Neoplasia

Definition:-

Neoplasia literally means new growth. (Neoplasm)

Neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of normal tissue & persists in the same excessive manner after cessation of the stimuli which evoked the change

FOUR CLASSES OF NORMAL REGULATORY GENES :-

1) Proto-oncogenes - growth promoting → RAS oncogene
2) Anti-oncogene - growth inhibiting or growth suppressor eg: RB, P53
3) Apoptosis regulatory genes - control the programmed cell death eg BCl2, CD95
4) DNA repair genes
   eg- p53 - detects & repair of damaged DNA.

VIRAL ONCOGENESIS :

1) DNA -

i) Replication - virus may replicate in host cell with consequent lysis of infected cells & release of virion.

ii) Integration - viral DNA may integrate into host cell.

Host cell transformation - expression of virus specific (T) antigen

2) Mode of RNA viral oncogenesis

i) Reverse transcriptase is RNA dependent DNA synthetase. that acts as a template to synthesise a single strand of matching viral DNA.

ii) single strand of viral DNA copies by DNA dep DNA synthetase → dsDNA

iii) provirus → DNA of host cell genome

iv) Integration of host cell genome with provirus. Transcription of proviral genes → messenger RNA forms component of virion

gag gene → core
RT → polgene
env gene → envelope glycoprotein

* Differences between benign & malignant tumors.

I. Clinical & gross features :- (4)

	Benign	Malignant
1) Boundaries :	Encapsulated Well-circumscribed	Poorly circumscribed Irregular
2) Surrounding tissue :	often compressed	Invaded
3) Size :	small	larger
4) 2° changes :	less often	more often

II. Microscopic features (10)

	(B)	(M)
1) Pattern	resembles tissue of origin closely	poor resemblance to TOO
2) Basal polarity	Retained	lost
3) pleomorphism	Absent	Present
4) N/C	Normal	↑
5) Anisonucleosis	Absent	Present
6) Hyperchromatism	Absent	Present
7) Mitoses	Present but typical	Abnormal
8) Tumor giant cell	Present w/o nuclear atypia	Present with nuclear atypia
9) Chromosomal abnormalities	Infrequent	Frequent
10) Function	Maintained	lost

III) Growth Rate	Slow	rapid
IV) Local invasion	Compress w/o invading	Infiltrat
V) Metastasis	Absent	Presen
VI) Prognosis	Local complicatn	local & metastat complic

II) METASTASIS

Definition :-

Spread of tumor by invasion in such a way that discontinuous 2° tumor are formed at the site of lodgement.

Benign → ⊗ metastasise

Malignant ✓

Exceptions :- gliomas
Basal cell carcinoma

Routes :-

1) Lymphatic - carcinomas
2) Hematogenous - sarcomas } generally
3) Spread along body cavities

1) Lymphatic Spread :- m/c carcinomas.

i) Lymphatic permeation - walls of lymphatics in the region of cancer are readily invaded by cancer cells and form a continuous growth within the lymphatic channel.

ii) Lymphatic embolli - malignant cells may detach to form tumour emboli and are carried to regional LNs. Tumor emboli enter through aff. lymphatics at its convex surface & lodge & grow in subcapsular sinus.

[iii] Skip metastasis :- when local LNs are bypassed & lymphatic metastases develop in LN distant from the site of 1° tumour.

Example:- Abdominal cancer → enlarged supraclavicular node
Virchow's Node.

(iv) Retrograde metastasis :- tumors spreading against flow of lymphatics. Eg: Ca prostate metastasize to supraclavicular LN.

2) Hematogenous :-
found in osteosarcoma, choriocarcinoma, RCC.

Vessels :- Capillaries & venules

Tumors with affinity for renal invasion :- RCC → Renal vein (malignant)
IVC → Right side of heart
• HCC - portal & hepatic vein

• Pattern Of Involvement -
Target Organs :-
Liver & lungs :-
Systemic veins → VC → lungs
Portal vein → liver
Pulmonary veins → L Heart → systemic circ
Bone - prostate, lung, breast, liver, intestine, kidney thyroid.
VC → paravertebral plexus.
Resistant organs :- Spleen & skeletal muscle

3) Spread along body cavities -
i) Transcoelomic
a) Malignant tumors arising in organs adjacent to body cavities
eg - Ca stomach → both ovaries
Krukenberg tumor
Ca of ovary → peritoneal cavity
Ca of bronchus → pleura & pericardium
2) Spread along lining epithelium
3) Spread via CSF.
4) Implantation

Chemical Carcinogenesis

The phenomena of cellular transformation by chemical carcinogens is a progressive process – 3 stages.

1) Initiation -

i) Directly acting carcinogens (alkylating & acylating agents) which can induce cellular transformation w/o undergoing any prior activation,

(ii) Indirectly acting or procarcinogens

↓

target cell (DNA)

↓

Reactive electrophiles

↓

target molecules (chiefly DNA)

↓

Permanent DNA damage or initiated cell

↓

clonal proliferation of altered cell

↓

cancer phenotype

↓

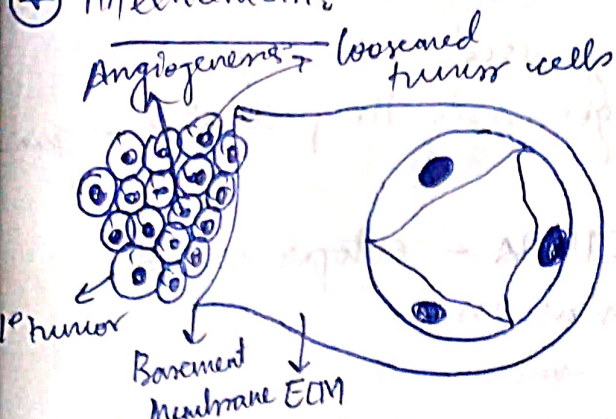
malignant tumors

Initiation

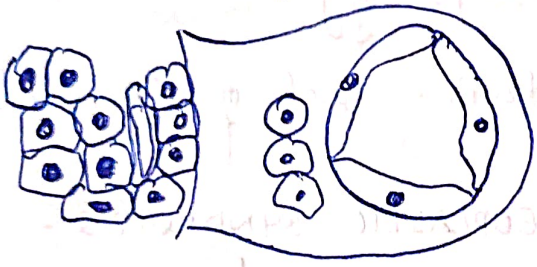
Promotion

Progression

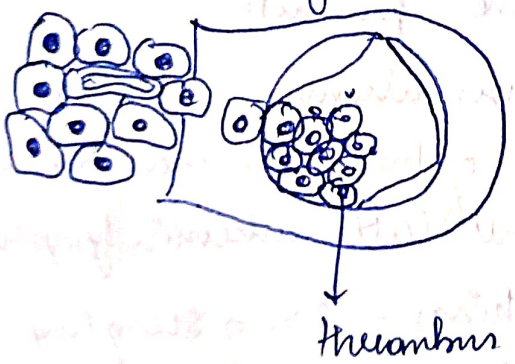
Mechanism:



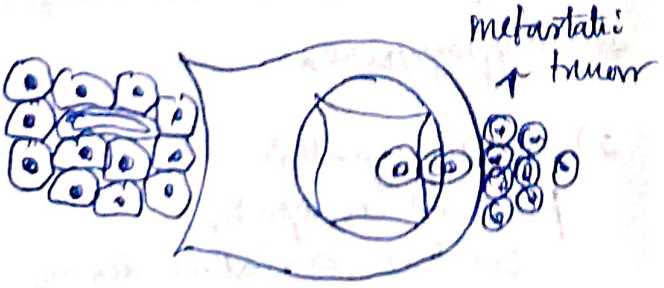
1,2) Aggressive clonal proliferation + angiogenesis + loosening of tumor cells



3,4 Tumor cell ECM interaction, Degradation of ECM



5,6 Entry of tumor cells in lumen Thrombus formation



7, 8 Extravasation of tumor cells Formation of metastases

Radiation carcinogenesis:-

1) Ultraviolet light -

→ Source - Sun

Effect limited to epidermis.

Eg: of UV light ∝ 1/melanin

Mechanism:- Induction of mutation, inhibition of cell division, inactivation of enzymes.

* most imp :- formation of pyrimidine dimers in DNA.

→ Xeroderma pigmentosum - skin cancer
→ Ataxia telangiectasia → leukemia
→ Bloom → All types of cancer

2) Ionizing:- X rays, α, β, γ.

All forms of leukemia (except CLL) cancer of thyroid, skin, breast, many tissues, lung, oral cavity & SCC.

Mech:- 1) Direct alteration of cellular DNA
2) formation of free radicals → Highly reactive

Damage to DNA → mutagenesis

leukemia, Colorectal, Chromosomal breakage, translocation, point mutation
Ca thyroid
Ca breast
Ca skin
Ca lung
nephritis
congenital anomalies
Sterility
Radiodermatitis

HAMARTOMA - mature but disorganised cells of tissues indigenous to the particular organ

CHORISTOMA - ectopic island of normal tissue

Differentiation - extent of morphological & functional resemblance of parenchymal tumor cells to corresponding normal cells.

Anaplasia - lack of differentiation

PARANEOPLASTIC SYNDROMES:-
Seen in advanced cancer.

i) Endocrine syndrome - ectopic hormone production

a) hypercalcemia - PTH by SCC of lung, Ca kidney, breast, Adult T cell leukemia lymphoma

b) Cushings - 10 % of SCC of lung - ACTH or ACTH like substance

c) Polycythemia - EPO - RCC, HCC cerebellar hemangioma

d) Hypoglycemia -

2) neuromyopathic syndromes -
peripheral neuropathy
cortical cerebellar degeneration
myasthenia gravis
polymyositis

(3) hypertrophic pulmonary osteoarthropathy & clubbing of fingers in bronchogenic carcinoma.

(iv) Hematologic - venous thrombosis (Trousseau's phenomenon), non-bacterial thrombotic endo., disseminated intravascular coagulation

(v) GIT syndromes - malabsorption

(vi) Renal - RVT or systemic amyloidosis → nephrotic syndrome

Pathogenesis

BURKITT'S LYMPHOMA

High grade, rapidly progressive B cell malignancy.

⇒ Strong association with Epstein-Barr virus.

90 % of BL are EBV positive

Immunosuppression: HIV, transplant patient, malaria → higher incidence

Cytogenic abnormalities - (MYC) on chromosome (8)

Morphology

Tumor cells are intermediate in size, non-cleaved, homogenous in size & shape. Nuclei - round to oval and contain 2-5 nucleoli.

Cytoplasm - basophilic + lipid vacuolation

Tumor cells have high mitotic rate → high cell death.

Starry sky app → macrophages containing phagocytosed tumor debris.

The BREAST

Carcinoma of the Breast:-

Presents as solitary, painless, palpable lump.

Early diagnosis by = (3) technique

palpation | mammography | FNAC

* RISK FACTORS:

1) Geographic & racial factors - higher in developed countries
2) Family h/o - 1° degree relatives of women with BC.
3) Menstrual & obstetric h/o -
   → Early menarche
   → delayed menopause
   → nulliparity
   → late age of 1st childbirth
4) Fibrocystic history - fibrocystic changes particularly when associated with atypical epithelial hyperplasia

5) Miscellaneous factors -

Interruption of large amount of animal fat

Cigarette smoking

Alcohol

breast augmentation surgery

high breast density

Exposure to ionizing radiation during breast development.

BRCA1 & BRCA2 → inactivated (heterozygous)

↓

for development of BC.

c) Mutation in p53 tumor suppressor gene on chromosome 17 → abn seen in Li-Fraumeni syndrome.

Pathogenesis:-

1) Hormonal -

Excess endogenous estrogen or exogenously administered estrogen for prolonged duration.

- Women with prolonged reproductive life
- Unmarried & nulliparous women
- HRT
- OCPs

Lactation & breastfeeding ↓ risk

BL oophorectomy → ↓ risk

2) Genetic factors :-

a) BRCA1 - ch17 - DNA repair gene

BRCA1 deletion → 2/3 rd of patient

BRCA1 mutation → uncommon in sporadic cases.

b) BRCA 2 gene - Ch 13, DNA repair gene

↓

mutation → 1/3 rd cases.

Classification

- Non-invasive carcinoma
  - Intraductal
  - Lobular
- Invasive carcinoma
  - Invasive ductal
  - Invasive lobular
  - Tubular
  - Medullary
  - Colloid (mucinous)
  - Papillary Ca
  - Adenocystic
  - Secretory
  - Inflammatory
  - Metaplastic
- Paget's disease of nipple

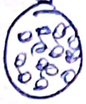
Morphology :-

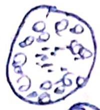
A) Intraductal Ca :-

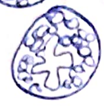
Grossly - small poorly defined focused to 3-5cm diameter mass

CLs - cystically dilated ducts containing solidly necrotic material (Comedo pattern) or tumor maybe polypoid & friable

Histologically :-

1) Solid  filling & plugging of ductal lumina with tumour cells.

2) Comedo  centrally placed necrotic debris

3) Papillary  intraductal papillary projections of tumor cells

4) Cribriform pattern  neat punched out fenestrations

B) Lobular Carcinoma in situ :-

Gross - no visible tumour

Histo - filling up of terminal ducts & ductules or acini by uniform cells.

C) Invasive ductal Ca :-

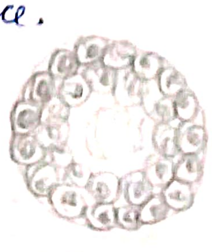
Gross :- tumour - irregular (1-5cm) in diameter, hard - cartilage like mass that cuts with grating sound.

C/S - greywhite to yellowish with chalky streaks

Histology :- i) Anaplastic tumour cells - solid nests, cords, poorly formed glandular structures.

(ii) Infiltration into fibrous stroma & fat

(iii) Invasion into perivascular & perineural space.



d) Infiltrating lobular Ca :-

Gross :- well defined scirrhous mass to poorly defined area of induration

Histo :- i) Pattern :- Single file (Indian file) linear arrangement of stromal infiltration of tumour cells.

ii) Tumor cytology - Resembles insitu lobular Ca. Signet ring cells.

* Prognostic Markers :-

Factor	Favorable prognosis	Poor prognosis
Routine HP criteria :-		
1) Histologic type	Medullary, tubular mucinous, lobular	inflammat
2) size	≤ 1cm size 10 year → 90%	Size >1cm
3) Grading Nottingham	low grade - 3-5 med grad - 6-7	high grad 8-9
4) Axillary nodal status	node - negative Recurrence after 10yrs : 10-30%	Node - +ve Recurrence => 70%
5) lymphatic & vascular	negative for both : good	positive for one or both - bad
6) Others :-		
Tumour angiogenesis	good	poor
Inflammatory	may have some role	controversial
Stromal elastosis	Absence	Presence
Intraductal	Presence	Absence
Skin involvement	Absence	Presence

	Favourable	Poor
II. Hormone receptor status:-		
ER PP	positive	negative
HER-2/neu	nuclear expression	over
III. Biological		
i) Mitotic Index	low	high
ii) DNA ploidy	diploid	aneuploidy
iii) Angiogenesis	low	high
iv) BRCA1 CA2	negative	positive
p53	positive	neg.
Bcl2	positive	neg.
Cathepsin D	Absence	Presence

* Fibroadenoma :-
benign → mc
Age : 15 - 30
Solitary, discrete, freely mobile nodules within the breast.
Morphology -
Gross - Small (2-4cm) solitary, well encapsulated, spherical shaped mass.
Cls - firm, greyish white, slightly myxoid

* Phyllodes tumor :-
Age : 30 - 70
Gross = Giant fibroadenoma, large 10-15cm in diameter, round ovoid, lobulated
Cls - grey white cystic cavities areas of hemorrhage, necrosis & degenerative Δs.
Histo - hypercellular stroma
To distinguish btw benign, borderline & malignant - 1) frequency of mitoses
2) cellular atypia
3) cellularity
4) Infiltrative margins.