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Case Report

Diabetes Mellitus and Concurrent Colon Cancer Complicated with Intrahepatic Cholangiocarcinoma - Case Report

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Abstract

Many earlier studies reported a slight high risk of colon cancer in individuals with type 2 diabetes. An increasing evidence that determinants of insulin resistance and of high insulin-like growth factor 1 (IGF-1) levels account for risk factors of colon cancer. Here, a case of type 2 diabetes and concurrent colon cancer with the metastasis of intrahepatic cholangiocarcinoma is presented. In discussion, the mechanism that insulin and especially IGF-1 stimulated in vitro epithelial growth of colonic carcinoma cells, which was mediated by oncogenic receptor activated IGF-1R,eventually contributed to the increased risk of colonic neoplasias in acromegaly even in type 2 diabetes, and further growth hormone (GH)-IGF-SST (somatostatin) system in hepatocarcinogenesis, and its targeting therapy.

Keywords: *Diabetes Mellitus; Colon Cancer; Insulin and IGF-1/Oncogenic IGF-1 Receptor; Target Therapy*

Introduction

Insulin and IGFs (IGF-1 and IGF-II) play essential roles in the regulation of cell metabolism, survival, growth, proliferation and differentiation in life span [1]. IGF-I is known as major regulation of postnatal growth. Treatment with human rIGF-I has been introduced in primary growth hormone insensitivity [2,3] or IGF-1 deficiency (Laron syndrome) [4-9], even in treatment of type I diabetes with lower IGF-I and others [10,11]. IGF-II plays a fundamental role in embryonic and fatal growth. It is conceivable therefore that maintaining a balance within the GH/IGF-I/insulin axis is a crucial determinant of normal going, whereas aberrant alterations in this system may underline the development of cancer and other age-related disorder. Cohort studies have demonstrated increase risk of colorectal cancer in those with insulin resistance [12]. In the prospective Nurse's Health Study [12,13], type 2 diabetes was associated with an elevated risk of colon cancer. Here, a case of type 2 diabetes and concurrent colon cancer with metastasis of intrahepatic cholangiocarcinoma is presented.

Case Report

A 55-year-old man consulted on August 01, 2018, with chief complaints of abdominal distension and abdominal pain for one month duration. He had a past history of 13+ years of type 2 diabetes mellitus. The temperature was 36.8°C, and blood pressure 100/82 mmHg. On physical examination his abdomen was markedly protuberant with subcutaneous varicose vein. The abdomen was greatly distended with a flat percussion in almost all areas. The flanks were bulging, and a fluid wave was elicited. There was abdominal tenderness. On CT examination revealed in his right middle abdomen there was extensive peritoneal thickening, with terminal ileum wall thickening and stenosis. A mass was detected in the left lobe of his liver. Ascites +++. A metastatic intrahepatic cholangiocarcinoma was noted. Laboratory data showed blood sugar 10.45 mmol/l, plasma glycosylated hemoglobin HbA1C 8.2%. Serum AFP (-), HBsAg (+), CEA 583.91 ng/ml.

Ascitic Fluid Tests: AFP 1.11 ng/ml, CEA > 1000.0 ng/ml, CA125 1067.0 u/ml, CA19-9 4.89 u/ml. Ascites smear showed adenocarcinoma cells derived from intestinal (colon) origin (See figure 1). IHC stain: CK5/6 (-), CK20 (-), CK19 (+), CDX-2 (weak positive), Calretinin (-), WT1 (-), Ki67 5%, villin (+), CK7 (+), MUC5AC (-), MUC2 (-). Now the patient is under investigation.

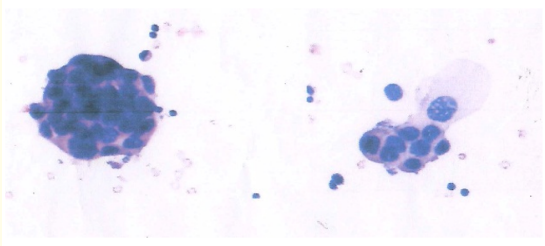

Figure 1: *Adenocarcinoma cells in ascites smear.*

Discussion

Many studies reported a slightly higher risk of colon cancer in individuals with type 2 diabetes, particularly in men [14,15], the relative risk (RR) for colon cancer among those with type 2 diabetes was 1.7. One study examined risk of adenomas of the sigmoid colon and showed a modestly elevated risk associated with type 2 diabetes(including new type 2 diabetes and type 2 diabetes under treatment) [16]. Among prospective studies, the largest was the cancer prevention study [17], which encompassed 13 yr of follow up among 15,487 subjects with diabetes and 850,946 subjects without diabetes. An increased risk of colorectal cancer was noted in men (RR = 1.3). In the prospective Nurses' Health Study [13], type 2 diabetes was associated with an elevated risk of colon cancer (age-adjusted RR = 1.6). Colorectal cancer risk increased with increasing levels of C-peptide, a marker for insulin secretion. Accumulated data, determinants of insulin resistance and of high IGF-1 levels are consistently related with high risk of colon neoplasia [12]. From animal models which were treated with insulin injections, insulin enhanced the growth of aberrant crypt foci, a colorectal cancer precursor [18] and increased the number and size of tumors [19]. In this case report, the patient had a 13 years of diabetes followed by colon cancer with metastasis of intrahepatic cholangiocarcinoma.

Most promising is the increased risk of both benign and malignant tumors in acromegaly [20-29]. Acromegaly is a condition characterized by excessive production of growth hormone and IGF-1. In a report of 222 patients at a repeat coloscopy, serum IGF-1 levels were significantly higher in those with a recurrent adenoma than in those without (IGF-1, 390 ug/l vs 244 ug/l, $p < 0.005$). In a cohort of 14,275 women in New York, baseline IGF and IGFBP were assayed from the serum of 102 women who subsequently developed colorectal cancer and 200 match controls [30]. Colorectal cancer showed a modest but positively increased risk with higher levels of IGF-1 [30-32]. Therefore, people with type 2 diabetes and people with acromegaly and who have high levels of insulin and IGF-1 respectively are at elevated risk of colon cancer in most studies.

The mechanism that IGF-1 and insulin stimulate *in vitro* growth of normal colonic and carcinoma cells [33] might be mediated through IGF-1 receptor [34,35] or possibly hybrid IGF-1 and insulin receptor [36]. Several laboratories clearly showing that constitutively active insulin-like growth factor I receptor cause transformation and xenograft growth of immortalized mammary epithelial cells with an epithelial-to-mesenchymal transition (EMT) [37,38]. The results uncovered that aberrant activated IGF-1R is oncogenic. This oncogenic receptor IGF-1R (or oncogenic IGF-1R) [39-48] is crucially required for the establishment and maintenance of the transformed phenotype [49]. Transgenic mice provide evidence that aberrant IGF-1R overexpression is sufficient to induce mammary epithelial hyperplasia and tumor formation *in vivo* [50]. Increased epithelial cell proliferation [51] and induction of vascular endothelial growth factor (VEGF) [52] are most probably due to a direct stimulatory effect of especially IGF-1, which contributes to the increased risk of colonic neoplasms in acromegaly and even in type 2 diabetes.

In circulation IGF-1 and insulin-like growth factor binding protein (IGFBP)-3 are mainly produced in the liver, and up-regulated by growth hormone [1]. Alternatively, growth hormone (GH) is the primary regulator for hepatic production of IGF-1 and hepatic GH receptor number is partly regulated by insulin [12]. GH-IGF-SST (somatostatin) system plays a central role in liver growth and development, and also as regulators of hepatocarcinogenesis (HCC) [53]. IGF1R overexpression in HCC facilitates IGF2 oncogenic activity. IGF1R is considered the main receptor responsible for the mitogenic effects of the IGF axis, representing an attractive target for anti-cancer therapy. Nowadays, a phase 2 study on IMC-A12, also known as cixutumumab (binds oncogenic IGF1R with high affinity), in combination with sorafenib in advanced HCC, are going. OSI-906 is a potent and selective small molecular receptor tyrosine kinase (RTK) inhibitor, targeting oncogenic IGF-1R and IR. Recently a randomized placebo-controlled double-blind phase 2 study has been concluded on patients with advanced HCC after failure of first-line treatment with sorafenib, but the results of this study are awaited. Promising effect of somatostatin analogue Octreotide reduces circulating IGF-1 levels, retards colonic tumor growth. The long-acting release formulation of octreotide (Octreotide LAR) has been proven to be useful in the treatment of HCC [53]. This is testable.

Conclusion

In conclusion, A patient with type 2 diabetes and concurrent colon cancer complicated with the metastasis of intrahepatic cholangiocarcinoma was reported here. In this case, circulating increased IGF-1 and local IGF-1 concentration, and its oncogenic receptor IGF-1R overexpression were considered as his risk factor of colon cancer. Due to his severe condition and dead 2 days ago, there was unable to detect his IGF-1 concentration. This is our care as to the clinical investigation.

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