

Oncological Pathology of The Endocrine System

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Abstract

Our endocrine glands produce hormones, which are like the body's messengers—they move through the bloodstream until they reach their target organ, and then they deliver instructions telling that organ exactly how to behave. These “messages” trigger important processes, like metabolism, growth, reproduction and even mood. Occasionally, in one of the endocrine glands, a change in the DNA (known as a mutation) causes abnormal cells to grow, and a tumor form. Most endocrine tumors are benign (not cancerous), but a few will become cancerous. Collectively, endocrine cancers are much less common than other kinds of cancer. However, thyroid cancer, which is an endocrine cancer, is the fifth most common cancer among women in the United States.

Keywords: Thyroid; Cancer; Carcinoma; Papillary; Tumor.

Introduction

Tumors can occur in any of the major endocrine glands, including the thyroid, parathyroid, pituitary and adrenal glands, and the pancreas. The most common sites are as follows:

- **Thyroid gland:** Most endocrine cancers develop in the thyroid gland (a butterfly-shaped organ in the lower neck). Thyroid cancer is far more common in women than men. Statistics show that the annual rate of thyroid cancer is on the rise, both in

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the United States and worldwide. The good news is, most tumors (referred to as nodules) of the thyroid are not cancerous.

- **Pituitary gland:** A pea-sized organ attached to the brain, the pituitary gland produces hormones that influence growth and fertility. Pituitary tumors are almost always benign but can result in too much or too little of one or more hormones, which in turn can upset the balance of other glands.

- Adrenal gland: The two adrenal glands, which reside just above the kidneys, produce hormones that regulate metabolism (cortisol), the stress response (adrenaline), blood pressure (aldosterone) and certain sexual characteristics (androgens).
- Pancreas: Though the pancreas plays an active role in the digestive system, it's also the source of important hormones, including insulin. Rare tumors can produce too much insulin or other related hormones, which can impact blood sugar levels.

Though some cases are inherited, the cause of most endocrine cancer is usually unclear.

Thyroid cancer

Thyroid carcinoma is the most frequent endocrine neoplasia, without considering ovarian tumors. It represents, however, 1% of all human cancers. In autopsies, the estimated prevalence is 1 to 30% depending on the series. It is one of the few neoplasms that occurs more frequently in women with an M:M ratio of 0.36. The incidence, in different regions of the world, is from 0.5 to 10/100,000 inhabitants/year.

The average age of presentation is between 45-50 years. The prognosis of thyroid carcinoma varies from lesions with very low mortality to extremely aggressive tumors, depending on the histology. However, in most cases the prognosis is good, accounting for only 0.5% of all cancer deaths. Thyroid cancer usually presents as an asymptomatic nodule or, less frequently, due to the appearance of cervical adenopathy. The prevalence of carcinoma in a single nodule or

in a polynodular gland is 10-20%, a figure that increases to 30-50% if there is a history of cervical irradiation. Therefore, the evaluation of thyroid nodular pathology is part of the systematic study of thyroid carcinoma. Various factors that have been associated with the genesis of thyroid carcinoma. Cervical irradiation is clearly related to a significant increase in the incidence of differentiated carcinoma. The risk increases after an average dose of 10cGy, particularly if it was administered during childhood or adolescence. In survivors of Hiroshima and Nagasaki, rates have been found to be 5 to 10 times higher in irradiated people than in those who were not.

The latency time between the moment of irradiation and the appearance of the tumor can reach 20-30 years. On the other hand, there does not seem to be an increase in the incidence of these tumors due to the diagnostic or therapeutic use of radioactive iodine. A relative increase in the incidence of follicular carcinoma has been reported, in relation to other histological variants in areas with iodine deficiency. Molecular biology studies demonstrated the presence of recombination's of the tyrosine kinase domain of the RET proto-oncogene with an uncharacterized gene called H4, both located on the short arm of chromosome 10.

This would produce a constitutive activation of the RET proto-oncogene. This alteration has been found in 3 to 33% of patients with papillary carcinoma not associated with cervical irradiation and in 80% of those with this history, while it has not been found in other forms of thyroid carcinoma. In addition, a nonsense mutation (V599E) in the BRAF gene has been found in 40% of patients with

this histological variant. Not so in follicular or anaplastic tumors. These mutations have been associated with the genesis of this tumor lineage, but no correlation was found with age at diagnosis, sex, size or local invasion, lymph node metastases or tumor stage. In areas with

iodine deficiency, a high incidence of mutations in codon 61 of the Ras gene has been described in thyroid tumors, a fact that could involve some environmental factor in the possible molecular alterations associated with thyroid carcinoma.

Differentiated	Papillary	Good prognosis	Micropapilar
			Encapsulated
			Solid
			Follicular variant
		Poor prognosis	High cell
			Columnar
			Diffuse sclerosant
			Insular
	Follicular	Minimally invasive	
		Invasive	
From Hürtle cells to oxyphilic cells			
Anaplastic			
Medullary			
Other	Lymphoma		
	Sarcomas		
	Metastasis		

Table 1: Histological classification of thyroid cancer.

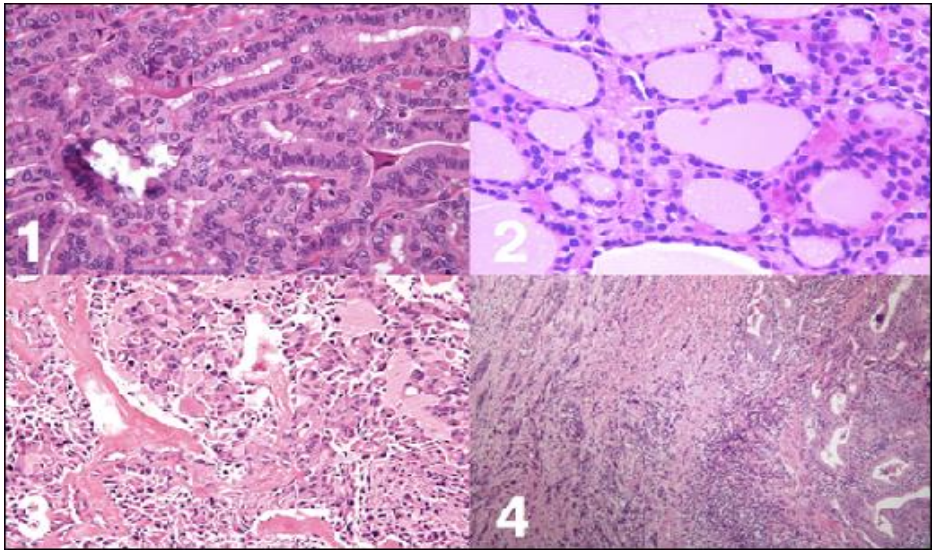


Figure 1: Adapted from work by Nephron (1,3,4), Yale Rosen (2) [CC BY-SA 3.0], via Wikimedia Commons and Flickr.

Histopathologically

Table 1 thyroid cancers are classified into differentiated carcinomas: papillary (1) and follicular (2), and anaplastic carcinoma (4). All these tumors derive from the follicular epithelium. A particular group is made up of medullary carcinoma (3), derived from parafollicular cells (or C cells), with different manifestations and evolution in Figure 1.

Differentiated thyroid carcinoma

Papillary carcinoma

Papillary carcinoma accounts for 50-70% of thyroid cancers. In autopsies, the finding of a micropapillary carcinoma can reach up to 11%. It occurs more frequently in women and in children and young adults (under 40 years of age). Papillary carcinoma is usually a non-

capsulated tumor and histologically it is made up of papillary structures (hence its name) composed of a fibrovascular pedicle, on which the epithelial cells are arranged; Usually, some follicular component is also found. The cells have nuclei with a ground glass appearance, and inclusions and indentations in the nuclear membrane are characteristic. It is common to find calcium structures arranged in concentric sheets called Psammoma bodies. Some tumors may present large cells with a clear acidophilic cytoplasm and a well-defined nucleus, called Hürtle cells. These tumors are slow growing and depend, to some extent, on TSH stimulation. In older people they have a more aggressive evolution, they may do undergo transformation into anaplastic carcinoma.



Figure 2: CT scan of the neck with large tumor image of the right lobe of the thyroid, which causes displacement of the anatomical structures of the neck.

Papillary carcinoma extends locally and spreads predominantly via the lymphatics. Between 30 and 80% multicentricity has been described, with tumor foci in both thyroid lobes. Cervical nodes are the most common

sites of metastasis. Although 30-40% of patients with papillary carcinoma have metastases in cervical lymph nodes, at the time of surgery, their presence does not alter the prognosis of recurrence or mortality.

Hematic dissemination is rare, but when it occurs, distant metastases may be made up of the follicular elements that are associated with these tumors.

Poor prognostic factors in papillary carcinoma are:

- Age over 50 years
- male gender
- Tumor greater than 4 cm.
- capsular involvement
- Distant metastases (non-cervical)
- Absence of thyroiditis in adjacent tissue

Mortality from papillary carcinoma is low (less than 5%), with lung or brain metastases and airway invasion being the most frequent causes.

Follicular carcinoma

It represents 10-15% of thyroid carcinomas. It occurs most often in people over 40 years of age. Like papillary carcinoma, it is more frequent in women.

It is usually a capsulated tumor and is made up of follicular structures that may be identical to normal thyroid tissue (although with less colloid content) and therefore difficult to differentiate from follicular adenomas by cytological techniques. Other times it forms compact plates of tumor cells with mitoses of varying degrees.

It can also present Hürtle cells, and some variants are made up almost exclusively of this cell type. Invasion of adjacent and vascular tissue is common, and the degree of invasion determines the prognosis. Considering that follicular adenomas and carcinomas have a similar structure, the

difference between the two is based on the absence or presence of capsular involvement or vascular invasion, or the finding of distant metastases [4]. Follicular carcinoma has a more aggressive course than papillary carcinoma. Lesions larger than 3.5cm. are associated with an increased risk of recurrence or metastasis. It spreads via the lymphatics and mainly via the blood, with the cervical lymph nodes, lungs, liver, and bone being the most frequent sites of metastasis. Mortality is 5 to 15%, but survival of these tumors can be several decades.

Diagnosis

Thyroid cancer usually presents as an asymptomatic nodule or, less frequently, due to the appearance of cervical adenopathy. As mentioned in previous paragraphs, the prevalence of carcinoma in a thyroid nodule is 10-20% and increases to 30-50% if the gland has been irradiated. Therefore, during the interrogation it is essential collect the history of cervical irradiation.

Family history of thyroid carcinoma is also useful information, since cases of familial papillary carcinoma have been described, and it is essential if the possibility of medullary carcinoma is considered. A single nodule, in men, especially children or adults over 60 years of age, is more likely to be a carcinoma. The same happens if it has had a rapid growth. On palpation, thyroid cancers tend to be stony-hard in consistency, and in some cases adherent to neighboring structures, with limited mobility during swallowing. The presence of a cervical node increases the chance of malignancy of a thyroid nodule.

Thyroid hormone measurement is not very useful in the systematic diagnosis of thyroid

carcinoma since most patients are euthyroid. If it is, the dosage of calcitonin in cases of medullary carcinoma.

Thyroglobulin is a more useful determination in the postoperative follow-up of these tumors than as an initial diagnostic element. Ultrasound is useful to determine the number of thyroid nodules, their size, and the cystic, solid-cystic, or solid structure of the nodules, to assess the presence of lymphadenopathy, and to guide fine-needle puncture when necessary. Thyroid scintigraphy is not very useful in differentiating benign or malignant lesions, since, although most carcinomas occur in cold nodules, only 10% of them correspond to thyroid cancer.

Fine-needle aspiration is the initial method of choice to make the cytological diagnosis of a thyroid nodule. Those completely benign lesions will not require surgery. Tumors whose cytology turns out to be malignant will be treated surgically.

However, there is a subgroup of nodules in which the puncture does not yield a definitive diagnosis (indeterminate cytology) or the material is insufficient. In the latter case, a second puncture can be used, but, in both

situations, it is usually necessary to resort to surgery to obtain a more certain histological diagnosis [1-10].

Staging

There are several systems used to stage thyroid carcinomas. One of the most used is the TNM system Table 2.

T (tumor size) X: The primary tumor cannot be evaluated

o: No evidence of primary tumor

- <1 cm.
- 1-4 cm.
- 4cm
- Extension beyond the capsule

N (Nodes) o: No metastasis

With metastases

- 1 to Ipsilateral
- 1 b Bilateral, midline, contralateral or mediastinal

M (distant metastasis) o: No metastasis

- With metastases

Stage	Age	
	<45 years old	>45 years old
I	Any T, any N, Mo	T ₁ , Mo, No
II	Any T, any N, M ₁	T ₂ the T ₃ , No, Mo
III		T ₄ , N ₁ , Mo
		Any T, any N, M ₁

Table 2: TNM System for Staging Differentiated Thyroid Carcinoma.

Treatment

The treatment of thyroid carcinoma is based on 3 fundamental pillars:

- The surgery
- Ablation with iodine ¹³¹
- TSH inhibitory treatment with thyroid hormone.

Surgery

Surgery is the initial treatment for thyroid carcinoma. Although there is controversy as to what degree of extension it should have in cases of microcarcinomas, there is agreement that in tumors equal to or greater than 1 cm. the indication is total or almost total thyroidectomy (leaving a remnant of thyroid tissue no greater than 2-3gr.). In 5,584 patients with differentiated thyroid carcinoma from 1,500 US centers. 77.4% of them underwent total thyroidectomy, regardless of histological type or stage.

Total thyroidectomy has low morbidity and mortality in the hands of experienced surgeons and allows the identification and removal of contralateral lesions, common in cases of papillary carcinoma. The fact of not removing part of the gland under the pretext of conserving a certain degree of residual thyroid function is of little consequence in patients with thyroid cancer, since they will still have to be treated with levothyroxine to inhibit TSH. And finally, total thyroidectomy facilitates subsequent follow-up with iodine and thyroglobulin.

After a follow-up of 16.6 years, the most aggressive surgery was an independent variable in reducing mortality from differentiated carcinoma by 50%. Leaving a minimum remnant of thyroid tissue (almost total surgery) aims to preserve the irrigation of at least one of the 4 parathyroid glands, to minimize the risk of post-surgical hypoparathyroidism. However, a remnant greater than 2 g decreases the success of ablation with. Patients undergoing more conservative surgery (lobectomy plus isthmectomy) presented 5-14% of local recurrence (2% in cases of total

thyroidectomy), 19% of lymph node metastases (6% in patients with total thyroidectomy) and 11% of lung metastases. In any case, those who promote this type of surgery recommend it only in cases of low-risk tumors: papillary carcinoma <1.5 cm, unifocal and interlobar.

At the time of surgery, two-thirds of patients with papillary carcinoma and 35% of patients with follicular carcinoma have lymph node metastases, which in 80% of cases are in the central compartment of the neck. Routine lymph node dissection is not indicated, but only in those cases where there is evidence of metastasis. If evidence of high risk is found after conservative surgery (tumor larger than 1 cm, tumor in the resection margins, metastasis, or recurrence), the indication is to complete the surgery, since, when doing the scan to subsequent ablation with too large a remnant can mask the presence of distant metastases, due to competition in radioisotope uptake.

The greater the thyroid remnant, the greater the risk of radiating thyroiditis when attempting ablation. If the remnant has sufficient hormone production, it can prevent TSH elevation, which decreases the therapeutic success of the therapeutic dose of. Complications of thyroid surgery are recurrent nerve injury (3%) and transient post-surgical hypoparathyroidism (10%) or, more rarely, definitive (2.6% in adults and up to 10% in children).

Ablation with iodine

After a successful total thyroidectomy, hyper-uptake may appear in the thyroid bed, indicating the presence of glandular or tumor tissue, not macroscopically visible. Removing

it by using is called ablation of the remnant. The purpose of this procedure is to: Eliminate possible foci of microcarcinoma not removed during surgery, destroy the remaining normal thyroid tissue, to facilitate follow-up of patients with scan and increase the specificity of thyroglobulin determinations, reduce the possibility of masking Distant metastasis due to the persistence of a local remnant that competes with the uptake of , and facilitate the elevation of TSH to carry out successive sweeps and therapeutic doses in adequate conditions.

Ablation with is performed between 4–6 weeks after surgery. The patient must not receive levothyroxine treatment during this period and must have been placed on a low-iodine diet. It is necessary to verify the elevation of TSH ($>35\mu\text{U/ml}$) to consider that the procedure will be done under normal conditions It's adequate.

Then, 2 mCi are administered and a total body scan is performed between 48 and 72 hours after receiving it. If hyper uptake is detected in the thyroid bed, the indication is to administer a therapeutic dose of. This varies from 30 to 100 mCi depending on the centers. A meta-analysis found that using doses of 30 mCi, the ablation failure rate was 46% versus 27% when doses of 100 mCi were used ($p<0.001$). If there is evidence of lymph node involvement, the suggested dose is 150 mCi and it is recommended to administer 200 mCi in the case of distant metastases. It is advisable to carry out a new body scan every week, to detect the possible presence of lymph node or distant metastases, which would not have been recognized with 2 mCi but which become evident with a higher dose, such as the therapeutic dose. From this

moment, the patient can start levothyroxine therapy. Ablation is verified by performing a new 2-5 mCi whole body scan at 6 to 12 months.

If any type of increased uptake is evident, the indication is to repeat a new therapeutic dose. It has recently been shown that lithium carbonate administered at a dose of 10 mg/kg during the week prior to the dose increases its uptake in metastatic lesions, with minimal increases in uptake in normal thyroid tissue. Lithium would act by inhibiting the release of radioiodine from the follicular cells and thus increase the exposure time.

This adjuvant treatment is discontinued one week after receiving the dose. Complications of treatment with can be early or late. In the days after treatment with iodine, edema or hemorrhage may appear at the peritumoral level, particularly serious in injuries that compromise the airway, the spinal canal, or the central nervous system. Radiant thyroiditis occurs in 20% of patients during the first week after receiving the dose and is proportional to the size of the treated thyroid remnant; Acute or chronic radiant sialadenitis may also occur, the incidence of which is reduced by adequate hydration and the indication of consuming sour candies. Transient changes in platelet and white blood cell counts have been described.

Bone marrow damage and induction of tumors and leukemia are the most serious late complications of iodine radiation therapy. Cumulative doses greater than 1000 mCi produce a slight but significant increase in mortality from bladder cancer and leukemia. In the latter case, the prevalence is 0.5%, with acute myeloid leukemia being the most frequent.

However, the estimated risk of death from recurrent thyroid cancer is 4 to 40 times that of leukemia, depending on the age at which the patient receives treatment. If administration is at 12-month intervals and the cumulative dose does not exceed 600-800 mCi, long-term effects on bone marrow are minimal. Pulmonary fibrosis may occur in patients receiving lung metastases, particularly if it is miliary spread of carcinoma.

TSH inhibitory treatment with levothyroxine

Tumor cell growth depends, in part, on TSH stimulation. Treatment with levothyroxine to keep thyrotropin inhibited improves recurrence and survival rates. It is indicated in all patients with thyroid carcinoma, regardless of its extension, in doses of 2.2-2.8 µg/kg, to achieve TSH levels <0.1 µU/ml, with free T₄ concentrations within the normal range.

Follow up

Although the prognosis of differentiated thyroid carcinoma is good, 20% of patients have local recurrences and 10-15% distant metastases. In relation to locoregional recurrences, the factors associated with lower survival.

Aspects related to the initial tumor (age >45 years, follicular carcinoma, and capsular invasion), the non-ablation of the thyroid remnant after surgery, the presence of distant MTS before the diagnosis of locoregional recurrence and 2 factors related to the local recurrence itself (the lack of uptake of and the location in the thyroid bed). Therefore, it is important to identify patients at higher risk who would benefit from closer monitoring

and early intervention. Although recurrences usually occur in the first few years, follow-up should be lifelong. The most useful parameters are:

Thyroid hormone dosage

It is necessary to ensure correct TSH inhibition to reduce recurrence or metastasis rates.

Thyroglobulin dosage

Thyroglobulin is a protein produced almost exclusively by thyroid follicular cells. When total thyroidectomy and ablation of the remnant have been in successful cases, thyroglobulin is undetectable (<2ng/ml in hypothyroid conditions and <5ng/ml under treatment with levothyroxine). Elevations in its levels, particularly in the presence of high TSH, should lead to suspicion of recurrence or metastasis. It should be considered that the presence of antithyroglobulin antibodies (15-25% of patients) alters its values and invalidates the determination.

Thyroglobulin levels at the time of ablation have prognostic value: Undetectable thyroglobulin concentrations, in conditions of hypothyroidism, have been related to the absence of recurrence in long-term follow-up; in 268 patients treated with total thyroidectomy and ablation of the remnant with I₁₃₁, the positive predictive value of recurrence in patients with thyroglobulin >2µg/l at the time of ablation was 23.1% (95% CI 16.4-30.8 %) while the negative predictive value in patients with figures <2µg/l was 98.4% (95% CI 94.4-99.8%) .

Total body sweep with

It is recommended to perform it between 6-12 months after the post-surgical ablative

dose. The patient must discontinue treatment with levothyroxine at least 4 weeks before, to achieve an elevation of TSH to more than 35µU/ml. To minimize symptoms of hypothyroidism, triiodothyronine can be used for the first 2 weeks of levothyroxine discontinuation.

Another alternative is the administration of recombinant TSH (rTSH) intramuscularly, 48 hours before the scan, without the need to suspend levothyroxine. There do not seem to be significant differences in the results of the scans performed after the administration of rTSH or in conditions of hypothyroidism, but the experience with the former is still limited. In either case, the patient should be instructed to receive a low-iodine diet. The scan is performed by administering 2-5 mCi of I₁₃₁ and proceeds in the same way as in the post-operative study.

The results of the determination of thyroglobulin and the total body scan with I₁₃₁ provide complementary information. A problematic situation is the finding of an elevated thyroglobulin in the context of a negative scan. Tumor cells may suffer from a loss of the ability to concentrate I₁₃₁. This results in a 20% false negative whole-body scan in patients with metastatic disease. Ultrasound, computed tomography and, more recently, PET, can be useful in locating lesions that do not enhance and that are manifested only by elevated thyroglobulin levels. Some of these patients could benefit from the use of retinoic acid.

In vitro, a redifferentiation of tumor cells has been seen with the use of this drug. However, in clinical practice, the number of patients treated with retinoic acid who respond by showing uptake of and increasing

thyroglobulin levels (which leads one to think of redifferentiation) is not so encouraging. In these cases, the possibility of blindly administering a therapeutic dose is raised, which, being higher than conventional scanning, could reveal a lesion with poor uptake capacity.

Positron emission tomography (PET)

PET has become a functional imaging technique, with increasing importance in clinical oncology. In thyroid cancer, the greatest utility of PET is to allow the location of lesions that do not uptake of, whose presence is suspected by elevated thyroglobulin values (false negatives of PET uses glucose uptake (in this case, fluorine deoxyglucose-FDG-) by tumor cells and has a sensitivity of 60-94% for detecting recurrent or metastatic disease in patients who have negative uptake.

The sensitivity is lower when it comes to detecting minimal residual disease in cervical nodes. Specificity is 25-90% since some inflammatory processes can concentrate FDG the elevation of TSH does not increase the ability of these tissues to capture FDG

Prognosis

Differentiated thyroid carcinoma generally has a good prognosis. Survival at 10 years is 85 to 90%.

The prognostic factors are:

- The age of the patient
- The tumor stages
- The initial treatment.

Low-risk patients are those under 45 years of age, with a low-grade non-metastatic tumor, confined to the thyroid gland, between 1-5

cm, whose survival, at 20 years, reaches 97-100% even treated with surgery alone. The highest risk factors are age over 45 years, high-grade tumors, locally invasive or metastatic, larger than 1-2 cm. In these patients the survival rate is 55% at 20 years. Treatment by total thyroidectomy and ablation is an independent prognostic factor that favorably influences the rate of local or distant recurrence and mortality rate. Delay in treatment for more than 12 months from diagnosis worsens the prognosis [11-25].

Anaplastic carcinoma

It constitutes 2% of thyroid carcinomas. It predominantly affects women, occurs in people over 50 years of age and has an extremely aggressive evolution both locally and at a distance, with a survival of between 7 to 12 months from diagnosis. A high percentage of these tumors arise in the context of long-standing differentiated carcinoma, and the incidence is higher in areas of endemic goiter.

They are usually non-capsulated tumors, made up of atypical cells, with numerous mitotic figures, distributed in an undetermined pattern and with a great tendency to invade adjacent structures, resembling a sarcoma. Infiltration by polymorphonuclear cells and extensive areas of necrosis are frequent findings. At the time of diagnosis, the average size of the tumor mass is 8 cm, with lesions that can be larger than 20 cm. Local compression symptoms include dysphagia, hoarseness, stridor, dyspnea, and local pain. Regional lymphadenopathy is found in more than 40% of cases; one out of every three patients consult for vocal cord paralysis.

The diagnostic system is like that described in cases of differentiated thyroid carcinoma. In these tumors, it is also useful to perform a CT scan of the neck and chest to define the degree of local extension and the presence of metastases. This will allow the extent of the resection to be assessed. Several studies of patient series have tried to establish different prognostic factors. The size of the tumor, the speed of onset of symptoms and the presence of metastases are the clinical variables that influence survival. Treatment of anaplastic carcinoma is surgical.

However, in many cases, surgery is for palliative purposes only, to preserve the integrity of the airway. The therapeutic use of is not useful in these tumors since many of them have lost the ability to capture it. In addition, due to their large size, surgical resection is usually incomplete, leaving a large tumor remnant, with a high risk of radiating thyroiditis after the administration of. The use of radiotherapy and/or postoperative chemotherapy have not been able to establish a significant benefit, although the design of the studies and their retrospective nature are limiting to define the real usefulness [26-33].

Medullary thyroid carcinoma

Medullary carcinoma comprises 5-10% of thyroid neoplasms. It originates from parafollicular cells, or C cells, derived from the neuroectoderm, which produce calcitonin. This tumor can occur sporadically (80%) or in a hereditary variant, forming part of the multiple endocrine neoplasia syndrome type 2 (MEN 2) in 20% of cases. Familial medullary carcinoma occurs in younger people, is usually bilateral and behaves more benignly, and is preceded by an alteration

that is considered pre-neoplastic: parafollicular cell hyperplasia.

Pathology

Medullary carcinoma behaves more aggressively than differentiated thyroid carcinomas. It is usually a non-capsulated tumor, composed of round, polyhedral or spiculated cells, which appear undifferentiated and exhibit mitoses of varying degrees.

The distribution pattern is irregular, and they do not form follicles or papillae. These tumors present abundant hyaline connective tissue that stains positively for amyloid, a characteristic element of this histological variant. Immunohistochemistry is positive for calcitonin and foci of carcinoma are usually found in other sectors of the gland and it is possible to see lymphatic and vascular invasion.

Clinical manifestations

These tumors are manifested by the presence of a thyroid nodule, the appearance of cervical adenopathies or paraendocrine manifestations because of hypersecretion of calcitonin and other neuropeptides (ACTH, serotonin, prostaglandins, VIP, etc.). Patients may present with attacks of watery diarrhea, vasomotor symptoms, and even typical Cushing's syndrome. In cases of medullary carcinoma associated with MEN 2, the typical manifestations of the components of the different variants of this syndrome can also be found (see chapter Multiple Endocrine Neoplasia Syndrome)

Diagnosis

Calcitonin is elevated in one to two thirds of individuals with medullary carcinoma. The

pentagastrin or calcium gluconate stimulation test produces an exaggerated calcitonin response in these patients. The association with pheochromocytoma and hyperparathyroidism must be ruled out, to exclude the presence of MEN 2. In cases of MEN 2 there may be hypercalcaemia, hypophosphatemia and PTH elevation, due to hyperparathyroidism. Associated increase in catecholamines and/or their metabolites, because of the coexistence of a pheochromocytoma. The diagnosis is confirmed by puncture of the lesion.

Treatment

The treatment of choice for medullary thyroid carcinoma is total thyroidectomy, with cervical lymph node dissection. Given the suspicion of a possible association of medullary carcinoma with MEN 2, the coexistence of a pheochromocytoma must be ruled out, since, in this case, the adrenal tumor must first be removed. Follow-up to detect recurrence or metastasis is done with serial calcitonin doses.

Forecast

Medullary carcinoma has a 10-year survival rate of 40-60%. These figures improve if the diagnosis is made in early stages, before the tumor is palpable. Patients with stage I tumors have a 10-year survival rate of 95%, while those patients with stage IV tumors have a 10-year survival rate of less than 15%

Multiple endocrine neoplasia syndrome (MEN)

Multiple endocrine neoplasia (MEN) syndrome is a complex, hereditary, multiglandular disease that has allowed the

study of some of the molecular mechanisms involved in tumor genesis.

MEN 1

MEN 1 is an autosomal dominant hereditary disease characterized by the presence of parathyroid hyperplasia or tumors, enteropancreatic neuroendocrine tumors, and pituitary adenomas. At least 2 of these alterations must be demonstrated to consider that an individual is a carrier of MEN 1. In familial cases, there must be at least one first-degree relative with a history of this disease.

Hyperparathyroidism

It occurs in 90% of MEN 1 individuals. In most cases it is multiglandular hyperplasia. However, there may be monoclonal or polyclonal tumors.

Enteropancreatic tumors

Occur in 60% of MEN 1 cases. They are usually small and nonfunctioning. In order of frequency, insulinomas and gastrinomas follow. While the first 2 are usually located almost exclusively in the pancreas, gastrinomas can be pancreatic or originate in the duodenal submucosa. Some of these enteropancreatic tumors have malignant behavior.

Pituitary tumors

The prevalence is 30% in patients with MEN 1 and are usually microprolactinomas.

Other tumors

In association with MEN 1, the presence of bronchial, gastrointestinal, or thymic carcinoids, adrenocortical tumors, lipomas, angiofibromas and collagenomas has also been described.

The clinical manifestations are related to the hyperfunction of these tumors or the symptoms of an occupying mass. Patients may present with hypercalcaemia, a consequence of parathormone excess, hypoglycaemia in the case of an insulinoma, refractory ulcerative syndrome in the case of a gastrinoma, vasomotor disorders related to the synthesis of other neuropeptides, and amenorrhea-galactorrhea syndrome or infertility in patients with prolactinomas. MEN 1 is associated with mutations in the MEN 1 gene.

This is a 9-kb tumor suppressor gene that is located on chromosome 11, has 10 exons, and codes for a protein called menin. Menin is made up of 610 Aa and is expressed in endocrine and non-endocrine tissues, particularly those with high proliferation, such as the endometrium. This protein is in the nucleus of the cells that express it and is retained in this subcellular compartment by means of 2 anchoring sites. Its function would be to intervene in the repair and synthesis of DNA, through interaction with certain growth factors. Menin binds JunD and inhibits its transcriptional properties.

Tumor suppressor genes are recessive at the tumor level, that is, both alleles must be inactivated for cell proliferation to occur as a clonal tumor. Knudson proposes the theory of the 2 hits to explain the mechanism of tumorigenesis.

The appearance of a tumor can occur after two consecutive mutations that affect both alleles of the same gene. In the first place, there would be a heterozygous germline mutation, which would be combined with a second mutation at the somatic level, which would affect the other allele, giving rise to the

dominant expression of the tumor. According to the two-hit theory and taking into account that the menin gene is a tumor suppressor gene, MEN 1 would be caused by an inactivating germline mutation of this gene, followed by frequent "second hits" at the somatic level, which would lead to the appearance of multiple endocrine tumors. Treatment corresponds to the tumor type found in a particular individual.

MEN 2

There are 3 subtypes of this entity

MEN 2A (60%)

Determined by the association of medullary thyroid carcinoma (70%), pheochromocytoma (50%) and hyperplastic hyperparathyroidism or less commonly the presence of an adenoma (15-30%).

MEN 2B (5%)

Association of medullary thyroid carcinoma (70%), pheochromocytoma (50%), marfanoid habitus and ganglioneuromatosis of the gastrointestinal tract. In this case, the spinal tumor is usually more aggressive and presents earlier [34-45].

Familial medullary carcinoma (35%)

Defined by the presence of this tumor in 4 or more members of the same family and in the absence of other manifestations of MEN 2.

MEN is clearly associated with mutations of the RET (Rearranged during Transfection) proto-oncogene. This proto-oncogene has 21 exons and encodes a receptor tyrosine kinase (RTK), which is expressed in neural crest and urogenital precursor cells. Like other RTKs, it has 3 domains: extracellular, transmembrane,

and intracellular. The first one has a structure rich in cysteine residues, highly conserved between species, essential to determine the secondary and tertiary structure of this protein.

The RTK encoded by the RET proto-oncogene is activated by the binding of a ligand: glial cell-derived neurotrophic factor (of the TGF β family) which, in turn, requires a cofactor bound to the cell surface to be able to activate the receptor. It is involved in renal morphogenesis, in the maturation of cell lines of the peripheral nervous system and in the differentiation of spermatogonia.

In MEN, mutations have been found in different regions of the RET proto-oncogene, a fact that produces ligand-independent constitutive activation, with autophosphorylation. A clear association has been seen between different mutations and the expressed phenotype.

MEN 2A

RET mutations have been found in 95% of cases. 93-98% correspond to mutations in exon 10 (codons 609-611-618 and 620) and in exon 11 (codon 634), which involve the cysteine residues of the extracellular domain of the RTK.

MEN 2B

98% of cases present mutations of the RET proto-oncogene, 95% of which occur at codon 918 of exon 16, which involves the intracellular domain of the receptor. Familial medullary carcinoma: 88% have some RET mutation, with 80-96% located in exon 10 (codon 620 and 618) and exon 11 (codon 634). Mutations in exons 13, 14 and 15 and duplications in exon 8 have also been found in this subgroup of

MEN. Therefore, in cases of medullary thyroid carcinoma, the study of the RET proto-oncogene should be extended to all these exons. Once the diagnosis of medullary thyroid carcinoma is made, the molecular study of the RET proto-oncogene should be performed on the individual carrying this pathology. If any mutation associated with this gene is found, the entire family group is studied. In those "healthy" individuals in whom a mutation of the RET proto-oncogene is found, prophylactic total thyroidectomy is indicated (even in children), since in many cases, the pathological study of the gland demonstrated the presence of C-cell hyperplasia or foci of microcarcinoma. In these cases, attention must be paid to the appearance of other tumors associated with this syndrome and, if this occurs, treatment must be early and according to the type of tumor diagnosed.

Carcinoid

Generalities

Carcinoid tumors (CT) are very rare tumors derived from pluripotential cells of the embryonic digestive and respiratory tract. It affects both sexes equally and can occur at any age. About 75% originate in the digestive system, with the appendix being the site of origin in more than 50% of cases; followed in order of frequency by the small intestine and the rectum.

Primitive carcinoids of the lung account for 25% of all cases and represent only 2% of all neoplasms of the organ. TCs are characterized by the production of serotonin and the excretion of its most important metabolite, 5-hydroxy indole acetic acid (5-HIAA). However, several substances and hormones have been detected as products of CT scans, including bradykinin, histamine, prostaglandins, ACTH, vasopressin, chorionic gonadotropin, insulin, growth hormone-releasing factor.



Figure 3: Contrast radiology image of small intestine with a terminal ileum mass corresponding to a carcinoid tumor.

Pathology

Carcinoid tumors have traditionally been classified according to their place of origin in

the embryonic intestine. Those derived from the first portion, affect the bronchial tree, lungs and stomach; from the second, those of the small intestine, appendix and proximal

colon; and from the third, those located in the distal colon and rectum.

Histopathologically, tumors are composed of small, round cells arranged in uniform sheets. Immunohistochemical techniques show positivity for neurospecific enolase, chromogranin A, and synaptophysin. Those CT scans that have positive staining for CEA are considered mixed, with an adenocarcinoma component that is the determinant of their worst prognosis; They are called adenocarcinoids. Of all of them, the appendicular location is the most frequent. Characteristically, the lesions that settle in the appendix affect younger people, are usually benign, and originate from the neuroendocrine cells of the subepithelium. The clinical presentation of these cases with carcinoid syndrome is very rare. Of lung CT, the histopathological distinction between typical and atypical is very important due to the implications for the biological behavior of the tumor and the worse prognosis of the latter. Several prognostic factors have been considered useful in carcinoid tumors: the location of the primary tumor, its size, the locoregional extension of the disease, and the presence of distant metastases. From a clinical point of view, malignant carcinoid syndrome and severe cardiac involvement are more adverse indicators. High levels of Ki 67 and p53 alterations have been described in patients with more aggressive diseases.

Clinic

The description of carcinoid syndrome, characterized by flushing, diarrhea, abdominal pain and/or bronchospasm, is due to the release of serotonin and other mediators mentioned above. Flushing, one of the cardinal symptoms, can present as a slight

redness that affects the face and upper chest, to generalized vasodilation that can cause hypotension and syncope. The triggering of flushing can be spontaneous or secondary to the intake of alcohol, drugs such as catecholamines, stress situations, etc. The duration of the episodes is usually minutes but can continue for hours in some patients. The frequency of attacks is highly variable. Carcinoid tumors that originate in the lung produce more intense and prolonged flushing. Because the syndrome occurs in patients with intestinal tumors and hepatic metastatic involvement, hepatomegaly is usual in these cases.

Diarrhea is very common (more than 70% of cases), rarely very bulky, and is due to intestinal motility disorders mediated by excessive serotonin, and infiltration of the digestive mucosa (tumors of the small intestine). Sometimes it is accompanied by abdominal pain, which can be intense, caused by various causes: intestinal sub-obstruction, ischemia, or fibrosis of the mesentery.

According to different studies, heart disease affects 35-50% of patients with carcinoid syndrome, compromising the right cavities due to endocardial fibrosis; it can present with involvement of the pulmonary and tricuspid valves. Physiopathogenically, it is considered likely with excess serotonin. Bronchospasm during flushing appears in 1 out of 5 patients. Bradykinin and histamine are the mediators of its appearance.

Diagnosis

Clinical suspicion is the key to making the diagnosis. It should be clarified that most CT scans are benign, and their discovery is

accidental, in the histopathological study of the appendectomy pieces.

Faced with a symptomatic picture with flushing and diarrhea, the urine dosage of 24 hours HIAA allows diagnosis.



Figure 4: Surgical piece of broad resection of the carcinoid tumor with right hemicolectomy and lymphadenectomy. The arrow points to the neoplasm.

It is necessary to respect compliance with a diet and avoid those medications that can cause false positives. Elevated plasma serotonin and chromogranin A levels are also used for diagnosis.

Imaging studies, computed tomography, and magnetic resonance imaging are used to determine the location of the primary tumor and assess the extent of disease.

Octreotide scintigraphy and other indium-111-labeled derivatives have shown greater sensitivity compared to ultrasound and tomography to determine the location of primary CT and extrahepatic metastases (71% vs. 61%), whereas it is lower for secondary liver cancer. Its usefulness also lies in the fact that according to the level of uptake presented by the patients, those cases that would benefit from treatment with somatostatin analogs can be considered.

Treatment

Surgery plays a fundamental role in the approach to the different stages of CT. For CT located in the appendix smaller than 2 cm, appendectomy is the treatment of choice with excellent results. For larger tumors, right hemicolectomy with lymphadenectomy is the indicated procedure. The same criterion of surgical resection with adequate margins next to the regional lymph nodes is indicated for lesions of the small intestine and rectum.

Lung, gastric, and gonadal CT scans should be resected in cases of localized disease meeting the criteria.

Metastatic disease must be evaluated together with the patient's symptoms to define the benefits of the therapy to be used. Patients suffering from carcinoid syndrome should be considered candidates for hepatic resection due to the high frequency of

involvement of this organ. Unlike resections for metastases of other origin (for example adenocarcinoma of the colon or rectum) in which the removal of secondary lesions must be complete, partial reductions in CT cases have shown significant clinical benefit.

Palliative surgery can also take place for those patients who present with abdominal pain due to the tumor mass or fibrosis associated with CT scans of the small intestine despite presenting with disseminated disease.

Local resection or intestinal bypass allow symptomatic relief. Local treatment with chemoembolization, radiofrequency ablation or cryotherapy, to reduce the tumor mass and therefore the excessive production of serotonin and other substances produced by CT. The presence of membrane receptors for somatostatin has allowed it to be considered for the treatment of CT.

Octreotide, a somatostatin analog composed of 8 amino acids, is the most active agent in

symptomatic treatment. A derivative with a longer half-life than the native hormone, it can be administered subcutaneously 2 or 3 times a day. The daily dose ranges between 100 and 600 micrograms and must be individualized for each patient. It allows an evident improvement not only of the usual manifestations of carcinoid syndrome, but it can also avoid severe hypotension associated with the crisis.

The response from the oncological point of view is scarce, although isolated cases of partial responses and even a complete response have been reported in a recent review. Its tolerance is good but chronic administration can cause gallstones, steatorrhea, digestive intolerance, hyposaline retention and glucose intolerance. Long-acting somatostatin derivatives, such as lanreotide applied intramuscularly at intervals of 2 to 4 weeks, maintain adequate therapeutic activity like daily octreotide, optimizing quality of life.

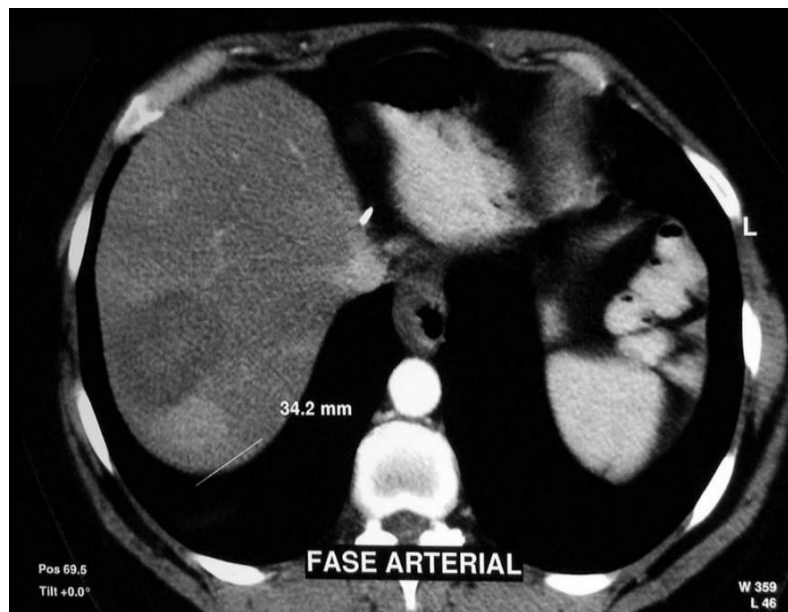


Figure 5: Liver metastasis in the right hepatic lobe of carcinoid tumor.



Figure 6: Computed tomography prior (A) and subsequent (B) to chemoembolization of liver metastases.

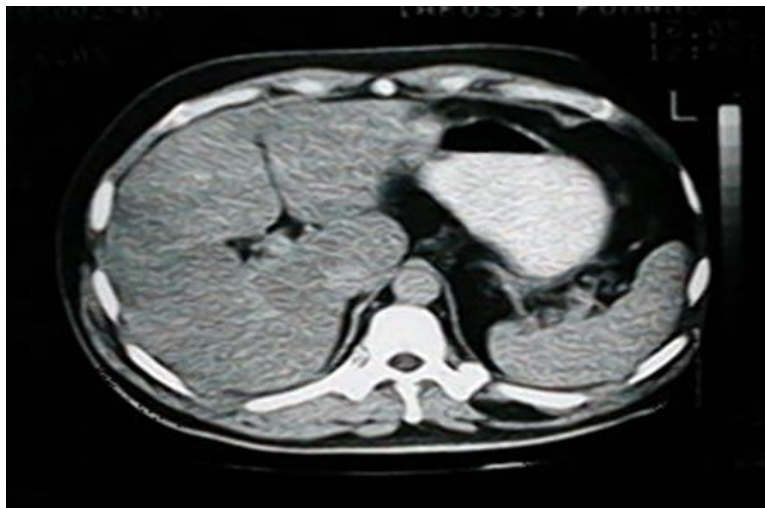


Figure 7

Radioisotopes conjugated to somatostatin analogs have been used in patients with high uptake on in 111 scintigraphy. Interferon alpha 2 has shown responses in some cases; It has also been used in combination with analogues in cases of progression to the latter and with chemotherapy. Symptomatic treatment of patients is carried out according to the severity of the clinical picture.

For diarrhea and abdominal pain, mild cases are managed with general measures and opioids and atropine derivatives. In more

severe cases, antiserotonergic drugs such as methysergide or cyproheptadine are indicated. In patients with dermatitis and dementia due to tryptophan deficiency, supplementation with niacin is indicated.

Systemic treatment with chemotherapy, either with monodrugs or in combination, has shown response rates between 10 and 35%. The selection of patients to be treated should be properly assessed due to the limited clinical benefit and the deterioration in quality of life that it can cause in many

patients. Those tumors with a more aggressive behavior, multiple metastatic organs, or symptoms not controllable by other means are indicated for systemic chemotherapy. Single agents such as 5-fluorouracil, streptozotocin, doxorubicin, or dacarbazine, or combinations of them, have shown response rates ranging between 13% and 33%). Considering the indolent nature of CT in many patients and the good response that the symptoms of carcinoid syndrome have to somatostatin derivatives, it is a priority to thoroughly consider the benefit of the indication for chemotherapy versus toxicity.

Hepatic arterial embolization has been used since TCs, like other neuroendocrine tumors, are highly vascularized and receive their irrigation through the hepatic artery almost exclusively. Because the hepatocyte can be nourished through the portal vein, the occlusion of the artery or its branches through selective catheterization makes it possible to reduce the tumor mass and improve the symptoms of patients. The local use of chemotherapy (cisplatin, doxorubicin or mitomycin) together with embolization has shown very satisfactory results in some case series, with disappearance or attenuation of flushing and diarrhea for prolonged periods. Patients may present with fever and leukocytosis in half of the cases, and local pain of variable intensity is practically constant [46-55].

Parathyroid cancer

Generalities

Parathyroid cancer (PC) is a very rare pathology. Reported cases have been associated with alterations in parathyroid

hormone secretion, representing 1% of primary hyperparathyroidism diagnoses in Western countries. Although serum calcium levels tend to be higher in the case of parathyroid cancer, there is no cut-off value or specific determination that confirms the nature of the tumor. The disease does not present a difference in incidence between women and men and affects more frequently before people in the fifth and sixth decades of life.

Pathogeny

The pathogenesis of PC is not clearly understood. Several case reports have described parathyroid cancer in patients who had received radiotherapy to the neck and in patients undergoing hemodialysis for chronic renal failure, after several years of replacement therapy.

Chromosomal studies have found more than 40% unbalanced deletions of chromosomes 1p and 13q. In the evaluation of molecular alterations, in a series of 9 cases of PC, inactivation of the retinoblastoma (RB) suppressor gene has been described in 88% of them, compared to normal levels of the nuclear protein in cases of adenomas. Alterations in the protein encoded by the suppressor gene p53 have also been described in some patients with LC. two

Cyclin D₁ protein has been found to be overexpressed in more than 90% of parathyroid cancers and in less than 10% of parathyroid adenomas, because of chromosomal changes in the long arm of chromosome 11. The alterations it produces in control of the cell cycle may participate as a factor in the oncogenic process.

Clinic

The clinical manifestations are due to those produced by hyperparathyroidism and the consequent hypercalcemia. Weakness, weight loss, polyuria, polydipsia, and digestive problems are the most common general symptoms. Clinical palpation of a cervical mass has been reported in 30% to 76% of patients with parathyroid carcinoma. Renal (lithiasis, nephrocalcinosis) and bone (osteopenia, fractures) alterations caused by parathormone hypersecretion appear in more than 50% of patients, a much more frequent clinical situation in tumor etiology than in other causes of hyperparathyroidism.

Pathology

From a histological point of view, as occurs in other glandular oncological diseases, it is not easy to distinguish between PC and parathyroid hyperplasia or adenoma. The presence of mitoses and the invasion of blood vessels in the microscopic examination is relatively frequent, but there are no pathognomonic elements that allow it to be defined. During surgery, the finding of a tumor that invades other anatomical structures increases the possibility of malignant disease.

Treatment

The treatment of PC confirmed at surgery should be in bloc resection of the tumor and the neighboring structures involved. Due to the low incidence of lymphatic spread, routine lymph node removal is not considered necessary, except for obvious tumor involvement.

In those cases of diagnosis of malignancy in the postoperative histopathological study

after exclusive resection of the gland, surgical exploration should only be considered if there is evidence of high local aggressiveness such as significant capsular invasion, or if there is persistence of hypercalcemia.

In the event of a relapse, identifying the presence of local recurrence with imaging methods, or even with hormone dosages via selective venous catheterization, is of fundamental importance to evaluate the possibility of surgical resection. In cases of distant involvement, surgical therapy should also be considered as the ideal to achieve control of the disease.

In those cases of unresectable disease, the primary objective is the control of hypercalcemia. Treatments with bisphosphonates (pamidronate, etidronate, zoledronate), calcitonin, mithramycin, and gallium nitrate have been used with unsatisfactory responses, confirming the ominous prognosis of this disease. The response to chemotherapeutic agents is low. The positive response has been described both in the level of calcinemia and in the partial remission of pulmonary metastases with immunization with PTH. The indication for radiotherapy is limited to analgesic control in the presence of symptomatic bone compromise.

Prognosis

The prognosis of PC, which can metastasize to the lung, liver, and bone, is more devastating from the metabolic point of view due to the production of parathormone and the consequent hypercalcemia that is very difficult to control pharmacologically and is frequently fatal. Although the figures for survival at 5 and 10 years vary between 29 and

85% and 20 and 69%, respectively, surgery with oncological criteria is the fundamental pillar that determines the prognosis of PC.

Pheochromocytoma

Generalities

Pheochromocytoma is a rare tumor associated with a wide variety of symptoms, although arterial hypertension is the cardinal manifestation. The estimated prevalence is considered close to 0.1% of patients with arterial hypertension, although the figures vary in different regions with much lower figures in Japan or Scandinavia. More than 80% of cases originate in the adrenal medulla; Of extra-adrenal pheochromocytomas, the most frequent site is the organ of Zuckerkandl, a structure with chromaffin cells located in the anterior region of the aorta prior to its bifurcation. With a peak incidence that occurs in the 3rd and 4th. decades of life, the disease can affect at any age and in both sexes equally.

The presence of multiple lesions (adrenal and extra adrenal) is greater in childhood (35%) than in the adult population (8%). Pheochromocytoma associated with family diseases with hereditary transmission (VHL and MEN2) represents 10% of cases; Bilateral glandular involvement is much more frequent (75%) in this population, and they are usually diagnosed at younger ages than sporadic cases.

The malignant variant of this tumor is around 10%, with a poor prognosis. Multiple endocrine neoplasia 2 has two subtypes' MEN 2 A and MEN 2 B (90% and 10%, respectively). The syndrome is characterized by medullary thyroid carcinoma (in 95% of cases) and pheochromocytoma (50%), in both subtypes.

Parathyroid gland hyperplasia occurs exclusively in MEN 2 A (15-30%); on the other hand, marfanoid habitus and mucosal neuromas affect individuals with MEN 2 B. Genetic mutations affect the RET proto-oncogene, causing an uncontrolled activation of various cellular stimulation mechanisms. VHL disease is an autosomal dominant disease, characterized by the presence of hemangioblastomas of the central nervous system and retina, renal cell cancer, endocrine tumors of the pancreas, and pheochromocytoma. The gene involved in this pathology is located on chromosome 3p and belongs to the group of suppressor genes.

Pathophysiology

Pheochromocytomas begins to produce catecholamines, a product made from the amino acid tyrosine. At the level of the adrenal medulla, 75% of norepinephrine is transformed into epinephrine by the action of phenyl ethanolamine N-methyltransferase, an enzyme stimulated by glucocorticoids produced in the adrenal cortex. Norepinephrine is the main product of extra adrenal pheochromocytomas and paragangliomas.

Dopamine secretion is produced by tumors that are generally large and do not present the symptoms of pheochromocytomas. Much less frequently, these tumors produce other peptides capable of giving clinical manifestations of other syndromes because of such hypersecretion. The production of VIP (vasoactive intestinal peptide), endorphins, somatostatin, ACTH, substance P and parathormone, among others, has been demonstrated.

Clinical manifestations

The clinical manifestations are the result of hypersecretion of catecholamines. The most frequent symptoms are persistent arterial hypertension or in crisis, frequently refractory to treatment. The severity of arterial hypertension can generate cardiac (angina, myocardial infarction, arrhythmias), cerebral (hypertensive encephalopathy, cerebral vascular accident) or vascular (aortic dissection) complications. The episodes of paroxysms characteristic of the disease occur

in half of the patients and can be triggered spontaneously or associated with many different factors or circumstances: exercise, Valsalva maneuver, apnea induction, aesthetics, smoking, abdominal palpation, etc. Different types of drugs can also cause a hypertensive crisis due to pheochromocytoma such as corticosteroids, opioids, histamine, dopaminergic antagonists, tricyclic antidepressants. The frequency of presentation of symptoms in patients with pheochromocytoma is shown in Table 1.



Figure 8: Pheochromocytoma macroscopy, showing hyper vascularized tumor with areas of necrosis.

Table 1

Pheochromocytoma

Chart of clinical manifestations

- Arterial hypertension
- Usually, >90
- Sustained 50
- Intermittent 50
- Orthostatic hypotension 50-70
- Weight decreases 80
- Headache 40-80
- Sweating 40-70
- Palpitations 45-70
- Paleness 40-45
- Anxiety/Nervousness 40
- Nausea/Vomiting 10-50

- Abdominal pain
- chest pain
- tremors

Pathology

Pheochromocytomas are usually encapsulated tumors, and larger tumors on section may show areas of hemorrhage and necrosis. Microscopically they are made up of chromaffin cells, arranged in cords or with an alveolar pattern. The differential diagnosis between a benign or malignant pheochromocytoma is difficult: neither the macroscopic appearance nor the histopathological characteristics allow a clear differentiation. The presence of visceral metastases is the only certainty criterion of malignancy.

Diagnosis

Diagnosis is made based on urinary and plasma levels of catecholamines and their derivatives (metanephrines and vanillin mandelic acid [VMA]). Unlike the normal glandular secretion of the adrenal medulla, which is 85% adrenaline, pheochromocytomas primarily secrete norepinephrine [NE].

The suspected diagnosis can be confirmed or excluded with catecholamines and their metabolites in 24-hour urine. The collection should be carried out, as far as possible, during a period of symptoms, following strict guidelines that reduce the possibility of false negatives, avoiding those antihypertensive medications that may interfere with the result. Diuretics, calcium blockers and ACE inhibitors do not seem to alter the measurements significantly. Free catecholamines, metanephrines and AVM are

determined, the latter being less specific than the former; sensitivity increases if at least 2 of them are considered.

Location

The localization of the pheochromocytoma is carried out with CT or MRI, allowing tumors of up to 1 cm to be detected. diameter. The behavior of these tumors in the MRI (hyperintense in T₂) can facilitate the differentiation between a pheochromocytoma and an adrenal adenoma. Another auxiliary method is the scintigram with IMBG, a substance with behavior like NE that is concentrated in the chromaffin tissue. By determining tissue activity, it allows clarifying the nature of the images found on CT or MRI, in patients with inconclusive hormonal dosages.

Treatment

The treatment of choice for pheochromocytoma is surgery. Alpha adrenergic receptor blockade is part of preoperative therapy; Phenoxybenzemia, the drug of choice, allows a double alpha blockade: postsynaptic type 1 and presynaptic type 2 receptors. The appropriate dose is one that controls blood pressure and prevents paroxysmal crises. In those cases where patients develop tachycardia (rare with current medication), a beta-blocker will be added.

The alpha 1-selective quinazoline blockers, such as prazosin or doxazosin, a structural analog of the former but with a longer half-life, are widely used today. They do not usually produce reflex tachycardia. The start of medication 1 or 2 weeks before surgery allows the normalization of intravascular volume, avoiding intraoperative hypotension.

During surgery, blood pressure levels, intravascular volume, and pH are carefully monitored. The management of possible sudden changes in blood pressure, especially during tumor manipulation, with intravenous fast-acting drugs has managed to significantly reduce intraoperative and perioperative morbidity and mortality. Phentolamine is used in boluses of 2 to 5mg, or sodium nitroprusside in infusion, a drug with rapid onset and short duration of its pharmacological action.

Treatment of pheochromocytoma consists of surgical resection, which in current practice is performed by laparoscopic surgery in most cases. With the progress of less invasive techniques, specialists have successfully achieved tumor removal of the adrenal gland in benign and malignant pathologies of different etiologies. The consideration of the size of the lesion and the etiology are only relative factors when deciding the technique to develop.

The therapeutic approach for malignant pheochromocytomas does not differ from that mentioned above. As already mentioned, the macroscopic or histopathological characteristics of the tumor do not allow us to discriminate with certainty whether it is benign. Thus, the appearance of local recurrence or distant metastasis are the elements that confirm the presence of malignant pheochromocytoma. Although 10% of pheochromocytomas are malignant, some follow-up studies have shown reappearance of the pathology in between 36 and 46% of cases; For this reason, some authors propose an annual control with computed tomography, magnetic resonance imaging and IMBG.

In these patients, surgical resection of the recurrence is the treatment of choice. In the case of painful bone metastases, radiotherapy allows adequate symptomatic control. The administration of systemic cytotoxic agents has shown relative utility. Due to the rarity of this disease, the experience we have is only based on clinical studies of a few patients.

I131 IMBG has been used with variable results as a radiopharmaceutical targeting tumor cell due to its ability to concentrate the drug. Complete responses have not been reported, but a clinical benefit due to decreased plasma and urinary levels of catecholamines, and partial reduction of metastases have been described in up to 60% of patients. Due to certain biological and secretory similarities between neuroblastoma (aggressive tumor that occurs in childhood) and malignant pheochromocytoma, a combination of chemotherapeutic drugs has been used in the latter pathology, which has shown good results in neuroblastoma. A scheme with cyclophosphamide, doxorubicin and dacarbazine with clinical responses greater than 50%.

Adrenal cancer

Treatment

The therapy of choice for adrenal tumors is surgery.

Adenomas

Surgical removal of the involved gland is the definitive treatment for adenomas. Currently, laparoscopic surgery is the treatment of choice, reducing the rate of complications, postoperative ileus, and hospital statistics. In cases of functioning tumors, the hypothalamic-pituitary-adrenal axis may

remain suppressed for several months; hormone replacement with glucocorticoids should be implemented during and after surgery until normalization of axis function is verified.

Carcinoma

A complete staging that includes CT and/or MRI of the abdomen, CT of the chest and bone scintigraphy is necessary to propose an adequate therapeutic strategy. In some patients with probable compromise of vascular structures, preoperative angiography or Doppler ultrasound of the aorta or inferior vena cava should also be included. Surgery is the treatment of choice in all cases, regardless of stage. The therapeutic objective is the resection of the entire tumor mass, requiring in many cases the partial or total removal of neighboring compromised structures (kidney-liver-pancreas-spleen-diaphragm and/or great vessels).

An aggressive surgical approach can achieve healing in patients with lesions it is locally advanced. Since more than half of the cases present at diagnosis with metastatic disease, evaluating their resection with oncological criteria allows to improve survival. The most frequent complications are local bleeding and undiagnosed adrenal insufficiency.

In different series, recurrence rates after successful surgery of the primary tumor range between 35-85%. Surgical treatment of tumor recurrences, local or distant, has shown prolonged remissions, with superior results in patient survival, compared with exclusive systemic cytotoxic treatment. Partial resections with palliative criteria must be analyzed individually. In patients with unresectable, metastatic, or recurrent disease, response with mitotane (o,p'DDD) is the systemic treatment of choice.



Figure 9: Adrenal carcinomas can reach a large size. The image shows an important tumor mass that displaces the kidney (left and bottom).

This cytotoxic drug produces alterations in the functioning of the 11β hydroxylase enzyme involved in adrenal steroidization and alters the extra-adrenal metabolism of cortisol and androgens. It is bio transformed in the liver and kidney into water-soluble metabolites. The administered dose ranges between 10-20 g/day orally, according to the patient's tolerance, although the toxicity is generally mild. The starting dose of 2-6g/d is administered at night to reduce the incidence of digestive intolerance. The most frequent adverse effects are neurological, 40-60% (drowsiness, lethargy, confusion, headache, and vertigo), constitutional (anorexia, weakness), gastrointestinal 70% (nausea, vomiting and diarrhea), skin (rash). Hepatogram changes or leukopenia are occasional findings.

Tumor regression with mitotane ranges between 25-30% but a decrease in hormonal hypersecretion is achieved in 3 out of 4 patients. The onset of the response generally occurs after the 6th. week of starting therapy. Unfortunately, the responses are transient with a mean duration of remission of one year. Due to the adrenolytic profile of this drug, the concomitant administration of hydrocortisone in hormone replacement doses is required. Due to the low frequency of adrenal cancer, the results with the use of other chemotherapy agents correspond to studies with a small number of patients.

Agents such as cisplatin, etoposide, doxorubicin and 5-fu, as monodrugs or in combination, have been used with variable results, with isolated reports of responses and survival greater than one year. Suramin, which interferes with the activity of several growth factors, gossypol, and streptozotocin

have been used in patients with progression to mitotane. In cases of hormonal hypersecretion that are difficult to control, drugs that inhibit steroidogenic enzymes, such as ketoconazole and aminoglutethimide, allow symptoms to be controlled.

Prognosis

Adrenal adenocarcinoma is a highly aggressive pathology with a 5-year survival rate that ranges from 15 to 47%. The anaplastic histopathological variant, more frequent in males, is associated with a mean survival of 5 months. Tumor stage is an important prognostic factor: with mean survival at 5 years: 45% E I, 30% E II, 10% E III and 0% E IV. In conclusion, adrenal cancer is a rare pathology, with a poor prognosis, which has surgery as its therapeutic pillar.

Endocrine tumors of the pancreas

Generalities

Endocrine tumors of the pancreas (PNET) share histopathological and biological characteristics with carcinoid tumors; both are within the classification of Apudomas. More than 50% of PNETs are malignant except for insulinomas (only 10% of these). They are classified as functional or not, according to the association with the clinical manifestation of a syndrome caused by hormonal secretion caused by the tumor, although there is no histological distinction between the two groups. The prevalence of these cases is low, with reports of 1:100,000 people with functioning tumors, although autopsy findings are much higher (1%).

The possible reasons for this important difference are because most of the post-

mortem findings correspond to non-functioning neoplasms, or they secrete a very low amount of hormone that does not generate clinical alterations, or the symptomatology, of variable magnitude, was not associated with a probable tumor disease. Within PNETs, gastrinomas are one of the most frequent variants. The main characteristics of the different types of PNET are described below.

Gastrinoma

It represents 30% of PNETs. The initial description was made in 1955 by Zollinger and Ellison when they presented 2 patients with severe ulcerative disease and the presence of a tumor in the pancreas that produces a powerful peptic acid secretagogue. Biochemical studies identified that the product secreted by the tumor was gastrin, hence the name gastrinoma. Gastrin is a polypeptide normally secreted by G cells located in the gastric antrum. The most frequent active forms found in the circulation are those with 17 and 34 amino acid residues (G₁₇ and G₃₄, respectively), although other molecular variants derived from a large protein precursor are currently known.

The most frequent clinical manifestations are due to gastric acid hypersecretion due to hypergastrinemia levels: gastric and duodenal ulcer disease or even other areas of the digestive tract (esophagus or jejunum) and diarrhea that is generally intermittent and occasionally accompanied by steatorrhea. Therefore, all medical or surgical treatment is aimed at controlling such excess peptic acid. In the late stages of the disease, the size of the primary tumor or the presence of metastases are responsible for the pain, weight loss or cachexia that patients may experience.

Personal or family history of MEN-1 is important as up to 50% of these cases have gastrinoma.

Most cases of gastrinoma occur in the pancreas, duodenum, or peripancreatic lymph nodes. However, they have also occasionally been described in the liver, stomach, jejunum, mesentery, spleen, and more rarely in the ovary. The organ of settlement of the primary tumor (pancreas or duodenum) has no prognostic value regarding the malignancy of the tumor tissue. The diagnosis of ZES involves the actual determination of pathologically elevated gastrin levels in the context of basal acid secretion greater than 15meq/h.

A serum gastrin value of 1,000pg/mL or more is pathognomonic. Compared to non-categorical levels, the secretin test allows confirming the pathology with elevations greater than 200pg/ml with respect to the baseline serum value. The evaluation of the peptic ulcer disease (in case it was not the reason for the patient's study), the location of the tumor and the determination of whether it is malignant, constitute the steps to follow. Abdominal ultrasound, CT, MRI, digital arteriography, and gastrin determination by selective venous catheterization are the complementary methods used in daily practice.

Treatment

Since the introduction of the first drugs that effectively control acid secretion by the stomach, the H₂ antagonists (cimetidine, ranitidine, famotidine), and in recent years the proton pump inhibitors (omeprazole, lansoprazole, pantoprazole, etc.), the need for

gastric resection for adequate control of the disease was greatly reduced.

Due to the fact that 70% or more of gastrinomas are malignant, the evaluation of the possibility of surgical resection of the primary tumor, as well as of the metastases in case of advanced disease at the time of diagnosis, must be the objective to define in the therapeutic plan. Patients with oncological resections have a survival at 5 and 10 years greater than non-operated patients (62 and 27% at 10 years, respectively). The treatment must achieve complete resection and include the peripancreatic lymph nodes due to the risk of tumor involvement. Although in some cases enucleation of the pancreatic lesion is sufficient, partial, or total pancreaticoduodenectomy is the most commonly used procedure. The removal of liver metastases simultaneously or later clearly improves the survival of these patients. In patients with gastrinoma, the response to octreotide is not satisfactory and only a small percentage of cases present an objective response or symptomatic remission.

Local procedures on hepatic metastases have shown an excellent rate of improvement of the tumor and of the symptoms caused by hypersecretion in PTE. The peculiarity of secondary liver lesions in that they receive their nutrients from the hepatic artery, allows selective catheterization and embolization of the branch that supplies the tumor. In addition, the administration of chemotherapy can be added locally, achieving better results in non-randomized studies.

Vipoma

The vasoactive intestinal peptide (VIP) is a polypeptide structure of 28 amino acids that

participates in many functions of the organism since its production and secretion is by the cells of the endocrine system of the digestive tube, various neuronal structures, and T lymphocytes; It thus participates in the regulation of arteriolar tone (vasodilator), digestive processes at the intestinal level, peptidergic neurotransmission and in the complex mechanisms of immunomodulation. VIP hypersecretion generates a syndrome characterized by profuse watery diarrhea, accompanied by hypokalemia, hypochlorhydria, and metabolic acidosis. In most cases, the presence of a pancreatic tumor lesion and secondary lesions, generally in the liver, is found, with the possibility of surgical cure being exceptional. Palliative treatment with octreotide or chemotherapy and therapeutic procedures on liver lesions generate significant improvement in patient symptoms.

Insulinoma

Insulinoma is a rare tumor, but the most frequent of the PE. Its incidence varies in different countries, ranging from 1 every 250,000 to 1,000,000 inhabitants per year; the average age corresponds to the fifth decade of life. Its origin is in the beta cell of the pancreas, and its topographic distribution is similar and is homogeneous in the head, body, and tail of the pancreas.

Characterized by symptoms of hypoglycemia, usually fasting, accompanied by relatively high levels of serum insulin, the diagnosis of insulinoma emerges from a high clinical suspicion in the context of symptoms that can be confused with other pathologies. In any case, Whipple's triad must be present: symptoms of hypoglycemia, plasma glucose levels less than 50 mg/dl and improvement of

the clinical picture with glucose supplementation. Unlike other PTEs, most insulinomas are benign; only 10% are malignant and another 10% are multicentric lesions. As mentioned above, they are not easily distinguished by histopathological characteristics but by the presence of secondary lesions from the initial diagnosis or throughout their medical follow-up. The appearance of a nodular image in the pancreas in imaging studies is the most common way of presenting the disease. CT and MRI allow to identify the location and characterize the lesion. In cases of doubt, arteriography and insulin dosage by selective portal catheterization clarify the tumor topography. In cases of insulinoma associated with MEN-1, the lesions are generally multiple, diffuse, small, associated with endocrine cell hyperplasia, or even nesidioblastosis. Simple surgical resection allows for cure in most cases due to the usually small size and benign biology of insulinomas. The use of intraoperative ultrasound together with palpation of the pancreas allows the location of the lesion to be identified and curative resection to be achieved, including laparoscopically (in lesions located in the body or tail). Distal or partial pancreatectomy and pancreaticoduodenectomy are necessary in some patients. In those cases of unresectable malignant insulinoma or non-surgical recurrence, a hyperhydrocarbonated diet should be achieved together with pharmacological treatment that prevents the appearance of hypoglycemia.

Glucagonoma

Glucagon is a hormone that plays a fundamental role in the metabolism of

carbohydrates; It is produced by the alpha cells of the islets of Langerhans. Rare tumor characteristically presenting in the fifth or sixth decades of life. It affects the body or tail of the pancreas or diffusely infiltrates it. Glucagon hypersecretion determines the appearance of a distinctive dermatological clinical picture: migratory necrotizing erythema, associated with weight loss and insulin resistance syndrome; glossitis and cheilosis may occur.

The rash predominantly affects the thighs, groin, perineum, and buttocks. Due to the reduction of intestinal motility caused by glucagon, constipation frequently appears. Diagnosis of the disease is generally late, and the majority of patients (50 to 80%) have metastases.

Markedly elevated plasma glucagon levels (normal value up to 200pg/ml) are typical of the disease. Some complementary hormonal tests confirm the diagnosis, such as the lack of glucagon suppression by glucose infusion. Therefore, intentional resection is achieved in a third of patients, although lymphatic or hepatic recurrence is common. As in other PNETs, the use of octreotide causes a notable benefit with reduction of the tumor mass and, more importantly, of the rash [56-59].

Conclusion

Endocrine system is indispensable for life in addition to the nervous system. Fundamental biological functions such as reproduction, growth, salt-water balance and emergency responses such as fight or flight are regulated to a fine tuning by the endocrine system in young and adulthood. This article reviews the most common tumors, their diagnosis and available treatments.

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