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Thyroid cancer in a patient with a germline *MSH2* mutation. Case report and review of the Lynch syndrome expanding tumour spectrum

Rein P. Stulp[1], Johanna C. Herkert[1], Arend Karrenbeld[2], Bart Mol[1], Yvonne J. Vos[1], Rolf H. Sijmons[1]

[1]Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[2]Department of Pathology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

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Corresponding author: Rein P. Stulp, Department of Genetics, University Medical Center Groningen, PO-Box 30.001, 9700 RB Groningen, The Netherlands, phone: +31 50 361 72 29, fax: +31 50 361 72 31, e-mail: r.p.stulp@medgen.umcg.nl

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Abstract

Lynch syndrome (HNPCC) is a dominantly inherited disorder characterized by germline defects in DNA mismatch repair (MMR) genes and the development of a variety of cancers, predominantly colorectal and endometrial. We present a 44-year-old woman who was shown to carry the truncating *MSH2* gene mutation that had previously been identified in her family. Recently, she had been diagnosed with an undifferentiated carcinoma of the thyroid and an adenoma of her coecum. Although the thyroid carcinoma was not MSI-high (1 out of 5 microsatellites instable), it did show complete loss of immunohistochemical expression for the MSH2 protein, suggesting that this tumour was not coincidental. Although the risks for some tumour types, including breast cancer, soft tissue sarcoma and prostate cancer, are not significantly increased in Lynch syndrome, MMR deficiency in the presence of a corresponding germline defect has been demonstrated in incidental cases of a growing range of tumour types, which is reviewed in this paper. Interestingly, the *MSH2*-associated tumour spectrum appears to be wider than that of *MLH1* and generally the risk for most extra-colonic cancers appears to be higher for *MSH2* than for *MLH1* mutation carriers. Together with a previously reported case, our findings show that anaplastic thyroid carcinoma can develop in the setting of Lynch syndrome. Uncommon Lynch syndrome-associated tumour types might be useful in the genetic analysis of a Lynch syndrome suspected family if samples from typical Lynch syndrome tumours are unavailable.

Introduction

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant disorder associated with a germline mutation in one of the DNA mismatch repair (MMR) genes, most commonly *MLH1* and *MSH2* and less frequently *MSH6* and *PMS2*. Lynch syndrome is characterized by a strongly increased risk of developing colorectal cancer and several extra-colonic malignancies including carcinomas of the endometrium, ovary, ureter, stomach and small intestine. Tumours develop at a relatively young age. Although the risks for some common types of cancer, for example breast cancer [1-3], or rarer tumour types, for example malignant fibrous histiocytoma (MFH) [4], do not appear to be significantly increased in Lynch syndrome, MMR deficiency in the presence of a corresponding germline defect has been demonstrated in incidental cases of these tumours.

Here we report a 44-year-old woman from a Lynch syndrome, Amsterdam positive family who was referred for DNA testing. She had a recent history of a colorectal adenoma and an undifferentiated carcinoma of her thyroid and was shown to carry the truncating *MSH2* mutation that was known to segregate in her family. Traditionally, thyroid cancer is not considered to be part of the Lynch syndrome tumour spectrum. Our findings, however, suggest that this tumour was not coincidental, but likely developed in association with the underlying germline defect in the *MSH2* gene. We reviewed the literature on unusual manifestations of inherited mismatch repair gene mutations.

Methods

After genetic counselling, DNA analysis of the *MSH2* gene was performed in this 44-year-old woman by extracting DNA from lymphocytes, followed by a PCR amplification of exon 11 of the *MSH2* gene. The PCR product was analyzed by denaturing gradient gel electrophoresis (DGGE) and compared with DNA from a family member carrying the mutation [5].

Immunohistochemical staining for MLH1, PMS2, MSH2 and MSH6 protein expression was performed on formalin-fixed, paraffin-embedded sections of tumour as described previously [6].

DNA was extracted from both tumour and normal tissue. Microsatellite instability analysis was performed on formalin-fixed, paraffin-embedded sections of tumour and corresponding normal tissue. Following DNA amplification using fluorescent labelled primers, a panel of five microsatellites recommended by the NCI [7] and consisting of BAT25, BAT26, D2S123, D5S346 and D17S250 was analyzed for allelic shift. The amplified PCR products were analyzed on an ABI Genetic Analyzer.

We searched the English literature through Entrez PubMed (www.ncbi.nlm.nih.gov/sites/entrez) using sets of keywords to identify publications on tumours reported in patients with germline mismatch repair gene mutations. The reference lists of publications found through this approach were searched for additional relevant papers.

Results

Genetic analysis of the *MSH2* gene in the patient revealed the c.1704_1705delAG mutation, already known to segregate in her family. Her undifferentiated thyroid carcinoma showed complete loss of immunohistochemical expression of the MSH2 and MSH6 protein in the presence of normal positive internal controls, and no loss of the MLH1 and PMS2 protein. Of the five microsatellite markers tested, BAT26 showed instability. Therefore the thyroid tumour was classified as MSI-low.

The acknowledged Lynch syndrome tumour spectrum is shown in Table 1. The cumulative risks and

Table 1. Lynch syndrome tumour spectrum. Cumulative risks and average ages at diagnosis

Tumour site	*MLH1*		*MSH2*		*MSH6*	
	male	female	male	female	male	female
Colorectum	22-65% (41-47 years)	18-54% (41-47 years)	30-73% (44-46 years)	25-54% (44-46 years)	60-70% (50-54 years)	30-40% (50-54 years)
Endometrium	25-65% (59 year)		22-61% (59 year)		60-70% (54 year)	
Small intestine	7%		4%		n.a.	
Stomach	2%		4%		n.a.	
Ovary	3%		10%		10-28%	
Ureter and renal pyelum	1%		12%		n.a.	
Brain	n.a.		1%		n.a.	
Sebaceous glands Pancreas Biliary tract	n.a.		n.a.		n.a.	

n.a. – not available

Shown in brackets are the ranges of average ages at diagnosis. For the *PMS2* gene no cumulative risks are available.

Modified from a table developed by D Voskuil and RH Sijmons for the Dutch National Guidelines on Hereditary Colorectal Cancer (Menko F, ed. Richtlijn Erfelijke Darmkanker, VKGN, VIKC and CBO, 2007), used with permission

average ages of diagnosis shown in this table were retrieved from papers reporting these data in proven mutation carriers [8-17], rather than from papers that had included untested patients and/or first-degree relatives in their analyses. The reports on 'unusual' tumours in Lynch syndrome patients are presented in Table 2. For comparison, we list the tumour spectrum associated with bi-allelic MMR gene germline mutations in Table 3.

Discussion

Undifferentiated thyroid carcinoma is not commonly associated with Lynch syndrome. In our patient the immunohistochemical loss of expression for the MSH2 and MSH6 protein suggested that this tumour was not coincidental, but due to the underlying mutation in the *MSH2* gene. Loss of *MSH6* expression in tumours is often observed in case of germline *MSH2* mutations and can be explained by loss of its stabilizing partner MSH2. Broaddus et al. [18] contended that for both an adrenal and a thyroid carcinoma an *MSH2* gene mutation was causally linked because the tumour showed loss of MSH2 protein with immunohistochemical staining, but retained expression of *MLH1*. This staining pattern was similar to that seen in the more common Lynch syndrome related malignancies in these families. Although both adrenal and thyroid carcinoma showed loss of *MSH2* immunohistochemical expression, neither tumour was microsatellite instable (MSI-high). Loss of protein expression in the absence of MSI has been observed before in Lynch syndrome, most notably in patients with *MSH6* mutations [6, 19].

In the past, the Lynch syndrome tumour spectrum has primarily been defined through an epidemiological and statistical approach. From a clinical point of view this approach is of course still very valid as many clinicians will be primarily interested in tumours that

Table 2. Unusual tumours in patients with Lynch syndrome

Tumour type	Age	Gene	Mutation	MSI	IHC MLH1	IHC MSH2	IHC MSH6	Ref.
Non-Hodgkin's lymphoma	48	*MSH2*	large rearrangement	high	+	–	–	45
Rhabdomyosarcoma, pleomorphic	34	*MSH2*	not published	high	+	–	ND	46
Breast carcinoma, ductal	49	*MSH2*	c.1705-1706 del GA	high	+	–	–	3
Fibrous histiocytoma, malignant	45	*MSH2*	p.G429X	high	+	–	ND	4
Adrenal cortical carcinoma	34	*MSH2*	c.IVS10+1G>A	low	+	–	ND	18
Thyroid carcinoma, anaplastic	39	*MSH2*	p.Q824X	low	+	–	ND	18
Thyroid carcinoma, undifferentiated	44	*MSH2*	c.1704_1705 del AG	low	+	–	–	[C]
Pancreatic medullary carcinoma	63	*MSH2*	c.C1147T p.R383X	high	+	–	–	47
Prostate adenocarcinoma	61	*MSH2*	c.del exon 5	high	+	–	–	48
Liposarcoma	40	*MSH2*	c.del AT codon 677	ND	+	–	ND	49
Hepatic cholangiocarcinoma, mucinous	41	*MSH2*	c.T2026C	high	+	–	–	50
Uterine carcinosarcoma	46	*MLH1*	c.G1896C p.E632D	ND	–	+	ND	51
Renal cell carcinoma, clear cell[A]	51	*MLH1*	c.C1528T	high	–	ND	ND	1
Breast carcinoma[A], ductal	34	*MLH1*	c.C1528T	high	–	ND	ND	1
Breast carcinoma, male ductal	71	*MLH1*	4 bp dup in codon 755-756	high	ND[B]	ND	ND	52
Breast carcinoma, male	46	*MLH1*	c.2215-2218 dup AAAC	high	ND[B]	ND	ND	2

ND – not determined, IHC – results from immunohistochemical staining of the tumour for the protein coded by that gene, MSI – classification of the tumour microsatellite instability test results

[A]in this South-African family 5 breast cancer patients and a relative with renal cell cancer all carried the same mutation and showed microsatellite instability and loss of MLH1 protein in their tumours

[B]in this tumour loss of heterozygosity for MLH1 was detected

[C]patient reported in this paper

Table 3. Tumours observed in patients with bi-allelic MMR gene germline mutations

Tumour type	*MLH1* mean age (range), N	*MSH2* mean age (range), N	*MSH6* mean age (range), N	*PMS2* mean age (range), N
Acute leukaemia	2, 1/14			
Acute myeloid leukaemia	6, 1/14		7, 1/15	
Atypical chronic myeloid leukaemia	1, 1/14			
B-acute lymphatic leukaemia				10 (10), 1/43
T-acute lymphatic leukaemia/ T cell leukaemia		2, 1/7		2 (2), 1/43
Lymphoblastic lymphoma			5, 1/15	9 (6-15), 3/43
NHL/T-cell lymphoma	3, 1/14	1.7 (1-2), 3/7	10, 1/15	11 (3-17), 4/43
Small bowel carcinoma, not specified				15.5 (15-16), 2/43
Adenocarcinoma duodenum	11, 1/14			
Breast cancer	35, 1/14			
Colorectal cancer	22 (9-35), 3/14	11.5 (11-12), 2/7	16.6 (8-31), 5/15	15.9 (11-24), 10/43
Endometrial cancer			24, 1/15	23.5 (23-24), 2/43
Brain tumour, not specified				24 (24), 1/43
Glioma	4, 1/14			15 (15), 1/43
Astrocytoma/glioblastoma (multiforme)	4, 1/14	3, 1/7	8 (7-9), 3/15	7.1 (2-17), 8/43
Glioblastoma of the spinal cord			2, 1/15	
Oligodendroglioma			10, 1/15	16.5 (14-19), 2/43
Infantile myofibromatosis				1 (1), 1/43
Medulloblastoma	7, 1/14		7, 1/15	
Neuroblastoma				13 (13), 1/43
Primitive neuroectodermal tumour (PNET) of brain or ovary				11 (4-21), 5/43
Sarcoma	65, 1/14			
Ureter/renal pelvis carcinoma				15 (15), 1/43
Wilms' tumour	4, 1/14			
Total	**14 (11 patients)**	**7 (7 patients)**	**15 (10 patients)**	**43 (28 patients)**

For each MMR gene and each of the tumours, the mean age at diagnosis is given in years. If more than one tumour was reported for each type then the range of ages at diagnosis is shown between brackets. The number of each of the tumour types observed for a particular MMR gene is shown as number/total of tumours reported for that gene in bi-allelic mutation carriers. Multiple primary tumours were reported frequently and the total number of reported tumours and total number of patients are presented in the last row for each of the genes [20-44]

have a significantly increased risk of developing in their patients. Cumulative cancer risks for Lynch syndrome were usually based on retrospective cohort analysis of families meeting the Amsterdam criteria, often including families without proven mutations and untested first-degree relatives. More recently studies have focused on proven mutation carriers only. The risk figures listed in Table 1 are based on the latter type of studies [8-17]. Interestingly, the risk for gastric, ovarian, ureter/renal pyelum and brain tumours appears to be higher for carriers of *MSH2* mutations than for carriers of *MLH1* mutations. In addition to the statistical

approach, the tumour spectrum can be broadened through analysis of tumours occurring in MMR gene mutation carriers. Again, patients with atypical Lynch syndrome tumours as listed in Table 2 more often have been reported to carry an *MSH2* than an *MLH1* mutation. Also a wider range of tumours is observed for *MSH2* than for *MLH1* in these patients. At this point we can only speculate on the reason for these differences. *MLH1* and *MSH2* each create a heterodimer with different partners and have different roles in the detection and repair of DNA mismatches. For each of these protein complexes, deficiency might have a different impact on types and quantity of mismatches left unrepaired and the effect deficiency has on different target genes. The absence of *MSH6* and *PMS2* mutations in Table 2 might simply be caused by the fact that these mutations have been less frequently observed in Lynch syndrome in general. Ascertainment bias, however, cannot be excluded as laboratories did not test *MSH6* and *PMS2* in their analyses of Lynch syndrome suspected patients until fairly recently. Nevertheless, the absence of *MSH6* and *PMS2* from the listed reports might also reflect a true difference in associated tumour spectrum.

The tumours listed in Table 2 are not known to develop significantly more frequently in MMR gene mutation carriers than in the general population. Loss of MMR function may or may not have contributed significantly to tumour development in these particular cases. Generally, in these organs loss of the wild type allele in MMR gene mutation carriers and/or subsequently the accumulation of clinically important unrepaired mutations in cancer-associated target genes are apparently relatively rare. It is interesting to look at the types of cancer that develop in patients who have inherited bi-allelic MMR gene mutations (Tabele 3.). These patients are born with a mismatch repair deficiency and can present with tumours that rarely occur in carriers of single allele MMR gene mutations who need to lose their WT allele in their tissues first. Several studies have demonstrated that these bi-allelic mutations can lead to a phenotypically distinct recessive syndrome with predominantly childhood onset brain tumours, leukaemia and lymphoma, bowel tumours and endometrial carcinoma [20-44]. A striking feature of these patients is that nearly all of them display some features, spotty hyperpigmentation of the skin and Lisch nodules of the irides, usually observed in neurofibromatosis type I. Some of the reported tumour types, sarcoma, NHL and early-onset breast cancer match the types incidentally reported in patients with single allele MMR gene mutations, which further supports the notion that these tumour types could be causally linked to inherited MMR gene mutations. Whether or not MMR deficiency contributed significantly to development of the types of cancer occasionally seen in Lynch syndrome patients remains to be determined. From a practical point of view, we conclude that unusual tumours in Lynch syndrome can show loss of immunohistochemical staining that corresponds to the MMR germline mutation. Therefore these tumours, especially of those types that rarely occur in the general population, could be useful when trying to predict MMR gene mutations in Lynch syndrome suspected families for mutation analysis [6, 19] if the typical Lynch syndrome-associated tumours are unavailable.

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