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CASE REPORT

Appearance of attenuated intestinal polyposis during chronic non-steroidal anti-inflammatory drugs use

Hugh James Freeman

Hugh James Freeman, Department of Medicine, University of British Columbia, Vancouver, BC V6T 1W5, Canada
Author contributions: Freeman HJ solely contributed to this paper.
Correspondence to: Hugh Freeman, MD, FRCPC, FACP, Department of Medicine, University of British Columbia, 2211 WesbrookMall, Vancouver, BC V6T 1W5, Canada. hugfree@shaw.ca
Telephone: +1-604-8227216 Fax:+1-604-8227236
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Abstract

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDS) may prevent sporadic colonic neoplasia and reduce the polyp burden in familial adenomatous polyposis. A 41-year-old pharmacologist with no family history of intestinal polyps or cancer chronically consumed daily aspirin and other non-steroidal anti-inflammatory drugs for decades despite recurrent and multiple gastric ulcers. A cancerous polyp in the colon was endoscopically resected. Over the next 2 decades, almost 50 adenomatous polyps were removed from the rest of his colon and duodenum, typical of an attenuated form of adenomatous polyposis. Chronic and habitual use of aspirin or NSAIDS may have important significance in delaying the appearance of adenomas. The observations here emphasize the important implications for clinical risk assessment in screening programs designed to detect or prevent colon cancer.

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Key words: Colon cancer; Duodenal adenoma; Colon adenoma; Aspirin; Non-steroidal anti-inflammatory drugs; Attenuated polyposis; Chemoprevention of colon cancer

Peer reviewer: Narasimham Laxmi Parinandi, PhD, Associate Professor, Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, the Ohio State University College of Medicine, 473-W 12th Avenue, Ohio State University, Columbus, OH 43210, United States

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INTRODUCTION

Several studies in the past 3 decades, recently reviewed, support a role for aspirin and some non-steroidal anti-inflammatory drugs (NSAIDS) in reducing risk for sporadic colorectal cancer and adenomas[1]. Similar conclusions were reached in a recently conducted meta-analysis[2]. These studies have also suggested similar conclusions for familial adenomatous polyposis (FAP) or FAP[3]. Some proposed mechanisms for NSAIDS to reduce cancer risk include COX-2 inhibition, inhibition of nuclear factor kappa B, apoptosis induction by p38 kinase activation, and polyamine catabolism[1]. For those categorized as average risk for colon cancer, harm from NSAIDS may exceed benefit and their routine use has not been recommended[4]. Besides added cardiovascular events, the risk of gastrointestinal ulceration and bleeding from NSAIDS is significant[5]. For those thought to be high-risk, however, further studies have been suggested[6,7].

CASE REPORT

A 41-year-old pharmacology professor was evaluated in 1985 for epigastric pain. Past history included recurrent duodenal ulcers over a 20 year period associated with continuous daily NSAIDS use for joint pain, positive antinuclear antibodies (titer, 1:320) and anti-DNA antibodies consistent with systemic lupus erythematosus. There was no family history of neoplastic disease. Endoscopy

showed gastric and duodenal erosions. He was prescribed ranitidine, but he self-medicated with daily aspirin.

In June 1991, dysuria and pneumaturia with fever, chills and flank pain developed requiring antibiotics. Cystoscopy, contrast and computed tomography imaging studies of the urinary tract and colon showed diverticulosis and a colo-vesical fistula while 2 sigmoid colon polyps were detected with colonoscopy: a 1.5 cm benign tubular adenoma, completely excised by snare polypectomy, and a 3 cm adenoma with a well-differentiated adenocarcinoma in the cautery line. Left hemicolectomy with removal of the fistulous tract and bladder repair were done. No residual cancer or additional colon polyps were present in the resected colon.

In December 1991, epigastric pain recurred. However, he continued to self-medicate with continuous daily aspirin and multiple NSAIDS: piroxicam, rofecoxib and tolmetin. He tried to control his pain with added misoprostol, antacids and sulcralfate. Endoscopy showed a benign gastric ulcer. Silver stains were negative for *Helicobacter pylori* and gastrins were normal. Daily omeprazole was prescribed. Endoscopy in April 1993 showed gastritis alone. He continued to use aspirin with codeine each day for his joint pain along with omeprazole. Colonoscopies in June 1992 and March 1993 showed a well-healed anastomosis with no new polyps.

From 1994 to 2000, colonoscopies led to endoscopic removal of 5 small tubular adenomas. In September 2001, endoscopy revealed another separate benign gastric ulcer and omeprazole was prescribed. Colonoscopic excision of a 1 cm villous adenoma in the ascending colon was done. In December 2002, endoscopy and colonoscopy showed inflammatory and reactive gastric polyps, a normal duodenum and multiple tubular adenomas in the cecum. Although some were excised, a right hemicolectomy was required to remove a large flat adenoma in the cecum along with 23 tubular adenomas in the cecum and ascending colon, all with low grade dysplasia, estimated to be 3-15 mm in size. In September 2003, upper endoscopy showed inflammatory gastric polyps and a 3-4 mm sessile polypoid lesion in the duodenum while colonoscopy of the residual colon showed 6 colonic polyps, each measuring about 3-4 mm; all were completely excised and defined as tubular adenomas.

Based on the large number of adenomas and multiple sites in colon and duodenum, an attenuated intestinal polyposis syndrome was diagnosed. No dermatologic, dental or ocular manifestations were present. Gene testing in 2 independent centers for adenomatous polyposis coli (protein truncation test) and mutY homolog (MYH) were both negative. Over the next 6 years, additional small colon tubular adenomas were excised during annual colonoscopies. In addition, recurrent benign gastric ulcers were detected. The patient continued to self-medicate with aspirin and other NSAIDS on a daily basis.

DISCUSSION

Despite background gastric ulcers attributed to ongoing "toxic" self-medication with aspirin and other NSAIDS, this patient initially appeared with an invasive colon carcinoma followed only later by the appearance of numerous duodenal and colonic neoplastic polyps in multiple sites. This was a distinctly unusual presentation, and only retrospectively, after many years of careful clinical follow-up, could be attributed to the classical phenotype of an attenuated intestinal polyposis syndrome. Classical FAP and MYH were excluded[8] by genetic testing through 2 independent laboratories. Likely, a lower penetrance susceptibility gene as a cause for this clinical presentation was present[9]. Recent genome-wide association studies have also identified numerous other loci that may account for up to 6% of all colorectal cancer cases. In addition, certain genetic variants or polymorphisms may be associated with increased colon cancer risk[10]. These may serve to modify the expression of intestinal adenomatous polyps and colon cancer such that gene-gene or gene-environment interactions may be responsible. For example, one of these genetic variants, ornithine decarboxylase 1 (locus 2p16.3)[11], may modify neoplasia risk, and interestingly, also interact with NSAIDS to modify the risk of adenoma development.

Multiple studies[1-3] have already documented reduced adenoma formation in polyposis syndromes with this broad class of NSAIDS, and these may well have played a role in the time of appearance of different adenomas in the small and large bowel. As suggested here, however, aspirin or other NSAIDS, used on a long-standing and continuous basis, may mask or delay the appearance of intestinal polyps, even in the setting of a polyposis syndrome.

A more important implication here relates to surveillance programs in populations at risk for colon cancer. Clearly, clinicians may increase their level of concern (and frequency of procedures) for later colon cancer development if multiple polyps are detected. Here, the reverse occurred with the emergence of numerous adenomas over time, even after presentation with a malignant polyp. In screening programs for colonic neoplasia, chronic use of daily NSIADS may be a confounding variable in the evaluation of individual risk.

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