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Hereditary Non Polyposis Colon Cancer - A case report

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Abstract : A 43 year old male presented with a history of altered bowel habits for 4 months. He was treated elsewhere as a case of amoebiasis. History revealed a strong family history of colorectal malignancies. His father and 3 of his brothers had colonic malignancy. The patient was suspected to have colonic malignancy and evaluated. Hepatic flexure growth was found in CT and confirmed by colonoscopy. A diagnosis of HNPCC was made. The patient was explained of the condition and total procto colectomy was advised. The patient refused radical procedure. Hence segmental resection extended right hemicolectomy was done. Histopathology showed Infiltrating moderately differentiated adenocarcinoma with clear surgical margins. The patient was discharged and started on Chemotherapy. 1 year follow up showed no new lesions. Hereditary nonpolyposis colorectal cancer (HNPCC accounts for about 5-8 of colorectal cancers. Lynch syndrome I is an autosomal dominant inherited disorder characterized by early onset of colorectal cancer, predominance of proximal and multiple tumors, and microsatellite instability. In order to identify HNPCC, the international Amsterdam criteria have been used

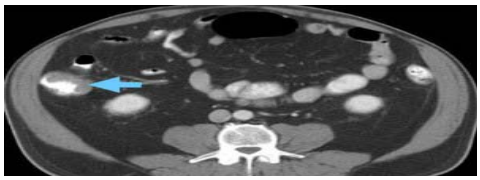
Keyword :HNPCC, Lynch syndrome, microsatellite instability

Introduction:

Hereditary nonpolyposis colorectal cancer (HNPCC) accounts for about 5-8%% of colorectal cancers. Lynch syndrome I of which HNPCC is a part, is an autosomal dominant inherited disorder characterized by early onset of colorectal cancer, predominance of proximal and multiple tumors, and microsatellite instability. In order to identify HNPCC, the international "Amsterdam criteria" have been used

Abstract:

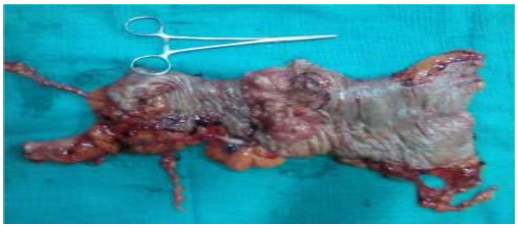
A 43 year old male presented with a history of altered bowel habits for 4 months. There was frequent episodes of loose stools – not blood stained which partly responded to medical therapy with anti amoebics. He was treated elsewhere as a case of amoebiasis or colitis. There was history of dull aching pain of lower abdomen which was at times colicky. There was no fever. There was a significant weight loss and loss of appetite. There were no urinary symptoms. There was no jaundice. History revealed a strong family history of colorectal malignancies. Patient's father and elder brother had history of colonic malignancy. His father had died at the age of 45 years. An elder brother had succumbed to the disease at the age of 46 years. Both of their medical records showed metastatic colonic cancer. There were another younger brother aged 38 years and sister aged 40 years who had no significant illness. On examination , the patient was well built . Vitals were stable. Per abdominal examination revealed a non tender, hard mass of size 5*5 cm palpable in the right hypochondrium . Surface was irregular and margins well defined. Moved with respiration. Per rectal examination was normal. There was no lymphadenopathy. A provisional diagnosis of Colonic growth was made- probably hereditary colon cancer. Base blood investigations showed Hb – 9 g/dl. Fecal occult blood test was positive. X ray chest and abdomen were unremarkable. USG abdomen came out to be normal. CECT abdomen showed Heterogenous enhancing endoluminal growth 5.5*4.7 cm involving hepatic flexure causing significant luminal narrowing with a few enlarged adjacent pericolonic lymph nodes – suggestive of neoplasm. Colonoscopy showed a hepatic flexure growth . Biopsy showed a moderately differentiated adenocarcinoma. CEA was elevated to 8mcg/dL.



CECT abdomen shows hepatic flexure growth

Based on Modified Amsterdam criteria, patient was dignosed to have Hereditary Non Polyposis Colon Cancer. The patient was explained of the condition , its genetics and the nature of treatment. As HNPCC was diagnosed, the patient was explained the need for total procto colectomy. The patient refused radical procedure despite the life time risk of metachronous or recurrent disease citing compromise of lifestyle Hence a segmental resection - extended right hemicolectomy was done. Per operatively, Hepatic flexure growth 6*5 cm was found .Multiple Mesocolic, pericolic, epicolic lymphnodes hard in

consistency largest being 2*2 cm were found. There were no hepatic / peritoneal mets and no free fluid.



Operative specimen laid open to show the growth

Histopathology showed Infiltrating moderately differentiated adenocarcinoma with clear surgical margins. The patient was discharged and started on Chemotherapy based on FOLFOX 4 regimen. 1 year follow up with colonoscopy showed no new lesions. CEA levels were found to be within normal limits. Patients siblings were counselled and screened for Colonic and extra colonic malignancies. The patient and his siblings are under regular follow up

Discussion:

Hereditary Non Polyposis cancer is a rare cause of Colo Rectal Cancer (CRC) in India with incidence about 3% of CRC. It is a part of family of inherited colorectal cancers comprising of :

1.Hereditary non-polyposis colorectal cancer (3- 5% of cases of CRC)
2.Familial adenomatous polyposis and attenuated FAP(1%)
3.Familial colorectal cancer (10-15%)
4.Peutz-Jeghers syndrome (<1%)
5.Juvenile polyposis syndrome (<1%)

In 1985, the chairman of pathology at the University of Michigan, Dr. Alder Warthin, recognised this syndrome. Dr. Henry Lynch fully investigated this entity in the early 1990's and 2 hereditary syndromes were described: Lynch I and Lynch II.

Lynch syndrome 1 is charecterised by Cancer of the colon occurring at a relatively young age (mean, 44 years), with proximal distribution (70% of cancers located in the right colon), predominance of mucinous or poorly differentiated (signet cell) adenocarcinoma, and the presence of tumourinfiltrating and peritumoural lymphocytes and increased number of synchronous and metachronous cancers Despite all the these poor prognostic indicators, there is a relatively good outcome after surgery.

Lynch syndrome 2 is charecterised by high risk for colorectal cancer and extracolonic cancers such as endometrial, ovarian, gastric, small intestinal, pancreatic, ureteral, renal pelvic. HNPCC and Lynch syndromes are diagnosed with Modified Amsterdam Criteria or Bethesda criteria:

Modified Amsterdam Criteria:

At least 3 relatives with HNPCC-associated cancer (colon, endometrium, small bowel, ureter, renal pelvis) and all of the following:

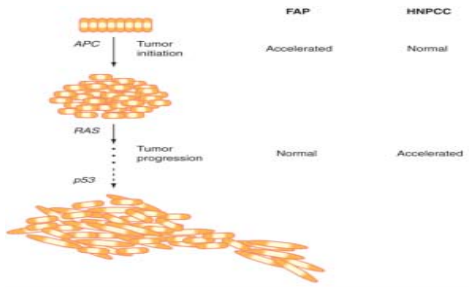
¨One affected person is a first-degree relative of the other 2 affected persons
¨ 2 successive generations affected
¨ At least one case of cancer diagnosed before age 50 years
- FAP excluded

Bethesda Criteria:

The Amsterdam criteria or one of the following:

¨ 2 cases of HNPCC-associated cancer in one patient, including synchronous or metachronous cancer
¨ Colon cancer and a first-degree relative with HNPCC-associated cancer and/or colonic adenoma (one case diagnosed before age 45 years and adenoma diagnosed before 40 years)
¨ Colon or endometrial cancer diagnosed before 45 years
¨ Right-sided colon cancer that has an undifferentiated pattern (solid -cribriform) or signet-cell histopathologic features diagnosed before 45 years
¨ Adenomas diagnosed before age 40 years

HNPCC is inherited in an autosomal dominant fashion. HNPCC accounts for 5-7% of colorectal cancers, it is the most frequent inherited CRC syndrome in the West. Results from a mutation in one of the **DNA mismatch repair (MMR) genes** (**MLH1**, **MSH2**, MSH6, PMS1, PMS2, MLH3, MSH3). Only 50-70% of patients meeting clinical criteria for HNPCC have an identifiable germline MMR mutation which suggests that one or more unidentifiable genes or other genetic events (e.g., large germline deletions) may be involved that result in **microsatellite instability** in 80-90% of cases.



Tumour pathway

Clinical Features:

Marked by early-onset CRC. There is predominance of lesions proximal to the splenic flexure (60 - 70%). Associated benign and malignant extracolonic tumours present. There is predilection for synchronous and metachronous colorectal tumours. The lifetime risk of CRC in HNPCC patients is approx. 80%. It does have a better prognosis for cancer patients with HNPCC than for non-HNPCC patients with cancer of the same stage.

Investigations:

Colorectal cancer, or an HNPCC-related cancer, arising in a person < 50 years should raise the suspicion of this syndrome. The mainstay of the diagnosis of HNPCC is a detailed family history, yet 20% of newly discovered cases are caused by spontaneous germline mutations. CRC patients who belong to known HNPCC kindreds, who have a pedigree suggestive of HNPCC, or who meet the Bethesda criteria should be offered screening by MSI testing. Patients with MSI-high tumours should undergo testing for germline MMR mutations. If a mutation is identified then other family members can be tested after obtaining genetic counselling.

Screening and surveillance :

If a family member has tested negative for a specific MMR mutation identified in an index case he is an average risk subject. If no genetic counselling, or positive for a given MMR mutation then screening recommendation is as follows:

HNPCC	Screening tool	Recommendation
CRC	Colonoscopy	Every 2 years beginning age 20 years, annually after 40 or 10 years younger than earliest case in family
Endometrial cancer	Pelvic exam, transvaginal ultrasound, endometrial aspirate, CA 125	Every 1-2 years beginning age 25-35 years
Upper urinary tract cancer	USS, U/A	Every 1-2 years beginning at age 30-35 years
Gastric cancer	Upper GI endoscopy	Annual after age 25-35 years
CNS cancer	-	-
Small bowel cancer	-	-

Surgical Management:

1.Total abdominal colectomy with ileo-rectal anastomosis.

This option is open only to patients with normal rectal reservoir function a normal anal sphincter function with no evidence of rectal involvement. Life long follow up is must.

2. **Total proctocolectomy with ileal pouch-anal anastomosis**
Indicated in patients with rectal cancer that is amenable to sphincter -preserving resection. The risk of developing a metachronous lesion in the remaining colon with an index rectal cancer in HNPCC patients is 17-45% at 10-12 years. The patient's will to undergo extensive surveillance and concern on bowel function is decisive.

3.Segmental colectomy with yearly colonoscopic surveillance.
This option is the standard of care in terms of quality of life and preserved bowel function. The need for extensive surveillance on a one-yearly basis cannot be overemphasised. An accelerated adenoma-carcinoma sequence and microsatellite instability may lead cancers to develop in less than one-year intervals.

Conclusion:
HNPCC is rarely diagnosed in Indian scenario. Yet, every patient presenting with a malignant tumor involving the colon, rectum, stomach, uterus, ovaries, renal pelvis or ureters under the age of 50 years is to be screened or at least counseled for a possible inherited carcinoma syndrome. He/she and their first-degree relatives are to be counseled appropriately with the aid of a geneticist, if possible.

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