



Successful Preoperative Treatment with Plasmapheresis of Patients with Hyperthyroidism

Hipertiroidili Hastaların Plazmaferez ile Başarılı Preoperatif Tedavisi

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Abstract

Anti-thyroid drugs are used as the first line treatment in the majority of patients with hyperthyroidism, but side effects such as severe hepatotoxicity and agranulocytosis may occur in some rare cases. For patients suffering from such severe side effects and in need of emergent surgical interventions, the removal of circulating thyroid hormones and thyroid antibodies by preoperative plasmapheresis has been reported as an effective adjunct. In this study, we report two patients, one with Graves' disease who underwent a liver transplantation, and the second with a toxic multinodular goiter and acute cholecystitis due to suspected pancreatic cancer.

Keywords: Hyperthyroidism; plasmapheresis; operation

Özet

Hipertiroidili hastaların büyük çoğunluğunda anti-tiroid ilaçlar ilk basamak tedavi olarak kullanılmaktadır, fakat ciddi hepatotoksikite ve agranülositoz gibi yan etkiler nadir olarak meydana gelebilmektedir. Antitiroid ilaç kullanımı sonrası şiddetli yan etki görülen ve acil cerrahi müdahale ihtiyacı gelişen hastalar için serbest tiroid hormon ve antikorlarını uzaklaştırmak üzere yapılan preoperatif plazmaferez etkili bir uygulama olduğu rapor edilmiştir. Bu çalışmada; ilki karaciğer nakil öyküsü olup, Graves' hastalığı tanısı alan ve ikincisi pankreas karsinomuna sekonder olduğu düşünülen akut kolesistit kliniğinde toksik multinodüler guatrli iki olguyu sunulmuştur.

Anahtar kelimeler: Hipertiroidizm; plazmaferez; operasyon

Introduction

Thyrotoxicosis is characterized by an excess of circulating thyroid hormones that may affect thermoregulatory central nervous and gastrointestinal, hepatic and cardiovascular systems and result in a thyroid crisis along with a high mortality rate (1). There are three treatment options: antithyroid drug therapy, radioactive iodine therapy, and surgery (2). The choice of which depends on the underlying cause. Anti-thyroid drugs are used as the first line treatment in the majority of patients with hyperthyroidism, but side effects such as severe hepatotoxicity and

agranulocytosis may occur in some patients (<1%), which can lead to serious consequences (3). Thyroidectomy is the definitive treatment for thyrotoxicosis, especially in patients resistant to other medical treatments or unsuitable for RAI treatment (4). The plasmapheresis an alternative and effective therapeutic option in situations where restoring euthyroidism for the short-term period (5). In this study, we report two patients, one with Graves' disease who underwent a liver transplantation and the second with a toxic multinodular goiter and acute cholecystitis due to suspected pancreatic cancer.

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Patients

First patient

A 43-year-old male presented with symptoms like weight loss (of 7-8 kg), palpitation, weakness and excessive sweating since three months. His physical examination revealed a heart rate of 100 beats/min, blood pressure of 120/80 mmHg, respiratory rate of 18 breaths per min, 36.5 °C body temperature, and generalized icterus and tremor. Additionally, diffuse palpable thyroid gland was found in the patient. The resulting laboratory test values were as follows; FT4: 45.9 (11.5-22.7 pmol/L), FT3: 12.5 (3.5-6.5 pmol/L), TSH: 0.01 (0.27-4.2 IU/mL), TRAB: 2.43 (<1 IU/L). Ultrasonography of the thyroid gland indicated mild diffuse enlargement of the thyroid gland, with heterogeneity and the ^{99m}Tc scan showed diffuse high uptake activity (4.9%) (normal reference range: 0.5-3.75%). These findings were consistent with the diagnosis of Graves' disease. According to the patient's history, he had cadaveric liver transplantation due to primary sclerosing cholangitis in the year 2011. After three years, due to persistent ulcerative colitis and high-grade dysplasia from the colon polyps, he had to undergo total colectomy. Antibody profiles including ANA, ASMA, AMA, anti-LKM, and p-ANCA were negative in his earlier report. He had continued treatment with cyclosporin, prednisolone, ursodeoxycholic acid, metoprolol, and cholestyramine as immunosuppressive agents for hepatic transplantation, until the date of admission. During the follow-up, the patient was admitted with symptoms like weakness, weight gain and overt hypothyroidism (TSH: 28 IU/mL, fT4: 8.63 pmol/L) and he had a high level of anti-TPO >1300 with urine iodine in the normal range (121 µg/L). His thyroid ultrasonography was found to be consistent with autoimmune thyroiditis. Levothyroxine therapy was started by gradually increasing the doses up to 100 mcg and once the TSH was suppressed, after three months, the drug was discontinued gradually. Graves' disease was diagnosed. During this time, the total and direct bilirubin levels were found to be higher (19.69 and 13.48 mg/dL, respectively) and the MELD score was 24. In addition, liver biopsy suggested the recurrence of primary sclerosing cholangitis. Based on these findings, a liver transplantation surgery was planned; however, due to the patient's high bilirubin levels, anti-thyroid medications and ra-

dioactive iodine therapy could not be commenced. Plasmapheresis (4 sessions) was performed using an intermittent flow device (Fresenius-COM.TEC) with the removal of (40 mL/kg) 3100 mL of plasma volume during each plasmapheresis cycle and 5% human albumin/saline solution combined with fresh frozen plasma was employed as the replacement fluid. The levels of free T3 and T4 returned to normal range and a total thyroidectomy was performed. No major complication was observed during surgery but a minor postoperative bleeding at the incision site occurred on the day after the operation that was controlled with a fresh frozen plasma infusion and mechanical tamponade. The pathology results revealed diffuse hyperplasia.

Second patient

A 79-year-old woman was hospitalized for abdominal and back pain and malaise. Physical examination of this patient revealed epigastric tenderness, defense and rebound tenderness and Murphy's sign for abdominal palpation was found to be positive. The resulting laboratory test values were as follows; ALT: 73 (12-59 u/L), AST: 70 (10-37 u/L), GGT: 307 (5-55 u/L), ALP: 206 (46-116 u/L), T.blb: 0.46 (0.2-1.2 mg/dL), D.blb: 0.3 (0.0-0.2 mg/dL), Amylase: 66 (25-115 u/L), Lipase: 136 (73-393 u/L), CA 19-9: 5273.08 (0-37 U/mL). Abdominal ultrasonography was consistent with acute cholecystitis and the ERCP and EUS investigation showed bile duct strictures with the presence of atypical cells in the biopsy. The patient's medical history indicated that a toxic multinodular goiter was present for which she had previously used different doses of propylthiouracil during various treatment courses and had later discontinued this therapy on her own. Upon admission we observed that her thyroid test values were as follows TSH: <0.008 (0.25-4.55 uIU/mL), fT4: 46.9 (11.5-22.7 pmol/L), fT3: 7.33 (3.5-6.5 pmol/L), Anti-TPO: <28.0 (0-60 IU/mL), TRAB: 0.27 (<1.0 IU/L). Increased vascularity, with the largest nodule of 39×21 mm dimensions in the right lobe and a second large nodule of 25×19 mm dimensions in the left lobe and multiple hyperechoic nodules, were observed during thyroid ultrasonography. We could not use anti-thyroid drugs because of the presence of acute cholecystitis and the probability of pancreatic cancer. There was not enough time to treat hyperthyroidism, because

the patient had to undergo an emergent surgery. Thus, in her case therapeutic plasmapheresis was employed for three cycles. The plasma volume exchange was performed with 5% concentration of albumin/ saline solution and the total volume of plasma that was exchanged at each cycle was 2000 mL. After the third cycle, the free T3 and T4 concentration in her serum were 1.4 pmol/L and 6.07 pmol/L, respectively. Twenty-four hours after the last plasmapheresis the patient underwent a thyroid surgery in which near-total thyroidectomy was performed successfully. Although preoperative screening coagulation tests (prothrombin time, activated partial thromboplastin time and platelet count) were within normal limits, the patient had excessive postoperative bleeding from the operation site leading to a cardiac arrest that necessitated resuscitation and urgent re-operation for bleeding control. After re-operation and supportive treatment with fresh frozen plasma, she recovered completely. The pathology showed multinodular colloid hyperplasia.

Discussion

In Graves' disease, TSH-receptor antibodies stimulate the TSH-R to produce excessive amounts of thyroid hormone that lead to hyperthyroidism. The most common treatments for hyperthyroidism are antithyroid drug therapy, radioactive iodine therapy, and thyroidectomy. The most widely used antithyroid drugs cause minor and transient adverse effects like skin rash, itching, and mild leucopenia, in certain cases. The most dangerous effect is agranulocytosis, while other major adverse effects like aplastic anemia, thrombocytopenia, lupus-like syndrome and vasculitis are rare in nature (6). In addition, disturbances of hepatic function is also a complication of antithyroid drug treatment (7). The spectrum of observed changes in such condition ranges from a mild and asymptomatic elevation of cholestatic and cytosolic liver enzymes to fulminant and fatal necrotizing hepatitis (8, 9). Immuno mediated hepatocellular damage may be seen in patients when treated with propylthiouracil, while cholestasis, due to impaired intracellular drug metabolism, may occur in case of treatment with imidazole derivatives. Drug-induced intrahepatic cholestasis results from abnormal bile flow arising from disruption of subcellular actin filaments and interruption of proton pumps and mitochondria.

Most severe cases of imidazole-induced cholestasis have reported fulminant hepatic failure leading to liver transplantation and other fatal outcomes (10).

Our first patient presented with jaundice and extremely high levels of serum bilirubin due to the rejection of liver transplantation while the second patient presented an acute cholecystitis with suspected pancreatic cancer. We could not use antithyroid drugs in either of these situations and radioactive iodine therapy was not an acceptable choice because these patients could not wait until euthyroid. The first patient was awaiting surgery for an urgent liver re-transplantation and the second patient needed urgent cholecystectomy and probably even the Whipple procedure. In order to perform thyroidectomy, these patients were required to be euthyroid. Therapeutic plasma exchange (TPE) is an alternative treatment that has been proposed since the 1970s for hyperthyroidism and, more precisely, for the thyroid storm, since it leads to rapid clinical response and rapid normalization of circulating thyroid hormone levels, irrespective of the etiology (11). During plasma exchange, the plasma is extracted from the patient's blood, and a colloid replacement solution (in our cases, FFP and albumin) is infused back to the patient in place of the plasma. TBG along with bound thyroid hormones also gets removed from the plasma during this procedure and the colloid replacement provides new binding sites for the circulating free thyroid hormone. Although albumin binds thyroid hormone with less avidity than TBG, it provides a much larger capacity for low-affinity binding that may contribute to lower levels of free thyroid hormone (12). Even though plasmapheresis has been used mainly for the treatment of thyroid storm, it can be used as a preferred therapy for the prevention of thyroid storm in selected patients in whom thyroid hormone concentrations do not decrease to safer levels in spite of employing medical treatment strategies such as iopanoic acid, lithium, beta blockers or combinations (13).

In thyrotoxic patients with severe complications, TPE should be considered as a valuable pre-operative therapeutic option. However, TPE involves complications like hypotension, hemolysis, anaphylactic or allergic reactions, infection, vascular injury and coagulopathy (14). In addition to this, coagulation proteins and platelets are removed during plasmapheresis and this step is important because when the removed plasma is restored by

colloidal solutions other than fresh frozen plasma, it leads to coagulopathy in the immediate post-plasmapheresis period. After plasmapheresis, factors such as prothrombin time, activated partial thromboplastin time and thrombin time are found to be markedly prolonged (15). In the report by Ezer et al., in 2009, intraoperative bleeding from operation sites occurred in one out of 11 patients who were studied (11). Ozbey et al., in 2004, reported in their investigation that two patients had perioperative unusual bleeding despite normal screening coagulation tests (13). Therefore, bleeding complications should be monitored carefully.

In the patients from our study, TPE in combination with standard supportive measures provided safe, rapid and effective treatment for hyperthyroidism.

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Author Contributions

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