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Thyroid

Relationship of *PPARG* overexpression with prognostic parameters in papillary thyroid carcinoma

Correlazione fra iperespressione della proteina PPARG e parametri prognostici nel carcinoma papillare della tiroide

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SUMMARY

Objectives. *PAX8/PPARG* chromosomal rearrangement is frequently seen in thyroid cancer, and *PPARG* overexpression has been shown in the follicular variant of papillary thyroid carcinoma, but not in papillary thyroid carcinoma other than the follicular variant. The main aim of this study was to investigate the frequency of *PPARG* overexpression among papillary thyroid carcinoma and if there were any variants of papillary thyroid carcinoma with *PPARG* overexpression other than the follicular variant.

Methods. Immunohistochemical analysis of *PPARG* overexpression was performed using a *PPARG* monoclonal antibody in a series of 111 paraffin-embedded blocks of thyroid tumours. Of the patients in our study, 100 were diagnosed with papillary thyroid carcinoma, 9 with follicular adenoma and 2 with follicular carcinoma.

Results. *PPARG* staining was detected in 19 of the 111 cases. Sixteen patients with *PPARG* overexpression had papillary thyroid carcinoma and 3 had follicular adenoma.

Conclusion. *PPARG* overexpression was detected mainly in follicular-variant papillary thyroid carcinoma. Vascular invasion, lymphatic invasion, thyroid capsule invasion and lymph node positivity were lower in patients with *PPARG* overexpression.

KEY WORDS: papillary thyroid carcinoma, *PPARG* overexpression, prognostic parameters, PAX8/PPARG fusion protein (PPFP), pioglitazone

RIASSUNTO

Obiettivi. *Il riarrangiamento cromosomico PAX8/PPARG è frequentemente osservato nel cancro della tiroide, la sovraespressione della proteina PPARG è stata già dimostrata nella variante follicolare del carcinoma papillare della tiroide, ma non nelle varianti del carcinoma papillare della tiroide, diverse da quella follicolare. L'obiettivo principale di questo studio è stato quello di indagare la sovraespressione di PPARG nel carcinoma papillare della tiroide e se ci sia qualche variante del carcinoma papillare della tiroide, diversa da quella follicolare, con sovraespressione di PPARG.*

Metodi. *È stata eseguita una analisi immunoistochimica della sovraespressione di PPARG, utilizzando un anticorpo monoclonale PPARG in una serie di 111 campioni di tumori tiroidei inclusi in paraffina. In 100 casi, è stato diagnosticato un carcinoma papillare della tiroide, in 9, adenoma follicolare e 2, carcinoma follicolare.*

Risultati. *La proteina PPARG è stata rilevata in 19 dei 111 casi. Sedici di quei pazienti con sovraespressione di PPARG avevano carcinoma papillare della tiroide e 3 pazienti avevano adenoma follicolare.*

Conclusione. *La sovraespressione di PPARG è stata rilevata principalmente nella variante follicolare del carcinoma papillare della tiroide. L'invasione vascolare, l'invasione linfatica, l'invasione della capsula tiroidea e la positività dei linfonodi sono risultate inferiori nei pazienti con sovraespressione di PPARG.*

PAROLE CHIAVE: *carcinoma papillare della tiroide, sovraespressione di PPARG, parametri prognostici, proteina di fusione PAX8/PPARG (PPFP), pioglitazone*

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Introduction

The majority of thyroid cancers are well-differentiated tumours that develop from thyroid follicular cells [1]. These tumours are histologically classified as papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) and Hurthle cell carcinoma [2]. Of all thyroid cancers, 79% are PTC, 13% FTC and 3% Hurthle cell carcinoma [1]. The prognosis is excellent in most patients with well-differentiated thyroid carcinomas who receive proper diagnosis and treatment. The 5-year relative survival in PTC is higher than 99% in women at age 15-55 years and higher than 96% in men at age 15-55 years [3]. Some subtypes of well-differentiated thyroid cancers are known to be more aggressive, and clinical and pathological prognostic factors are helpful in determining which patients will develop aggressive or recurrent disease [4].

The *PAX8/PPARG* oncogene occurs as a result of stable translocation between *PAX8*, a transcription factor required for thyroid differentiation, and peroxisome proliferator receptor gamma (*PPARG*), a member of the steroid/thyroid nuclear receptor family (t [*2; 3*] [*q13; p25*]) [5]. The existence of this translocation was detected only in FTC and follicular adenoma (FA) in one study [6], whereas in other studies the translocation was also detected in the follicular variant of PTC (FVPTC) [5,7]. In the study by Nikiforova et al., it was observed that FTCs with *PAX8/PPARG* translocation were associated with more aggressive pathological prognostic parameters [6]. The translocation of PPARG has been shown with PCR-based methods with better clarity, although the technique is too expensive to apply in all laboratories and settings. Immunohistochemistry (IHC) is an easy and inexpensive method to reveal protein expression in tissues and cells.

In this study, we investigated the presence of *PPARG* overexpression in PTC, FTC and FA with IHC. We also evaluated the histologic subtypes of tumours with PPARG overexpression and the relationship with prognostic parameters. The present study was performed to investigate the frequency of PPARG overexpression among PTC and if there were any variants of PTC with PPARG overexpression other than the follicular variant.

Materials and methods

Patient selection

Pathology specimens were examined from 124 patients who had thyroid surgery during 2012-2017 at a single tertiary referral centre with a diagnoses of PTC, FTC, or FA. Thirteen patients were excluded because the tumour focus was too small for IHC analysis, and thus a total of 111 patients were included. Of these, PTC was found in 100 patients, FA in 9 patients and FTC in 2 patients. Pathology reports and haematoxylin and eosin (H&E) slides of all patients were obtained from the archives of the Department of Pathology. The preoperative examination, intraoperative surgical findings and postoperative follow-up findings of the patients were obtained by accessing medical records.

Pathological evaluation and immunohistochemistry

Haematoxylin-eosin stained slides of 111 patients with PTC, FTC, or FA were re-examined by a pathologist experienced on thyroid (P.B.), who was blinded to the patient's clinical information and pathology results. In addition to the thyroid, slides of metastatic foci (neck metastases) were also examined. Tumour foci that were suitable for IHC were marked and highlighted. Two distinct tumour foci were marked for each patient on at least 2 separate slides. The paraffin blocks of the selected slides were pulled from the archives of pathology.

All IHC staining processes, including deparaffinisation and antigen retrieval, were performed on a fully automated staining device (Ventana BenchMark Ultra, Ventana Medical Systems, Tucson, AZ, USA). Cross-sections were incubated for 30 minutes at 1/800 dilution with *PPARG* rabbit monoclonal antibody (Cell Signaling, Danvers, MA, USA). Nuclear staining in omental adipose tissue of 3 patients without thyroid carcinoma was used as the external control as defined in the user manual by the manufacturer. Similarly, nuclear staining of perithyroidal fat cells was observed in some of the thyroid specimens and used as an internal control.

PPARG monoclonal antibody staining was scored as weak (1+), moderate (2+), or strong (3+) and as focal (less than half of tumour cells were stained) or diffuse (more than half of tumour cells were stained) (Tab. I) [6].

Statistical analysis

IBM SPSS version 15 was used to perform the analysis. When descriptive analysis was presented, mean, standard deviation, median and 25-75 percentile values were

Table I. Immunohistochemical scoring of tumours stained with PPARG.

Staining and score of stained tumour cells	
Strong staining	3+
Moderate staining	2+
Weak staining	1+
Percentage of tumour cells stained	
Diffuse staining	> 50% of tumour cells positive
Focal staining	< 50% of tumour cells positive

Table II. Number of cases stained with PPARG antibody in IHC and degree of staining.

		n	%
PPARG staining	Positive	19	(17.1)
	Negative	92	(82.9)
Degree of PPARG staining	1 + diffuse staining	5	(4.5)
	2 + diffuse staining	10	(9.0)
	3 + diffuse staining	3	(2.7)
	3 + focal staining	1	(0.9)
	No staining	92	(82.9)

used. The normal distribution of variables was examined by histogram graphs and the Kolmogorov-Smirnov test. When normally distributed (parametrical) variables were compared between groups, the one-way analysis of variance (ANOVA) test was used. Post hoc analysis was done according to *PPARG* staining of tumour cells between the PTC classical and follicular variants. Chi-square and Fisher's exact tests were used to compare categorical data. For statistical significance, $p < 0.05$ was accepted.

Results

The study included 111 patients, of whom 33 were men (29.7%) and 78 women (70.3%). The mean age of patients was 42.0 ± 15.3 years. Nineteen of the 111 cases were stained with *PPARG* monoclonal antibody (Tab. II). Among these 19 cases, nuclear staining was found in only one case with PTC classical variant, and in all other 18 cases there was cytoplasmic staining of tumour cells (Figs. 1-3).

The pathological prognostic parameters of patients were examined according to *PPARG* monoclonal antibody staining. According to a post-hoc analysis, *PPARG* staining was higher in FVPTC than in the classical variant. Vascular invasion ($p = 0.039$), lymphatic invasion ($p = 0.019$) and thyroid capsule invasion ($p = 0.002$) were found to be lower in patients with *PPARG* staining (Tab. III).

There was no lymph node metastasis in any tumour that stained with *PPARG* monoclonal antibody in our case series ($p = 0.012$). Lymph node metastasis was detected in 22 of 111 patients. Nuclear or cytoplasmic PPARG immunoreactivity was not observed in any of these 22 cases. Therefore, we could not examine whether there is a relationship between PPARG and lymph node positive or negative cases in terms of recurrence. There was no relationship between tumour size and positive staining of tumours ($p = 0.654$) (Tab. IV).

There was also no relationship between *PPARG* positive tumours and stage, postoperative need of radioactive iodine (RAI), or recurrence ($p > 0.05$). There was no statistically

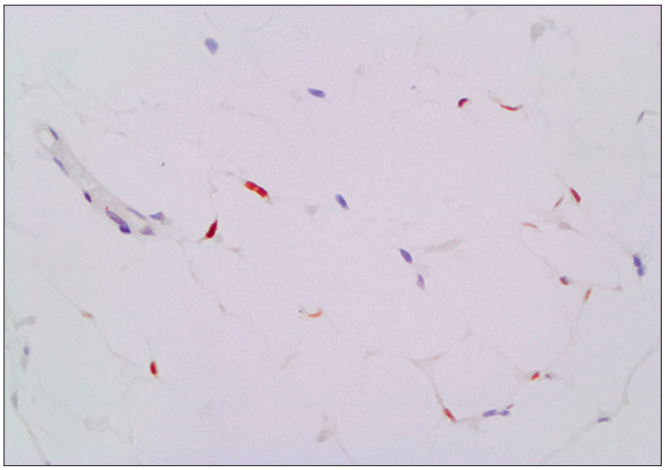

Figure 1. Nuclear staining of omental adipose tissue cells with PPARG monoclonal antibody (external control), X40.

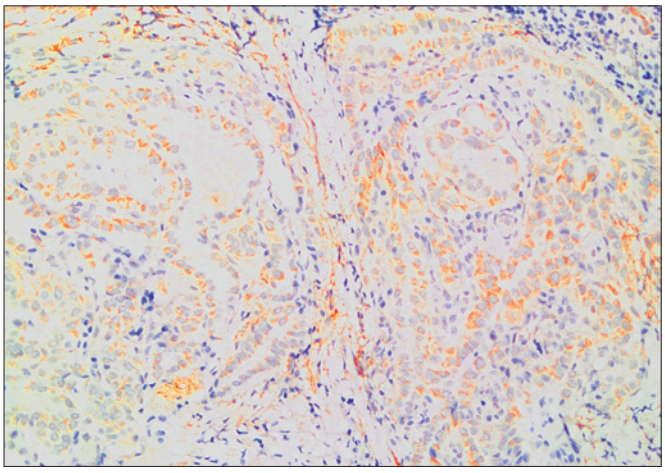

Figure 2. Diffuse 3+ cytoplasmic staining of tumour cells with PPARG monoclonal antibody, X20.

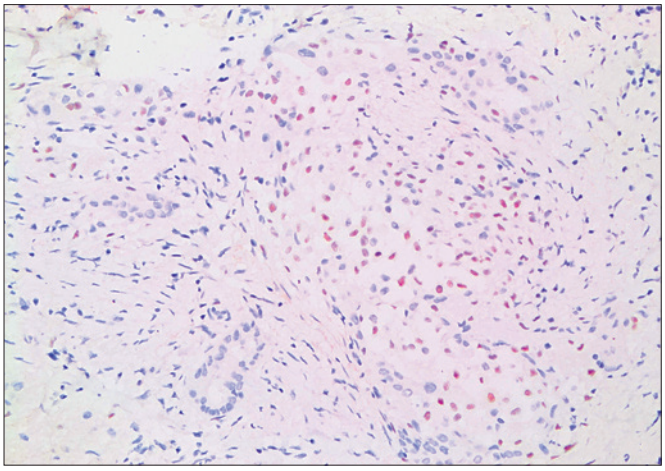

Figure 3. Focal nuclear staining of tumour cells with PPARG monoclonal antibody, X40.

Table III. Histological types of tumours stained with PPARG and relationship with pathological prognostic parameters.

		PPARG staining				p
		Positive		Negative		
		n	%	n	%	
Histopathology	Classical variant of PTC	2	10.5	48	52.2	0.004[b]
	FVPTC	9	47.4	19	20.7	
	Other variants of PTC	5	26.3	17	18.5	
	FA	3	15.8	6	6.5	
	FTC	0	0.0	2	2.2	
Vascular invasion	Positive	1	5.3	26	28.3	0.039[b]
	Negative	18	94.7	66	71.7	
Lymphatic invasion	Positive	1	5.3	29	31.5	0.019[a]
	Negative	18	94.7	63	68.5	
Perineural invasion	Positive	0	0.0	13	14.1	0.120[b]
	Negative	19	100.0	79	85.9	
Thyroid capsule invasion	Positive	3	15.8	51	55.4	0.002[a]
	Negative	16	84.2	41	44.6	
Extrathyroidal soft tissue invasion	Positive	3	15.8	26	28.3	0.391[b]
	Negative	16	84.2	66	71.7	

[a] Chi-square test, [b] Fisher's exact test (n: number of patients; %: percentage of patients).

Table IV. Relationship of PPARG positive tumours with tumour size, lymph node metastasis and distant metastasis.

		PPARG staining				p
		Positive		Negative		
		n	%	n	%	
T (tumour size)	T1a	4	21.1	18	19.6	0.654[a]
	T1b	9	47.4	35	38.0	
	T2	2	10.5	22	23.9	
	T3a	1	5.3	8	8.7	
	T3b	0	0.0	2	2.2	
	T4a	0	0.0	1	1.1	
	FA	3	15.8	6	6.5	
N (lymph node)	Nx	16	84.2	64	69.5	0.166[a]
	N0a	3	15.8	6	6.5	
	N0b	0	0.0	0	0.0	
	N1a	0	0.0	8	8.7	
	N1b	0	0.0	14	15.3	
M (metastasis)	M0	19	100.0	88	95.7	> 0.999[a]
	M1	0	0.0	4	4.3	
Lymph node positivity	Negative	19	100.0	70	76.1	0.012[a]
	Positive	0	0.0	22	23.9	

[a] Fisher's exact test.

significant difference between *PPARG* staining and multifocality or multicentricity ($p > 0.05$).

The ultrasonographic characteristics of tumour nodules were investigated according to the American Thyroid Association (ATA) Guideline for thyroid nodule sonographic patterns and estimated risk of malignancy. *PPARG*-positive tumours were found to be more related with low-to-moderate risk nodules ($p = 0.009$) (Fig. 4).

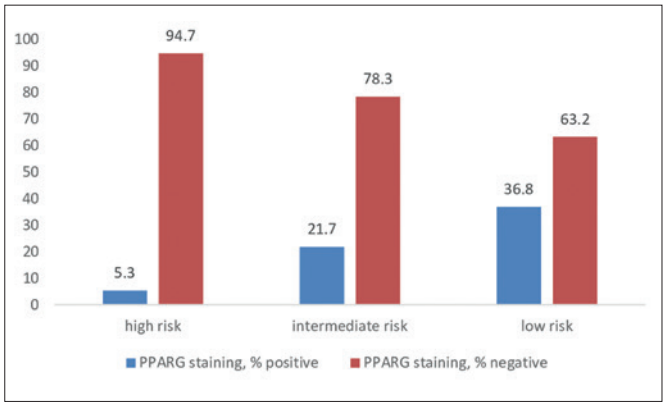

Figure 4. Relationship between PPARG staining and ATA nodule sonographic patterns and risk of malignancy.

Discussion

PPARG staining was detected in 19 of 111 cases studied herein. Sixteen of the patients with *PPARG* overexpression had PTC (9 follicular variant, 3 oncocytic variant, 2 classical variant, 1 solid variant and 1 Warthin-like variant), and 3 patients had FA.

Even though nuclear staining of *PPARG* has been found to be meaningful in recent studies [6,8], 18 of our cases showed cytoplasmic staining as well. The antibody used in the immunohistochemistry was a monoclonal antibody which means it has less background staining and higher specificity for the target compared to polyclonal antibodies. Omental tissues of non-PTC cases were used as external controls, and perithyroidal fat tissues were used as internal controls to compare and adjust the staining (Figs. 1-3). Despite these calibrations and adjustments, the difference in the brands and clones of the antibodies might have affected these results. This might also explain the confusing results in the current literature. One might consider that mitochondrial rich cells can show background staining as their organelle burden is too high, but only 3 of the positive cases were oncocytic PTCs, so this cannot explain the cytoplasmic staining (Figs. 1-3). According to the Human Protein Atlas [9] results, *PPARG* immunohistochemical staining is seen in the nucleus as well as in cytoplasmic/membranous parts of thyroid cancer cells. As a result, cytoplasmic staining in our cases might be interpreted as a verification or new contribution to the literature.

As far as we can determine from the literature, *PPARG* overexpression has been detected in FTC, FVPTC and FA, but there is no study showing *PPARG* overexpression in PTC other than in the follicular variant. Thus, in our study we demonstrated *PPARG* overexpression in both FVPTC and other variants of PTC with IHC. In a study by Nikiforov et al., *PPARG* overexpression was found in FTC and FA, but not detected in PTC [6]. In that study, the authors pointed out that *PAX8/PPARG* translocation may be specific to follicular lesions of the thyroid gland and may be used as a molecular marker. In addition, it was reported that FTC cases with this translocation showed a more aggressive growth pattern and more vascular invasion [6]. In a study by Wreesmann et al., *PPARG* overexpression was detected in FVPTC as well as in FTC and FA [10]. In that study, an immunohistochemical analysis of *PPARG* monoclonal antibody was performed, and *PPARG* overexpression was detected in 2 of 3 patients with FTC, in 8 of 11 patients with FA and in 3 of 17 cases with FVPTC, but not detected in any of the 25 cases with the classical variant of PTC. In our study, *PPARG* overexpression was detected in some cases with FA, as in the literature, but, in contrast, there was no overexpression in the 2 FTC cases in our database. *PPARG* overexpression in FVPTC has been shown in some studies but not in others, while it was observed in 9 of 28 patients with FVPTC in our study. In contrast to what is known in the literature, *PPARG* overexpression was also found in PTC variants other than the follicular variant in our series.

Although the immunohistochemical detection of *PPARG* overexpression in tumour cells may be a sign of *PAX8/PPARG* translocation, a definitive diagnosis is established by RT-PCR or FISH. In addition, Nikiforova et al. reported that they detected PAX8/PPARG rearrangement in all tumours that stained diffuse and strong with PPARG monoclonal antibody, but not in patients with focal or weak staining [6]. In the context of that study, we detected diffuse and strong cytoplasmic staining with *PPARG* monoclonal antibody in three cases, which may be a sign with the translocation being found in 1 patient with FA, 1 patient with the PTC oncocytic variant, and 1 patient with the PTC solid variant. In contrast, Lacroix et al. found that in the 17 FTCs in which no PAX8/PPARG translocation was found, nuclear staining with PPARG monoclonal antibody was diffusely positive and intense in five samples [11].

Vascular invasion ($p = 0.039$), lymphatic invasion ($p = 0.019$), thyroid capsule invasion ($p = 0.002$) and lymph node positivity ($p = 0.012$) were found to be lower in PTC patients with PPARG overexpression than in PTC patients without overexpression. This suggests that PTCs with *PPARG* overexpression may be associated with less aggressive behaviour in terms of the pathological prognostic parameters. In the study by Nikiforova et al., it was found that thyroid capsule invasion, extrathyroidal soft tissue invasion and vascular invasion were more common in FTC cases with PPARG overexpression [6]. However, in our study we had only two cases of FTC and there was no staining with these two cases. Galusca et al. reported that PTCs

with lymph node metastasis showed a significantly higher percentage of PPARG-positive cases than those without, and they highlighted that PPARG expression might be related to tumour progression [8]. Contrary to the two aforementioned studies, Lacroix et al. found no relationship between PAX8-PPARG rearrangement and the clinical status of patients such as age, TNM stage and radioactive iodine uptake [11].

In 12 of the 111 patients in our study, variable degrees of immunoreactivity were observed with *PPARG* in the non-tumoural thyroid parenchyma. In 2 of those cases, immunoreactivity together with non-tumour thyroid parenchyma was observed in tumour cells, while in other cases immunoreactivity was observed only in non-tumour thyroid tissue. Among the cases with varying degrees of immunoreactivity in the non-tumoural areas, 6 had lymphocytic thyroiditis, 1 had nodular hyperplasia, 1 had Hashimoto's thyroiditis and 1 had Graves' disease, while 3 had staining in normal thyroid tissue. Similarly, in the study by Nikiforova et al. moderate or strong immunoreactivity with *PPARG* was observed in some cases with Hashimoto's thyroiditis. This condition was attributed to the probability of wild-type *PPARG* expression in these areas [6].

Well-differentiated thyroid cancer is usually treated surgically, with radioactive iodine therapy as needed, as well as thyroid stimulating hormone suppression [12-14]. In case of recurrence, repeated radioiodine administration may be beneficial when the tumour takes radioiodine [15,16]. In cases refractory to radioiodine therapy, palliation of local symptoms can be achieved by external beam radiotherapy with or without a multikinase inhibitor [17-20]. Because thyroid cancer is a chemotherapy refractory disease [21], new agents or new treatment modalities are necessary to treat patients with radioiodine refractory metastatic disease in thyroid carcinoma. Pioglitazone is an antidiabetic agent used to treat type 2 diabetes through *PPARG* [22]. A study investigating the efficacy of pioglitazone in thyroid carcinoma in a transgenic mouse model with *PAX8/PPARG* translocation was conducted by Dobson et al. [23]. In that study, it was reported that pioglitazone transdifferentiated thyroid tumour cells containing *PAX8/PPARG* fusion protein (*PPFP*) to adipocyte-like cells, decreased tumour size and prevented metastatic disease. In light of the possible effect of pioglitazone in animal models, it was thought that pioglitazone might have an effect on human thyroid tumour cells harboring *PPFP*. In a phase 2 multicentre study investigating the efficacy of pioglitazone in patients with progressive thyroid cancer refractory to RAI treatment, *PPFP* was detected in only 1 patient [24]. That patient had a 6 cm painful metastatic focus at the right acetabulum, had thyroglobulin levels above the thousands and had to use a wheelchair. Despite receiving 30 Gy external beam radiotherapy in 10 fractions, the patient showed no improvement [17]. In that study, pioglitazone decreased the size of the metastatic lesion, decreased the level of thyroglobulin in the patient with *PPARG* overexpression and decreased pain related to metastatic disease.

Well-differentiated thyroid cancers respond well to surgical treatment. Radioactive iodine treatment is very effective in treating both local and distant metastases after surgical treatment and in relapses. Although well-differentiated thyroid cancers respond superbly to surgical treatment and radioactive iodine therapy, new treatment modalities are needed in patients with progressive disease refractory to radioactive iodine. The response to pioglitazone of the patient with a radioactive iodine refractory progressive thyroid carcinoma harbouring *PPFP* [24] shows the importance of molecular pathways in thyroid cancers and suggests possible new treatment modalities in selected cases.

Conclusions

In our study, *PPARG* overexpression was detected with IHC in FA and in some variants of PTC, including the follicular, classical, solid, oncocytic and Warthin-like variants. *PPARG* overexpression in PTC was found to be associated with less lymphovascular invasion, less thyroid capsule invasion and less lymph node metastasis. PTC cases with cytoplasmic or nuclear immunohistochemical overexpression of *PPARG* monoclonal antibody might be good candidates to further analyse *PAX8/PPARG* translocations with PCR-based methods, if necessary.

Conflict of interest statement

The authors declare no conflict of interest.

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Authors' contributions

All authors contributed in design, data collection and processing, analysis, literature review, writing and critical review.

Ethical consideration

The study was approved by Marmara University Medical Faculty Ethics Committee for Clinical Research (Approval number 09.2017.489 on 14/07/2017).

The research was conducted ethically, with all study procedures being performed in accordance with the require-

ments of the World Medical Association's Declaration of Helsinki.

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