A case of intractable pruritus in Turner’s syndrome successfully treated with molecular adsorbent recirculating system

Elena Silvagni · Luigi Coli · Barbara Stagni · Sergio Stefoni · Luigi Bolondi

Pruritus is the most disabling symptom in patients with cholestatic liver diseases, such as primary biliary cirrhosis, primary sclerosing cholangitis and drug induced cholestasis.

Many drug therapies have been used for treating pruritus in these patients, such as histamine antagonists, ursodeoxycholic acid, cholestyramine, enzyme inducing agents as rifampicin or phenobarbital, for inactivation of putative peripheral pruritogens, and finally opioid antagonists as naloxone or naltrexone, which modulate altered central neurotransmission.

Other methods have been tried in patients who do not respond to medical therapies.

Extracorporeal albumin dialysis with the molecular adsorbent recirculating system (MARS) is used for the treatment of acute decompensation of chronic liver disease, acute liver failure, liver failure after surgery or liver transplantation [1, 2]. It has also been claimed that it may be useful in intractable pruritus in cholestatic syndromes [1, 3, 4].

We report the effect of this treatment in a patient with Turner’s syndrome and drug induced cholestasis refractory to medical therapy.

A 54-year-old woman came to our attention because of intractable pruritus. She was affected by Turner’s syndrome (karyotype 45, X0) and hypothyroidism. Since the age of 23 years she had suffered of amenorrea and she had been treated with estro-progestinic therapy for many years. One year before hospitalisation, her therapy was changed into tibolone at a dose of 2.5 mg once daily. Approximately 6 months later, the patient presented itching and mild jaundice, she was admitted to the hospital and a percutaneous liver biopsy was performed; it revealed a pattern of drug induced cholestatic hepatitis. She was treated with ursodeoxycholic acid, cholestiramine and histamine antagonist, and a resolution of jaundice occurred. After an initial improvement of pruritus, later on she suffered from a severe relapse, in spite of continuing medical therapy.

Six months later she was admitted to our hospital; the patient presented scratching skin lesions on arms and legs and sleep deprivation that made worse her quality of life.

Our laboratory data demonstrated a normal liver function (Child-Pugh-Turcotte: A5), a moderate elevation of transaminases (GOT: 55 U/L, GPT: 51 U/L) and elevated AP: 863 U/L and gGT: 53 U/L. Bilirubin level was within normal values. Autoimmune liver disease was excluded because of negative antimitochondrial antibodies, antinuclear antibodies, antineutrophilic cytoplasm antibodies, smooth muscle antibodies, C-reactive protein, rheumatoid factor. Hepatic ultrasonography was normal.

Taking into account the unsuccessful previous medical treatment we decided to treat the patient with the extracorporeal albumin dialysis (MARS).

The MARS system (MARS module: Teraklin AG, Rostock, Germany) was used in combination with a standard dialysis machine. The blood flow was set to 185 ml/min, the flow in the closed albumin dialysate...
A circuit was 150 ml/min and the dialysate flow was 500 ml/min. Vascular access was obtained by insertion of a double-lumen catheter into the right femoral vein. For anticoagulation, a bolus of low-weight heparin (64 I.U. anti Xa/kg, calcic-nadroparin) was injected into the extracorporeal system at the beginning of the treatment.

Two consecutive treatments of 5 h were performed in this patient.

Intensity of pruritus was assessed by a visual analogue scale (VAS) ranging from 0 to 10; 0 corresponding to no pruritus, 10 corresponding to severe pruritus. Table 1 reports the clinical and laboratory parameters detected 1 h before and 24 h after treatments. A significant improvement of pruritus occurred after two sessions of MARS treatment (Fig. 1) and also serum bile acid levels decreased (Table 1). However, after the first treatment there was a rebound in serum bile acid levels. Other laboratory data (transaminases, albumin, prothrombin time) (Table 1) did not show significant changes.

During follow-up, even if the patient did not restart therapy with tibolone, pruritus and bile acids levels progressively increased, and after 6 months the patient complained pruritus, similar to that experienced before the first MARS treatment, but she did not present scratching skin lesions.

This case report shows that MARS treatment can improve pruritus of cholestasis; the significant improvement of pruritus and also the decrease of serum bile acid levels observed after two sessions of MARS treatment confirmed that the method is able to remove substances that are accumulated as a consequence of impaired biliary secretion. The rebound in serum bile acid levels, suggests that part of these bile acids might originate from those previously retained in the skin and other tissues.

Since MARS treatment only replaces the detoxication properties of the liver and has no effect on liver synthetic function transaminases, albumin, prothrombin time did not show significant changes.

The role of bile acids in the development of cholestatic pruritus is still under debate: in some studies the improvement of the perception of pruritus do not closely correlate with the decrease of circulating bile acids, but more recent data support a probable association between bile acids and pruritus [5]. However, data are scarce and definitive conclusions cannot be made.

In our case cholestasis and pruritus were probably drug induced (tibolone) in the setting of a predisposing condition (Turner’s syndrome).

Among the side effects of tibolone, cholestatic hepatitis has not been described until now, even if it is recommended to watch over women that presented cholestasis and pruritus during pregnancy, and to suspend the therapy if cholestatic jaundice appears.

As reported in different studies, the incidence of biochemical liver cholestasis in patients with Turner’s syndrome is high [6–8]; estrogen therapy and autoimmune disorders do not seem to be the responsible causes [9]. Liver diseases associated with Turner’s syndrome increase

<table>
<thead>
<tr>
<th>Table 1 Laboratory data</th>
<th>Before 1st MARS</th>
<th>After 1st MARS</th>
<th>Before 2nd MARS</th>
<th>After 2nd MARS</th>
<th>After 1 month</th>
<th>After 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus VAS</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2.5</td>
<td>4</td>
</tr>
<tr>
<td>CCDCA (mmol/l) n.v. &lt; 2</td>
<td>4.1</td>
<td>7.1</td>
<td>1.8</td>
<td>1.7</td>
<td>3.8</td>
<td>4.3</td>
</tr>
<tr>
<td>CCA (mmol/l) n.v. &lt; 1</td>
<td>6.8</td>
<td>13.6</td>
<td>4.2</td>
<td>6.9</td>
<td>9.4</td>
<td>9.2</td>
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<td>Bilirubin (mg/dl)</td>
<td>1.10</td>
<td>1.12</td>
<td>0.85</td>
<td>1.12</td>
<td>0.65</td>
<td>0.78</td>
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<tr>
<td>GOT (U/L)</td>
<td>55</td>
<td>71</td>
<td>61</td>
<td>62</td>
<td>60</td>
<td>69</td>
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<tr>
<td>GPT (U/L)</td>
<td>51</td>
<td>59</td>
<td>53</td>
<td>52</td>
<td>54</td>
<td>51</td>
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<tr>
<td>Gamma-GT (U/L)</td>
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<td>139</td>
<td>62</td>
<td>56</td>
<td>57</td>
<td>42</td>
</tr>
<tr>
<td>AP (U/L)</td>
<td>871</td>
<td>717</td>
<td>897</td>
<td>869</td>
<td>1,066</td>
<td>1,008</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.63</td>
<td>0.55</td>
<td>0.69</td>
<td>0.55</td>
<td>0.55</td>
<td>0.54</td>
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<tr>
<td>PT (%)</td>
<td>100</td>
<td>94</td>
<td>97</td>
<td>96</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.6</td>
<td>3.8</td>
<td>3.8</td>
<td>4.0</td>
<td>4.2</td>
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<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.8</td>
<td>10.3</td>
<td>10.5</td>
<td>9.9</td>
<td>11.2</td>
<td>12.0</td>
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<td>Platelets (× 10^3/μL)</td>
<td>326</td>
<td>278</td>
<td>336</td>
<td>328</td>
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</tr>
</tbody>
</table>

VAS visual analogue score, CCDCA chenodesoxycholic coniugated acid, CCA cholic coniugated acid, AP alkaline phosphatase

![Fig. 1 Visual analogue scale (VAS)](image-url)
with age and 80% of patients with Turner’s syndrome over the age of 35 are reported to have abnormal liver enzymes, predominantly the gGT. [10]. It has also been reported that pruritus may be the presenting symptom in Turner’s syndrome, and histological features of bile duct proliferation may be found on liver biopsy [8]. The pathogenesis of chronic cholestasis reported to occur in Turner’s syndrome has not been clarified.

We may suppose that in this patient the pathogenesis of liver cholestasis and pruritus was multifactorial: in a patient with predisposition to cholestasis, a medical therapy with tibolone, may be considered the second hit responsible to give rise to cholestasis.

The approach to patients with pruritus due to cholestasis usually consists of medical therapies aimed at reducing the concentration of putative pruritogens, either by removing the substances through anion exchange resins, such as cholestyramine, or by increasing their metabolism through hepatic enzyme inducing drugs, such as rifampicin and phenobarbital. Also 5HT3 serotonin receptor subtypes antagonists, such as naloxone and naltrexone, have a role in the treatment of hepatic pruritus [11, 15].

More invasive approaches, aimed at removing pruritogens, have been tried including phototherapy, partial external biliary diversion, plasmapheresis and charcoal plasma perfusion, and finally the extracorporeal albumin dialysis with MARS [12–15]. Based on these observations, we treated the patient with two sessions of the MARS system.

In this patient the beneficial effect of treatment of pruritus was sustained for several months, despite an early (1 month) increase of serum bile acids (Fig. 1, Table 1); we can suppose that bile acids are not the single responsible of pruritus but other pruritogens may also contribute. These results suggest that MARS treatment removes albumin bound substances, such as bile acids, together with other pruritogens, which still remain unknown. In this patient the beneficial effect of MARS was maintained for about 6 months, a period which is longer than in other reported cases [3, 12].

In conclusion, MARS treatment seems to be an effective alternative option for patients with pruritus due to cholestasis who do not respond to standard medical therapies. Further studies are required to establish the frequency and the duration of treatments. The procedure also opens new perspectives for understanding the pathogenesis of pruritus in cholestasis, since it may be possible to elute and characterize the potential pruritogen substances from the albumin dialysate.

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References