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Case Report

Role of plasma exchange in autoimmune hyperthyroidism complicated by severe tiamazol-induced cholestatic jaundice

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ABSTRACT

Therapeutic plasma exchange (TPE) is an alternative treatment for hyperthyroidism, resulting in a rapid decline in plasma thyroid hormones and anti-thyroid antibodies. TPE has also been used both in primary liver disease and in drug-induced cholestasis. Data on thyrotoxic patients with severe hepatic complications are scarce. Cholestasis induced by imidazol-derived anti-thyroid drugs is extremely rare. The use of TPE for treating this complication was not previously reported. We report the experience of one such patient with a favorable response to TPE. A 45-year-old male patient with Graves' disease, presented with severe jaundice and extremely high serum bilirubin levels due to hepatotoxicity induced by tiamazol. Through extensive investigation primary liver disease, including viral, metabolic, neoplastic and autoimmune disease, as a cause of cholestasis were all ruled out. The patient underwent total of 6 TPEs which in combination with low dose of glucocorticoids and standard supportive measures, resulted in normalization of thyroid hormones and normal liver function tests. TPE provided a safe, rapid and effective treatment of severe drug-induced cholestasis and auto immune hyperthyroidism. From this case we conclude that TPE should be considered as a valuable alternative therapeutic option in thyrotoxic patients with severe complications. Guidelines and indication criteria for TPE treatment in patients with hyperthyroidism are still lacking.

1. Introduction

Cholestatic jaundice is a very rare complication of imidazol derived thyreosupressive drugs. It results from impaired intracellular drug metabolism and only 30 cases have been published so far. Therapeutic plasma exchange (TPE) is an alternative treatment for hyperthyroidism achieving rapid decline in plasma thyroid hormones and anti-thyroid antibodies. TPE can also be effective in removing other harmful plasma constituents. It has been used both in primary liver disease and in drug-induced cholestasis with variable success. Guidelines and indication criteria for therapeutic plasma exchange (TPE) treatment in patients with hyperthyroidism are still lacking, although numerous reports on TPE treatment in thyrotoxic patients have been published [1,2]. However, data on thyrotoxic patients with severe hepatic complications are scarce [3,4]. Cholestasis induced by imidazol-derived anti-thyroid drugs is extremely rare and so far TPE has not been used in patients with this complication. We share our experience of one such patient with favorable response to TPE.

2. Patient

A 45-year-old male patient was hospitalized for extreme malaise, jaundice and nausea. He was diagnosed

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Table 1
Thyroid hormones, anti-thyroid antibodies and liver function tests on admission and after four therapeutic plasma exchange (TPE) sessions.

Parameter (reference range)	Admission	1st TPE	2nd TPE	3rd TPE	4th TPE
FT4 (12–22 pmol/l)	64	36.4	34.9	17.5	12.4
FT3 (2.8–7.10 pmol/l)	9.8	7.0	6.3	3.2	2.5
TSH (0.4–4 mU/l)	<0.15	0.18	0.23	0.25	0.26
TR-Ab (0–1.5 U/l)	12.52	10.0	3.2	1.3	1.1
TPO-Ab (0–10 IU/ml)	375.2	227.1	128.5	50	33
Tg-Ab (0–25.2 IU/ml)	1853	1420.7	971	620	489
Bilirubin total/direct (0–20.5 μmol/l)	453/250	425/264	376/256	360/229	231/82
AST (0–40 U/l)	83	47	45	38	35
ALT (0–40 U/l)	107	104	53	51	44
Alkaline phosphatase (40–120 U/l)	220	206	164	145	95

with Graves' disease and treated for a month with tiamazol, interrupted because of jaundice. On admission, jaundice was the most prominent feature while other findings were unremarkable. Laboratory investigations revealed abnormally high free T4 (64 pmol/l, reference range 12–22) and free T3 sera (9 pmol/l, reference range 2.8–7.10) and low thyroid stimulating hormone serum (TSH <0.15 μIU/ml, reference range 0.4–4). Autoantibody profile included elevated titre of anti-thyreoglobuline antibodies (1853 IU/ml, reference range 0–25.2), anti-thyroid peroxidase (375.2 IU/ml reference range 0–10) and anti TSH receptor antibodies (12 U/l, referance range 0–1.5). Ultrasound showed mild diffuse enlargement of the thryoid gland. Liver function tests showed elevated transaminase and alkaline phosphatase levels with marked hyperbilirubinemia (up to 453 μmol/L, reference range 0–20.5). Coagulation tests, tests for hepatitis ABC, ABV and CMV, CRP, ferritin, ceruloplasmin, copper, alpha-1 antitrypsin levels were normal. Autoantibody profiles for ASMA, LKM, AMA, ANCA, ANA and anti dsDNA were negative. Serum protein electrophoresis was normal. The liver and spleen size was normal with no signs of portal thrombosis or ascites.

Patient underwent total of 6 TPEs (2 L plasma volume, every four days) with 20% human albumin, fresh frozen plasma and Ringer solution as replacement fluid. After the 4th TPE normalization of thyroid hormones was evident (Table 1) and 15 mg of prednisolone was added to block new anti-thyroid antibody production. Two more courses of TPE were performed in order to normalize elevated bilirubin levels. Patient refused the offered thyroid surgery. On the control visit, two months later, normal thyroid status (FT4 13.4 pmol/l, FT3 3.2 pmol/l TSH 1.5 μIU/ml) negative anti-thyroid antibody profile (TR-Ab <1 U/l, TPO Ab 3.4 U/ml, Tg Ab 25 U/ml) and normal liver function tests (AST 16 U/l, ALT 19 U/l, alkaline phosphatase 83 U/l bilirubin total/direct 11/2.9 μmol/l) were found.

3. Discussion

Anti-thyroid drugs are the first line treatment in the majority of patients with hyperthyroidism, but severe hepatotoxicity is rare, affecting less than 1% of patients [5]. Immuno-mediated hepatocellular damage may occur in patients treated with propylthiouracil, while cholestasis induced by imidazol derivates is due to impaired intracellular drug metabolism. Drug-induced intrahepatic cholestasis results from abnormal bile flow due to disruption of subcellular actin filaments and interruption of proton pumps and mitochondria. In most severe cases of imidazol-induced cholestasis fulminant hepatic failure leading to liver transplantation and fatal outcomes have been reported [6,7]. The natural course of the disease is prolonged with jaundice slowly resolving over the period of three to six months.

Our patient presented with severe jaundice and extremely high serum bilirubin levels due to hepatotoxicity induced by tiamazol. Extensive investigation was done to rule out primary liver disease, including viral, metabolic, neoplastic and autoimmune disease, as a cause of cholestasis. The successful use of TPE for severe cholestasis, drug-induced or in primary liver disease, has been reported before [8,9]. However, in thyrotoxic patients with hepatic complications use of TPE has been described in only two patients: one caused by severe hepatitis B [3] and another with fulminant hepatic failure induced by propylthiouracil treatment [4] both with favorable outcomes.

In our patient, TPE in combination with low dose of glucocorticoids and standard supportive measures, provided safe, rapid and effective treatment of severe drug-induced cholestasis and auto immune hyperthyroidism. TPE should be considered as a valuable alternative therapeutic option in thyrotoxic patients with severe complications. This case further stresses the role of TPE in the treatment of thyrotoxic patients with life threatening complications.

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References

[1] Ezer A, Caliskan K, Parlakugumus A, Belli S, Kozanoglu I, Yildrim S. Preoperative therapeutic plasma exchange in patients with thyrotoxicosis. J Clin Apheresis 2009;24:11–114.
[2] Muller C, Perrin P, Faller B, Richter S, Chantrel F. Role of plasma exchange in the thyroid storm. Ther Apheresis Dial 2011;15:522–31.
[3] Soares DV, Nakamura LT, Ladeira MC, Brito SM, Henriques JL. Acute hepatic failure in a patient with hyperthyroidism and virus B hepatitis: recovery after plasmapheresis and thyroidectomy-A case report. Arq Bras Endocrinol Metab 2008;52(3):566–7.
[4] Aydemir S, Ustundag Y, Bayraktoglu T, Tekin IO, Peksoy I, Unal AU. Fulminant hepatic failure associated with propylthiouracil: a case

report with treatment emphasis on the use of plasmapheresis. J Clin Apheresis 2005;20(4):235–8.
[5] Cooper DS. Anti-thyroid drugs. New Engl J Med 2005;352:905–17.
[6] Russo MW, Galanko JA, Srestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug induced liver injury in the United States. Liver Transplant 2004;10:1018–23.
[7] Sein Anand J, Chodorowski Z. Drug-induced liver failure caused by thiamazole and methimazole: a case report.. Prezgl Lek 2007;64: 320–1.
[8] Chou JW, Yu CS, Chuang PH, Lai HC, Hsu CH, Cheng KS, et al. Successful treatment of fosinopril-induced severe cholestatic jaundice with plasma exchange. Ann Pharmacother 2008;42(12):1887–92.
[9] Matloff DS, Kaplan MM. D-penicillamine-induced Goodpasture's-like syndrome in primary billiary cirrhosis successful treatment with plasmapheresis and immuno-suppressants. Gastroenterology 1980;78:1046–9.