



Image 1 – (A) Unfiltered image demonstrating an inflammatory conglomerate in the theoretical location of the left ureter; (B) ICG enhancement in the lumen of the ureter after retrograde injection through the ureteral catheter.

uneventful. The patient currently lives a normal daily life and is monitored in follow-up appointments.

The use of ICG provides very good results in the field of colorectal surgery for the real-time evaluation of the perfusion of the proximal end of the intestinal loop and the distal end before anastomosis, thereby avoiding, *a priori*, a potential anastomotic leak in the postoperative period.⁴

The extension of its use to identify structures that are difficult to visualize in complex surgeries in which the field is distorted and unstructured is illustrated in the intraoperative localization of the ureter, thus preventing injury to it.

This technique is useful and easy to reproduce; the most complex part of the process is the administration of the dye and the technological infrastructure necessary for visualization.^{5,6}

Even so, more studies are needed with a greater degree of scientific evidence in order to consolidate the use of ICG in daily practice.

REFERENCES

1. Luo S, Zhang E, Su Y, Cheng T, Shi C. A review of NIR dyes in cancer targeting and imaging. *Biomaterials*. 2011;32:7127–38.
2. Frasson M, Flor-Lorente B, Ramos Rodríguez JL, Granero-Castro P, Hervás D, Alvarez Rico MA, et al., ANACO Study Group. Risk factors for anastomotic leak after colon resection for cancer: multivariate analysis and nomogram from a multicentric, prospective, national study with 3193 patients. *Ann Surg*. 2015;262:321–30.
3. Liu DZ, Mathes DW, Zenn MR, Neligan PC. The application of indocyanine green fluorescence angiography in plastic surgery. *J Reconstr Microsurg*. 2014;27:355–64.
4. Blanco-Colino R, Espin-Basany E. Intraoperative use of ICG fluorescence imaging to reduce the risk of anastomotic leakage in colorectal surgery: a systematic review and meta-analysis. *Tech Coloproctol*. 2018;22:15–23. <http://dx.doi.org/10.1007/s10151-017-1731-8>.
5. Jafari MD, Lee KH, Halabi WJ, Mills SD, Carmichael JC, Stamos MJ, et al. The use of indocyanine green fluorescence to assess anastomotic perfusion during robotic assisted laparoscopic rectal surgery. *Surg Endosc*. 2013;27:3003–8.
6. Braun JD, Trinidad-Hernandez M, Perry D, Armstrong DG, Mills JL. Early quantitative evaluation of indocyanine green angiography in patients with critical limb ischemia. *J Vasc Surg*. 2013;57:1213–8.

Antonio Gila-Bohórquez*, Julio Gómez-Menchero, Joaquín Luis García-Moreno, Juan Manuel Suárez-Grau, Juan Francisco Guadalajara-Jurado

Servicio de la Unidad de Cirugía, Hospital General de Riotinto, Minas de Riotinto, Huelva, Spain

*Corresponding author.

E-mail address: antonio@gilabohorquez.es (A. Gila-Bohórquez).

2173-5077/

© 2018 AEC. Published by Elsevier España, S.L.U. All rights reserved.

Persistent Disease and Recurrence in Medullary Thyroid Carcinoma: A Case Series[☆]

Enfermedad persistente y recaída en el carcinoma medular de tiroides. Serie de casos



Medullary thyroid carcinoma (MTC) is a rare disease that is silent and usually diagnosed in advanced stages, representing

2%–5% of all thyroid cancers. After years of study, we have been able to better understand its relationship with genetic

[☆] Please cite this article as: Tejera Hernández AA, Gutiérrez Giner MI, Rocca Cárdenas JC, Rodríguez Rodríguez F, Hernández Hernández JR. Enfermedad persistente y recaída en el carcinoma medular de tiroides. Serie de casos. *Cir Esp*. 2019;97:234–237.

factors and the presence of lymph node invasion. It can occur sporadically (70%–80%) or associated with a complex group of familial endocrinopathies (20%–30%).¹ Mutations of the RET proto-oncogene located on chromosome 10q11.2 cause an alteration of the transmembrane receptor tyrosine kinase, resulting in clinical manifestations in the thyroid (in the sporadic type) and in different organs (when associated with familial syndromes).² MTC affects parafollicular cells, increasing the secretion of calcitonin and making these levels a useful marker to evaluate the response to treatment and during follow-up. At the time of diagnosis, lymph node or distant involvement were detected in half of patients, which reduced the average survival in the latter to 3 years, with high rates of persistent disease and locoregional recurrence.³ We present a series of 12 cases that analyzes the characteristics related with the persistence and recurrence of the disease.

Between 2000 and 2016, 12 patients underwent surgery for MTC at our hospital, with an average follow-up of 86 months and a mean overall survival of 7.1 years. The majority were women (58%), with a mean age of 52 years and no family history of carcinoma; the study reported mutations of the RET proto-oncogene in only 3 cases. Clinically, 33% started with palpable cervical lymphadenopathies associated with other symptoms, such as goiter, nodules or dyspnea. In more than half of the patients, the diagnosis was obtained incidentally in the histological study of the piece, consequently requiring more than 2 surgical interventions for its treatment (Table 1). Analytical studies (to rule out other endocrine tumors),

cervical ultrasounds (to evaluate lateral lymph node chains) and cervical–thoracic CT scans were performed systematically as extension studies in all patients during the preoperative period and were completed before totalization surgery in patients with incidental diagnoses. Total thyroidectomy was performed in all patients, with bilateral central lymph node dissection in 7; 57% were during the same surgery, and the rest were in a second operation; lateral compartment dissection was done in only 4 (cases 8–11). In 4 patients, surgery was palliative treatment as they had extensive muscular or esophageal invasion, associated with metastatic disease (mainly mediastinal or pulmonary). Three patients presented complications (Table 1): bilateral recurrent nerve paralysis (case 3), transient hypoparathyroidism (case 8) and asphyxia hematoma (case 9), the latter resulting in reoperation.

Persistent disease was defined as maintained elevated calcitonin levels 6 months after surgery, and recurrence was the increase of calcitonin after its descent or normalization in this period of time.⁴ Seventy-one percent of patients with disease persistence or recurrence had calcitonin levels higher than 500 pg/mL at diagnosis (Table 2). Four patients had persistent disease (cases 4, 5, 9 and 10); in 2 of them (cases 4 and 5), no decrease in calcitonin levels was observed after surgery, and during follow-up they increased progressively. In the remainder (cases 9 and 10), these levels initially decreased but increased again after a few months. The maintained high levels of the first group are explained by the presence of unresected metastatic disease and the appearance of involvement in new locations,^{5,6}

Table 1 – Characteristics of the Patients Treated (n=12).

Case	Age	Sex	Type	Reason for Consultation	Diagnosis	Surgery	Complications	Histology	Adjuvancy
1	50	F	S	Nodule+goiter	Postoperative	TTE		MTC 25 mm	
2	53	M	S	Nodule+goiter	Postoperative	TT		MTC 35 mm, multifocal, VI and PI	Iodine
3	66	F	S	Goiter+dyspnea	Preoperative	TTB	Paralysis recurrence	MTC 12 mm, multifocal, CI and LI	Iodine Radiotherapy
4	72	F	MEN	Lymphadenopathies +dyspnea	Preoperative	TTB ^a		MTC 50 mm, multifocal, VI, PI and LI	Radiotherapy
5	51	M	S	Nodule +lymphadenopathies	Postoperative	TTB ^a		MTC 50 mm, multifocal, bilateral, CI, VI, PI, MI and LI	Radiotherapy
6	46	F	S	Nodule	Postoperative	TT		MTC 22 mm	
7	43	M	S	Nodule+goiter	Preoperative	TTE		MTC 40 mm and CI	
8	44	F	S	Nodule	Postoperative	TTE	HypoPTH transient	MTC 11 mm	
9	57	M	S	Lymphadenopathies	Preoperative	TTE ^a	Asphyxia hematoma	MTC 20 mm, multifocal, bilateral, CI, VI, PI, MI and LI	Radiotherapy
10	35	M	Fa	Lymphadenopathies	Preoperative	TTE ^a		MTC 35 mm, multifocal, bilateral, CI, VI, PI, MI and LI	Radiotherapy vandetanib
11	62	F	S	Nodule+goiter	Postoperative	TTE		MTC 12 mm	
12	51	F	S	Nodule	Postoperative	TTE		MTC 80 mm	

MTC: medullary thyroid carcinoma; S: sporadic; Fa: familial; CI: capsular invasion; LI: lymphatic invasion; MI: muscle invasion; PI: perineural invasion; VI: vascular invasion; F: female; MEN: multiple endocrine neoplasia; TT: total thyroidectomy; TTE: total thyroidectomy, extended; TTB: total thyroidectomy+lymph node biopsy; M: male.

^a Palliative surgery.

Table 2 – Correlation of Calcitonin Levels With Persistent Disease and Locoregional Recurrence (n=12).

Case	Recurrence/Persistence	Calcitonin Levels (pg/mL)			Metastasis	Survival (yrs)
		Diagnosis	<6 m	>6 m		
1		50	↓	↑		17 [†]
2	Recurrence(3 y)	70	↓	↑	Hepatic, pulmonary	12 [†]
3	Recurrence(10 y)	768	↓	↑	Mediastinal	17 [†]
4	Persistence	48,000	=	↑	Mediastinal ^a	<1 [†]
5	Persistence	7,900	=	↑	Pulmonary ^a	7 [†]
6	Recurrence(3 y)	109	↓	↑	Mediastinal	17
7		15	↓	↑		5
8		8	↓	↑		4
9	Persistence	1,534	↓	↑	Mediastinal ^a pulmonary	3
10	Persistence	6,027	↓	↑	Pulmonary ^a	2
11		140	↓	↑		1
12		19	↓	↑		<1

y: yrs after initial surgery; m: months; ↓: descent; ↑: increase; =: equal; †: exitus.
^a Appearance at the time of diagnosis.

while the decrease in tumor burden would explain the initial decrease in calcitonin in the second group.⁶ Although it is widely accepted that calcitonin levels are related with the prognosis of these patients, they do not always coincide with the amount of metastatic deposits, and disseminated disease can be observed even with lower levels of this parameter.⁷

As for recurrences (cases 2, 3 and 6), we observed that the initial surgery was limited to the thyroid, with selective biopsy of certain lymphadenopathies. Furthermore, although there was capsular, vascular or lymphatic invasion in the histology study, no other surgical procedure was performed at that time. This could confirm the need for bilateral central lymph node dissection in all patients, especially those with high levels of calcitonin and suspicious lymphadenopathies on ultrasound,⁸⁻¹⁰ leaving lateral compartment dissection for selected cases (evidence of pathological central and lateral lymphadenopathies).⁹ Over time, it has been shown that the implementation of standard bilateral central lymph node emptying decreases locoregional recurrence rates, so that “berry-picking” techniques are not recommended.^{8,9}

We observed common characteristics in both groups of patients (persistent and recurrent). Most had pathological lymphadenopathies at the beginning of the disease and had undergone incomplete initial thyroid surgery. In addition, the tumors were larger, multifocal and with capsular or vascular invasion, all of which were unfavorable prognostic factors identified in the literature.^{1,8,9,11} Case 6 would be an exception, as it was a smaller solitary tumor (22 mm), with no capsular or vascular invasion and with a long survival, despite having relapsed 3 years after the initial surgery. External radiotherapy was the most common adjuvant option, especially in the 4 palliative patients and in one patient with recurrence. Vandetanib was used in one of the most recent cases, providing a good response until the present time. Radioactive iodine was used as adjuvant therapy in 2 patients who had associated papillary carcinoma. All the patients with recurrence presented metastatic disease during follow-up, and the first cause of general death was related respiratory insufficiency.

Calcitonin levels remain a cornerstone in the follow-up of patients, which, associated with other characteristics (incom-

plete surgical treatment, presence of lymph node infiltration, tumor size and unfavorable anatomic pathology characteristics of the tumor), can predict their prognosis. New therapies like tyrosine kinase inhibitors are being used with good initial results, but their use is limited only to patients with a large tumor burden and evidence of disease progression.² Until new lines of treatment appear, surgery will be the only effective treatment for this disease, and prognostic factors will help us select the best therapeutic option for each type of patient.

Authorship

All the authors have participated in the study design, data collection, analysis and interpretation of the results, article composition, critical review and approval of the final version.

REFERENCES

1. Douglas Ball W. Medullary thyroid cancer: monitoring and therapy. *Endocrinol Metab Clin North Am.* 2007;36: 823-37.
2. Grande E, Santamaría S, Capdevila J, Navarro E, Zafón C, Ramón Y, et al. Consensus on management of advanced medullary thyroid carcinoma on behalf of the Working Group of Thyroid Cancer of the Spanish Society of Endocrinology (SEEN) and the Spanish Task Force Group for Orphan and Infrequent Tumors (GETHI). *Clin Transl Oncol.* 2016;18:769-75.
3. Song H, Lin C, Yao E, Zhang K, Li X, Wu Q, et al. Selective ablation of tumor suppressors in parafollicular C cells elicits medullary thyroid carcinoma. *J Biol Chem.* 2017;292:3888-99.
4. Machens A, Dralle H. Benefit-risk balance of reoperation for persistent medullary thyroid cancer. *Ann Surg.* 2013;257: 751-7.
5. Villar JM, Soria V, Colina A, Flores B, Gutiérrez MT, Ortega J, et al. Clinical pathway for thyroidectomy. *Cir Esp.* 2015;93:283-99 [article in English, Spanish].
6. Wells SA, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American Thyroid Association guidelines for the

- management of medullary thyroid carcinoma. *Thyroid*. 2015;25:567-610.
7. Pelizzo MR, Torresan F, da Roit A, Merante I, Chondrogiannis S, Rampin L, et al. Mild to moderate increase of serum calcitonin levels only in presence of large medullary thyroid cancer deposits. *Rev Esp Med Nucl Imagen Mol*. 2015;34:378-82.
 8. Momin S, Chute D, Burkey B, Scharpf J. Prognostic variables affecting primary treatment outcome for medullary thyroid cancer. *Endocr Pract*. 2017;23:1053-8.
 9. Jin LX, Moley JF. Surgery for lymph node metastases of medullary thyroid carcinoma: a review. *Cancer*. 2016;122:358-66.
 10. Magracha LA, Varela A, Barceloa B, Lozoyoa R, Garijoa J. Cirugía de la recidiva del carcinoma medular de tiroides. *Cir Esp*. 2000;68:183-4.
 11. Ríos A, Rodríguez JM, Acosta JM, Balsalobre MD, Torregrosa N, Sola J, et al. Prognostic value of histological and immunohistochemical characteristics for predicting the recurrence of medullary thyroid carcinoma. *Ann Surg Oncol*. 2010;17:2444-51.

Ana Alicia Tejera Hernández^{a*}, María Isabel Gutiérrez Giner^a, Juan Carlos Rocca Cárdenas^b, Fructuoso Rodríguez Rodríguez^a, Juan Ramón Hernández Hernández^a

^aServicio de Cirugía General y del Aparato Digestivo, Hospital Universitario Insular de Gran Canaria, Universidad de las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Las Palmas, Spain

^bServicio de Medicina Física y Rehabilitación, Hospital Universitario de Gran Canaria Dr. Negrín, Universidad de las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Las Palmas, Spain

*Corresponding author.

E-mail address: anath15@hotmail.com

(A.A. Tejera Hernández).

2173-5077/

© 2018 AEC. Published by Elsevier España, S.L.U. All rights reserved.

Acute Gastrointestinal Bleeding, Multiple GIST and Intestinal Ganglioneuromatosis in a Patient With Neurofibromatosis[☆]



Hemorragia digestiva aguda en paciente con neurofibromatosis tipo 1 afecto de múltiples GIST y ganglioneuromatosis intestinal

Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary syndrome with an incidence of 1:3000 births; it is caused by alterations in the NF1 gene, which involve the development of different tumors.^{1,2} Its gastrointestinal manifestations can lead to acute gastrointestinal hemorrhages, which endanger the life of the patient.^{3,4} Although this situation is exceptional, diagnostic suspicion is essential to establish appropriate treatment, and decision making should be individualized.

We present the case of a 74-year-old man with COPD and home oxygen therapy. He had been diagnosed with NF1 at the age of 35, but refused follow-up. The clinical symptoms began with syncope, so the patient was admitted for further studies. An abdominal computed tomography scan demonstrated images of cutaneous nodules, a solid retroperitoneal mass (neurofibroma), neuroendocrine tumors in the pancreaticoduodenal groove, and gastrointestinal stromal tumors (GIST) in the jejunum and duodenum. The patient presented an episode of rectal bleeding with hemodynamic instability, requiring transfusion of packed red blood cells and perfusion of noradrenaline.

Colonoscopy and gastroscopy discovered no pathological findings. After another episode of rectal bleeding, we decided to perform urgent surgery. During the operation, multiple fibrous-looking lesions (more than 30) were identified from the angle of Treitz to the ileocecal valve, all of different sizes (up to 3 cm). Suspecting that these lesions were causing the hemorrhage, we removed the 7 largest tumors in the jejunum and intestine. A large, umbilicated and fibrous lesion was observed in the cecum, and ileocectomy and ileocolic anastomosis were performed. The gallbladder was large and the bile duct dilated, although no mass was detected in the head of the pancreas. The postoperative period was uneventful.

The pathological anatomy of the ileocectomy piece reported diffuse intestinal ganglioneuromatosis. The pathology study of the resected jejunal tumors reported multicentric GIST with multiple nodules measuring 0.5-5 cm; the predominant cell type was fusiform, histological grade 1, and resection margins were involved in more than one nodule.

Immunohistochemistry reported abnormal proliferation of fibers and enteric nerve plexuses in the submucosa and

[☆] Please cite this article as: de la Fuente N, Rodríguez Blanco M, Cerdán G, Artigas V. Hemorragia digestiva aguda en paciente con neurofibromatosis tipo 1 afecto de múltiples GIST y ganglioneuromatosis intestinal. *Cir Esp*. 2019;97:237-239.