Increased Incidence of Tumors With the IKBKAP Gene Mutation? A Case Report and Review of the Literature

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Abstract

An increased incidence of neoplasia was recently reported in patients with familial dysautonomia. This suggests that, in addition to its role in neuronal development, the IKBKAP gene may also influence DNA repair. Here we report the case of a 28-year-old male with familial dysautonomia who was found to have neoplastic lesions detected post mortem as incidental findings. This case indicates that the prevalence of tumorgenesis within this population may be underestimated.

Keywords: Familial dysautonomia; IKBKAP; Tumorgenesis

Introduction

Familial dysautonomia, also known as Riley-Day syndrome and hereditary sensory and autonomic neuropathy type III, is a rare autosomal recessive disorder. Over 99.5% of cases are homozygous for a point mutation in the 5' splice site of the IKBKAP gene located on the long arm of chromosome 9 (9q31), which encodes IkB kinase complex associated protein (IKAP) [1, 2]. The carrier rate among Ashkenazi Jews is approximately 1 in 27. The disorder is characterized by sensory and autonomic dysfunction as a result of an abnormality in the development in the sensory and autonomic neuronal pathways [3].

Case Report

The decedent was a 28-year-old Ashkenazi Jewish man diagnosed with familial dysautonomia by genetic testing. At 6 weeks of age he presented with hypothermia and severe feeding problems. He had alacrima and other characteristic features of familial dysautonomia including unstable blood pressure and gastrointestinal dysfunction with oral incoordination and gastroesophageal reflux. He underwent a Nissen fundoplication and gastrostomy at age 2, suffered three episodes of intestinal obstruction, requiring bowel resection, and multiple bouts of pancreatitis and cholecystitis, persistent esophageal dysmotility leading to multiple episodes of aspiration pneumonia. Cinesophagram demonstrated marked esophageal dilation with poor peristaltic wave and narrowed spastic esophagogastric junction. He had kyphoscoliosis and underwent spine fusion at the age of ten; he also had equinovarus deformity and osteoporosis with multiple bone fractures. He was classified as learning disabled. He suffered several seizures associated with hyponatremia and hypoxia. Because of obstructive sleep apnea and nocturnal oxygen desaturations and hypercapnia that persisted after tonsillectomy and adenoidectomy, non-invasive posi-
tive pressure respiration was recommended but refused. In the months preceding his death, his condition was stable and there was no obvious change in his status on the evening that preceded his unexpected death during sleep.

The salient findings at autopsy were the esophagus distended with partially undigested food and evidence of aspiration pneumonia with associated foreign body giant cell reaction on the lung sections. Taken together in a context of swallowing difficulty and esophageal dysmotility, these findings were consistent with aspiration as a cause of death.

The unexpected findings were multiple well-circumscribed unencapsulated, pale yellow tumors in the subcapsular portions of both kidneys ranging from 0.2 to 0.4 cm in greatest dimension (Fig. 1). H&E sections revealed densely packed papillae or tubules lined by small, regular, cuboidal cells with rounded, uniform nuclei that lacked cytologic anaplasia and mitoses, making a diagnosis of tubulopapillary adenomas (Fig. 2).

Discussion

The mechanism of tumorgenesis in familial dysautonomia is unknown. A recent retrospective review indicates that two percent of patients with familial dysautonomia had a neoplasm [11]. All were detected prior to death between the ages of 7 to 49, which suggests that mutations in the IKBKAP gene may be predisposed to neoplasia at an early age. Therefore, considering that most of these patients succumb to the complications of their disease at a young age and that religious Jews often refuse to allow autopsy, it is likely that other patients with familial dysautonomia, like our own case, may also have died with unrecognized tumors which would increase the incidence of neoplasias even further. Notably, the father of this patient passed away at a young age of unknown cancer. It may be of significance since carriers are known to have reduced levels of the IKBKAP gene. In one study, a strong correlation was found between the IKBKAP

Figure 1. Autopsy revealed multiple well-circumscribed unencapsulated, pale yellow tumors in the subcapsular portions of both kidneys.

Figure 2. H&E sections revealed densely packed papillae or tubules lined by small, regular, cuboidal cells with rounded, uniform nuclei that lacked cytologic anaplasia and mitoses.
mRNA levels of the 22 familial dysautonomia patients and their parents [12], suggesting that the efficiency of the splicing is controlled by genetic mechanisms.

In our case, we found multiple bilateral tubulopapillary adenomas, which are low-grade papillary lesions with striking histological and genetic similarities to papillary carcinomas and are distinguished from the latter on the basis of size under 0.5 cm [13]. These small renal cortical epithelial neoplasms may be found incidentally. However, bilateral multifocal lesions are uncommon, unless they develop as a part of von Hippel-Lindau syndrome [14]. Although the previous review of neoplasms in familial dysautonomia included some low-grade neoplastic lesions [11], with time these proliferative lesions may have evolved into malignancy if the decedents had a full life expectancy.

The relationship between our findings and the IKBKAP gene mutations is unclear. Cytogenetic and molecular techniques demonstrated balanced translocations involving chromosome 9p and 9q (q34) in both clear cell and papillary renal cell carcinoma, the malignant counterparts of the adenomas [15, 16]. Perhaps, the proximity to the causative gene renal cell carcinoma, the malignant counterparts of the adenomas and 9q (q34) in both clear cell and papillary carcinomas may play a role in this association. Alternatively, by virtue of affecting the critical part of the transcriptional machinery, IKBKAP gene expression may be involved in crucial signaling cascades affecting expression of multiple secondary genes, the effects of which are yet to be discovered. Finally, defective repair of damaged DNA may provide yet another mechanism for accelerated tumorgenesis in patients with familial dysautonomia.

Conflict of Interest

The authors declare that they have no conflict of interest.

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