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EPIDEMIOLOGY AND PATHOGENSIS OF THYROID NODULES

Summary: Thyroid nodules encompass all structural tissue changes that differentiate them from a normal thyroid tissue. Palpatory detected nodules' prevalence is about 3%, echosonographicaly detected about 60%, and during autopsy thyroid nodules are detected in about 50% of the examined glands. 5% of thyroid nodules, regardless of their size, are a consequence of a thyroid gland carcinoma. In humans ionizing radiation is the only known initiator and TSH is the only known promoter of thyroid tumour development. Use of radioiodine for the treatment of hyperthyroidism is not associated with increase of thyroid malignancies. In thyroid tumours numbers of mutations are found. Most frequent mutation in papillary thyroid carcinoma is BRAF gene mutation and PTC (papillary thyroid carcinoma) gene. PTC gene originates due to translocation in which ret oncogene is attached to one of three different promoters, producing retPTC-1, retPTC-2, and retPTC-3. Fusion gene produced by fusion of the thyroid specific transcription factor PAX8 with PPARγ gene. Anaplastic carcinomas are caused by dedifferentiation of papillary of follicular carcinoma. In this carcinoma TP53 gene inactivation occurs frequently in anaplastic carcinoma. RAS mutation is often found in anaplastic carcinoma. Non-medullary thyroid carcinoma can occur as a familiar form or as a part of hereditary cancer syndrome. Scintigraphycaly hot nodules characterise constitutional activation of TSH receptor, monoclonality and point mutations, while cold nodules are characterized by dedifferentiation and polyclonality.

Key words: thyroid carcinoma, thyroid adenoma, BRAF, RET, hereditary cancer syndrome.

Thyroid nodules represent focal lesions different from the normal gland. They can be cysts, adenomas, carcinomas, or lobules of normal tissue.[1] Epidemiological

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data on thyroid nodule prevalence are critically depending on method of detection, population characteristics, especially iodine intake. Nodules whose diameter is smaller then ten millimetres are usually not palpabile.[2] Therefore, it is not unexpected that prevalence of palpable nodules is smallest.

Prevalence of thyroid nodules detected by palpation is about 3% u the whole population, 6.4% in females and 1.5% in males.[3, 4] However, echosonographic screening of the general population detects presence of the thyroid nodules in about 60% of subjects.[5] During autopsy thyroid nodules are detected in about 50% of the examined thyroid glands.[6] Thyroid nodule prevalence increases with age, iodine deficiency and exposure to ionizing radiation.[7] Thyroid nodule incidence is 100 cases per 10000 persons per year.[4] It is important to note that 5% of all thyroid nodules, regardless of size are thyroid carcinoma.[7]

Oncogenesis is a process which involves sequence of genetic and environmental events, which cause changes in the control of cell growth and differentiation. These factors are classified as initiators and promoters. In humans, ionizing radiation is the only known initiator and TSH the only known promoter of thyroid tumors.[8] Thyroid nodule and carcinoma incidence is linearly correlated with ionizing radiation doze, and increased risk is found forty years after exposition.[9, 10] Therefore safety of radioiodine treatment is questioned. Still, there is no proof that use of radioiodine for hyperthyroidism treatment increases prevalence of thyroid malignances.[8] However, use of radioiodine for the treatment of thyroid carcinoma is associated with the increased risk of leukaemia, salivary gland and digestive tract cancer, and soft-tissue and bone sarcomas. Unfortunately, very little is known about the risk of second cancers, especially in children and young adults.[11]

Thyroid follicular cells, even when they belong to the same follicle, are very heterogeneous in their thyroglobuline iodination capacity, peroxidase expression and growth capacity.[12-15] Therefore, thyroid adenomas and carcinomas have different presentations and different evolution. Thyroid carcinomas are characterised by more or less specific genetic changes, but genetic changes are also found in thyroid adenoma and goitre. Genes involved in tumorognesis are called oncogenes. Usually these genes are not active, but mutation activates them and causes transformation of the cell to malignant one. Usually activation of only one gene is not enough to cause malignancy, and expression of an oncogene is necessary. Another path to oncogenesis is inactivating mutation of a suppressor gene.

One of the most frequent mutations in papillary thyroid carcinoma is mutation of the BRAF gene. BRAF gene codes a protein that belongs to serine/treonine protein kinase and is involved in signal transduction from cell membrane to nucleus. This gene influences cell division and differentiation.[16] V600E BRAF mutation is detected in more than 50% papillary thyroid carcinomas. On the other hand, this mutation has not been detected in hypofunctioning thyroid nodules, follicular carcinomas or in the healthy thyroid tissue.[17] It is interesting to note that in 40% of multifocal pa-

pillary carcinomas discordant BRAF mutations have been found.[18] V6000E BRAF mutation positive papillary carcinomas have aggressive behaviour and unfavourable outcome.[19] Also, in papillary thyroid carcinoma PTC (papillary thyroid carcinoma) is often expressed. This oncogene is created by an intrachromosomal rearrangement of the tyrosine kinase domain of the ret oncogene so that it is attached to one of three different promoters, producing retPTC-1, retPTC-2, and retPTC-3. One of these translocation products is found in 20-70% of papillary cancers, but not in follicular, anaplastic and medullary carcinomas, nor in benign nodules.[20]

Translocation t(2;3)(q13;p25) is found in follicular carcinoma. This translocation creates fusion gene fusing thyroid specific transcription factor PAX8 with PPARγ gene[21]. However this gene is not specific as it is also found in follicular adenoma and in the follicular for of papillary carcinoma[22-24].

Anaplastic carcinoma is probably consequence of papillary and follicular cancer dediferentiation.[25] In this cancer inactivation of the TP53 gene occurs. The transcription factor p53 responds to diverse cellular stresses to regulate target genes that induce cell cycle arrest, apoptosis, DNA repair, or changes in metabolism.[26] TP53 mutations are found in 20 to 86% of anaplastic thyroid carcinoma.[27] Another, often found mutation, is RAS gene mutation which is found in 13 to 60% of anaplastic thyroid carcinoma.[27] RAS mutations are associated with very aggressive tumours and poor prognosis.[28] N-RAS mutation positive undifferentiated thyroid carcinomas have a significant propensity to haematogenous (particularly bone) metastases.[29, 30] Non-medullary thyroid carcinomas also occur in familiar forms, or associated with other tumours forming hereditary cancer syndromes (table 1).[8]

Scintigraphic classification of thyroid nodules to hot and cold also has genetic correlates. Hot nodules are characterised by constitutional activation of TSH receptor, monoclonality and point mutations. These mutations involve the extracellular loops of the transmembrane domain and the transmembrane segments, and are proven to induce hyperfunction. However these mutations are not associated with cancer formation.[31] Mutations of the stimulatory GTP binding protein subunit are also present in some patients with hyperfunctioning thyroid adenomas.[32] However, TSH receptor mutations are unusual in thyroid cancer, and persistence of TSH receptor expression is associated with a better prognosis.[33, 34] On the other hand cold nodules are associated with mutation of dedifferentiation genes. These nodules are mostly polyclonal.[27] In about 20% of cold nodules RAT proto-oncogene are found.[35, 36]

Thyroid nodules represent one of the most frequent pathologies in medicine. More than half of the population have a thyroid nodule and it is often cause of serious patient's anxiety. Contemporary genetic research has contributed to the evaluation of thyroid nodule pathogenesis and better understanding of the differences and similarities between malignant and benign alterations.

References

1. De Groot LJ, Pacini F. Thyroid Nodules. http://www.thyroidmanager.org/Chapter18/18-nodulesframe.htm 1-5-2006. 13-2-2009.
2. Tan GH, Gharib H, Reading CC. Solitary thyroid nodule. Comparison between palpation and ultrasonography. Arch Intern Med 1995; 155(22): 2418–2423.
3. Tunbridge WM, Evered DC, Hall R et al. The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf) 1977; 7(6): 481–493.
4. Vander JB, Gaston EA, Dawber TR. The significance of nontoxic thyroid nodules. Final report of a 15-year study of the incidence of thyroid malignancy. Ann Intern Med 1968; 69(3): 537–540.
5. Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Intern Med 1997; 126(3): 226–231.
6. Mortensen JD, Woolner LB, Bennett WA. Gross and microscopic findings in clinically normal thyroid glands. J Clin Endocrinol Metab 1955; 15(10): 1270–1280.
7. Gharib H, Papini E. Thyroid Nodules: Clinical Importance, Assessment, and Treatment. Endocrinol Metab Clin N Am 2007; 36(3): 707–735.
8. Pacini F, De Groot LJ. Thyroid Cancer. http://www.thyroidmanager.org/Chapter18/18-cancerframe.htm . 14-3-2008. Endocrine education Inc. 16-2-2009.
9. Maxon HR, Thomas SR, Saenger EL, Buncher CR, Kereiakes JG. Ionizing irradiation and the induction of clinically significant disease in the human thyroid gland. Am J Med 1977; 63(6): 967–978.
10. Sadetzki S, Chetrit A, Lubina A, Stovall M, Novikov I. Risk of thyroid cancer after childhood exposure to ionizing radiation for tinea capitis. J Clin Endocrinol Metab 2006; 91(12): 4798–4804.
11. de VF. The carcinogenic effects of radioiodine therapy for thyroid carcinoma. Nat Clin Pract Endocrinol Metab 2008; 4(4): 180–181.
12. Gerber H, Studer H, von GC. Paradoxical effects of thyrotropin on diffusion of thyroglobulin in the colloid of rat thyroid follicles after long term thyroxine treatment. Endocrinology 1985; 116(1): 303–310.
13. Peter HJ, Studer H, Forster R, Gerber H. The pathogenesis of "hot" and "cold" follicles in multinodular goiters. J Clin Endocrinol Metab 1982; 55(5): 941–946.
14. Studer H, Peter HJ, Gerber H. Natural heterogeneity of thyroid cells: the basis for understanding thyroid function and nodular goiter growth. Endocr Rev 1989; 10(2): 125–135.
15. Studer H, Derwahl M. Mechanisms of nonneoplastic endocrine hyperplasia--a changing concept: a review focused on the thyroid gland. Endocr Rev 1995; 16(4): 411–426.
16. BRAF v-raf murine sarcoma viral oncogene homolog B1. http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=retrieve&db=gene&list_uids=673 . 12-2-2009. 18-2-2009.
17. Ameur N, Lacroix L, Motte N et al. Mutational status of EGFR, BRAF, PI3KCA and JAK2 genes in endocrine tumors. Int J Cancer 2009; 124(3): 751–753.
18. Giannini R, Ugolini C, Lupi C et al. The heterogeneous distribution of BRAF mutation supports the independent clonal origin of distinct tumor foci in multifocal papillary thyroid carcinoma. J Clin Endocrinol Metab 2007; 92(9): 3511–3516.

19. Lupi C, Giannini R, Ugolini C et al. Association of BRAF V600E mutation with poor clinicopathological outcomes in 500 consecutive cases of papillary thyroid carcinoma. J Clin Endocrinol Metab 2007; 92(11): 4085–4090.
20. Santoro M, Carlomagno F, Hay ID et al. Ret oncogene activation in human thyroid neoplasms is restricted to the papillary cancer subtype. J Clin Invest 1992; 89(5): 1517–1522.
21. Kroll TG, Sarraf P, Pecciarini L et al. PAX8-PPARgamma1 fusion oncogene in human thyroid carcinoma [corrected]. Science 2000; 289(5483): 1357–1360.
22. Castro P, Rebocho AP, Soares RJ et al. PAX8-PPARgamma rearrangement is frequently detected in the follicular variant of papillary thyroid carcinoma. J Clin Endocrinol Metab 2006; 91(1): 213–220.
23. Cheung L, Messina M, Gill A et al. Detection of the PAX8-PPAR gamma fusion oncogene in both follicular thyroid carcinomas and adenomas. J Clin Endocrinol Metab 2003; 88(1): 354–357.
24. Marques AR, Espadinha C, Catarino AL et al. Expression of PAX8-PPAR gamma 1 rearrangements in both follicular thyroid carcinomas and adenomas. J Clin Endocrinol Metab 2002; 87(8): 3947–3952.
25. Neff RL, Farrar WB, Kloos RT, Burman KD. Anaplastic thyroid cancer. Endocrinol Metab Clin North Am 2008; 37(2): 525–38, xi.
26. TUMOR PROTEIN p53; TP53. http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=191170 . 26-11-2008. 18-2-2009.
27. Sobrinho-Simoes M, Maximo V, Rocha AS et al. Intragenic mutations in thyroid cancer. Endocrinol Metab Clin North Am 2008; 37(2): 333–62, viii.
28. Garcia-Rostan G, Zhao H, Camp RL et al. ras mutations are associated with aggressive tumor phenotypes and poor prognosis in thyroid cancer. J Clin Oncol 2003; 21(17): 3226–3235.
29. Basolo F, Pisaturo F, Pollina LE et al. N-ras mutation in poorly differentiated thyroid carcinomas: correlation with bone metastases and inverse correlation to thyroglobulin expression. Thyroid 2000; 10(1): 19–23.
30. Manenti G, Pilotti S, Re FC, Della PG, Pierotti MA. Selective activation of ras oncogenes in follicular and undifferentiated thyroid carcinomas. Eur J Cancer 1994; 30A(7): 987–993.
31. Parma J, Duprez L, Van SJ et al. Somatic mutations in the thyrotropin receptor gene cause hyperfunctioning thyroid adenomas. Nature 1993; 365(6447): 649–651.
32. Suarez HG, du Villard JA, Caillou B, Schlumberger M, Parmentier C, Monier R. gsp mutations in human thyroid tumours. Oncogene 1991; 6(4): 677–679.
33. Matsuo K, Friedman E, Gejman PV, Fagin JA. The thyrotropin receptor (TSH-R) is not an oncogene for thyroid tumors: structural studies of the TSH-R and the alpha-subunit of Gs in human thyroid neoplasms. J Clin Endocrinol Metab 1993; 76(6): 1446–1451.
34. Shi Y, Zou M, Farid NR. Expression of thyrotrophin receptor gene in thyroid carcinoma is associated with a good prognosis. Clin Endocrinol (Oxf) 1993; 39(3): 269–274.
35. Esapa CT, Johnson SJ, Kendall-Taylor P, Lennard TW, Harris PE. Prevalence of Ras mutations in thyroid neoplasia. Clin Endocrinol (Oxf) 1999; 50(4): 529–535.

36. Motoi N, Sakamoto A, Yamochi T, Horiuchi H, Motoi T, Machinami R. Role of ras mutation in the progression of thyroid carcinoma of follicular epithelial origin. Pathol Res Pract 2000; 196(1): 1–7.

Table 1. Thyroid carcinoma familiar forms and syndromes with hereditable thyroid tumours. PTC=papillary thyroid carcinoma, APC=adenomatous polyposis of the colon, PRKAR1A=protein kinase A regulatory subunit-1-alpha gene, CNC1=Carney complex, type 1, CNC2=Carney complex, type 2

Syndrome	Clinical Presentation	Thyroid Pathology	Gene and Location
Familial Papillary Carcinoma	associated with papillary renal ca	PTC	1q21
Familial non-medullary thyroid ca		PTC	2q21
Thyroid tumours with oxyphilia		Benign nodules and PTC	19p13.2
PTC without Oxyphilia		PTC	19p13
Familial Polyposis	Large intestine polyps and other GI tumours	PTC	APC on 5q21
Gardner's Syndrome	Small and large intestine polyps, osteomas, fibromas, lipomas	PTC	APC on 5q21
Turcot's Syndrome	Large intestine polyps Brain tumours	PTC	APC on 5q21
Cowden's Disease	Multiple hamartomas and breast tumours	Follicular adenoma and cancer	Unknown
Carney Complex	Pigmented adrenal nodules, pituitary adenomas, spotty skin pigmentation, myxomas	Thyroid adenomas	CNC1=PRKAR1A on 17q23-q24 CNC2=2p16