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EDİTÖRE MEKTUP / LETTER TO THE EDITOR

Resistance to multiple therapeutic apheresis attempts in a patient with Graves' disease

Graves hastalığı olan hastada çoklu terapötik aferez direnci

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To the Editor,

In many countries, the most common cause of hyperthyroidism is Graves' disease (GD). The disease is more screen between the ages of 30 and 50, with an annual incidence of 20-50 / 100.000[1]. GD is an autoimmune disorder that is characterised by the infiltration of thyroid-stimulating hormone receptor autoantibodies (TSH-R-ab) in thyroid tissue[2]. Circulating TSH-R-ab binding to the TSH-R increases the production of intracellular cyclic AMP, causing the release of thyroid hormones and growth of thyroid tissue. Although major genetic compound of GD is also known major histocompatibility complex (HLA DR3, DR4), novel susceptibility genes including cytotoxic T lymphocyte antigen-4 (CTLA-4), protein tyrosine phosphatase non receptor 22, basic leucine zipper transcription factor 2 and CD40 are related with this autoimmune disease[3].

According to the European Thyroid Association guidelines, the treatment of GD mainly includes reducing TSH synthesis by using antithyroid drugs (ATD) or reducing thyroid tissue by performing ablative therapy (surgery or RAI). Although ATDs are indicated as the first line of therapy, relapse of disease or side effects of ATD are often seen in these patients. While all treatment modalities (ATD, RAI and surgery) have advantages and disadvantages, the main goal of antithyroid therapy is to provide a quick euthyroid status. Given that the thyroid function test should be at or near normal to avoid potential aggravation of thyrotoxicosis during surgery or RAI therapy, assistive treatment is often required to achieve a euthyroid status[4]. Although the use of an iodine solution is quite effective, long-term use could lead to the escape phenomenon. In addition, several case reports dating back to the 1970s recommend plasmapheresis[5,6]. In the literature, there were only upto six sequential sessions of plasmapheresis used for treating hyperthyroidism[7].

Here, we detail an unusual case presentation where the patient was allergic to methimazole and propylthiouracil. After eight sessions of therapeutic plasma exchange, a euthyroid status was achieved for this patient. An informed consent has been taken from the patient for this case report.

A 36-year-old woman with a history of GD presented with severe thyrotoxicosis. She was treated with methimazole followed by propylthiouracil over 12 months and suffered repeated episodes of rash and redness on the skin from both medicines. On physical examination, she was tachycardic to 132 bpm and had nausea and vomiting. Her blood pressure was stable at 127/80 mmhg. An electrocardiogram showed a sinus rhythm. The remainder of the physical examination was unremarkable. Notably, neither thyromegaly nor tender thyroid was appreciable on physical examination. She had a normal complete blood count and liver and kidney function tests, but her TSH was low, measuring <0.05 μIU/mL (reference range, 0.38–5.3mIU/L). Her free thyroxine (T4) was 5.17 ng/dl (reference range, 0.6–1.12 ng/dl), and her free triiodothyronine (T3) was 21.2 pg/ml (reference

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range, 2.3–4.2 pg/ml). Her anti-thyroglobulin and antimicrosomal antibodies were positive at a titre of 6.2 U/ml(reference range, 0–4 U/ml) and 25.8 U/ml (reference range, 0–9 U/ml), respectively. A thyroid uptake scan showed diffusely increased uptake, indicating GD, and an ultrasound examination showed hypoechogenicity and heterogeneity with no nodules. The treatment plan was reviewed, and surgical therapy was chosen. To reach a euthyroid status without ATDs, eight sequential sessions of therapeutic apheresis were conducted. At each session, 1.5 to 2 L of plasma were exchanged, and fresh-frozen plasma was used as the replacement fluid. The patient's vital signs were monitored, and her biochemical and haematological parameters were re-evaluated during each session. Table 1 demonstrated thyroid hormones during therapeutic apheresis.

Table 1. Thyroid hormones during therapeutic apheresis

	fT3 pg/mL (2,3-4,2 pg/mL)	fT4 ng/dL (0,61-1,2 ng/dL)	TSH mIU/L (0,38-5,33 mIU/L)	Anti-TPO AB U/mL (0-9 U/mL)	Antithyroglobulin AB U/mL(0-4 U/mL
Day 1. Before TPE	23,95	4,58	<0,005	24,3	7,4
Day 1. After TPE	14,77	3,91	0,42	9,9	2,9
Day 2. After TPE	7,06	2,83	0,32	7,6	1,5
Day 3. Before TPE	7,45	4,44	<0,005		
Day 4. After TPE	7,1	2,3	<0,005	2,3	0,4
Day 5 After TPE	3,6	2,24	<0,005		
Day 6 After TPE	5,05	2,3	<0,005		
Day 7. After TPE	4,07	1,75	0,01		
Day 8. After TPE		1,1	0,43		

FT3 5= Free Triiodothyronine, FT4= Free Thyroxine, Anti-TPO AB=Antimicrosomal Antibodies, TPE= Therapeutic Plasma Exchange

After eight sessions,a euthyroid state was achieved,and a total thyroidectomy was performed. Her pathological diagnosis was diffuse hyperplasia of the thyroid gland (GD).

This unusual case report shows the efficacy and tolerability of therapeutic apheresis and its benefit in cases where a pharmacological approach is either contraindicated or unavailable. Notably, the effect of apheresis is staggered and temporary, lasting less than 3–4 days. Repeated plasma exchange sessions are often needed to reach euthyroidism, especially in resistant cases. Multiple sessions (eight) of plasmapheresis may be required for patients with refractory thyrotoxicosis.

Therapeutic plasmapheresis has been shown to have a clear benefit in cases of severe hyperthyroidism related to GD and toxic multinodular goitre[8]. The therapeutic benefit of apheresis stems from the withdrawal of cytokines, hormones and other pathological substances[9]. Therapeutic apheresis also removes 5-monodeiodinase, which converts T4 toT3 and thus decreases T3 production. Autoimmune-based thyroid diseases show more positive results from therapeutic plasmapheresis, and its ability to achieve a euthyroid state is probably not only by direct thyroid hormone removal but also clarified by the removal of the anti-TSH and antithyroid antibodies[10]. Multiple case reports associated with GD have demonstrated the use of apheresis, and all showed rapid clinical response and rapid normalisation of thyroid hormone level circulation[11,12]. In 2018, Simsir et al.[13]demonstrated that 46 patients with hyperthyroidism were treated with plasmapheresis, and the mean number of sessions needed to reach euthyroidism was 4.

Baser et al.[14] presented 18 patients with hyperthyroidism; plasmapheresis was performed on 2 patients to achieve euthyroidism before surgery, and the mean of the plasmapheresis sessions was5.35. One of two patients was diagnosed with GD, and the number of needed plasmapheresis sessions for this patient was four. Another retrospective multi-centre study revealed the result of plasmapheresis in 22 patients with hyperthyroidism. In that study, a mean of four plasmapheresis sessions were performed to reach euthyroidism[15].

In summary, we were able to achieve euthyroidism with eight sequential plasmapheresis sessions for our patient. Because the effectiveness of plasmapheresis can be transient, several sessions are needed for resistant hyperthyroid patients. Increasing the circulating plasma cytokines in patients with GD

might contribute to the need for multiple sessions of therapeutic plasmapheresis. Further prospective studies are needed to clarify the overall effectiveness of plasmapheresis.

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