiopurine, and identifies the need for
additional research focused on the mechanism of thio-
purine-induced hepatic injury in patients treated with
thiopurines for inflammatory bowel disease. Cirrhosis
may be an exceptional complication of thiopurine drugs.

Knowledge of such side effect could justify the routine
use of abdominal ultrasound in monitoring patients on
thiopurine as liver function tests may be normal.

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**LIST OF ABBREVIATIONS**

AZA: azathioprine  
6 MP: mercaptopurine  
IBD: inflammatory bowel disease  
6-TGNs: 6-thioguanine nucleotides  
TPMT: thiopurine methyl transferase  
6-MMP: 6-methylmercaptopurine  
6TG: 6-thioguanine