Gastro Hep Advances 2024;3:333–335

CASE REPORT

Metastatic Colon Cancer in an Individual Following Prolonged Daily Inulin Consumption

Beng San Yeoh,[1] Andrew T. Gewirtz,[2] and Matam Vijay-Kumar[1]

[1]Department of Physiology and Pharmacology, The University of Toledo College of Medicine & Life Sciences, Toledo, Ohio; and [2]Center for Inflammation, Immunity & Infection, Institute for Biomedical Sciences, Georgia State University, Atlanta, Georgia

Studies in rodents suggest that inulin supplements may be carcinogenic. We present a case implicating that this risk extends to humans. A healthy male from a family lacking history of cancer had his first cancer-screening colonoscopy at age 56. No intestinal polyps/abnormalities were detected. A second colonoscopy, performed 7 years later, revealed a tumor in the cecum, with evidence of metastasis to lymph nodes. The only known change in patient's lifestyle during that seven-year period was the addition of 4g of inulin powder as a daily supplement during the last 2 years. Such inulin consumption is a plausible contributor to his disease.

Keywords: Gut Microbiota; Supplemental Fermentable Fiber; Dietary Inulin; Colon Cancer

Introduction

Inulin, a nondigestible, plant-derived carbohydrate is a prebiotic fiber that is readily degraded and fermented by gut bacteria. The products of such fermentation, namely, short chain fatty acids, can have numerous beneficial properties resulting in inulin being marketed as a supplement that promotes gut health. However, studies in both rodents[1,2] and humans[3] report that inulin can trigger chronic inflammation of the lining of the colon that may lead to cancer. We present a case that may reflect this notion.

Case Report

A lean (body mass index = 19) adult male had his first colonoscopy at age 56, with no intestinal polyps detected. A second colonoscopy 7 years later revealed a large 4–5 cm tumor in the cecum. The patient's family history (paternal, maternal, immediate, and extended) had no record of tumors of any kind. The patient reported a healthy lifestyle, including frequent consumption of organic home-grown vegetables, naturally rich in fiber, and no use of drug, tobacco, or alcohol. The only noted lifestyle change between colonoscopies was the initiation of 4 grams of agave inulin powder daily in his morning beverage for the last 2 years of that seven-year period. The consumption of inulin each morning produced noticeable bowel gas by late afternoon, indicating rapid, intense fermentation of the inulin.

The tumor required a right hemicolectomy where the patient lost roughly 12 inches of his colon, including the appendix and ileocecal valve. The tumor was a mucinous (colloid) adenocarcinoma (>50% mucinous component), poorly differentiated, with a size of 3.5 × 4.0 × 2.3 cm. The tumor invaded through the muscularis propria into the pericolorectal tissues but did not extend to the serosal surface. Immunohistochemistry for DNA mismatch repair proteins revealed positive staining for mutL homolog 1, mutS homolog 2, mutS homolog 6, and PMS1 homolog 2 in the tumor. Memorial Sloan Kettering's Integrated Mutation Profiling of Actionable Cancer Targets estimated that the patient's tumor mutation burden was 10.7 mutations per megabase and had identified 13 mutations (Table). One lymph node out of 36 was metastatic, leading to 3 months of chemotherapy with capecitabine and oxaliplatin. The patient was then free of cancer for 1.5 years. During this cancer-free period, the tumor marker carcinoembryonic antigen level was between 1 to 2 ng/mL, indicating no cancer was present. However, during a six-month interval, the cancer returned as metastatic colon cancer (peritoneal metastasis), a terminal cancer with no cure. During this interval, his serum carcinoembryonic antigen level had climbed to 40 ng/mL. He is now being treated with systemic chemotherapy and is exploring options for cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy.

Discussion

The human gastrointestinal tract harbors >500 bacterial species, generally categorized into 3 groups – beneficial, mutualistic, and opportunistic. The marketing of inulin as health promoting is based on the idea that it feeds the

Most current article

Copyright © 2024 The Authors. Published by Elsevier Inc. on behalf of the AGA Institute. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

2772-5723
https://doi.org/10.1016/j.gastha.2023.12.003

Table. Somatic Mutation Detected in the Patient's Tumor

Gene	Type	Alteration	Location	MAF
Kirsten rat sarcoma viral oncogene homolog (KRAS)	Missense mutation	G12D *(c.35G>A)*	Exon 2	17.2%
G protein, alpha stimulating activity polypeptide (GNAS)	Missense mutation	R201H *(c.602G>A)*	Exon 8	40.1%
Inositol polyphosphate phosphatase like 1 (INPPL1)	Missense mutation	R70H *(c.209G>A)*	Exon 2	19.9%
		E887K *(c.2659G>A)*	Exon 23	18.2%
SRY-box transcription factor 9 (SOX9)	Frameshift insertion	Q496fs *(c.1486dupC)*	Exon 3	15.2%
Axis inhibition protein 2 (AXIN2)	Nonsense mutation	E384[a] *(c.1150G>T)*	Exon 5	20.0%
		P690[a] *(c.2063_2067dupTGACC)*	Exon 8	16.9%
DNA methyltransferase 1 (DNMT1)	Missense mutation	T1163M *(c.3488C>T)*	Exon 32	24.9%
Inhibin subunit beta A (INHBA)	Missense mutation	R379W *(c.1135C>T)*	Exon 3	25.3%
Mediator complex subunit 12 (MED12)	Missense mutation	R1148H *(c.3443G>A)*	Exon 24	47.8%
Notch receptor 3 (NOTCH3)	Missense mutation	R578C *(c.1732C>T)*	Exon 11	16.2%
PiggyBac transposable element derived 5 (PGBD5)	Missense mutation	A368V *(c.1103C>T)*	Exon 5	18.5%
Phosphatidylinositol-3,4,5-trisphosphate dependent Rac exchange factor 2 (PREX2)	Missense mutation	Q1201K *(c.3601C>A)*	Exon 30	21.1%

Sequencing reads supporting the mutation/total number of reads.
Amino acid substitution and nucleotide substitution (in bracket) are indicated under the alteration column.
dup, duplication; fs, Frameshift; MAF, mutant allele frequency.
[a]Stop codon.

beneficial bacteria in the gut, ignoring the fact that those harmful bacteria will also use inulin as a carbon source or via cross-feeding. A study published in 2020 found that people with colorectal cancer had almost 4 times higher levels of the genotoxic polyketide synthase–expressing *E. coli*,[4] implicating its role in colon cancer pathogenesis. Recently published animal experiments indicated that, in the presence of this same strain of *E. coli*, inulin induces generation of the genotoxin colibactin encoded by polyketide synthase that causes DNA damage and tumorigenesis.[5,6] The unique DNA mutational signature induced by colibactin has been recently reported,[4] thus raising the prospect of its potential use to identify individuals who are at higher risk of developing colorectal cancer and ultimately to help in disease prevention.

If the natural balance of gut microbes is disturbed, a condition known as dysbiosis, bacteria that are normally harmless can become pathogenic and contribute to a wide range of serious illnesses that include cancer, obesity, and inflammatory bowel disease.[7] Clinical trials have demonstrated that there is a shift in bacterial populations in the human gut with inulin consumption,[8] one of the reasons people with inflammatory bowel disease should abstain from consuming inulin and other fermentable oligosaccharides that are constituents of a class of carbohydrates known as fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.[9]

The cellular and molecular mechanisms that lead from chronic inflammation to serious diseases like cancer are not yet completely understood, but the connection is well established and includes bacteria-induced inflammation and their immunosuppressive metabolites that dampen immunosurveillance.[7] While inulin itself may not be a DNA mutagen, preclinical studies indicate that it supports tumorigenesis by promoting the growth of adenomas and their progression to malignancy.[10–12] It is possible that the tumor arose from a preexisting polyp that was not detected in previous colonoscopy, which was then transformed in an environment wherein inulin elevated the abundance of gut bacteria that express the protumor genotoxin colibactin,[5,6] and impeded antitumor immunosurveillance[13,14] through the generation of gut bacteria–derived immunosuppressive metabolites such as short chain fatty acids[15–17] and bile acids.[18–20]

It is, of course, impossible to discern with certainty whether this patient's daily inulin consumption contributed to his intestinal cancer, but because it is plausible, we hope that reporting this case will encourage broader investigation of whether consumption of purified fermentable fibers as supplements is associated with tumorigenesis. Meanwhile, we suggest that highly refined fermentable fibers like inulin as daily dietary supplements may not be without risk, and those seeking to improve gut health would be better served by eating whole foods naturally rich in fiber.

References

1. Miles JP, et al. Inflamm Bowel Dis 2017;23:1133–1143.
2. Singh V, et al. Gut 2019;68:1801–1812.
3. Armstrong HK, et al. Gastroenterology 2023;164:228–240.
4. Pleguezuelos-Manzano C, et al. Nature 2020;580:269–273.
5. Oliero M, et al. Front Microbiol 2023;14:1067505.
6. Oliero M, et al. BMC Cancer 2021;21:172.
7. Levy M, et al. Nat Rev Immunol 2017;17:219–232.
8. Lancaster SM, et al. Cell Host Microbe 2022;30:848–862 e7.
9. Gibson PR, et al. J Gastroenterol Hepatol 2010;25:252–258.
10. Misikangas M, et al. Br J Nutr 2008;99:963–970.

11. Misikangas M, et al. J Nutr Biochem 2005;16:402–409.
12. Pajari AM, et al. Int J Cancer 2003;106:653–660.
13. Singh V, et al. Cell 2018;175:679–94 e22.
14. Yeoh BS, et al. Gastroenterology 2022;163:1658–1671 e16.
15. Arpaia N, et al. Nature 2013;504:451–455.
16. Furusawa Y, et al. Nature 2013;504:446–450.
17. Smith PM, et al. Science 2013;341:569–573.
18. Arifuzzaman M, et al. Nature 2022;611:578–584.
19. Campbell C, et al. Nature 2020;581:475–479.
20. Ma C, et al. Science 2018;360(6391):eaan5931.

Received October 17, 2023. Accepted December 5, 2023.

Correspondence:
Address correspondence to: Andrew T. Gewirtz, PhD, Center for Inflammation, Immunity & Infection, Institute for Biomedical Sciences, Georgia State University, Atlanta, Georgia 30303. e-mail: agewirtz@gsu.edu. Matam Vijay-Kumar, PhD, University of Toledo College of Medicine & Life Sciences, Toledo, Ohio 43614. e-mail: MatamVijay.Kumar@Utoledo.edu.

Conflicts of Interest:
The authors disclose no conflicts.

Funding:
The authors report no funding.

Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research. The authors have received consent/permission from the patient to share his case to *Gastro Hep Advances*.

Reporting Guidelines:
CARE.