Acromegaly and Colorectal Cancer

Beat R. Buehler, MD[*]
Christoph M. Henzen, MD[†]
Maria Teresa de Zulueta, MD[‡]
Rudolf A. Joss, MD[§]

[*]*Department of Oncology, Kantonsspital Luzern, Luzern, Switzerland*
[†]*Consultant Endocrinology, Kantonsspital Luzern, Luzern, Switzerland*
[‡]*Department of Oncology, Kantonsspital Luzern, Luzern, Switzerland*
[§]*Department of Internal Medicine, Kantonsspital Luzern, Luzern, Switzerland*

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ABSTRACT

Acromegaly results from an excessive secretion of growth hormone. Recently, a 2.4 fold increased mortality rate of colorectal cancer was shown in acromegalics. Over a 2-year period 186 new cases of colorectal cancer were diagnosed at our institution, and acromegaly was diagnosed in 3 (males) of 182 patients, yielding a prevalence of 1.6%. Clinical presentation and diagnosis of acromegaly are discussed.

INTRODUCTION

Acromegaly results from a prolonged, excessive secretion of growth hormone (GH), mostly due to a GH-secreting adenoma of the anterior pituitary gland. Rarely acromegaly is caused by excessive secretion of growth hormone-releasing hormone (GHRH) by hypothalamic tumors, ectopic GHRH secretion by nonendocrine tumors such as carcinoid tumors or small-cell lung cancers, and ectopic secretion of GH by nonendocrine tumors. The incidence of acromegaly is 3 to 4 cases per million persons, and the prevalence is 50 to 70 cases per million, equally occurring in both sexes.[1]

The mortality rate of patients with acromegaly is 2 to 3 times the expected rate, mostly due to cardiorespiratory disease, hypertension, diabetes mellitus, and cancer.[2] The excess mortality rate in acromegalics due to cancer was shown in a large multicenter retrospective study of 1362 patients in which there was a 2.4 fold increase in the mortality rate of colorectal cancer, and an almost two-fold increase in breast cancer.[2 3]

CASE REPORTS

Patient A

In this 61 year old man presenting with typical acromegalic features (Figure 1) a large carcinoma of the descending colon with infiltration of the psoas muscle and the lateral abdominal wall was diagnosed. Colonoscopy revealed several more colonic polyps. In his medical history there was a right-sided pyelolithotomy due to nephrolithiasis. Subsequently, he suffered from recurrent kidney stones, which once were treated by extracorporeal shock wave lithotripsy (ESWL). Seven years ago he was operated on for bilateral carpal tunnel syndrome. A large euthyroid multinodular goitre was removed one year ago. Because of low back pain, a magnetic resonance imaging (MRI) of the lumbar spine was performed and showed an infiltrating process within the psoas muscle eventually leading to the diagnosis of colorectal cancer. Left-

Table 1. Laboratory Findings*

	Patient A	Patient B	Patient C
IGF-1 (5.7-41.6 nmol/L)	96.4	139.1	84.5
TSH (0.2-4.2 mU/L)	1.6	0.85	1.5
fT4 (12-22 pmol/L)	13.8	11.8	16.1
Cortisol, stimulated (>550 nmol/L)	520	223	519
LH (1.7-8.6 U/L)	3.4	1.1	2.8
Free testosterone (19-66 pmol/L)	11.5	10.2	24.3
Prolactin (2-16 µg/L)	23.6	284	8.9

*TSH indicates thyroid-stimulating hormone; fT4, free thyroxine (T4); and LH, luteinizing hormone.

Table 2. Acromegalic features

	Patient A	Patient B	Patient C
Acral growth	+	+	+
Hyperhydrosis	+	+	+
Pathologic glucose tolerance	-	+	-
Carpal tunnel syndrome	+	-	-
Systemic hypertension	+	+	+
Goitre	+	+	-
Sleep apnea syndrome	+	+	+
Loss of libido	+	-	-

sided hemicolectomy was performed and chemotherapy with capecitabine was initiated.

An MRI of the skull demonstrated a macroadenoma of the pituitary gland. The assessment of the pituitary function revealed elevated IGF-1 and prolactin levels, a normal thyroid axis, hypogonadotrophic hypogonadism, and a partial insufficiency of the hypothalamic-pituitary-adrenal axis (Table 1).

Patient B

This 56-year-old male patient was referred to our outpatient clinics because of poorly controlled diabetes mellitus type 2, that was diagnosed 6 years ago and complicated by diabetic retinopathy and nephropathy. There was a history of non-metastatic colorectal cancer 4 years ago that was treated by right-sided hemicolectomy only. On colonoscopic routine follow up 3 years ago, several colonic polyps were removed. Two years ago obstructive sleep apnea was diagnosed and treatment with nasal continuous positive airway pressure (CPAP) was installed successfully.

On physical examination he presented with typical acromegalic features (Table 2), and the diagnosis was confirmed by excessively high levels of IGF-1 and growth hormone, and a macroadenoma of the pituitary gland was demonstrated by MRI. The laboratory findings are summarised in Table 1.

Patient C

In this 68-year-old male patient, colonoscopy was performed because of refractory iron deficiency anemia. Colorectal cancer with liver metastasis and peritoneal carcinosis was diagnosed. Right-sided hemicolectomy was performed and chemotherapy with irinotecan, 5-fluorouracil, and calciumfolinate was initiated. In his medical history uvuloplasty was performed 11 years ago, due to obstructive sleep apnea syndrome.

On admission the patient reported that his feet had been growing over the past

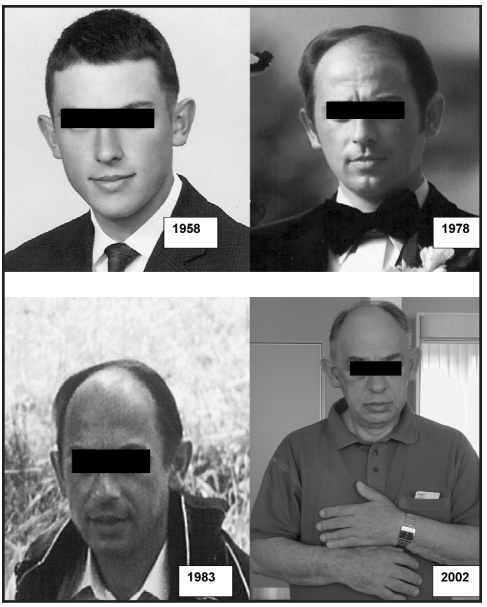

Figure 1. Typical acromegalic changes in patient A.

few years and that his rings had to be enlarged. The acromegalic features and the laboratory findings are summarised in Table 1. The MRI showed macroadenoma of the pituitary gland with a diameter of 1.5 cm.

DISCUSSION

Over a 2-year period 182 new cases of colorectal cancer have been diagnosed at our institution. The diagnosis of acromegaly has been made in 3 of them, suggesting a prevalence of 1.6%. In all 3 patients the diagnosis of colorectal cancer preceeded the diagnosis of acromegaly by one to 4 years. However, the typical acromegalic features and the medical history suggested the diagnosis of acromegaly much earlier. Our findings concur with several studies that demonstrated an increased risk of colorectal cancer in acromegalics.[2 4] The prevalence of 1.6% of acromegaly in our patients with colon cancer is considerably high, compared to the prevalence of familial adenomatous polyposis of less than 1% and to the prevalence of hereditary non-polyposis colorectal cancer of 5 to 8%.[5]

Excessive secretion of growth hormone (GH) leads to the increased synthesis of IGF-1, which is mainly produced in the liver and, by the activation of a tyrosine kinase, and leads to the phosphorylation of several intracellular structures ultimately resulting in the stimulation of cell growth, protein synthesis, cell proliferation, cell differentiation, and inhibition of apoptosis.[6]

The initial step in adenoma formation is an increased cell proliferation that also entails the risk of oncogenic mutation. Actively dividing cells are found at the bottom of the colonic crypts and move toward the luminal surface, where they eventually become apoptotic. In acromegaly the increased proliferation of the colonic epithelium correlates to the serum IGF-1 level, supporting the clinical findings that adenomatous colonic polyps occur more frequently in patients with acromegaly and behave more aggressively with accelerated progression to malignancy.[3] Moreover, IGF-1 reduces apoptosis by impairing the function of antiapoptotic proteins and by inadequate induction of transcription.[7]

Recently, screening guidelines for colorectal cancer and polyps in patients with acromegaly have been published. Following these guidelines regular colonoscopic screening should be offered to these patients from the age of 40 years. The interval of colonoscopy should depend on the original findings and the activity of the acromegaly, for instance, patients with an adenoma or an elevated IGF-1 level should be screened at 3-year intervals. In patients with negative findings screening at 5-year intervals should be offered. Total colonoscopy is required but may be associated with technical difficulties. In these patients the colon is of increased length and circumference with a more than doubled transit time. Therefore

twice the standard bowel preparation is required.[8]

Considering the surprisingly high proportion of acromegaly in our patients with colorectal cancer, physicians should be aware of acromegalic features in the patients with colorectal cancer, and IGF-1 levels should be measured if there is a high index of suspicion.

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