Somatic SDHB Mutation in an Extraadrenal Pheochromocytoma

TO THE EDITOR: As many as 25% of pheochromocytomas — catecholamine-producing tumors located along the sympathetic nervous system, including the adrenals — occur in hereditary tumor syndromes that include von Hippel–Lindau disease (VHL gene), multiple endocrine neoplasia type 2 (RET gene), neurofibromatosis type 1 (NF1 gene), and the pheochromocytoma–paraganglioma syndrome (SDHB and SDHD genes). The last two genes are also associated with extraadrenal pheochromocytoma. 

To date, except for one sporadic SDHD mutation, only germ-line mutations in SDHB and SDHD have been described, even among reported mutations in these genes in apparently sporadic pheochromocytomas and paragangliomas.

We present a case of a 25-year-old woman with an extraadrenal pheochromocytoma in the wall of her urinary bladder. Mutational analysis of the pheochromocytoma candidate genes RET, VHL, SDHB, and SDHD was performed in tumor and normal DNA present in the same tissue specimen. (The NF1 gene was not investigated, since the patient had no clinical signs of neurofibromatosis type 1 disease.) A single aberration was found: an SDHB 299C→T transition in tumor DNA but not in the patient’s normal DNA. This finding was confirmed by allele typing of the DNA samples and repeating the entire procedure, starting with the isolation of DNA from tumor and normal tissue. This somatic SDHB gene mutation results in a substitution of phenylalanine for serine at position 100 (S100F). Functional consequences of the S100F mutation can be anticipated, given the large physical differences between the two amino acids: substitution of a nonpolar side chain (F) for an uncharged polar side chain (S). In addition, the region of the SDHB gene that includes the S100F mutation is highly conserved at the protein level. Moreover, an SDHB germ-line missense mutation of the S100 neighboring amino acid (C101Y) has been described in a patient with an extraadrenal pheochromocytoma.

From the sequence analysis of the tumor DNA, it is apparent that the mutated allele is in excess of the wild-type allele, indicating amplification of the mutated allele or loss of the wild-type allele. Comparative genomic hybridization, loss of heterozygosity of the SDHB locus, and chromosome 1p fluorescence in situ hybridization all showed the loss of one 1p allele. These findings point to the biallelic inactivation of SDHB in this tumor: the mutation of one SDHB allele and the loss of the second SDHB allele. In addition, we found that there was an absence of SDHB expression in tumor cells, indicating complete loss of SDHB function.

We think it is likely that the somatic S100F mutation played a causal role in the tumorigenesis of the extraadrenal pheochromocytoma. Our
Figure 1. Molecular and Immunohistochemical Results.

Sequencing chromatograms of SDHB exon 4 of tumor and normal DNA from the patient show the relative signal intensities at position 299 of the wild-type nucleotide C and the substituted nucleotide T, indicating relative loss of the wild-type allele in the tumor DNA (Panel A). Panel B shows polymerase-chain-reaction–single-strand conformation polymorphism analysis of the patient’s normal (N) and tumor (T) DNA, as compared with control (C) DNA from a healthy subject. The aberrant migration pattern in the tumor DNA is apparent (arrowhead). In Panel C, the loss of heterozygosity is shown on an autoradiograph of chromosome 1p with a marker in proximity to the SDHB gene, indicating relative loss of tumor DNA (arrowhead), as compared with the patient’s normal DNA and control DNA from a healthy subject. Immunohistochemical staining of the patient’s tumor for SDHB shows unstained tumor cells surrounded by endothelial cells with speckled staining (Panel D), in contrast to the staining pattern in a pheochromocytoma without the SDHB mutation (Panel E).
findings suggest that the SDHB gene not only plays a role in the pathogenesis of a subgroup of inherited pheochromocytomas but also can be involved in a subgroup of truly sporadic pheochromocytomas.

Francien H. van Nederveen, M.D.
Esther Korpershoek, B.Sc.
Erasmus University Medical Center
3000 CA Rotterdam, the Netherlands

Jacques W.M. Lenders, M.D., Ph.D.
Radboud University Medical Center Nijmegen
6525 GA Nijmegen, the Netherlands

Ronald R. de Krijger, M.D., Ph.D.
Winand N.M. Dinjens, Ph.D.
Erasmus University Medical Center
3000 CA Rotterdam, the Netherlands
w.dinjens@erasmusmc.nl

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Dietary Supplement–Induced Vitamin D Intoxication

TO THE EDITOR: Vitamin D intoxication that is associated with the consumption of dietary supplements is reported rarely.¹ In 2004, the Food and Drug Administration (FDA) learned of the following case.

A 58-year-old woman with diabetes mellitus and rheumatoid arthritis began taking a dietary supplement called Solutions IE Ageless Formula II on January 12, 2004. Fatigue, constipation, back pain, forgetfulness, nausea, and vomiting soon developed. On March 15, 2004, she was hospitalized because her speech was slurred, and a blood glucose reading taken at home was 30 mg per deciliter. On admission, her serum levels were as follows: calcium, more than 3.75 mmol per liter; 25-hydroxyvitamin D, 1171 nmol per liter (normal range, 22 to 135); 1,25-dihydroxyvitamin D, 305 pmol per liter (normal range, 36 to 144); parathyroid hormone, 12 ng per liter (normal range, 10 to 65); calcitonin, 4.5 ng per liter (normal range, 0 to 4.6); albumin, 31 g per liter; phosphorus, 0.81 mmol per liter; blood urea nitrogen, 18.6 mmol per liter; and creatinine, 221 μmol per liter. The patient died from a cause unknown to us on January 8, 2005.

Laboratory analysis of the product by the FDA, obtained from one of two lots reportedly over-fortified with vitamin D₃, revealed 186,906 IU of vitamin D₃ in each serving size of six capsules, indicating that the patient had consumed roughly 90 times the recommended safe upper limit of 2000 IU per day. Long-term daily vitamin D consumption of more than 40,000 IU (1000 μg) is needed to cause hypercalcemia in healthy persons.² In March 2004, the product distributor announced that during the previous month it had received three complaints from customers who had been hospitalized for hypercalcemia and vitamin D toxicity. The same month, the product manufacturer recalled 1600 bottles of the product. The case described here underscores the need for the manufacturers of dietary supplements to

1. Data from the Food and Drug Administration, retrieved from their website.
2. Data from the American Society for� Medical Nutrition and Metabolism, retrieved from their website.

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