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Occurrence of neoplasms in individuals with congenital, severe GH deficiency from the Itabaianinha kindred

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ABSTRACT

Growth hormone (GH) and the insulin-like growth factor I (IGF-I) have cell proliferative and differentiation properties. Whether these hormones have a role in mutagenesis is unknown. Nevertheless, severe IGF-I deficiency seems to confer protection against the development of neoplasms. Here, we report five cases of adult patients with severe and congenital isolated GH deficiency (IGHD) due to the c.57+1G > A mutation in the GHRH receptor gene, who developed tumors. Four GH-naïve subjects presented skin tumors: a 42-year-old man with a fibroepithelial polyp, a 53-year-old woman and two men (59 and 56 years old) with epidermoid skin cancers. One of these died from it after three surgeries and radiotherapy. The fifth patient was a 25-year-old woman, who had intermittently received GH replacement therapy (GHRT) from age 11 to 18, who developed an ependymoma extending from the fourth ventricle to the end of the thoracic spine. She underwent three surgical procedures, without obvious evidence of tumor recurrence during the six years follow up. These observations suggest that severe IGHD does not protect completely from development of tumors.

1. Introduction

Growth hormone (GH) and its effector, the insulin-like growth factor I (IGF-I), are the principal regulators of somatic growth. They have additional biological functions, exhaustively studied since the demonstration of GH existence, near a century ago [1]. Since that date, a remarkable controversy persists on whether the proliferative actions of these peptides carry a risk of mutagenesis. This risk is difficult to assess, since the pathogenesis of cancer involves environmental factors and the accumulation of genetic alterations, and cancers have different pathways of growth regulation [2].

The historical concept of increased risk of malignancy in acromegaly, mainly colorectal, thyroid and urinary tract [2–5], has been recently challenged [6]. Conversely, severe IGF-I deficiency in mice [7] or in men (congenital GH insensitivity or Laron's syndrome, LS), seems to confer protection against cancer [8]. Accordingly, mice studies showed upregulation of GH receptor transcripts in melanoma cells [9] associated to increased resistance to anti-cancer drugs [10]. Conversely, GH receptor knockdown seems to attenuate human melanoma cell proliferation [11]. On other hand, models of human IGF-I deficiency with some residual GH secretion and function, like the autosomal recessive isolated GH deficiency (IGHD) type IB [12] due to GHRH receptor (GHRHR) gene (*GHRHR*) mutations [13], may have different consequences in terms of cancer development when compared to LS.

Intriguingly, recent data suggested a protective role of IGF-I against the development of non-melanoma skin cancer. IGF-I secreted by skin fibroblasts acts on keratinocytes, stimulating DNA repair and regeneration, thereby promoting cellular survival [14,15]. Thus, perhaps the IGF-I reduction that occurs during the aging process may result in inefficient DNA repair and uncontrolled proliferation of mutated cells.

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Table 1
Skin tumors in severe IGHD due to the c.57 +1 G > A *GHRHR* mutation.

Patients	Gender	Age	Place	Profession	AP	Death	Surgeries
1	Male	59	Nose	Farmer	Epidermoid cancer	No	1
2	Male	56	Thorax	Farm worker	Epidermoid cancer	Yes	3
3	Female	53	Chin	Housewife/teacher	Epidermoid cancer	No	1
4	Male	42	Left thigh	Farm worker	Fibroepithelial polyp	No	1

GHRHR: growth hormone releasing hormone receptor; IGHD: isolated growth hormone deficiency.

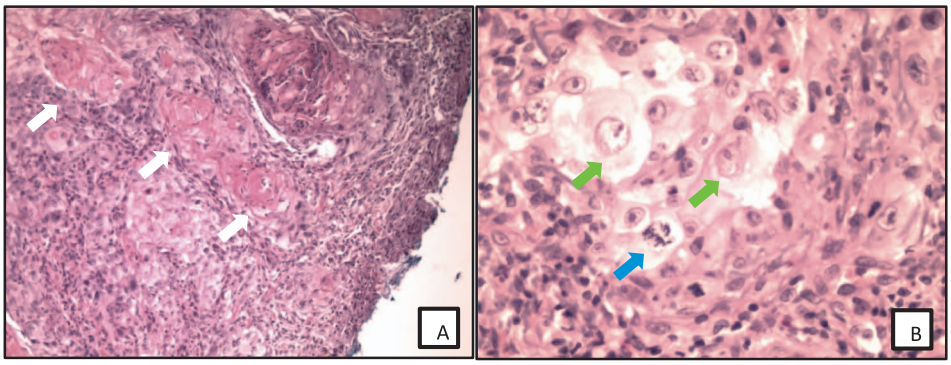

Fig. 1. Histopathological exam (hematoxylin-eosin stain) of one skin epidermoid cancer (case 3). (A) Stratified squamous epithelium with evidence of abundant keratin and corneal pearls (white arrows) (100x magnification). (B) Neoplastic squamous cell with large nuclei and prominent nucleoli (green arrows). Mitoses are also evident (blue arrow) (400x magnification).

In Itabaianinha County, in the northeastern Brazilian state of Sergipe, we have described large IGHD type IB kindred, with low to undetectable serum IGF-I levels and very low but detectable GH secretion [16]. This population lives in a rural environment, with low economic revenues originated by pottery and crops. They are Caucasian, likely of Portuguese ancestry. In this highly inbred kindred IGHD is due to the homozygous c.57 + 1G > A *GHRHR* mutation [17]. Most of the adult IGHD subjects from this kindred have not been treated with GH replacement therapy (GHRT). They exhibit severe short stature, doll facies, a high-pitched voice, central obesity and a wrinkled and prematurely aged skin [13]. Here we report that four GH-naïve subjects (three males) of this cohort developed skin tumors (three non-melanoma skin cancers), one resulting in death. The fifth patient is IGHD woman who had intermittently received GHRT during childhood and developed a large ependymoma.

2. Case reports

The cases we report were diagnosed due to patient-generated medical exams, and not by a systematic research-driven surveillance. Table 1 shows the clinical and anatomo-pathological features of the four IGHD patients with skin tumors. None of these patients had received GHRT at any point of life. Three had skin cancers, and one of them died due to progression of the tumor despite three surgeries and radiotherapy. The fourth one had a skin tag in the left thigh that by pathological examination was a fibroepithelial polyp. Fig. 1 shows the typical pathological example of one skin cancer (case 3). Fig. 2 shows the pathological exam of the patient with the fibroepithelial polyp (case 4).

The case 5 was a 25-year-old IGHD woman. She received intermittent GHRT between 11 and 18 years of age (approximate cumulative GH dose of 3000 mg). She presented to medical attention in March 2011 complaining of 5 years of pain in the cervicothoracic spine, one year of urinary incontinence, and 5 months of progressive left hemiparesis and hemiparesthesia. Magnetic resonance imaging (MRI) showed a tumor in the fourth ventricle extending through the medulla to the end of the thoracic spine. The patient underwent surgery in April 2011. Pathology showed a grade II ependymoma (Fig. 3). In May 2011, a C3–C7 laminectomy was performed, and in August 2011, a T1–T7 spinal cord lesion was removed. The postoperative MRI performed in September 2011 demonstrated only signs of the surgical approach from the posterior fossa. There were cystic areas extending throughout the spinal cord, denoting sequelae areas, as well as signs of medullary atrophy and cavitation areas. In 2015, a 6 mm nodule was observed in the posterior portion of the cervical spinal cord at C6–C7 level, suggestive of relapse, although the patient was clinically asymptomatic.

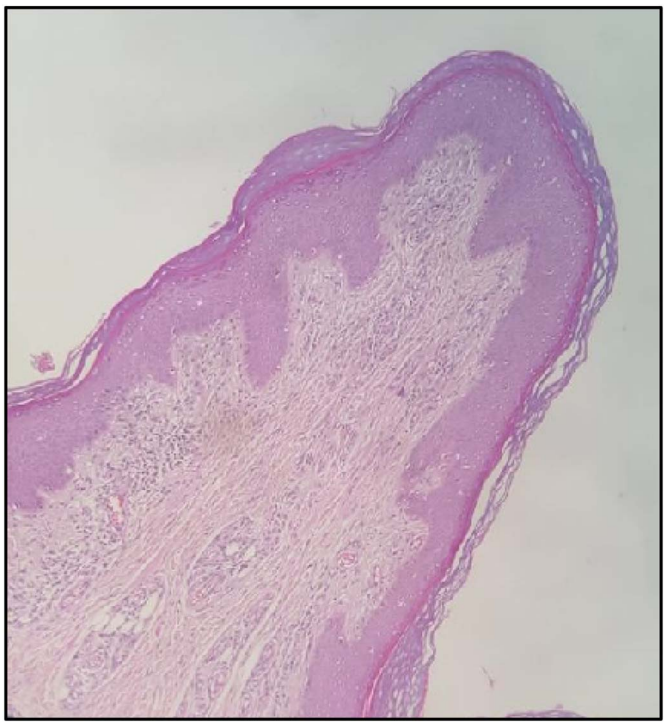

Fig. 2. Histopathological exam (hematoxylin-eosin stain) of the case 4 revealing a fibroepithelial polyp. Epidermal hyperplasia and connective tissue stalk composed of well-vascularized, loosely arranged collagen (4 x magnification).