Incidentally-diagnosed type IIa multiple endocrine neoplasia (Sipple syndrome) with bilateral pheochromocytoma and medullary thyroid carcinoma. Report of one case

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Abstract

Multiple endocrine neoplasia IIa, also known as Sipple syndrome, is a rare entity, difficult to diagnose and potentially fatal, caused by RET proto-oncogene mutations. The importance of diagnosis and determination of this mutation in the patient and their consanguineous relatives lies in avoiding the appearance of medullary thyroid cancer by prophylactic thyroidectomy and the follow up before development of pheochromocytoma and/or parathyroid adenoma. We present the case of an asymptomatic patient with a tail gut cyst 634 AGC (Cys 634 Arg) mutation who was diagnosed with medullary thyroid carcinoma, bilateral pheochromocytoma, family history of deaths from thyroid and adrenal tumors who was treated for curative purposes and in whom the diagnosis was suspected through screening studies.

Key words: Multiple endocrine neoplasia IIa. Medullary thyroid carcinoma. Pheochromocytom. Proto-oncogen-RET.

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Introduction

Sipple syndrome, an eponym by means of which type IIa multiple endocrine neoplasm (OMIM #1721400)¹ is designed, is a rare, but potentially fatal condition that affects one out of every 40,000 people. It is a dominant autosomal condition, and its clinical spectrum includes the presence of pheochromocytoma, thyroid medullary carcinoma and parathyroid adenomas².

The description of this disease dates from 1961, when Sipple presented a series of 537 pheochromocytoma cases, out of which five were strongly associated with thyroid gland carcinoma³. Subsequently, in 1965, Schimke⁴ demonstrated the association of pheochromocytoma with medullary thyroid carcinoma. Finally, this duo and the presence of parathyroid adenomas have distinguished this entity.

Clinical diagnosis is rarely suspected and mostly it occurs during the diagnostic workup of patients that may have: a) high blood pressure secondary to pheochromocytoma; b) hypercalcemia in the causal study of pyeloureteral lithiasis, or c) during the screening of a thyroid nodule that turns out to be medullary cancer and family history of this type of neoplasms. However, many times, the syndrome goes unnoticed and the patient dies undiagnosed, which puts familiar integrity at risk, since the disease is transmitted to up to 50% of the offspring. If, on the other hand, we consider that the diagnosis of this syndrome forces to contemplate prophylactic extirpation of the thyroid gland at ages as early as five years, given that these patients will develop medullary thyroid cancer in up to 95% of cases, we can regard Sipple syndrome as being a highly important entity.

The *RET* proto-oncogene was associated in 1998 with medullary thyroid carcinoma by means of studies carried out by Shirahama et al⁵. In the year 2000, Huang⁶ and Koch⁷ discovered molecular mechanisms probably involved in the development of tumors by mutations in this proto-oncogene. Currently, it is accepted that the cause of the Sipple syndrome is a mutation in the *RET* proto-oncogene, which encodes for a tyrosine kinase receptor located in chromosome 10q11.21. There are 52 documented allelic variants⁸, with 17 of them being related to the development of the Sipple syndrome. Between 73% and 85% are found in codon 634 of exon 11 (C634R and C634Y) and 10-20%, in exon 10 codons 609, 611, 618 and 620.

Molecular diagnosis of this syndrome can be established by demonstrating mutations in the *RET* gene, which constitutes the gold standard; however, the

diagnosis can also be established by demonstrating the presence of two neoplasms in a single individual or else in a first-degree relative. Impossibility to perform the genetic study should not delay diagnosis and treatment^{9,10}.

Wells et al.¹¹ demonstrated that total thyroidectomy in asymptomatic patients with mutations in the *RET* proto-oncogene may prevent or cure medullary thyroid carcinoma, with this neoplasia having multifocal, bilateral presentation and spreading early to the lymph nodes. Currently, there are protocols that warrant this surgery in certain types of mutations in *RET*¹²⁻¹⁴.

This syndrome is usually accompanied by pheochromocytoma and parathyroid adenoma. Other features that may also be present are Hirschsprung's disease and Cushing syndrome¹⁵.

We present the case of a female patient diagnosed with Sipple syndrome (multiple endocrine neoplasia, type IIA) who was asymptomatic, had a medullary thyroid carcinoma and bilateral pheochromocytoma, as well as a family history of deaths related to thyroid and adrenal tumors, who was treated for curative purposes.

Clinical case

This is the case of a 50-year old woman with a family history of thyroid tumors in her great-grandmother, grandfather, aunt and mother, all in her maternal family, who had lactate dehydrogenase and aspartate and alanine aminotransferase elevated levels discovered in a routine annual test, which prompted the performance of a hepatic ultrasound, where lesions were detected at hepatorenal and splenorenal spaces. A liver triphasic tomography showed tumors that were dependent on both adrenal glands. Metanephrin plasma levels were elevated. Finally, a meta-iodobenzylguanidine-I¹³¹ uptake test generated sufficient evidence for the bilateral pheochromocytomas diagnosis to be considered, with surgery therefore being indicated.

Preoperatively, the patient underwent α -adrenergic receptors blockage, followed by β -blockage for surgical extirpation by means of laparoscopy, which was performed without accidents or incidents, and with right and left adrenal tumors being found, of 3 and 5 cm in their longest diameter, respectively. Histopathological study results indicated bilateral pheochromocytoma.

Although the tomography, the bone ultrasonography and the meta-iodobenzylguanidine-I¹³¹ uptake study allowed for the presence of catecholamine-producing tissue other than that identified in the adrenal glands

to be ruled out, these studies, together with serum calcium and calcitonin elevated levels, enabled the detection of a lesion in the right lobe of the thyroid gland. Thyroid function tests were normal.

Continuing the diagnostic workup with a neck tomography was decided, which revealed the presence of bilateral thyroid nodules and adenomegalies in the right hemineck. This prompted the performance of an ultrasound-guided fine-needle aspiration biopsy, the results of which were highly suspicious of malignancy.

In view of these findings, the patient was subjected to total thyroidectomy and type III radical right-side neck and central compartment dissection. The surgery involved the excision of both parathyroid glands. Histopathology results showed a bilateral medullary thyroid carcinoma metastatic to right-side lymph nodes and two parathyroid glands without alterations. With these findings, the Sipple syndrome diagnosis was established and the patient was referred to genetic counseling with the purpose to include the family in a protocol in order to determine the performance of prophylactic thyroidectomy.

Sequencing studies for the *RET* gene showed a thymine-adenine mutation at position 634 (TGC634A-GC → Cys634Arg), heterozygous.

Currently, the patient is asymptomatic on thyroidal replacement treatment, steroid complementary therapy and management for thyroidal disease. Calcitonin levels are currently at 137 pg/mL, and genetic sequencing study will be practiced to her blood relatives.

Discussion

Sipple syndrome or type IIa multiple endocrine neoplasia is a rare condition that commonly produces initial clinical data that, for the most part, can be grouped in four types of presentation.

The first one corresponds to those symptoms resulting from an increase in the amount of blood-circulating catecholamines due to the presence of functioning tumors deriving from chromaffin cells proliferation. Patients initially experience headache, sweating, tachycardia, nervousness and irritability, weight loss and, occasionally, abdominal or chest pain. Many of them are diagnosed with high blood pressure, and cases are not uncommon where symptoms can be mixed up with panic attacks, generalized anxiety syndrome or other similar disorders that, ultimately, are lately diagnosed as pheochromocytomas¹⁶, in the case of this syndrome, sometimes when patients have already developed medullary thyroid cancer.

A second spectrum corresponds to the patient that, being asymptomatic, accidentally perceives a cervical growth or palpates one or several lymph nodes that grow in number and size over time, and where a thyroid nodule is discovered that, after the corresponding workup, is diagnosed as medullary thyroid cancer¹⁷.

The third type of manifestation corresponds to those patients with generalized joint pain, abdominal pain, depression or urolithiasis in whom the diagnostic workup unveils the presence of hypercalcemia, which leads to the suspicion of hyperparathyroidism and parathyroid adenoma¹⁸.

Finally, there is one type of patients in whom, indirectly, one or more of the three Sipple syndrome components develops manifestations that direct the diagnostic workup towards other entities such as peptic ulcer¹⁹, cutaneous lichen amyloidosis²⁰, Cushing syndrome²¹, catecholamine-induced heart disease²², and thyroidectomy for a cause other than medullary thyroid cancer has even been reported to result in parafollicular cell hyperplasia, which elicits the suspicion and, subsequently, the diagnosis²³. There is even one case reported by Casey et al.²⁴ where carrying out a diagnostic workup was decided in a 35-year old female patient who presented with fatigue and weight loss, with an hepatic masses being discovered that turned out to be medullary thyroid cancer metastases, which makes it different from our case, where distant metastases were not demonstrated. However, no entirely asymptomatic case has been yet reported in the medical literature.

The presence of bilateral pheochromocytoma and medullary thyroid cancer at diagnosis is uncommon, but it is necessary per se for type IIa medullary thyroid cancer diagnosis to be established and this is why excision of the pheochromocytomas and total thyroidectomy was performed.

In the presence of a medullary thyroid cancer index-case, familiar genetic study is essential. Prophylactic thyroidectomy is the only curative treatment, although it depends on the type of mutation^{25,26}. Given that concordance between the presence of the disease and the mutation carrier status is higher than 95%, the study should be practiced to blood relatives as well.

Conclusions

Sipple syndrome is a rare disease, with varied presentations, and potentially fatal, and its diagnosis has not only consequences for the patient's life, but to that of his/her relatives as well, since this is a dominant autosomal familial syndrome.

In most cases, the diagnosis is based on suspicion or is established when there is presence of pheochromocytoma, medullary thyroid carcinoma and/or parathyroid adenoma, especially if any of these conditions is recurrent in the family.

Even when demonstration of a specific mutation in the *RET* proto-oncogene is the gold standard, diagnosis and treatment of the disease should not be delayed in patients in whom this cannot be established.

Conflict of interests

The authors declare not having any conflicts of interests of the social, economic, ethical and/or moral types relevant to the investigation, development and presentation of this work.

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