Case Report

Orbital metastasis from thyroid cancer: a case report and review of the literature

Giulia Sapuppo[1,2]^, Federica Martorana[2], Elena Tirrò[2,3], Rosario Le Moli[1], Romilda Masucci[4], Lelio Baldeschi[5], Corrado Spatola[6], Antonino Belfiore[1], Paolo Vigneri[2], Gabriella Pellegriti[7]

[1]Endocrinology, Department of Clinical and Experimental Medicine, University of Catania, Garibaldi-Nesima Medical Center, Catania, Italy; [2]Center of Experimental Oncology and Hematology, Department of Clinical and Experimental Medicine, Policlinico "G. Rodolico-San Marco" Medical Center, Catania, Italy; [3]Department of Surgical, Oncological and Stomatological Sciences, University of Palermo, Palermo, Italy; [4]Clinical and Diagnostic Center, G.B. Morgagni, Catania, Italy; [5]Department of Ophthalmology, Hospital Saint Luc, Catholic University of Louvain, Brussels, Belgium; [6]Department of Oncological Radiotherapy, "G. Rodolico-San Marco" Medical Center, Catania, Italy; [7]Endocrinology, Garibaldi-Nesima Medical Center, Catania, Italy

Correspondence to: Giulia Sapuppo, MD, PhD. Endocrinology, Department of Clinical and Experimental Medicine, University of Catania, Garibaldi-Nesima Medical Center, Via Palermo 636, 95122 Catania, Italy. Email: giuliasapuppo@hotmail.it.

Background: Differentiated thyroid cancer (DTC) is generally associated with an excellent prognosis. However up to 20% of DTC patients have disease events during subsequent follow-up; rarely patients present an aggressive disease with distant metastases (DM), mainly in the lung and bone. Metastases at unusual sites may also occur, generally in patients with disseminated disease. Orbital localization is rare and only few cases have been described so far.

Case Description: A 36 years-old man, treated with chemo and radiotherapy during childhood for non-Hodgkin lymphoma, was referred for suspicious lymph node (LN) and multiple lung metastases. Total thyroidectomy and latero-cervical (LC) lymphadenectomy were performed: papillary thyroid cancer (PTC), 25 mm, 11/17 LN metastases; pT2N1bM1. Post-treatment total body scan with I-131 showed LN and lung uptake. Eighteen months from diagnosis he presented progressive diplopia, proptosis and right exophthalmos due to an 18 mm orbital metastasis. Hence, due to I-131 refractoriness for structural disease progression despite I-131 therapy, he started therapy with Lenvatinib for 6 months, with initial partial response followed by disease progression, and then with Cabozantinib, which he stopped after 6 months for adverse events and disease progression after therapy reduction. Currently, the patient is receiving Lenvatinib, rechallenge therapy, with disease stabilization and biochemical response. Molecular analysis, performed on both primary and relapsed tumor didn't show any significant pathogenic alteration.

Conclusions: This case of DTC with an unusual metastasis in the orbit, may suggest that patient's exposure to chemo- and radiotherapy during pediatric age might have played a role in the subsequent development of this unusually aggressive tumor, reinforcing the recommendation of long-term and intensive follow-up of these patients.

Keywords: Thyroid cancer; case report; orbital metastases; chemo and radiotherapy; non-Hodgkin lymphoma

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^ ORCID: 0000-0002-8471-7310.

Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy (1,2). Over 85% of cases have a papillary thyroid cancer (PTC) histotype and are generally associated with an excellent prognosis, with a 5-year survival rate of about 100% for localized, 98% for regional and 56% for metastatic disease (https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2021.html) (3). However, up to 20% of DTC patients have persistent or recurrent disease (4,5). These tumors frequently spread to the lymph nodes (LN) of the neck compartment (12–81% of cases) (6,7). Moreover, 7–23% of DTC patients develop distant metastases (DM) (8,9) which represent a strong negative prognostic factor and markedly reduce survival (8,10,11). In most cases (about 60–70% of subjects), DM occur during the first decade of follow-up but in a smaller proportion of cases they are present at diagnosis (6–20%) (8,9,11,12) or may develop up to 30–40 years after diagnosis (9). The most frequent DM sites are lungs and bones (10), followed by central nervous system, skin and liver. Metastases at unusual sites (e.g., adrenal glands, kidney) may also occur, generally in patients with disseminated disease. Metastatic thyroid carcinoma rarely involves the orbit and few cases are described in the literature (13). Of all orbital neoplasms, only about 3–5% originate from DTC (14-16).

Here we report an uncommon case of orbital metastasis of DTC in a 36-year-old man, with a previous diagnosis of non-Hodgkin's lymphoma treated with chemo and radiotherapy at 18 months of age. Data from molecular analysis, performed on both primary and relapsed tumor (nodal metastases) are also available.

The molecular characterization was performed using Next Generation Sequencing approach.

Genomic DNA was extracted from five unstained 5-micron-thick sections using the QS Gene Read FFPE Treatment kit and QIAsymphony DNA Mini Kit (both from Qiagen, USA) employing the automated QIAsymphony instrument according to manufacturer's instruction. DNA was then quantitated by Qubit 3.0 fluorometer (ThermoFisher Scientific, USA) and libraries preparation was performed using Ion AmpliSeq library kit plus (ThermoFisher Scientific) and a custom DNA panel. Massively parallel sequencing was carried out using Ion GeneStudio S5 Plus System according to manufacturer's instruction (ThermoFisher Scientific). Torrent Suite v.5.10.1 (ThermoFisher Scientific) was used to perform initial quality control while Ion Reporter v5.18.0.2 (ThermoFisher Scientific) was employed to single nucleotide variant (SNV) annotations.

Finally, we performed a thorough literature review about the previously reported cases of orbital metastasis from DTC. We searched on PubMed for English-language articles and case reports published between January 1977 and October 2021, using various combinations of the following keywords: thyroid, cancer, thyroid carcinoma, DTC, papillary thyroid carcinoma, orbital metastases, and ocular metastases. Reports of metastasis involving orbital skeleton were included. We present the following case in accordance with the CARE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-61/rc).

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

A 36-year-old man, treated at 18 months of age with chemotherapy and radiotherapy for a non-Hodgkin's lymphoma, presented with dysphonia and left latero-cervical (LC) swelling. Neck ultrasound showed pluri-nodular goiter, with the largest nodule measuring 38 mm in the right lobe, and bilateral enlarged LN. Fine needle aspiration biopsy revealed a papillary carcinoma with LN metastases [positive Thyroglobulin (Tg) in the wash-out fluid]. Computed tomography (CT) confirmed the presence of the nodule in the right thyroid lobe with tracheal shift without infiltration, along with bilateral cervical pathological nodes and multiple sub-centimetric metastases in both lungs. The patient underwent total thyroidectomy with central and right LC lymphadenectomy. Pathology report showed a 25 mm papillary thyroid carcinoma (follicular variant), with adipose tissue infiltration and 11/17 metastatic nodes (pT2 N1b M1, stage II). At the first post-operative evaluation, the patient presented elevated Tg value (410 ng/mL), negative Tg antibodies (TgAb) and several suspicious LN in the left LC compartment.

Hence, he underwent ^{131}-I treatment (100 mCi) after levothyroxine (LT4) withdrawal with the evidence of

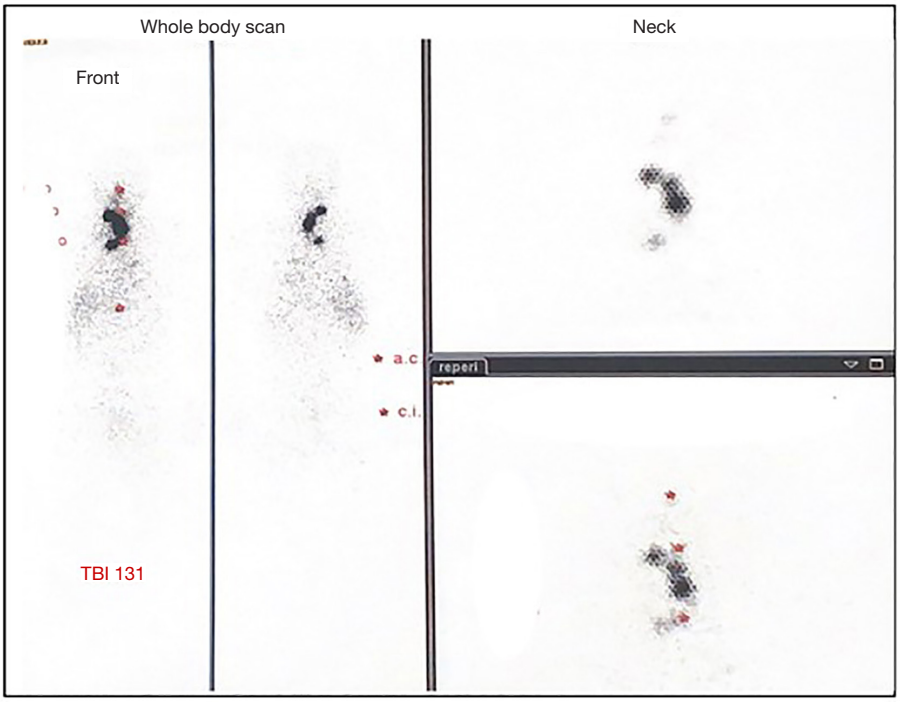

Figure 1 Whole body scan after ^{131}-I treatment. TBI, traumatic brain injury.

elevated Tg value (125 ng/mL) and negative TgAb and neck and diffuse bilateral lung uptake at post-treatment whole body scan (*Figure 1*). Contextually, at neck ultrasound, several suspicious areas are highlighted (left LC, right paramedian and submandibular). After 3 months, left cervical nodes dissection was performed with 10/17 of metastatic LN retrieved. However, small bilateral metastatic LNs were still evident at the following ultrasound examination. A second ^{131}-I treatment was planned but during LT4 withdrawal before second radioiodine treatment; 18 months after the initial diagnosis, the patient developed diplopia, proptosis, right exophthalmos, and paralysis of the right common oculomotor nerve. On physical examination, reduced elevation of the right eyeball and variable diplopia according to Gorman was evident, as well as first degree right eyelid edema, Hertel measurement 17-17 mm and reduced elevation motility on the right (b-0). LT4 therapy was immediately restarted and was decided to not carry out the planned ^{131}-I treatment. A brain and orbits CT scan (*Figure 2*) showed an 18 mm lesion adherent to the lateral rectum muscle, displacing the optic nerve.

An excisional biopsy of this lesion confirmed the diagnosis of orbital metastasis from thyroid carcinoma, with a poorly differentiated component, positive for Paired box 8 (PAX8) expression. The patient received retro-orbital radiotherapy [total dose 46 Gray (Gy), daily fractionation of 2 Gy] with radiological response (orbital metastasis's size decreased gradually from 18 to 4 mm) and clinical improvements (ocular symptoms enhanced a few weeks after the end of the radiotherapy). To date the patient still shows mild eyelid ptosis.

However, CT scan demonstrated disease progression in the right supraclavicular paratracheal region (37 mm), involving the first tracheal ring with reduction of air tracheal lumen, along with right LC nodal metastases and numeric and dimensional increase of the pulmonary metastases, the largest 12 *vs.* 8 mm. Moreover, a bone scan showed an extensive skeletal involvement (sternum, sacrum, right scapula, left upper acetabular roof, femoral neck and ipsilateral pubic branch; spine).

Given the refractoriness to ^{131}-I (extensive disease progression despite ^{131}-I) and the multiple secondary localizations, the patient started first-line therapy with Lenvatinib 14 mg/die, with a partial response lasting 6 months. Subsequently, because of tumor relapse with local and lung localizations the patient received Cabozantinib 140 mg/die. However, dose reductions to 60 and 20 mg were needed due to unacceptable gastro-intestinal toxicities,

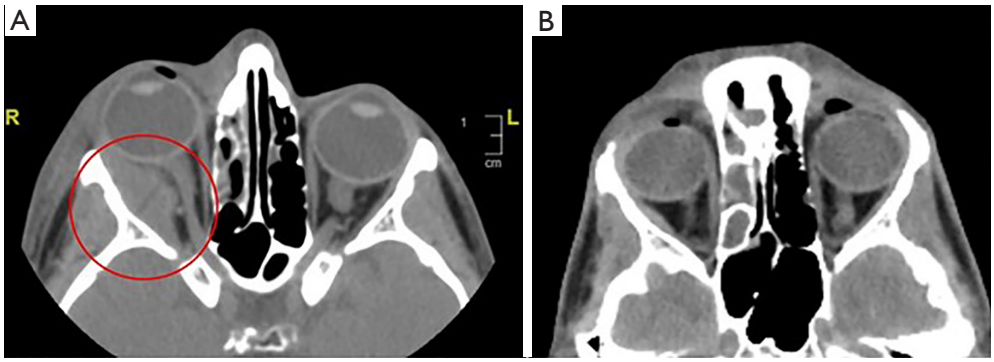

Figure 2 Computerized tomography image of the orbital metastasis (red circle). (A) Before retro-orbital radiotherapy. (B) After retro-orbital radiotherapy (total dose 46 Gray).

asthenia, and weight decrease. The patient showed an initial partial response followed by disease progression at 6 months, probably due to dose reductions. For progressive dysphagia due to esophageal obstruction "ab extrinsico" a percutaneous endoscopic gastrostomy was placed for enteral feeding, improving the nutritional status.

Currently, the patient is receiving Lenvatinib re-treatment started 4 months ago, with a morphological disease stabilization and biochemical response (last Tg value 360 ng/mL).

Mutational analysis

We performed a genomic analysis on formalin fixed/paraffin embedded tissue from primary tumor and from LC nodal metastases obtained with the second surgery employing a customized NGS panel including 24 genes related to PTC (including *BRAF* and *TERT*).

In the primary tumor, an alteration of TP53 emerged (c.853G>A, p.Glu285Lys) with a median allele frequency of 3.25% However, this findings was not present at relapse. We also analyzed the benign and likely benign SNV present in both samples with an allele frequency >3% (n=63) (Table S1) and performed a literature search to identify, among these variants, the potential polymorphisms related with PTC. Pre-existing evidences emerged for RET (p.Gly691Ser, p.Leu769=, p.Ser904=), TG (p.Asp1312Gly) and TP53 (p.Glu727Asp) SNVs.

Discussion

DTC is generally associated with an excellent prognosis, especially if it remains localized in the neck. Up to 20% of DTC patients have disease events after surgery (4,17,18); and 7–23% of DTC patients develop DM (8,9), a strong negative prognostic factor for disease specific survival (8,10,11). The most frequent sites for DM are lung and bone (10). Metastases at unusual sites may also occur generally in patients with disseminated disease.

Here we report the case of a man with a history of non-Hodgkin lymphoma, treated with chemotherapy and radiotherapy, at the age of 18 months, who was diagnosed a metastatic papillary thyroid carcinoma at the age of 36. After the initial treatment, the patient developed an unusual orbital metastasis from the thyroid tumor. Orbital metastases are more frequently related with breast, prostate and lung cancer, with thyroid tumors representing the primary malignancy only in 3% cases (19). According to the available literature, these lesions are preferentially located in the bony margins of the orbit rather than in the eye-ball, probably due to the lymphatic connections between thyroid and the orbit, as indicated by a study using radioisotope thyroid-lymphography and orbito-lymphography (20,21). The presence of orbital metastases is usually associated with advanced and widespread metastatic disease with poor prognosis. Clinical presentations include diplopia (48%), proptosis (26%), pain (19%), decreased vision (16%), ptosis (10%), and palpable mass (22).

A recent study (23), including 80 patients with OB from solid tumors, showed a survival limited to 1.5 years after diagnosis of OB, independent of the histological type, with less than one third (29%) of patients alive at 17 months and that the orbit was the first presentation in 15% of the cases. In this cohort, the mean interval between primary cancer diagnosis and onset of orbital metastases was 52 months. However, orbital metastases can occur at any time after

initial cancer diagnosis, even after decades (24).

In our case, the latency between PTC diagnosis and orbital metastasis onset was only 10 months, underlying its aggressiveness (local invasion and lung metastases). To our knowledge, this is the first report of an orbital metastasis from DTC in a previously irradiated patient described in the literature. Thyroid is very radiosensitive and functional or morphological thyroid diseases are relatively frequent after exposure to therapeutic doses of external ionizing radiation for head and neck cancers (25-28). Direct irradiation of the thyroid may produce a broad spectrum diseases, with a dose-effect relationship, both functional (hypothyroidism, thyroiditis, Graves' disease) and morphological (single or multinodular goiter and thyroid carcinoma) (29). The latency interval between radiation exposure and the development of thyroid dysfunction varies greatly, ranging from 6 months to 40 years. The risk of thyroid cancer in children exposed to neck irradiation is 15 to 30 fold higher compared to not-exposed subjects and it is inversely related to the age of patient, being maximum for children before 4 years of age (30,31). The correlation between irradiation and thyroid carcinoma, as analyzed in a pooled analysis of 12 studies (31), has shown that the risk of developing a thyroid carcinoma increases after exposure to a dose of at least 2–4 Gy, remains stable between 10 and 30 Gy and declines, still remaining significantly high, at a dose >50 Gy. This risk remains elevated for a long period after irradiation (up to 50 years) (32,33).

The biological mechanisms underlying radiation-induced thyroid disease is related to genomic alterations, to an ischemic damage of small vessels and to immune-mediated factors. DNA is susceptible to radiation-induced damage and this consequently lead to cell toxicity, apoptosis and loss of cell cycle control with uncontrolled proliferation (32,34). The aggressive clinical behaviour of radio-induced thyroid tumors is also probably associated with the genomic alterations induced by ionizing radiation (35).

Unfortunately, the mutational analysis performed on both tumor and nodal relapse of our patients failed to identify relevant prognostic or therapeutic molecular targets. The TP53 alteration retrieved at a low allelic frequency (3.25%) in the primary tumor is likely a passenger event, without a real transforming significance. Of note, RNA sequencing failed due to the poor quality of biological material and we were not able to rule out the presence of gene fusions. The lack of data about gene rearrangements represents a major limitation for the biological interpretation of this case. On the other hand, an interesting framework emerged from the non-pathogenic molecular variants identified. Five of them are potential polymorphisms, previously correlated with PTC onset or with its clinical behaviour. The RET variants (p.Gly691Ser, p.Leu769=, p.Ser904=) apparently determined an increased PTC risk in a Portuguese and Indian population (36), while a study conducted on Iranian subjects correlated the p.Asp1312Gly TG variant with DTCs incidence (37). Additionally, the RET p.Gly691Ser and the TP53 p.Glu727Asp variants were associated with tumors' dimensions >1 cm at diagnosis in a Chinese and Iranian cohort, respectively (38). Whether the simultaneous presence of these variants might play a role in our patient's clinical history remains undetermined and further studies are needed.

Reviewing all previous papers, to our knowledge 23 cases of thyroid carcinomas with orbital metastases have previously been described (13-16,19,21,39-53) (*Table 1*).

The most common primary tumor was papillary thyroid carcinoma, which occurred in 11 patients, followed by follicular thyroid carcinoma reported in 7 patients and insular carcinoma in 1 patient. Four patients displayed a non-specific histology (thyroid carcinoma of follicular origin). Patients'age ranged from 16 to 76 years, with a median of 59 (IQR range, 55.5–68.5) years. Most patients presented evidence of disseminated metastatic disease. Indeed, 16 patients had multiple metastatic sites (mainly bone and lung) and 4 presented the orbital metastasis only, while data were not available for 3 patients. Almost all patients presented symptoms and signs of orbital metastases at diagnosis (diplopia, proptosis, pain, decreased vision and ptosis as first sign of disease). All patients were treated with ^{131}-I and showed orbital uptake and 6 patients also received external-beam radiation.

Data about patients' outcome are largely incomplete as they were missing in 10 of them. Six subjects died for DTC or had disease progression, 5 were free of disease at the last evaluation (2 with multiple metastases at diagnosis and 3 without other disease localizations), 2 were alive at last follow-up (with disease status unknown).

In conclusion the present report describes a peculiar and rare case characterized by the onset, in a patient exposed to previous thyroid irradiation and chemotherapy for a non-Hodgkin lymphoma, of a papillary thyroid tumor with ab initio aggressive characteristics and subsequent onset of an orbital metastasis. In the literature no other cases of PTC with orbital metastases have been described by analyzing the mutations/polymorphisms to find a "biological" explanation to these unusually and often aggressive tumors. Further

Table 1 Orbital metastases from thyroid cancer: review of literature

Study	Gender, age (y)	Clinical presentation	Surgery	Histotype	Treatment	Concomitant distant metastases	Outcome
Bidari-Zerehpoosh F, 2014 (39)	F, 70	Bilateral exophtalmus at diagnosis	Partial thyroidectomy (nodular goiter in thyroid examination)	FTC	Tumor resection and chemo-radiotherapy	Facial skin lesion	Not known
Ozpacaci T, 2012 (40)	F, 76	Loss of vision at diagnosis	Total thyroidectomy + left LN dissection	Insular	Enucleation	Metastasis to choroid and retina, lungs (bilateral)	Died
Besic N, 2013 (13)	F, 69	Impaired vision after 7 months from diagnosis	Total thyroidectomy	FTC (hurtle cell)	^{131}-I treatment and external-beam radiation	Bone metastases	Progression
Slim I, 2012 (41)	F, 67	Pain and slow-growing painless swelling on her left cheek	Emithyroidectomy 7 years before (unspecified histology). Completion of thyroidectomy with central lymph node dissection	PTC (follicular variant)	^{131}-I treatment and mono-head gamma camera	Zygomatic bone, lung metastases	Remission
Betharia SM, 1985 (15)	F, 16	Diplopia, gradual protrusion of the right eye along with progressive diminution of vision	Total thyroidectomy	Thyroid cancer (histotype not known)	Palliative treatment	Extradural mass in the right middle cranial fossa	Progression
Repanos C, 2011 (19)	M, 75	Eye diplopia, proptosis and reduced visual acuity	Total thyroidectomy, neck dissection, orbital exenteration	PTC	Tumor resection and ^{131}-I treatment	Lung metastasis	Probably remission
Pagsisihan DA, 2015 (42)	F, 49	Slowly enlarging right supraorbital mass	Total thyroidectomy	PTC (follicular variant)	^{131}-I treatment	Right posterior parietal, left shoulder and left hip areas	Alive
Rocha Filho FD, 2008 (43)	F, 66	Proptosis on the right eye	Total thyroidectomy	PTC	Radiotherapy and chemotherapy	Thoracic vertebrae, multiple bone metastases	Palliative care
Daumerie C, 2000 (16)	F, 59	Gradual left upper eyelid swelling associated with progressive painless exophthalmos and blurred vision.	Total thyroidectomy with neck dissection	PTC (follicular variant) and FTC	^{131}-I treatment	Mediastinum and in iliac bones	Not known
Cacha LCA, 2018 (44)	F, 68	Left ocular protrusion	Total thyroidectomy + right neck dissection	PTC (follicular variant)	None	None	Dead

Table 1 (*continued*)

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Study	Gender, age (y)	Clinical presentation	Surgery	Histotype	Treatment	Concomitant distant metastases	Outcome
Eldesouky MA, 2015 (45)	2 F and 1 M, Mean age 59.3	Not known	Not known	Not known	Not known	Not known	Not known
Yethadka R, 2014 (21)	F, 70	Right orbital proptosis	Total thyroidectomy	PTC	Radiotherapy	Left lower limb	Alive
Okere PC, 2012 (46)	M, 63	Double vision after 21 months from diagnosis	Near-total thyroidectomy	FTC	^{131}-I treatment	None	Remission
Hornblass A, 1987 (14)	F, 35	Gradual swelling along her right temple associated with tearing and painless progressive proptosis of the right eye	Total thyroidectomy	PTC	Tumor resection	Temporal fossa	Not known
Malhotra G, 2010 (47)	F, 55	Unilateral proptosis	Total thyroidectomy with lymph node dissection	FTC	Excision of the tumor, ^{131}-I treatment	Left maxillary, bilateral shoulder, right humerus, mediastinum, bilateral pelvic bones and bilateral femurs	Not known
Palaniswamy SS, 2018 (53)	M, 58	Swelling close to the right eye (not present at diagnosis)	Total thyroidectomy	PTC	^{131}-I treatment	None	Remission
Basu S, 2001 (48)	F, 54	Left-sided proptosis with epiphora and blurred vision	Total thyroidectomy	FTC	Tumor debulking, ^{131}-I treatment	Right shoulder joint	Not known
Vanderpump MP, 1992 (49)	M, 61	Unilateral proptosis, double vision and painful swelling in the right eye	Total thyroidectomy	FTC (hurtle cell)	Debulking of the tumor, ^{131}-I treatment and external-beam radiation	Diffuse bone metastases	Died
Boughattas S, 2005 (50)	F,25	Asymptomatic, right-sided uptake	Total thyroidectomy	PTC	^{131}-I treatment	Lung	Not known
Bernstein-Lipschitz L, 1990 (51)	F, 56	Diplopia, ptosis, And discomfort in her right orbit	Debulking of the tumor, total thyroidectomy	FTC	Debulking of the tumor and ^{131}-I treatment	Ethmoid and maxillary	Not known
Shyla PR, 2007 (52)	F, 70	Loss of left eye vision	Total thyroidectomy	PTC	Excision of mass, external-beam radiation and ^{131}-I treatment	None	Remission

FTC, follicular thyroid cancer; PTC, Papillary thyroid cancer; LN, lymph node; y, years; M, male; F, female.

studies on molecular characterization are needed in order to better understand these types of tumors.

The role of previous radiotherapy in the pathogenesis of thyroid carcinogenesis is well established, however its influence in our case remains unknown. This report indicates the need of periodic morpho-functional thyroid evaluation in patients treated with neck irradiation particularly in childhood, in order to promptly diagnose secondary malignancies.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-61/rc

Peer Review File: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-61/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-61/coif). PV reports that he received research funding from Novartis and Pfizer; honoraria from Astra-Zeneca, Celgene, Italfarmaco, Incyte, Novartis, Pfizer, Tesaro, and Teva. FM reports that she received honoraria for lectures and support for meeting attendance from Istituto Gentili, Lilly, Novartis and Pfizer in the last three years. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Table S1 Benign or likely benign single nucleotide variations present in both primary and relapsed tumor

	Locus	Gene	Amino Acid Change	Coding
1.	chr6:157405930	*ARID1B*	p.Ala807=	c.2421G>A
2.	chr11:108122729	*ATM*	p.Asn591=	c.1773T>C
3.	chr11:108175462	*ATM*	p.Asp1853Asn	c.5557G>A
4.	chr11:108183167	*ATM*	p.Asn1983Ser	c.5948A>G
5.	chr5:70800475	*BDP1*	p.Arg757Cys	c.2269C>T
6.	chr5:70805664	*BDP1*	p.Thr915=	c.2745G>A
7.	chr5:70806711	*BDP1*	p.Ile1264Met	c.3792C>G
8.	chr5:70806958	*BDP1*	p.Val1347Met	c.4039G>A
9.	chr5:70818150	*BDP1*	p.Gln1676Glu	c.5026C>G
10.	chr5:70837295	*BDP1*	p.Ile2013Leu	c.6037A>C
11.	chr5:70858194	*BDP1*	p.Arg2530=	c.7590C>T
12.	chr20:60348084	*CDH4*	p.Ala141Val	c.422C>T
13.	chr20:60485627	*CDH4*	p.Asp446=	c.1338C>T
14.	chr20:60504734	*CDH4*	p.Ile691=	c.2073C>T
15.	chr17:40860080	*EZH1*	p.Tyr519Cys	c.1556A>G
16.	chr11:534242	*HRAS*	p.His27=	c.81T>C
17.	chr11:118344418	*KMT2A*	p.Gly848=	c.2544G>C
18.	chr7:151864305	*KMT2C*	p.Phe3226Leu	c.9676T>C
19.	chr7:151877997	*KMT2C*	p.Ser2316=	c.6948T>C
20.	chr7:151878950	*KMT2C*	p.Ile1999Val	c.5995A>G
21.	chr7:151945128	*KMT2C*	p.Leu797=	c.2391G>T
22.	chr7:151945140	*KMT2C*	p.Ser793=	c.2379G>A
23.	chr7:151945167	*KMT2C*	p.Ser784=	c.2352C>A
24.	chr7:151962257	*KMT2C*	p.Pro350=	c.1050G>A
25.	chr7:151962265	*KMT2C*	p.Asp348Asn	c.1042G>A
26.	chr7:151962269	*KMT2C*	p.Val346=	c.1038G>A
27.	chr7:151970931	*KMT2C*	p.Leu291Phe	c.871C>T
28.	chr7:151970951	*KMT2C*	p.Arg284Gln	c.851G>A
29.	chr12:25362776	*KRAS*	p.?	c.*5598T>C
30.	chr12:25368462	*KRAS*	p.Arg161=	c.483G>A
31.	chr11:64572018	*MEN1*	p.Thr546Ala	c.1636A>G
32.	chr11:64572557	*MEN1*	p.His438=	c.1314T>C
33.	chr11:64572569	*MEN1*	p.Thr434=	c.1302G>A
34.	chr11:64572602	*MEN1*	p.Asp423=	c.1269C>T
35.	chr17:29422305	*MIR4733, NF1*	p.?	c.-22G>C
36.	chr10:43595968	*RET*	p.Ala45=	c.135A>G
37.	chr10:43597840	*RET*	p.Thr130Ala	c.388A>G
38.	chr10:43610119*	*RET*	p.Gly691Ser	c.2071G>A
39.	chr10:43613843*	*RET*	p.Leu769=	c.2307G>T
40.	chr10:43615633*	*RET*	p.Ser904=	c.2712C>G
41.	chr17:47677867	*SPOP*	p.Leu333Ter	c.998T>A
42.	chr8:133899160	*TG*	p.Gln515Glu	c.1543C>G
43.	chr8:133900252	*TG*	p.Ser734Ala	c.2200T>G
44.	chr8:133900386	*TG*	p.Pro778=	c.2334T>C
45.	chr8:133909974	*TG*	p.Met1028Val	c.3082A>G
46.	chr8:133920518*	*TG*	p.Asp1312Gly	c.3935A>G
47.	chr8:133931748	*TG*	p.Ala1502=	c.4506T>C
48.	chr8:133984058	*TG*	p.Arg1999Trp	c.5995C>T
49.	chr8:134108546	*TG*	p.Trp2501Arg	c.7501T>C
50.	chr8:134144113	*TG*	p.Tyr2640=	c.7920C>T
51.	chr17:7577085	*TP53*	p.Glu285Lys	c.853G>A
52.	chr17:7579472*	*TP53*	p.Pro72Arg	c.215C>G
53.	chr14:81534635	*TSHR*	p.Ser94Pro	c.280T>C
54.	chr14:81610583	*TSHR*	p.Glu727Asp	c.2181G>C
55.	chr16:72821475	*ZFHX3*	p.Glu3567Gly	c.10700A>G
56.	chr16:72827758	*ZFHX3*	p.Gly2941=	c.8823A>G
57.	chr16:72828265	*ZFHX3*	p.His2772=	c.8316C>T
58.	chr16:72832135	*ZFHX3*	p.Ala1482=	c.4446A>T
59.	chr16:72984636	*ZFHX3*	p.Ser983Ter	c.2948C>G
60.	chr16:72991660	*ZFHX3*	p.Pro795=	c.2385G>C
61.	chr16:72992138	*ZFHX3*	p.Ser636Leu	c.1907C>T
62.	chr16:72992269	*ZFHX3*	p.Asp592=	c.1776C>T
63.	chr16:72993251	*ZFHX3*	p.Asp265Gly	c.794A>G

*, with a potential role in tumor's pathogenesis according to pre-existing evidence.

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