{ Oncology }

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Neoplasia: means 'new growth'.

A Neoplasm is a growth of new cells that proliferate without Control, serve no useful function, & has no orderly arrangement.

They are basically transformed cells that ignore inhibitory Control that regulate normal cell growth.

Neoplasm behave as a parasite that Competes with normal cells for their metabolic need & patient undergoes wasting.

Neoplasm is generally referred to as tumour but its a misnomer ∵ tumour means swelling & all swellings are not tumours.

Nowdays tumour term is used only for neoplastic masses that cause swelling

Tumours are of 2 types i.e, Benign & Malignant.

Benign; A tumour is said to be benign when it remains localised, doesn't spread to other sites, can be removed surgically & doesn't Cause death, unless it interfers with an imp. body function.

Malignant; They can invade & destroy other adjacent structures, spread to ~~adjacent~~ distant sites (metastasize) & Cause death. They are termed as Cancers.

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Nomenclature :

i) Benign - Cell type + 'oma'

- Epithelial
  - Glandular → Adenoma
  - Squamous → Papilloma
- Non-epithelial → Tissue + oma

except : Melanoma → M.T.
Glioma → MT of Glial cells
Seminoma → " " seminal vesicles
Mesothelioma → " " Mesothelial cells

ii) Malignant :

- Epithelial
  - Sq. epithelium → Sq. cell Carcinoma
  - Glandular epithelium → Adenocarcinoma
- Non-epithelial → Tissue + Sarcoma

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Aetiology of Cancer;

Can be divided into 2 types i.e. Intrinsic factors & Extrinsic factors.

i) Intrinsic factors:
a) Heredity
b) Age
c) Pigmentation
d) Sex.

a) Heredity; Most of the tumours are non-heredity, but for some tumours genetic predisposition is seen.
e.g. Breast Cancer in humans, Ovarian tumours
Lymphoid leukosis in Chicken.

b) Age; In general, the frequency of Cancer increases with age due to the accumulation of somatic mutations over a period of time that are needed for devp. of Cancer.
But some tumours occur in young ones e.g. Sarcomas, Carcinomas occur in old age.

c) Pigmentation;
Melanin pigment produced by the melanocytes protect the skin from UV rays. Hence, lack of pigmentation may lead to occurence of tumours.
e.g. In white & Grey horses → melanosarcomas are more.
In Herefold Cattle → sq. cell Carcinoma of eye is more.

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d) Sex : Tumour incidence of genital organs shows incidence for particular sex. due to diff. hormones.
→ Mammary tumour, → more in females.

ii) Extrinsic factors ;

a) Chemicals ; A no. of chemicals are labelled as Carcinogens & are inform of 2 types i,e, Direct acting — that don't require chemical transformation for producing Cancer.
& Indirect acting — that become active only after metabolic Conversion. They are referred to as 'pro carcinogens' & their active end products are called ultimate Carcinogens.

Chemical Carcinogenisis ;
Carcinogenisis is the prod. of Cancer, It is a multistep process. Chemical Carcinogenesis Can be divided into 2 stages i,e, initiation & promotion.

· Initiation results from the exposure of Cells to a Carcinogen, which Causes permanent DNA damage & Can give rise to tumour.

· Promotion ; Certain promoters Can induce tumour prod. in initiated cells but they aren't tumour producing themselves. The promoters cause cellular changes

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Date ..../..../.....

making them prone to transformation but don't affect DNA.

⇒ Mechanism of Chemical Carcinogenesis:

i) All direct & indirect Carcinogens are highly reactive electrophiles, & they react with nucleophilic sites in cell. (e.g. DNA base)

ii) The rxn leads to formation of addition product, & causes DNA damage. But changes in DNA don't lead to initi-ation necessarily because some damage is repaired by cellular enzymes.

iii) But any damage to certain specific genes e.g. ras gene in rats, TP53 gene lead to permanent changes, which is the ist step in initiation.

iv) For the change to be heritable, the damaged DNA must be replicated. Ther-efore for initiation to occur, Carcinogen induced cells must undergo at least one cycle of proliferation, so that the damage in DNA becomes fixed.

v) Permanent DNA damage is not still enough for transformation. The DNA damage only gives preneoplastic lesions/ hyperplastic lesions.

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Date ..../..../.....

vi) Subsequent application of promoters causes proliferation & clonal expansion of initiated cells.
Initiated cells respond differently to promoters than normal cells & expand selectively. Such cells require less amount of growth factor.

vii) Thus initiated cells proliferate and develope into a malignant neoplasm.

Initiation:

Carcinogen → Detoxification → Excreation

↓ metabolic conversion.

Electrophilic intermediates → Detoxification → Excreation

↓

Binding to DNA → DNA repair → Normal cell.

↓

formation of addition product → Cell death.

↓

Permanent DNA lesion.
(initiated cell).

Promotion:

↓

Cell proliferation
(due to promoters).

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Date ..../..../.....

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Preneoplastic clone.

| Additional mutations

↓

Malignant neoplasm.

b) Radiation;
e.g. X rays, UV rays.
Either they directly ionize the particular critical components of cell or react with water or molecular oxygen to produce free radicals that mediate the carcinogenesis.
UV rays cause damage to the DNA by forming pyrimidine dimers, which lead to mutation e.g. of TP53 gene.

c) Hormones; It is seen that some hormones also cause malignant transformation of cells
e.g. High Oestrogen levels associated with milk retention in bitch lead to mammary tumour.

d) Biological agents
- Parasites → They cause cancer by virtue of causing chronic irritation
  e.g. Habronema megastoma → Gastric adenoma in horses.
  Eimeria stiedae → Bile duct cancer in rabbit.
- Viruses e.g. Retroviruses.

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Characteristics of Benign & Malignant neoplasms.

Date

- The characteristics of B & M.T are discussed under 4 different headings.

i) Differentiation & Anaplasia:

Benign	Malignant.
* B.T are composed of well differentiated cells that closely resemble normal cells, i.e, they have same morphology as that from which it originated.	* M.T exhibit a wide range of parenchymal cell differentiation from well-differentiated to completely undifferentiated cells.
* The tumour cells show minimal evidence of anaplasia. Mitotic figures few or absent.	* The Tumour cells show lack of differentiation or anaplasia. Due to which tumour cells loss their structural & functional differentiation. These cells show pleomorphism, large & hyperchromic nuclei, N:C ratio 1:1, Giant cells present in neighbour Nucleoli extremely large, & ↑sed no. of mitotic figures.

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ii) Local Invasion.

Date ..../..../.....

B.T	M.T
The tumour is Confined by adjacent tissues. It doesn't extend beyond the basement membrane or basal layer of cells.	· The Tumour is not Confined by adjacent tissues. They grow by progressive infiltration, destruction & penetration of surrounding tissue.
The Tumour doesn't pen-trate, or infiltrate Conn-ective tissue Capsule.	Microscopic exam. reveal tiny, Crab like feet penetrating the margin & infiltrating the neigh-bouring structure.
iii) Rate of Growth;	
* Rate of Growth is slow over a period of months to years	Rate of Growth is gener-rally fast, & they spread to other locations also.
· Since rate of Growth is slow blood supply meets the growing de-mands easily & there is no degenerative & necrotic changes within the tumour.	Since rate of Growth is fast blood supply Can't meet the needs & there are extensive degenrative and necrotic changes.
· There is also no invasion of blood vessels or lymphatics.	· Invasion of blood vessels & lymphatics Occurs.

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Date ..../..../.....

iv) Metastasis;

· Metasis is lacking	· Metastasis is the Characteristic feature.

v) Some other Characteristic features.

· They occur singly ∵ they don't spread & hence a single tumour is found.	· These may appear as single or multiple tumours. This is on account of metastase.
· Shape is round, eliptical, wart like ∵ as the tumour grows slowly pressure is equal on all directions.	· Shape is irregular. ∵ it grows rapidly & extends in all directions.
· Encapsulation is present generally	· Encapsulation is absent.
· Removal is not difficult ∵ of encapsulation & lack of local invasion.	· Removal is difficult: This is on account of local invasion & metastasis & also lack of encapsulation.
· There is no recurrence of tumour	· Tumour tends to recur after apparent removal.
· Death doesn't occurs	· Death occurs ∵ of invasion, metastasis & tissue destruction.
· Tumour is not toxic ∵ the deg. & necrotic changes that liberate toxic material don't occur.	· Tumour is toxic, ∵ of extensive deg & necrotic changes that liberate toxic spiral products.

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{Metastasis & Spread of neoplasm Date..../..../.....

Metastasis is a property of malignant tumour by which malignant cells spread from its primary site to another place through blood or lymph vessels & form Secondary growth there.

The Secondary growths formed at distant organs or tissues are called metastases.

Pathways of Spread;

1) **Hematogenous spread** :-
The spread through blood & blood vessels. Mainly through veins as arteries are resistant to invasion due to ↑se in thickness, ↑ elastin content & due to secreation of protease inhibitors.
- Lungs & Liver are the most commonly involved secondary site in hematogenous spread.
- Favoured for Sarcomas, also Carcinomas.

2) **Lymphatic spread** :-
- Common route for Carcinomas.
- This route involes regional lymph nodes, because lymph nodes act as filter & trap the cells.

3) **Seeding within body cavities** :- It is the transfer of tumour cells from one serous or mucous membrane to another by spread

Date ..../..../.....

direct contact.

e.g. in Cancer of Ovary,

Grading & Staging of Cancers;

i) Grading; It is done to know about the level of malignancy.

- Based on Cytological differentiation & no. of mitotic figures
- These two will tell us about the level of anaplasia & accordingly Grade I, II, III or IV is given to different tumours.

ii) Staging;

It is on the bases of

a) Size of primary tumour at the site of Origin

b) Extent of spread to regional lymph nodes

c) Presence or Abscence of metastases.

& is given name as TNM System.

on increasing order of size of 1° tumour

$T_4 > T_3 > T_2 > T_1$

Based on involvement of regional lymph nodes as $N_0 < N_1 < N_2 < N_3$.

Metastases → M_0, M_1 { M_1 → secondary growth.

e.g. $T_1 N_0 M_0$ → Early stage

$T_2 N_1 M_0$ → Intermediate

$T_4 N_3 M_1$ → Last stage

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{ Tumour Immunity }

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There are some antigens which are present on tumour cells. These are of two types i.e. Tumour specific antigens present only on tumour cells & not on any other cell & Tumour associated antigens present on both tumour cells & on some normal cells.

i) TSA :- May be due to mutation of genes which give rise to some abnormal proteins c̄ when combined with MHC forms / becomes an antigen.

e.g. Tumour suppressor gene products.
Oncogene products.
Mutated gene products.

ii) TAA :- e.g. oncofetal antigen → which are normally expressed in developing embryos.
Some proteins : of their overprod. are expressed on the surface.

These antigens help in provoking some Immunity but not full. the mechanism of "Anti-tumour" are as.

Anti-tumour Effector mechanisms;

i) Cytoxic - T - lymphocyte mediated ($CD8^+$);
They destroy the tumour cell by recognizing MHC class I antigen expressed on tumour cells & release granezymes, perforins c̄ cause cell death or

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Date ..../..../.....

induce apoptosis especially in Virus associated neoplasm cells.

ii) Nature Killer cells ;
These cells destroy tumour cells with prior sensitization & thereby provide first line of defense against tumour cells.
They basically recognize the low MHC- I levels on the surface of tumour cells which are very low in these cells.

iii) Macrophages :
They cells get activated by IFN IFN-γ c̄ is released by cytotoxic T- cells & NK cells when they destroy the tumour cells. After c̄ they (the macrophages) so kill the tumour cells by prod. of reactive oxygen species or TNF secreation.

iv) Antibody dependent cell mediated ~~toxic~~ cytotoxicity ;
- Antibodies bind with the antigen on T cells c̄ then activate neutrophils, eisnophils to kill these cells.

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Date ..../..../.....

Escape mechanism of Immuno Survillance:

i) Tumour cells fail to express normal levels of MHC-I & thus escape attack by cytotoxic T-cells.

ii) Many Tumour cells produce many products e.g. TGF (Tumour growth factor-β). This causes apoptosis of nearby cells & angiogenesis is neighbouring cells & is also immunosuppressant.

iii) Lack of Co-stimulation;
Sensitization of T-cells require 2 signals, one by peptide antigens presented by MHC & the other by Co-stimulatory molecule.

Although Tumour cells express peptide antigen with class-I molecules, they don't express Co-stimulatory molecules & thus can't sensitize T-cells.

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{ Diagnosis of Cancer } Date ..../..../.....

i) Clinical diagnosis based on the gross features (papilloma, cystic, fibrotic) etc.

ii) Histological & Cytological methods;

a) Biopsy :- here a section of tissue can be seen under microscope for cellular characteristics of anaplasia, invasion, loss of polarity.

b) Cytology; Examination of cells which can be used for diagnosis.
Cells can be collected by fine needle aspiration biopsy. other methods include scraping, brushing. Cellular characteristics are then seen.

c) Exfoliative Cytology; Neoplastic cells are less cohesive (sticking together) than others & so are shed into fluids or secreations. The shed cells are evaluated for features of anaplasia.

iii) Biochemical Assays; Based on assays of tumour-associated enzymes, hormones & other useful tumour markers in blood.
e.g. Alfa-feotoprotein & Carcino-embryonic antigen are 2 markers seen in humans.

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Date ..../..../.....

iv) Molecular methods ;

e.g. PCR which helps to differentiate b/w monoclonal (neoplastic) & polyclonal proliferations.

- FISH (fluorescent in situ hybridisation) technique.

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