Case report
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Familial papillary thyroid carcinoma

ABSTRACT

Familial papillary carcinoma of the thyroid has been reported rarely. This report describes a motherand her duaghter with papillary thyroid carcinoma. The speculation of authors is that some gene-related factors might play an important role in familial occurrence of papillary thyroid carcinoma.

Key words: *Thyroid tumor; Familial occurrence; Papillary thyroid carcinoma; Modern genetic studies; RET protooncogene*

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INTRODUCTION

Papillary carcinoma of the thyroid is the most prevalent malignancy of thyroid gland. A review of the literature of twenty years ago, reported few cases of papillary carcinoma of thyroid in families. The occurrence of familial medullary carcinoma in the thyroid is a well-known entity, but cases of familial papillary carcinoma have been rarely reported. Recent studies indicated that a familial or genetic factor contributes to the causation of papillary carcinoma of the thyroid.

The characteristics of familial thyroid carcinoma are: (a) predominantly papillary type, (b) early age of cancer onset (mean age about 35 years), and (c) smaller size of carcinoma and higher frequency of multicentric cancer occurrence (1,2).

This report describes a mother and her daughter with papillary thyroid carcinoma. Our cases show autosomal dominant inheritance.

CASE REPORT

The 24 year-old woman was admitted at Institute of Endocrinology in March 1995, with neck swelling which lasted for nine years. Physical examination confirmed the presence of a hard nonencapsulated nodule on the right lobe of the thyroid. The diagnosis was papillary carcinoma of the thyroid with bilateral cervical lymph node metastases. Microscopically, tissue of a tumor consisted of numerous branching papillae that had a fibrovascular core covered by a layer of cuboidal cells with irregularly distributed vesicular nuclei. Psammoma bodies, fibrosis and prominent lymphocytic infiltration are also present including intraglandular spread in the contralateral lobe.

Her 52 year-old mother had a papillary thyroid carcinoma too. She was admitted at the Institute of Endocrinology in December 1999, with swelling of which lasted for ten years, at the frontside of her neck. Physical examination showed an encapsulated nodule on the right lobe and a hard, ill-defined nodule on the left lobe of the thyroid. After total thyroidectomy, a diagnosis of papillary carcinoma was made on the left lobe and adenomatous nodule on the right lobe. Morphologically, this papillary carcinoma consisted of predominantly follicular and rare papillary structures lined by a layer of cuboidal cells having nuclei with ground-glass appearance. Numerous psammoma bodies have also been found.

DISCUSSION

The literature on familial papillary thyroid carcinoma was reviewed.

The occurrence of this neoplasm at an advanced stage in closely related individuals, early in life, suggests that underlying genetic factors may predispose this malignancy.

Papillary carcinoma of the thyroid in a family was first discussed in 1967, by Smith, who felt it was coincidental to familial polyposis of the colon. Further study suggests that there may be two groups of familial papillary carcinomas: one, as a part of a syndrome of multiple polyposis associated with papillary carcinoma; the other, a familial papillary carcinoma free of accompanying disorders (3).

Familial papillary carcinoma of the thyroid may have a hereditary basis independent of its association with the syndromes of multiple polyposis and of multiple hamartomas, and thus may represent a new entity with characteristics which distinguish it as a distinct subset of the more common disease.

Modern genetic linkage studies show that familial papillary thyroid carcinoma is genetically distinct from familial adenomatous polyposis coli.

Cancer is a genetic disease, arising from an accumulation of mutations that promote clonal selection of cells with increasingly aggressive

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behaviour. More than 20 different hereditary cancer syndromes have now been defined and attributed to specific germline mutations in various inherited cancer genes. The vast majority of mutations in cancer are somatic and are found only in an individual´s cancer cells. Somatic mutations in sporadic cancers frequently alter the inherited cancer genes, and the functions of cell signalling pathways have been illuminated by the study of the affected genes. Although rare, the inherited cancer syndromes are of vast biological importance. Studies of the specific mutations responsible for these syndromes and the cellular signalling pathways disrupted by the mutant proteins have begun to provide unprecedented insights into the molecular origins and pathogenesis of inherited and sporadic forms of cancer. The proteins encoded by inherited cancer genes have been implicated in a diverse array of cellular processes, including proliferation, differentiation, apoptosis, and maintenance of genomic integrity (4).

Cancer is a genetic disease caused by the ”gain of function” mutations of oncogenes and the ”loss of function” mutations of tumor suppressors, and of genes involved in DNA repair mechanisms (5).

The RET proto-oncogene encodes a protein receptor tyrosine kinase. The RET mutations are associated with dominantly inherited cancer syndromes multiple endocrine neoplasia (MEN, familial medullary thyroid carcinoma and also, with sporadic thyroid carcinomas (6).

The activation of RET protooncogene, through chromosomal translocation, is unique to papillary thyroid carinomas. Rearrangement of the RET kinase domain to 3 partner genes, has been mentioned, of which RET/ptc1 is the most common; RET/ptc2 and RET/ptc3. RET rearrangement is an important genetic lesion underlying the development of thyroid papillary carcinoma. Oncogenic rearrangements of the ret proto-oncogene (RET/PTC) are found uniquely in papillary thyroid carcinomas (7). The prevalence of RET/PTC in these tumors varies widely. The very high prevalence of RET/PTC in tumors arising in children after the Chernobyl nuclear accident has generated speculation that this oncogene may be an indicator of overt or inadvertent radiation exposure (8).

RET is a paradigmatic example of how different mutations of a single gene can lead to different neoplastic phenotypes. Indeed, gene rearrangements, often caused by chromosomal inversions, activate the oncogenic potential of RET in a fraction of human thyroid papillary carcinomas.

A combined cytogenetic and molecular analysis of thyroid tumors has indicated that these neoplasms might represent a significant model for analysing human epithelial cell multistep cancerogenesis. Thyroid tumours comprise a broad spectrum of lesions with different pehnotypes and variable biological and clinical behaviour. Molecular analysis has detected specific genetic alterations in these different tumours types. In particular, the well-differentiated carcinomas of the papillary type are characteristised by the activation of the tyrosine kinase receptors (TKRs)RET and NTRK1 protooncogenes. Cytogenetic analysis of these tumours has contributed to defining the chromosomal mechanisms leading to the TKRs′ oncogenic activation.

Exposure to ionising radiation is associated with papillary carcinomas, and RET activation has been suggested to be related to this event. Molecular characterisation of specific genetic lesion could provide significant information about the association betweenthe ionising radiation and the RET oncogene activation (9).

Recent studies have provided evidence that germline mutations of the RET gene are the underlying genetic events responsible for MEN 2, too.

The RET staining could be a useful marker for papillary thyroid carcinoma (10).

The pathology of thyroid tumours shows an autosomal mode of inheritance linked to a gene that maps to chromosome 19p13.2 (11). McKay et al. (12) reported that there are at least three susceptibility genes that predispose families to familial papillary thyroid carcinoma.

Investigation of inherited mutations that affect susceptibility to cancer will aid efforts to effectively prevent, detect, and treat the disease.

CONCLUSION

We speculate that some gene-related factors might play an important role in familial occurrence of papillary thyroid carcinoma. This report describes a mother and her daughter with papillary thyroid carcinoma.

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