Severe Ticlopidine-Induced Cholestatic Syndrome

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Key Words
Ticlopidine-induced cholestasis · Toxico-pathogenous liver insufficiency · Iatrogenic cholestasis · Liver-kidney transplantation · Intrahepatic cholestasis

Introduction

Ticlopidine, widely used in the prevention of stroke or myocardial infarction and in the reduction of cardiovascular risk [1–3], is also often used in the prevention of thrombotic events involving the arterio-venous fistula. The drug is a powerful antithrombotic agent that seems to act by inhibiting the platelet aggregation induced by ADP and by blocking the fibrinogen membrane receptors. Among the drug’s side effects, the following can be mentioned: hemorrhage, gastrointestinal disorders, hemocytopenia (from medullar aplasia), thrombotic thrombocytopenic purpura, hepatopathy (asymptomatic increase in the hepatic enzymes), skin rash [1, 2]. More rarely, hepatic complications of an acute intrahepatic cholestatic syndrome type can occur that normally regress with drug withdrawal [4].

We here describe a serious as well as unusual case of jaundice with a ‘malignant’ clinical evolution.

Case

A 53-year-old man, non-drinker and hypertensive, with a diagnosis of end-stage kidney disease (ESKD) given in the previous year, started replacement dialysis treatment at our Dialysis Unit in June 2002. At the age of 40 (1989), he had been submitted to the removal of the left kidney as a result of obstructive hydronephrosis. The laboratory tests relating to liver function were normal (bilirubin 0.36 mg/dl, γ-GT 14 U/l, AST 12 U/l, ALT 8 U/l). The drugs being administered were carvedilol 12.5 mg/die, omeprazol 20 mg/die, calcium carbonate 3.6 g/die, ticlopidine 250 mg/die for
prophylactic anti-thrombotic purposes (after the construction of arterio-venous fistula as a vascular access for the hemodialysis treatments), and erythropoietin 12,000 IU/week.

About a month after the start of the dialysis treatment, we observed the appearance of deepening jaundice and a squamous skin reaction with diffuse pruritus, accompanied by the emission of deepening jaundice and a squamous skin reaction with diffuse pruritus, accompanied by the emission of itchings and widespread lesions caused by scratching.

We then took the toxico-pathogenetic hypothesis into consideration. The chronic therapy administered to the patient until then had been in progress for some time and as concerns the drugs taken no similar toxic phenomena is described. We had already made sure that the patient was not taking any other potentially hepato-damaging drugs on his own initiative (e.g. benzodiazepine or tricyclic antidepressives).

As the only recent therapeutic variation was the addition of ticlopidine, which had started 10 days before the appearance of the jaundice, a relationship was hypothesized between the clinical picture and the toxicity of the drug that was thus withdrawn after 17 days of therapy.

However, the condition of hyperbilirubinemia persisted reaching values up to 40 mg/dl with alkaline phosphatase of 3,050 U/l. The patient thus started symptomatic therapy with ursodeoxycholic acid 900 mg/die and cetirizine 20 mg/die, to which methyprednisolone 4 mg/die was also associated. The general clinical conditions were, however, progressively worsening up to the caffetic state with bronze-colored skin, jaundiced sclera, incessant itching and widespread lesions caused by scratching.

In order to avoid the overlapping of complications from persistent hyperbilirubinemia (first and foremost neurological), besides the regular hemodialysis sessions the patient was submitted to specific extracorporeal treatments of selective plasmapheresis in order to drastically reduce the bilirubin.

Three months after the withdrawal of the drug there was still no sign of a functional recovery of the organ and the levels of bilirubin showed no signs of dropping (table 1). Liver transplant seemed to be the only possible solution. The patient was thus placed on the waiting list for combined liver-kidney transplant.

The patient received the transplant in November 2002, 4 months after the onset of the clinical picture. The functional recovery of the two transplanted organs was rapid and optimal with a progressive improvement in all the hematic parameters both of hepatic and renal function (at 24 h: bilirubin 11 mg/dl, creatinine 0.9 mg/dl).

The removed liver was submitted to microscopic investigation that confirmed the massive cholestasis with collapse of the portal spaces, fibrosis and signs of hepatocytary degeneration (fig. 1).

### Table 1. Main clinical (hemodynamic and hematologic) parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>At presentation</th>
<th>After 3 months</th>
<th>Pre-transplant</th>
<th>Post-transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic arterial pressure, mm Hg</td>
<td>130 ± 11</td>
<td>150 ± 16</td>
<td>145 ± 18</td>
<td>130 ± 13</td>
</tr>
<tr>
<td>Diastolic arterial pressure, mm Hg</td>
<td>80 ± 8</td>
<td>80 ± 9</td>
<td>80 ± 5</td>
<td>80 ± 5</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66 ± 6</td>
<td>72 ± 4</td>
<td>66 ± 4</td>
<td>64 ± 5</td>
</tr>
<tr>
<td>Bilirubin, mg/dl</td>
<td>16.5</td>
<td>29.3</td>
<td>48.6</td>
<td>4.4</td>
</tr>
<tr>
<td>Direct bilirubin, mg/dl</td>
<td>2.2</td>
<td>23.4</td>
<td>37.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Indirect bilirubin, mg/dl</td>
<td>13.4</td>
<td>5.8</td>
<td>11.2</td>
<td>1.4</td>
</tr>
<tr>
<td>γ-GT, U/l</td>
<td>672</td>
<td>180</td>
<td>320</td>
<td>67</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/l</td>
<td>2,356</td>
<td>1,521</td>
<td>2,514</td>
<td>504</td>
</tr>
<tr>
<td>AST, U/l</td>
<td>133</td>
<td>97</td>
<td>106</td>
<td>20</td>
</tr>
<tr>
<td>ALT, U/l</td>
<td>162</td>
<td>68</td>
<td>57</td>
<td>31</td>
</tr>
<tr>
<td>Ammonium, µmol/l</td>
<td>63</td>
<td>66</td>
<td>54</td>
<td>41</td>
</tr>
<tr>
<td>Amylases, U/l</td>
<td>325</td>
<td>284</td>
<td>172</td>
<td>107</td>
</tr>
<tr>
<td>Lipases, U/l</td>
<td>791</td>
<td>695</td>
<td>706</td>
<td>486</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>2.6</td>
<td>3.2</td>
<td>3.1</td>
<td>3.3</td>
</tr>
<tr>
<td>Total proteins, g/dl</td>
<td>4.8</td>
<td>5.6</td>
<td>5.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>10.8</td>
<td>10.1</td>
<td>7.8</td>
<td>11.9</td>
</tr>
<tr>
<td>Ferritin, ng/ml</td>
<td>1,082</td>
<td>2,830</td>
<td>10,820</td>
<td>860</td>
</tr>
</tbody>
</table>
Discussion

A patient with chronic renal insufficiency started dialysis treatment and developed deepening jaundice with histological evidence of acute cholestatic hepatitis. In the differential diagnostic phase we excluded viral, alcoholic and metabolic causes, and the mechanical obstruction of the extra- and intrahepatic biliary pathways. We also excluded primitive biliary cirrhosis and autoimmune cholangitis as, in our case, the antinuclear antibodies (ANA) were slightly positive, but not the anti-mitochondrial antibodies (AMA); there was no association with any other autoimmune pathologies and the histological evidence showed no damage to the biliary ducts or portal vein inflammation [5, 6]. For the same reasons, we also excluded autoimmune hepatitis [7] and sclerosing primitive cholangitis that is associated to intestinal inflammatory illnesses and to positivity of the ANCA in 80% of the cases (negative in our patient) [8, 9]. The absence of hepatic granulomatose lesions and build-up of epithyloid cells at biopsy associated to the clinical and laboratory picture led us to exclude the possibility of cholangitis due to granulomatose hepatitis or sarcoidosis [10]. The biopic evidence also excluded idiopathic adulthood ductopenia [11]. The laboratory and the biopic picture, without hepatic infiltration and destruction of the portal tract, excluded the possibility of a form secondary to lymphoma [12]. A septic picture following bacterial infection, which could be associated to slight hyperbilirubinemia and a modest rise in the transaminases [13], was not present either.

We thus formulated an etiological hypothesis of cholestatic jaundice having a toxic-iatrogenic nature and induced by ticlopidine in particular, as no cases of cholestasis were described for the other drugs assumed by the patient. From a theoretical standpoint, the only possible pharmacological interaction could occur between carvedilol and ticlopidine, since they are both metabolized by the CYP 450 enzymatic system. However, in spite of the wide use of these two drugs in association, to our knowledge no clinical case report about their interference is present in the scientific literature. Carvedilol per se has been associated only with mild liver abnormalities and cholestasis, which had never taken any clinical aspects similar to our case [14]. Moreover, if an interaction does occur, the liver abnormalities would seem to be due to a gene polymorphism of CYP 450 isozymes, rather than to drug interaction [15].

The diagnosis of ticlopidine-induced cholestasis is essentially arrived at by exclusion and the positive response to the drug discontinuation usually confirms the diagnostic hypothesis. The onset of alterations in the liver function is documented in about 4% of the patients undergoing ticlopidine [1] treatment, while the incidence of ticlopidine-induced cholestatic hepatitis ranges between 0.1 and 1%. This is a severe complication that presents with jaundice, anorexia, abdominal pain, acholic feces, tea-colored urine and itching. The latency time between the drug intake and the appearance of the symptoms (10 days) supported our hypothesis. The ticlopidine-induced hyperbilirubinemia indeed occurs from 1 week to 6 months after the start of the drug intake; in most of the patients it appears between 2 and 12 weeks [16]. In 2 cases a late onset was described about 1 month after drug discontinuation [17, 18].

Patient ages can vary. A higher incidence has been reported among elderly patients (mean age 67.5 years with a range of 29–92 years) [19]. However, this could be attributed to the more frequent exposure to the drug in this age group owing to age-related pathologies. Other authors have reported the onset of hyperbilirubinemia, particularly in those patients aged between 50 and 60 years [17, 20] and with a negative medical history for hepatic pathologies [21]. The alteration in hepatic function indexes includes an increase of up to ten times in alkaline phosphatase and γ-GT. The bilirubin can reach values of up to 30 mg/dl (conjugated bilirubin 18 mg/dl) [20]. From the evidence in the literature, liver biopsies have only been performed in a small number of patients and show

Fig. 1. Removed liver: hepatocytary degeneration and fibrosis due to prolonged cholestasis.
a picture of intralobular intrahepatic cholestasis with moderate hepatocytary and portal vein damage [3, 17]. In one case, complete resolution of the damage was described once the clinical complication had achieved a resolution [16]. The pathogenetic mechanisms are unknown. Tsai et al. [22] describe the presence of antinuclear antibodies in the serum of the patient affected by such a pathology, suggesting a probable underlying autoimmune mechanism. In the case described by Amaro et al. [20], the test for the lymphocyte transformation demonstrated a significant reaction to ticlopidine and a negative response to the other drugs taken by the patient described. The hepatic damage could thus be mediated by idiosyncratic mechanisms, in which the toxic metabolites appear to act upon the cellular proteins determining the necrosis, or by phenomena of hypersensitivity in which antigenic complexes (aptene-drug) are thought to stimulate the T lymphocytes by triggering an immune-mediated reaction with the consequent hepatic damage. Cholestasis is not dose dependent [21] and is not related to the treatment duration [17]. There are no prophylactic measures and the treatment is essentially symptomatic, consisting of reducing the itching with ursodeoxycholic acid and antihistaminic drugs such as hydroxyzine [20]. In some cases, the use of steroids has accelerated the remission and improved the symptomatology [21]. The duration of the symptoms varies between 10 days and 4 weeks [16, 17] without treatment, while treatment with steroids appears to reduce the duration to 4 days [21]. In 2 cases the cholestasis lasted for more than 1 year after discontinuation of the drug but always with a benign trend [20, 23]. There is no test available that can confirm the diagnosis, so it can only be based on exclusion criteria.

The case we observed has presentation characteristics that largely overlap with those described in the literature but with a frankly atypical trend, having extremely serious stigmata characterized by the persistence of very severe cholestasis with severe systemic repercussions after drug withdrawal. He was 53 years old at the time the symptoms appeared and had no hepatic pathologies. There was positivity in the antinuclear antibodies, suggesting an immunological pathogenetic basis. However, our case assumed a different valence because the picture was particularly severe. The bilirubin values were much higher (as much as 40 mg/dl). From the histological point of view, the biopsy picture substantially overlaps that described in the literature, with addition of perivenular bilirubinosis. The evidence on the explanted organ shows, however, a failure to resolve the picture, which had indeed acquired a progressive nature. Finally, about 4–5 months after the start of the therapy there was a serious and progressive decline in the patient’s general clinical condition that led us to advise a combined liver-kidney transplant to the patient.

In our case, the diagnosis of ticlopidine-related hepatotoxicity was based on the exclusion of other possible causes of intrahepatic cholestasis, such as viral infection and ischemic damage, and the onset of symptoms concurrent with ticlopidine treatment since no other new drugs have been administered in that period.

It was not possible for us to test ticlopidine in culture with the patient’s peripheral blood mononuclear cells in order to detect a specific cellular stimulation. The peculiarity of our case is the severity of the clinical trend in the form of reaction to ticlopidine that is generally much more benign. In this regard, we asked ourselves what could have interacted with the uremia to worsen the clinical and metabolic picture because the drugs that can interfere with the hepatic metabolism itself can often present an enhancement of the toxicity in the dialysis patient [24].

Generally, a picture of aspecific nodular lesions has been described with ticlopidine attributable to phenomena of an idiosyncratic kind [25]. In our case, an abnormal immune response, related to the uremic status, could have determined a prolonged intrasinusoidal lymphocytic infiltration with consequent perivenular bilirubinosis.

In conclusion, the case we have described suggests the need for careful monitoring of liver function indexes in patients with renal insufficiency being treated with ticlopidine for whatever reason. Nevertheless, ticlopidine is a valuable drug in cardiovascular prophylaxis, although uremia could accentuate its hepatotoxicity. More data are necessary to investigate the pathogenesis of ticlopidine-induced hepatotoxicity and to assess the mechanism of enhancement in uremic patients.

References


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