

## Thyrotoxicosis Associated with Cholestatic Jaundice Treated with Therapeutic Plasma Exchange—Case Report

Irfan Ahmeti<sup>1,5\*</sup>, Viktorija Chalovska<sup>2,5</sup>, Nevena Manevska<sup>3,5</sup>, Pavlina Dzekova-Vidimliski<sup>4,5</sup>, Vladimir Avramoski<sup>2,5</sup> and Daniela Pop Gjorceva<sup>3,5</sup>

<sup>1</sup>University Clinic of Endocrinology, Diabetes and Metabolism, Skopje, Macedonia

<sup>2</sup>University Clinic of Gastroenterohepatology, Skopje, Macedonia

<sup>3</sup>Institute of Pathophysiology and Nuclear Medicine "Acad. Isak S. Tadzer", Skopje, Macedonia

<sup>4</sup>University Clinic of Nephrology, Skopje, Macedonia

<sup>5</sup>University of "Ss. Cyril and Methodius", Skopje, Macedonia

\*Corresponding author: Irfan Ahmeti, MD, University Clinic of Endocrinology, Diabetes and Metabolism, Skopje, Macedonia, Tel: +389 70239607; E-mail: iahmeti@yahoo.com

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### Abstract

Thyroid disorders, especially thyrotoxicosis, are commonly associated with hepatic dysfunction, but cholestasis is rarely reported. Heart failure, infection, weight loss may play role in the pathogenesis of cholestasis. Cholestasis could be worsened by treatment of hyperthyroidism using Thiamazole, but cholestasis in undiagnosed thyrotoxicosis is uncommon. We present 23 year old female with jaundice, goiter, palpitation and confirmed thyrotoxicosis associated with hepatomegaly, hepatocellular damage and cholestasis. Liver biopsy excluded the suspicion of autoimmune hepatitis. Therapeutic plasma exchange was performed 5 days after starting the treatment with thyroid suppressive therapy, and hepatoprotective therapy due to progressive increase of serum levels of bilirubin (conjugated/direct) and liver enzymes. The patient treatment continued with low doses of thyroid suppressive therapy. Patient achieved euthyroid state after 2 months with normalization of the serum levels of liver enzymes and bilirubin. The final treatment option for our patient was surgical total thyroidectomy.

**Keywords:** Thyrotoxicosis; Cholestasis; Therapeutic plasma exchange; Thiamazole

### Introduction

Thyroid disorders, especially thyrotoxicosis, are commonly associated with hepatic dysfunction, but cholestasis is rarely reported [1]. Undiagnosed and untreated hyperthyroidism, in 45%-90% of the affected population leads to liver enzyme abnormalities [2].

The association of thyrotoxicosis with hepatic injury is well documented in the literature. Hepatic injury can be presented with mild hepatic dysfunction with enzyme abnormalities to severe central hepatic ischemia. Hyperthyroidism can be rarely complicated by a severe cholestatic syndrome that may dominate the clinical presentation. Other atypical clinical presentations of thyrotoxicosis, especially Graves disease (GD), include anemia, vomiting, right heart failure, infection and weight loss, which could also contribute in the pathogenesis of liver dysfunction and cholestasis [3]. Forms of anemia that are associated with GD include pernicious anemia, iron deficiency anemia of celiac disease and autoimmune hemolytic anemia [4]. Iron deficiency anemia could contribute in the pathogenesis of liver dysfunction and cholestasis. This type of anemia resembles anemia of chronic disease and may be termed GD anemia.

Therapeutic plasma exchange is rarely used treatment modality in the management of thyrotoxicosis. It is safe procedure where the patient blood is separated via filtration into plasma and cells. The cells are returned to the patient circulation, replacing the plasma with fresh frozen plasma or albumin solution, aiming for a lower level of the circulating thyroid hormone to be achieved [5]. In the absence of clear

guidelines and recommendations on the use of plasma exchange in treatment of patients with severe thyrotoxicosis, the decision to utilize this treatment modality has to be made by the treating physician [4].

### Case Presentation

A 23 year old female with clinical presentation of cholestatic syndrome ("overnight yellowing"- extreme jaundice, frequent diarrheic stools, dark urine, and decreased appetite) was admitted to the Clinic of Gastroenterohepatology. A hemolytic anemia and viral hepatitis were excluded as a cause of the jaundice. Intermittent body temperature was up to 38.3°C. Skin and mucous membranes were jaundiced with present excoriations, with moderately expressed pretibial and perimalleolar edema. The result from the upper gastrointestinal endoscopy was normal. The abdominal ultrasonography showed slightly enlarged liver with rounded edges and inhomogeneous structure. The laboratory findings revealed gradual increase in the liver enzymes, as well as both conjugated and unconjugated bilirubin. Analysis of thyroid hormones showed high values of total thyroxine (TT4), free thyroxine (fT4), free triiodothyronine (fT3) and thyroid autoantibodies (TPOab) and low/suppressed values of thyroid stimulating hormone (TSH), (Table 1).

Diffusely enlarged, soft and mobile thyroid gland, with a systolic murmur on auscultation was detected by endocrinologist. Thyroid ultrasound revealed diffusely enlarged thyroid gland with a volume >70 cm, expressed hypoechoic structure with hyperechoic tracks and marked diffuse vascularization. An electrocardiogram (ECG) showed sinus tachycardia of 120/min with ST depression in D2, aVL, V2-V4.

Liver biopsy excluded autoimmune hepatitis and cirrhosis (microscopic findings, chronic hepatitis with Kodel Score 1, inflammation, fibrosis 0, isolated necrosis 0, bridging necrosis 0). Presence of Wilson disease was also excluded. 24-h urinary copper excretion value was 19.31 µg/day (reference range less than 50 µg/day). Presence of cholestatic jaundice secondary to thyrotoxicosis was diagnosed by the treating physicians. An immediate treatment was started with thyroid suppressive therapy (Thiamazole 30 mg/day), 2-3 liters of liquid/day and beta-blocker (Propranolol 60 mg/day). Therapy with Thiamazole was discontinued, five days after starting the treatment, due to higher increase of the serum levels of liver enzymes.

The treating physicians (endocrinologist, nuclear medicine specialist, nephrologist and gastroenterologist) decided to start with therapeutic plasma exchange (TPE) because of the risk of development of acute hepatic failure. Three courses of TPE were performed with plasma filter 2000N (Gambro). Vascular access: catheter in femoral vein. Heparin was used as anticoagulation drug during each procedure. About 2800 ml of plasma was extracted on each procedure and replaced with 3000 ml fresh frozen plasma, because of the existing hypoalbuminemia (26 g/l). There was continuous monitoring of the patients' vital signs and possible adverse events during the procedure. A transfusion reaction was registered and treated during the second course of TPE. Slight elevation of plasma bilirubin and thyroxin was registered early after plasma exchange treatment. Hypoproteinemia with hypoalbuminemia were detected as an adverse event of plasma exchange procedure, which were corrected with fresh frozen plasma (proteins 50 g/L vs. 62 g/L, respectively and albumin 24 g/L vs. 40 g/L, respectively). After three courses of TPE, there was decrease in the serum levels of total and direct bilirubin around 60% (Table 1), as well as the level of fT4 (around 40%), (Table 1).

The patient treatment continued with orally therapy with Thiamazole 5 mg (once a day), Propranolol 20 mg (three times a day), schema with Prednisone for 2 weeks (10 mg, 7.5 mg, 5 mg and 2.5 mg as a maintaining dose), tablets Iron III hydroxide polymaltose 100 mg (twice a day), Vitamin C 500 mg (twice a day), and Ursodeoxicholic acid (twice a day).

Afterwards, the patient was treated at Clinic of Endocrinology with clinical presentation of lack of interest, with symptoms of fatigue, dizziness, palpitations, sweating, heat intolerance, weight loss, jaundice, and swelling of the lower extremities. The treatment prescribed afterwards was almost identical: Tbl. Thiamazole 5 mg (twice a day) until normalization of serum levels of thyroid hormones and Propranolol 20 mg (three times a day), Prednisone 2.5 mg (once a day), Ursodeoxicholic acid (twice a day), Iron III hydroxide polymaltose 100 mg (twice a day), Vitamin C 500 mg (twice a day) until normalization of the serum levels of liver enzymes and bilirubin. Patient achieved euthyroid state after 2 months with normalization of the liver enzymes. The final treatment option in our patient was surgical, total thyroidectomy.

## Discussion

Hepatic dysfunction is a rare complication of hyperthyroidism and was first recognized and reported by Hamershon in 1874. Thyroid hormones are metabolized in the liver and thyroid disorders may lead to derangement of the liver profile. The etiology of liver injury in patients with hyperthyroidism covers a broad diagnostic spectrum, and more than one cause may be identified at presentation. Sometimes the diagnosis is possible only after a long period of monitoring.

Raised levels of thyroid hormones leads to increased activity of Na<sup>+</sup>/K<sup>+</sup> pump in cells and of the metabolic cell state. If no concomitant elevation of hepatic blood flow occurs, then hepatocytes are subjected to metabolic stress and damage [6]. Another proposed theory is the decreased activity in the enzyme UDP-glucuronyl transferase, with a defect in the bilirubin metabolism causing hyperbilirubinemia, with focal hypoxemia and hepatic dysfunction [7].

A number of diseases can affect both, the liver and the thyroid, simultaneously. Hyperthyroidism complicated by congestive heart failure and secondary hepatic dysfunction develops jaundice, a very uncommon clinical entity. As the hyperthyroid state becomes euthyroid, the cholestasis improves. If treatment includes antithyroid drug, such as Thiamazole, cholestasis can be worsened [8]. Thionamides induce cholestasis, as an idiosyncratic reaction to the drug [9]. An elevation of the bilirubin, alkaline phosphatase, and  $\gamma$ -glutamyl transpeptidase levels are the predominant abnormalities. Such liver dysfunction usually presents within 2 to 3 weeks of the initiation of treatment, and can persist for several months despite discontinuation of the drug [10].

Drug-induced or autoimmune liver dysfunction should be evaluated, when jaundice appears as a secondary consequence of cholestasis due to hyperthyroidism [11]. Although less frequent, symptomatic cholestasis and hepatitis of variable intensity may also occur [12,13]. The predominant feature on liver biopsy is intrahepatic cholestasis.

The association of the imbalance in thyroid hormone levels and hepatic injury is well documented in the literature. It may vary from mild hepatic dysfunction with enzyme abnormalities to severe central hepatic ischemia. Cholestatic syndrome may dominate the clinical presentation and course.

In our case the patient developed cholestasis with widest possibilities of differential diagnosis at clinical presentation. The serum levels of aminotransferases were increased before thyroid suppressive therapy was started, leading to an initial diagnosis of liver damage, secondary to thyroid hyperactivity. Furthermore the long-term previous anemia in our patient could participate in the development of thyrotoxicosis-induced cholestasis and jaundice. Therefore the anemia was intensively treated. The real diagnose has been masked by the symptoms of the anemia, with delay of the appropriate treatment of thyrotoxicosis.

Although low dose of Thiamazole was started in the treatment of clinically manifested overt hyperthyroidism, the drug could also contribute to the progressive course of the hyperbilirubinemia and high liver enzyme concentrations in the blood. This fact directed us towards plasma exchange as a short-term therapeutic approach, to reduce the thyrotoxic effect on hepatocytes, without applying thyroid suppressive therapy. The therapeutic plasma exchange efficiently improves thyrotoxicosis by rapidly removing and exchanging the serum proteins to which approximately 99% of the thyroid hormones bind. Plasma or human albumin solutions used for replacement also provide new binding sites for circulating free hormones. At least 1-1.5 times of plasma volume should be changed with plasma or human albumin for the effective procedure. However, this effect is usually transient and thyroid hormone levels increase within few days after plasmapheresis. Öztürk et al. performed seven sessions of plasmapheresis in a 54-year old patient with toxic multinodular goiter who successfully afterwards underwent thyroid surgery [14].

Treatment of the thyrotoxicosis with TPE was for the first time described by Ashkar et al. in 1970. They have started treatment with TPE in three patients with thyrotoxicosis because they did not respond to the conventional treatment [15]. In the period of 2006-2012, Keklik et al. retrospectively reviewed 22 patients who had severe thyrotoxic values despite anti-thyroid drug use and underwent therapeutic plasma exchange due to hyperthyroidism. After TPE, they observed a significant decrease in free thyroxin (FT4) ( $p < 0.001$ ) and free triiodothyronin (FT3) ( $p < 0.004$ ) levels. There was statistically significant increase in the mean values of TSH levels after TPE ( $p < 0.001$ ). Clinical improvement was achieved in hyperthyroidism by TPE in 20 cases (91%) [16].

In 2009, Ezer et al. published TPE case series which included 11 patients with thyrotoxicosis, scheduled for surgery with plasmapheresis at their institution. They observed a marked decrease in free thyroxin (FT4) and free triiodothyronin (FT3) levels in the preoperative period, enabling patients to undergo surgery more safely [17].

Forty-three years later, the American Society for Apheresis (ASFA) 2013 guidelines on the use of therapeutic apheresis listed thyroid storm as a category III indication (optimum role of apheresis therapy is not established, decision making should be individualized for therapeutic apheresis) [18]. To date, no randomized study has verified the usefulness of TPE in the treatment of thyroid storm because it is a rare endocrine condition. However, based on many case reports from Japan and other countries in which the efficacy and safety of TPE have been demonstrated, Japan Thyroid Association and Japan Endocrine Society in 2016 recommend that TPE should be considered if thyrotoxicosis has not improved within 24-48 hours after the start of initial treatment. It is recommended that fresh frozen plasma should be used as the replacement solution in TPE to treat thyroid storm. The fresh frozen plasma is expected to reduce thyroid hormones more efficiently than albumin solution. TPE should be performed daily or every 2 to 3 days until clinical improvement has been observed [19].

In a recent systemic review summarizing 126 case reports of thyroid storm treated with TPE, the recommended indications for TPE in thyroid storm were described as 1) severe symptoms (cardiothyrotoxicosis, neurological manifestations, disturbances in consciousness, and severe myopathy), 2) rapid clinical worsening, 3)

contraindication to other therapies (including agranulocytosis, renal insufficiency, asthma, and heart failure), and 4) failure of conventional therapy [20]. This study recommended that TPE should be performed daily with 40-50 ml/kg of replacement solution until clinical improvements are noted, and levels of both fT3 and fT4 should be sampled before and after each session. TPE should not be discontinued if there is no reduction in fT3 or fT4 levels because of biologic-clinical dissociation. The side effects of TPE are mostly reversible, with an incidence of approximately 5%. They include transfusion reaction, citrate-related nausea and vomiting, vasovagal or hypotensive reactions, respiratory distress, tetany, and convulsions. Death was also rarely observed and was commonly attributed to the underlying disease.

When reconstruction of results and facts for thyroid storm was made, our young patient became >45 points (50) [21]. The therapeutic plasma exchange was a suggestive treatment because of the risk for development acute hepatic failure and life threatening thyroid storm. Co-treatment with low doses of Thiamazole and Propranolol contributed to the normalization of the levels of thyroid hormones and aTPO, as well as decrease of serum levels of bilirubin and liver enzymes. The possibility of radioiodine treatment was considered but it was excluded because of the risk of hepatic injury relapse and potential pregnancy of the patient.

In a report similar to our patient, Belassoued and colleagues reported a case of thyrotoxic hepatitis and steatosis with favorable outcome after I131 therapy [22].

Kubota et al. showed similar case where six month post I131 treatment, the liver enzymes improved gradually with the reduction in fT4 level, but they showed picture of hepatocellular derangements that was most likely attributed to obesity associated non alcoholic fatty liver disease [23].

Taking into consideration the possible risk of potential pregnancy (a reason to exclude radioiodine treatment) as well as the diffusely enlarged thyroid gland our team decided for surgical treatment – thyroidectomy to be the definitive treatment of the thyrotoxicosis in our patient. In the two reported cases by Hull and colleagues the jaundice resolve completely after thyroidectomy [24].

Laboratory findings	6 weeks before TPE	3 weeks before TPE	1 week before TPE	Started TPE	5 days finished TPE	2 weeks after TPE	3 weeks after TPE	5 weeks after TPE	8 weeks after TPE	3 months after TPE	8 months after TPE
<b>Bilirubin total (3-22 µmol/L)</b>	25	221	457	548	264	266	83	26	12	18	17
<b>Bilirubin direct (&lt;7 µmol/L)</b>		203	407	471	228	247	74	18	7	10	6
<b>Bilirubin indirect (5.1-13.6 µmol/L)</b>		18	50	77	36	19	9	8	5	8	11
<b>AP (38-126 U/L)</b>	187	173	91	105		103	90				
<b>AST (15-46) U/L</b>	36	175	53	105		53	105				
<b>ALT (11-66) U/L</b>	45	98	42	58		61	55				
<b>LDH(313-618) U/L</b>	404	524	249	947		299	278				

<b>TSH</b> mU/L)	<b>(0.4-4.5</b>			0.004	0.004	0.004		0.004	0.004	0.004	0.04	0.325
<b>FT4</b> pmol/L)	<b>(10.3-24.45</b>				73.2	51.5	20.3	14,7	39.1	22.8	7.07	10.9
<b>FT3</b> pmol/L)	<b>(4.2-8.1</b>				12.4				18.9		6.27	
<b>ATP-O</b> iU/ml)	<b>(10-50</b>				>1000				384.1			27.51

AP: Alakaline Phosphatase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; ATP: Adenosine Triphosphate

**Table 1:** Laboratory findings before and after therapeutic plasma exchange (TPE)-six weeks before TPE, during TPE and 8 months after TPE.

## Conclusion

A good differential diagnosis is very important in a case of severe cholestatic syndrome. A clinician should always bear in mind thyrotoxicosis as a possible entity in the developing of hepatic injury and cholestasis. The therapeutic plasma exchange efficiently improves thyrotoxicosis by reducing the serum levels of thyroid hormones.

## Consent

Consent was obtained from the patient before publication of this case report and the images presented.

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