აღნიშნება მსოფლიო მოსახლეობის 1%-ს. მისი ეტიოლოგია ჰეტეროგენურია და მოიცავს გენეტიკურ, სტრუქტურულ და მეტაბოლურ მიზეზებს, თუმცა ზოგ შემთხვევებში მისი პათოგენეზი უცნობია. უკანასკნელი 20 წლის მანძილზე აქტიურად მიმდინარეობს კვლევები ანთების, როგორც ეპილეფსიის შესაძლო მექანიზმის განხილვის შესახებ. ჩატარებული ექსპერიმენტული მოდელებით დამტკიცდა ანთების როლი ანგიოგენეზსა და ეპილეპტოგენეზში, თუმცა კლინიკურ ეპილეპტოლოგიაში ამ თვალსაზრისით კვლევები საკმაოდ მცირეა. პედიატრიული ეპილეფტოლოგიის განსაკუთრებით მნიშვნელოვან ნაწილს წარმოადგენს ეპილეფსიური ენცეფალოპათიები, რადგან ამ დროს განვითარებული გულყრები მნიშვნელოვან ნეგატიურ ზეგავლენას ახდენს ბავშვის არა მარტო მოტორულ, არამედ კოგნიტურ განვითარებაზეც. გარდა ამისა, ეპილეფსიური ენცეფალოპათიების დროს აღმოცენებული გულყრების მართვა ძალზე ძნელია, რადგან ისინი ხასიათდება მაღალი რეზისტენტობით ანტიეპილეფსიური მკურნალობისადმი. შესაბამისად, ყველა ეტიოლოგიური ფაქტორი, რომელიც შესაძლოა მონაწილეობდეს ეპილეფსიური ენცეფალოპათიის განვითარებაში საჭიროებს მნიშვნელოვან შესწავლას.

კვლევის მიზანს წარმოადგენდა პროინფლამატორული ციტოკინების შესწავლა სხვადასხვა სახის ეპილეფსიის დროს ბავშვებში.

შესწავლილია 0-დან 16 წლამდე ასაკის 56 ბავშვი: 20 - საკონტროლო ჯგუფიდან, 20 - წამალდაქვემდებარებული გულყრებით, ხოლო 16 - რეზისტენტული ეპილეფსიით. სისხლის შრატში განისაზღვრა შემდეგი პროინფლამატორული ციტოკინების კონცენტრაცია: VCAM-1, CCL2, CCL3, CCL11 და მათი კონცენტრაციის კავშირი გულყრების განმეორების სიხშირესთან. დადგინდა, რომ როგორც საკონტროლო, ისე საკვლევი ჯგუფის იმ პირებში, რომელთაც აღენიშნებოდათ წამალდაქვემდებარებული გულყრები, ყველა მათგანის კონცენტრაცია იყო ნორმის ფარგლებში, ხოლო CCL11 იყო ნორმული კონცენტრაციით საკონტროლო ჯგუფსა და წამალდაქვემდებარებულ პირებში, მისი კონცენტრაცია კი მნიშვნელოვნად იყო მომატებული ბავშვებში რეზისტენტული ეპილეფსიით. შესაბამისად, პროინფლამატორული ციტოკინები შესაძლოა განვიხილოთ, როგორც მნიშვნელოვანი ეტიოლოგიური ფაქტორი რეზისტენტული ეპილეფსიების, მათ შორის ეპილეფსიური ენცეფალოპათიების დროს. აღნიშნული შესაძლოა გახდეს ახალი, დამხმარე თერაპიული საშუალებების შექმნის საფუძველი ანტიეპილეფსიურ პრეპარატებთან ერთად.

DISTRIBUTION OF STEM CELLS IN DIFFERENT THYROID LESIONS IN PATIENTS OF REPRODUCTIVE, MENOPAUSAL AND POST-MENOPAUSAL AGE

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Several lines of evidence show that cancer stem cells (CMC) play the major role in the progression and therapy resistance in various tumor types [1]. CSCs are characterised with the similarity to normal stem cells, including their ability for self-renewal and differentiation, which gives rise to heterogeneous cancer cells [1]. There are many different markers which are associated with CSCs, including CD44, which represents one of the important markers of CSCs. CD44 is the glycoprotein which is encoded by CD44 gene [2]. CD44 is widely distributed in normal adult and foetal tissues. In normal tissues CD44 regulates the hyaluronic metabolism, wound healing and keratinocyte proliferation [2]. In vitro studies also have shown that CD44 causes the increase of metastatic potential of different cell lines. However, the role of CD44 in the development of metastases in human malignancies is still under investigation [2]. In addition, there is less known about the distribution of CD44 in different types of inflammatory, premalignant and malignant lesions, including the lesions of thyroid gland.

Thyroid carcinoma represents the fifth most frequent cancer in the world [3]. The frequency of thyroid cancer is higher in women between 20-55 years old. Several studies indicate that oestrogen might play and important role in the development of thyroid cancer [4], from which papillary thyroid carcinoma (PTC) represents the most frequent subtype [5]. Frequently, PTC is found in association with Hashimoto's thyroiditis [6]. However, the causal link between Hashimoto's thyroiditis and PTC is not yet clear.

The aim of our study was to investigate the distribution of CSCs, marked by CD44 in different types of thyroid lesions, in different age groups, including reproductive, menopausal and post-menopausal women. In addition, we wanted to compare the expression of CD44 with other markers of malignancy, including proliferation marker – Ki67, apoptotic marker – Bcl2 and other markers such as CK19, CD56 and ER.

Material and methods. Study included 200 formalin-fixed and paraffin-embedded tissue material from the teaching, research and diagnostic laboratory of Tbilisi State Medical University. Study material was divided into following histopathological groups: normal thyroid gland (45 cases), Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) (n=34), Hashimoto's thyroiditis (50 cases), classic papillary carcinoma (n=42), and the co-occurrence of Hashimoto's thyroiditis and papillary carcinoma (n=29). In addition, each group was divided into following three age groups: reproductive age (15-44 y), menopausal age (45-55 y) and post-menopausal age (>55 y) (according to WHO Women Health, Fact Sheet №334, Updated September 2013). The detailed distribution of patient numbers into each group is given in Table 1.

Table 1. Distribution of patients into groups

	Total n=200
Normal Thyroid Gland	
Reproductive Age	15
Menopause	15
Post-Menopause	15
NIFTP	
Reproductive Age	15
Menopause	11
Post-Menopause	8
Hashimoto's thyroiditis	
Reproductive Age	25
Menopause	15
Post-Menopause	10
PTC	
Reproductive Age	20
Menopause	14
Post-Menopause	8
Hashimoto's thyroiditis and PTC	
PTC component	
Reproductive Age	14
Menopause	9
Post-Menopause	6
Thyroiditis Component	
Reproductive Age	14
Menopause	9
Post-Menopause	6

Immunohistochemistry. 4μ FFPE tissue sections were deparaffinized in xylene, rehydrated by using serial dilutions of ethanol (96%, 80%, 70%) and heat mediated antigen retrieval has been performed. Ready to use antibodies against the following antigens were used: Ki67, BCL2, CK19, CD56, ER, CD44. Staining and visualization has been performed using Bond polymer refine detection system. The number of positive cells were counted in 20HPF and the percentage of marker positive cells were estimated. Ki67 and Bcl2 labelling index was defined as the percentage of marker positive cells. In addition, Ki67 and Bcl2 labelling index ≤3% was considered as low and >3% was considered as high. In cases of CK19, CD44 and CD56 the positivity in ≤10% cells was considered as low expression and positivity in >10% of the cells was considered as high expression. ER expression was evaluated as following: ≤10% of positive cells was considered as low expression, 11-50% of positive cells was considered as moderate expression and >50% positive cells was considered as high expression.

Comparisons between groups were made using Kruskal-Wallis test. The Kruskal-Wallis test is a nonparametric (distribution free) test, and is used when the assumptions of one-way ANOVA are not met. The Kruskal-Wallis test can be used for both continuous and ordinal-level dependent variables. Correlations were assessed using Spearman's rank correlation. The Spearman's rank correlation is also used when data is non-parametrically distributed. P values <0.05 were considered as significant. All statistical tests were performed using SPSS software V19.00.

Results and discussion. The study showed the following results: In normal thyroid gland the Ki67 labelling index was low (≤3%) in all cases 15/15 (100%) cases in all age groups. In NIFTP 12/15 (80%) cases were characterised with low and 3/15 (20%) cases were characterised with high Ki67 labelling index in reproductive age. In menopause 9/11 (81.8%) cases were characterised with low and 2/11 (17.2%) cases were characterised with high Ki67 proliferation index and in post-menopause all 8/8 (100%) cases were characterised with low Ki67 labelling index. In Hashimoto's thyroiditis 7/25 (28%) cases were characterised with low and 18/25 (72%) cases were characterised with high Ki67 labelling index in reproductive age. In menopause 6/15 (40%) cases were characterised with low and 9/15 (60%) cases were characterised with high Ki67 labelling index. In post-menopause, 3/10 (30%) cases were characterised with low and 7/10 (70%) cases were characterised with high Ki67 labelling index. In cases of papillary thyroid carcinoma 8/20 (40%) cases were characterised with low and 12/20 (60%) cases were characterised with high Ki67 labelling index reproductive age. In menopause 6/14 (42.9%) cases were characterised with low and 8/14 (37.1%) cases were characterised with high Ki67 labelling index. In post-menopause 3/8 (37.5%) cases were characterised with low and 5/8 (62.5%) cases were characterised with high proliferation index. In Hashimoto's thyroiditis and PTC co-occurred cases, 3/14 (21.4%) were characterised with low and 11/14 (78.6%) were characterised with high Ki67 labelling index in reproductive age. In menopause 2/9 (22.2%) cases

were characterised with low and 7/9 (78.8%) cases were characterised with high Ki67 labelling index and in post-menopause 2/6 (33.3%) cases were characterised with low and 4/6 (66.7%) cases were characterised with high Ki67 labelling index.

The Bcl2 labelling index was high in all cases of normal thyroid gland in all age groups. In NIFTP 5/15 (33.3%) cases were characterised with low (≤3%) and 10/15 (66.7%) cases were characterised with high (>3%) Bcl2 labelling index in reproductive age group. In menopause 4/11 (36.4%) cases were characterised with low and 7/11 (63.6%) cases were characterised with high Bcl2 labelling index. In post-menopause all 1/8 (12.5%) case was characterised with low and 7/8 (87.5%) cases were characterised with high Bcl2 labelling index. In Hashimoto's thyroiditis 19/25 (76%) cases were characterised with low and 6/25 (24%) cases were characterised with high Bcl2 labelling index in reproductive age. In menopause 11/15 (73.3%) cases were characterised with low and 4/15 (26.7%) cases were characterised with high Bcl2 labelling index and in post-menopause 5/10 (50%) cases were characterised with low and 5/10 (50%) cases were characterised with high Bcl2 labelling index. in PTC 11/20 (55%) cases were characterised with low and 9/20 (45%) cases were characterised with high Bcl2 labelling index in reproductive age. In menopause 7/14 (50%) cases were characterised with low and 7/14 (50%) cases were characterised with high Bcl2 labelling index. In Hashimoto's thyroiditis and PTC co-occurred cases, 12/14 (85.7%) cases were characterised with low and 2/14 (14.3%) cases were characterised with high Bcl2 labelling index in reproductive age. In menopause 8/9 (88.9) cases were characterised with low and 1/9 (11.1%) case were characterised with high Bcl2 labelling index. In post-menopause 6/8 (75%) cases were characterised with low and 2/8 (25%) cases were characterised with high Bcl2 labelling index (Table 2).

In all cases of normal thyroid gland CK19 expression was low (≤10%) in all age groups. In NIFTP 10/15 (66.7%) cases were characterised with low CK19 expression and 5/15 (33.3%) cases were characterised with high CK19 expression in reproductive age. In menopause 8/11 (72.7%) cases were characterised with low and 3/11 (27.3%) cases were characterised with high CK19 expression. In post-menopause 5/8 (62.5%) cases were characterised with low and 3/8 (37.5%) cases were characterised with high CK19 expression. In Hashimoto's thyroiditis 19/25 (76%) cases were characterised with low and 6/25 (24%) cases were characterised with high CK19 expression in reproductive age. In menopause 11/15 (73.3%) cases were characterised with low and 4/15 (26.7%) cases were characterised with high CK19 expression. In post-menopause 7/10 (70%) cases were characterised with low and 3/10 (30%) cases were characterised with high CK19 expression. In PTC all cases were characterised with high expression of CK19 in all groups, as well as in Hashimoto's thyroiditis and PTC co-occurred cases.

In all cases of normal thyroid gland CD56 expression was high (>10%). In NIFTP 8/15 (53.3%) cases were characterised with the low expression of CD56 and 7/15 (46.7%) cases were characterised with high expression of CD56 in reproductive age. In menopause 6/11 (54.5%) cases were characterised with low expression of CD56 and 5/11 (45.5%) cases were characterised with high expression of CD56. In post-menopause 5/8 (62.5%) cases were characterised with low expression of CD56 and 3/8 (37.5%) cases were characterised wit high expression of CD56. In Hashimoto's thyroiditis 5/25 (20%) cases were characterised with low and 20/25 (80%) cases were characterised with high CD56 expression in reproductive age. In menopause, 3/15 (20%) cases were characterised with low and 12/15 (80%) cases were characterised with high expression of CD56. In post menopause 2/10 (20%) cases were characterised with low and 8/10

Table 2. The distribution of proliferation and apoptosis markers in study groups

	Total N	**Ki67**		**Bcl2**	
Normal Thyroid Gland		**Low ≤3**	**High >3**	**Low ≤3**	**High >3**
Reproductive Age	15	15	0	0	15
Menopause	15	15	0	0	15
Post-Menopause	15	15	0	0	15
NIFTP					
Reproductive Age	15	12	3	5	10
Menopause	11	9	2	4	7
Post-Menopause	8	8	0	1	7
Hashimoto's thyroiditis					
Reproductive Age	25	7	18	19	6
Menopause	15	6	9	11	4
Post-Menopause	10	3	7	5	5
PTC					
Reproductive Age	20	8	12	11	9
Menopause	14	6	8	7	7
Post-Menopause	8	3	5	6	2
Hashimoto's thyroiditis and PTC					
Reproductive Age	14	3	11	12	2
Menopause	9	2	7	8	1
Post-Menopause	6	2	4	5	1

Table 3. The distribution of CK19 and CD56 in study groups

	Total N	CK19		CD56	
Normal Thyroid Gland		**Low ≤ 10**	**High >10**	**Low ≤ 10**	**High >10**
Reproductive Age	15	15	0	0	15
Menopause	15	15	0	0	15
Post-Menopause	15	15	0	0	15
NIFTP					
Reproductive Age	15	10	5	8	7
Menopause	11	8	3	6	5
Post-Menopause	8	5	3	5	3
Hashimoto's thyroiditis					
Reproductive Age	25	19	6	5	20
Menopause	15	11	4	3	12
Post-Menopause	10	7	3	2	8
PTC					
Reproductive Age	20	0	20	20	0
Menopause	14	0	14	14	0
Post-Menopause	8	0	8	8	0
Hashimoto's thyroiditis and PTC					
Reproductive Age	14	0	14	14	0
Menopause	9	0	9	9	0
Post-Menopause	6	0	6	6	0

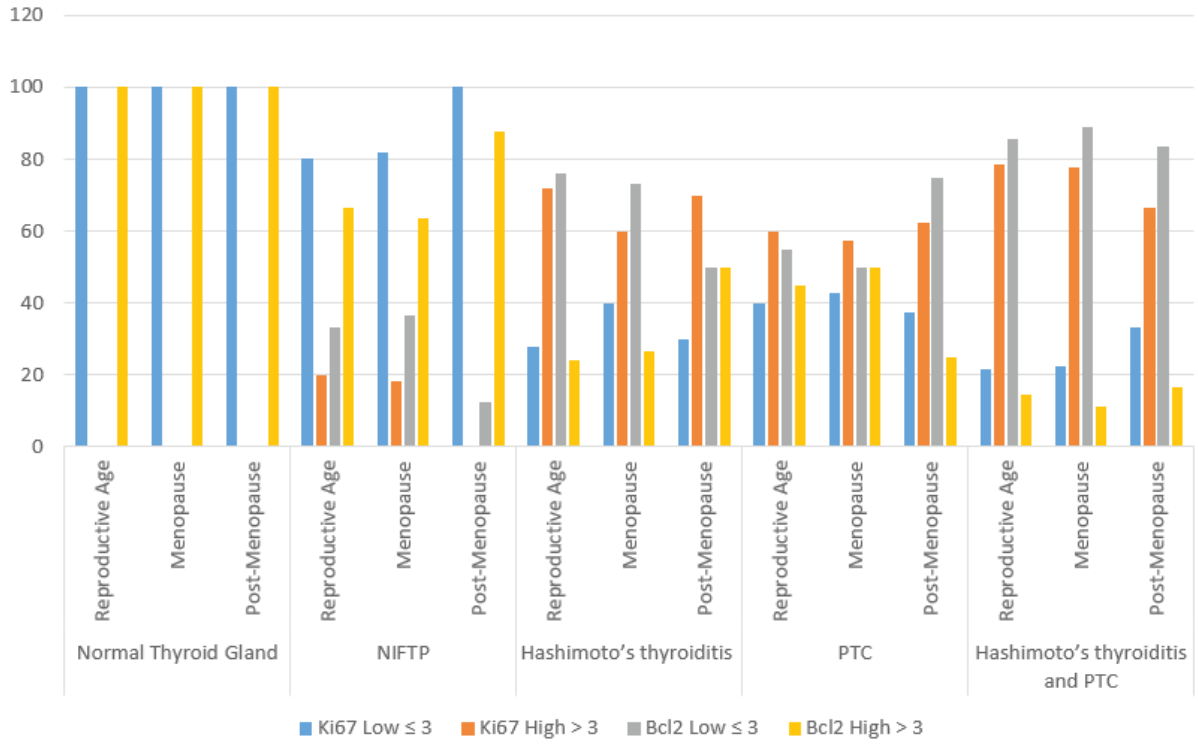
(80%) cases were characterised with high expression of CD56. In PTC all cases were negative for CD56 in all groups, as well as in Hashimoto's thyroiditis and PTC co-occurred cases (Table 3).

CD44 was characterised with low expression (≤10%) in 8/15 (53.3%) cases and it was negative in 7/15 (46.7%) cases in reproductive age. In menopause, low expression of CD44 was detected in 6/15 (40%) cases and in post-menopause 4/15 (26.7%) cases. The rest of the cases were negative. In NIFTP, in reproductive age 6/15 (40%) cases showed low and 9/15 (60%) cases showed high CD44 expression. In menopause 4/15 (26.7%) cases showed low and 7/15 (46.7%) cases showed high expression, 3/15 (20%) cases were negative. In post-menopause 2/10 (20%) cases showed low expression and 8/10 (80%) cases were negative. In Hashimoto's thyroiditis in reproductive age 5/25 (20%) cases showed low and 6/25 (24%) cases showed high expression of CD44, 14/25 (56%) cases were negative. In menopause 2/15 (13.3%) cases showed low and 2/15 (13.3%) cases showed high expression, whilst 11/15 (73.3%) cases were negative for CD44. In post-menopause 2/10 (20%) cases showed low expression and 8/10 (80%) cases were negative for CD44. In PTC, in reproductive age 2/20 (10%) cases showed low expression and 14/20 (70%) cases showed high expression of CD44 whilst 4/20 (20%) cases were negative. In menopause 1/14 (7.14%) case showed low and 6/14 (42.9%) cases showed high expression of CD44, whilst 7/14 (50%) cases were negative. In post-menopause 1/8 (12.5%) case showed low and 4/8 (50%) cases showed high expression of CD44, whilst 3/8 (37.5%) cases were negative. In Hashimoto's thyroiditis and PTC co-occurred cases, in reproductive age 2/14 (14.3%) cases showed low and 12/14 (85.7%) cases showed high expression of CD44. In menopause 1/9 (11.1%) case showed low and 8/9 (88.9%) cases showed high expression of CD44. In post-menopause 2/6 (33.3%) cases showed low and 2/6 (33.3%) cases showed high expression of CD44, whilst 2/6 (33.3%) cases were negative.

In normal thyroid gland in reproductive age 10/15 (66.7%) cases showed low and 5/15 (33.3%) cases showed moderate ER expression. In menopause 12/15 (80%) case showed low and 3/15 (20%) cases showed moderate ER expression. In post-menopause 13/15 (86.6%) cases showed low and 2/15 (13.4%) cases showed moderate ER expression. In NIFTP, in reproductive age, 10/15 (66.7%) cases showed moderate and 5/15 (33.3%) cases showed high ER expression. In menopause 9/11 (81.8%) cases showed moderate and 2/11 (18.1%) cases showed high ER expression, in post-menopause 7/8 (87.5%) cases showed moderate and 1/8 (12.5%) cases showed high ER expression. In Hashimoto's thyroiditis, in reproductive age 11/25 (44%) cases showed low and 14/25 (56%) cases showed moderate ER expression. In menopause 9/15 (60%) cases showed low and 6/15 (40%) cases showed moderate ER expression. In post-menopause 7/10 (70%) cases showed low and 3/10 (30%) cases showed moderate ER expression. In PTC, in reproductive age 9/20 (45%) cases showed low, 5/20 (25%) cases showed moderate and 6/20 (35%) cases showed high ER expression. In menopause 7/14 (50%) cases showed low, 3/14 (21.4%) cases showed moderate and 4/14 (28.6%) cases showed high ER expression. In post-menopause 4/8 (50%) cases showed low, 2/8 (25%) cases showed moderate and 2/8 (25%) cases showed high ER expression. In Hashimoto's thyroiditis and PTC co-occurred cases, in reproductive age 2/14 (14.3%) cases showed low, 7/14 (50%) cases showed moderate and 5/14 (35.7%) cases showed high ER expression. In menopause 4/9 (44.4%) cases showed low, 3/9 (33.3%) cases showed moderate and 2/9 (22.2%) cases showed high ER expression. In post-menopause 3/6 (50%) cases showed low, 2/6 (33.3%) cases showed moderate and 1/6 (16.7%) case showed high ER expression (Table 4).

Table 4. The distribution of stem cell marker CD44 and ER in study groups

	Total N	CD44		ER		
Normal Thyroid Gland		**Low ≤ 10**	**High >10**	**Low ≤ 10**	**Medium 10-49**	**High >50**
Reproductive Age	15	8	0	10	5	0
Menopause	15	6	0	12	3	0
Post-Menopause	15	4	0	13	2	0
NIFTP						
Reproductive Age	15	6	9	0	10	5
Menopause	11	4	7	0	9	2
Post-Menopause	8	3	5	0	7	1
Hashimoto's thyroiditis						
Reproductive Age	25	5	6	11	14	0
Menopause	15	2	2	9	6	0
Post-Menopause	10	2	0	7	3	0
PTC						
Reproductive Age	20	2	14	9	5	6
Menopause	14	1	6	7	3	4
Post-Menopause	8	1	4	4	2	2
Hashimoto's thyroiditis and PTC						
Reproductive Age	14	2	12	2	7	5
Menopause	9	1	8	4	3	2
Post-Menopause	6	2	2	3	2	1



Graph 1. The distribution of Proliferation and apoptosis markers in groups

The analysis of proliferation and apoptotic markers showed that normal thyroid gland is characterised with an extremely low proliferation activity, whilst apoptotic activity is mostly high. The highest proliferation activity is detected in PTC cases in reproductive age, whilst in the same group the apoptotic activity is low. Interestingly the proliferation index was higher in PTC and Hashimoto's thyroiditis co-occurred cases, compared to PTC only. The apoptotic index was also lower in PTC and Hashimoto's thyroiditis co-occurred cases compared to only PTC.

The analysis of CK19 and CD56 showed that all PTC cases are characterised with the loss of CD56 in all age groups. With regards to CK19 the highest expression was seen in PTC in reproductive age. The loss of CD56 was also present in some thyroiditis component in cases with Hashimoto's thyroiditis and PTC.

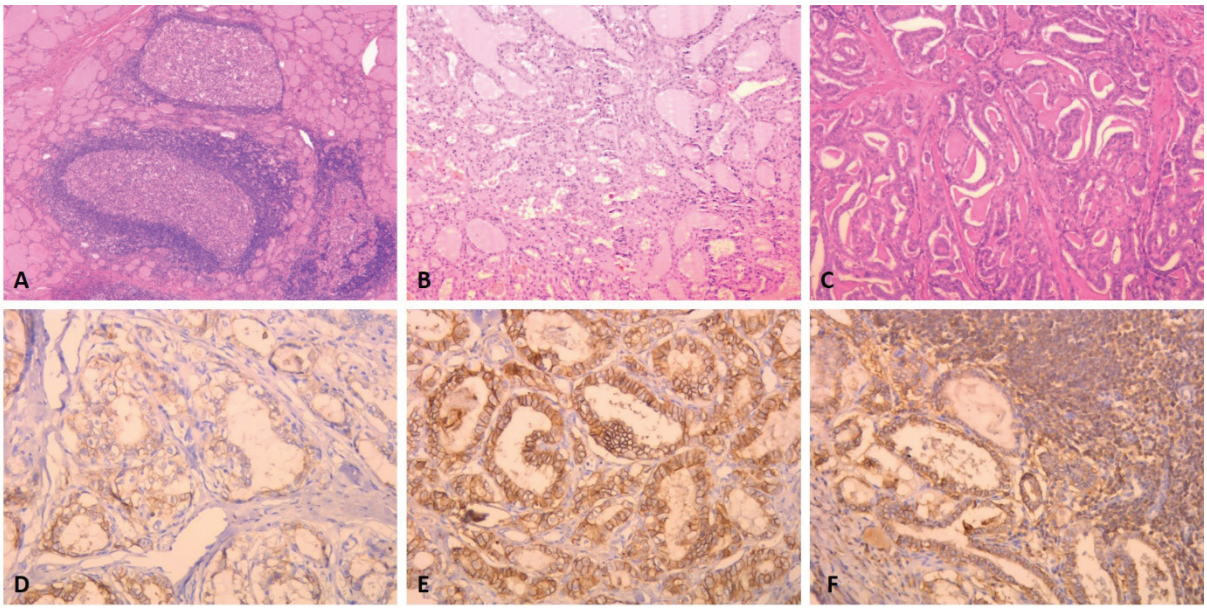
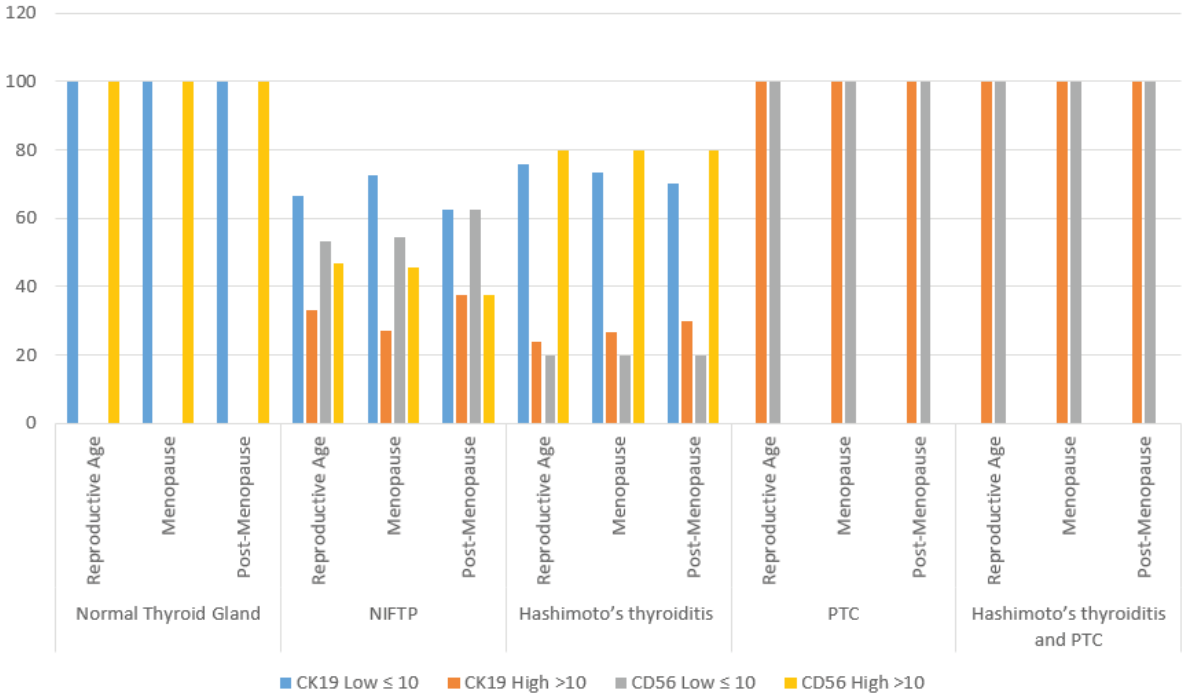
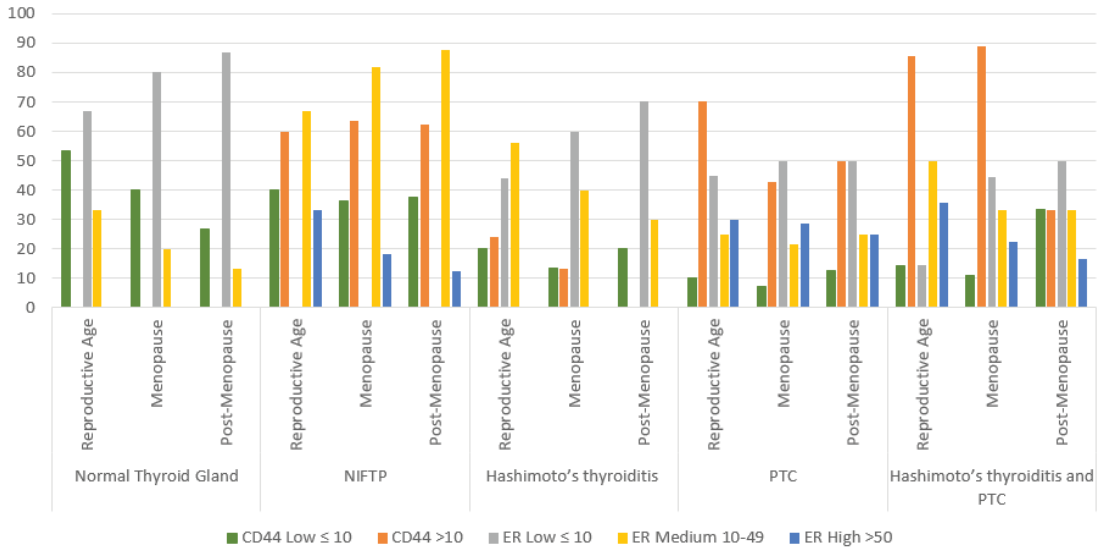


Fig. 1. A. Hashimoto's thyroiditis, B. NIFTP, C. Papillary thyroid cancer, H&E, x200; D. CD44 weak expression in PTC, E. CD44 strong expression in PTC and F. CD44 Strong expression in PTC and Hashimoto's thyroiditis co-occurred cases, IHC, x200



Graph 2. The distribution of CK19 and CD56 in study groups

The analysis of stem cell marker CD44 in groups showed that the highest expression of CD44 is present in PTC in reproductive age. CD44 expression is also relatively higher in PTC and Hashimoto's thyroiditis co-occurred cases, compared to only PTC cases in reproductive age. The lowest expression of CD44 is seen in patients with post-menopause in the same groups. The analysis of ER expression, also showed that the highest expression of ER is present in PTC cases, in reproductive age and in Hashimoto's thyroiditis and PTC co-occurred cases.



Graph 3. The distribution of CD44 and ER in study groups

The correlation analysis indicated that CD44 expression positively correlates with the expression of ER in all groups ($r=0.37$, $p<0.05$). In addition, the expression of CD44 is positively associated with the Ki67 labelling index ($r=0.033$, $p<0.05$) and negatively associated with the apoptotic index, measured as Bcl2 expression ($r=-0.025$, $p<0.05$).

The analysis of marker expression in different age groups indicated that the expression of CK19 and CD56 does not differ significantly in reproductive, menopausal and post-menopausal age patients. However, the expression of Ki67 is significantly higher in reproductive age patients, compared to menopausal and post-menopausal patients in all groups. Whilst Bcl2 is significantly lower in reproductive age patients, compared to menopausal and post-menopausal patients in all groups. CD44 is also significantly higher in patients in reproductive age in all study groups, compared to patients with menopausal and post-menopausal age. ER expression is significantly higher in reproductive age in all groups as well.

Kiziridou and colleagues investigated the expression of the CD44 in different types of thyroid lesions by immunohistochemistry[7]. The results of their study showed the increased expression of CD44 in papillary thyroid carcinoma, similar to our study results. In addition, Kim at all, also demonstrated the increased expression of CD44 in thyroid papillary carcinoma[8]. However, with the difference from our study they did not find a significant correlation between CD44 and Ki67, which might be explained by the difference in study cohorts. To the best of our knowledge, we are first who studied the stem cell marker expression in PTC and in PTC/Hashimoto's thyroiditis co-occurred cases. The results of our study indicates that the expression of CD44 is markedly higher in PTC/Hashimoto's thyroiditis co-occurred cases, compared to cases with PTC only. Previous analysis from Tang et al., indicated that Ki67 represents an important marker which can distinguish malignant from benign thyroid lesions[9]. Indeed, in our study we have also found a significant upregulation of Ki67 in PTC cases and especially in cases with PTC and Hashimoto's thyroiditis co-occurrence.

Conclusions. The results of our study indicates that CD44 stem cell marker, as well as proliferation marker Ki67 is significantly upregulated in PTC cases in all age groups. However, the expression of CD44 and Ki67 is significantly higher in reproductive age patients, compared to patients in menopause and post-menopause. In addition, the expression of CD44 and Ki67 is significantly higher in PTC and Hashimoto's thyroiditis co-occurred cases, compared to cases with PTC only.

REFERENCES

1. Ayob A.Z., Ramasamy T.S. Cancer stem cells as key drivers of tumour progression.// J. Biomed. Sci. 2018; 25(1): 20.
2. Senbanjo L.T., Chellaiah M.A. CD44: A Multifunctional Cell Surface Adhesion Receptor Is a Regulator of Progression and Metastasis of Cancer Cells. // Front. cell Dev. Biol. 2017; 5; 18.
3. Siegel R.L., Miller K.D., Jemal A. Cancer statistics, 2019. CA. // Cancer J. Clin. 2019; 69(1): 7–34.
4. Derwahl M., Nicula D. Estrogen and its role in thyroid cancer. // Endocr. Relat. Cancer 2014; 21(5): T273–T283.
5. Gilmartin A., Ryan M. Incidence of Thyroid Cancer among Patients with Thyroid Nodules. Ir. Med. J. 2018; 111(8): 802.
6. Graceffa G. et al. Association between Hashimoto's thyroiditis and papillary thyroid carcinoma: a retrospective analysis of 305 patients. // BMC Endocr. Disord. 2019; 19(1): 26.
7. Kiziridou A., Pantidou A., Destouni C., Toliou T. Immunohistochemical expression of CD44 in thyroid gland lesions. // Arch. Oncol. 2003; 11(1): 5–8.
8. Jung Y. Kim, J. Yoo, and H. Cho. Preferential Expression of CD44 in Thyroid Papillary Carcinoma. // J Pathol Transl Med .2001; 35(4): 314–318.
9. Tang J., Gui C., Qiu S., Wang M. The clinicopathological significance of Ki67 in papillary thyroid carcinoma: a suitable indicator? // World J. Surg. Oncol. 2018; 16(1): 100.

SUMMARY

DISTRIBUTION OF STEM CELLS IN DIFFERENT THYROID LESIONS IN PATIENTS OF REPRODUCTIVE, MENOPAUSAL AND POST-MENOPAUSAL AGE

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Different studies indicate that cancer stem cells (CSCs) play an important role in the progression and therapy resistance in

different cancer types. The aim of our study was to analyse the distribution of CSCs in different thyroid lesions, in reproductive, menopausal and post-menopausal women. Study included altogether 200 formalin-fixed and paraffin-embedded tissue material, with the diagnosis of NIFTP, Hashimoto's thyroiditis, papillary thyroid carcinoma (PTC) and PTC and Hashimoto's thyroiditis co-occurred cases. Normal thyroid gland was used as a control tissue. Stem cell marker – CD44, as well as other markers including Ki67, BCL2, CK19, CD56, ER were investigated with standard immunohistochemical procedure.

The results of our study indicated that CD44 stem cell marker, as well as proliferation marker Ki67 is significantly upregulated in PTC cases in all age groups. However, the expression of CD44 and Ki67 is significantly higher in reproductive age patients, compared to patients in menopause and post-menopause. In addition, the expression of CD44 and Ki67 is significantly higher in PTC and Hashimoto's thyroiditis co-occurred cases, compared to cases with PTC only.

Keywords: thyroid lesions, cancer stem cells, expression of CD44 and Ki67, CD44 stem cell marker, proliferation marker Ki67, papillary thyroid carcinoma.

РЕЗЮМЕ

ОСОБЕННОСТИ РАСПРЕДЕЛЕНИЯ СТВОЛОВЫХ КЛЕТОК В РАЗЛИЧНЫХ ПАТОЛОГИЯХ ЩИТОВИДНОЙ ЖЕЛЕЗЫ У ЖЕНЩИН РЕПРОДУКТИВНОГО, МЕНО- И ПОСТМЕНОПАУЗАЛЬНОГО ВОЗРАСТА

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Ранее проведенными исследованиями показано, что опухолевые стволовые клетки играют значимую роль в прогрессии опухолей и в их резистентности к лечению.

Целью исследования явилось изучение особенностей распределения стволовых клеток при различных патологиях щитовидной железы у женщин репродуктивного, мено- и постменопаузального возраста.

Исследование включало 200 фиксированных в формалине и залитых в парафиновые блоки тканевых образцов со следующими гистопатологическими диагнозами: фолликулярная тиреоидная неоплазия с ядерными признаками, напоминающими папиллярную карциному, тиреоидит Хашимото, папиллярная карцинома, папиллярная карцинома в сочетании с тиреоидитом Хашимото. В качестве контрольной группы использованы образцы нормальной щитовидной железы. Стандартным иммуногистохимическим методом изучен маркер стволовых клеток CD44, а также молекулярные маркеры Ki67, BCL2, CK19, CD56 и ER.

Результаты исследования показали, что эксперссия маркеров CD44 и Ki67 значительно увеличивается в случаях карцином, это увеличение значительно выше при папиллярных карциномах в сочетании с тиреоидитом Хашимото. Экспрессия этих маркеров выше в репродуктивном возрасте в сравнении с мено- и постменопаузальным возрастом. Полученные результаты могут быть использованы в клиническом менеджменте женщин с данными патологиями с учетом их возраста.

რეზიუმე

ღეროვანი უჯრედების განაწილების თავისებურებანი ფარისებრი ჯირკვლის სხვადასხვა პათოლოგიებში რეპროდუქციული, მენოპაუზური და პოსტმენოპაუზური ასაკის ქალებში

თ.მუზაშვილი, მ.გაჩეჩილაძე, გ.ბურკაძე

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

სხვადასხვა კვლევებით ნაჩვენებია, რომ სიმსივნის ღეროვანი უჯრედები მნიშვნელოვან როლს თამაშობენ ავთვისებიანი სიმსივნეების პროგრესიასა და მკურნალობისადმი რეზისტენტობაში.

კვლევის მიზანს შეადგენდა ღეროვანი უჯრედების განაწილების თავისებურებების შესწავლა ფარისებრი ჯირკვლის სხვადასხვა ტიპის დაზიანებებში, რეპროდუქციული, მენოპაუზური და პოსტმენოპაუზური ასაკის ქალებში.

საკვლევი ჯგუფი მოიცავდა 200 ფორმალინში დაფიქსირებულ და პარაფინში ჩაყალიბებულ ქსოვილოვან ბლოკს, შემდეგი ჰისტოპათოლოგიური დიაგნოზებით: ფოლიკულური თირეოიდული ნეოპლაზია პაპილური კარცინომის მსგავსი ბირთვული მახასიათებლებით, ჰაშიმოტოს თირეოიდიტი, პაპილური კარცინომა და პაპილური კარცინომის და ჰაშიმოტოს თირეოიდიტის თანაარსებული შემთხვევები. საკონტროლო ჯგუფად აღებული იყო ფარისებრი ჯირკვლის ნორმალური ქსოვილი. სტანდარტული იმუნოჰისტოქიმიური მეთოდით გამოვლენილია ღეროვანი უჯრედების მარკერი - CD44, ასევე Ki67, BCL2, CK19, CD56 და ER.

კვლევის შედეგებმა აჩვენა, რომ CD44-ის და Ki67-ის ექსპრესია მნიშვნელოვნად არის მომატებული კარცინომის შემთხვევებში. ამასთან იგი გაცილებით უფრო მაღალია პაპილური კარცინომის და ჰაშიმოტოს თირეოიდიტის თანაარსებობისას. გარდა ამისა, აღნიშნული მარკერების ექსპრესია მაღალია რეპროდუქციულ ასაკში მენოპაუზურ და პოსტმენოპაუზურ ასაკთან შედარებით. ჩატარებული კვლევის შედეგები შესაძლებელია გამოყენებულ იქნას აღნიშნული პათოლოგიებით ქალების კლინიკურ მენეჯმენტში მათი ასაკის გათვალისწინებით.