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Therapy-associated polyposis – a novel form of acquired gastrointestinal polyposis

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Abstract

Survivors of childhood cancers are at increased risk of developing secondary gastrointestinal cancers, including colorectal cancer later in life, possibly due to abdominopelvic radiotherapy and/or alkylating chemotherapy exposure. Profuse gastrointestinal polyposis is associated with rare, inherited colorectal cancer predisposition syndromes, most commonly caused by mutations in the *Adenomatous Polyposis Coli (APC)* and *MutY Homolog (MYH)* genes. We report five patients with gastrointestinal polyposis developing many years after radiotherapy and chemotherapy for a childhood cancer. All had normal genetic testing of the *APC* and *MYH* genes. Childhood chemotherapy and/or radiotherapy exposure may be an unrecognized cause of acquired gastrointestinal polyposis.

Introduction

Childhood cancer survivors are at increased risk for secondary gastrointestinal cancers, including colorectal cancer (CRC), later in life.¹⁻⁶ While the pathogenic mechanisms remain

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poorly-understood, various studies have suggested an association with alkylating chemotherapy and/or abdominopelvic radiotherapy exposure.¹⁻⁴ Due to this increased risk, the Children's Oncology Group recommends that childhood cancer survivors exposed to at least 30 Gy of abdominal radiotherapy undergo screening colonoscopy every 5 years beginning at age 35, or 10 years after radiation exposure.⁷

Gastrointestinal polyposis is the primary manifestation of various rare, high-penetrance hereditary CRC syndromes, most notably familial adenomatous polyposis (FAP), attenuated FAP (AFAP), *MYH*-associated polyposis (MAP), and the hamartomatous polyposis syndromes. Although many patients undergoing genetic evaluation for hereditary polyposis syndromes are not identified to have germline mutations,^{8,9} there are virtually no known forms of acquired gastrointestinal polyposis. Other loosely-described forms of hereditary polyposis include serrated polyposis and mixed polyposis, though their genetic basis remains undefined.¹⁰⁻¹⁴

We present five cases of non-familial gastrointestinal polyposis occurring many years after chemotherapy and radiotherapy for childhood cancer. None of the patients carry detectable *APC* or *MYH* mutations. We hypothesize that alkylating chemotherapy and/or radiation exposure may be an unrecognized risk factor for acquired gastrointestinal polyposis.

Methods

All five subjects were referred to the Dana-Farber Cancer Institute's Cancer Genetics & Prevention Program for clinical evaluation of possible familial polyposis, based on their personal history of gastrointestinal polyposis. All subjects or their legal guardians provided informed consent to participate in an IRB-approved institutional research registry developed for the purposes of investigating possible genetic and biologic factors that contribute to cancer risk. As part of this protocol, subjects were asked to provide an optional one-time blood sample.

Clinical information, including gender, age, medical, and family histories were obtained from medical records developed as part of the subjects' routine clinical care. All gastrointestinal polyp information was obtained from available medical records, including official pathology reports, endoscopy reports, and operative notes issued as part of the subjects' routine medical care. A gastrointestinal pathologist (J.L. Hornick) reviewed all available and relevant gastrointestinal pathology specimens to confirm the histologic classification. All subjects underwent comprehensive germline testing with full sequencing and large rearrangement analysis of the *APC* gene and full sequencing of the *MYH* gene by a commercial laboratory (Myriad Genetics Laboratories Inc; Ambry Genetics), either as part of their routine clinical care or through research-based testing. Patients 1, 2, 4, and 5 also underwent large rearrangement analysis of the *MYH* gene. Patient 3 had insufficient germline DNA for *MYH* rearrangement analysis.

Cases

Patient 1 was diagnosed with adrenal neuroblastoma at nine months of age, with liver, bone marrow, and skull metastases. He was treated with doxorubicin, vincristine, and dacarbazine

chemotherapy, as well as radiation to the cranium, abdomen, and liver. He developed severe neurocognitive dysfunction, presumed to be from radiotherapy. The development of hematochezia from compulsive rectal digging prompted colonoscopies at ages 24 and 26, which revealed an aggregate of 4 inflammatory/hamartomatous polyps, 2 adenomas, and one hyperplastic polyp. In total, he has had 9 colorectal adenomas and 5 colorectal inflammatory/hamartomatous polyps throughout his life. His first esophagogastroduodenoscopy (EGD) at age 28 revealed at least 20 gastric polyps and 15 duodenal polyps, all of which were inflammatory/hamartomatous on biopsy (Figure 1A). Subsequent EGDs have continued to show dozens of small gastroduodenal inflammatory/hamartomatous polyps (Figure 1E). He has had multiple other neoplasms within his radiation field, including an intra-abdominal desmoid tumor (age 9), a rib osteochondroma (age 16), an occipital bone osteoma (age 22), multiple meningiomas (age 27), a parathyroid adenoma, and bilateral papillary thyroid cancer at age 28 (Table 1). Family history is unknown, since the patient is adopted. Germline sequencing and rearrangement testing of the *APC* and *MYH* genes was normal. He is currently 36 years old and being managed with annual colonoscopies and EGDs.

Patients 2-5 were diagnosed with Hodgkin lymphoma at ages 15-21. All received MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) chemotherapy and radiotherapy to the mantle and para-aortic lymph nodes (Table 1). All were found to have colorectal polyposis on their first screening colonoscopies: Patient 2 had “>30-40” sessile serrated adenomas/polyps (Figure 1B); Patient 3 had “approximately 40” adenomas (Figure 1C); Patient 4 had “approximately 50” polyps which were a mix of adenomas, inflammatory polyps, and mixed hyperplastic polyps/mucosal perineuriomas (Figure 1D); Patient 5 had “many ... flat, carpet-like” sessile serrated adenomas/polyps throughout the entire colorectum. All four have had continued polyp formation on follow up colonoscopies (Figure 1F). Three patients had multiple fundic gland polyps on EGD; one had a chest wall desmoid tumor in her prior radiation field (age 44); one had papillary thyroid cancer (age 32). Three of these patients are being managed by annual endoscopic surveillance whereas the fourth underwent total proctocolectomy. Table 1 provides further information regarding other neoplastic and non-neoplastic findings in these patients. Genetic testing of Patients 2-5 revealed no germline abnormalities in either the *APC* or *MYH* genes.

Discussion

This report brings to light a potentially novel etiology of acquired gastrointestinal polyposis, which we hypothesize to be therapy-associated polyposis (TAP). These five patients were recognized to have gastrointestinal polyposis at a mean of 24.8 years (range 13-35 years) after exposure to alkylating chemotherapy and abdominal radiotherapy for a childhood cancer. Intriguingly, one patient showed predominantly upper GI inflammatory/hamartomatous polyposis, two fulfilled 2010 World Health Organization (WHO) clinical criteria for serrated polyposis syndrome,¹⁴ and two showed a phenotype of AFAP (defined as 20-99 lifetime colorectal adenomas), suggesting potentially different mechanisms of neoplasia. To the best of our knowledge, this is the first report suggesting an association between chemoradiotherapy exposure and the development of acquired gastrointestinal polyposis.

We recognize that the small number of patients and their heterogeneous phenotypes are significant limitations to this report, and we clearly cannot claim any definitive causality between chemoradiotherapy and our patients' polyposis. In spite of such limitations, however, we feel that these patients' striking phenotypes raise an important and biologically plausible hypothesis of an association between their polyposis and chemoradiotherapy exposure, which itself generates intriguing questions and theories about the pathophysiology of acquired polyposis and of therapy-related toxicities. There are, for example, multiple reports linking chemotherapy and radiotherapy exposure to the risk of subsequent colorectal and gastric cancers,^{1,2} prompting the hypothesis that gastrointestinal epithelium can be induced to undergo accelerated neoplasia. The mechanisms underlying such neoplasia are speculative, but may involve abnormalities in *Wnt* signaling. The *APC*^{Min/+} mouse is a well-studied animal model of FAP in which mice carrying a truncating *APC* mutation demonstrate rapid multifocal colorectal neoplasia due to unchecked *Wnt* signaling activation. Intriguingly, prior work has shown that radiation exposure increases the burden of intestinal tumor development in *APC*^{Min/+} mice in a dose-dependent manner, possibly through additional downstream effects on *Wnt* signaling.¹⁵

All five subjects exhibited extracolonic features associated with FAP within their radiation fields, including three with fundic gland polyps, two with desmoid tumors, two with papillary thyroid cancer, and one with an osteoma (Table 1), which raise the question as to whether these subjects could simply have unrecognized FAP/AFAP. We acknowledge that our data do not eliminate the possibility of one or more of these subjects having FAP/AFAP from an unidentifiable germline mutation, although their mixed polyp histologies are inconsistent with classically-defined FAP/AFAP with underlying germline *APC* mutations. This illustrates a common problem in the clinical evaluation of patients with moderate degrees of polyposis, where most are not identified to have germline *APC* or *MYH* mutations.⁸ In such situations, counseling recommendations for patients and their family members usually rely on the assumption that the polyposis is hereditary, though our intent in presenting this series is to raise the hypothesis of the existence, in a subset of such patients, of an acquired form of polyposis.

Curiously, four subjects experienced significant toxicities beyond these FAP-like manifestations, presumably also related to chemoradiation: three have young-onset cardiovascular disease, one has severe neurocognitive deficits, and two had young-onset breast cancer. These findings raise speculation that such patients may have a systemic predisposition to chemotherapy and/or radiotherapy toxicities beyond their gastrointestinal epithelium.

To summarize, we present five cases of therapy-associated polyposis occurring many years after exposure to alkylating chemotherapy and radiotherapy for a childhood cancer. All five patients display extracolonic features mimicking FAP/AFAP, though none have family history or genetic testing results suggesting an inherited syndrome. Our data are insufficient to determine the optimal management of patients with TAP. The fact that none of these patients have had a gastrointestinal malignancy and that four are being managed with aggressive endoscopic surveillance, however, suggests that some TAP patients may be able to avoid prophylactic colectomy, which is considered to be a standard risk-reducing

intervention for FAP patients. Furthermore, family members of TAP patients may be reassured that the predisposition to polyps may not be hereditary. These findings and proposed hypotheses should be studied in larger cohorts of childhood cancer survivors to better understand the prevalence, pathophysiology, and management of TAP.

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Abbreviations

APC	<i>Adenomatous Polyposis Coli</i>
AFAP	Attenuated familial adenomatous polyposis
CRC	Colorectal cancer
EGD	Esophagogastroduodenoscopy
FAP	Familial adenomatous polyposis
MOPP	Mechlorethamine, vincristine, procarbazine, prednisone
MYH	<i>MutY Homolog</i>
MAP	<i>MutY Homolog</i> -associated polyposis
TAP	Therapy-associated polyposis
WHO	World Health Organization

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Figure.

A, gastric inflammatory/hamartomatous polyp from Patient 1 (original magnification, 40 $\times$). B, ascending colon sessile serrated adenoma/polyp from Patient 2 (original magnification, 200 $\times$). C, descending colon tubular adenoma from Patient 3 (original magnification, 200 $\times$). D, descending colon mixed hyperplastic polyp/mucosal perineurioma from Patient 4 (original magnification, 200 $\times$). E, esophagogastroduodenoscopy from Patient 1 showing

multiple gastric body inflammatory/hamartomatous polyps. F, colonoscopy from Patient 3 showing multiple rectal adenomas.

Table 1

Gastrointestinal polyposis and other clinical characteristics in five survivors of childhood cancer

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	Male	Female	Female	Male	Female
Original cancer/stage	metastatic neuroblastoma	stage IIIA Hodgkin lymphoma	stage IIB Hodgkin lymphoma	stage IIA Hodgkin lymphoma	stage IIA Hodgkin lymphoma
Age at original cancer	9 months	21 years	15 years	18 years (para-aortic relapse at age 20)	16 years
Chemotherapy	doxorubicin, vincristine, dacarbazine	MOPP (mechlorethamine, vincristine, procarbazine, prednisone)	MOPP	MOPP (age 20)	MOPP
Sites of radiation therapy	Cranium, abdomen, liver	Mantle, para-aortic nodes	Mantle, para-aortic nodes	Mantle (age 18); para-aortic, iliac, inguinal nodes (age 20)	Mantle, axilla, para-aortic, pelvic lymph nodes
Age at recognition of first polyp	24 years	47 years	43 years	33 years	51 years
Latency between chemoradiation and recognition of polyposis	22 years	26 years	28 years	13 years	35 years
Primary polyp manifestation	Gastroduodenal hamartomas	Colorectal sessile serrated polyps	Colorectal adenomas	Colorectal adenomas	Colorectal sessile serrated polyps
Other GI neoplasia	Multiple colorectal adenomas and hamartomas	Multiple colorectal adenomas and hyperplastic polyps; Barrett's esophagus	Multiple colorectal sessile serrated and hyperplastic polyps; multiple fundic gland polyps	Multiple colorectal mixed hyperplastic polyp/mucosal perineuriomas; multiple fundic gland polyps	Multiple fundic gland polyps
Family history	Adopted/unknown	No known GI cancers; mother with <10 lifetime colorectal polyps	No known GI cancers; two siblings each with <5 colorectal polyps	Adopted/unknown	No known GI cancers or polyps
Current management of polyposis	Annual EGD and colonoscopy	Annual colonoscopy	Annual colonoscopy	Annual colonoscopy	Status-post total proctocolectomy
Other neoplasia	Retroperitoneal desmoid tumor (age 9); occipital osteoma (age 22); papillary thyroid cancer (age 28); multiple meningiomas; parathyroid adenoma	Invasive ductal breast cancer (age 32); extra-abdominal desmoid tumor (age 44)	Papillary thyroid cancer (age 32); unilateral invasive breast cancer and bilateral DCIS (age 40)	None	None
Non-neoplastic medical history since chemoradiation	Cognitive/behavioral deficits; osteopoikilosis	High-grade heart block requiring pacemaker	Pneumonitis; early-onset coronary artery disease; aortic stenosis; cardiomyopathy	None	Hypothyroidism; cardiomyopathy