Lecture no. 9

Thyroid Surgery - Hyperthyroidism

The syndromes associated with elevated levels of thyroid hormones are generally defined as *thyrotoxicosis*: these may arise in the thyroid gland, and thus rightly be termed hyperthyroidism, also known as *primary hyperthyroidism*. Other Authors use *secondary hyperthyroidism* to refer to causes external to the thyroid (e.g., iatrogenic thyrotoxicosis, thyrotoxicosis factitia, from hypothalamus-pituitary damage, etc.).

The organ-specific autoimmune form of the disorder is the most frequent cause of primary hyperthyroidism: Flajani's (1802), Graves' (1835), Basedow's (1840) disease - or diffuse toxic goiter (DTG) - and, at times, Hashimoto lymphocytic thyroiditis at disease onset.

Hyper- or neoplastic disease may also be responsible for hyperthyroidism: toxic adenoma or toxic nodular goiter (TNG), toxic multinodular goiter (TMG) or Plummer's disease. Even a euthyroid goiter may evolve (or become complicated) in hyperthyroid goiter (i.e., "*Gravesized or basedowized goiter*").

DTG, hereinafter Graves' disease, TNG (it, too, referred to simply as toxic adenoma) and TMG are all of surgical interest and thus constitute the content of this chapter; Hashimoto hyperthyroidism, by contrast, becomes a surgical problem only with the advent of complications (e.g., compression phenomena, nodulation).

Graves' disease is the single most common cause of primary hyperthyroidism in persons under 40 years of age. Its frequency in the general population ranges from 1.5 to 2%, with significant geographic variations, while incidence amounts to 20 cases per 1,000,000 every year, affecting above all females (F: 5-7; M: 1). The disease can occur at any age, but it is most commonly seen in the 3rd and 4th decade and above 60 years of age. Childhood cases have been seen, albeit with it a lower frequency (0.15% in school-aged children). A particular genetic predisposition has been described.

The disease is the focus of intense multidisciplinary research, since numerous issues of an etiological-pathogenetic nature remain unsolved. Beyond the already mentioned - and sporadic - observation of a genetic basis, much investigation has centered on infective, also viral, causes, without any apparent involvement of the thyroid itself. Psychic stimuli have also been implicated, and the parallelism with periods of high hormonal activity (puberty, pregnancy, menopause).

Graves' disease is an organ-specific condition triggered by a number of possible immunological alterations. At present, it seems that a defect of suppressor T cells in the thyroid induces the lost inhibition of abnormal lymphocyte clones, thereby leading to the immune action against thyroid autoantigens. The thyroid is thus stimulated by antibodies against the thyroid-stimulating hormone (TSH) receptor (anti-Tr), such as the immunoglobulins TS-ab or *thyroid-stimulating immunoglobulin* (TSI), or those that inhibit the binding of TSH (TBI-ab), or still those that block the stimulation of TSH (TSB-ab), namely, *long-acting thyroid-stimulator* (LATS) and LATS-protector. The thyrocyte itself, following stimulation, which may be either viral and/or bacterial, expresses antigenic peptides belonging to the major histocompatibility complex (MHC) class I; the aberrant expression of MHC class II peptides presumably then leads to an abnormal presentation of thyroid autoantigens in helper T cells, thereby triggering the immune reaction (*antigen presenting cells, APC*).

From an anatomo-pathological standpoint, the gland may be uniformly increased in size and without nodular formations (parenchymatous goiter). Relatively rarely, however, does the thyroid enlarge excessively, and, at times, may even be normal in size (a form of Graves' without goiter); in appearance, it shows an increased consistency and an opaque surface that often adheres to adjacent tissues. Vascularization is visibly intense, above all in an untreated gland.

Histologically, hyperplasia and hypertrophy of epithelial follicular cells are evident, with small folliculi and endofollicular papillary proliferation (a diagnostic differential for papillary neoplasm). Colloid is scarce, fluid, vacuolized ("*wormholed" colloid*), especially in areas coming into contact with the epithelium. In the stroma, lymphocytic infiltrates with the formation of germinating centers are seen: in some areas the lymphocytic infiltrates resemble what occurs with Hashimoto thyroiditis (common autoimmune pathogenesis).

Classic Graves' disease is characterized by the involvement of numerous systems: it is a multiorgan disease. Onset is often insidious, and for several months may detract attention away from the true nature of symptoms. During this phase the patient complains especially of psychic disorders: excessive emotiveness, irritability, restlessness, anxiety, easily worried about unimportant or nonexistent reasons, depression, psychasthenia, difficulties of ideation, insomnia and tremors. Such symptomatic mimicking jeopardizes the correct diagnosis: nevertheless, bearing in mind that a thyrotoxicosis may account for these symptoms is enough to warrant further investigation (hormone assays).

The hallmark symptoms, in addition to the above-mentioned neuropsychic signs, include asthenia, heat intolerance, increased sweating (always excessive after even light

physical exertion, and even at rest), flushing episodes of the face and neck, menstrual disorders until amenorrhea, abdominal problems with episodes of diarrhea, cardiopathies, dyspnea (especially after exertion, even slight), substernal compression.

At physical examination, the patient is often thin, hyperkinetic, with trembling of the hands (rapid, fine, irregular oscillations), bright, shiny eyes, often fair unless they are protruding and staring, i.e., sporadic exophthalmos, at times asymmetric. The skin is often moist with sweat, and the neck may be enlarged due to the goiter (not constant). The pulse is increased, as is the differential arterial pressure. Tachycardia may be raised (120 beats/minute), arrhythmias are frequent, eventually leading to total arrhythmia from atrial fibrillation. The thyroid is often palpable, even if not enlarged, due to its increased consistency; a constant thrill and a systolic murmur are frequently experienced (due to increased vascularization and activation of arterial-venous shunts).

Ophthalmopathy nearly always manifests, even if an evident exophthalmos is not present. The most common ocular symptoms are conjunctival/corneal irritation (lagophthalmos during sleep, with rare blinking: corneal ulcer), photophobia, painful gritty sensation in the eyes. Ophthalmopathic conditions may worsen into diplopia and weakened eyesight, ultimately resulting in amaurosis (complete loss of vision).

Specific ocular signs are:

- lifting of the upper eyelid (Dalrymple's sign) and retraction of the lower lid;
- infrequent/incomplete blinking (Stellwag's sign);
- lag of the upper eyelid fails as it follows rotation of the eyeball downwards (von Graefe's sign);
- ocular-frontal asynergy (Jeffroy's sign);
- impairment of ocular convergence (Möbius's sign);
- horizontal nystagmus.

In elderly subjects the disease may arise without the above-mentioned signs and symptoms (*apathetic thyrotoxicosis*), and if present attenuated by cardiovascular and myopathic features.

The diagnostic workup necessarily includes assays for thyroid hormones: free triiodothyronine (FT3), free thyroxine (FT4) and thyroid-stimulating hormone (thyrotropin - TSH); and antithyroid antibodies: antithyroglobulin (anti-Tg), antithyroidal peroxidase (anti-TPO), thyrotropin receptor antibodies (anti-TSH).

Ultrasound (US) examination of the thyroid is advisable to confirm the parenchymatous make-up of the gland and the possible presence of nodules. While generally not useful, a thyroid scintigraphy will reveal homogenous and increased uptake curves, with rapid discharge. Other complementary and normally not performed exams include colesterolemia (reduced), alkaline phosphatase and hydroxyprolynuria (increased).

The natural history of the disease has a course that may be slow and erratic, with critical exacerbations alternating with periods of relative remission and relapse. Antibody aggression, which brings about parenchymal destruction and/or inactivation, may induce a gradual attenuation of the hyperthyroidism and a potential evolution into hypothyroidism. Nonetheless, the features of the multiorgan damage caused by the disease may lead to serious alterations in various systems, and may condition the onset or the worsening of potentially dangerous complications. Episodes of relapse may manifest as *thyrotoxic crisis* (*thyroid storm)*.

This life-threatening syndrome is a sudden and acute exacerbation of the hyperthyroidism: it arises in untreated thyrotoxic patients, following surgery, during a serious disease, following a trauma or even after radiometabolic treatment for hyperthyroidism. Other triggering factors have been described, including serious

infectious episodes, cardiovascular diseases, diabetes mellitus, dehydration and metabolic imbalance. Symptoms include high fever (> 40 C°), which rapidly induces dehydration; tachycardia and often tachyarrhythmia; initial stage arterial hypertension and congestive heart failure, with progressive deterioration of conditions due to shock brought on chiefly by dehydration. Vomiting, diarrhea, abdominal pain and jaundice may also appear. Conscience is altered, with erethism (irritability) and confusion leading to symptoms of psychosis, stupor and coma. In essence, the multiorgan involvement typical of Graves' disease are exacerbated to a life-threatening extent. The following sections covering therapy will discuss, with descriptions based on personal experiences, actions to take to prevent thyroid storm and to treat it should it arise.

The treatment of Graves' disease is challenging, hampered as it is by the still uncertain and undefined etiological and pathogenetic interpretations of the condition. As has been practiced for some time now, most practitioners today hold that the primary purpose of therapy is to make the patient euthyroid by inducing permanent or at least long-term remission without provoking hypothyroidism. This is the primary objective of medical therapy, through the use of antithyroid drugs (methimazole, propylthiouracil, and as second choice, lithium carbonate and propanolol). Theoretically, ^{131}I therapy should achieve this goal, but this approach, be it at short- or at long-term, often leads to the onset of hypothyroidism.

In most countries, including Italy, antithyroid drugs are the treatment of choice for DTG ; until recently, physicians in the United States preferred radioactive iodine, but this trend has given way to strategies based on antithyroid medication and on surgical treatment. This latter normally represents a second therapeutic option, although some authors still insist on its use as treatment of choice.

Near total thyroidectomy (NTT), the most commonly adopted procedure for DTG, achieves euthyroidism in nearly 60% of treated patients, while hypothyroidism and recurrence, according to published series, do not exceed 20-40% and 2-15%, respectively. Our experience (Surgical Clinic, University of Genoa) confirms these data, with long-term findings of:

- Euthyroidism: 60.5%;
- Hypothyroidism (considered as such also those cases with only increased TSH): 29.2%;
- Recurrence: 8.3% (clinical: 5.2%; serum levels: 3.1%).

It is noteworthy that the risk of hypothyroidism is greater in the first year after surgery, that it decreases in the second year and that it remains constant over the years that follow. The risk of postoperative recurrence is high during the first three years, and declines thereafter.

In Lecture no. 8 on the surgery of euthyroid goiter, care was taken to distinguish between subtotal thyroidectomy (STT) and NTT. Regretfully, the literature continues to speak of the former as an alternative to total thyroidectomy (TT), but the term is too vague and broad, and for numerous authors (including us), it denotes a procedure that leaves a residual parenchymal volume equal to normal, which is certainly excessive in the treatment of high-risk Graves'. As was mentioned in the previous lecture, with NTT parenchymal demolition leaves a residual posterior glandular wall no greater than 1 centimeter in thickness, above all towards the inferior pole (to better safeguard the parathyroid glands and the recurrent nerve). This approach presumably guarantees a remaining glandular tissue of approximately 4 to 10 grams in weight, i.e., the range thought to be acceptable to achieve the greatest possible measure of euthyroidism.

Here, however, the etiological uncertainties surrounding the disease come into play again: the extent of postsurgical hypo- or hyperthyroidism that has impacted negatively

in some way on all published series is seemingly contingent less on errors made in "weighing" the parenchyma to preserve and more on the "quality" of the gland in relation to the extent that factors causing the disease are maintained, namely, the varying degree of functional activation of thyrocytes and the complex of responsible autoimmune factors. Nevertheless, as occurs with every organ-specific autoimmune disorder, a correlation between the amount of residual parenchyma and the functional outcome of treatment has been demonstrated. One of our studies investigating an activity specifically correlated to the autoimmune nature of the disease (autologous mixed lymphocyte reaction - AMLR) in groups of patients who became euthyroid after treatment with methimazole, ^{131}I or NTT revealed that only the ablative, not total, approaches like NTT allowed reverting the autoimmune reaction to parameters within the norm, on the condition that sufficient active parenchyma was removed.

Beyond this specific finding, this research seems to corroborate the legitimacy of non-total intervention, as long as it is *adequate*. Obviously, better results could be achieved were it possible to establish in each individual patient the degree of exeresis to perform, and thereby design targeted treatment strategies. Attempts have been made, utilizing available data (epidemiological, clinical, biochemical and histopathological) to identify predictive factors of possible disease relapse or of evolution towards hypothyroidism. There is little consensus in the literature, above all due to the different clinical settings of patient series and the different methods of evaluation. The parameters most often analyzed are age, sex, duration of preoperative treatment, size of the goiter, free T3 serum levels and thyroid autoantibodies. Among these, only the following correlations would seem to emerge: an increased frequency of postsurgical hypothyroidism in patients with a prolonged clinical history of disease and a higher chance of recurrence in younger subjects.

Even though we have at present no reliable criteria to help *calibrate* the extent of excision, the above data would seemingly enable us to address younger patients in

whom recurrence is more likely to more radical procedures, while a more conservative approach could be reserved for elderly patients with a longer history of symptoms, in whom signs of a spontaneous progressive functional breakdown will presumably be found.

One predictive element could also derive from the correlation between the intraglandular lymphocyte makeup and postsurgical hypothyroidism, as was already proposed by some authors nearly fifty years ago. Indeed, the notion that a DTG with strong "*hashimotian*" features will more likely succumb to functional breakdown with time is intriguing.

A great deal of information on the state of functional activation of infiltrating lymphocytes in autoimmune thyroid disease has derived from both phenotypic and functional studies. In particular, we know that in Hashimoto thyroiditis (HT) cytotoxic T cells are prevalent, while in TDG T helper cells predominate, and are able (through activation of B cells and macrophages) to generate antibodies stimulating TSH. Nevertheless, in TDG clones with cytotoxic activity against thyroid cells are also present. Still other findings putatively ascribe to the thyrocyte in TDG the ability, albeit to a lesser extent than in HT, to express adhesion molecules (ICAM-1), and that such activity could depend on the amount of activated infiltrating lymphocytes present.

In light of these data, the strategy of treating hyperthyroidism by TT, thereby imposing complete hypothyroidism and condemning patients to substitute therapy for life, seems a dismal one at best. This same outcome is achieved to a fair degree at long term after ^{131}I therapy. Although complications from TT (hypoparathyroidism, recurrent nerve paralysis) are limited in expert hands, such radical therapy offers no advantages over ^{131}I, except in specific groups of patients in which radioactive iodine is ill-advised or in which compliance issues would arise.

From a cost/benefit standpoint (not to mention potential medical-legal pitfalls), TT, because it intrinsically entails greater complications for the same outcome, would seem unwarranted compared to ^{131}I therapy. The euthyroidism that is achieved in reasonable share of cases is the only reason in our view that would justify the risks of surgical intervention. Even the objection coming from advocates of TT, namely, that a sub- or near total procedure does not resolve the causes of the disease, is debatable, in view of what has been said about the adequate parenchymal excision and its ability to overcome in a large number of cases the autoimmune aggression.

Leaving aside the technical details and potential complications of NTT (already detailed in the previous Lecture), it is worthwhile rather to delve into preoperative treatment strategies aimed at preventing perioperative hemorrhaging and postoperative thyroid storm. It should be borne in mind that forestallment of this latter complication must be guaranteed prior to any other planned surgical procedure.

The patient, already euthyroid thanks to antithyroid medication (note this state must be carefully ascertained as the procedure approaches), should be given iodine in the form of Lugol's solution or potassium iodide at gradually increasing doses. This therapy (the Wolff-Chaikoff effect) leads to i) a noteworthy decrease in the vascularization of the gland (the thrill must disappear; perioperative, and often serious, hemorrhage is prevented), ii) a reduction in the volume of and an increase in the firmness of the parenchyma (thereby facilitating surgical maneuvers) and iii) the inhibition of the release of thyroid hormones into circulation.

Thyroid storm is managed medically, both aspecifically and specifically. The former is meant to contrast systemic effects (fever, dehydration, shock, etc.), while the latter entails the administration of antithyroid agents, iodine or β-blockers. Given that

the syndrome carries a serious prognosis, even with these adopted provisions, the absolute need for appropriate preventive care cannot be stressed enough.

Two personal experiences

The first was an observation during my residency in surgery. The patient was a 40-year-old male with a Graves' goiter transferred from the Endocrinology Division, where he had undergone a presumably appropriate preoperative workup. Surgeons of the day, trustworthy of the work done by their endocrinologist colleagues, proceeded to perform a thyroidectomy. Thyroid storm occurred in the first postoperative hours and quickly led to the patient's death despite attempts otherwise. This distant experience taught me to personally control not only the euthyroidism of the patient being operated, but also the clinical conditions (e.g., the thyroid murmur, etc.) and the effectiveness and development of the iodine therapy.

The second case involved a 60-year-old female patient with a previous Graves' goiter treated with antithyroid medication and subsequently with radioactive iodine. The patient came under our observation for an obstructive jaundice caused by biliary and gall stones. A cholecystectomy and choledocholithotomy were scheduled. Surgery was performed after having ascertained that thyroid function values (beyond the specific examinations for the procedures) were normal. Thyroid storm developed with mitigated symptoms during the immediate postoperative period, and was successfully resolved using β-blockers (propanolol) and antithyroid drugs. The sudden and unexpected onset of this complication raised a number of questions in us as to its cause: was it possible that surgical stress had triggered autoimmune phenomena in the thyroid, which once presented a Graves' goiter but was now normalized through ^{131}I therapy, as if the gland somehow remained susceptible to such an event? This experience prompted us be wary in any surgical circumstance of previous events of hyperthyroidism.

The effects of total or partial surgical procedures on Graves' ophthalmopathy are still widely debated, with little consensus emerging from published experiences: according to some, NTT guarantees improvement of ophthalmopathic symptoms in as many as 70% of cases, while others hold that the procedure is ineffective or even detrimental. Analogous contrasting results are reported for TT. Leading to such difficulties are factors such as moment of onset (more favorable results in more recent cases), and the degree of ophthalmopathy, which ranges from simple exophthalmos to the more serious lesions mentioned earlier. The rate of "malignant exophthalmos" reaches as high as 8%.

In our experience, ophthalmopathy was present in 78% of cases. In our hands, NTT achieved the following outcomes:

- Approx. 70% - nearly complete regression over a time span of 3 to 18 years;
- Approx. 16% - improvement;
- 2% - only monolateral regression;
- Approx. 8% - failed regression;
- Approx 4% - worsening.

As far as **Graves' euthyroid goiter** is concerned, apart from the variations in gland volume and the possible compressive symptoms, unusual for DTG, the pathogenetic mechanisms and treatment do not differ from those described for Graves' disease proper.

Toxic thyroid adenoma (thyrotoxic adenoma or toxic nodular goiter - TNG), called by some authors Plummer's adenoma (erroneously, in my view, since Plummer described toxic multinodular goiter, a.k.a. Plummer's disease), is a benign tumor that only exceptionally (1/10,000) presents signs of malignancy. A distinction between Plummer's disease and toxic adenoma must be made, as they are two different disorders: the former is a hyperplastic goiter, while the latter is a neoplasm.

This topic has been the focus of numerous investigations. These solitary, encapsulated, nodules have a follicular structure and, as such, differ from hyperplastic growths in which the structure is similar to what is found in a euthyroid goiter. They have been shown to have a monoclonal proliferation (which attests to their neoplastic nature), compared to the polyclonal proliferation found in hyperplastic nodules. The follicular cells that make up the nodule proliferate and function more and independently compared to the other cells. A TNG is also functionally autonomous, and this autonomy is clearly apparent (as we will see) on scintigraphy, where uptake curves independent of the remaining thyroid parenchyma are visible.

From a clinical standpoint, symptoms, especially at onset, are often misleading and insidious when (as frequently occurs) the nodule is not manifest, let alone palpable. This is often the case because of the small size of the growth and because the hyperthyroidism is oligosymptomatic: indeed, disturbances usually affect the neuro-psychic and/or cardiovascular system, and the simultaneous compromise of other, including the ophthalmic, systems (as with Graves' disease) is regularly absent. Patients often present complaining of anxiety, depression, psychosis (one case in our experience was transferred from the psychiatric ward, and removal of the nodule promptly restored

the patient's neuropsychic equilibrium); tachycardia, at times paroxysmal, arrhythmia and atrial fibrillation may also be present. Cardiovascular and neuro-psychic disturbances often coexist. Such a clinical presentation obviously undermines a correct diagnosis. Symptoms may also be absent in pre-toxic TNG.

Diagnosis is based on clinical grounds, if the nodule is palpable (the thyroid murmur of Graves' disease is absent), on US imaging and on levels of thyroid hormones (free T3, free T4), TSH and antithyroid antibodies: demonstration of a solitary nodule ("solid" on US), increased FT3 and FT4 with decreased TSH (which may be the only sign should FT3 and FT4 levels result normal), and normal antibody findings provide the convincing grounds for a suspected TNG. This diagnosis is confirmed by thyroid scintigraphy, which reveals a round ("hot" nodule) corresponding to the palpable growth and/or what was detected on US, and by the absent visualization (no uptake) of extranodular parenchyma. Such a scintigraphic picture is the only certain sign of pre-toxic solitary nodule. If scintigraphy is repeated after administration of exogenous TSH, the extranodular parenchyma - which showed no uptake in the previous examination - is visualized, thereby demonstrating the nodule's autonomous nature. This procedure is not routine, and is indicated when doubts arise (for instance, a possible thyroid dysgenesis).

Certainty about the benign nature of TNG does not require preoperative biopsy by fine needle aspiration (FNA) or perioperative sample examination: postoperative histo-morphological control normally suffices. Apart from exceptional cases, preoperative pharmacological measures (imperative in Graves' disease) are not needed.

The treatment of choice is surgery, and following that, radioactive iodine. This latter, however, carries with it some noteworthy drawbacks and complications, namely

radiation induced thyroiditis, exacerbation of thyrotoxic symptoms with the ensuing possibility of thyroid storm and long-term hypothyroidism.

Surgical intervention entails removal of the nodule (see **video**; legend at the close of the Lecture); with a large nodule a lobectomy may become necessary. Because TNG is a benign neoplasm, which differs completely, as mentioned above, in constitution and growth from the surrounding normal parenchyma - not only by definition, but also by preoperative findings - radical procedures (as suggested by some surgeons and prescribed by some textbooks, are meaningless and are to avoid.

Our series of thyroid surgery patients has numerous cases of TNG, which we always managed with conservative approaches: postoperative complications were irrelevant and short- and long-term outcomes always satisfactory in our experience. Some patients in whom the TNG had been removed developed a thyroid disorder decades later: these were, however, unrelated pathogenetically and nosologically to the previous disease.

Toxic multinodular goiter (TMG) corresponds to a hyperplastic goiter, much the same way as what was described in Lecture no. 8, in which one or more of the nodules is (are) functionally independent of the remaining parenchyma. The diagnosis of TMG, therefore, is grounded - beyond physical examination (the goiter) and hormone levels - on US and scintigraphy, which reveal the presence of high-uptake nodules ("hot"), thereby formulating the scintigraphic definition of "multi-hetero-nodular goiter".

The indications and methods of the surgical treatment of TMG we described in Lecture no. 8. The preoperative preparation required for Graves' disease is not necessary for TMG.

Video Legend

The video illustrates the surgical procedure for the excision of a TNG from the right thyroid lobe using bipolar instrumentation (scissors, harmonic scalpel). The following are the different stages of the operation.

- Incision of the skin and platysma muscle.
- Use of bipolar scissors.
- Section of the prethyroid muscles.
- Exposure of the gland.
- Exploration with fingers.
- The nodule in the right lobe.
- Use of the harmonic scalpel.
- Removal of the nodule.
- Aspirating tubular drainage.
- Suture of the prethyroid muscles with absorbable synthetic materials.
- Suture of the platysma muscle and the skin.