Advances in Medicine and Engineering Interdisciplinary Research, 2025, Volume 3, Issue 4
DOI: 10.32629/ameir.v3i4.4853
ISSN Online: 2972-3825
ISSN Print: 2972-3833

First case of renal metastases in a pediatric patient with differentiated thyroid carcinoma in Venezuela

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Abstract: Thyroid cancer is the most common endocrine malignancy and is rarely diagnosed during childhood, representing approximately 4% of all pediatric cancers. At the time of diagnosis, these patients often present with more advanced disease, larger tumors, frequent extrathyroidal extension, lymph node involvement, and distant metastases. We present a case of a 10-year-old male schoolchild diagnosed with papillary thyroid carcinoma presenting with metastatic pulmonary disease at debut. He was treated with total thyroidectomy, bilateral cervical lymph node dissection, radioiodine, sorafenib, and levothyroxine. During total body scanning, increased concentration of the radiotracer was observed in both kidneys, coinciding with hyperrefractive areas on computed tomography, confirming the diagnosis of renal metastasis. This pathology has been observed in less than 1% of cases of differentiated thyroid carcinoma in pediatric patients worldwide and is the first such case reported in the Venezuelan literature.

Key words: papillary thyroid cancer; metastasis of the neoplasm, kidney; nuclear medicine; iodine radioisotopes

1 Introduction

Thyroid cancer is the most common endocrine malignancy, with differentiated thyroid carcinoma (DTC) being rarely diagnosed during childhood and accounting for approximately 3%-4% of all pediatric cancers. Around 90% of pediatric patients with DTC have papillary thyroid carcinoma (PTC), while less than 10% are diagnosed with follicular thyroid carcinoma (FTC) [1].

Before puberty, the incidence is similar in terms of the male-to-female ratio, but after puberty, it changes in favor of women, with a ratio of 1:2 to 1:5 [2,3]. This incidence has increased since 2000, from 0.001 to 0.02 in children under 10 years old, and to 0.02 in the 10-14 age group, especially among survivors of neoplasms who received radiation therapy to the neck [4]. Deficiency of iodine, a family history with a diagnosis of DTC, and genetic mutations are also risk factors [5].

Regarding the symptoms in pediatric patients, they most frequently present with an asymptomatic solitary thyroid nodule or increased volume in the neck, compressive symptoms (such as hoarseness, dysphagia, dyspnea) [6], in children between 10%-25% of these nodules are malignant, and in adolescents 10%-20% [6,7].

At diagnosis, children present with more advanced disease compared to adults. Children with DTC have larger primary tumors, extracapsular extension with tracheal invasion (20%-60%), and are more frequently diagnosed with lymph node and distant metastases (DM) in up to 90% of cases. They also present with recurrent laryngeal nerve invasion (30%). Among DM, the lungs are the primary site, but DM also occurs in the bones and brain (10%-28%). The risk of DM

correlates with the presence and extent of lymph node metastases. Despite the more extensive disease at presentation, children have an extremely low disease-specific mortality rate, even though most patients with DM from pediatric DTC do not achieve remission, with a 30-year survival rate of 99% [8,9,10].

2 Clinical case

This case involves a 10-year-old male schoolboy whose family member reported the onset of the current illness in February 2022, when he presented with persistent headache. They went to a health center in December of that same year, and after clinical evaluation, they found an oxygen saturation of 70%. Therefore, they requested a high-resolution computed tomography (CT) scan of the chest, where numerous small, well-defined nodules were observed, distributed uniformly in both lung fields and pleural thickening (Figure 1). They concluded that it was bilateral pneumonia due to miliary tuberculosis vs. lymphocytic interstitial pneumonia. He was admitted with a diagnosis of granulomatous vs. fungal lower respiratory infection.

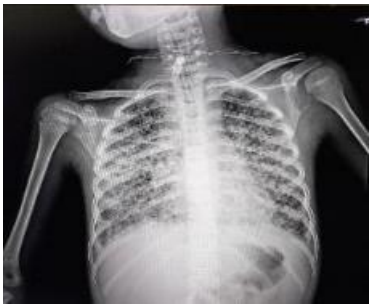

Figure 1. Chest X-ray, December 2022.

During his hospitalization, a pleural biopsy was taken, which was negative for malignancy, and studies were performed to rule out a diagnosis of cystic fibrosis. Subsequently, he developed complications from pleural effusion, which led to his admission to the Intensive Care Unit (ICU). During his stay, a physical examination of his neck revealed a thyroid nodule; an ultrasound (US) was performed, which reported a nodule with TIRADS-5 characteristics and lateral cervical lymphadenopathy. A fine-needle aspiration biopsy (FNAB) was performed, with findings consistent with malignancy, and a biopsy of the right lateral cervical lymph node confirmed metastatic carcinoma. A magnetic resonance imaging (MRI) scan was performed in January 2023, which showed an extra-axial infratentorial lesion measuring 1.92 cm x 2.48 cm x 3.97 cm, hypointense on T1 and hyperintense on T2, without enhancement after contrast administration, which could be related to transependymal migration.

In January 2023, he underwent a total thyroidectomy (TT) with bilateral lymph node dissection. The postoperative biopsy revealed a single nodule with papillary thyroid carcinoma in the lower pole of the right lobe and isthmus, measuring 2 cm x 1.5 cm, with vascular infiltration, capsular infiltration, and extrathyroidal infiltration specifically into the sternocleidomastoid muscle (SCM). No lymphatic or perineural infiltration was observed. Regarding the bilateral lymph node dissection, two right and ten left lymph nodes were positive for metastatic papillary carcinoma. Following surgery, he experienced immediate postoperative complications and was transferred back to the ICU for 10 days, where he suffered four assisted cardiac arrests requiring high levels of ventilation. During his stay in the ICU, he started treatment with tyrosine kinase inhibitors (TKIs) such as sorafenib 50 mg orally (PO) twice a day (BID), levothyroxine 62.5 mcg PO once a day (OD) and chemotherapy (CT) with doxorubicin at 15 mg/m² (which he received for only two days); showing improvement and finally being discharged in February 2023.

In July 2023, the patient attended the Nuclear Medicine Unit, attached to the Chair of Radiotherapy and Nuclear Medicine of the University Hospital of Caracas (HUC). Following evaluation and case discussion with international

specialists (Nuclear Medicine Physicians), his condition was classified as a high-risk Papillary Thyroid Carcinoma (CPT), pT4 pN1b M1 (11) according to the 2015 American Thyroid Association (ATA) pediatric guidelines [12]. It was decided to administer a dose of 50 mCi of radioactive iodine (RAI 131I). One week after the ablative therapy, a total body scan (TBS) was performed, which revealed: presence of iodine-avid tissue in the anterior neck region related to postsurgical remnant, intense uptake in both lung fields, and scattered uptakes in the skeletal system (skull, dorsal spine, left shoulder, pelvis, coxofemoral joint, and right femur). Additionally, focal uptake was observed in the anterior abdominal wall and in both kidneys (Figures 2 and 3).

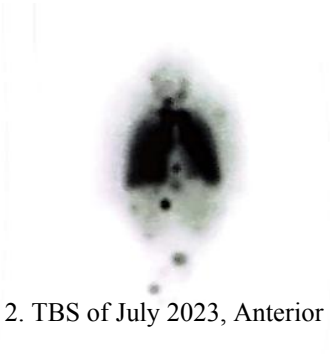

Figure 2. TBS of July 2023, Anterior View

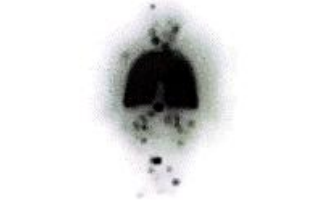

Figure 3. TBS of July 2023, Posterior View

In August of the same year, imaging studies were complemented with abdominal ultrasound, where an image in the hepatic segment was observed, possibly related to hemangioma and vesicular lithiasis. Additionally, a CT of the cranium, neck, thorax, abdomen, and pelvis with intravenous contrast was performed, revealing: residual thyroid tissue, bilateral cervical ganglionic disease, a thorax with a diffuse centrilobular micronodular pattern and bilateral fissural nodular thickening (Figure 4), a central lytic lesion with a thick sclerotic halo at the T11 level (Figure 5), and a festooned appearance of the endostium of the left glenoid (Figure 6); at the renal level, hyperrefractive areas were considered, not yet categorized (Figure 7), but which coincided with the areas of radiofármaco hypercaptation in the TBS. The kinetics of the values of thyroglobulin (Tg) and thyroid-stimulating hormone (TSH) are shown in Figures 11 and 22.

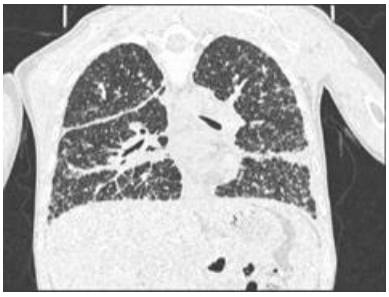

Figure 4. CT of cranium, neck, thorax, abdomen and pelvis with intravenous contrast, pulmonary window, August 2023

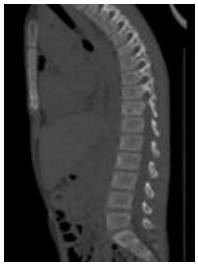

Figure 5. CT scan of skull, neck, thorax, abdomen and pelvis with intravenous contrast, bone window, August 2023

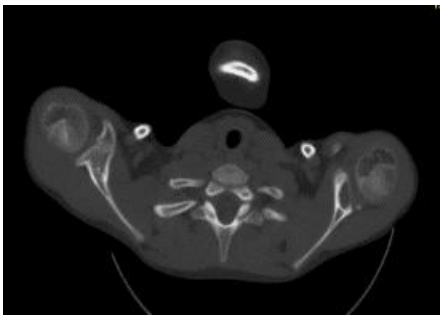

Figure 6. CT scan of skull, neck, thorax, abdomen and pelvis with intravenous contrast, bone window, August 2023

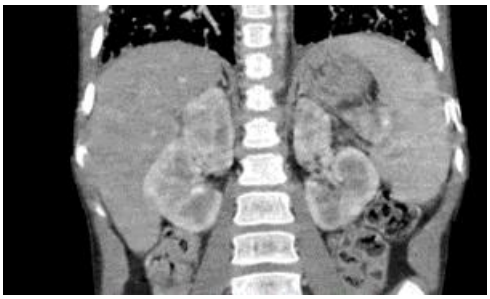

Figure 7. CT scan of the skull, neck, thorax, abdomen and pelvis with intravenous contrast, abdominal window, August 2023.

Figure 11. Kinetics of thyroglobulin values

Figure 12. Kinetics of TSH values

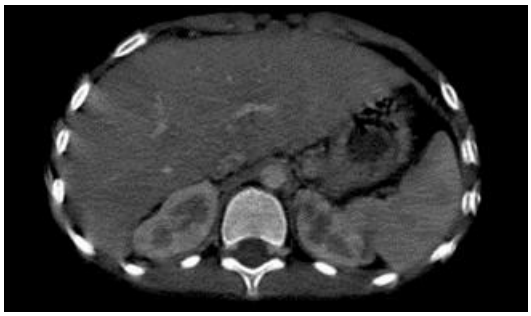

Figure 8. CT scan of the skull, neck, thorax, abdomen and pelvis with intravenous contrast, abdominal window, August 2023

In April of this year, a second therapeutic dose of 50 mCi of 131I was administered, and the TBS performed one week after treatment (Figures 9 and 10) concluded: residual thyroid tissue in the thyroid bed and bilateral laterocervical lymph node involvement, predominantly on the right side, of lesser intensity compared to the previous study; bilateral metastatic disease with high avidity for RAI; secondary bone involvement in the described sites, of lesser intensity compared to the previous scan, as well as probable secondary renal involvement. The patient was subsequently evaluated by the endocrinology service, which decided to increase the levothyroxine dose to 125 mcg orally once daily. The patient was scheduled to receive another dose of RAI around October of this year. Clinically, he is asymptomatic and continues with his normal daily routine.

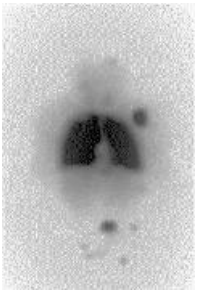

Figure 9. TBS of March 2024, Anterior View

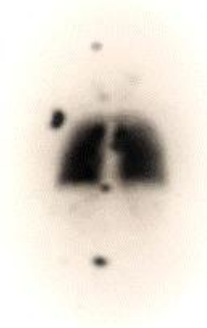

Figure 10. TBS of March 2024, Posterior View

3 Discussion

Lung and bone metastases are the main sites of distant metastasis from DTC, followed less frequently by the CNS, liver, skin, and muscles; in contrast, renal metastases from DTC are extremely rare. A publication by Ahmed et al. reports that from 1975 to 2005, only one case was found in a 24-year-old female patient with DTC and renal metastasis among 3,500 patients with DTC at their institution. Eight years after her initial treatment, she presented with persistently elevated Tg levels despite multiple negative CT, RCT, and PET scans. Two renal lesions were finally found via abdominal ultrasound, supplemented by CT. Resection of the lesion was performed, and Tg levels remained stable until the time of publication of the study. Internationally, only approximately 26 cases were reported in the literature [13].

An article published by Cheong et al. in 2010 highlights the importance of differentiating between renal cell carcinoma (RCC) and renal metastasis to determine surgical indications. Due to their high specificity, whole-body scans (WBS) with 131I are suggested for diagnosing renal metastases from DTC. Of the 20 cases they identified, only five case reports showed renal metastasis from DTC demonstrated on post-131I TBS (and these tend to be categorized as physiological uptake from the digestive tract due to their rarity). In general, metastatic renal tumors are asymptomatic, small, multiple, bilateral, wedge-shaped, located within the renal capsule, and accompanied by metastatic disease in another location [14].

A study conducted at the University of Texas, MD Anderson Cancer Center, including pediatric patients with DTC between the years 1946 and 2019 and metastatic disease (MD) diagnosed in childhood or adulthood, identified a total of 148 patients, of whom 97% had PTC, 70% were female, and the median age at diagnosis was 13.4 years. They received a median of 2 treatments with RAI, with a median administered cumulative activity of 238.0 mCi. At the last evaluation, 93% had persistent disease. The median overall survival and disease-specific survival after the diagnosis of DTC were 50.7 and 52.8 years, respectively. Of the 5% who died of the disease, it occurred after a median of 30.7 years [9].

The molecular pathogenesis of DTC, especially PTC, has been better elucidated over the years. Point mutations and fusion genes that activate the mitogen-activated protein kinase (MAPK) pathway play a crucial role in the development and progression of thyroid cancer. In pediatric PTC, chromosomal rearrangements involving the proto-oncogene RET (rearranged during transfection) and the genes of the Neurotrophic Tyrosine Kinase Receptor (NTRK1 and NTRK3) are the most common oncogenic drivers [9].

In children, rearrangements in the RET/PTC-1 and RET/PTC-2 genes, particularly the RET/PTC-3 oncogene, are associated with PTC in 20%-30% of cases. However, if there was exposure to ionizing radiation, this increases to 74%-87%. In adults, the oncogene most related to PTC after radiation is RET/PTC-1, and mutations in BRAF and RAS are associated with 40% of PTC and 10% of follicular carcinoma [4].

The BRAF V600E point mutation also prevails in pediatric PTC, but at a much lower rate than in adults. These differences in molecular pathogenesis likely explain the differences in clinical behavior observed between older and younger patients with PTC. Knowledge of the tumor genotype can inform the expected clinical course, response to RAI, and potential for targeted gene therapy for progressive DM. However, information is limited in relation to pediatric DTC [9].

It can be concluded that in pediatric patients with DTC, the disease is often more extensive at the time of diagnosis. However, disease-specific mortality is extremely low, regardless of the fact that remission is not always achieved. Due to its rarity and variability in imaging studies, DTC-derived renal metastases can be camouflaged as another primary tumor (such as RCC), which may lead to inadequate treatment. Added to this, there is scarce literature on this presentation in pediatric patients. Therefore, the use of complementary studies is necessary so that findings can be correlated (metastases are generally observed as small, multiple, bilateral, wedge-shaped lesions located within the renal capsule) and/or biopsy is taken for confirmation. This approach guarantees the most appropriate treatment and thus increases the quality of life for patients.

Conflicts of interest

The author declares no conflicts of interest regarding the publication of this paper.

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