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ORIGINAL ARTICLE

THYROID CANCER IN SARDINIAN PEDIATRIC PATIENTS: REPORT OF 63 CASES AND A REVIEW OF THE LITERATURE

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ABSTRACT

Thyroid cancer is considered uncommon in pediatrics, yet it is the most common endocrine malignancy among them. The aim of this study was to analyze pediatric thyroid carcinomas diagnosed in Sardinian children and adolescents in order to find a possible association with autoimmune diseases.
We studied 63 consecutive 10-20-years-old patients who underwent surgery for thyroid cancer between January 2001 and April 2020 in our hospital.
No evidence of risk factors including external radiation was found. All cases were follicular-derived neoplasms: 45 PTCs (72%), 9 FTCs (14%), 2 well differentiated carcinomas not otherwise specified (3%), 2 poorly differentiated carcinomas (3%), 5 cases of encapsulated PTC-FV were re-diagnosed as NIFTP (8%), according to the last WHO classification. Autoimmune thyroid diseases were detected in the 29 PTCs (64% of PTCs). BRAF V600E mutation was found in 21 PTCs (47% of PTCs). Our study shows that thyroid cancer in Sardinian children and adolescents is characterized by peculiar features: our cohort is composed only by Follicular-derived differentiated thyroid cancer without medullary carcinomas; PTC seems to be more frequent and strongly associated with autoimmune thyroid diseases in our population. Those evidences, together with the absence of any exposure to radiation in our patients, support the possibility that autoimmune diseases became an important event to be considered also in the evolution of pediatric thyroid carcinogenesis.

KEY-WORDS

Pediatric thyroid carcinomas; BRAF V600E; PTC; autoimmune thyroid diseases.

IMPACT STATEMENT

A twenty-year study with a large number of cases of thyroid cancer in pediatric patients in the particular genetic scenario of Sardinia.

INTRODUCTION

Even if differentiated thyroid cancers have always been considered rare in pediatric population (1, 2), recently an increasing incidence of thyroid cancer in adults as well as in children and adolescents was reported (3). In the pediatric population, the only consolidated risk factor is the exposure to radiation. The scientific interest on radiation-associated risk of thyroid cancer, increased in pediatric population after the Chernobyl and Fukushima nuclear accident, was extended to radiation exposure regarding therapeutic procedures. In fact, youngest children are more sensitive to radiation-induced carcinogenesis, the minimal latent period for thyroid cancer development after exposure is as short as 4 years and is dose dependent (1, 2). The reasons associated with this progressive trend are controversial because the incidence growth of thyroid cancer in children may not be justified only by an increase of radiation risk (4).

Other risk factors are involved in thyroid diseases and, among these, we can distinguish genetic (thyroid disease like autoimmune thyroid disorders) and epigenetic events (iodine nutritional deficiency) (4-7). Even though there is no indication of ethnic or race susceptibility in pediatric thyroid cancer, an increased trend was found in different geographic regions of the United States and some genetic peculiarities associated with this cancer are present in the Sardinian Island population (8, 9). In particular, Sardinians are more sensible to autoimmune diseases, strongly associated with papillary thyroid carcinoma (10-12). The recent years have seen an increasing focus on the genes implicated in carcinogenesis, also for the thyroid tumors (13, 14). The genetic mutations are important for understanding the nature of the tumors and they have an implication in the therapy and in the follow-up. One of the most important gene mutations on thyroid cancers is the BRAF V600E mutation (15). This mutation, thought to mimic phosphorylation of the activation site (15, 16), is important not only for the prognosis, but also for the therapeutic response. In fact, radioactive iodine therapy normally has a good response, but its efficacy is variable in BRAF V600E + cases (17). The mutated BRAF V600E protein in fact causes a resistance to iodine absorption, thus making radioactive iodine ineffective (17, 18). Recently it was proposed a specific targeted therapy for thyroid cancer (a BRAF inhibitor) used for both, pediatric and adult population, according to the adult guidelines, and thyroid cancer is not classified differently in children compared to young adults (2). All together these data underline that pediatric and adult's thyroid cancer tend to have a different evolution (more advanced disease and an excellent overall survival rate in children and adolescents); however, most of the studies have been performed in radiation-exposed pediatric thyroid carcinoma and there is no clear explanation for these differences. Therefore, there is a strong need for studies in pediatric population and, for this reason, the aim of this study is to analyze 63 Sardinian pediatric clinical cases of thyroid cancer.

PATIENTS AND METHODS

This retrospective study was approved by the ethics committee of the University Hospital of Cagliari. We examined 63 consecutive cases. All thyroid samples were formalin-fixed and paraffin-embedded. 3-micron thick paraffin sections were stained with Hematoxylin and Eosin for histology. All cases have been reviewed by two experienced pathologists (MLL and AS) and histopathological assessment was performed and re-diagnosed according to the fourth edition of the WHO classification (22). BRAF mutational status was determined using the Diatech Pharmacogenetics piro-sequencing system (Diatech Pharmacogenetics, www/diatechpharmacogenetics.com) performed on formalin-fixed, paraffin-embedded tumor tissues. Neoplastic and non-neoplastic (surrounding) formalin-fixed tissues were microdissected from hematoxy-

lin-stained thyroid tissue and genomic DNA was extracted using the MagCore Automated Nucleic Acid Purification system (RBC. Bioscience Corp., www/rbcbiocience.com). For Immunohistochemical analysis, 3 µm thick sections were obtained from each paraffin block. All reagents were purchased from Ventana Medical Systems Inc. 1910 E. Innovation Park Drive Tucson, Arizona 85755 USA.

All immunostaining procedures were performed using the UltraView Universal DAB Detection Kit (Ref. 760-5000) on the BenchMark Ultra instrument, according to the manufacturer's instructions.

RESULTS

The vast majority of cases was incidentally diagnosed by ultrasonography in the setting of a follow-up for a preexisting autoimmune thyroid disease or during screening programs in schoolhouses. At clinical examination, few patients presented a painless or tender thyroid nodule.

No risk factor, including exposure to ionizing radiation or ingestion of radioiodine, was present in any patient's history. No family history of thyroid cancer was reported in our patient's clinical information.

Distant metastases were never detected. At histology all cases were follicular-derived neoplasms (**table I**). In 58 cases a diagnosis of malignancy was made; 5 cases, already diagnosed as encapsulated follicular variants of papillary thyroid carcinoma, were re-classified as NIFTP (8%), according to the new classification of the WHO (19). The malignant cases included 45 papillary thyroid carcinomas (PTCs) (72%), 9 follicular thyroid carcinomas (FTCs) (14%), 2 well differentiated carcinomas not otherwise specified (3%) and 2 poorly differentiated carcinomas with focal areas of differentiated PTC (3%). PTCs were predominantly observed in females (F/M = 36/9), with a median age of 16.8 years (range 10-20 y); 10 cases were multifocal (22% of PTCs), 1 presented intravascular invasion (2% of PTCs) and 25 showed lymph node metastases (55.5% of PTCs). The extrathyroid invasion was present in 17 PTCs (38% of PTCs) and 29 were associated with autoimmune thyroid diseases (64% of PTCs).

About the 9 cases of FTCs, 7 were in females and 2 in males, with a median age of 17.7 years, ranging from 13 to 20 years at presentation. In 5 patients, intravascular invasion was detected (55% of FTCs), but none presented with lymph node metastases. 2 FTCs presented extrathyroid invasion (22% of FTCs) and 4 were associated with autoimmune thyroid diseases (44% of FTCs). The 5 patients with NIFTP were all females, with a median age of 17 years old, ranging from 12 up to 20 years old at presentation. None of them were multifocal, nor did they present intravascular invasion or lymph node metastases or extrathyroid invasion, as indeed it must be for the diagnosis of NIFTP. One was associated with autoimmune thyroid diseases.

The two cases of well differentiated carcinomas not otherwise specified (WDC-NOS) were found in a 15 and a 19-years-old patients, (median age 17 y), respectively a male and a female. 1 of them presented intravascular invasion (50% of WDCs-NOS). None of them were multifocal, nor did they show lymph node metastases or extrathyroid invasion or association with autoimmune thyroid diseases. The two patients with a diagnosis of poorly differentiated carcinoma

HISTOTYPE	N. (% PER COLUMN)	F/M	MEDIAN AGE (RANGE)	MULTIFOCAL (% PER ROW)	IVI (% PER ROW)	LN METASTASES (% PER ROW)	EXTRATHYROID INVASION (% PER ROW)	ASSOCIATED AITD (% PER ROW)
PTC	45 (72%)	36/9	16.8 (10-20 y)	10 (22%)	1 (2%)	25 (55,5%)	17 (38%)	29 (64%)
FTC	9 (14%)	7/2	17.7 (13-20 y)	0 (0%)	5 (55%)	0 (0%)	2 (22%)	4 (44%)
NIFTP	5 (8%)	5/0	17.0 (12-20 y)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (20%)
WDC-NOS	2 (3%)	1/1	17.0 (15-19 y)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)
PDC	2 (3%)	2/0	17.5 (17-18 y)	0 (0%)	2 (100%)	1 (50%)	2 (100%)	2 (100%)

Table I. *Cases.*

PTC: Papillary Thyroid Carcinoma; FTC: Follicular Thyroid Carcinoma; NIFTP: NonInvasive Follicular Thyroid neoplasm with Papillary like nuclear features; WDC-NOS: Well Differentiated Carcinoma – Not Otherwise Specified; PDC: Poorly Differentiated Carcinoma; IVI: IntraVascular Invasion; AITD: AutoImmune Thyroid Disease.

(PDC) were both females, one 17- and the other 18 years old (median age 17.5 y). In both cases we found intravascular invasion (100% of PDCs) and extra-thyroidal extension (100% of PDCs). In one patient lymph nodal metastases were present (50% of PDCs). Both patients had autoimmune thyroid diseases (100% of PDCs). Regarding the subtypes of PTCs (**table II**), 17 showed features of the Classical Variant (PTC-CV) (38% of PTCs), 11 were Follicular Variant (PTC-FV) (24% of PTCs), 8 were diagnosed as Tall Cell variant (PTC-TCV) (18% of PTCs), 6 as Diffuse Sclerosis variant (PTC-DSV) (13.5% of PTCs), 2 were diagnosed as Solid Variant (PTC-SV) (4.5% of PTCs) and 1 as Cribriform variant (PTC-CrV) (2% of PTCs). The distribution of BRAF V600E mutation in papillary thyroid carcinomas (**table III**) was found in 21 out of 45 cases (47%), with a median age of 16.3 years old (range 11-20 years). 7 cases were multifocal (33.3%), 1 case showed intravascular invasion (5%), lymph-nodes metastases were present in 13 cases (62%) and extrathyroid extension in 9 cases (42%). The BRAF V600E mutation was associated with autoimmune thyroid diseases in 15 out of 21 cases (71%). BRAF V600E negative PTCs patients had median age 17.4 years old (range 10-20 years), association with autoimmune thyroid disease was found in 14 out of 24 cases (58%), extra thyroid extension in 8 out of 24 cases (33%) and lymph-node metastases in 12 out of 24 cases (50%). No BRAF V600E mutation was found in any cases of FTCs, well differentiated carcinomas not otherwise specified, poorly differentiated carcinomas and NIFTPs.

DISCUSSION

The trend of the incidence rates for sporadic PTC in childhood and adolescence shows a constant growth (3). The prevalent risk factor for thyroid cancer are the ionizing radiations but other genetic, environmental and lifestyle factors are emerging (20). In fact, an increased proportion of mutations less associated to radiation exposure (BRAF and RAS point mutations) was described in different studies (21-24).

VARIANTS	N. (% PER COLUMN)	F/M	MEDIAN AGE (RANGE)	MULTIFOCAL (% PER ROW)	IVI (% PER ROW)	LN METASTASES (% PER ROW)	EXTRATHYROID INVASION (% PER ROW)	ASSOCIATED AITD (% PER ROW)
CV	17 (38%)	15/2	17.2 (10-20y)	6 (35%)	0 (0%)	7 (41%)	5 (29%)	13 (76%)
FV	11 (24%)	9/2	18.4 (16-20y)	1 (9%)	0 (0%)	3 (27%)	2 (18%)	3 (27%)
TCV	8 (18%)	5/3	15.6 (11-19y)	3 (37.5%)	1 (12,5%)	8 (100%)	4 (50%)	5 (62,5%)
DSV	6 (13.5%)	4/2	16.0 (14-19y)	0 (0%)	0 (0%)	6 (100%)	4 (66,6%)	6 (100%)
SV	2 (4.5%)	2/0	14.0 (13-15y)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	1 (50%)
CrV	1 (2%)	1/0	15.0 (15y)	0 (0%)	0 (0%)	1 (100%)	1 (100%)	1 (100%)

Table II. *PTC Variants.*
CV: Classic Variant; FV: Follicular Variant; TCV: Tall Cells Variant; DSV: Diffuse Sclerosing Variant; SV: Solid Variant; CrV: Cribriform Variant; IVI: IntraVascular Invasion; AITD: AutoImmune Thyroid Disease.

	N. (% PER COLUMN)	F/M	MEDIAN AGE (RANGE)	MULTIFOCAL (% PER ROW)	IVI (% PER ROW)	LN METASTASES (% PER ROW)	EXTRATHYROID INVASION (% PER ROW)	ASSOCIATED AITD (% PER ROW)
BRAF V600E mutated	21 (47%)	16/5	16.3 (11-20y)	7 (33.3%)	1 (5%)	13 (62%)	9 (43%)	15 (71%)
BRAF V600E not mutated	24 (53%)	20/4	17.4 (10-20y)	3 (12.5%)	0 (0%)	12 (50%)	8 (33%)	14 (58%)

Table III. *BRAF Mutation in PTCs.*
PTC: Papillary Thyroid Carcinoma.

In any cases, more multicenter studies are necessary to better understand the relevance of different risk factors thyroid carcinogenesis (25).

This study made in Sardinia, a Mediterranea island without any evidence of radiation contamination, in 63 clinical cases without head and neck radiation exposure, represent one of the firsts example of a possible association between pediatric thyroid cancer and autoimmune thyroiditis. This association was more evident in PTC samples (64% of the cases) but seems to be present also in the 4 out of 9 FTC cases examined (44%). The presence of autoimmune thyroiditis was already described in adults thyroid cancers, in PTC and even if in reduced frequency also in FTC (26-28), in the general population or in areas with an high prevalence of Hashimoto's disease (11-13, 29-31).

These thyroid cancers have been described as less aggressive and with a better prognosis and more frequent in younger patient. On the contrary, our pediatric PTC samples with autoimmune diseases showed, as all pediatric thyroid tumors, a more aggressive pattern (55,5% with LF metastasis and 38% of exstrathyroid invasion), confirming that relevant differences between pediatric and adult thyroid tumor may exist.

In our study, thyroid carcinoma affected more girls than boys, with a 4-fold predominance, in line with more recent studies (2, 3, 32, 33) supporting previous hypotheses on a relevant role played by hormonal determinants in the pathogenesis of thyroid carcinoma (2, 34). The median age at diagnosis, in our cohort, was 17 years (ranging from 10 up to 20) different of that observed in others studies (13.5-14.6-14.7 years) suggesting a possible elderly clinical manifestation in our population (3, 32, 33).

The relationship between chronic autoimmune thyroiditis and thyroid carcinogenesis are still controversial but seems that they could share the same molecular pathogenesis and therefore, these inflammatory events could be considered as preneoplastic lesions (35-37).

Some studies (38) estimated that the BRAF V600E mutation has a lower incidence in thyroid pediatric cancers than in adults, while other studies reported a higher incidence (38-41). In line with the latter, in our cohort, BRAF V600E mutation was frequently detected (47% of PTCs). Even if Hardee *et al*. specify that the BRAF V600E mutation is not associated with a more aggressive clinical course in the pediatric people (41), our and other studies indicated a more aggressive behavior, such as described in adults. Therefore, the relevance of the BRAF V600E mutation seems to be relevant also for the diagnosis of the PTC in the pediatric patients, in particular because is indicative for specific therapy strategies.

PTC was the most common histological subtype diagnosed in our children and adolescents, accounting for 70% of the total. No case of anaplastic/undifferentiated carcinoma was found in our series, confirming the rarity of this entity in young people. In our population, follicular derived differentiated carcinomas represent 100% of thyroid cancers originating in children and adolescents. This finding contrasts with previous reports, indicating medullary thyroid carcinoma appearing in about 10% of patients affected by thyroid cancer in childhood, mostly correlated with MEN2B syndrome (42).

CONCLUSIONS

This study represents one of the first example of pediatric thyroid carcinoma made in a population genetically predisposed to autoimmune diseases. The high percentage of clinical cases associated with autoimmune thyroiditis clearly indicate the opportunity of a screening campaign in these pediatric patients in order to prevent a possible insurgence of this type of cancer and to obtain more diagnostic and therapeutic recommendations. Finally, this and other studies highlights the need to establish a more personalized approach in these clinical cases.

ETHICS

Fundings

There were no institutional or private fundings for this article.

Conflict of interests

The authors have declared no conflict of interests.

Availability of data and material

All the data supporting the findings of this study are available within the article and can be shared just before a reasonable request to the corresponding author.

Authors' contribution

All the authors contributed equally to conception, data collection, analysis and writing of this paper.

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