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Case Report

First reported case of a squamous cell carcinoma arising in the duodenum in a patient with Lynch syndrome

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Abstract: A 58 y/o male with Lynch syndrome, who was diagnosed with a squamous cell carcinoma (SCC) arising in the duodenum, is described. Previous malignancies included two metachronous colorectal adenocarcinomas, and a known family history of Lynch syndrome associated with deletion of exons 8-15 of the *MSH2* gene. Analysis of his small bowel SCC revealed loss of MSH2 and MSH6 protein expression, suggesting a pathogenic role of the germ-line deletion. While small bowel adenocarcinomas have previously been reported in Lynch syndrome, to our knowledge this is the first report of Lynch syndrome-associated squamous histology. As patients with Lynch syndrome live longer with early detection and treatment of their cancers, unusual sites and histology of previously unreported cancers may emerge. It is also important to recognize variant histologies that otherwise might not prompt pursuing a diagnosis of Lynch syndrome in the appropriate clinical setting.

Keywords: Hereditary non-polyposis colorectal cancer, Lynch syndrome, squamous cell carcinoma, small bowel cancers, duodenal cancers

Case presentation

A 58-year-old Caucasian male presented with two days of nausea and vomiting from an upper gastrointestinal tract obstruction. Imaging and endoscopy showed a mass arising in the duodenum (**Figure 1**). A biopsy of this mass revealed squamous cell carcinoma. He underwent resection of his duodenum with a distal gastrectomy and Billroth II gastrojejunostomy. Pathology revealed an invasive, moderately differentiated keratinizing squamous cell carcinoma (**Figure 2A-C**) with a focal glandular differentiation measuring 11 cm. The tumor transmurally invaded the duodenal wall with involvement of the subserosa. There was angiolymphatic invasion but no perineural invasion. The tumor was immunoreactive for the squamous cell markers p40 and CK5/6, and demonstrated very focal positivity with mucicarmine. One of 17 lymph nodes was positive for carcinoma. Surgical resection margins were free of tumor. Pathologically, it was staged as a pT3 N1 tumor. Immunohistochemistry for mismatch repair proteins demonstrated loss of MSH2 (**Figure 2D**) and MSH6, with preserved MLH1 and PMS2 staining. Imaging was negative for distant metastasis. Because of the diagnosis of squamous cell carcinoma, an upper airway endoscopy, complete skin exam and radiographic search for any other potential primary sources were performed. No other lesions were found.

The patient had a history of Lynch syndrome secondary to a known germ-line deletion of exons 8-15 in the *MSH2* gene. He had been treated 16 years earlier for adenocarcinoma of the rectum (**Figure 4**) with neoadjuvant chemoradiation followed by surgical resection and close follow up. Ten years later he was found to have early stage adenocarcinoma of the colon (**Figure 5**) and subsequently had a total colectomy.

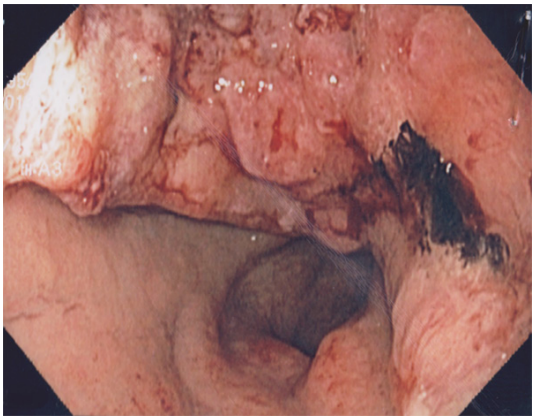

Figure 1. Endoscopic picture showing obstructing and bleeding mass arising from the duodenum.

His ancestry was notable for German-Scottish descent. His mother and maternal grandmother both were successfully treated for colorectal cancer at the ages of 49 and 55 years, respectively. His mother also had a hysterectomy for unclear reasons. His brother was diagnosed with colorectal cancer at the age of 49 years and later with a bladder cancer at the age of 60 years. His brother was also treated for multiple skin adenomas over his lifetime. One of his maternal first cousins died at the age of 35 years from metastatic colorectal cancer (**Figure 3**). There was no history of cancers on the paternal side of the family.

Because his histology was with a squamous cell carcinoma, we elected to adjuvantly treat him with three monthly cycles of infusional 5-fluorouracil in combination with cisplatin. He experienced no complications and is currently following an individualized plan of surveillance with annual upper gastrointestinal endoscopy and small bowel capsule endoscopy.

Discussion

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is the most common form of hereditary colorectal cancer. It is characterized by an autosomal dominant inheritance pattern with incomplete penetrance and accounts for 2-5% of all colorectal cancers [1]. Patients with HNPCC are also at an excess risk of extracolonic malignancies including endometrial, ovarian, stomach, small bowel, pancreas, hepatobiliary, brain and urothelial cancers. Some patients with HNPCC have the Muir-Torre variant and present with recurrent sebaceous adenomas, sebaceous carcinomas and/or multiple keratoacanthomas [2]. Lynch syndrome is caused by germ-line defects in mismatch repair genes, with *MLH1* and *MSH2* accounting for approximately ninety percent of identified mutations [1].

We report a case of a patient with known Lynch syndrome who was diagnosed with a squamous cell carcinoma arising in the duodenum and previously treated for two metachronous colorectal adenocarcinomas. The patient's inherited cancer predisposition was due to a previously identified germ-line *MSH2* deletion of exons 8-15. His duodenal squamous cell carcinoma showed loss of MSH2 and MSH6 by immunohistochemistry, suggesting a pathogenic role for his *MSH2* germ-line mutation in this tumor. To the best of our knowledge, our patient seems to be the first report of a duodenal squamous cell carcinoma, since Love and Lynch first recognized Lynch syndrome-associated small bowel cancers in the late 1980s [3, 4].

Given the glandular differentiation of the lining of the gastrointestinal tract, pathogenesis of squamous cell cancers remains elusive. One may speculate that these cancers arise from pre-existing adenomas and adenocarcinomas, as historically evidenced by areas of squamous differentiation sometimes seen in gastrointestinal adenocarcinomas.[5] We retrieved and reanalyzed the two prior colorectal adenocarcinoma specimens and found no squamous features (**Figures 4** and **5**). However, there was focal glandular differentiation of the squamous carcinoma specimen from the duodenum. Another proposed theory is squamous metaplasia of pluripotent basal cells which then undergo malignant transformation to form squamous cell cancers [6]. Whether this finding relates to mismatch repair defect in Lynch Syndrome is unknown.

We performed an extensive literature search to review published data on HNPCC-associated small bowel cancers (**Table 1**). In the largest reported cohort of Lynch syndrome patients (from German and Dutch national registries), small bowel cancers comprised 2.5% patients (54 of 2,118), more commonly affecting males (HR 2.5; p 0.002) with a cumulative lifetime risk of 12.0% (95% CI 5.7 to 19.3). *MSH2* gene mutation was not associated with higher incidence of small bowel cancers (compared with

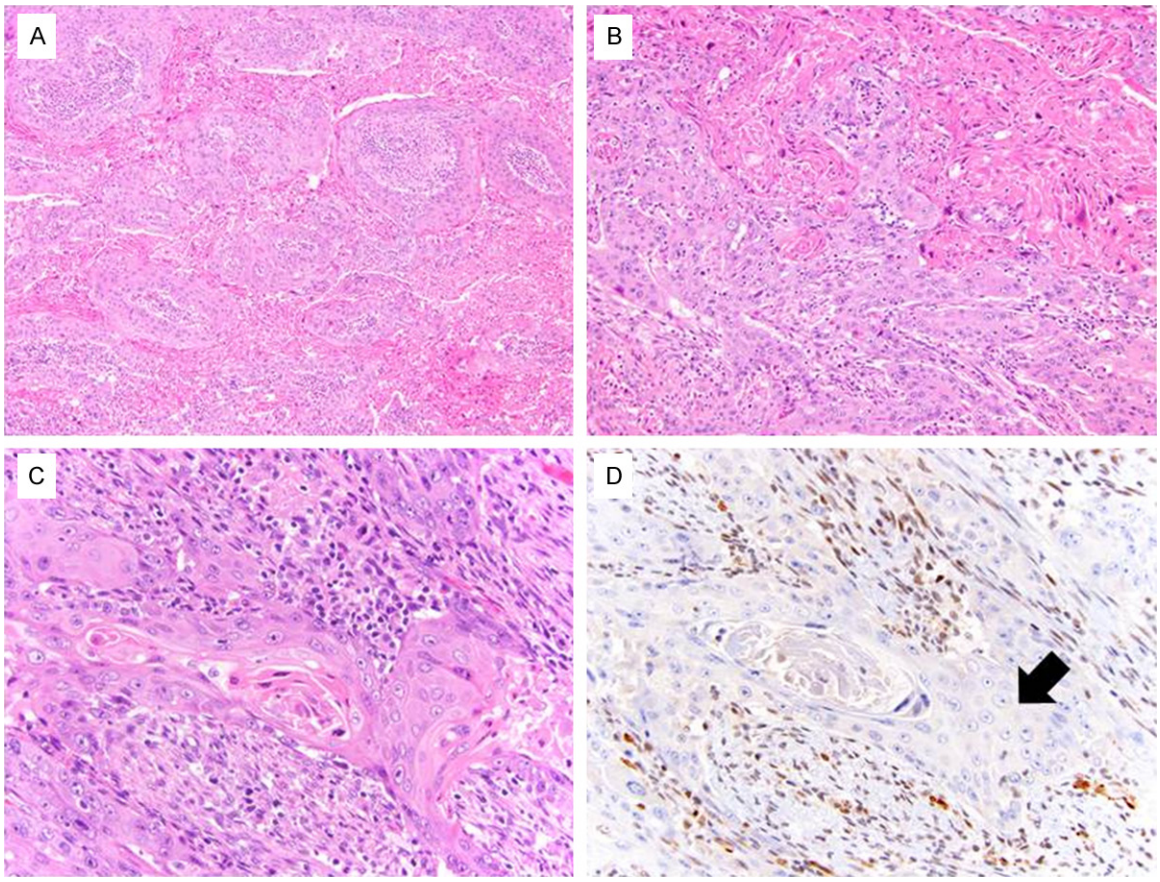

Figure 2. Histopathology of the patient's duodenal tumor demonstrated (A-C) moderately-differentiated keratinizing squamous cell carcinoma with focal glandular differentiation. Immunohistochemical stains for MSH2 (D) and MSH6 showed loss of nuclear expression (arrow), while the surrounding stroma had preserved staining.

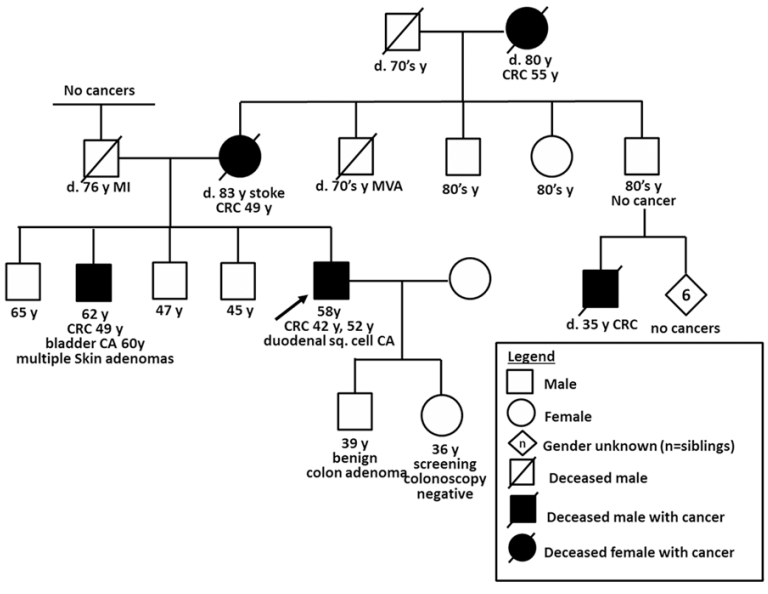

Figure 3. Pedigree of patient (index case indicated by arrow). Abbreviations: d: deceased. CRC: colorectal cancer. sq: squamous. CA: cancer.

MSH6 and *MLH1* HR 1.0; p = 0.993) [7]. Histology of the small bowel cancers were not reported in this cohort.

Another large study (reporting proven and probable mutation carriers from Denmark, Holland, Finland and USA) quotes a frequency of small bowel cancers of 0.93% (56 of 6,041 patients), more likely in males (HR 3.1, p = 0.0002) with a lifetime risk of 4.3% (95% CI 3.1-6.0). The small bowel cancers included adenocarcinoma and neuroendocrine tumors. No squamous cell histology was reported [8]. Other smaller retrospective studies have quoted a

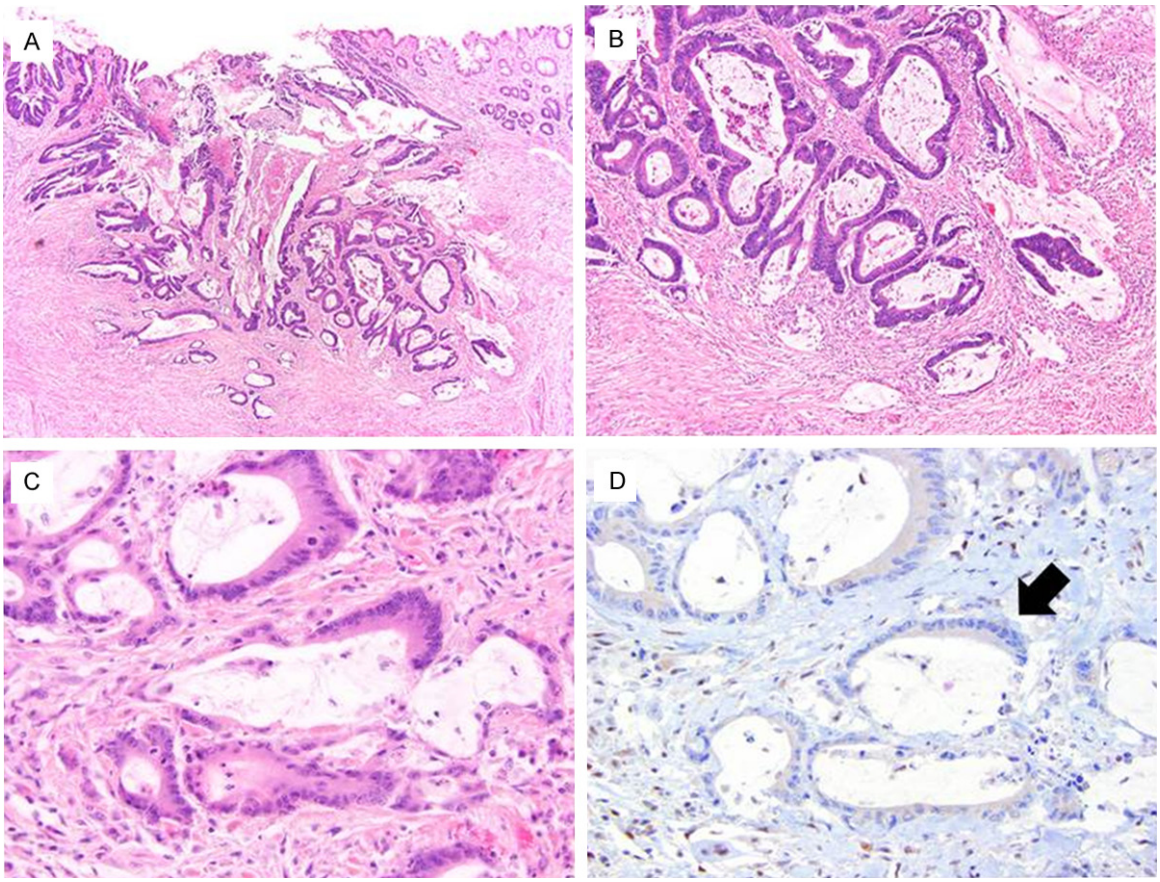

Figure 4. The patient's first cancer was diagnosed at the age of 42 years and located within the rectum. The histopathology (A-C) was consistent with an invasive moderately-differentiated adenocarcinoma with mucinous features that extended through the mucosa, submucosa and into the muscularis propria. Immunohistochemical stains demonstrate the tumor had loss of both MSH2 (D, arrow) and MSH6.

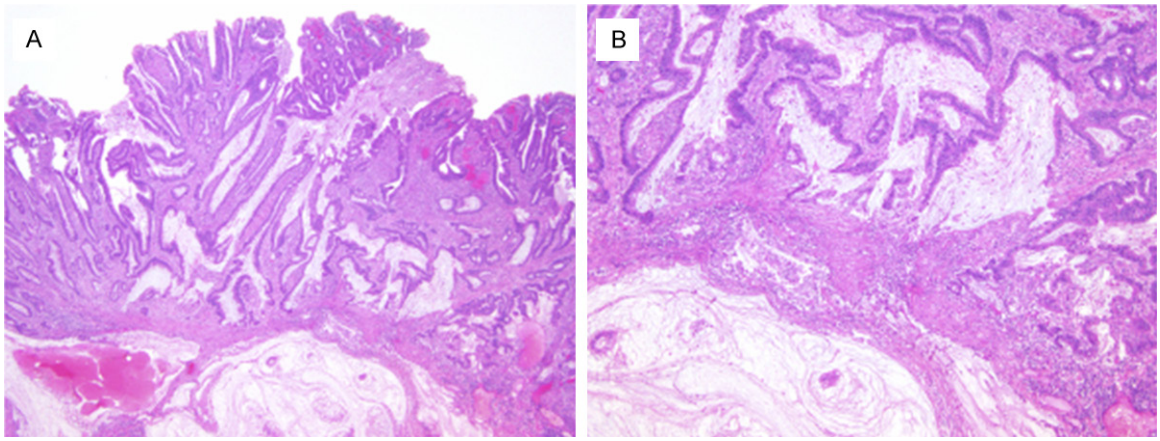

Figure 5. The patient's second colon cancer was diagnosed when the patient was 52 years of age and consistent with (A and B) an invasive moderately-differentiated mucinous adenocarcinoma arising in association with a tubular adenoma.

lifetime cumulative incidence of small bowel cancers ranging from 2.5% to 7.2% with none resembling the histology of our patient [9-11].

The largest dedicated series of small bowel cancers in Lynch syndrome was published by Park et al in 2006 [12]. This was a question-

Table 1. Review of clinical characteristics of patients from published case series of small bowel cancers associated with Lynch syndrome

Characteristics	HNPCC-associated Small Bowel Cancer (SBC) Case Series			Current patient
Study Identification	Park et al. (2006) [12]	Rodriguez-Bigas et al. (1998) [13]	Schulmann et al. (2005) [14]	Amjad et al. (2015)
Source of patient (s)	Questionnaires mailed to 55 members of InSiGHT* from 21 countries	Questionnaires mailed to members of ICG-HNPCC+ from 6 countries	Patient data retrieved from German HNPCC Consortium	University of Pittsburgh Cancer Institute
Patient Demographics				
No. of patients	85	42	31	
No. of Small bowel cancers	90	49	32 + 1 adenoma	
Males	51/85 (60.0%)	32/42 (76.2%)	22/31 (70.9%)	Male
Age at diagnosis, years	Mean 48 (range 11-81)	Mean 49 (range 25-88)	Mean 44 (range 15-73)	58
Met Amsterdam criteria	60/85 (70.6%)	34/43 (80.9%)	16/31 (51.6%)	Yes (Met Amsterdam I criteria)
Disease Characteristics				
Histology				Squamous cell carcinoma (first scientific report to the best of our knowledge)
Adenocarcinoma	74/90 (82.2%)	41/49 (83.7%)	24/33 (72.7%) + 1 adenoma	
Carcinoid	2/90 (2.2%)	3/49 (6.1%)	1/33 (3.0%)	
Not specified	14/90 (15.6)	5/49 (10.2%)	7/33 (21.2%)	
Squamous cell carcinoma	None reported	None reported	None reported	
Location				
Unknown	18/90 (20.0%)	2/49 (4.1%)	3/33 (9.1%)	
Known	72/90 (80.0%)	47/49 (95.9%)	30/33 (90.9%)	
Duodenum	31/72 (43.1%)	17/47 (36.2%)	16/30 (53.3%)	Duodenum
Jejunum	31/72 (43.1%)	18/47 (38.3%)	10/30 (33.3%)	
Ileum	10/72 (13.9%)	12/47 (25.5%)	4/30 (13.3%)	
Synchronous	None reported	7/42 patients (16.6%)	1/31 patient	Capsule endoscopy negative for synchronous SBC. Patient will be offered surveillance
Metachronous	4/85 patients (4.7%) One patient had 2 metachronous SBCs	4/42 patients (9.5%)	None reported	
Other HNPCC-associated cancers	(Information available for 41 patients)	(Information available for 42 patients)	Not reported	
Total number of other cancers	59	77	Not reported	
Colorectal	51 in 27 patients	59 in 25 patients		2 prior colorectal cancers
Endometrial	5	NR		
Renal pelvis/ureter	4	NR		
Ovarian	3	NR		
Pancreatic	1	NR		
SBC as the first HNPCC-associated cancer	14/41 patients (34.1%)	24/42 patients (57.1%)	14/31 (45.1%)	No
Genetics	All patients were known mutation carriers (inclusion criteria)	No. of patients who were mutation carriers unknown	27 patients underwent genetic testing	
Mutations in mismatch repair genes	69 different germ-line mutations identified			
MSH2	34/69 (49.3%) in 38 patients	6 patients	9 patients	Exon deletion 8-15 in MSH2
Truncation	28/34 (82.4%)			
Missense	6/34 (17.6%)			

MLH1	31/69 (44.9%) in 42 patients	9 patients	16 patients
Truncation	25/31 (80.6%)		
Missense	6/31 (19.4%)		
MSH6	3/69 (4.3%) in 3 patients		2 patients
Truncation	2/3		
Missense	1/3		
PMS2	1/69 (1.4%) in 2 patients		

*ICG-HNPCC: International Collaborative Group on Hereditary non-polyposis. colorectal cancer. +InSiGHT: International Society for Gastrointestinal Hereditary Tumors Incorporated.

naire-based survey with collaboration of members of the International Society for Gastrointestinal Hereditary Tumors from 21 countries. They identified 85 patients with 90 small bowel cancers with characteristics as reported in **Table 1**. One interesting finding from this study was that in patients with small bowel cancers and *MSH2* mismatch repair gene mutations, the distribution of the mutations within the gene was significantly different as compared to their HNPCC controls. There was an increased frequency of mutations in the Walker-A region, comprising codons 626-733, (26.5% versus 2.8%, $p < 0.001$) and fewer mutations in the MutL homologue interaction domain (2.9 versus 19.9%, $p = 0.019$). Our patient's large deletion encompasses the Walker-A region and part of the MutL homologue interaction domain. Two other similar studies by Rodriguez-Bigas et al and Schulmann et al are summarized in **Table 1** [13, 14]. We were especially interested in the reported tumor histology and none of the small bowel cancers were of squamous cell origin.

Conclusion

Based on our review of literature, this is the first report of squamous cell carcinoma arising in the duodenum in a patient with Lynch syndrome. As patients with Lynch syndrome live longer with early detection and treatment of their cancers, unusual sites and histology of previously unreported cancers may emerge, as is illustrated by this case. It is also important to recognize alternative histologies that otherwise might not prompt pursuing a diagnosis of Lynch syndrome in the appropriate clinical scenario.

Disclosure of conflict of interest

None to disclose.

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