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Lynch Syndrome: Diagnostic Challenges and Management - A Case Report

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Abstract

Aim and objective: To highlight a rare case of Lynch Syndrome and the challenges associated with its diagnosis and management.

Materials and methods: A 68-year-old male who had a family history of colonic neoplasms came with complaints of left loin pain and altered bowel habits. Clinical examination showed a large palpable mass of size 8 cm × 5 cm in the left lumbar region. On evaluation, CECT Abdomen and pelvis showed a large circumferential lumen occluding growth in descending colon; with a synchronous mass lesion in left pelvic ureter causing upstream hydroureteronephrosis and a polypoidal lesion in urinary bladder. Patient underwent staged Laparoscopic left hemi colectomy with left nephrourterectomy and transurethral resection of bladder tumor. A diagnosis of hereditary non polyposis colorectal cancer (HNPCC) was made according to Revised Bethesda criteria. Immunohistochemistry for microsatellite instability (MSI) in the resected specimen showed unstable MSI. Genetic testing done showed Germ line mutation of MSH2 gene confirming lynch syndrome. Patient had an uneventful post-operative recovery.

Results and Conclusion: Lynch syndrome is one of the most common hereditary cancer susceptibility syndromes. A deleterious mutation in one of the DNA mismatch repair gene is responsible for cases. In our case we identified a family member with synchronous HNPCC tumors; genetic testing identified causative MSH2 mutation. This allowed us to formulate personalized screening program for the successive generation.

Keywords: ***Lynch syndrome; Hereditary cancer syndromes***

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1. Background

Lynch syndrome is the most common cause of inherited colorectal cancer (CRC). It is characterized by a significantly increased risk for CRC and endometrial cancer as well as a risk of several other malignancies. It accounts for approximately 3 percent of newly diagnosed cases of CRC and 2 to 3 percent of endometrial cancer [1]. Lynch syndrome refers to patients and families with a germ line mutation in one of the DNA mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*) [2]. We report a case of Lynch syndrome, and the challenges associated with its diagnosis and management.

2. Case Presentation

A 68-year-old male who has a family history of colonic neoplasms in second degree relatives, came with complaints of left loin pain and altered bowel habits. No History of bleeding per rectum. Clinical examination showed a large palpable mass of size 8 cm × 5 cm in the left lumbar region.

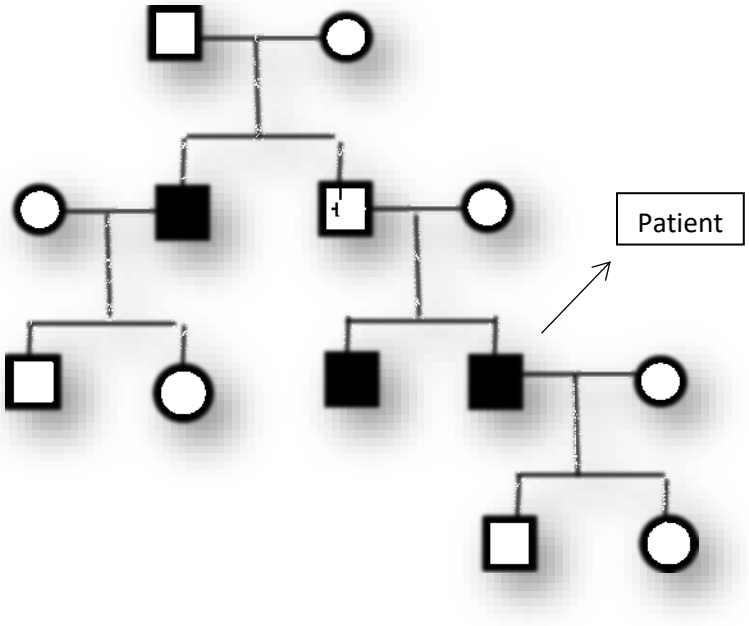


FIG. 1. **Family tree of patients showing affected second-degree relatives are marked in black.**

On evaluation, his blood investigations were normal, CEA-1.4 ng/dl. CECT Abdomen and pelvis showed a large circumferential lumen occluding growth in descending colon; with a synchronous mass lesion in left pelvic ureter causing upstream hydroureteronephrosis and a polypoidal lesion in urinary bladder. Colonoscopy done showed a Semi circumferential

Mass lesion in descending colon, Biopsy from colonic growth showed features of well differentiated adenocarcinoma. Cystoscopy and Transurethral resection of bladder tumour showed noninvasive papillary urothelial neoplasm. Left ureteric stenting attempted during cystoscopy was not possible due to intraluminal ureteric growth.

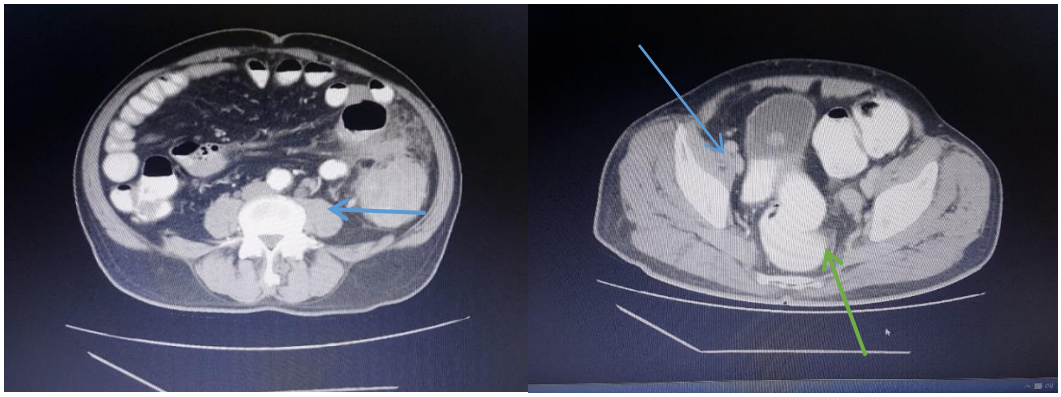


FIG. 2 and 3. **Axial CT images showing Descending Colon mass lesion (blue arrow), Intraluminal Urinary bladder growth (blue arrow) and Left Ureteric mass (orange arrow).**

Three synchronous malignancies (colonic and urothelial) along with family history of colorectal carcinoma in second degree relatives raised suspicion of hereditary cancer syndrome. Patient underwent Laparoscopic left hemi colectomy with left nephrourterectomy. Histopathology revealed colonic adenocarcinoma grade 2 (T3N0) and high grade invasive papillary urothelial carcinoma (T2). A diagnosis of lynch syndrome was made according to Revised Bethesda criteria. Immunohistochemistry for microsatellite instability (MSI) in the resected specimen showed unstable MSI. Genetic testing done showed, Germ line mutation of MSH2 gene confirming lynch syndrome. Patient had an uneventful post-operative recovery. He was discharged on 9th post-operative day and is doing well.

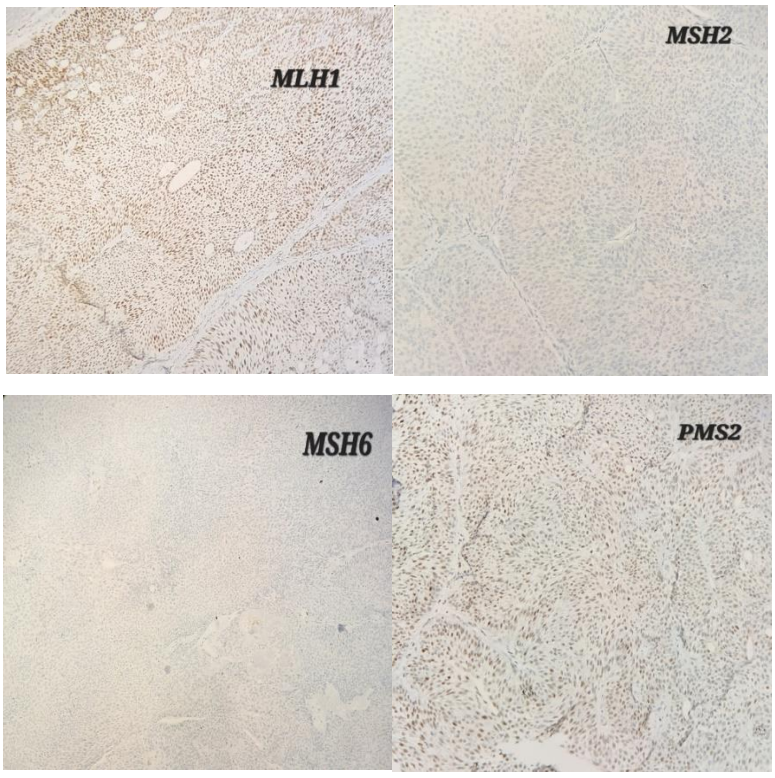


FIG. 4-7. **Moderate nuclear reactivity is seen in tumour cells of MLH1 and PMS2 with loss of MSH2 and MSH6, Suggestive of MSH2 gene mutation.**

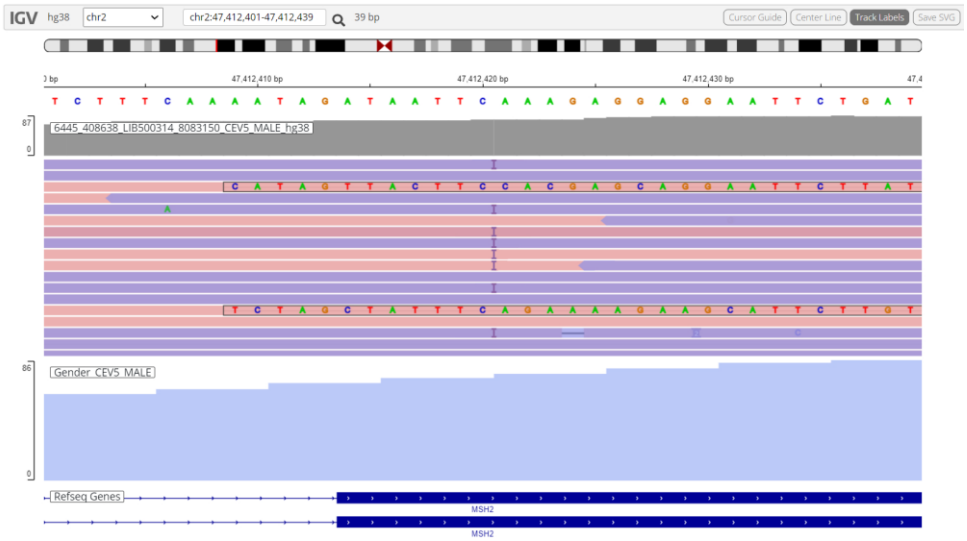


FIG. 8. **Pictorial representation of Genomic Sequencing in Chromosome 2 Showing abnormal base pair insertion/duplication in MSH2 gene locus.**

3. Discussion

Lynch syndrome is one of the most common hereditary cancer susceptibility syndromes. A deleterious mutation in one of the DNA mismatch repair gene is responsible for cases. These are identified by a positive family history, their occurrence at an early age and by the development of synchronous/ metachronous cancers in same individual.

Even though the syndrome was named after Henry Lynch, an American physician; first reports of these familial cancer syndrome were reported by Aldred Warthin, renowned American pathologist who elucidated the autosomal dominant pattern of inheritance [3].

3.1 Terminology

Hereditary nonpolyposis colorectal cancer (HNPCC) refers to patients and/or families who fulfill the Amsterdam / Bethesda criteria. A portion of these patients will have Lynch syndrome on germline molecular testing. Lynch syndrome refers to patients and families with a germline mutation in one of the DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*). It has an autosomal dominant pattern of inheritance, making 50% offspring's of affected individuals at risk of HNPCC related tumors.

3.2 Amsterdam II Criteria [4]

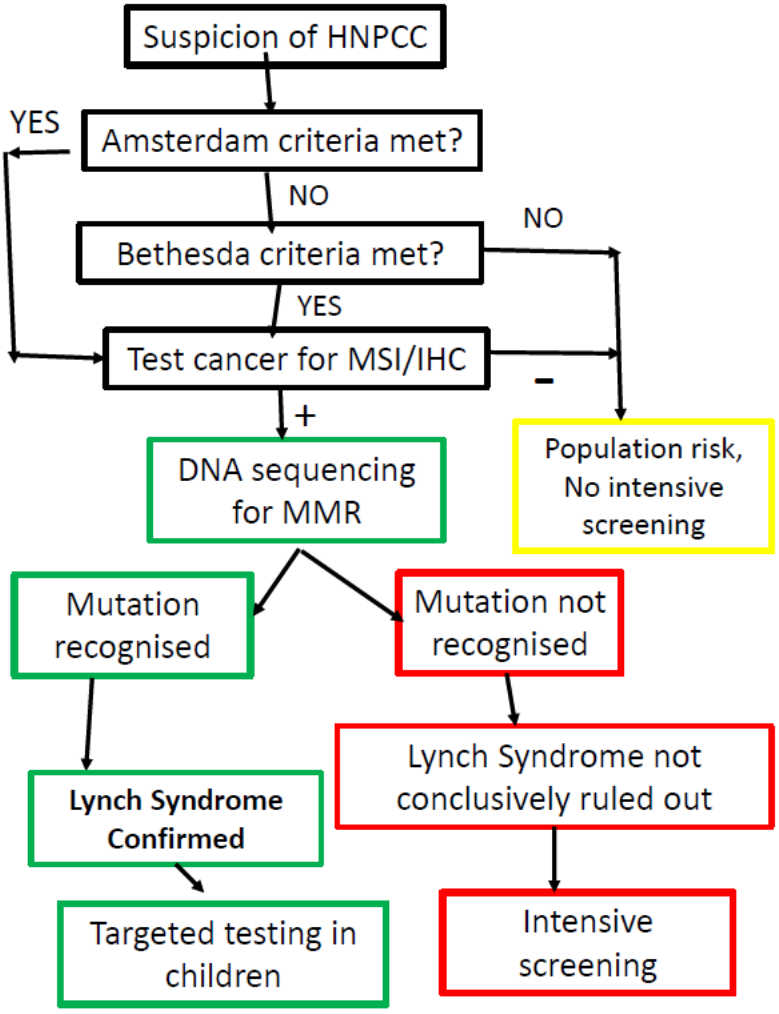
Require at least three relatives with an LS-associated cancer (that is, CRC and cancers of the endometrium, stomach, ovary, ureter or renal pelvis, brain, small bowel, hepatobiliary tract and skin (sebaceous tumours)): 1. One is a first-degree relative of the other two; 2. At least two successive generations are affected; 3. At least one of the LS-associated cancers should be diagnosed at <50 years of age; 4. FAP should be excluded in any CRC cases; 5. Tumours should be verified by pathology whenever possible.

3.3 Revised Bethesda Criteria [5]

1. Colorectal cancer is diagnosed in a patient who is less than 50 years of age.
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors, regardless of age.
3. Colorectal cancer with the MSI-H-like histology diagnosed in a patient who is less than 60 years of age.
4. Colorectal cancer is diagnosed in a patient with one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years.
5. Colorectal cancer diagnosed in a patient with two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma) tumours, sebaceous gland adenomas and keratocanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

3.4 Diagnostic Algorithm in Lynch Syndrome [2]



Previously, blanket screening programs were employed in these families to diagnose and treat cancer early. But with widespread availability of genetic testing, identifying mutated gene in the cancer patient can help in screening for same mutation in their offspring's. In our case we identified a family member with synchronous HNPCC tumors; genetic testing identified causative MSH2 mutation. This allowed us to formulate a personalized screening program for the successive generation.

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