Sporadic Multiple Endocrine Neoplasia Type 2A

Clinical syndromes associated with multiple endocrine neoplasia (MEN) have been well established; these are inherited in an autosomal dominant manner and classified according to the pattern of involvement (1). The clinical features of MEN type 2A syndrome, first described by Sipple in 1961 (2), include bilateral and multilicentric medullary thyroid carcinoma (MTC), unilateral or bilateral pheochromocytoma, and parathyroid neoplasia. Genetic findings of MEN type 2A are characterized by the recent evidence of germline mutations in ret proto-oncogene (ret) which have been identified in more than 95% of the patients (3). The most common mutation, found in 80% of all MEN type 2A, is a codon 634 mutation in exon 11.

In contrast, from the viewpoint of MTC, the type of tumor can be classified into 4 subgroups; sporadic, MEN type 2A, type 2B and familiar. Sporadic MTC has no associated abnormalities and no underlying defect of germline ret mutation but tumor DNA may have mutations; a high frequency of a common point mutation of ret at codon 918 in exon 16, however, a mutation at codon 634 is rare (4).

Based on these background of clinical and genetic advances, a somewhat puzzling but very informative report appeared in this issue. Akama et al (5) reported a case of MEN type 2A without germline mutation of ret but with identical somatic mutation at codon 634 in both tumors derived from MTC and pheochromocytoma, suggesting a sporadic case of MEN type 2A.

See also p 145.

How can we understand the genetic background of coincident tumor development of MTC and pheochromocytoma with an identical ret mutation in tumor tissues, not in germline DNA? First, sampling and polymerase chain reaction (PCR) contamination should be carefully excluded. Data with regard to ret mutations in sporadic pheochromocytoma is sparse and it is difficult to compare the results with other sporadic MTC and pheochromocytoma associated with ret mutations (6). The accidental coexistence of both sporadic tumors is very unlikely and the mosaic chromosomal pattern of ret mutation is also denied due to the intactness of the leukocyte and normal thyroid tissue ret. Developmental abnormalities induced by common environmental factors can be considered. Alternatively other types of ret mutation, other than exon 10 and 11, or the involvement of other genetic abnormalities may be a primary cause. Several possible mechanisms have been discussed but the important thing is the accumulation of cases such as this with the relationship between clinical and genetic features precisely analyzed. This the first unique report concerning a sporadic case of MEN type 2A, which provides a hint to realize another novel mechanism of the development of this syndrome.

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References