A clinical case of hereditary papillary thyroid carcinoma associated with a germline DICER1 gene mutation

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Here, we report a clinical case of isolated papillary thyroid cancer associated with a germline DICER1 gene mutation in a boy and his father. The father underwent surgery for a euthyroid multinodular goiter at the age of 7 and 9 years. On examination at the age of 27 years, he was diagnosed with papillary thyroid cancer. At the age of 7 years, the boy was suspected of having a multinodular goiter (based on thyroid ultrasonography findings); he underwent total thyroidectomy. A histological examination of the surgical material revealed encapsulated papillary carcinoma. Neither boy nor his father had been exposed to radiation or chemotherapy before the diagnosis of papillary thyroid cancer. To clarify the etiology of disease, a molecular genetic testing was performed using next-generation sequencing (NGS). The proband and his parent had a heterozygous thymine deletion in the exon 4 at position 380, which led to a shift in the reading frame with the formation of a premature stop codon (c.380delT p.L127QfsX3).

Keywords: case report, thyroid cancer, papillary, DICER1 protein, human.

Malignant neoplasms are among the most common causes of childhood mortality all over the world. High-differentiated carcinomas, such as papillary and follicular cancer, account for more than 90% of cases of thyroid malignancy [1]. According to the literature, the recurrence rate of thyroid cancer in children after primary surgical treatment depends on the morphological structure of the tumor and varies in a wide range from 7 to 47% [2–4]. The study of the molecular mechanisms underlying the development of these tumors is extremely important, since it will not only improve the diagnosis and prognosis of the disease, but also will form the basis for the development of new targeted chemotherapeutic agents in the future.

This article reports a rare case of the familial form of papillary thyroid cancer (PTC). Molecular genetic studies using the next generation sequencing (NGS) have established the relationship between the PTC in that family and DICER1 gene defect.

Case report

The patient A. was first admitted to the genetic endocrinopathy unit of the Endocrinology Research Center of the Ministry of Health of the Russian Federation at the age of 8 years with a diagnosis of papillary thyroid carcinoma, pT1bNxMx stage, after thyroidectomy and radioactive iodine ablation. The patient was hospitalized due to increasing blood level of thyroglobulin (TG), signs of submandibular and cervical lymphadenopathy, suspected preservation of residual glandular tissue at the thyroid bed.

According to the history, the child was born of the 2nd pregnancy at the age of 21; there was threatening miscarriage at 24 weeks. The child was born prematurely, weighing 760 g and having length of 48 cm. Apgar score was 7/7 points. The early development was normal. Mother has no family history of oncological and endocrinological diseases. The child’s father was operated on for multinodular euthyroid goiter at the age of 7 and 9 years. PTC
was histologically diagnosed at the age of 27 years, after the third surgery for disease recurrence. Ultrasound changes in thyroid structure were detected in patient’s younger brother at the age of 4 years and he is followed by endocrinologist.

History of the disease: the tumor on the left side of the neck was detected by palpation at the age of 7 years. Multinodular goiter was suspected based on ultrasound findings (2 masses in the left lobe sized 10 mm to 16 mm and a single nodular mass in the right lobe sized 4 mm in diameter), the total volume of the gland was 4.7 cm³, TIRADS II. Multiple enlarged lymph nodes in the right and left submandibular areas. Fine-needle aspiration biopsy of the mass in the left thyroid lobe was carried out, cytological description corresponded to colloid goiter pattern (Bethesda II). Taking into account the rapid growth of nodes, suspected thyroid capsule invasion by one tumor node, as well as burdened family history, total thyroidectomy was carried out at the age of 7 years. Histological examination of resected tissue found encapsulated papillary carcinoma with pronounced focal changes, signs of focal invasive growth into the capsule and slightly beyond. Radiodine ablation was carried out 3 months after surgery, whole-body scintigraphy showed accumulation of the radiopharmaceutical in the projection of the thyroid bed (residual thyroid tissue?), no other foci of abnormal accumulation of radioactive iodine were detected. Preoperative TG level was not assessed. TG level 7–8 months after surgery was up to 0.2 ng/ml with underlying suppression. Stimulated TG level (4 weeks after withdrawal of L-thyroxin with TTG > 100 mIU/l was 9.0 ng/ml, antibodies to TG <3 IU/ml).

Neither the child nor his father were exposed to radiation or chemotherapy before PTC was diagnosed. There was no evidence of other tumors in the family history.

The patient was examined at the pediatric department of the Endocrinology Research Center, growth and somatic development are within the age norm, subcutaneous fat is moderately developed (height SDS = 0.71; BMI SDS = −0.29). Patient’s condition is relatively satisfactory. Postoperative scar is located on the anterior surface of the neck in its lower third. No tumors were detected in projection of the thyroid gland during palpation. There are multiple palpable submandibular, anterior and posterior cervical lymph nodes sized up to 1.5—2 cm, palpation is painless. No abnormalities of other organs and systems were detected.

The results of physical, laboratory, and instrumental studies

Ultrasound examination of the neck was carried out at the department; thyroid gland and space-occupying masses have not been detected. Multiple lymph nodes sized 0.5 cm to 1.8×0.8×0.4 cm and characterised by low echogenicity and homogeneous structure were observed on both sides of the neck along the vessels. CT of the chest showed no focal or infiltrative changes in the lungs. According to the results of scintigraphy with 99mTc-pertechnetate, there were no sites of pathological hyperfixation of radiopharmaceutical in projection of thyroid bed. No pathological inclusion of radiopharmaceutical in the lungs and skeleton were found. No signs of functioning residual thyroid tissue was detected.

Molecular genetic studies

Molecular genetic analysis using next-generation sequencing (NGS) was carried out to clarify the etiology of the disease. The panel of primers Ion Ampliseq Custom DNA Panel («LifeTechnologies», USA) developed at the department of hereditary endocrinopathies of Endocrinology Research Center was used, covering the coding regions of the following genes: SDHB, SDHC, CDKN2C, MEN1, AIP, SDHD, SDKN1B, DICER1, PRKAR1A, PRKCA, GNAS, POU1F1, PTG2, SDHA, CDKN2A. Sequencing was carried out on PGM semiconductor se- quencer (Ion Torrent, «LifeTechnologies», USA). Bioinformatic processing of sequencing results was carried out using a TorrentSuite 4.2.1 software module (Ion Torrent, «LifeTechnologies», USA) and Annovar software package (version 2014Nov12) (http://www.openbioinformatics.org/annovar/) [K. Wang, M. Li, H. Hakonarson ANNOVAR: Functional annotation of genetic variants from next-generation sequencing data. Nucleic Acids Research, 38: e164, 2010]. NGS data were confirmed by Sanger sequencing. NM_177438.2 transcript was used as a reference sequence of the coding region of the DICER1 gene (http://www.ncbi.nlm.nih.gov/sites/entrez).

Heterozygous deletion of thymine at position 380 in exon 4, leading to a shift in reading frame to form a premature stop codon (c.380delTp.) was detected in the proband. The same mutation was detected in the patient’s father.

Discussion

DICER1 gene is located on the long arm of chromosome 14 (14q32.13) and consists of 36 exons. In recent years, increasingly more attention is being paid to this gene and DICER protein encoded by the gene due to the study of microRNA (miRNA), a class of small non-coding RNA molecules of about 22 nucleotides in length, which were discovered by V.Ambros in 1993 [5]. MicroRNAs are negative regulators of gene expression at the post-transcriptional level and are actively involved in many biological processes, including cell proliferation and apoptosis. [6,7]. In the RISC (RNA-induced silencing complex) complex with Argonaute (Ago) protein they interact with the non-coding portion of the 3'-end of mRNA, which prevents its translation or results in complete degradation of the molecule [8, 9]. One of the stages of miRNA biosynthesis includes cutting of pre-miRNA (pre-miRNA) molecules and involves DICER ribonuclease, which is subsequently included in formation of RISC complex
for its binding to mRNA [10]. DICER contains two RNase III domains and one PAZ domain. The distance between these portions in the molecule is determined by the length and angle of pre-miRNA connecting loop. DICER binds to pre-miRNA molecule and removes fragments of the molecule, which results in formation of miRNA and small interfering RNA (siRNA), gene expression regulators at the post-transcriptional level.

Several authors noted the role of microRNA biosynthesis disorders in the occurrence and progression nature of some types of tumors, including various morphological variants of thyroid cancer [11]. World literature provides no reliable data on the effect of inactivating mutations in DICER1 gene on the development of malignant thyroid tumors. Several authors suggested that history of chemotherapy could be one of the contributory causes of the development of differentiated thyroid cancer in these patients of [12—14].

Two germline heterozygous mutations in exons 8 and 25 of DICER1 gene associated with PTC [15, 16] have been described so far. Family case of papillary thyroid cancer has been described in a female and her two daughters aged 12 and 14 years [15]. The female was first operated on for nodular goiter at the age of 13 years, and then for follicular thyroid cancer at the age of 18 years. She also underwent a sinistrous oophorectomy for the Sertoli-Leydig cell tumor at the age of 7 years and dextral partial resection of the ovary at the age of 18 years. One of her daughters was diagnosed with androblastoma of the left ovary and cystic nephroma of the right kidney a month after thyroidectomy. Heterozygous missense mutation c.5441C>T; p.S1814L in exon 25 was detected in the mother and five of her children. Another two of her younger children were operated on for nodular goiter at the time of writing this case report.

There is also case report describing manifestation of papillary thyroid cancer in a 29-years-old female [16]. A year earlier, the patient was examined for the low-differentiated Sertoli-Leydig cell blastoma of the right ovarian.

Several authors suggested that family history of the patient is uncharacteristic of thyroid tumors. Several authors suggested that history of chemotherapy could be one of the contributory causes of the development of differentiated thyroid cancer in these patients [12—14].

Conclusion

This clinical case proves the causal relationship between the nodular thyroid pathology, including malignancy, and germlinal mutation in DICER1 gene. The case like this was described in Russian literature for the first time. Further studies are required to evaluate the incidence, penetrance, and prognostic impact of carriage of mutant DICER1 gene in familial variants of non-medullary thyroid cancer. The present case emphasizes the importance of considering family history as the only way to identify genetic variants of nodular thyroid pathology.

ADDITIONAL INFORMATION

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