Oncologic Surveillance for Subjects With Biallelic Mismatch Repair Gene Mutations: 10 Year Follow-Up of a Kindred

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BACKGROUND

Lynch syndrome (LS), also known as hereditary nonpolyposis colorectal cancer (HNPCC), is the most common inherited colorectal cancer (CRC) syndrome with an estimated lifetime CRC risk of 12–48% [1]. Affected individuals are also predisposed to extra-colonic malignancies, primarily endometrial cancer and to a lesser extent, other gastrointestinal, gynecological, and genitourinary cancers [2]. LS is caused by heterozygous germline mutations in the DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6, or PMS2 and is characterized by high frequency of tumor microsatellite instability (MSI-H).

Over the last decade, a novel childhood cancer syndrome associated with biallelic MMR gene mutations (bMMR) has been described [3,4]. This distinct syndrome is characterized by brain tumors, leukemias, lymphomas, and gastrointestinal polyposis with early-onset colorectal and small bowel cancer, often associated with café-au-lait spots (CALS) and other stigmata of IBD [3]. These children usually succumb to multiple cancers before adulthood. We developed a surveillance protocol aiming at early detection for these individuals and report the 10-year experience with a kindred. Methods. On the basis of genetic testing and early age tumors, the kindred started a cancer surveillance protocol based on the crude estimates of cancer risks and available cancer screening: imaging, endoscopy, and hematologic tests. Results. Over the 10-year follow-up period, the screening protocol detected 15 tumors. These included three high-grade adenomatous colonic polyps and two colon cancers. In one child, MRI revealed an asymptomatic anaplastic astrocytoma which was treated by complete resection and radiation. All three cancers identified during surveillance were small and asymptomatic at diagnosis. The two sisters are currently 16 and 18 years of age with no evidence of malignant disease. Both parents have annual colonoscopies and the father at 43 years had two colonic adenomatous polyps.

Conclusions. We report on the long-term outcome in patients with biallelic MMR mutations who benefited from prophylactic cancer surveillance. Genetic screening and subsequent surveillance led to earlier recognition of asymptomatic tumors at stages more amenable to resection and probable cure. Multicenter collaboration and implementation of surveillance guidelines is necessary to further determine genotype-phenotype correlations.

Key words: biallelic germline mismatch repair gene mutations; brain tumors; cancer surveillance; gastrointestinal cancer

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TABLE I. Management Recommendations for Biallelic MMR Carriers

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Surveillance strategy</th>
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<tbody>
<tr>
<td>Children</td>
<td>Colon: Colonoscopy annually&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Upper GI tract and small bowel: EGD annually&lt;sup&gt;a&lt;/sup&gt;, video capsule endoscopy annually</td>
<td></td>
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<tr>
<td>Brain&lt;sup&gt;b&lt;/sup&gt;: Ultrasound at birth then MRI brain every 6 months</td>
<td></td>
</tr>
<tr>
<td>Leukemia&lt;sup&gt;b&lt;/sup&gt;, lymphoma&lt;sup&gt;b&lt;/sup&gt;: Complete blood count, erythrocyte sedimentation rate, lactate dehydrogenase every 4 months</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>Uterus: Ultrasound annually</td>
</tr>
<tr>
<td>Urinary: Ultrasound annually</td>
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EGD, esophagogastroduodenoscopy. <sup>a</sup>Beginning at 3 years of age or at diagnosis; <sup>b</sup>Brain, leukemia/lymphoma screening should commence at birth if diagnosed prenatally.

METHODS

A surveillance protocol was established for this bMMR kindred based on age and crude estimates of cancer risks and available cancer screening modalities (Table I). Management and surveillance strategies were developed based on reports of hematologic and lymphoid malignancies, brain tumors, gastrointestinal, and gynecological cancers in homozygous or compound heterozygous MMR-deficient families [4,5,10–16]. During childhood, the screening protocol focused on detection of brain tumors, leukemias, lymphomas, and gastrointestinal malignancies. A rapid total body MRI was our initial recommendation. However, since brain tumors appear to be the most common solid tumor diagnosed in patients with bMMR gene mutations, the protocol was altered to include a more sensitive focused brain MRI. For hematologic malignancies including leukemias and lymphomas; complete blood count, erythrocyte sedimentation rate, and lactate dehydrogenase were performed every 6 months as previously described by our group [6]. Gastrointestinal surveillance included annual upper and lower endoscopy and capsule endoscopy. Upon reaching adulthood, our protocol added the general recommendations for individuals with LS to include gynecological and urinary tract screening [1,8].

To assess the protocol in this family, reviews of the medical records of the siblings and parents were performed. All diagnostic imaging, endoscopy, operative, and pathology reports were reviewed. Informed consent was obtained for performing the surveillance and for reporting the follow-up. The parents were advised to have colonoscopy every 1–2 years per LS guidelines and the mother was referred for yearly CA-125 blood test and transvaginal and pelvic ultrasonography with consideration of TAH-BSO after childbearing years. We describe here the surveillance results of the proband’s siblings and parents over the last 10 years.

RESULTS

Clinical and Molecular Diagnosis of bMMR in the Kindred

The proband was diagnosed at 11 years of age with duodenal adenocarcinoma metastatic to the liver. He died rapidly of disseminated disease. His 9-year-old sister presented months later with mild abdominal pain, and was noted to have café-au-lait macules and axillary freckling. She was investigated extensively because of her brother’s history. Abdominal ultrasonography and computerized tomography demonstrated a 1.6 cm x 1.4 cm x 2 cm left upper quadrant mass which, upon biopsy was confirmed to be metastatic adenocarcinoma consistent with a primary intestinal tumor. Colonoscopy confirmed three malignant colonic polyps. She underwent total colectomy with ileorectal anastomosis and chemotherapy and remains in remission 8½ years later. The 6-year-old sister had café-au-lait macules, hairy nevi, and a plexiform neurofibroma of the tongue. The parents are first cousins (Fig. 1). The young ages of these children and the rarity of their gastrointestinal cancers led to the search for a heritable genetic mechanism.

The proband’s metastatic duodenal cancer and his sister’s malignant colon polyps exhibited high-frequency microsatellite instability but had detectable MLH1, MSH2, and MSH6 protein expression by immunohistochemistry. The plexiform neurofibroma in the youngest sister showed intact protein expression and was microsatellite stable. As germline DNA MMR gene deficiency may be associated with intact immunohistochemical DNA MMR gene expression in tumors, DNA sequencing was undertaken. All three children harbored a germline homozygous MLH1 missense mutation in exon 18 (c.2059C>T, p.Arg687Trp), and both parents were heterozygous for this mutation.

Malignant and Premalignant Neoplasms Detected by the Surveillance Protocol

Over the 10-year follow-up period, the surveillance protocol detected 15 tumors in the two sisters with biallelic MLH1 mutation (Table II). The two sisters have survived three malignant neoplasms detected at an early stage of the disease and three tumors showed high grade dysplasia. Both sisters, currently 16 and 18 years old of age, are alive and well.

The youngest sister (IV-3, Fig. 1) had preventive total colectomy and ileorectal anastomosis at age 9. Seven years after starting the surveillance protocol, she was diagnosed with an asymptomatic malignant brain tumor by surveillance rapid whole-body MRI (Fig. 2) at 13 years of age. This small lesion was completely resected. Pathology revealed anaplastic astrocytoma with clear microscopic margins. She was treated with focal radiation to a dose of 54 Gy with no evidence of recurrence 3½ years later. At 16 years of age, a 0.5 cm jejunal adenocarcinoma was diagnosed within an adenomatous polyp, with a metastatic duodenal lymph node. She underwent resection of the tumor.
and a limited lymph node dissection and at the time of this report is nearing completion of chemotherapy. Additionally, five premalignant gastrointestinal lesions were resected over the last decade not requiring further therapy. She is currently free of disease.

Additional Findings Detected During Surveillance

For the younger sister, a left renal cortical cyst (1.5 cm × 1.4 cm) seen on initial baseline ultrasound and CT imaging of the abdomen has remained unchanged after 10 years. Pelvic ultrasound shows functional ovarian cysts. For the older sister, annual rapid whole-body MRI had identified hepatic lesions that were biopsied previously and found to be consistent with hepatic adenoma [17]. These have remained unchanged in follow-up imaging.

**Surveillance for the Asymptomatic Parents**

The father had two tubular adenomas with low-grade dysplasia removed from the ileocecal valve and the left colon at age 43. He also had a benign paracalyceal cyst in the right kidney identified by abdominal ultrasound. The mother had no evidence of adenomatous polyps or CRC. She had a vaginal hysterectomy at age 39 which showed a benign endocervical polyp. She continues to have annual pelvic and abdominal ultrasounds to monitor her ovaries.

**DISCUSSION**

We demonstrate the feasibility and efficacy of this comprehensive clinical protocol which can detect asymptomatic neoplasms in carriers of bMMR gene mutations, potentially leading to reduced cancer mortality. All tumors detected were asymptomatic,

**TABLE II. Asymptomatic Tumors Detected During Surveillance (n = 15)**

<table>
<thead>
<tr>
<th>Family member</th>
<th>Tumor and site</th>
<th>Pathology</th>
<th>Age at diagnosis (years)</th>
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<tbody>
<tr>
<td>Sister IV-3</td>
<td>Cecum and transverse colon polyps&lt;sup&gt;b&lt;/sup&gt; (n = 3)</td>
<td>Adenomatous high grade dysplasia</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Renal mass</td>
<td>Cyst</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Duodenal polyp</td>
<td>Adenomatous low grade dysplasia</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Brain tumor&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Anaplastic astrocytoma</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Duodenal polyp</td>
<td>Adenomatous low grade dysplasia</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Jejunal tumor</td>
<td>Adenocarcinoma</td>
<td>16</td>
</tr>
<tr>
<td>Sister IV-2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hepatic mass</td>
<td>Hepatic adenoma</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Gastric polyp</td>
<td>Hyperplastic</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Gastric polyp</td>
<td>Hyperplastic</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Ileal nodules (counted as 1 in total)</td>
<td>Adenomatous low grade dysplasia</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Duodenal polyp</td>
<td>Adenomatous low grade dysplasia</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Duodenal polyp</td>
<td>Adenomatous low grade dysplasia</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Rectal polyp</td>
<td>Adenomatous low grade dysplasia</td>
<td>16</td>
</tr>
</tbody>
</table>

<sup>a</sup>Diagnosed with adenocarcinoma of the colon prior to starting the screening protocol; <sup>b</sup>Underwent total colectomy and ileorectal anastomosis.

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and all of the malignant or high-grade dysplastic tumors identified were small, enabling complete surgical resection. Of note, complete resection of anaplastic astrocytoma when symptomatic is rare. Moreover, although both sisters underwent preventive total abdominal colectomy with ileorectal anastomosis, they continue with annual rectal surveillance and upper endoscopy with capsule endoscopy which recently detected an early asymptomatic jejunal carcinoma.

Protocols for genetic testing and evidence-based surveillance and prophylactic surgery have been developed for predisposition syndromes including Familial Adenomatous Polyposis (FAP) [2]. The long-term outcome in FAP has significantly improved since the implementation of these surveillance guidelines. Adenocarcinoma of the small bowel has been reported in patients with bMMR gene mutations at a mean age of 20 years [5]. Surveillance of the small bowel for polyps is challenging. This is relevant for both the FAP population and patients with biallelic MMR mutations. Patients from other kindred with biallelic MMR mutations that we follow with this surveillance protocol have had duodenal polyps diagnosed with high-grade dysplasia. Follow-up in other kindreds is less than 5 years. The polyps have been removed successfully by endoscopy and/or surgical intervention.

We recently reported survival benefit with early detection of brain tumors for another familial cancer predisposition syndrome [6]. Since most malignant gliomas in the context of bMMR have been reported to be fatal [13,14], our patient surviving long term following early detection is striking and suggests a benefit of pre-symptomatic early detection.

This family highlights the challenges and heterogeneity of bMMR syndromes. First, most children with bMMR present with malignant brain tumors or lymphomas/leukemias. In this kindred, the gastrointestinal phenotype is remarkably penetrant and similar among the three siblings. All were diagnosed with very early onset gastrointestinal cancer, metastatic to regional lymph nodes when the adenocarcinomas were still very small.

The first-cousin parents have remained unaffected by cancer. Despite having a large extended family, there are only two LS-related cancers reported in the extended family including over the

![Fig. 2.](image.png) Surveillance MRI reveals an asymptomatic malignant glioma. A: Routine total body MRI reveals a small asymptomatic lesion in the left parieto-occipital lobe. B: T1 weighted MRI demonstrating the lobulated left parietal intra-axial tumor.
past decade. This type of family history is common in bMMR families making the diagnosis possible only after the first affected child is diagnosed. High index of suspicion in cases of consanguinity and a child with features of NF1 would be life-saving in this context. The reasons for lack of LS presentations in these families are still unclear, however, many of the MMR mutations in these families are likely less functionally deleterious than most mutations in typical LS families [3,5].

The use of rapid whole-body MRI and DNA analysis for T-cell and B-cell rearrangement for lymphoma and leukemia are still controversial, though they may be considered in a research setting [18]. Interestingly, the rapid total body MRI detected additional structural anomalies in other organs. Although these were nonmalignant and did not progress over the past several years, ongoing studies may uncover new tumors in other tissues which will change the spectrum of the known phenotype of bMMR. This is especially important since currently most bMMR patients are not surviving to adulthood and the spectrum of their tumors in later years is therefore unknown. Brain MRI and endoscopic evaluation will require anesthesia in young children with known potential complications of sedation. The surveillance protocol is time consuming with potential for stress and anxiety. We recommend that families entering any clinical surveillance protocols have access to psychosocial support.

In summary, 10-year experience of prolonged survival and good functional outcome with this kindred in spite of the high frequency of tumors detected supports the implementation of a clinical surveillance protocol for bMMR carriers. We demonstrate that a comprehensive clinical surveillance protocol can detect asymptomatic cancers and high-grade dysplastic lesions in biallelic MMR gene mutation carriers, leading to improved survival. Prospective multi-center experiences will help to determine the feasibility and genotype–phenotype correlations in patients with biallelic MMR gene mutations.

ACKNOWLEDGMENT

Dr. Alain Lagarde was responsible for identifying the MLH1 mutation in this kindred.

REFERENCES