

Lynch Syndrome- a Case Report with Review of Literature

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ABSTRACT

Introduction: Hereditary non polyposis colorectal cancer(HNPCC)was originally described based on familial clustering of cancers at several sites.

Case report: The authors report a case of HNPCC in a 55 year old male, who presented with bleeding per rectum and hematuria. Total colectomy specimen revealed an adenocarcinoma and nephroureterectomy specimen revealed a high grade urothelial carcinoma. Subsequently the family history revealed a history of cancers of colon, endometrium and larynx in close relatives.

Conclusion: This case is reported in view of its rarity, and also to emphasize the importance of screening family members in colonic cancers.

Keywords: colon, polyposis, cancer, lynch syndrome

INTRODUCTION

Hereditary non polyposis colorectal cancer syndrome (HNPCC) is also known as lynch syndrome.¹ It is inherited in an autosomal dominant fashion and is due to defects in at least one of a family of DNA mismatch repair genes like hMLh1, hMSH2, hMSH6, or PMS2. Mutations in these enzymes lead to micro satellite instability and an accumulation of mutations in genes that are believed to control the progression of tumor development. People with mutations in these genes have a risk of developing cancers in endometrium, colon, stomach, ovary, ureters, brain, small bowel, liver, skin etc.

CASE REPORT

A 55 year old male patient presented to the surgical clinic with complaints of loss of weight and appetite, bleeding per rectum and hematuria. On colonoscopy there was a friable growth in the colon and on ureteroscopy a growth was also seen in the ureter.

Under general anesthesia total colectomy and left radical nephrectomy with ureterectomy was done with ileorectal anastomosis.

Gross morphology

Specimen 1: We received large intestine of length 90 cms, cut section of which showed two growths, one in the ascending colon measuring 7x7x6 cms, polypoidal, ulcerated, grey white, and a second growth measuring 4x3x2 cms, mucoid in nature and predominantly located in the wall of sigmoid colon. No other polyps were seen in the colon.(fig 1A, fig2 A)

Specimen 2: Kidney with attached ureter of length 6 cms, cut section of which revealed papillary, grey white tumors multifocally in the pelvis, calyces and ureter.(fig 3A)

Microscopy

The tumor in the right colon showed histological picture of a well differentiated adenocarcinoma and sigmoid colon a mucinous adeno carcinoma. No tumor immune lymphocytes, no

lympho vascular invasion was found. It was staged as T3 N0 M0. Tumors in the pelvis of kidney and ureter revealed a high grade urothelial carcinoma. No lymph nodes were submitted. It was staged as TaN0 M0, stage 0a. Immunohistochemistry was done using markers MLH1,MSH2 markers. Slides were positive for MLH1 and negative for MSH2. Because the patient had multiple cancers, slides were positive for MLH1, on further probing three of his relatives suffered from cancer- the case was diagnosed as lynch syndrome.

DISCUSSION

Lynch syndrome is a syndrome of cancer predisposition linked to inherited mutations of genes in post replicative DNA mismatch repair.² Multiple generations are affected with colorectal cancer(CRC) at an early age with a predominance of right sided colorectal cancer. There is an excess of synchronous (multiple colorectal cancers at or within six months after surgical resection for colorectal cancer) and metachronous colorectal cancers. (Colorectal cancer occurring more than six months after surgery). In addition extra colonic cancers namely, carcinoma of the endometrium, ovary, stomach, small bowel, pancreas, hepato biliary tract, brain and upper urothelial tract also occur. Patients may also have sebaceous adenomas; keratoacanthomas etc.³ sebaceous gland tumors along with HNPCC is called as Muir Torre syndrome. Cerebral gliomas along with multiple colorectal adenomas is called as Turcot syndrome. In one case report soft tissue sarcoma and male breast carcinoma are also reported.¹ In the present case the patient had multifocal urothelial carcinoma of renal pelvis, ureter along with well differentiated adenocarcinoma of the ascending colon and mucinous carcinoma of the sigmoid colon.(figure 1,2,3) Bladder was not involved. Though the slides were positive for MLH1, there are no tumor immune lymphocytes, no crohns like lymphocyte reaction. This is in contrast with the literature which says that in MLH1 positive cases tumor immune lymphocytes, and crohns like lymphocyte reaction are seen generally.⁴ He was treated with "FolFox4" regime which contains, oxaliplatin 85mg/m² IV on day1, leucovorin 200mg/m² IV on days1 and 2 as a two hour infusion, 5fluorouracil400 mg/m² IV bolus, followed by 600mg/m² IV continuous infusion for 22 hours on days 1and2, Repeat cycle every two weeks. Twelve such cycles were given. His paternal uncle was af-

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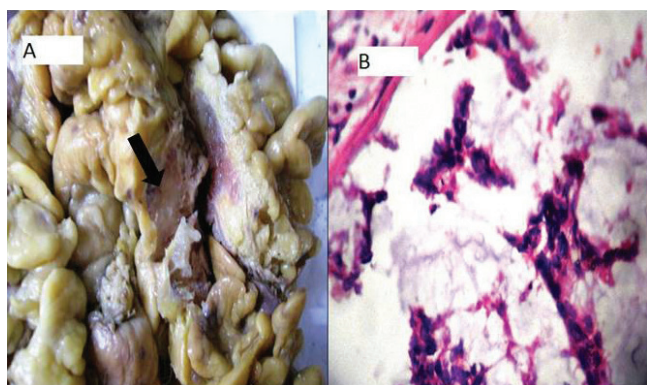


Figure-1: (A) Gross picture of sigmoid colon with mucinous growth (B) Microscopic picture of mucinous adenocarcinoma (Hand E x400)

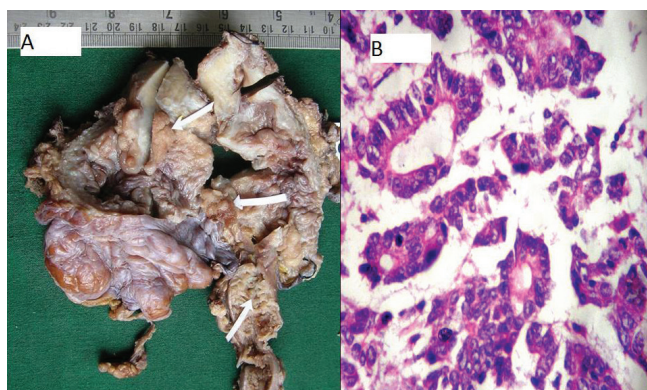


Figure-2: (A) Gross picture of ascending colon with polypoid growth (B) Microscopic picture of a well differentiated adenocarcinoma (Hand Ex400)

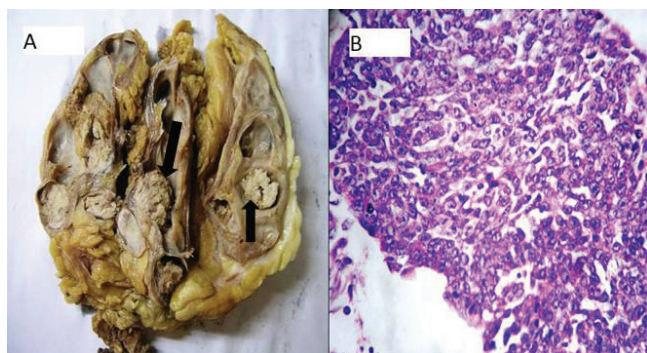


Figure-3: (A) Multifocal papillary tumors in kidney (B) Microscopic picture of a papillary urothelial carcinoma (H and Ex400)

ected by colonic carcinoma at the age of 50 years, his sister was affected by endometrial carcinoma before 45 years, and another brother died of carcinoma of larynx before 45 years. There are sets of criteria to diagnose lynch syndrome as the Amsterdam criteria and the revised Bethesda guidelines. (table 1 and 2)

The present case fits very well into the criteria. A hallmark of tumors in HNPCC is micro satellite instability.³ Micro satellites are genomic regions in which short DNA sequences or a single nucleotide is repeated. During DNA replication, mutations occur in some micro satellites owing to mis alignment of their repetitive subunits and result in contraction or elongation (instability). These are repaired by mismatch repair proteins. (MMR). However repair is inefficient in tumors

1	There should be at least three relatives with a lynch syndrome associated cancer: cancer of the endometrium, small bowel, ureter or renal pelvis.
2	One patient should be a first degree relative of the other two,
3	At least two successive generations should be affected
4	At least one tumor should be diagnosed before the age of 50 years
5	Familial adenomatous polyposis should be excluded in the CRC cases if any,
6	Tumours should be verified by histopathological examination.
Table-1: The Amsterdam criteria 2 ⁴	

1	Colorectal carcinoma diagnosed in a patient aged < 50 years. ⁵
2	Presence of synchronous or metachronous colorectal or other Lynch syndrome – related tumors regardless of age.
3	CRC with MSI-1 phenotype diagnosed in a patient aged <60 years.
4	Patient with CRC and a first degree relative with a Lynch syndrome-related tumor, with one of the cancers diagnosed at age <50 years.
5	Patient with CRC with two or more first degree or second degree relatives with a Lynch syndrome- related tumor regardless of age.
Table-2: The revised Bethesda guidelines	

with a deficiency of these proteins. Though genes including hMLH1, hMLH3, hMSH2, hMSH3, hMSH6, hpMS1, and hPMS2 all participate in this process. Approximately 90% of the cases have hMLH1 and hMSH2 deficiency and only 10% of the cases have hMSH6 deficiency.²

Many lynch syndrome associated cancers also manifest loss of staining of the protein encoded by whichever MMR gene is mutated, making immunohistochemistry (IHC) of tumors, a helpful first step in the evaluation of a possible MMR deficient tumor. It was proposed that all newly diagnosed CRC should be subjected to IHC staining for MLH1, MSH2, MSH6, PMS2. Of every thirty five CRCs one has lynch syndrome.⁵ Unaffected carriers are subjected to colonoscopy every two years from age 25. At an international meeting in Bethesda in 2004, most participants considered HNPCC as inappropriate, since the syndrome is also associated with other tumors. It was proposed that the name lynch syndrome should be used. The European group suggests that families that meet the Amsterdam criteria but do not have evidence for MMR deficiency are referred to as having familial CRC.⁴ In the present study we have advised other family members to undergo screening for colorectal and endometrial cancers.

CONCLUSION

Lynch syndrome is a syndrome of cancer predisposition. Patients present with colorectal cancer and or multiple organ cancers. Hence it is important to council the family members of this patients to undergo screening tests for cancer.

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