COLORECTAL ADENOCARCINOMA:

Adenocarcinoma of the colon is the most common malignant tumor of GIT tra

RISK FACTOR:

1) → Dietary factors:
→ Low intake of dietary fibre - (unabsorbable vegetable fibers)
→ slower transit of fecal contents
→ These change may ↑ the synthesis of toxic oxidative.
↓
Remain in contact with colonic mucosa for longer periods. → development of colorectal cancer

2) High intake of Refined carbohydrate And fat:
↳ High fat intake ↑s the hepatic synthesis of secretion of bile into the intestine
↓
Conversion of normal bile Acid And cholesterol into carcinogens by Anaerobes in the gut microflora.
↓
↑ Risk of colorectal cancer.

3) Insulin Resistance:

Factors that Reduce the Risk:
→ Diets Rich in cruciferous vegetables (Brussels sprouts,
→ Protective effect of Aspirin or other NSAIDs

Hereditary factors And syndrome:
- MYH - Associated polyposis
- Nonpolyposis syndrome (Lynch syndrome)
- familial Adenomatous polyposis.

IBD - Crohn disease, Ulcerative colitis.

Other → ↑ Age, Family History, Streptococcus bovis bacteremia
Alcohol consumption, Tobacco.

Gardner syndrome – (FAP + extra colonic lesions)
Turcot syndrome – (FAP + medulloblastoma)

PATHOGENESIS:

develop from the combination of multiple molecular Alterations.

- genetic Abnormalities
  - APC/β-catenin pathway
    - Activated in classical Adenoma carcinoma sequence
  - MSI pathway
    - Defect in DNA mismatch Repair
    - Accumulation of mutation in microsatellite Repeat Regions
- epigenetic Abnormalities (factor beyond the genetic code)
  - → external modification to DNA that turn gene on or off.
  - Methylation Induced gene silencing
  - enhance progression in both Pathways

APC/β-catenin Pathway: APC – Adenomatous Polyposis coli gene → Tumor suppr gene → downregulate pro-proliferative (gate keeper of colonic Neoplasia).

key negative Regulator of β-catenin — bind to & promote degradation of β-catenin, promote differentiation, counteracts proliferation, facilitate Apoptosis

① Inactivation of APC tumor suppr gene.
→ negative Regulator of β-catenin

② Inactivation of both copies of APC gene → either by mutation or epigenetic silencing (Methylation)

Associated with familial Adenomatous polyposis
Non familial colorectal carcinomas & sporadic Adenomas.

→ APC is a component of the WNT signalling Pathway
– Role in controlling cellular growth and differentiation during embryonic development

NON - HODGKIN LYMPHOMAS.

– Non Hodgkin.

↑ p61 island is hypermethylated
↓
Methylation lead to silencing of tumor suppressor gene
↓
MLH1 promoter become hypermethylated → Reduce MLH1 expression & repair function

Normal

The APC bind with β catenin And form a destruction complex
↓
degradation of β catenin (As it is needed for the translocation)
↓
→ no translocation into nucleus
↓
No proliferation

↓ APC gene mutated ... lead to prolonged degradation of β catenin

WNT signals the deactivation of destruction complex
↓
↑↑ Accumulation of β catenin
↓
Activate translation of gene (MYC, cyclin D1)
↓
proliferation ↑↑↑ of colonic epithelial cell.

This β catenin bind to TCF to form transcription activation complex

⇒ when mutation of APC (no proper formation destruction complex) ↑↑ Accumulation → same → same just like WNT signaling

AKS?

Sequence

Normal Mucosa → Germline or somatic mutation of cancer suppressor gene (1st HIT)
↓
APC at 5q21

Mucosa at Risk → Abnormalities: Methylation Abnormality → 2nd HIT (CpG islands) Inactivation of normal allele.
APC / β catenin

early Adenoma → Protooncogene mutation KRAS
↓
promote growth, prevent Apoptosis
~~overexpression of COX-2~~
↓
Late Adenoma

Adenoma hypothesis

Homozygous loss of Additional cancer suppressor gene, Overexpression of COX2
← main SMAD2, SMAD4, TP53 gene Mutation

CARCINOMA
← Addition Mutation.
→ Activation of Telomerase & other oncogenes.

Tumor progression of Metastasis

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MICROSATELLITE INSTABILITY PATWAY:

Microsatellite Repeats:

Short segment of DNA . 1 to 6 or more base pair in length which Repeats multiple times in succession.

Eg: TATATA , GTCGTCGTC

Microsatellite Instability — Condition of genetic hypermutability.

↑ Due to impaired DNA mismatch Repair And Accumulation of mutation in microsatellite Repeats.

MSI involving

MSH2, MLH1 (DNA) mismatch Repair gene } Normal colon

↓

Sessile serrated Adenoma

(Microsatellite instability (MSI) mutator phenotype.

↓

Carcinoma

Epigenetic Area

→ Methylation of CpG Rich zones or CpG islands

↓

islands are Regions of genome that contain large Number of CpG dinucleotide Repeats.

Normal Mucosa

Germline or somatic mutation of mismatch Repair gene.

MLH1, MSH2 MSH6, PMS1,

→ **Mucosa at Risk**

Alteration of wend allel by2nd mutation or promoter methylation

→ sessile serrated Adenoma.

Accumulation of mutated in gene that Regulate growth differentiation or Apoptosis

TGFBR-2 BAX BRAF

Accumulation of DNA mismatch mutation in microsatellite Repeats.

↓

Carcinoma

DDH1

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MORHOLOGY:

Location → ① Right sided or proximal colon carcinomas.
② Left sided colon carcinomas.
③ Rectal carcinomas.

GROSS:

1) → exophytic polypoid mass in the Right side of colon
→ exophytic (cauliflower-like) - polypoid masses
They have sharp dividing line with the normal bowel.
- doesn't cause Intestinal obstruction

2) Annular And constricting tumor in the left side of the colon
- napkin-Ring or Apple core constrictions
- cause Intestinal obstruction

3) Infiltrative & ulcerating tumor → usually Raised, have irregular edge have a central excavated ulcerated area.

MICROSCOPY:

Adenocarcinoma NOS (not otherwise specified)
→ Differentiation → well differentiated, grade(I) ... ...
→ Microscopic feature → show glands of variable size & configuration.
The glands are composed of tall columnar cells that Resemble dysplastic epithelium found in Adenomas.
→ The lumen of the gland is usually filled with infiltrated eosinophilic mucus & nuclear & cellular debris.
Mitotic figures are usually Abundant.
→ components of their tumor may show stromal desmoplasia. & cause firm consistency.

→ Mucinous Adenocarcinomas: composed of Abundant pools of extracellular mucin.

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Signet Ring carcinoma

→ A colonic carcinoma is called SRC.

They have prominent intracytoplasmic mucin.

C.F

→ Cancer in the caecum and other Right sided colon.

→ Left sided colorectal cancer

Methods of investigation of colon

→ Occult blood loss in stool by Guaiac test

→ Tumor marker.

→ Flexible sigmoidoscopy

→ colonoscopy

Radiology → D.C barium enema

→ U.sound

→ Spiral C.T

Direct spread:

→ Transverse spread:

→ Longitudinal spread:

→ Radial spread.

→ Lymphatic spread.

→ Blood spread – Venous invasion

→ Transcoelomic spread.

– Non Hodgkin's

NON - HODGKINS LYMPHOMA: