Colorectal Carcinoma

* etiopathogenesis
* gross and microscopy
* Serological markers

- adenocarcinoma of colon is the most common malignancy of GI tract.
- peak 60-70 years.

Etiology and Risk factors

Dietary factors

→ Increased Risk:

- low intake of dietary fibre.
  ↓ (unabsorbable vegetable fibre)
  decreased stool bulk
  ↓
  slower transit of fecal content through colon.
  and altered microbiota
  ↓
  synthesis of toxic oxidative byproducts that remains in contact with colonic mucosa for long period.
- high intake of refined carbs and fat.

Ingestion of animal fats
↓
increased proportion of anaerobe in gut flora and increased hepatic synthesis of bile.
↓
Conversion of normal bile acids and cholesterol into carcinogens by anaerobes in gut microflora.
↓
↑ risk of colorectal cancer.

reduced Risk:

- diets rich in cruciferous vegetables & vit A.
- protective effect of aspirin and NSAIDs.
  ↓
  ⊖ COX 2.

Hereditary factors and Syndromes

→ familial adenomatous polyposis

- (5q) mutations of APC gene.

→ MYH - associated polyposis (MAP).

- mutations in MUTYH gene.

→ HNPCC / Lynch syndrome

- IBD
- ↑ age
- familial H/o in 1st degree relative.
- prior H/o CA colon.
- Tobacco smoking.
- alcohol & obesity.

PATHOGENESIS

~~genetic abnormalities~~

Molecular Pathogenesis

- genetic & epigenetic (more) abnormalities.

2 Genetic pathways.

- APC/β-catenin pathway.
- MSI pathway.

epigenetic events, the most common of which is methylation-induced gene silencing, may enhance progression along either pathway.

APC/β-catenin pathway.

- adenoma - carcinoma.

Sequence is seen in about 80% of sporadic colonic cancers

Normal function of APC:

APC gene → (5q 21).

↓

APC protein.

↓

negative regulator of β catenin, a component of WNT signaling pathway.

Early event - first hit & 2nd hit.

Inactivation of both copies of APC gene. {mutation or methylation etc}

↓

no APC protein

↓

β-catenin accumulation

↓ migrate to nucleus.

forms complex with TCF.

↓

activates myc & cyclin D.

↓

cell proliferation & adenoma formation.

Late events

- additional mutations accumulate.

① proto oncogene KRAS

↓

oncogene KRAS.

↓

promote cell proliferation & prevents apoptosis.

② SMAD2, SMAD4 mutations

↓

loss of TGF-β mediated growth inhibition.

③ TP53 mutations

④ telomerase activation.

Microsatellite Instability Pathway. (MSI) MSI

DNA mismatch repair (MMR) deficiency.

loss of function mutations in MMR gene.

(MLH1, MSH2, MSH6, MSI-H)

↓

accumulation of mutations in microsatellite sequence.

effects of MSI on key genes.

TGF-β receptor type II mutation.

↓

loss of TGF-β receptor function.

↓

uncontrolled epithelial cell proliferation.

BAX mutations

loss of apoptosis regulation

↓

survival of abnormal clones.

CpG island hypermethylation phenotype. (CIMP)

hypermethylation of MLH1 promoter gene

↓

decreased MMR function.

↓

BRAF oncogene activation.

sessile serrated adenoma

↓

Carcinoma.

Morphology of CA COLON

GROSS

(1) Exophytic polyploid mass (Right side) in → proximal colon.

(2) Annular and constricting tumours in distal colon (left side).
↓
apple core constriction.
↓
luminal narrowing.

(3) Infiltrative & ulcerating tumours.

MICROSCOPY.

- most of the tumours show glands of variable size and configurations.
↓
Composed of tall columnar cell
↓
lumen of glands.
↓
eosinophilic mucus, nuclear & cellular debris.

mucinous adeno carcinoma

- produce abundant mucin that accumulates within the intestinal wall.
- poor prognosis.

Signet ring carcinoma.

nucleus pushed to periphery due to mucin.

METHODS OF INVESTIGATION OF COLON CANCER

1. Occult blood loss in stool by Guaic test
2. Tumour markers
↑ Lvl of : carcino embryonic Antigen
CEA
&
CA 19-9
3. flexible sigmoidoscopy
4. fibreoptic colonoscopy.
5. Radiology - Barium enema.
↓
apple core appearance
6. ultrasonography

Test to know

- tumor in caecum & right side
↓
iron def anemia
fatigue, weakness.
- Left sided
altered bowel habits,
occult bleeding.
abdominal pain

Draw MICROSCOPY