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Pediatric manifestations of Lynch Syndrome: A single center experience

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Abstract

Lynch syndrome is an autosomal dominant condition caused by a heterozygous variation in one of the DNA mismatch repair (MMR) genes that pre-disposes individuals to early onset colorectal cancers and other malignancies. Lynch syndrome is generally considered an adult-onset disorder, with malignancy rarely manifesting in childhood. Colorectal cancer is extremely rare in children, but hereditary syndromes including Lynch syndrome are an important cause. We aimed to assess the frequency and clinical course of children with Lynch syndrome associated pediatric colorectal cancers at our institution over the last 20 years.

In this retrospective study, we describe four cases of children with Lynch syndrome-associated colorectal cancers age 14–17 years at diagnosis. All patients were diagnosed with Lynch syndrome after diagnosis, despite three of them having family histories consistent with Lynch syndrome.

This series highlights a rare but important cause of pediatric malignancy and points to the need for early education on colorectal cancer warning symptoms and open discussion about this condition in affected families. It also illustrates the need for a thorough family history and a high level of suspicion for Lynch syndrome in children based on family background, as early detection may be key to improving cancer outcomes.

Keywords

Pediatric; Cancer; Colorectal; Lynch syndrome; HNPCC; Genetics; Surgery

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Authorship

All authors attest that they meet the current ICMJE guidelines for authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

1. Introduction

Lynch syndrome, also known as hereditary non-polyposis colon cancer (HNPCC), is an autosomal dominant genetic condition that pre-disposes individuals to early onset colorectal cancers, as well as several other extra-intestinal cancers including endometrial, ovarian, gastric, pancreas, biliary, skin, and central nervous system tumors [1,2]. Lynch syndrome is due to heterozygous germline pathogenic variants in one of five recognized DNA mismatch repair (MMR) genes: MLH1, MSH2, MSH6, PMS2, and EPCAM. Lynch syndrome was first described by Dr. Henry Lynch in 1985, and is now recognized as the most common inherited cause of colorectal cancer, with a prevalence of about 1 in 300 in the adult population [1–3]. Lynch syndrome is typically considered an adult-onset disorder with a mean age of colorectal cancer diagnosis of 45 years, with malignancy only rarely manifesting in children [1,3].

In children, primary colorectal cancer is an exceedingly rare condition that affects less than 2 in 1 million children [4]. However, in those children who do develop colorectal cancer, it is generally diagnosed at late stages with a poor prognosis [5,6]. Though colorectal cancer is uncommon in children, Lynch syndrome is an important cause of this and other malignancies in pediatric patients, and it is essential that providers recognize this condition in order to pursue appropriate genetic screening of at risk and affected children and their families [3]. Here, we describe four cases of children with Lynch syndrome (heterozygous DNA MMR mutations, as described above) and associated early onset colorectal cancers managed at our center.

2. Methods

In this retrospective, institutional review board (IRB) approved study, we searched our center's internal patient database using International Classification of Diseases (ICD) codes. We searched for all patients ≤ 18 years from January 2000–December 2020 with diagnosis codes for genetic susceptibility to unspecified neoplasms, genetic susceptibility to breast and ovarian neoplasm, and all diagnosis codes for benign and malignant neoplasms of the colon. Review of the electronic medical record was conducted for all patients. Patients with other genetic syndromes, non-genetic cases of colorectal cancer, or patients for whom genetic studies were not obtained were excluded. Patients 18 years or younger with an established genetic diagnosis of Lynch syndrome were included. Consent to publish this series was not required by our IRB and was not obtained as this report does not contain any personal information that could lead to identification of the patients.

3. Results

We identified 147 patients in our search, 23 of whom were found to have Lynch syndrome, as described in Table 1. Median age of Lynch syndrome diagnosis was 16 years, with the youngest patient being 6 years old (patient age range: 6–18 years). The majority (91.3%) had a known family history of Lynch syndrome at the time of diagnosis, and/or had a family history of Lynch associated cancers (82.6%).

Of these 23 children and adolescents identified with Lynch syndrome, four developed colorectal cancer, as summarized in Table 2 and described in the following cases. One additional patient developed Stage IV proximal stomach/gastroesophageal junction adenocarcinoma (diffuse type). This was a 17-year-old male with Crohn's disease, congenital cleft lip and palate and a known family history of Lynch syndrome due to a pathogenic variant in MSH6, specifically c.3939_3940dupTC. The patient underwent panel based genetic testing from a commercial genetic testing laboratory and was found to carry the familial MSH6 pathogenic variant and a pathogenic CDH1 variant, specifically c.1565 + 2_1565+3insTT. Pathogenic variants in the CDH1 gene are associated with autosomal dominant hereditary diffuse gastric cancer syndrome. This patient ultimately passed away from the cancer following chemotherapy. The rest of the children identified with Lynch syndrome in this cohort (n = 18) did not develop any malignancy during the study period, though two of those patients were lost to follow up.

Among the 18 patients diagnosed with Lynch syndrome who did not develop cancer, the majority (16, 88.9%) underwent testing due to a known family history of Lynch syndrome. The two patients who did not undergo testing based on a family history of Lynch syndrome included one patient who underwent testing due to their parent developing early onset colon cancer and skin cancer. The parent underwent testing simultaneously and was also diagnosed with Lynch syndrome. The other patient underwent genetic testing for unrelated reasons, and was incidentally found to have Lynch syndrome, which was then subsequently diagnosed in the patient's father. Ten (55.6%) of these 18 patients were undergoing colonoscopic screening during the study period, with the age at first screening ranging from 11 to 21 years. The youngest patient to begin screening at age 11, did so because of a colorectal cancer diagnosis in a sibling at age 21. Seven (38.9%) of the patients did not have any documented screening plan, and one patient (5.6%) planned to begin screening at age 25.

Case 1.

17-year-old previously healthy male who presented to the ED with abdominal pain and nausea and was found to have perforated invasive mucinous adenocarcinoma of the transverse colon (Stage IIIC), requiring emergent transverse colectomy. He had a family history of Lynch Syndrome and associated cancers in his mother and several other relatives. He was referred to genetic counseling and underwent panel based genetic testing from a commercial genetic testing laboratory which identified that he carried the known familial MSH2 pathogenic variant, specifically c.942+3A > T. He had not undergone screening or genetic testing prior to the cancer diagnosis. He received chemotherapy (FOLFOX), then immunotherapy (nivolumab and ipilimumab), followed by tumor debulking and resection of an isolated liver lesion. Presently, he has no evidence of disease (NED) with followup of approximately one year.

Case 2.

14-year-old previously healthy female who presented with colonic obstruction and was diagnosed with moderately differentiated rectal adenocarcinoma (Stage IV), with no known family history of Lynch Syndrome or Lynch associated cancers. She underwent sigmoid and small bowel resections for metastatic disease in addition to end colostomy. The

patient underwent panel based genetic testing from a commercial genetic testing laboratory which identified a heterozygous pathogenic variant in MLH1, specifically c.2157dup. Immunohistochemistry (IHC)was subsequently performed on the tumor and showed loss of MLH1 and PMS2 expression. MLH1 promotor hypermethylation was completed and was present. Parental testing for the MLH1 pathogenic variant was consistent with a de novo mutation. The patient underwent chemotherapy (FOLFOXIRI), followed by immunotherapy (pembrolizumab), then completion total colectomy with surgical resection as well as tumor debulking and management of liver lesions. She has ongoing disease requiring continued immunotherapy (pembrolizumab) with followup of approximately 16 months.

Case 3.

15-year-old previously healthy male diagnosed with invasive mucinous rectal adenocarcinoma (Stage IIIC). IHC testing completed on his tumor identified loss of MSH2 and MSH6 expression. He did not have an established family history of Lynch syndrome but did have several family members with potentially Lynch associated cancers. Testing for the MSH2 and EPCAM genes was completed through a commercial genetic testing laboratory which identified a pathogenic variant in MSH2, specifically c.942+3A > T. It was not documented if the patient's parents underwent genetic testing. The patient underwent surgical resection of the tumor, chemotherapy (capecitabine and oxaliplatin), and radiation, and currently has NED with followup of approximately three years.

Case 4.

15-year-old previously healthy female who presented with abdominal pain and anemia and was found to have invasive mucinous sigmoid adenocarcinoma (Stage IV). IHC testing completed on her tumor identified loss of PMS2 expression. Genetic testing was unable to be completed due to lack of insurance coverage for genetic consultation. The patient had a family history significant for her paternal grandfather with a history of colon cancer at age 75. She underwent chemotherapy (FOLFOX + Cetuximab), followed by surgical resection, and immunotherapy (pembrolizumab for one year, followed by nivolumab and ipilimumab). She continues to undergo treatment with followup of approximately two years.

4. Discussion

Lynch syndrome accounts for about ~2–3% of colorectal cancers in the adult population, but its prevalence among children is not well defined, due in part to the rarity of pediatric colorectal cancers [8]. Herein we describe four cases of children with Lynch syndrome associated colorectal cancers, all of whom were diagnosed with Lynch syndrome at the time of cancer diagnosis. Two of these patients had likely de novo pathogenic variants, one patient had a known family history of Lynch syndrome, and one patient had a family history of Lynch syndrome related cancers, but no prior genetic evaluation in other family members. The patient with a family history of Lynch syndrome had not undergone screening or genetic testing prior to cancer diagnosis. This case series adds to the very limited literature describing cases of pediatric colorectal cancer associated with Lynch syndrome [9,10].

Current guidelines call for screening colonoscopy to begin in patients with Lynch syndrome between age 20–25, with repeat colonoscopies to occur every two years unless findings dictate otherwise [2,12–14]. In families with particularly early-onset colorectal cancers, screening should begin two to five years prior to the earliest colorectal cancer diagnosed before age 25 [2,13,14]. Genetic testing is typically offered after age 18 in families with known Lynch syndrome, though the appropriate age for testing has been debated [2]. In families with early-onset Lynch syndrome associated malignancies, young children have been referred for genetic counseling [15]. This raises some challenging ethical issues surrounding genetic testing in children, including psychological consequences of health anxiety in parents and children related to cancer predisposition syndromes, and concern for discrimination in obtaining life or health insurance as adults [15–17]. For these reasons, hesitancy around genetic testing persists for some, and there remain large numbers of at-risk individuals even in families with an established Lynch syndrome diagnosis [18].

Current criteria for genetic evaluation for Lynch syndrome includes a personal history of a tumor with mismatch repair deficiency at any age, the diagnosis of colorectal cancer or uterine cancer before the age of 50 years, a synchronous or metachronous Lynch syndrome related cancer at any age, a first degree relative or second degree relative with a Lynch syndrome related cancer diagnosed before 50 years, or a family history of two or more first or second degree relatives with a Lynch syndrome related cancer regardless of age [13,14]. Early detection of cancer in Lynch syndrome has been shown to improve outcomes, and this could be particularly important in pediatric cases where baseline prognosis is already poor due to typically advanced stage at diagnosis [6,19].

In the adult population, most Lynch syndrome associated colorectal tumors are poorly differentiated with mucinous or medullary features and lymphocyte infiltration, due to the extensive mutation burden seen in these tumors [20,21]. This held true in our series with three of the four cancer cases having tumors with mucinous pathology. Despite this, adult colorectal cases with DNA MMR mutations tend to have earlier detection and lower rates of metastasis than MMR proficient tumors, and those with metastatic disease tend to have better outcomes than in stage-matched MMR proficient colorectal cases.

In children, Lynch syndrome associated colorectal cancers remain rare so these trends are not well defined. However, it is notable that despite advanced stage at diagnosis, all patients in this series are still alive, with two achieving NED status. This further supports the importance of early detection in these cases, as there may be a similar survival advantage in pediatric cases of Lynch associated colorectal cancers, if appropriately managed. This supports the need for pediatric providers to take a thorough family history during patient consults, and maintain a level of suspicion for Lynch Syndrome, even in young patients. Additionally, this highlights the importance of colorectal cancer symptom education in families with known Lynch Syndrome as well as open discussion in affected families about the diagnosis with children to facilitate early cancer detection.

In cases where Lynch syndrome is suspected, either based on family history or IHC testing results, strong consideration should be given to genetic panel-based testing, as even in a family with a known single pathogenic variant there may be other variations contributing

to cancer risk as well, as was the case here in the child with both MSH6 and CDH1 variations. Pathogenic variants in MLH1 and MSH2 have been reported to account for 60–80% of Lynch syndrome associated colorectal cancers, and that held true in this series with 3 of 4 cancer cases being associated with one of these [20]. However, other MMR pathogenic variants can be associated with risk of extraintestinal Lynch syndrome-associated malignancies as well. For instance, MSH6 and PMS2 pathogenic variants have been shown to double breast cancer risk by age 60, and there is population-based data to suggest that these variants are more prevalent in the general population than MLH1 and MSH2 [22,23]. As such, panel-based testing may help individuals better understand their overall cancer risk, even in the context of a known familial MMR variation.

5. Conclusion

Colorectal cancer remains rare in the pediatric population, but Lynch syndrome can be an important cause of this and other pediatric malignancies. Though small, this case series supports the need for thorough education on symptoms of colorectal cancer in affected families as well as open discussion of this diagnosis with children, to best facilitate early detection and improve outcomes. Additionally, given the frequency of Lynch syndrome in pediatric colorectal cancers, it is important that specimens from these cases undergo IHC testing in order to screen for DNA MMR pathogenic variations. Further studies are merited to better delineate the frequency with which Lynch syndrome truly does contribute to pediatric colorectal cancers.

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Table 1

Description of all Lynch syndrome patients.

	Patients ≤ 18 Years at Lynch Syndrome Diagnosis (n = 23)
Age at Lynch syndrome Diagnosis (years)	Range: 6–18
	Median: 16 [15,18] *
Sex (M/F)	10 Female (43.4%)
	13 Male (56.5%)
Known Lynch syndrome Pathogenic Variant	MHL1: 6 (26.1%)
	MSH2: 7 (30.4%)
	PMS2: 5 (21.7%)
	MSH6: 2 (8.7%)
	>1 Pathogenic Variant: 3 (13.0%)
Known family history of Lynch syndrome at Diagnosis	21 (91.3%)
Family History of Lynch syndrome related cancers	Yes- 19 (82.6%)
	No- 2 (8.7%)
	Unclear- 2 (8.7%)
Cancer at time of Lynch syndrome Diagnosis	5 (21.7%)

Table 1: Results are expressed as raw counts with percentage of total patients, unless otherwise specified.

* Median with quartiles [Q1, Q3].

Table 2

Description of patients with Lynch syndrome that developed colorectal cancer (n = 4).

Age at Cancer Diagnosis (Years)	Sex (M/F)	Lynch syndrome Associated Pathogenic Variant	Known Lynch syndrome Prior to Cancer Diagnosis?	Known Family History of Lynch syndrome at Diagnosis?	Cancer Type	Cancer Stage at Diagnosis	Current Status
17	M	MSH2 c.942+3A > T	No	Yes	Colon Adenocarcinoma	IIIC	No evidence of disease (NED) (~1 year)
14	F	MLH1 c.2157dup	No	No	Rectal Adenocarcinoma	IV	Ongoing treatment
15	M	MSH2 c.942+3A > T	No	No (but likely)	Rectal Adenocarcinoma	IIIC	NED (~4 years)
15	F	Likely PMS2	No	No	Colon Adenocarcinoma	IV	Ongoing treatment