JOD-BASEDOW EFFECT DUE TO PROLONGED USE OF LUGOL SOLUTION-CASE REPORT

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JOD-BASEDOW EFFECT DUE TO PROLONGED USE OF LUGOL SOLUTION-CASE REPORT (Abstract): Graves' disease is the most common form of hyperthyroidism, accounting for 60-80% of all cases of thyrotoxicosis. If left untreated, it may lead to severe thyrotoxicosis with cardiovascular, ocular, psychiatric complication, and in extreme cases thyrotoxic crisis with a high mortality rate. We present the case of a 50-years-old woman diagnosed in another service with Graves' disease and treated for many years with antithyroid drugs (ATDs), admitted to our service for a relapse due to treatment discontinuation. The surgical treatment was planned and the preoperative preparation with Lugol solution was initiated. Due to a misunderstanding, the administration of iodine solution was extended for a period of about 30 days, thus generating the so-called Jod-Basedow effect, with the exacerbation of the manifestations of thyrotoxicosis and risk of thyroid storm. The patient received treatment with high ATDs doses, glucocorticoids, and beta-blockers, resulting in the progressive improvement of symptoms. She was discharged from hospital and given the risk of thyrotoxic crisis the surgery was postponed. After a month, the patient underwent thyroidectomy without preoperative preparation with iodine solution. The operative and postoperative courses were uneventful. Keywords: GRAVES' DISEASE, SURGICAL TREATMENT, LUGOL SOLUTION, THYROTOXIC CRISIS

Graves' disease is the most common form of hyperthyroidism, accounting for 60-80% of all cases of thyrotoxicosis. Its prevalence is estimated to be about 0.6% of population, with a female-to-male ratio of 7:8/1. The disease mainly affects young women, aged 30-60 years (1, 2).

It is an autoimmune disorder due to thyroid receptor autoantibodies (TRAb), also named thyroid-stimulated immunoglobulins (TSI), which stimulate growth of the thyroid gland and overproduction of thyroid hormones. The main clinical manifestations are hyperthyroidism, diffuse goiter, ocular signs, and more rarely dermopathy and acropachy (3). If left untreated it may lead to severe thyrotoxicosis with cardiovascular, ocular, psychiatric complication, and in extreme cases thyrotoxic crisis, with a high mortality rate of about 20% even in our days (4).
The optimal therapy for Graves' disease is still a subject of debate. The main treatment options are represented by antithyroid drugs (ATDs) and ablation therapy: radioactive iodine (RAI) or surgery (5). The used ATDs are methimazole, carbimazole, and propylthiouracil. They are acting by blocking thyroid hormone synthesis and may also control hyperthyroidism by immune suppression (6). A major disadvantage of ATDs treatment, which has traditionally been the first-line treatment in Europe, is the high risk of relapse after discontinuation (50-80% of patients) (5, 7). Surgery is an alternative therapeutic option for Graves' disease in many circumstances. Total thyroidectomy has negligible recurrence rates and high cure rates (8, 9, 10). Preoperative preparation with iodine is used by most surgeons in order to prevent thyrotoxic crisis and complications during thyroidectomy (11, 12).

**CASE REPORT**

We present the case of a 50-years-old woman, living in an urban area, non-smoker, diagnosed in 2006 in another service with Graves' disease. She was treated with variable doses of methimazole. The patient was admitted to our service in January 2014 for agitation, sinus tachycardia, significant weight loss, and diarrhea. The patient discontinued the treatment with ADTs for 10 months without consulting her physician. Hormone profile revealed severe thyrotoxicosis: TSH < 0.004 µU/ml, FT4 = 4.88 ng/dl, FT3 = 21.1 pg/ml, positive antithyroid antibodies (AAT) and TRAb. Thyroid ultrasound: increased thyroid volume (40 ml), intense hypoechoic appearance "hell-like" vascularization. ECG: sinus tachycardia. Given the long course of Graves' disease, high thyroid volume and high TRAb levels, surgery was recommended. The preoperative preparation with Lugol solution 20 drops x 3/day for 9 days was initiated. Due to intercurrent respiratory infection surgery was delayed, but without discontinuing the administration of Lugol solution; the patient continued the administration of iodine solution at home for 30 more days. Readmitted for surgical treatment, the patient developed more severe symptoms of thyrotoxicosis (pulse = 140/min, intense sweating, agitation), the surgery being once again delayed, and the patient transferred to the Endocrinology Department. Clinical and laboratory assessments confirmed the diagnosis of Graves' disease; thyroid scan demonstrated the characteristic features of Jod-Basedow effect (large thyroid, highly increased thyroid uptake). Cardiac assessment: hyperkinetic heart, without signs of ventricular dysfunctions (fig. 1, 2).

The patient received treatment with high methimazole doses (Thyrozol 60mg/day), glucocorticoids (Prednisone 30 mg/day) and beta-blockers (Propranolol 40 mg x 2/day). Due to leukopenia (white blood cell count to 2730/µl) with neutropenia (neutrophil count to 920/ µl) methimazole administration was temporary discontinued and continued the administration of corticosteroids with gradual return to normal of leukocyte formula that allowed resumption of high ATDs doses. The clinical signs had progressively improved and the patient was discharged after 14 days. The surgical treatment was once again postponed, given the risk of thyrotoxic crisis. The patient was ambulatory monitored every 2 weeks. In April 2014 thyroidectomy was performed without preoperative preparation with iodine solution. The operative and postoperative courses were
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uneventful. The patient developed postoperative hypothyroidism, and currently she is under thyroid replacement therapy. Histopathology confirmed the Graves' disease.

**DISCUSSION**

In patients with Graves' disease treated for many years with ATDs, with an increased number of relapses, large goiter and high TRAb level, surgery may be a safe therapeutic option. Also, surgery provides rapid treatment and permanent cure of hyperthyroidism in most patients (8). Preoperative preparation of patients with hyperthyroidism to achieve euthyroid state is extremely important for avoiding perioperative complications due to severe thyrotoxicosis (13). This can be done using a combination of ATDs, beta-blockers and sometimes glucocorticoids (11). Thyroid storm is an exaggerated state of thyrotoxicosis that occurs in patients who have an inadequately treated thyrotoxicosis and a precipitating event such as thyroid surgery, with a mortality rate that has decreased over time from nearly 100% to approximately 20% in our days (4). Most surgeons administer iodine (as Lugol solution) to provide ≥ 30 mg of iodine/day for 10 days before surgery to decrease thyroid vascularity, the rate of blood flow, and intraoperative blood loss during thyroidectomy (12). These actions are explained by the Wolff-Chaikoff effect of excess iodine, an autoregulatory phenomenon that directly inhibits thyroid hormone synthesis and release. This effect lasts around 10 days, after which it is followed by an "escape phenomenon", with resumption of normal organification of iodine and normal thyroid function (14, 15).

In our patient, the preoperative preparation with Lugol solution was extended for a period of about 30 days (due to a misunderstanding), thus providing excessive amounts of iodine to the thyroid gland for a long period of time, and generating the so-called Jod-Basedow effect, with the exacerbation of thyrotoxicosis and risk of thyroid storm.
This condition has a steep onset with fever, marked tachycardia, and arrhythmias, which may be accompanied by pulmonary edema, congestive heart failure, gastrointestinal dysfunction, and central nervous system involvement (16,17). Knowledge of these aspects and careful monitoring of the patient are extremely important because the diagnosis is mostly clinical, the point at which thyrotoxicosis becomes thyroid storm being subjective (17). Even though some authors have proposed a clinical score to confirm the diagnosis, in current practice patients presenting with significant symptoms of thyrotoxicosis should be considered as being at risk for thyroid storm and undergo aggressive treatment, rather than waiting for a specific score threshold (17, 18). In our case, the patient presented an impaired general condition with aggravation of the cardiovascular, digestive and mental manifestations of thyrotoxicosis, thus prompt treatment with high doses of ATDs, beta-blockers, glucocorticoids and sedatives was initiated in an attempt to block the synthesis and peripheral conversion of thyroid hormones, and to control the clinical symptoms.

Besides minor adverse effects such as pruritus, skin rash, arthralgias, and slight elevations in liver enzymes levels, ATDs may rarely cause an aggravation of mild leukopenia that is common in Grave’s disease, with risk of agranulocytosis (granulocyte count below 500/mm³). Agranulocytosis may occur even in patients who previously tolerated ATDs, and multiple exposures may represent a risk factor for developing hematological disturbances (19, 20). This situation was met in our patient, who presented under methimazole a worsening of initial leukopenia, with granulocytopenia and risk of agranulocytosis, which forced us to temporarily discontinue the administration of ATDs, and continue only with glucocorticoids, which gradually normalized the absolute neutrophil count. Normalization of white blood count allowed us to resume the treatment with high doses of methimazole, in order to obtain a more rapid improvement of symptoms, by blocking the synthesis of thyroid hormones.

The clinical symptoms and hormone parameters gradually improved, and the patient was discharged after 14 days of hospital stay.

It is important to know that in thyrotoxicosis ATDs are blocking the thyroid hormone synthesis, not the release of preformed thyroid hormones. Euthyroidism is obtained only when intrathyroidal hormone and iodine stores are depleted, and this process requires up to 6 weeks. Large goiters with abundant deposits of thyroid hormone, especially when iodine excess is present, often show a delayed response to thioanmides (19, 21). In these circumstances, knowing the history of massive thyroid iodine load, confirmed by the increased scintigraphic uptake and the ultrasonographic aspect of the thyroid gland with high volume and intense vascularization, the surgical intervention was postponed again, due to the high risk of thyrototoxic crisis.

**CONCLUSIONS**

Our case highlights that although preoperative preparation with iodine solution is preferred by most surgeons in order to prevent complications during thyroidectomy, this treatment must be performed in hospital under close supervision by medical personnel, in order to avoid such complications like Jod-Basedow phenomenon and thyroid storm. Thus, surgery remains a safe therapeutic option for Graves’ disease in many circumstances.
REFERENCES