Idiopathic portal hypertension regarding thiopurine treatment in patients with inflammatory bowel disease

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ABSTRACT

Introduction: The possibility of developing idiopathic portal hypertension has been described with thiopurine treatment despite compromises the prognosis of these patients, the fact its true prevalence is unknown.

Material and methods: A cross-sectional study was conducted in a cohort of inflammatory bowel disease (IBD) patients followed at our unit, to determine the prevalence of diagnosis of idiopathic portal hypertension (IPH) and its relationship with thiopurine treatment.

Results: At the time of the analysis, 927/1,419 patients were under treatment with thiopurine drugs (65%). A total of 4 patients with IBD type Crohn’s disease with idiopathic portal hypertension probably related to the thiopurine treatment were identified (incidence of 4.3 cases per 1,000). Seventy-five percent of patients started with signs or symptoms of portal hypertension. Only one patient was asymptomatic but the diagnosis of IPH because of isolated thrombocytopenia is suspected. However, note that all patients had thrombocytopenia previously. Abdominal ultrasound with fibroscan, hepatic vein catheterization and liver biopsy were performed on all of them as part of the etiology of portal hypertension. In the abdominal ultrasound, indirect portal hypertension data were observed in all patients (as splenomegaly) cirrhosis was also ruled out. The fibroscan data showed significant liver fibrosis (F2-F3).

Conclusion: Idiopathic portal hypertension following thiopurine treatment in IBD patients is a rare occurrence, but it must be borne in mind in the differential diagnosis for early diagnosis, especially in patients undergoing thiopurine treatment over a long period. The presence of thrombocytopenia is often the only predictor of its development in the preclinical stage.

Key words: Idiopathic portal hypertension. Inflammatory bowel disease. Thiopurine treatment.

INTRODUCTION

Between the secondary hepatic adverse effects to the thiopurine treatment in patients with inflammatory bowel disease (IBD), there has been described the possibility of developing idiopathic portal hypertension (IPH). This pathology with uncertain etiology can compromise the prognosis of these patients, therefore, it is necessary to have a high degree suspicion for an early diagnosis.

IPH is a rare condition of unknown etiology that covers various syndromes with similar clinical characteristics. To make the diagnosis, one needs to establish unmistakable signs of portal hypertension and to rule out liver cirrhosis and other specific causes of liver disease. The definitive diagnosis is obtained with representative pathology revealing the presence of hepatopetal sclerosis and/or oblitative venopathy (obliteration of small venules portals in fibrous tracts) (1).

One variant of idiopathic portal hypertension is nodular regenerative hyperplasia (NRH). It has been reported in patients treated with thiopurine drugs for IBD. It is a type of dose-dependent injury characterized by damage to the endothelial cells of the sinusoids and hepatic veins, resulting in non-thrombotic occlusion of the blood vessels and the subsequent development of fibrosis and portal hypertension (1-3). Large data sets are not available and only isolated cases have been reported in which thiopurine treatment appears to be the main cause of the syndrome (4). The onset of IPH usually occurs between 3 months and 3 years into the thiopurine treatment. Although the pathogenic mechanism is unknown, it appears to be due to the depletion of glutathione by the use of azathioprine and mercaptopurine (5).

The HNR can produce non-cirrhotic portal hypertension with the onset of esophageal varices, splenomegaly and ascites. These changes can occur even when analysis does not reveal signs of abnormal liver function. This pathology should therefore be suspected in all patients who: a) are receiving thiopurine treatment (or who have received it
previously); and b) who exhibit portal hypertension but no other liver disease (6).

MATERIAL AND METHODS

A cross-sectional study was conducted in a cohort of IBD patients followed at our unit to determine the prevalence of diagnosis of IPH and its relationship with thiopurine treatment.

For that, the clinical histories of all the patients who are at present in pursuit in our IBD unit have been reviewed. There have been initially selected for the study those patients who were presenting a sign of liver disease (analytical, clinical or radiological alteration) and who were or had been low thiopurine treatment for their IBD.

It was considered to be a significant analytical alteration:
- Pronounced elevation of transaminases, understanding as such an elevation of at least the double of the top profile of the normality.
- Moderate elevation of liver test but remaining stable (for at least one month) or that it requires intervention in some sense for its correction (for example, stopping thiopurine treatment).
- Trombopenia not explained by hematological disorders, whose origin could be liver failure and/or portal hypertension.

We analyzed the baseline characteristics of patients with IPH which included a complete analysis (blood count and biochemistry) to study liver disease (serology, auto-immunity, lysosomal storage diseases protein, immunoglobulins and alpha-1-antitrypsin), and an abdominal ultrasound scan with transient elastography (fibroscan).

A study was also made of portal hypertension including hepatic vein catheterization, gastroscopy for screening of esophageal varices and magnetic resonance angiography (to rule out vascular pathology of the splenoportal axis) and transjugular liver biopsy for definitive diagnosis in all patients.

In the statistical analysis, values are represented as median and range, while categorical data is represented as frequencies (%) and range. Comparisons between groups on continuous variables were performed using Student’s t-test or ANOVA as appropriate. Categorical data were compared using the Chi square test. Statistical significance is set at a level of p < 0.05. Statistical analyses were carried out with SPSS 20.0 (SPSS inc., Chicago IL, USA) for Mac.

RESULTS

At the time of analysis, our centre had 1,419 patients being monitored for IBD (ulcerative colitis, Crohn’s disease and indeterminate colitis). Of these, 927 patients were under treatment with thiopurine drugs (or have been during the evolution of their disease), representing 65.3% of the population: 689 patients with azathioprine (74.3%) and 238 with 6-mercaptopurine (25.7%).

In the selected sample, 63 patients (6.8% of the patients who had received thiopurines) developed liver disease related to the thiopurine treatment, all other causes of liver disease having been excluded.

Most of them (59 patients, 93.6%) were diagnosed of hepatotoxic of thiopurines, producing in all of them an improvement of the liver test after the decrease of the dose and/or stopping the treatment. Nevertheless, it has to be emphasized that 11 patients were diagnosed of concomitant non alcoholic fatty liver disease.

A total of 4 patients with IBD type Crohn’s disease with idiopathic portal hypertension probably related to the thiopurine treatment were identified, representing 4.3% of the total (i.e. an incidence of 4.3 cases per 1,000 IBD patients treated with thiopurine). The baseline characteristics of the patients are described in table I.

Seventy-five percent of patients started with signs or symptoms of portal hypertension: one patient with hepatic encephalopathy and 2 patients with bleeding esophageal varices. Only one patient was asymptomatic but with a suspected diagnosis of IPH as a result of isolated thrombocytopenia. However, one should note that all patients previously had thrombocytopenia although diagnosis of portal hypertension was not suspected despite an exhaustive study.

Abdominal ultrasound with fibroscan, hepatic vein catheterization and liver biopsy were performed on all the patients as part of the etiology of portal hypertension. In the abdominal ultrasound, indirect portal hypertension data were observed in all patients (as splenomegaly) thus also ruling out cirrhosis. The fibroscan data showed significant liver fibrosis (F2-F3). In addition, all patients were subjected to resonance angiography where splenportal axis thrombosis was ruled out as a cause of IPH. Finally, the pathology of the liver biopsy ruled out the presence of liver cirrhosis, supporting the diagnosis of IPH (Table II).

After the diagnosis of IPH probably stemming from thiopurine treatment, all patients were monitored by the hepatology unit with diagnosis and therapeutic management following clinical practice for patients with portal hypertension. Cases of bleeding varices received endoscopic treatment by ligation of varices with bands and later secondary prophylaxis of gastrointestinal bleeding.

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Table I. Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Gender</th>
<th>3 males (75%)</th>
<th>1 female (25%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Average: 51.5 years</td>
<td>Range (42-72)</td>
</tr>
<tr>
<td>IBD development time (years)</td>
<td>Average: 20 years</td>
<td>Range (19-24)</td>
</tr>
<tr>
<td>Thiopurine time (months)</td>
<td>Average: 88 months</td>
<td>Range (30-120)</td>
</tr>
<tr>
<td>Analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOT (IU / L)</td>
<td>Average: 50.25</td>
<td>Range (18-73)</td>
</tr>
<tr>
<td>GPT (IU / L)</td>
<td>Average: 34</td>
<td>Range (21-65)</td>
</tr>
<tr>
<td>GGTT (IU / L)</td>
<td>Average: 175</td>
<td>Range (8-465)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>Average: 1.15</td>
<td>Range (0.4 to 2.2)</td>
</tr>
<tr>
<td>Platelets (x10²)</td>
<td>Average: 73.25</td>
<td>Range (60-100)</td>
</tr>
<tr>
<td>Prothrombin activity (%)</td>
<td>Average: 84.75</td>
<td>Range (76-100)</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>Average: 4.1</td>
<td>Range (3.6-4.5)</td>
</tr>
</tbody>
</table>
from esophageal varices with beta-blockers. In addition, treatment with thiopurine drugs was suspended in all cases and it was not re-introduced at any point.

**DISCUSSION**

IPH is an uncommon liver disease of unknown etiology that includes a group of disorders with similar clinical characteristics, encompassing a wide spectrum of histological alterations (hence the use of other terms to describe the condition, such as hepatoporal sclerosis, non-cirrhotic portal fibrosis, incomplete septal cirrhosis and nodular regenerative hyperplasia) (7,8). This fact probably reflects different stages of the disease or multiple pathological processes that converge in a syndrome with similar clinical characteristics.

The diagnosis of IPH is a diagnosis by exclusion (i.e., occurring in patients with clinical-radiological findings of portal hypertension without cirrhosis and without vascular changes (with permeability splenoporal axis and hepatic veins)) (9-11). The diagnosis is established by pathology, although this ranges from minor changes to the presence of NRH.

The literature shows cases of secondary IPH following treatment with thiopurine drugs in patients with IBD, mostly described as NRH. This and other adverse hepatic effects (such as veno-occlusive disease or peliosis) can arise from between 3 months and 3 years of treatment with thiopurine (12,13).

In our series, we identified 4 patients with unequivocal diagnosis of IPH, with the thiopurine treatment as the only objective causal factor. Nevertheless, although an exhaustive analysis was made to diagnose all possible cases, it has the limitations characteristic of a transversal study.

One should note that in our study all patients had long had IBD Crohn’s disease (mean 20 years) and had been treated with thiopurine drugs for a long period (mean 88 months, range 30-120 months). No adverse effects of this nature were found in patients who had not received at least two years of treatment.

IPH, unlike cirrhosis, does not usually lead to abnormal test results in the early stages of the disease. In the case of IPH, liver test results tend to be normal (in the absence of cholestasis or cytolysis) (14). Only the presence of thrombocytopenia may predict the development of IPH (15). In our series, in up to 100% of cases the presence of thrombocytopenia was the first sign of IPH, although as clinical suspicion was low probably due to the low incidence of this disease, the diagnosis was not established until there were other signs and symptoms of portal hypertension. That is, the isolated thrombocytopenia may have been a predictor for the development of portal hypertension. Therefore, in the presence of thrombocytopenia in patients suffering from IBD and treated with thiopurine drugs, exhaustive study of liver disease is needed to discriminate between patients with IPH (even when liver function tests are strictly normal). In fact, in patients with compensated cirrhosis, a figure of platelets

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal ECO</td>
<td>Smooth</td>
<td>Smooth</td>
<td>Smooth</td>
<td>Smooth</td>
</tr>
<tr>
<td>* Liver edge</td>
<td>Smooth</td>
<td>Smooth</td>
<td>Smooth</td>
<td>Smooth</td>
</tr>
<tr>
<td>* Base diameter</td>
<td>16 cm</td>
<td>13.5 cm</td>
<td>14.5 cm</td>
<td>14.4 cm</td>
</tr>
<tr>
<td>* Splenic hilum</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>collateral circulation</td>
<td>Others</td>
<td>Others</td>
<td>Others</td>
<td>Others</td>
</tr>
<tr>
<td>Fibroscan (MR: 100%; IQ: 1.3)</td>
<td>F2</td>
<td>F3</td>
<td>F3</td>
<td>F3</td>
</tr>
<tr>
<td>Hepatic haemodynamics</td>
<td>Sinusoidal PHT not clinically significant</td>
<td>Sinusoidal PHT not clinically significant</td>
<td>Sinusoidal PHT clinically significant</td>
<td>Sinusoidal PHT clinically significant</td>
</tr>
<tr>
<td>HVPG</td>
<td>7.5 mmHg</td>
<td>7 mmHg</td>
<td>7 mmHg</td>
<td>7 mmHg</td>
</tr>
<tr>
<td>DBP</td>
<td>7 mmHg</td>
<td>7 mmHg</td>
<td>7 mmHg</td>
<td>7 mmHg</td>
</tr>
<tr>
<td>PVCI</td>
<td>7.5 mmHg</td>
<td>7 mmHg</td>
<td>3.5 mmHg</td>
<td>7 mmHg</td>
</tr>
<tr>
<td>PSHE</td>
<td>15 mmHg</td>
<td>2 mmHg</td>
<td>3.5 mmHg</td>
<td>18 mmHg</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>Mild steatosis as only notable injury</td>
<td>No regenerative changes, fibrosis or inflammatory changes observed. No necrosis, inflammation, steatosis, cholestasis or other relevant changes were observed in the lobule</td>
<td>Non specific changes with no signs of cirrhosis or focal lesion. No hepatocyte dysplasia observed</td>
<td>Nodular architectural alteration compatible with the diagnosis of nodular regenerative hyperplasia</td>
</tr>
</tbody>
</table>

| Table II. Study for the diagnosis of idiopathic PHT |
lower than 150,000 platelets/mm³ was independently associated with the presence of esophageal varices (16). In our series, all patients had a platelet count of 100,000/mm³ or lower, so if the suspicion of portal hypertension had been high, it could have been a predictor.

Regarding liver function tests, our patients had no major alterations of liver function (GOT average: 50 U/L, average GPT: 34 U/L and average GGT 175 U/L).

This insidious, silent, presentation means that, in most reported cases, the first clinical manifestation is portal hypertension. In our study, 3 patients (75%) were diagnosed following a sign or symptom of portal hypertension, two due to gastric bleeding esophageal varices and the other due to an episode of hepatic encephalopathy. Although these symptoms are the proper ones of the portal hypertension for other causes, it has been reported that variceal bleeding is most frequent, affecting two thirds of the patients (17,18). This explains why the diagnosis of IPH is delayed by the difficulty of diagnosing early pre-clinical stages.

Characteristically, patients with idiopathic portal hypertension show higher values in transient elastography but these are below the threshold described for predicting the presence of clinically significant portal hypertension (18.4 Kpa) (19). In our study, no patient had a normal value in the fibroscan although, as discussed above, it was less than 13 Kpa (which corresponds to an F4 stage because all patients exhibited values corresponding to F2-F3).

All patients exhibited portal hypertension when their liver hemodynamic was analyzed, although not all of them showed clinically significant values of portal hypertension. Note that even in patients with clinical manifestations of portal hypertension (such as bleeding gastro-esophageal varices), the portal pressure gradient measured by catheterization of supra-hepatic veins was not clinically significant. In other words, patients with IPH exhibited lower clinical gradients than those estimated for patients with secondary portal hypertension due to cirrhosis, probably because the measurement of hepatic venous pressure gradient translates to sinusoidal pressure and does not allow one to infer the pre-sinusoidal pressure that is characteristic of IPH (20).

The clinical course of patients was similar to that of other patients diagnosed with non-cirrhotic portal hypertension from other causes. Fifty per cent of patients required diuretic therapy due to the presence of ascites. Response to such treatment was good.

CONCLUSION

We can conclude that IPH following thiopurine treatment in patients with inflammatory bowel disease is a rare occurrence but it must be borne in mind in the early differential diagnosis, particularly in patients undergoing thiopurine treatment over a long period. The presence of thrombocytopenia is often the only predictor of its development at the pre-clinical stage.

REFERENCES