IgG4-related thyroid disease. Endocr J. 2021;68(1):1–6, http://dx.doi.org/10.1507/endocrj.EJ20-0557.
8. Brito-Zerón P, Bosch X, Ramos-Casals M, Stone JH. IgG4-related disease: Advances in the diagnosis and treatment. Best Pract Res Clin Rheumatol. 2016;30(2):261–78, http://dx.doi.org/10.1016/j.berh.2016.07.003.
9. Rumyantsev PO, Kozlov IG, Kolpakova EA, Chukhacheva OS, Korenev SV, Goncharov AG, et al. [IGG4-related diseases in endocrinology]. Probl Endokrinol (Mosk). 2020;66(2):24–32, http://dx.doi.org/10.14341/probl12285.

Pamela Benítez Valderrama[a,*], Alejandro Castro Calvo[b], Laura Rodrigañez Riesco[b], Rita Regojo Zapata[c], Paola Parra Ramírez[a]

[a] *Servicio de Endocrinología y Nutrición, Hospital Universitario La Paz, Madrid, Spain*
[b] *Servicio de Otorrinolaringología, Hospital Universitario La Paz, Madrid, Spain*
[c] *Servicio de Anatomía Patológica, Hospital Universitario La Paz, Madrid, Spain*

* Corresponding author.
E-mail address: alexapamela.benitez@salud.madrid.org (P. Benítez Valderrama).

Thyroid gland metastases: 3 cases that illustrate their clinical, radiological and pathological characteristics

Metástasis en la glándula tiroidea. Tres casos ilustrativos de su presentación clínica, radiológica y anatomopatológica

Introduction

Thyroid metastases of extrathyroid neoplasms account for less than 3% of all malignant thyroid tumours.[1] Given their rarity, we report three cases that occurred in different clinical scenarios, before reviewing this condition and expounding upon its diagnosis in depth.

Case 1

A 59-year-old man who smoked 45 pack-years, came in with an anterior neck mass that had gradually enlarged over the past three months. Thyroid ultrasound was performed, showing an enlarged gland with a tïger-stripedäppearance, no nodularity and multiple pathological bilateral swollen lymph nodes (Fig. 1). Fine needle aspiration biopsy (FNAB) was performed on the gland and cytology and immunohistochemistry diagnosis confirmed PDL1-positive squamous cell lung metastasis. A computed tomography (CT) scan of the neck and chest was ordered, which revealed not only pathological thyroid and cervical lymph node findings but also a spiculated lung mass measuring 5 cm in the right upper lobe. At the same time, the patient was diagnosed with squamous-cell carcinoma of the oral cavity with cervical, submandibular and supraclavicular involvement.

Treatment was started with carboplatin and paclitaxel with cytoreductive intent, but after the first session the patient showed rapid clinical decline with dysphagia and dyspnoea, and therefore palliative sedation was pursued.

Case 2

A 50-year-old woman with a history of metabolic syndrome had undergone a right nephrectomy 10 years earlier due to low-risk clear cell renal cell carcinoma. She was in follow-up by urology and her disease was in remission. A follow-up CT scan detected a bilateral multinodular goitre. Thyroid ultrasound showed a solid, isoechogenic (ACR-TIRADS 3)[2] nodule on the left thyroid lobe (LTL) measuring 34 mm. FNAB was performed on this nodule and it was diagnosed as benign. The right thyroid lobe (RTL) had a solid, hypoechogenic nodule with limited vascularisation (ACR-TIRADS 4) measuring 8 mm. FNAB was not performed on this nodule due to lack of criteria. On a follow-up ultrasound after 18 months, the nodule on the RTL had doubled in size and increased in vascularisation. FNAB was performed on three occasions, all of which were unsatisfactory. As such, total thyroidectomy was performed to arrive at a definitive diagnosis. Sample analysis showed two foci of clear cell renal cell carcinoma (the larger one, on the right, measuring 17 mm), with positivity for vimentin and RCC and focal positivity for CD10 and CK7. A staging CT scan further revealed two lung metastases measuring less than a centimetre. Therefore, treatment was started with sunitinib, then suspended due to lack of tolerance. The patient's disease is currently stable and being treated with nivolumab.

Case 3

A 64-year-old man with a history of smoking (50 pack-years) and metastatic lung adenocarcinoma with lymphangitic carcinomatosis (T3N3M1a) was on treatment with pemetrexed with a partial response. He was referred due to rapid and progressive thyroid gland enlargement over the course of the past two months, causing significant dysphagia to both solids and liquids. Thyroid ultrasound revealed enlargement of both thyroid lobes due to two large, solid, isoechoic nodules with punctiform calcifications (ACR-TIRADS 4), one on the RTL measuring 37 mm and other on the LTL measuring 35 mm. In addition, bilateral pathological lymphadenopathy measuring up to 20 mm was found in the cervical lymph node

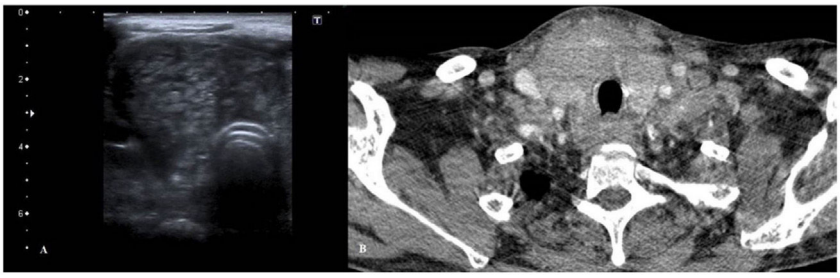

Figure 1 (A) Thyroid ultrasound. Enlarged right thyroid lobe with no clear nodularity. Heterogeneous echogenicity with a tiger-stripedäppearance. Lobe measuring 39 mm in length. (B) CT scan of the neck. Generalised enlargement of the thyroid gland with a heterogeneous appearance. Bilateral pathological cervical lymphadenopathy. Decreased tracheal calibre.

chains. FNAB was performed on the nodule on the RTL and on two swollen cervical lymph nodes, with a diagnosis of infiltration due to adenocarcinoma with an immunophenotype positive for TTF1 and negative for thyroglobulin, consistent with lung adenocarcinoma. The patient was admitted with complete dysphagia. As it was impossible to place a nasogastric tube, comfort measures were prioritised.

Discussion

Thyroid gland metastases have a low prevalence in clinical practice, accounting for less than 0.1% of nodules that undergo FNAB.[1] However, on autopsy, an incidence in oncology patients of 1.3%–25% of cases has been reported.[3]

The mechanism of metastatic involvement of the thyroid gland is usually through the haematogenous/lymphatic route and more rarely due to contiguity from adjacent structures.[4] Lung and breast cancer metastases are the most common metastases in autopsy series. By contrast, in clinical series, clear cell renal cell carcinoma is more typical[3]; it may metastasise to the thyroid gland long after primary resection,[4] as in Case 2.

Metastases may present as diffuse infiltration of the gland[3] or with the appearance of thyroid nodules on complementary tests in patients with a history of cancer. A presentation in the form of a neck mass due to bilateral thyroid enlargement in patients with no history of cancer is considered rare,[5] hence the peculiarity of Case 1. The essential clinical characteristic common to all the cases reported was rapid growth. This sign mandates suspicion of thyroid metastases, especially in patients with a history of cancer or risk factors.[4]

On ultrasound, generalised enlargement of the gland featuring a heterogeneous appearance with atypical hypoechoic lines is usually observed, and some series have reported pathological lymphadenopathy in up to 92% of cases.[6] No imaging tests distinguish between primary thyroid cancer and metastases.[7]

Therefore, for an accurate diagnosis, cytology or histology testing of a specimen obtained via FNAB (which enables diagnosis of up to 90% of thyroid metastases),[8] core needle biopsy (CNB) or surgical resection is indispensable. Clear cell renal cell carcinoma, lung adenocarcinoma and lymphoproliferative disorders may show morphological characteristics that overlap with primary thyroid neoplasms.[3] Given that they tend to be less differentiated cancers, immunohistochemistry techniques aid in differential diagnosis since each primary cancer presents different types of markers. Differentiated primary thyroid cancers express thyroglobulin, whereas metastases do not; lung adenocarcinoma shows positivity for napsin A; clear cell renal cell carcinoma shows positivity for RCC, vimentin and CD10; and lymphoproliferative syndromes express lymphocytic markers (CD45, CD3, CD20, CD30, etc).

In general, the prognosis is unfavourable. However, it is influenced by the extent of metastatic involvement and the nature of the primary cancer (two-year survival rates are 20% for lung carcinoma versus 70% if of renal origin). Total thyroidectomy, when possible, has a positive impact on survival.[9] Given its prognostic power, differential diagnosis between primary and metastatic lesions is key to proper decision-making.

Funding

No funding was received.

Conflicts of interest

None.

References

1. Papi G, Fadda G, Corsello SM, Corrado S, Rossi ED, Radighieri E, et al. Metastases to the thyroid gland: prevalence, clinicopathological aspects and prognosis: a 10-year experience. Clin Endocrinol (Oxf). 2007;66(4):565–71.
2. Tessler FN, Middleton WD, Grant EG, Hoang JK, Berland LL, Teefey SA, et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): white paper of the ACR TI-RADS committee. J Am Coll Radiol [Internet]. 2017;14(5):587–95. Available from: https://doi.org/10.1016/j.jacr.2017.01.046
3. Mistelou A, Papadatos SS, Kousi C, Lampri E, Mitsis M, Vougiouklakis T, et al. Thyroid gland as a target of secondary malignancies - an autopsy study and review data. Folia Med (Plovdiv). 2019;61(2):277–88.
4. Hegerova L, Griebeler ML, Reynolds JP, Henry MR, Gharib H. Metastasis to the thyroid gland: report of a large series from the Mayo clinic. Am J Clin Oncol Cancer Clin Trials. 2015;38(4):338–42.
5. Moghaddam PA, Cornejo KM, Khan A. Metastatic carcinoma to the thyroid gland: A single institution 20-year experience and review of the literature. Endocr Pathol. 2013;24(3):116–24.

6. Kim HK, Kim SS, Oak CY, Kim SJ, Yoon JH, Kang H-C. Diffuse metastasis to the thyroid: unique ultrasonographic finding and clinical correlation. J Korean Med Sci. 2014;29(6):818–24.
7. Nixon IJ, Coca-Pelaz A, Kaleva AI, Triantafyllou A, Angelos P, Owen RP, et al. Metastasis to the thyroid gland: a critical review. Ann Surg Oncol. 2017;24(6):1533–9.
8. Aron M, Kapila K, Verma K. Role of fine-needle aspiration cytology in the diagnosis of secondary tumors of the thyroid–twenty years' experience. Diagn Cytopathol. 2006;34(3):240–5.
9. Russell JO, Yan K, Burkey B, Scharpf J. Nonthyroid metastasis to the thyroid gland: case series and review with observations by primary pathology. Otolaryngol neck Surg Off J Am Acad Otolaryngol Neck Surg. 2016;155(6):961–8.

Irene de Lara-Rodríguez[a,*], Ana R. Romero-Lluch[a], Suset Dueñas-Disotuar[a], Esteban Castillo-Sánchez-Heredero[b], Elena Navarro-González[a]

[a] *Unidad de Gestión de Endocrinología y Nutrición, Hospital Universitario Virgen del Rocío, Sevilla, Spain*
[b] *Unidad de Gestión Clínica intercentros de Anatomía Patológica, Hospital Universitario Virgen del Rocío, Sevilla, Spain*

* Corresponding author.
E-mail address: irenedelara93@gmail.com
(I. de Lara-Rodríguez).

Successful pregnancy in a patient with multiple acyl-CoA dehydrogenase deficiency

Embarazo exitoso en una paciente con deficiencia de acil-CoA deshidrogenasa múltiple

Introduction

Multiple acyl-CoA dehydrogenase deficiency (MADD), also known as glutaric aciduria type II, is an autosomal recessively inherited metabolic disorder affecting the oxidation of fatty acids as well as the catabolism of branched-chain amino acids, lysine and tryptophan. MADD is caused by deficiency of either an electron-transfer flavoprotein (ETF, encoded by *ETFA* and *ETFB*) or an electron-transfer flavoprotein dehydrogenase (ETFDH, encoded by *ETFDH*).[1]

Patients with MADD have been classified into three groups: (1) neonatal onset without anomalies, (2) neonatal onset with anomalies and (3) mild or late-onset, with a wide range of clinical expression between the groups. Patients in the first group are often premature and present dysmorphic features with most of them dying in the first days of life. Patients in the second group do not present congenital anomalies but usually develop severe cardiomyopathy and die during the first weeks of life. The course and presentation in the third group, the late-onset patients typically include episodes of metabolic acidosis, non-ketotic hypoglycaemia and muscle weakness.[2,3]

The diagnosis of MADD consists in increased organic acid and acylglycine derivatives in the urine and medium- and long-chain acylcarnitines in the blood. Genetic analysis confirms the diagnosis.[4]

The treatment usually includes a high-carbohydrate, low-fat, low-protein diet associated with riboflavin and carnitine supplementation, without periods of fasting.[4,5]

Case

We present the case of a 31-year-old woman, diagnosed with MADD (mild or late-onset subtype) at the age of 10 years in the context of a family study because one of her brothers was hospitalised in the ICU in relation to a coma caused by metabolic acidosis and hypoglycaemia. Both of her parents were carriers of a mutation (R175H) in the ETFDH gene, and the three siblings were affected by the same condition. The patient is a product of non-consanguineous Spanish parents from the province of Ciudad Real. The paternal grandparents were first cousins (Fig. 1).

At the time of diagnosis she presented with high levels of acylcarnitines in her blood. Treatment with a diet restricted in fat and protein and associating supplementation of riboflavin and carnitine was started. Since the diagnosis to the present time the patient has been in good general condition, only suffering from occasional events of vomiting and muscle weakness (never requiring hospitalisations for metabolic decompensations).

Several echocardiograms have been performed throughout her life because of an increased risk of cardiomyopathy, which have all been normal.

At the age of 30, she became pregnant. She was not blood-related to her partner.

A normocaloric diet with most of the calories coming from carbohydrates (around 50/60%), similar to the diet she was already doing, was prescribed. The diet was divided into three main meals and periodic snacks, avoiding fasting periods of more than 4 h to prevent hypoglycaemia. The treatment also included riboflavin (300 mg/day) and L-carnitine (4 g/day).

Usual obstetric controls in the first, second, and third trimester were performed, with an estimated foetal weight of 2.4 kg (16% percentile) in the third trimester.

At the 39th week an elective caesarean was conducted to reduce the intrapartum risks (risk of metabolic decom-