The serrated neoplasia pathway: investigating the role of serrated polyps in colorectal cancer development
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Chapter 5

Serrated polyps and Lynch syndrome: are they associated?

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Submitted
ABSTRACT

Background and aims: Adenomas and colorectal cancers (CRCs) of Lynch syndrome patients display defective mismatch repair (MMR) associated with microsatellite instability (MSI). Serrated polyps have also been described, but previous studies investigating a causal relationship with Lynch syndrome by MMR testing have not been conclusive. Presence of a BRAF mutation is an alternative method to distinguish Lynch-associated CRCs from sporadic CRCs and may thus be of value to investigate Lynch association in serrated polyps. We studied the occurrence of defective MMR and BRAF mutations in serrated polyps occurring in 101 Lynch patients. Methods: Lynch patients with >1 serrated polyp were included. In all polyps of these patients, MLH1, MSH2, MSH6 and PMS2 protein expression was evaluated. In addition, APC-mutation cluster region, KRAS (exon 2) and BRAF (exon 15) mutation analysis was performed in adenomas and serrated polyps from these patients and from a control group of sporadic adenomas (n=17) and serrated polyps (n=42). Results: We identified 10/101 Lynch patients with >1 serrated polyp of whom 2/10 had multiple (≥10) and 8/10 occasional (<10) serrated polyps. A total of 69 polyps were available for analysis: 32 conventional adenomas and 37 serrated polyps. In 13/32 (40%) conventional adenomas and 0/37 serrated polyps, loss of MMR protein expression was observed. Overall, BRAF mutations were identified in 16/37 (43%) serrated polyps in Lynch compared to 20/42 (48%) serrated polyps in the control group (NS). In Lynch patients with occasional serrated polyps, BRAF mutations were significantly lower (23%) than control group serrated polyps (49%; p=0.04) Conclusions: Overall, serrated polyps do not seem to be a product of the MSI pathway in Lynch syndrome reflected by the absence of defective MMR in these polyps and a similarly high frequency of BRAF mutations as in sporadic serrated polyps. For occasional serrated polyps a causal relationship with Lynch syndrome can not be excluded.
INTRODUCTION

It is generally accepted that conventional adenomas of the colorectum are the main lesions with an undisputable malignant potential. The classical model describing colorectal cancer (CRC) development is the adenoma-carcinoma sequence associated with activation of the Wnt signalling pathway and chromosomal instability.(1;2) An alternative route to CRC, the microsatellite instability (MSI) pathway, was discovered in patients with Lynch syndrome.(3) Lynch syndrome is an autosomal dominant disorder associated with an increased risk (25-70%) of developing CRC.(4-6) Precursors of CRC in these patients are also conventional adenomas which are assumed to progress more rapidly to CRC than their sporadic counterparts.(7) The MSI pathway in these patients is initiated by a bi-allelic deletion or inactivation of one of the mismatch repair genes (MLH1, MSH2, MSH6 or PMS2). The hallmark of Lynch-associated tumors is microsatellite instability (MSI) and loss of immunostaining of the affected mismatch repair protein. MSI is found in more than 95% of Lynch associated CRCs as opposed to only 15% of sporadic CRCs.6,7 CRCs from Lynch patients harbour predominantly APC, KRAS and P53 mutations and virtually never a BRAF mutation.(3;8-13) BRAF testing has therefore been shown to be an ideal method to exclude Lynch associated tumors from sporadic tumors.(14;15) Recently, a newly proposed ‘serrated neoplasia pathway’ has been described involving the progression of serrated polyps to CRC through accumulation of genetic mutations, namely BRAF mutations and CPG-island methylation. Supporting clinicohistological and molecular evidence for such a pathway has been derived primarily from patients with serrated polyposis syndrome (SPS).(13;16-21)
In Lynch syndrome, serrated polyps (i.e. hyperplastic polyps, HPs; sessile serrated adenomas, SSAs; and traditional serrated adenomas, TSAs) have also been described.(7;22-27) In a number of previous studies, an attempt was made to verify whether these serrated polyps are causally related to Lynch syndrome, reflected by the presence of defective mismatch repair (MSI) and/or loss of immunostaining. These studies have thus far been inconclusive. Both conventional adenomas (24-93%)(23;28-37) and HPs/hyperplastic abberant crypt foci (0-100%)(26;29;35;38;39) express defective mismatch repair in highly variable frequencies. To analyze whether serrated polyps are causally related to Lynch syndrome, \textit{BRAF} mutation analysis may be a valuable adjunct to mismatch repair gene testing. Sporadic serrated polyps have been shown to display high (70-78%) levels of \textit{BRAF} mutations.\textsuperscript{33} It seems presumable that, like CRCs in Lynch, serrated polyps when causally related to Lynch syndrome, will display \textit{BRAF} mutations at a far lower frequency than their sporadic counterparts.

In this study, we describe the frequency of serrated polyps (HPs/SSAs/TSAs) in 101 patients with a genetically confirmed diagnosis of Lynch syndrome. We show that, overall, serrated polyps in Lynch syndrome lack defective mismatch repair (MSI and/or loss of immunostaining) and harbour a similarly high frequency of \textit{BRAF} mutations as their sporadic counterparts, strongly suggesting that they are not associated with the MSI-pathway. At sub-analysis, we show that occasional serrated polyps in Lynch patients have significantly lower levels of \textit{BRAF} mutations than their sporadic counterparts. Therefore, a causal relationship with the MSI-pathway can not be excluded in these polyps.
MATERIALS AND METHODS

Patients and specimens
For this study, 102 patients known at our centre with Lynch syndrome and an identified germline mutation in one of the MMR genes was analysed for the presence of serrated polyps. Patients were included if >1 serrated polyp was identified. These patients were then arbitrarily classified into two groups: patients with multiple serrated polyps (≥10); or patients with occasional serrated polyps (2-10).

Polyp characteristics were recorded retrospectively from previous colonoscopy reports or the gross description of the resection specimens at histopathology. All polyps were blindly re-evaluated and diagnosed by a single experienced pathologist (CvN) as HP, SSA, TSA or adenoma based on the histological features on H&E staining.(40-42) Lesions proximal from the caecum, ascending colon, transverse colon and descending colon were regarded as proximal and polyps from the sigmoid colon and rectum were regarded as distal. For the purpose of comparison, a previously selected control group consisting of sporadic HPs (n=24), SSAs (n=18) and conventional adenomas (n=17) from patients without a suspicion for Lynch syndrome was used to compare somatic mutations. This study was conducted in accordance with the research code of our institutional medical ethical committee on human experimentation, as well as in agreement with the Helsinki Declaration of 1975, as revised in 1983.

Molecular analysis
Mutation analysis
Using previously described primers and assays, DNA was analysed for mutations in the APC-mutation cluster region (APC-MCR), KRAS (exon 2) and BRAF (exon 15) of all polyps.37, 38 Previously performed
mutation analysis of these genes in a randomly selected sporadic polyps served as a control group. Detected mutations were confirmed in a second experiment.

*Immunohistochemistry*

Immunohistochemistry was performed on all polyps of the included Lynch patients. Unstained 5-µm sections were cut from paraffin blocks and the slides were deparaffinized. Primary monoclonal antibodies used were specific for MLH1(1:50 BD Pharmingen, San Diego, USA); MSH2(1:100 Oncogene Research Prod., San Diego, USA); MSH6(1:200 BD Transduction Lab., San Jose, USA); PMS2(1:250 BD Transduction Lab., San Jose, USA). Slides were immersed in 0.3% hydrogen peroxide in methanol for 20 minutes. Subsequently, antigen retrieval was carried out by 10 minutes of boiling in 10mM Tris/1mM EDTA (pH 9) followed by incubation with above mentioned diluted primary antibodies during 1 hour at room temperature. Post-antibody block (Immunologic) in PBS was performed followed by implementation of an antipolyvalent HRP detection system (Immunologic) to visualize antibody binding sites with 3,3'-diaminobenzidine as a chromogen. Sections were counterstained with haematoxylin. Stains for MLH1, MSH2, MSH6 and PMS2 were considered negative when there was complete absence of nuclear expression in all neoplastic cells. Negative staining in a part of a lesion or in a single crypt was registered separately.

*Microsatellite analysis*

In a subset of Lynch patients, harbouring many serrated polyps and conventional adenomas (>20), MSI analysis was performed. Microsatellite status was determined using an international standard
panel of 5 microsatellite markers (D17S250, D2S123, D5S346, BAT25 and BAT26) using standard techniques. A high degree of microsatellite instability (MSI-high) was defined as two (40%) or more unstable markers, MSI-Low as one unstable marker, and microsatellite stable (MSS) as no unstable markers.

Statistics
Statistical analyses were performed by using a statistical software package (Statistical Package for the Social Sciences 12.0.2; SPSS Inc, Chicago, Ill). Somatic mutations in polyps of Lynch patients were compared with those of the control group using a two-sided Fisher exact test. A p-value of < 0.05 was considered statistically significant.

RESULTS
From 101 Lynch syndrome patients with a known germline mutation, 10 (10%) patients were identified with >1 serrated polyp. Of these patients, 2 had ≥10 serrated polyps (table 1). The median age was 62 years (range: 44-75) with a male: female ratio of 3:7. In 10 patients, a total of 89 polyps were identified of which 69 were available for analysis: 32 conventional adenomas (21 tubular adenomas and 11 tubulovillous adenomas) and 37 serrated polyps (32 HPs and 5 SSAs). The median size of serrated polyps was 2mm (range: 1-10mm) and 4mm (range: 2-30mm) for conventional adenomas. Of 34/37 serrated polyps location could be ascertained. Nineteen of 34 (51%) serrated polyps were located proximal to the sigmoid colon. In 8/10 (80%) patients, serrated polyps were identified proximal to the sigmoid colon. In 1/11 tubulovillous adenomas (20mm) an adenocarcinoma was identified (at surgery: T2N0M0). The other 10 tubulovillous adenomas displayed low-grade dysplasia. In 6/22 tubular adenomas, features of
high-grade dysplasia were seen. In 1/10 patients a subtotal colectomy had been performed previously because of an adenocarcinoma (T3N0M0, tissue not available for analysis). Previously performed germline mutation analysis in patient 2 due to the high number of adenomas showed a mono-allelic mutation of the MUTYH gene.

<table>
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<th>Patient</th>
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<th>Germline mutation</th>
<th>Sex</th>
<th>Adenomas Analyzed/total</th>
<th>HPs Analyzed/total</th>
<th>SSAs analyzed/total</th>
<th>Location serrated polyps</th>
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<tr>
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Table 1: Number of histologically verified polyps and total number of detected polyps in Lynch patients.
Somatic *APC, KRAS* and *BRAF* mutation analysis

A total of 32 adenomas, 32 HPs and 5 SSAs were analysed for *APC-MCR, KRAS* exon 2 and *BRAF* exon 15 mutations. In adenomas, *APC* mutations were found in 6/32 (19%) of polyps. No *KRAS* mutations or *BRAF* mutations were detected in adenomas. No significant differences were seen compared to the control group regarding *APC* and *BRAF* mutations (table 2). More *KRAS* mutations were identified in sporadic adenomas (4/17) of the control group compared to Lynch adenomas (0/32: p=0.01). The adenocarcinoma identified in a tubulovillous adenoma displayed an *APC* mutation. In serrated polyps, no *APC* mutations were identified. *KRAS* mutations were identified 6/37 (16%) serrated polyps vs 7/42 (17%) in the control group. *BRAF* mutations were detected in 16/37 (43%) serrated polyps in Lynch patients compared to 20/42 (48%) in the control group (n.s.). There was no significant difference between proximal and distal serrated polyp location regarding *BRAF* mutation status.

When comparing patients with multiple serrated polyps and satisfying the criteria for SPS (n=2) to patients with occasional serrated polyps (n=8), we identified significantly (p=0.002) more *BRAF* mutations in SPS serrated polyps (11/15 =73%) than in occasional serrated polyps (5/22=23%). After subdivision, comparison of *BRAF* mutations showed that occasional serrated polyps in Lynch patients harboured a significantly lower *BRAF* frequency (23%) than the control group (49%; p=0.04). Comparison of SPS serrated polyps with control group serrated polyps showed no significant differences regarding mutations.
Table 2. Detected APC, KRAS and BRAF mutations in serrated polyps (HPs, SSAs) and adenomas (AD) compared to a control group. * significantly more KRAS mutations in sporadic adenomas than Lynch adenomas

**Immunohistochemistry and microsatellite analysis**

Loss of expression of one of the MMR proteins was observed in 13/33 (39%) conventional adenomas in Lynch patients which correlated in all cases with the germline MMR mutation. There was no correlation between histology (10 tubular adenomas and 3 tubulovillous adenomas) and loss of MMR expression (p=0.259). Also when grade of dysplasia was analyzed, no association was observed with MMR expression (p=0.672). The adenocarcinoma identified within a tubulovillous adenoma in a Lynch patient did not demonstrate loss of MMR expression. None of the serrated polyps showed loss of expression of one of the MMR proteins. MMR protein expression in the crypts of the serrated polyps was comparable to that of crypts in normal epithelium of the colorectum. Expression of all four MMR proteins was observed in most nuclei in the base of the crypts whereas few to none of the luminal nuclei expressed any of the MMR proteins.
Microsatellite analysis was performed in 30 polyps of Lynch patients 1 and 2, both with a germline mutation in \textit{MSH6} and \( \geq 10 \) serrated polyps, also satisfying the clinical diagnosis of SPS. Fifteen adenomas, 13 HPs and 2 SSAs were analyzed. In patient 1, both adenomas (2/2) were MSI-high and showed corresponding loss of the MSH6 protein at immunohistochemistry. All serrated polyps were MSS in this patient. In patient 2, 0/14 adenomas (including the adenocarcinoma) was MSI-H and none showed immunohistochemical loss of the MSH-6 protein. All serrated polyps were microsatellite stable in this patient.

**DISCUSSION**

In this comprehensive cohort study of Lynch syndrome patients with a proven germline MMR gene mutation, we demonstrated that a small proportion (2\%) of patients harbor multiple serrated polyps in addition to conventional adenomas, two of whom also satisfying the criteria for SPS. Using conventional immunohistochemistry and MSI analysis, previous studies have been performed to analyze whether serrated polyps are causally related to Lynch syndrome. Results from these studies have however been inconclusive. Based on the principle that \textit{BRAF} mutation testing is a highly sensitive method to distinguish sporadic CRCs (high frequency of mutations) from Lynch-associated CRCs (low frequency of mutations)(14;15;43), we demonstrated that serrated polyps most likely are not associated with Lynch syndrome, reflected by both a similarly high frequency of \textit{BRAF} mutations as sporadic serrated polyps and an absence of MMR deficiency in all of these polyps.

Our study is the first to utilize an alternative molecular approach involving mutation analysis (\textit{APC, KRAS} and \textit{BRAF}) in adjunct to
defective MMR testing to evaluate whether serrated polyps are causally related to Lynch syndrome. In addition, our study encompasses the largest analysis of serrated polyps (including SSAs) from Lynch patients who have been unambiguously defined by a germline mutation thus representing true Lynch syndrome patients. Prior reports evaluating solely defective MMR in serrated polyps defined Lynch syndrome in a broader sense: fulfilment of either genetic or clinical (Amsterdam) criteria. However, correlation between the Amsterdam criteria and a germline mutation are imperfect. Indeed, it has been shown that families satisfying the Amsterdam criteria may carry an alternative diagnosis such as Syndrome X or serrated polyposis syndrome (SPS).(19;44)

In Lynch syndrome, carcinogenesis is traditionally considered to proceed through an accelerated adenoma-carcinoma sequence driven by MMR deficiency. However, in the literature not all conventional adenomas in these patients have been shown to express defective MMR (24-93%). We also found loss of expression of one of the MMR proteins in only 13/33 (39%) conventional adenomas. It is conceivable that the remaining adenomas without loss of expression of one of the MMR proteins represent co-existing sporadic conventional adenomas. Concordantly, sporadic conventional adenomas show defective mismatch repair in far lower percentages: 0-3% of adenomas.(30;45) Nevertheless, independent of Lynch-association, removal of all conventional adenomas reduces the incidence of CRC and is therefore standard practice of care in these patients.(46;47)

Serrated polyps, which were traditionally considered to be benign lesions, have recently also been considered to be lesions with malignant potential through a serrated CRC pathway. The early genetic events of this route, as yet identified, are predominantly BRAF
Association between serrated polyps and MYH-associated polyposis

mutations and a generally enhanced CPG-island methylation status of multiple genes. Additional combined clinicohistological and molecular evidence supporting a serrated CRC pathway include right-sided carcinomas identified within serrated polyps harboring identical BRAF mutations as the serrated poly component (17) and increased incidence of serrated polyps in patients with sporadic microsatellite-unstable CRCs. Removal of these lesions, in particular large, right-sided serrated polyps, is therefore clinically important. However, serrated polyps associated with the accelerated MSI-pathway may represent present precursor lesions of MSI-CRC which evolve even faster than in the serrated CRC pathway alone. Investigation of an association between serrated polyps and Lynch is therefore clinically relevant. Three previous studies reported defective MMR in serrated polyps. In two studies, MSI was observed in hyperplastic aberrant crypt foci (4/4:100%) and HPs (2/17:11%). Finally, in one case report a Lynch patient was described with a mixed HP/adenoma in contiguity with a CRC. We found no defective MMR in serrated polyps which is in concordance with a number of prior studies also showing an absence of defective MMR in serrated polyps. In addition, the similarly high frequency of BRAF mutations in serrated polyps as their sporadic counterparts in this study further supports the notion that serrated polyps are not causally related to the MSI carcinogenesis pathway in Lynch syndrome.

It is possible that two oncogenic pathways, a MSI-pathway and a serrated CRC pathway, co-exist within Lynch syndrome patients with serrated polyps. However, considering that a large proportion of serrated polyps in our study were BRAF-mutated and thus far no CRCs with a BRAF mutation have been identified in Lynch patients, it
seems that the MSI pathway predominates over the serrated CRC pathway because of a relatively higher frequency of conventional adenomas in Lynch patients, favouring a stochastic process of carcinogenesis. Alternatively, the serrated CRC pathway may represent a slower route of carcinogenesis than the MSI pathway. 

*BRAF* mutations are more commonly associated with serrated polyps and the serrated CRC pathway than *KRAS* mutations. Nevertheless, a serrated CRC pathway, skewed towards initial *KRAS* mutations in a minority of serrated polyps can not be excluded.

Interestingly, after subdividing Lynch patients in SPS Lynch patients with multiple serrated polyps and non-SPS Lynch patients with occasional serrated polyps, we found that *BRAF* mutations were more common in serrated polyps of Lynch-SPS patients: 11/15 (73%) compared to 5/22 (23%) in non-SPS patients (p=0.002). Based on these findings we conclude that serrated polyps in SPS Lynch patients in particular are an expression of a serrated-CRC pathway. Alternatively, only 23% of serrated polyps in non-SPS patients were *BRAF* mutated. This proportion is significantly lower than control group serrated polyps (49%: p=0.04). Considering this low frequency of *BRAF* mutations in serrated polyps of non-SPS Lynch patients, a causal relationship with the MSI-pathway can not be excluded despite lack of defective MMR. Thus, these occasional serrated polyps, lacking *BRAF* mutations, may follow an accelerated route to CRC via the MSI-pathway.

SPS is a condition characterized by the presence of multiple serrated polyps spread throughout the colon and is associated with an increased CRC risk.(57-60) However, the heterogeneous phenotype of SPS such as the presence of different polyp histologies, differences in polyp localization and number of polyps, suggest that SPS can be
subdivided into separate (genetic) conditions. Two Lynch patients (patients 1 and 2) harboured ≥10 colorectal serrated polyps. While patient 1 satisfied the classical criteria for SPS with few classical adenomas(16), patient 2 had less serrated polyps and more conventional adenomas thus representing an intermediate SPS with a mixed phenotype. MSI analysis in adenomas of patient 1 showed high degree of MSI in all (2/2) adenomas as well as concordant lack of MSH-6 expression, indicating that these adenomas are a manifestation of Lynch syndrome. Interestingly, 0/14 adenomas of patient 2, including the adenocarcinoma, were MSI-H. The lack of MSI in all adenomas of this Lynch patient with a mixed SPS phenotype suggests that these adenomas are not associated with Lynch syndrome. To substantiate this, we selected a control group of conventional adenomas (n=15) which were matched for size, location, histology and grade of dysplasia from Lynch patients without serrated polyps to compare MSI status and found MSI-H in 9/15 adenomas (p=0.016, data not shown). Although less common, it is possible that the adenomas in patient 2 are an expression of mono-allelic MUTYH deficiency.(61) However, only 2/6 APC-mutated adenomas displayed G:C→T:A transversions, which are typical for MUTYH-deficiency. No KRAS mutations were identified in these adenomas. In the literature, a subset of serrated polyps has also been described to be causally related to bi-allelic MUTYH-deficiency.(62) This seems unlikely in patient 2 considering that of the mutated serrated polyps, 2 were BRAF mutated and only one KRAS mutated (although it did have a G:C→T:A conversion). Another explanation could be that these adenomas are in fact part of a mixed subtype of SPS. It remains however difficult to verify this hypothesis considering that no hallmark genetic characteristics of SPS have been identified. Alternatively,
these adenomas could simply be sporadic adenomas. However, considering the multitude of adenomas, this seems unlikely.

Based on our observations, we conclude that, overall, serrated polyps play an insignificant role in the MSI carcinogenesis pathway in Lynch syndrome. A causal relationship between occasional serrated polyps and the MSI-pathway can not be excluded. \textit{BRAF}-mutated serrated polyps may represent components of a co-existent serrated CRC pathway. The MSI pathway of carcinogenesis seems however to predominate over the serrated CRC pathway in these patients reflected by the described absence of \textit{BRAF} mutations in Lynch-associated CRCs.
REFERENCES


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