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RESEARCH ARTICLE

WHEN THE LARYNX PLEADS THE THYROID

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Abstract

We related the case of medullary thyroid carcinoma, revealed by multiple inaugural pharyngolaryngeal metastases, requiring the use of a rescue tracheotomy. Their histopathology confirmed by laryngeal biopsy performed during a panendoscopy of the upper aero-digestive tract. Following the exclusion of remote metastases by positron emission tomography scan, a mutation of the RET proto-oncogene was investigated, allowing the family nature of the carcinoma to be excluded. The patient received an external radiotherapy with a palliative aim in front of the inextricable character of the tumor. Therapeutic modalities of this rare form of pharyngolaryngeal localization of medullary thyroid carcinoma are discussed.

Introduction:

Medullary thyroid carcinoma is a rare neuroendocrine tumor, representing 5 to 8% of all thyroid cancers, from parafollicular C cells of the thyroid and associated with mutations of the RET proto-oncogene [1]. It develops at the expense of C cells secreting calcitonin, whose hyperplasia precedes the stage micro then macrocarcinoma. It is characterized by the secretion of calcitonin which is a sensitive and specific marker, carcinoembryonic antigen, and occasionally other peptides such as neuron specific enolase, chromogranin A, substance P, somatostatin and pro-opio-melanocortin derivatives [2].

Like any neuroendocrine tumor, it is manifested by symptoms due to locoregional or distant invasion, and / or symptoms directly related to neuroendocrine secretions.

The cervical ganglion invasiveness is common in this type of condition, the only curative treatment currently validated is radical surgery resection.

Thyroid cancer is generally associated with a high rate of recovery, but medullary thyroid carcinoma in particular is more aggressive and tends to metastasize. The prognosis depends on the clinical stage, with a survival rate at 10 years of 95.6% for patients with localized disease and 40% in patients with advanced disease [3].

We shall present the clinical case of a medullary thyroid carcinoma revealed by multiple inaugural pharyngo-laryngeal metastases, the pathways for the dissemination of visceral localizations, and the therapeutic advances made for the optimal management of this locally advanced type of carcinoma.

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Clinical case:
We report the case of a patient aged 36 years old, non alcoholic-tobago, with no notion of trauma or cervical irradiation, with a laryngeal dyspnea requiring the use of a rescue tracheotomy, whose tomodensitometric exploration revealed a voluminous tumor process rolling the thyroid parenchyma, with multiple bilateral lymphadenopathy adjacent to the jugular veina, and brachiocephalic trunks, and a secondary location.

The diagnosis of metastatic medullary thyroid carcinoma was suspected of having a higher serum calcitonin level at 300 ng / ml and confirmed histologically by laryngeal biopsy performed during a panendoscopy of the upper aero-digestive tract.

Immunohistochemical examination by immunoperoxidase reveals the presence of many neoplastic cells expressing massively calcitonin, the carcinoembryonic antigen and chromogranin A.

Positron emission tomography scan did not objectify distant metastases.

Negative research, RET proto-oncogene, has excluded the family nature of carcinoma.

In the face of the inextricable nature of the tumor, an external palliative radiotherapy was introduced.

Discussion:-

Two dissemination pathways explain visceral metastases of medullary thyroid carcinoma: Invasion of the visceral axis occurs either through direct contact with the thyroid body (neoplasia classified pT4) or starting from a metastatic ganglion in capsular rupture, with the important trend of medullary thyroid carcinoma to metastasize at the ganglion level [4].

This type of visceral metastases of medullary thyroid carcinoma is poorly described in the literature.

For Machens and al. [5] The most plausible explanation is that visceral invasion from the thyroid. In this case, tracheal damage are the most common. The invasion of the visceral axis starting from a ganglion is more rare, in this case reaching esophageal predominates.

Finally, invasion of the visceral axis of the neck is also associated with a higher probability of invasion of neurovascular structures.

From the stage microcarcinoma, lymph node invasion is present in 30% of cases. Metastatic diffusion occurs first in recurrent ganglion chains (50 to 80%), then jugulo-carotid homolateral to medullary thyroid carcinoma (50 to 75%). Indeed, lymph node metastases are found in over 10% of cases of medullary thyroid carcinoma less than 1 cm and in more than 40% of cases of larger size [6].

Significant differences are reported concerning the invasion of the recurrent nerve (7% vs 3%), the vagus nerve (14% vs 0%), the internal jugular veina (36% vs 2%) and the brachiocephalic trunk (14% vs 7%) [7].

Vilde and al. report the case of a patient with laryngeal metastases of a medullary thyroid carcinoma, similar to our patient [8]. The explanation they give is based on the anatomo-pathological discovery of carcinomatous vascular emboli at the level of the thyroid isthmus as well as at the level of the larynx. They hypothesize a metastatic implantation, by hematogenous route, in the larynx due to an unusual vascular report. They also insist on the differential diagnosis to be reported with primary laryngeal neuroendocrine carcinomas, or with possible metastases of primary extra-thyroid tumors secreting calcitonin.

Regarding primitive laryngeal neuroendocrine carcinomas, they are formed from Kultchisky ubiquitous cells or ectopic thyroid tissue. Their classification is based on their histological, epithelial or neural origin. In the latter group, we distinguish the typical small cell carcinoid tumor from the atypical one. This last histological type that lends the most confusing with medullary thyroid carcinoma. A histological analysis including a review histochemical, immunohistochemical and ultrastructural generally allows the diagnosis. In addition, medullary thyroid carcinoma is always accompanied by a high calcitonin, this is only exceptionally the case for primitive laryngeal neuroendocrine carcinomas [9].

Molecular analysis of the RET gene is systematically proposed, as it identifies in a third of cases an autosomal dominant germline mutation, conditioning monitoring of index case, family inverstigation, identification and management of subjects risk and age of prophylactic thyroidectomy.

The treatment of medullary thyroid carcinoma family without biological or radiological phrase consists of a total thyroidectomy is done preferably before the age of 6 [10].

When medullary thyroid carcinoma of the thyroid is suspected, before thyroidectomy - assuming multiple endocrine neoplasia Type 2A or 2B, even in the absence of evocative symptoms - we systematically eliminate the assessment of urinary catecholamines and their methoxylated derivatives and chromogranin A, a pheochromocytoma associated in half of cases and often bilateral (70%). Adrenalectomy then should precede thyroid surgery. Assuming multiple endocrine neoplasia Type 2A, we will measure the calcemia in search of a primary hyperparathyroidism associated in 5 to 20% cases and requiring peroperative exploration of the 4 parathyroid glands.

There is a good correlation between calcitonin levels and tumor volume. When the rate is above 100 or 250 pg / ml, an extension assessment looking for distant metastases, lymph nodes, pulmonary, hepatic or bone will be carried out.

Many radiopharmaceuticals are currently used to detect metastases of medullary thyroid carcinoma such as 131I or 123I meta-iodo-benzyl-guanidine (MIBG), the technetium-99m dimercaptosuccinic acid [DMSA (V)] and Technetium-99m methoxy isobutyl isonitrile (MIBI) [11].

The American Thyroid Association does not recommend somatostatin receptors imaging for initial metastatic assessment, despite the presence of high affinity somatostatin receptors in most metastatic neuroendocrine tumors. Indeed, there are II and III somatostatin receptors on the surface of neuroendocrine tumors; The diethylenetriamine pentaacetic acid (DTPA), pentetreotide or HYNIC-TOC in octreoscan binding to these receptors.

With regard to the residual tumor localization or recurrent medullary thyroid carcinoma, various radio-labeled molecules are used as the 99mTc-Sestamibi, 99m Tc-DMSA (V), 131I or 123I-MIBG, the 111- indium-DTPA-pentetreotide, 18F-fluoro-deoxy-glucose (FDG-PET) and the anti- carcinoembryonic antigen. However none has sufficient sensitivity and specificity for the final diagnosis.

Therapeutically, the pharyngo-oeso-laryngeal metastases of the medullary thyroid carcinoma, are a major surgical challenge. Indeed, if the chances of obtaining a local control seem slim, some symptoms such as dyspnea or aphasia justify a wide surgery of pharyngo-oesophago-laryngectomy. But some reconstruction techniques or prosthetic restoration of voice significantly moderate the functional consequences of such surgeries.

The benefit of radiotherapy and chemotherapy in these tumors is relatively limited and these therapeutic approaches should be reserved for cases of non-operable recurrence, metastatic disease or in addition to surgery in cases of locally invasive tumor not surgically curable as emphasizes our observation.

Radical surgery is the only curative treatment of medullary thyroid carcinoma [12], currently validated. It is therefore of utmost importance to establish the preoperative diagnosis.

Any surgery will include a total thyroidectomy, given the multiple primary tumors of medullary thyroid carcinoma with the presence of neoplastic cells in both thyroid lobes in 20-30% of sporadic forms and in 100% of familial forms [13].

view that the medullary carcinoma of the thyroid is particularly lymphophilic, total thyroidectomy is systematically completed in all cases, by a central cervical lymphadenectomy (zone VI according AAOHNS) [14] and pretracheal of the hyoid bone to the dome aortic, jugulo-carotid and spinal lymphadenectomy uni and homolateral in case of sporadic unilateral medullary thyroid carcinoma without macroscopic lymph node lesion, bilateral if necessary or in case of familial cancer.

Although bilateral jugular-carotid lymph node dissection is obviously recommended by many authors due to microscopic invasion of the lymph nodes at the cervical level even in the absence of palpable lymphadenopathy [15], the performance criterias are still controversal.

In this sense, some authors recommend the presence of a sporadic form without palpable lymph node, performing a total thyroidectomy with central lymph node dissection associated with a modified radical homolateral dissection of the neck comprising zones II, III, IV and V as described by AAOHNS, dissection of the contralateral region only being carried out in familial cases with elevated calcitonin.

Although surgery can cure localized disease, a remote tumor recurrency is likely in 4% of patients after a complete surgical resection. The presence of distant metastases reduces the overall survival to 5 year at 55%.

Therefore, palliative radiotherapy and Chemotherapy can be proposed in case of unresectable or metastatic medullary thyroid carcinoma in patients with progressive or symptomatic disease.

Chemotherapy and standard radiotherapy have no significant impact on overall survival of these patients carry a medullary thyroid carcinoma locally advanced or metastatic.

Immunotherapy (interleukin-2 (IL-2) and interferon-alpha (IFN-α)) and the similar treatment of somatostatin appear to provide a benefit in terms of symptoms and quality of life and temporarily reduce calcitonin levels [16]. In metastatic diseases, the use of metabolic radiotherapy using anti-carcinoembryonic antigen monoclonal antibody or somatostatin analogues or gastrin [17] appears promising.

Therefore, patients with progressive or symptomatic metastatic disease who cannot be treated with surgery or radiation therapy should be considered as candidates for systemic therapy.

In this case, the cytotoxic chemotherapy, including dacarbazine based protocols such as cyclophosphamide, vincristine, dacarbazine are indicated as first-line, however inhibitors of tyrosine kinase (TK) are an alternative for patients who do not respond to treatment..

Current chemotherapy for advanced medullary thyroid carcinoma include TK inhibitors such as sorafenib, sunitinib and pazopanib [18].

In recent years, many other kinase inhibitors, such as vandetanib, XL184 and motesanib were studied in several clinical trials.

Immunotherapy in the medullary thyroid carcinoma is promising but has not been many clinical applications.

In April 2011, vandetanib (Caprelsa) was the first agent approved by the Food and Drug Administration (FDA) for medullary thyroid carcinoma. Inhibitors of TK sorafenib (Nexavar), sunitinib (Sutent) and pazopanib (Votrient) were used outside the AMM.

In November 2012, the cabozantinib (Cometriq), an inhibitor of multiple tyrosine kinase receptor, has consistently shown efficacy, leading to its accelerated approval by the FDA for the systemic treatment of medullary thyroid carcinoma localy advanced or metastatic scalable.

The cabozantinib showed effectiveness based on the improvement of survival time increase compared to placebo in a Phase III trial. This drug also has an acceptable side effect profile for a favorable tumor response rate at the recommended dose of 140 mg.

Indeed, it has been reported that the results obtained on a model of highly vascularized tumors (pancreatic neuroendocrine tumor) showing that the anti-angiogenic drugs may increase tumor hypoxia through the vascular rarefaction induced by the inhibition of vascular endothelial growth factor (VEGF) [19]. This hypoxia increases the tumor expression of MET, leading to tumor aggression and the risk of metastatic progression. This shows the interest of simultaneously blocking the pathways of angiogenesis and HGF / MET, for example with cabozantinib

(XL184), an oral tyrosine kinase inhibitor targeting MET and VEGF, whose the first preclinical and clinical results are very promising.

In sum, cabozantininb is an important new treatment option for metastatic medullary thyroid carcinoma and opens the way for further research into therapies targeting both MET and VEGF [20].

However, these drugs have a suspensive effect and confer a clinical benefit that lasts only a few weeks or months.

In addition, in August 2017, Maciel and al. [21] demonstrated that the benefit / risk ratio is considered non-benificial because of the many side effects of both molecules. In this sense, since patients with medullary thyroid carcinoma and residual or recurrent disease can have an indolent evolution without systemic therapy, and these drugs are highly toxic, it is extremely important to select patients who receive these drugs .

In contrast, non responding patients to TK inhibitors may receive intravenous chemotherapy (cyclophosphamide, vincristine, and dacarbazine), but response rates are below 20%.

Recent experimental approaches are developed, consisting of the use of tumor vaccines, and the use of monoclonal antibodies coupled to radioisotopes as a vector for radiotherapy.

At present, there is no consensus for the management of localy advanced and unresectable medullary thyroid carcinoma.

Recent advances in biology and the current or potential treatment of medullary thyroid carcinoma were performed. However, gaps in our knowledge of the fundamental biology of cell C, its transformation into medullary thyroid carcinoma, and the mechanisms of resistance to therapy impede progress; new research in these areas would have a significant impact on the ground.

Note, a new understanding of developmental biology of the cell thyroid C, which was previously thought to be developed from the neural crest. The RET proto-oncogene proved to be a dual function kinase, thus widening their potential substrate directory. Promising new therapeutic developments are underway; many have recently progressed to clinical development.

Thus, there are new perspectives in the treatment of RET inhibitors.

In addition, new strategies are being developed to inhibit RAS proteins that are potential therapeutic targets in the medullary thyroid carcinoma.

In January 2018, Solarski and al. [22] stressed the importance of DICER1 gene in the function of the endocrine cells. They concluded that DICER1 mutations play a crucial role in the development, progression, cell proliferation, therapeutic response and behavior of several endocrine tumors. They reviewed the literature DICER1 gene mutations involved in tumorigenesis of various glands (thyroid, parathyroid, pituitary, endocrine pancreas, paraganglioma, adrenocortical, ovarian and testicular tumors). Although significant progress has been made in recent years, much more work is needed to fully understand the impact of DICER1 mutations.

Conclusion:-

Due to the scarcity of extensions Medullary thyroid carcinoma to the laryngotracheal axis, there is no consensus for its surgical management. Radiotherapy and chemotherapy are reserved for non-operable recurrencies, metastatic disease, or as a complement of localy invasive tumors surgically incurable. The cervical lymph node involvement is common in this type of condition whose only currently validated curative treatment is radical surgery resection. The pharyngo-oesophago-laryngeal metastases of medullary thyroid carcinoma are a major surgical challenge. Indeed if the chances of local control seem slim, some symptoms such as dyspnea or aphagia justify a large surgical excision.

Immunotherapy, chemotherapy with TK inhibitors and metabolic radiotherapy appear promising in these situations.

Declaration of interest:

The authors declare that they have no competing interest.

Author contributions:
All authors contributed equally to this manuscript

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