Q1. DEFINITIONS, PRENEOPLASTIC LEASIONS, PSEUDOTUMOURS

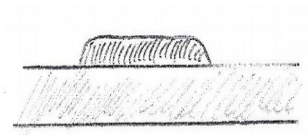
TUMOUR → / Neoplasm is a lesion resulting from the autonomous or relatively autonomous abnormal growth of cells which persists after the initiating stimulus has been removed.

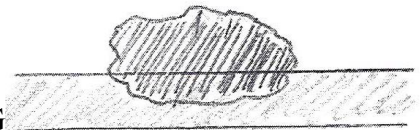
STRUCTURE OF TUMOURS

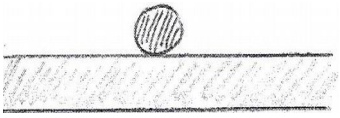
Solid tumours consist of neoplastic cells and stroma:

- NEOPLASTIC CELLS: result from neoplastic transformation of any nucleated cell in the body, although some cell types are more prone than others.
  By genetic alterations (mutations), cells escape permanently from normal growth regulatory mechanisms.
- STROMA: neoplastic cell populations is embedded in and supported by a connective tissue framework, called stroma, providing mechanical support and nutrition. It contains :
  - BLOOD VESSELS: which perfuse the tumour
  - FIBROBLASTS: which offer mechanical support and nutritive properties
  - LYMPHOCYTIC INFILTRATE may reflect a host immune reaction to the tumour.

GROSS APPEARANCE OF TUMOUR may be:

SESSILE 

FUNGATING 

POLYPOID 

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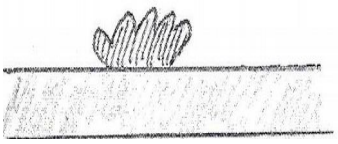
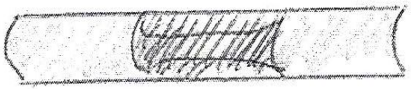
PAPILLARY 

ANNULAR 

1) Specification of the term tumour:

A tumour or neoplasm is a controlled growth formed by the unlimited multiplication of abnormal cells in one of the body tissue or organs.

a. Tumour forms a mass which has no useful function

b. Does not obey the biologic factors which control physiological and reparative growth. It growths even when the body is starved.

c. Any tissue may be the seat of tumour formation but it is rare in highly specialized cells (e.x nerve cells)

d. Cells of the tumour have a supporting stroma of fibrous tissue and supplying blood vessels derived from the host.

e. Activity of tumour is spent mainly in multiplication, however, functional may be present. The functional activity is unneeded and harmful.

f. Tumours are classified according to the behaviour into benign, malignant and locally malignant (question 3)

PRENEOPLASTIC LESION: is an identifiable local abnormality associated with an identifiable local abnormality risk of malignant and tumour developing at that site.

- It may be that these lesions represent the growth of partially transformed cells which have not yet achieved full neoplastic status.
- Premalignant condition is associated with risk for malignant

▪ Premalignant lesions:

- Adenomatous polyp of colorectom → Colorectal carcinoma
- Cervical epithelial dysplasia → Carcinoma of cervix
- Mammary ductal epithelial hyperplasia → Carcinoma of breast

▪ Premalignant conditions:

- Hepatic cirrhosis → Hepatocellular carcinoma
- Xeroderma pigmentosum → Skin cancer
- Ulcerative colitis → Colorectal carcinoma / bile duct carcinoma

PSEUDOTUMOUR → An enlargement of nonneoplastic character which clinically resembles a true neoplasm so closely as to often be mistaken as such.

▪ P. cerebri – a condition of the brain stimulating the presence of a intracranial tumour – usually in obese women

▪ Inflammatory p. – tumour – like mass in the lungs or other sites composed of fibrous or granulation tissue infiltrated by inflammatory cells

2. MICROSCOPIC STRUCTURE OF TUMOURS

Microscopically solid tumours consist of:
1) Neoplastic cells
2) Stroma

STROMA

Neoplastic cells are embedded in a connective tissue framework called stroma. The formation of stroma is called "desmoplastic reaction" and is due to induction of connective tissue proliferation by growth factors.

tumour stroma contains blood vessels upon which the nutrition of the tumour and so its growth depends. Angiogenesis in tumour is induced by "Vascular endothelial growth factor" and is therapeutically opposed by angiostatin and endostatin.

Fibroblasts (nutritive and supportive action) and myofibroblasts also may be abundant. Finally, stroma often contains a lymphocytic infiltrate of variable density, indicating immune reaction.

NEOPLASTIC CELLS

▪ In benign tumours.

The cells resemble those of tissue of origin. Their nucleus is small and mitotic figures are absent or few.

▪ In malignant tumours

The cells don't resemble so much those of tissue origin (loss of differentiation). The cells are larger, show polymorphism (variation in size and shape) while their nuclei vary in size, shape, position and are hyper chromic. There are many mitotic figures while in case of rapidly growing tumours, repeated disions of nucleus without divisions of cytoplasm results to multinucleated tumour giant cells. Malign tumours show loss of polarity.

3. CLASSIFICATION OF TUMOUR

The classification of tumours is based on 3 factors:
1) Behaviour
2) Hiostogenesis (= specific cell of origin)
3) Grade (= level of differentiation)

Behavioural classification

It divides tumour into:
i. Benign
ii. Malignant

The intermediate ones are called "border – line" tumours
(Check also table from question 5)

Histogenic classification

It includes numerous subdivisions but the major categories are:
i. from epithelial cells
ii. from connective tissue cells
iii. From lymphoid and haemopoietic organs

Differentiational classification

The term "differentiation" means the degree to which the tumor resembles histologicaly the parental tissue.

ATTENTION: THE HIGHER THE DIFFERENTIATION, THE HIGHER THE RESEMBLING TO THE PARENTAL TISSUE AND THE LOWER THE MALIGNANGY

So:
Grade 1 = high degree of differentiation (low malignancy)
Grade 2 = moderate degree of differentiation (moderate malignancy)
Grade 3 = low degree of… (high malignancy)
Grade 4 = very high malignancy

4. TUMOUR DIAGNOSIS, BIOPSY, CYTOLOGY

Diagnosis of tumor (benign, malignant) may be done by
→ blood tests
→ urine / stool tests
→ bone marrow aspiration
→ ultrasound
→ computer tomography
→ magnetic resonance imaging
→ x-rays
→ endoscopic exams

Laboratory diagnosis of cancer

1. Histologic + cytologic methods
- a) excision of biopsy
- b) fine needle Aspiration
- c) cytologic smears (PAP test)

2. Immunocytochemistry → detection of cell products or tumor surface markers by monoclonal Antibody used for categorization of undifferentiated malignant tumors.
Flow cytometry: categorization of leukemia + lymphomas, determination of site of origin of metastatic tumor.
3. Molecular diagnosis (Blot analysis) (southern, northern). Used for diagnosis + prognosis of malignant neoplasms, diagnosis of Hereditary predisposition to cancer, DNA micro array analysis + proteomics ⟹ used to obtain gene expression signature of cancer cells.
4. Flow cytometry → Measure several individual cell characteristics such as membrane Antigens + DNA content of tumor cells.
5. Tumor markers → Biochemical indicators of the presence of a tumor.
→ doesn't be constricted as primary modalities for the diagnosis of cancer.
→ These include cell surface antigens, cytoplasmic proteins, enzymes + Hormones.

5. BENIGNITY AND MALIGNITI OF TUMORS (LIST)

Feature	Benign	Malignant
Growth	slow	rapid
Mitotic activity	low	high
Resemblance to parent tissue	good	poor
Invasion	No, so there is formation of polyps and exophytic lesion	Yes, so there is formation of entophytic lesion
Metastases	No	Yes due to penetration of blood vessels and lymphatic channels wall by neoplastic cells
Nuclear morph.	Often normal	Hyperchromatic, pleomorphic, often multiple nucleoli with irregular outline
Border	Often circumscribed and encapsuled	poorly defined or irregular
Necrosis	Rare	Central due to defective vascular perfusion
Ulceration	Rare	Common in skin and mucosal surface

6. SPREAD OF MALIGNANT TUMOR

Definition: Metastasis is the development of secondary tumors discontinuous with primary one.

Not all tumors are equally metastasable. The most not metastatic are the basal cell carcinoma and primary CNS tumors while the most metastasable are the osteogenic sarcomas that usually metastize in lungs initially.
In general the larger and more anaplastic the tumor, the more it metastises.
The tumors in order to spread / metastize can use the following pathways:
1. By seeding within body cavities.
2. Lymphatic spread.
3. Hematogenous spread.

- Seeding within body cavities.

It occurs when neoplasm invade a natural body cavity. This kind of spread is most common in cancer of the ovaries which often cover the peritoneal surfaces widely.
Another example is the carcinoma of the gut that penetrates the wall and reimplants at distinct sites in peritoneal cavity.

- Lymphatic spread.

This pathway is more common for carcinomas although we should mark that cancers can use both lymphatic and Hematogenous spread.
The involvement of lymph modes depends on the site of the primary neoplasm and the natural lymphatic drainage of the site for example carcinoma of breast which appears at the upper guardant first spreads to the auxiliary nodes.

- Hematogenous spread.

This pathway is more common for sarcomas. As might be expected the veins are more easily penetrated than arteries.
Because of the fact that all portal area drainage flows to the liver and all cavol blood flows to the lungs, liver and lungs are the most frequent sites for metastasis at this kind of spread.

Q 6. CARCINOGENESIS, ETIOLOGY OF TUMORS

CARCINOGENESIS → Process which results in the transformation of normal cells to neoplastic cells by causing permanent genetic alterations.
Tumors arise from single cells that have become transformed by cumulative mutational events.

- Carcinogenesis → applies strictly to causation of malignant tumors..
- Oncogenesis → causation of all tumors, benign malignant.

CARCINOGENIC → agent known or suspected to participate in the causation of tumors.

- Carcinogenic → causing cancer
- Oncogenic → tumor causing

● Carcinogens may be identified by:
- Epidemiological evidence
- Assessment of occupational risks
- Direct accidental exposure
- Experimental testing in animals

● KNOW or SUSPECTED CARCINOGENS are:
a. chemicals
b. viruses
c. ionizing & non – ionizing radiation
d. hormones
e. bacteria, fungi, agents
f. miscellaneous agents

a. CHEMICAL CARCINOGENS

Some agents act directly, requiring no metabolic conversion. Others (procarcinogens) require metabolic conversion into active carcinogens (ultimate carcinogens).

- Polycyclic aromatic hydrocarbons (Lung/Skin cancer)
- Aromatic amines (Bladder cancers)
- Nitrosamines (Bladder & liver cancers)
- Azo dyes (liver angiosarcoma)
- Aklylating agents (Leukemia)

b. ONCOGENIC VIRUSES

Immunosupression favors viral Oncogenesis.

- Human Papilloma Viruses HPV (cervical carcinoma)
- Epstein – Barr Virus (Burkitt's lymphoma/ Nasopharyngeal cancer)
- Hepatitis B & C viruses (Hepatocellular carcinoma)

c. RADIANT ENERGY

a. Ultraviolet radiation (skin cancer) UVL, UVB, UVA.
b. Ionising radiation (- radiatory workers → leukemia
- military radiation → certain tumors
- radioactive uranium → carcinoma of lung
- radioactive iodine → thyroid cancer)

Tissues which appear sensitive to ionising radiation are: THYROID, BREAST, BONE, HAEMOPOIETIC TISSUE.

d. HORMONES

- oestrogens (mammary gland/endometrial carcinomas)
- androgenic & anabolic steroids (Hepatocellular tumors)

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PSEODOTUMOR ⇒ An enlargement of non-neoplastic character which clinically resembles a true neoplasm so closely as to often be mistaken as such.

● P. Cerebri – a condition of the brain stimulating the presence of an intracranial tumor – usually in obese women.
● Inflammatory p- tumor – like mass is the lungs or other sites, composed of fibrous or granulation tissue infiltrated by inflammatory cells.

Most common precancerous tissue changes.
1. Leukoplakia → white patch of altered superficial epithelium that wiped off focal squamous tissue changes with:
a. Hyperkeratosis → ↑ cornification
b. Parakeratosis → rapid cornification
c. Basal cell hyperplasia
d. Inflammation, lymphocytic infiltration
2. Intraepithelial neoplasia → refers to reversible histologic deviation of epithelia tissue from normal with 1) deranged differentiation, 2) controlled profile-ration
=> It's a precancerous lesion.
Shows → pleomorphism, mitoses with loss of functional epithelial orientation
3. Carcinoma in situ → severe epithelial Atypia + loss of polarity present with an intact basement membrane.
4. Microinvasive carcinoma → early forms of carcinoma that penetrates the basement mb + invades the tissue to a max 3-5mm.

Q7. EFFECTS OF TUMOR ON HOST

Clinical effects of tumors are attributable to their a) location, b) cell of origin, c) behaviour

- LOCAL EFFECTS

1. COMPRESION & DISPLACEMENT of adjacent tissues.
Even benign tumors eg. adenoma of pituitary gland may obliterate the adjacent functioning pituitary tissue, resulting in hypopituitarism.
2. DESTRUCTION, if malignant
3. INVASION & destruction of local structures
4. ULCERATION → ANEAMIA (loss of blood)
→ RISK OF INFECTION

- METABOLIC EFFECTS

a. Tumour – type specific effects

Pouraneoplastic syndromes: symptom complexes occur in patients with cancer and can not be readily explained by local or distant spread of tumour.

Well – differentiated endocrine tumour often retain the functional properties of the parent tissue.

- THYROTOXICOSIS, may result from a thyroid adenoma
- CUSHING'S SYNDROME may result from an adrenocortical adenoma.
- HYPERPARATHYROIDISM may result from a parathyroid adenoma. Sometimes we have inappropriate or unexpected consequences.
- Oat cell (small cell) carcinoma of long commonly secretes ACTH & ADH.
- Finger – clubbing & hyper tropic osteoatropathy in carcinoma of the lung.

b. Non – specific metabolic effects:

1. WEIGHT LOSS: sometimes leading to cachexia. It may be mediated by tumour – derived humoral factors that interfere with protein metabolism.
2. NEUROPATHIES / MYOPATHIES associated with some neoplasms mainly carcinoma of lung.

3. VENOUS THROMBOSIS associated with mucous-producing adenocarcinoma mainly pancreas.
4. GLOMERULAR INJURY from deposition of immune complexes in which one of the ingredients is tumour antigen.

9. BENIGN EPITHELIAL TUMORS

The benign epithelial tumors are either:
1. Papilloma
2. Adenomas

● Papilloma
It is a benign tumor of non – glandular or non- excretory epithelium such as squamous or transitional epithelium.
1. Basal cell Papilloma
It is a gap like projections. It arises in trunk, arms, face in older patients.
2. Squamous cell Papilloma
Branching growth of squamous epithelium. It arises in oral cavity, nose and larynx.
3. Transitional Papilloma
It arises in nasal and paranasal sinuses and in urothelium (urothelial Papilloma)
4. Papilloma of glandular excretory ducts. Mainly in breasts.

Papillomas are either exophytic or rarely entophytic

● Adenomas
Adenoma is a benign tumor of glandular or excretory epithelium
Examples include :
1. Solid adenomas → in glandular organs
2. Tubular adenomas → in intestinal tract
3. Villous adenoma → in intestinal tract
4. Cystadenomas → in ovaries and solivary gl.
5. Fibroadenoma → in breast

10. MALIGNANT EPITHELIAL TUMORS (LIST)

From squamous epith.
● Carcinomas
1. Squamous cell carcinomas
(Spinocellular and epidermoid carcinoma)
There is malignant transformation and proliferation of stratum spinosum. Stratification is lost with deposition of keratin in cells. Penetration of blood and lymphatic vessels may occur.
2. Basal cell carcinoma → Q.II 46
From Glandular epith.
1. Adenocarcinomas
It is the most common malignant tumor. It arises from transformation and proliferation of endocrine and exocrine glands epithelium or cylindrical epithelium of mucous membranes.
● Classification in parenchymatous organ
Irregular nodular structure often Ø capsule
i) Trabecular – equal proportion of stroma and parendyne
ii) Cirrhotic = stroma predominance
iii) Meddullary = parenchyne predominance

iv) Gelatinous = mucous
v) Cystic = cystic cavities
● Classification on the surface of organ with lumen
i) Entophytic
ii) Exophytic:
- papillar
- polypus
- villous
- disciform

● Classification according to mucous production
i) Carcinoma in signet – ring cells = mucous in cyptoplan
ii) Mucinous carcinoma = mucous in stroma

2. Ductal mammary carcinoma

It is a malignant proliferation of the ducts and is a cirrhotic, solid or tubular carcinoma

3. Lobular mammary carcinoma

13. CONNECTIVE TISSUE TUMORS

In general we should say that connective tissue tumors are uncommon.
The deeper a connective tissue tumor is situated the less likely is to be benign.

Benign connective tissue tumors

1. Lipoma
2. Inomyoma
3. Angioma
4. Granular cell tumor

● **Lipoma**

It is the most common usually subcutaneously located, comprising mature adiposities

● **Inomyoma**

They are commoner in uterus and gut while they arise from smooth muscle cells from the wall of blood vessels and in skin from our vector pilae muscles

● **Angioma**

Although they are benign they can cause clinical problems and recurrences that require surgery

● **Granular cell tumors**

Usually are superficial but when they occur beneath sq. epithelia induce epithelial hyper – plasia, mimicking carcinoma.

Malignant connective tissue tumors (sarcomas)

1. Liposarcoma
2. Angiosarcoma
3. Leiomyosarcoma
4. Synovial sarcoma
5. Epitheloid sarcoma
6. Rhabdomyo sarcoma
7. Fibrosarcoma
8. Peripheral neuroectodermal tumor

All of them they show the classic properties of local invasion and regional and distant metastasis preferring the Hematogenous route. Most of them develop as “spindle cell tumors” or “small blue round tumors”

Some comments are following:

● Synovial sarcomas

They usually occur close to joints and have a biphasic pattern of growth comprising spindle and epithelial cells. They are NOT derived from synovium

● Epitheloid sarcoma

Rare tumors in limbs that have the tendency to arise and grow along fascial sheaths.

● Peripheral neuroectodermal tumor

They occur most commonly in children

14. FIBROUS TISSUE TUMORS

At this case we meet with:

1. Nodular fasciites
2. Fibromatoses
3. Fibrosarcomas
4. Fibrohistocytic tumors

- Nodular fasciitis

It's not a real tumor but a self limited fibroblast proliferation. It's most common in upper limbs and trunk while represents as uncapsuled lesion subcutaneously, muscular or in fascia.

- Fibromatoses

They are also proliferations of fibroblasts distinguished from the fact that they grow in infiltrative fashion and vecur sometimes. They do not metastize.

There are:

1. Superficial fibromatoses

→ Polmar fibromatoses

→ Penile fibromatoses

that arise from superfischial fascias and are not serious characterized by large quantities of collagen.

2. Deep fibromatoses

→ Desmoid tumors

that arise in muscle and trunk and are serious.

- Fibrosarcoma

These are malignant lesions that are composed from fibroblasts. They arise mainly in deep tissues of thigh, knee and trunk.

- Fibrohistiocytic tumors

It's a group of tumors composed by amix of fibroblasts and phagocytic lipid – laden cells with histiocytic appearance.

  - Fibrous Histiocytoma

    They are benign lesions that appear as mobile nodules in dermes or subcutaneous tissue.

  - Dermatofibrosarcoma protuberans

    They are slowing growing lesions in dermis or subcutaneous tissue that in exceptional cases metastise.

  - Malignant fibrous histiocytoma

    These are the most common soft tissue sarcoma in adults. They arise in muscular tissues of the extremities or in the retroperitoneal areas. They are highly aggressive and metastise in 50% of cases.

    Morphologically, they are gray-white masses encapsuled.

Q11. LEIMYOMA, LEIOMYOSARCOMA, RHABDOMYOMA, RHABDOMYOSARCOMA.

LEIOMYOMA _ LEIOMYOSRACOMA connective tissue

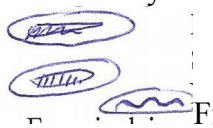
LEIOMYOMA → Benign tumor of smooth muscle cells

found: It may grow where smooth muscle is hollow organs, smooth muscle in vessels, skin, uterine corpus

It is found in 1/3 of females. In macroscopy, it resembles fibroma; it has tough consistency, white to gray color, is of round shape, sharply demarcated. Its size differs from several mm-15cm e.g. in uterus. It may be multiple as well-term for this is LEIOMYOMATOSIS

It may cause several problems: In vessels it may cause obstruction & thrombosis. In intestine it may lead to obstruction ileus, but most problems arise in uterine leiomyomas. If they are big enough, they may compress the ureters & may lead to pyelonephritis & renal insufficiency. In others they may cause infertility or in pregnancy they may lead to rupture of uterus. Their growth is oestrogen dependant; so they grow more rapidly in pregnancy & usually regress in dimacterium.

Microscopically, it consists of dtrands of smooth muscle cells, but we have problem in recognizing them as they are elongated cells with eosinophilic cytoplasm.



Fibrocytes: sharp end

Smooth muscle cells: nucleus has blunt end

Neurogenic cells in origin

Even in leiomyoma we may find fibrotic cells as they are a sign of aggression. Also, oedema & calcification may occur.

LEIOMYOSARCOMA (superficial: small, retroperitoneal: large) → Malignant tumor of smooth muscle cells.

There is presence of cellular atypias & ↑ mitotic activity. There is also ↑ risk of recurrence & metastases. Very rarely they my be a product of transformation of leiomyoma. Leiomyosarcomas are characterized by 10 or more more mitoses/ 10hp (high power fields), develop in skin, deep soft tissues of extremities. + pentoneum, mostly occur in adult females.

RHABDOMYOMA - RHABDOMYOSARCOMA

RHABDOMYOMA → Benign tumor of striated muscle

It arises usually in cardiac muscle & are often multiple. Many occur in newborn infants & cause stillbirth or death within the first days of life. Deddish grey soft growth which may be capsulated.

RHABDOMYOSARCOMA → Malignant tumor of striated muscle

It occurs in children & less commonly in adults. It is classified as i) embryonal, ii) alveolar (composed of loose aggregates of small round cells) or iii) pleiomorphic (containing rgabdomyoblasts).

Common in heart & bladder, head, neck, GIT.

Can present as soft gelatinous, grape-like masses or poorly defined, infiltrating masses.

16. VASCULAR TUMOR

Here we should mention

1. Hemangioma
2. Glomangioma
3. Hemangioendothelioma and Angiosarcoma.
4. Kaposi's sarcoma

- Hemangioma

These are masses of cavernous or capillary channels filled with blood or lymph.

- Cavernous hemangioma

They composed of large cavernous spaces filled with fluid blood. They are red-blu spongy lesions of 2-3cm, sharply defined. They mostly arise in blood vessels or lymphatics but may occur in skin mucosal surfaces and in viscera like spleen, liver, pancreas and rarely in brain.

- Cavernous hemangioma

They composed of capillaries separated by c.t. stroma filled with bluid flood. They are red-blue lesions of a few mm to several cm that occur in the skin or in mucosal surfaces of oral cavity and lips.

- Glomangioma

It's composed of branching vascular channels in ct stroma or aggragations of a glomus cells. They arise from modified smooth muscle cells of a glomus body and most often occurs in distal finger and toes specially under nails that appear as minute foci of hemorrhage.

- Hemangioendothelioma and Angiosarcoma

Hemanglioma is an intermediate grade b/w the benign hemangiomas and the malignant angiosarcoma.

Hemanglioma is composed of vascular channels in masses of well differentiated endothelial cells.

The angiosarcoma is composed of masses of anaplastic spindle spindle cell with scattered, poorly formed vascular channels. They are associated with specific carcinogens like arsenic compounds.

- Kaposi's sarcoma

It has variant forms:

1. Classic KS = among elderly men
2. African KS = among black African young men/chil
3. KS in immunossuppresed transplantation patients
4. Epidemic KS = common in AIDS patients

- Classic KS

It starts as blue – red lesion in distol low extremities and soon the lesions become more numerous and nodular 90% of patients die from intercurrent disease. It may involve also viscera like liver, lung, lymph node etc.

- Epidemic KS

It may start with a nodular skin or mucosa lesion but it soon spreads to viscera.

- Africa KS

The disease may be benign to highly aggressive.

- KS in immunossuppresed transplantation patients.

Tends to resemble classic KS

KS consists of 3 stages

1. Patches = Pinke macuoles in lower extremities
2. Plaques = dilated vascular channels lined by spindle cells
3. Nodules = skin and mucous membranes lesions become nodular

Q10. CHONDROMA, CHORDOMA, OSTEOMA (+SARCOMAS)

CHONDROMA – CHONDROSARCOMA – mesenchymal

CHONDROMA → Benign tumor of cartilage

Arises within the medvilary cavity of the bones of hands & feet. They are thought to develop from small nests of cartilage that are sometimes found close to metaphysic.

Commonly it grows in lungs. It arises there as an inborn tissue defect called HEMARCHIA, which is a focus of tissue not fully integrated into its surroundings & from this focus a tumor may arise called HEMARCHOMA.

Macroscopically, it looks like cartilage, is sharply demarcated, commonly is visible on X-ray as sharply demarcated shadow.
Microscopically, it contains cartilage but sometimes also muscle epithelial tissue – any tissue that we may find in lungs or close to them. All tissues are typical – mature tissues.

CHONDROSARCOMAS → Malignant tumor of cartilage
They grow slowly & arise only in long bones but also in the pelvis, ribs & spine. They may be well differentiated & can resemble normal cartilage. They may arise "de nova", but may develop in a preexisting benign cartilaginous leasion.
Surgical excision is the treatment of choice.

CHORDOMA – CHORDOSARCOMA – mesenchymal
CHORDOMA → benign tumor of skeletal tissue
Arise from notochordal remnands , usually in the base of the skull & or the sacral region.
Microscopically the constituent cells have often a characteristic "bubbly" appearance due to cytoplasmic vacuolation.
These tumor seldom metastise, but often recur locally.

OSTEOMA – OSTEOSARCOMA
OSTEOMA → Benign tumor of the bone
It is a mass of slowly growing, abnormally dense bone, usually in the paranasal sinuses, or the skull or mandible.
* OSTEOID OSTEOMA → solitary & characteristically painful leasion usually affecting femur & tibia. Histologically there is a central "nidus" of vascular tissue containing bone trabeculae formed be benign osteoblasts.

OSTEOSARCOMA → Malignant tumor of the bone
Aggressive, quick growing tumor affecting usually young adults & appearing often in distal femur, proximal tibia or humerous. It consists of malignant cells osteoblasts & bone matrix called OSTEOID. Sometimes there may be calcification & bone formation. It grows in bones & destroy them.
Macroscopic view depends on amount of bone in the tumor – sometimes white & tough. Less developed tumors are so often & red due to ↑ vascularization of tumor.
Microscopically we may have pleomorphic & mitotically active osteoblasts associated with osteoid. We may have foci of osteoid or bone formation surrounded by tumor cells – commonly there are foci of necrosis & haemorrhage.

21. MYELOID LEUKEMIAS

Introduction
Definition of leukemia: They are malignant neoplasm of hematopoietic stem cells characterized by replacement of bone marrow cells by neoplastic cells.
Classification:
Leukemias can be:
1. Acute, characterized by replacement of bone marrow cells with very immature cells (blasts) and by fatal course if untreated.
2. Chronic, associated with well differentiated leukocytes or
i. Lymphocytic
ii. Myelocytic

Chronic myeloid leukemias

It principally affects adults b/w 25-60 years old, while it accounts for 15-20% of all cases of leukemia.

Pathogenesis

The CML is associated with a unique chromosomal abnormality, the Ph^1 (Philadelphia)

The abnormality is caused by translocation from the long chromosomal arm 22 to, usually chromosome 9. This translocation gives rise to bcr-c-abl fusion gene, critical for the neoplasmic transformation.

In contrast to acute leukemias, there is no block in maturation of leukemic stem cells while the basis of increased myeloid stem cell mass seems to be in a failure to regulate their proliferation.

Clinical features

1. The Ph^1may be identified in granulocytic, erythroid, megakaryocytic precursors and B cells. This identification helps us to differentiate CML form LL.
2. Leukocyte count>100.000/μl .
3. The circulating cells are mainly neutrophills and myelocytes, also basophills and eosinophills, but there is also a small proportion of myeloblasts.
4. Splenomegoly
5. 50% thrombocytosis

Acute myeloid leukemias

It mainly occurs in adults while they are of diverse origin.

Pathogenesis

Some arise from transformation of multipotent stem cells, while others are associated with the common monocyte-granulocyte precursor giving rise to myelomonocitic leukemia.

So on base of differentiation and maturity are divided into eight groups in the used FAB classification.

From them, the Promyelocytic anema is of interest b/c is caused by a translocation that results in blockage of myeloid differentiation.

Clinical features

1. Myeloblasts and promyelocytes are predominant
2. Decrease in RBC, platelet and normal leukocytes
3. Fatique, breathing, problems

23. LYMPHOCYTIC LEUKEMIAS

I. CHRONIC LYMPHOCYTIC LEUKEMIAS

In general is an accumulation of long lived, non-functional B cells in blood, bone marrow, lymph nodes and other tissues. It affects persons older than 50 years old.

Pathogenesis

In 95% of cases it's a neoplasm of B cells. The leukemic cells express also the T-cell associated CDS.

Only 5% of CLL are real T-cell tumors which express CD2 and CD3 also. These rare T-cell leukemias are very aggressive.

Clinical signs

1. Hypogamaglobulinemia

b/c of non- stimulated B cells from antigen exposure

2. Haemolytic anemia

in some cases b/c of antibodies against RBC

3. Karyotype abnormalities

mainly trisomy 12

4. Splenomegaly, lymphadenopathy, anorexia, fatigue
5. Absolute lymphocytosis

II. ACUTE LYMPHOBLASTIC LEUKEMIA

In general ALL are diseases of children and young adults while represent the 80% of childhood acute leukemias.

Pathogenesis

These are s b subtypes according to the origin of leukemic lymphoblast and the level of differentiation.

NOTES:

- Most ALL are of B-cell origin
- All ALL express the pan-B-cell marker CD19
- T cell ALL are associated with mediastinal masses
- In 90% of cases there is a karyotypic abnormality

→ In "Early precursor B-cell ALL" most commonly hyperdipoidy

→ Philadelphia present in 25% of adults with ALL

- Prognosis is good fro children of 2-10 years old with "Early precursor B-cell ALL"

24. NON – HODGIN'S LYMPHOMA

NHL arise in lymphoid tissue, mainly in lymph nodes (65%) and also in lymphoid tissue of organ parenchyma (35%). All variants have the tendency to spread to other lymph nodes and to other tissues, specially to liver, spleen and bone marrow.

Most NHL are B-cell tumors (85%) while the rest may be T-cell tumors B-cell origin tumors may be nodular (follicular) compatible with long surviving without treatment but not curable while the diffuse are aggressive and fatal without treatment but curable.

NHL fall in a s subtypes

1. Small lymphocytic lymphoma

It's a non-nodular B-cell tumor. The cells are small unstimulated lymphocytes while bone marrow always is involved.

Clinical

Occurs in elderly characterized by general lymphadenopathy and mild enlargement of liver and spleen. It has good prognosis.

2. Follicular lymphoma

It's a nodular B-cell tumor and the most common NHL.

It has 3 histologic subtypes:

i) Follicular small cleaved cell lymphoma

The anaplastic B-cells are larger than the normal and have an angular cleaved nuclar contour.

ii) Follicular mixed small cleaved and large cell

When proportion of small cells and large cells are equal

iii) Follicular predominant large cell lymphoma

Clinical

It occurs in elderly people characterized by painless lymphadenopathy and usually bone marrow involvement

3. Mantle cell lymphomas

They are diffuse B-cell tumors that arise from mantle zone of lymphoid follicles

Clinical

They affect the elderly while also extranodal sites are involved like the GIT. They are aggressive and incurable.

4. Diffuse large cell lymphomas

They are diffuse B-cell (85%) or T-cell (15%) tumors. There are 3 histologic subtypes:

i) Diffused mix small and large cell

ii) Diffuse large cell

iii) Diffuse immunoblastic lymphomas

Clinical

It affects the elderly and is characterized by an rapid enlarging of a single nodal or extranodal site like GIT, skin, bone or brain. Bone marrow involvement is uncommon. They are aggressive and fatal.

5. Lymphoblastic lymphoma

It's a T-cell tumor of thymic origin.

Clinical

It accounts for 40% of childhood NHL. It's characterized by the presence of mediastinal masses that show its thymic origin. Bone marrow involvement is here. It has poor prognosis.

6. Small non-cleaved (Burket's lymphoma)

These are B-cell tumors associated with EBV. They are endemic in Africa or sporadic at other areas. Tumor cells are intermediate in size b/w small cells and non-cleaved large cells.

Clinical

It's more common in children while is the fastest growing human neoplasm.

Chronic myeloic leukemia

1. Polycytemia vera
2. CML
3. Essential thrombocytopenia
4. Chronic idiopathic myelofibrosis

Acute myeloic leukemia

AML with differentiation, without maturity

AML with maturity

Promyelocytic leukemia

Myelomonocytic leukemia

Acute megakaryocytic leukemia

25. HODKIN'S DISEASE

Introduction

Lymphomas are malignant neoplasms of native to lymphoid tissue cells.

They are separated to Hodkin's lymphomas and non-Hodkin's Lymphomas. Hodkin's lymphoma separation from other lymphomas is based on three facts:

1. The presence of RS cells
2. In involved nodes, the non-neoplastic inflammatory cells are more than neoplastic RS.
3. Presence of systematic manifestations like fever.

Classification

There are 4 subgroups:

1. Lymphocyte predominance –HD

The majority of cells are B-cells while RS are extremely difficult to find. Also common are the "popcorn" cells that have a multilobed nucleus. The prognosis is excellent.

2. Mixed cellularity –HD

Typical RS are abundant and also lymphocytes present but less than 1. Also eosinophills, plasma cells and benign histiocytes present

3. Lymphocyte depletion HD

RS are abundant and lymphocytes pause. There are 2 morphological forms:
i) Diffuse fibrosis = the node is hypocellular
ii) Reticular variant = the node is hypercellular.
It's aggressive

4. Nodular sclerosis

It's the most common form of the disease and is characterized by two facts:
i) The presence of a variant of RS cells called "Lacunar cells" (large cells, with hyperlobated nucleus and many nucleoli)
ii) Involvement of collagenous bands that separate the lymphoid tissue to nodules.
It's the only type of HD that occurs more frequently in woman than in men.

Etiology

The transformed component clearly is the RS cell.

- RS cell

  It's a multilobed cell. A characteristic appearance is the "two mirror image" that resembles the owl's eyes.

This transformation may have been caused by EBV since in 40-50% of cases EBV genome was found in RS cells.

Clinical course

The disease presents with painless enlargement of lymph nodes. The staging profile follows.
STAGE
I. Involvement of one lymph node region or one extra lymphatic organ or tissue.
II. Involvement of two or more lymph nodes on the same side of diaphragm alone, or with involvement of limited contiguous extra lymphatic organ or site.
III. Involvement of lymphatic regions on both sides of diaphragm, that may include spleen, limited extra lymphatic organ or site.

27. TUMORS OF SUPPORTIVE CELLS OF NERVOUS SYSTEM

Here we have to talk about 3 types of neoplasms:
1. Astrocytomas
2. Oligodendrogliomas
3. Ependymomas

Keep in mind that although brain is a site common for metastasis, the primary tumors of brain rarely disseminate to other parts of the body.

I. Astrocytomas

This group is the commonest tumors in CNS. We categorize them into two groups:
i) Fibrillary (infiltrating) astrocytic neoplasm
ii) Pilocytic astrocytomas

- Fibrillary astrocytic neoplasms

  They mostly occur in cerebral hemispheres and are subdivided according to the level of differentiation into:
  -Well – differentiated astrocytoma
  The cells are accompanied by intracellular accumulations of fluid called microcysts.
  - Anaplastic astrocytomas
  There are proliferating blood vessels inside the tumor.
  - Glioblastoma multiforme
  These are very aggressive while in this case there is formation of necrotic areas surrounded by tumor cells.

- Pylocytic astrocytomas

They mainly occur in cerebellum, optic nerve and 3rd ventricle. Their behaviour is less aggressive.

II. Oligodendrogliomas

They are mostly common in cerebral hemispheres. They are usually soft and gelatinous. Calcification is common together with "satelitosis" = tumor cells surrounding native neurons.

III. Ependymonas

They mainly occur at the ventricular cavities (mainly 4th ventricle) and in areas of central canal in spinal cord obstructing like this CSF flow.

28. NERVE CELL TUMORS

PNET

Primitive neuroectodermal tumors refer to a group of neoplasm composed of embryonal small cells.

PNET in CNS include medulloblastomas neuroblastomas, pineoblastomas and ependymoblastomas. Most important are the first two.

- **Medulloblastomas**

They are lesions of the cerebellum that occur mostly before 20 years. The lesions may project to ventricular system and spread through CSF (like ependymonas). The neoplastic cells often form rossetes.

Clinical

Increased intracranial pressure and walking problems are common.

- **Neuroblastomas**

Check QII47.

Other intraparenchymal CNS neoplasms

- CNS Lymphoma

They are usually B-cell tumors and highly associated with HIV positive patients.

- Neuronal neoplasms

The most common type is the ganglioglioma that arise in temporal lobes composed by mature but dysplastic ganglion cells mixed with glial cells.

- Hemangioblastomas

They occur in cerebellum and less in meninges and composed of vascular channels and lipid laden stromal cells.

Meningiomas

Meningiomas derived from meningothelial cells that surround arachnoid mater.

They are lobulated lesions including 3 hystologic types:

1. Syncytial
2. Fibroblastic
3. Transitional Meningiomas

→ mixture of 1 and 2

They may occur intracranial or in spinal cord and may be malignant invading brain parenchyma. Also here there is increased intracranial pressure.

Other meningeal neoplasms: 1) Meningeal hemangiopericytoma, 2) Meningeal sarcomas.

29. PIGMENT NEVUS MALIGNANT MELANOMA

I. Pigment nevus

They are tan-to brown, uniformly pigmented, small (up to 5mm), solid regions of elevated skin (papulloe) with well defined rounded borders.

They are formed by melanocytes that transformed from dendritic cells interspersed among basal keratinocytes to round-oval cells that grow in aggregates called nests, along the dermoepidermal junction.

From the dermoepidermal junction the nevi cells grow to underlying dermis by a process called "maturation". The superficial, large, immature cells produce melanin while those in deep tissues that are mature and small not or a little.

* In contrast with these benign nevi, melanomas show little or no maturation.

II. Malignant melanoma

Although most of these lesions arise in the skin, melanoms may arise in oral and anogenital mucosal surfaces, the esophagus, in meninges and notably in the eye.

The cause of malignant melanoma is not only the sunlight but also others:

1. Preexisting nevus.
2. Hereditary factors (melanoma tumor suppressor gene)
3. Exposure to other carcinogens although sunlight is the major one.

Pathogenesis

Concept of radial and vertical growth:

Radial growth indicates the tendency of melanoma to grow horizontally along epidermis and superficial dermal layers. During this stage melanoma does not metastize.

Vertical growth indicates a second stage during which melanoma cells grow downward into deeper dermal layers and now they can metastize.

The metastasis involves lungs, liver lymph nodes and any other site that can be seeded by the hematogenous route.

Clinical signs-warnings

The main sign is the change in color of a pigmented site. Melanomas may be black, brown, blue, gray while they may not have irregular borders.

Warnings include:

1. Itching, enlargement or pain of preexisting mole
2. New pigmented area during adult life
3. Variety of color within a pigmented area.

30. LUNG TUMORS

We have to say that 95% of b lung tumors arise from brochial epithelium (bronchogenic carcinoma) while 5% are some miscellaneous like mainly bronchial carcinoids, mesotheliomas, bronchial glands neoplasms etc.

I. Bronchogenic carcinoma

There are four histologic subtypes

1. Squamous cell carcinoma }
2. Adenocarcinoma
3. Bronchioalveolar carcinoma } NSCLC
4. Large cell carcinoma
5. Small cell carcinoma } SCLC

All of them appear as mucosal lesions and later invade the mucosa bronchial. Some forms cavitations due to central necrosis or develop focal areas of hemorrhage. Finally they spread to pleural cavity and chest wall or to more distant sites by the lymphatic or hematogenous route.

- Squamous cell carcinoma → The epithelium become squamous of metaplasia b/c of smoking
  - They are more common in men
  - They arise centrally in major bronchi and spread to hilar nodes.
- Adenocarcinoma
  - Most common in young women and non – smokers
  - Mainly they are more peripherally located although may occur centrally
- Bronchioalveolar carcinoma

Involve peripheral parts of the lungs, either as single nodule or as multiple ones

- Large cell carcinoma

Very undifferentiated, aggressive

- Small cell carcinoma
  - They are rapidly growing lesions that tend to infiltrate widely and metastize early in their course.
  - They are more common in men and in smokers
  - Very aggressive malignant

Etiology – Pathogenesis

SCLC are associated with:

1. Changes in oncogenes like myc family
2. Inactivation of TSG like pS3, Rb
3. Deletion of short arm of chromosome 3 NSLC are associated with:

1+2

3 Mutation in K-ras

Smoking is the leading cause

Clinical signs-course

Usually in the beginning is asymptomatic but later persistent cough and expectoration may call attention

* METASTISE TO: BRAIN, LIVER, BONES*

II. Bronchial carcinoids

They show the neuroendocrine differentiation of Kultsitsky cells in brochial mucosa and they may occur as part of multiple endocrine neoplasia.

They occur at early age and usually do not metastize elsewhere than hilar nodes.

Rarely metastize to liver.

32. TUMORS OF THE ORAL CAVITY AND THE ESOPHAGUS

I. Oral cavity

Squamous cell carcinomas the most predomint type of tumor in oral cavity.

These carcinomas originate from 3 major sites:

1. Vermillion border of lateral margins of the lower lip.
2. On the lateral borders of the mobile tongue.
3. From the floor of the mouth.

They may grow on edo- or exophytic manner while squamous cell carcinomas are usually moderate to well differentiated keratinizing tumors.

Spread to regional lymph nodes (submandibular, superficial and deep cervical) occurs mainly in cases of tongue cancers and cancers of the floor of the mouth. Metastases to liver, lungs and bone are rare.

II. Esophagus

Various benign tumors may arise here but mainly the malignant squamous cell carcinoma followed by the Adenocarcinoma.

- Squamous cell carcinoma

They are usually proceeded by a mucosal epithelial dysplasia to carcinoma. The early lesions become tumors taking one of the three forms.

1. Polypoid fungating masses.
2. Necrotizing cancerous ulcerations
3. Diffuse infiltrative neoplasms

20% of them arise in upper esophagus
50% in middle
30% in lower

Metastases occur to lung, liver and lymph nodes

- Adenocarcinoma

They arise from dysplastic mucosa in the setting of Barret's esophagus. Most tumors are mucin – producing glandular tumors.

Pathogenesis – risk factors

Whatever causes slowing down of food through esophagus is carcinogenic. Also tobacco and alcohol abuse, chronic esophagitis, gastroesophageal reflux (Barret's esophagus) and Tylosis.

33. TUMORS OF THE STOMACH

The most predominant are tumors that arise from the mucosa. These are classified to benign polyps and malignant carcinomas.

Gastric polyps

Polyp is any nodule or mass that projects above the surrounding mucosa. They are uncommon. The polyps can be:

1. Hyperplastic polyps (80%-85%)

→ Hyperplastic epithelium

2. Fundic gland polyps (10%)

→Collections of dilated corpus-type glands

3. Adenomatous polyps

→ It contains dysplastic epithelium and in contrast to the other two, they are true neoplasms.

Gastric carcinoma

Although is the predominant malignant case (90-95%) other exists like lymphomas, carcinoids and mesenchymal spindle cell tumors.

Classification

* According to depth of invasion:

1. Early gastric carcinoma

Confirmed to mucosa and sub mucosa and metastizing to regional lymph nodes (perigastric)

2. Advanced gastric carcinoma

It reaches the mucosal wall

* According to macroscopic growth

1. Exophytic
2. Flat or depressed
3. Excavated forming a crater on the wall of the stomach

* The histologic sub types

1. Intestinal

It arises from gastric mucous cells that have undergone intestinal metaplasia

2. Diffuse
It arises from de novo gastric mucus cells.
Pathogenesis –risk actors
The favored location for gastric carcinoma is the lesser antropyloric curvature. It spreads to regional and distant lymph nodes while it metastize widely. Krukenberg tumor arises from metastases to both ovaries.
Risk factors include H. pulori infectious chronic gastritis, tobacco, alcohol, diet, Pernicious anemia.

34. TUMORS OF COLON

I. Adenomas
Adenomas are neoplastic polyps. All Adenomatous lesions are results of profile-ration and dysplasia of epithelium.
We have to mark that probably all invasive colorectal carcinomas are secondary to preexisting adenomas.
There are 3 subtypes of Adenomatous polyps:
1. Tubular adenomas (90-95%)
Mostly tubular glands that may arise everywhere in colon but mostly in rectosigmoid. Their stalk is composed of normal colonic mucosa but their head of neoplastic epithelium.
2. Villous adenomas (1%)
Mostly villous projections that are the larger and the most aggressive. They occur mostly in rectum and rectosigmoid.
3. Tubulovillous adenomas (5%)
Mixed tubular and villous areas.
All adenomas may be considered potential malignant but we can say that, the larger the polyp the higher the risk.

II. Colorectal carcinoma
They are associated almost always with one of the following:
1. Adenomatous polyp, mostly
2. Iron deficiency anemia, in elderly men
25% occur in cecum and ascending colon
25% in rectum and distal sigmoid
25% in descending and proximal sigmoid
All colon carcinomas are adenocarcinomas that metastize to lymph nodes, liver, lungs, bones and peritoneal cavity.
3. Ulcerative colitis, in young

35. BENIGN BREAST DYSPLASIA

This question refers to fibrocystic changes of the breasts.
These are miscellaneous changes that vary from completely harmless to increasing the risk of carcinoma. They are consequences of exaggeration and distortion of those changes that normally occur during menstrual cycle.
These alterations are subdivided to proliferative and non-proliferative having as common characteristic the formation of lumps (=εξογκώματα).
1. Non-proliferative
* Cysts and fibrosis
It's the most common characterized by an increase in fibrous stroma, dilatation of ducts and formation of various size cysts.
2. Proliferative

* Epithelial hyperplasia

It's characterized by proliferative lesion in ductules, terminal ducts and sometimes breast lobules. Ducts, ductules and lobules become full filled with cuboidol cell within which glandular pattern may appear (so called fenestations).
Atypical hyperplasia we have in case that these cells are multilayered and disordered.
Atypical lobular hyperplasia is a term used to describe hyperplasias of terminal ducts and ductules. These hyperplasias are associated with development of invasive carcinomas.
* Sclerosing adenosis
It's less common and characterized by intralobular fibrosis and proliferation of small ductules and acini. The increased fibrous tissue may completely compress the lumina of acini and ducts, so that they appear as solid cords of cells. It's associated with minimal increase risk of progression to carcinoma.

36. BREAST TUMORS

There are several but the most important are the carcinomas.

Carcinomas

Carcinomas in the left breast are quite more common while mainly appear at the upper quadratant or at the central portion of the breast.
Carcinomas arise mainly (90%) in the ductol epithelium and sometimes ($\simeq$ 10%) in the lobular epithelium. We separate then to invasive and non-invasive.

A. Non-invasive

i. Intraductol carcinoma
ii. Intraductol carcinoma with Paget's disease
iii. Lobular carcinoma

B. Invasive

i. Ductol carcinoma
ii. Ductol carcinoma with Paget's disease
iii. Lobular carcinoma
iv. Medullary carcinoma
v. Colloid carcinoma
vi. Tubular carcinoma

We should note that invasive ductal carcinoma is by far the most common.

- Non-invasive carcinomas
  - Intraductal carcinoma

The ducts may be filled with masses of anaplastic tumor cells creating small glandular spaces called cribiform pattern. Sometimes there are central areas of necrosis that calcify. They may progress to invasion.

  - Lobular carcinoma

It arises in terminal ducts and ductules which become distended by tumor cells. Invasion may occur later in same or controlateral breast.

- Invasive carcinoma
  - Invasive ductal carcinomas

They are the most common breast cancers. They appear as hard rock masses of no more than 3-4cm. The masses consist of dense fibrous tissue with scattered nests of tumor cells. The tumors are infiltrative and go below surrounding fibrous fatty tissue invading frequently perivascular, perineurial spaces and blood vessels.

  - Paget's disease of breasts

It starts as typical Intraductal carcinoma but neoplastic cells called Paget's cells infiltrate the skin of nipple and areola.

  - Medullary carcinomas

They tend to be large (~ 10cm), soft and unlike invasive ductal carcinoma have scant (=ανεπαρκές) stroma. It's really rare.

- Colloid carcinoma

It's characterized by mucin production, intra or extracellular. They are soft.

- Infiltrating lobular carcinoma

They show characteristics of both ductal and lobular patterns. They have a high incidence of bilaterality.

NOTES of all **invasive** types

1. Non-metastizing = the non – invasive
- Rarely metastizing = colloid, medullary
- The rest metastize moderately to aggressively
2. The first site are usually the auxiliary lymph nodes. Hematogenously everywhere but usually to lungs, liver, bones, brain, adrenals, spleen and pituitary.

Risk factors for carcinomas

1. Age 30 to menopause
2. Estrogens
3. Smoking, alcohol abuse, obesity
4. Hereditary

Other benign tumors

1. Fibroadenoma = compressed ducts + hypercellular fibrocytic stroma
2. Phyllodes tumor
3. Intraductal pappiloma

37. TUMORS OF UTERUS

In this question we should mention tumors of cervix and uterine body although here we will talk for the second ones. For the first ones check Q38. More specifically we will talk about endometrium and muometrium tumors.

Benign tumors

- Endometrial polyps

They are usually hemispheric of 0,5 to 3cm that are composed of columnar cells while their neoplastic component is stroma. They are more common in menopause and rarely give rise to cancer.

- Leyomyomas and leiomyosarcomas

Leyomyomas are benign tumors of smooth muscle cells. They are composed of whaling (= ελικοειδής) bundles of smooth muscle cells that duplicate the histology of uterus wall. Estrogens and OC induce their growth.

Leiomyosarcomas arise from mesenchymal cells of myometrium and may develop in three patterns:

1. Burly masses infiltrating uterine wall.
2. Polypoid lesions projecting into the uterine cavity.
3. Deceptive discrete tumors.

Malignant tumors

- Endometrial carcinomas

Most of these tumors are adenocarcinomas that are:

1. Infiltrative causing thickening of uterine wall or
2. Exophytic

In both cases fill the endometrial cavity with soft partially necrotic tissue. Also adenocarcinomas with squamous METAPLASIA MAY OCCUR.

Pathogenesis – risk factors

In general we should say that endometrial carcinoma arise with endometrial hyperplasia. Also breast cancer appears usually together with endometrial carcinoma.

Risk factors include:

Obesity
Diabetes } ⟹ Estrogen stimulation
Infertility
Hypertension

+ About uterine cervix:

Malignant

1. Carcinoma of cervix

It arises from squamous epith. or less commonly from mucosa lining the cervical canal.

2. Leiomyosarcomas

Benign

1. Leyomyoma: Arise within wall of uterus. Is caused by excess estrogen stimulation.
2. Cervical polyp.
3. Condyloma accuminatum

- **ENDOMETRITIS**

→ Inflammation of endometrium

- ACUTE ENDOMETRITIS – Due to bacterial infections & is usually after parturition or miscarriage.
- CHRONIC ENDOMETRITIS - Occurs

1. In association with chronic gonorrheal pelvic disease
2. In tuberculosis (miliary spread or from drainage of tuberous salpingitis)
3. In postpartal or postbortal endometrial cavities, due to retained gestational tissue.
4. In patients with intrauterine contraceptive devices.

Spontaneously – no cause.

Microscopically, it is manifested by irregular proliferation of endometrial glands & presence of inflammatory cells: plasma cells, macrophages & lymphocytes in endometrial stroma.

- **ENDOMETRIOSIS**

→ Ectopic occurrence of endometrial tissue, frequently forming cysts containing altered blood.

Commonly present on pelvis, but may be also in lymph nodes, lungs, even heart & bone. Three possibilities to explain the origin of these leasions: (See KUMAR, p. 608, Fig. 19-10)

- FISRT REGURGITATION THEORY – proposes menstrual backflow through the fallopian tubes & subsequent + implantation – cannot explain leasions in lymph nodes & lungs
- SECOND METAPLASTIC THEORY – proposes endometrial differentiation of coelomic epithelium – origin of endometrium itself – cannot explain endometriatic leasion in lungs or lymph nodes.
- THIRD VASCULAR OR LYMPHATIC DISSEMINATION THEORY – TO EXPLAIN EXTRAPELVIC OR INTRANODAL IMPLANTS.

Extensive scarring of oviducts & ovaries → discomfort, dysuria, painful in recourse, severe dysmenorrheal & pelvic pain.

- Adenomyosis

It refers to growth of basal layer of endometrium into myometrium. Endometrial stroma and glands appear in myometrium while thickening and a reactive hypertrophy of myometrium may appear.

- Endometrium hyperplasia

It develops in estrogen excess and can cause simple complex hyperplasia or even atypical hyperplasia that can lead to endometrial carcinoma. The three levels have to do with the time of exposure to estrogens.

Whatever causes excess estrogen may cause hyperplasia:
eg. - Failure of ovulation
- Polycystic ovaries

40. TUMORS AND CYSTS OF OVARIES

A. Cysts

- **Lutean and follicle cysts**

These cysts are so common that may be considered as physiologic variants. They originate from unruptured follicles, they are small in diameter and filled with clear serous fluid. Sometimes they rupture causing intraperitoneal bleeding and acute abdominal symptoms.

- **Polycystic ovaries**

These multiple cystic follicles produce excess production of androgens and estrogens that may lead to oligomenorhea, infertility and obesity.

Morphology

The ovaries are twice in size. There is a thickened fibrosed outer tunica beneath which are many cysts lined by granulose cells with hypertrophic and hyperplastic theka interna.

B. Tumors

I. Surface epithelial stroma tumors

These neoplasms derived from coelomic epithelium. Other are strictly defined epithelial like serous and mucinous and other have a distinctive stroma component like cystadenofibroma and Brenner tumor. The tumors can be benign, low malignant potential or malignant.

- **Serous tumors**

These are the most common ovarian tumors and usually are cystic known as cystadenomas or cystadenocarcinomas. 60% are benign, 15% of low malignancy and 25% malignant.

Morphology

They are large spherical-ovoid tumors up to 30-40 cm 25% of benign forms are bilateral. In benign form serosa covering is smooth and glistering but in malignant there are nodular irregularities showing penetration to serosa. The cystic spaces are filled with serous fluid while papillary projections are more abundant in malignant forms.

The benign tumors are characterized by a single layer of columnar epithelium that lines the cysts. Psammoma bodies are common in tips of pappilae. In malignant form anaplasia of lining cells and invasion of stroma appears. In low malignant potential anaplasia appears but only a little stromal invasion.

Clinical features

The malignant form (cystadenocarcinomas) has a poor prognosis and spreads to pelvis and seeds to associated ascitic fluid.

The low malignancy potential may penetrate into peritoneal cavity.

- **Mucinous tumors**

These are analogous to serous but here the epithelium consists of mucin secreting cells. In majority 80% are benign. They are larger than serous with no much pappilary formations and no Psammoma bodies.

Morphology

Two types:

i. Endocervix like, resembling endocervical epithelium

ii. Intestine like, resembling intestinal epithelium

- **Endometroids tumors**

They are solid or cystic, distinguished by the formation of tubular glands within the linings of cystic spaces. They are usually malignant.

- **Cystadenofibroma**

It's like serous cystadenoma but with more pronounced proliferations of fibrous stroma. They are benign.

- **Brenner tumor**

They are uncommon solid unilateral tumors with abundant stroma containing nests of transitional epithelium resembling that of UT. Although most are benign, malignant and low malignancy potential forms exists.

41. TUMORS OF TESTIS

Introduction

These tumors arise mainly in ages 15-34. 95% arise from germ cells and virtually are all malignant. The non germ cells tumors (derived from sertoli or Leydig cells) are noticed from their ability to secrete steroid hormones that cause endocrine abnormalities.

Classification

Germ cell tumors are categorized into 2 categories on the base of whether they contain a single histologic pattern (40%) or multiple histologic patterns (60%).

1. Tumors with a single pattern:

Seminoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, teratomas.

2. Tumors with multiple patterns:

Teratocarcinoma = Embryonal most common carcinoma + teratoma.

Choriocarcinoma +other types

Other combinations

Types – Morphology

- **Seminomas**

They compose the 30% of testicular germ cell neoplasms.

They are large, soft, homogenous typically confined in testis.

Seminomas are composed of large cells with distinct borders, glycogen- rich cytoplasm and round nuclei and obvious nucleoli.

Cells are often arranged in lobules with intervening fibrous septa.

- **Embryonal carcinoma**

They are invasive masses containing foci of necrosis and haemorrhage. Larger lesions invade epididymis and spermatic cord.

EC are composed of large cells with indistinct cell borders, basophilic cytoplasm, large nuclei with prominent nucleoli.

- **Yolk sac tumor**

They are the most common in children younger than 3 years old. In adults are usually mixed with EC.

Their distinctive features are structures that resemble glomeruli, called Schiller- Duroll bodies.

- **Choriocarcinomas**

Represent differentiation of neoplastic germ cells along trophoblastic lines.

Choriocarcinomas are composed of small cuboidol cells (cytotrophoblatsic differentiation) and large eosinophillic cells (Synciotrophoblastic differentiation).

- **Teratomas**

Represent differentiation of neoplastic germ cells along somatic lines. Three variants are recognized:

i. Mature teratomas
Contain fully differentiated tissues from one or more germ cell layers.

ii. Immature teratomas
Contain immature somatic elements
iii. Teratomas with malignant transformation
Mostly in adults

Clinical features
Testicular germ neoplasms are usually painless. Seminomas remain confined to testis for long periods and metastases are seen in iliac and para-aortic lymph nodes. Hematogenous metastases are rare.
Non-seminomas metastize earlier by both lymphatic and hematogenous routes to liver and lungs.

42. TUMORS OF PROSTATE

- **Carcinoma of prostate**

It's the most common viscera cancer in men. The latent are more frequent than those that occur with clinical symptoms.
Most prostatic carcinomas are adenocarcinomas that usually arise in peripheral glands so may be palpable by vectol examination.
There are 2 histologic difference b/w prostate cancer and hyperplasia:
1. The glands in carcinoma are not encircled by collagen tissue but lie "back to back".
2. The neoplastic glands in carcinoma are lined by a single cell layer of cuboidol cells. The basal cell layer normally presents in normal or hyperplastic glands is absent.
Pathogenesis – Clinical signs
Mainly aged people are affected showing a relation to androgens. Also genetic factors play a role.
Metastases to regional lymph nodes may occur. Hematogenously, mainly to axial bones lungs and liver. By direct spreading to bladder and urethra.

43. TUMORS OF KIDNEYS

Benign tumors
Cortical adenomas
Medullary fibromas they are of no clinical importance.
Malignant tumors
● Renal cell carcinoma
It's adenocarcinomas that arise in tubular epithelial cells. These tumors are large 3-15 cm and may fungate through the walls of collecting system and may extend even to ureters. More commonly invade the renal veins. The tumor cells may be vacuolated with lipids (clear cells) or solid (granular cells).
Clinical – Pathogenesis
2/3 of patients with VHL syndrome develop carcinoma. Smokers and men are affected more.
Painless hematuria, fever and dull flank pain are the triad of symptoms. It mainly metastises to lungs and bones
● Willm's tumor
It's the most common tumor in children in most cases of 2 to 5 years old.
Willm's tumors are recognizable by the characteristic attempts to recapitulate different stages of nephrogenesis. The classic triphasic combination of blastemal, stromal and epithelial cell types is observed in most lesions.
Pathogenesis – clinical signs.
Three groups of congenital malformations are associated with Willm's tumor
1. WAGR syndrome

2. Deny's – Drash syndrome
3. Beck with Wiedmann syndrome
Patients complain for tumors enormous size.

44. TUMORS OF URINARY BLADDER

First we should mark that the entire urinary collecting system is lined with transitional epithelium.

Benign tumors

● Pappiloma

They are very small lesions that composed of fibro vascular cove covered by transitional well-differentiated epithelium

Malignant tumors

● Transitional cell carcinomas

They range from pappilary to flat, invasive to non- invasive, cell – differentiated to highly aggressive.

● Grade I TCC

They are always pappilary and rarely invasive but may recur.

● Grade II and III TCC

There is great degree of cellular Atypia and anaplasia, increase in size of lesion and invasion of sub mucosa and mucosa layers 5% of them are true squamous cell carcinomas although may show some face of squamous cell differentiation.

Pathogenesis – clinical signs

The bladder tumors are monoclonal in origin.

Clinical sign is painless hematuria. Smokers and men are more affected. Mainly the problems arise from obstruction and not from metastases.

46. TUMORS OF SKIN AND ADNEXA

Benign tumors

These tumors arise from the keratinizing squamous epithelium of epidermis. Except actinic keratosis the other do not progress to malignant situations

● Seborheic keratosis

These common neoplasms of epidermis are common for middle aged people and appear as flat coin-like plaques of some mm to several cm.

They are exophytic while they exhibit various pigmentation. Hyperkeratosis on the surface of keratoses and presence of small keratin cysts (horn-cysts) are characteristics.

● Keratoacanthoma

These rapidly developing neoplasms arise in men and sun exposed persons while appear as flesh colored nodules with a central keratin filled plug. It heals spontaneously without treatment.

● Verucae

They are caused by HPV and heal themselves in 6 months to 2 years.

Depending on the type of HPV different type of verrucae arises:

1. Veruccae Vulgaris

Mainly in hands

2. Veruccae plana

In face and hands

3. Veruccae plantaris

On the soles

4. Veruccae palmaris

On the palms

5. Condyloma accuminatum

In Penis, female genitalia, urethra perianal areas and rectum

Their common characteristics are epidermal hyperplasia and cytoplasmic vacuolization in the more: uperficial epidermal layers.

● Actinic keratosis

It's the result of sun exposure (actinic) and excess build – up of keratin (keratosis).They appear are 1cm brown, red or skin colored lesions mainly in face, arms and hands. There is cytologic Atypia (hyperplasia of basal epidermis cell). The dermis contains lots of elastin as a result of damaged fibroblasts. Usually actinic keratoses progress to skin cancer.

Malignant tumors

● Squamous cell carcinoma

It's the most common type of cancer of sun exposed sites in elderly people. The non- invading the basement membrane of dermoepidermal junction appear as red scalling plaques while the invading appears nodular with hyperkeratosis and may ulcerate.

Unlike actinic keratoses, here there is cell Atypia in all layers of epidermis. Chronic ulcers, sun, draining osteomyelitis tobacco, immunossuppresed due to radiation or transplantation, xeroderma pigmentosum are all risk factors.

● Basal carcinoma

These are common slow- growing tumors that appear as papules often containing sub epidermal blood dilated vessels.

Two patterns are seen:

1. Multifocal growths

Originates from epidermis and extending several cm^2 of skin surfaces.

2. Nodular lesions

Growing deeply into dermis as cords or islands of basophilic cells.

They rarely metastize and affects sun exposed and immunossuppresed persons. Also xeroderma pigmentosum

47. TUMORS OF CHILDHOOD

Benign tumors

Any tumor may be met in childhood although 3 of them are met more commonly:

1. Hemangiomas (check q. 16)

These are the most common usually arising on the face and scalp. They may enlarge or regress with age.

2. Lymphangioma

They represent the lymphatic counterpart of hemangiomas. They consist of cystic and cavernous spaces filled with pale fluid and lined by endothelial cells. They may occur on skin, regions of neck, axilla, mediastinum and retroperitoneal.

3. Sacrococcygeal teratomas

Check figure 7-32 in Robinson

Malignant tumors

In adults' heart, lungs, colon and prostate tumors are the most common. In contrast in children hematopoietic, neural and soft tissue tumors are the most common.

BIC of their primitive histologic appearance many childhood tumors are referred as small, blue, round cell tumors.

"Small round blue tumors" include nevroblastoma, lymphoma, rhabdomyosarcoma, Ewing's sarcoma and Willm's tumor for the three most common ones we will talk later. Common malignant tumors of childhood include:

1. Leukemia
2. Retinoblastoma
3. Hepatoblastoma
4. Soft tissue sarcoma
5. Teratomas
6. CNS tumors

● Neuroblastomas

It's the most common extra cranial tumor in childhood. Neuroblastomas may arise anywhere in SNS but 75% arise within abdomen half in adrenal glands and half in paravertebral autonomic ganglia.
Sometimes lack differentiation and can be distinguished by rosettes (=tumor cells line central spaces filled with fibrillar extensions of cells)
Better differentiated lesions may contain large cells resembling neurons. These lesions called neurogangliomas. Neuroblastomas metastasize mainly to liver, lungs and bones.
● Retinoblastomas
They arise from a cell of neuroepithelial origin in posterior part of retina. The tumors tend to be nodular while in familiar cases are multiple and bilateral while in non- heritable cases are unilateral and unifocal. Usually it metastasizes to CNS , skull, distal bones and lyph nodes.
● Willm's tumor
In kidneys (check Q. 43)

49. CHORIOCARCINOMA AND PLACENTAL SITE TROPHOBLASTIC TUMOR

The gestational trophoblastic tumors are divided into
1. Hydatiform mole → benign
2. Invasive mole → intermediate
3. Choriocarcinoma → malignant
All elaborate human chorionic gonadotropin (hCG) that in these cases is elevated.
● Hydatiform mole
It's a mass of swollen, cystically dilated chorionic villi that appear as grape like structure. There are 2 types.
1. Complete mole
It does not permit embryogenesis and so never contains fetal tissue. All chorionic villi are abnormal and epithelial cells are diploid. An empty egg is fertilized by 2 spermatozoa
2. Partial mole
It permits embryogenesis and so contains fetal tissue. Some Chorionic villi are normal and epithelial cells are triploid. Abnormal egg is fertilized by 2 spermatozoa. Hydatiform moles are common before 20 years old and after 40ies 10% of complete moles become invasive but only 2-3% progress to choriocarcinoma.

- Invasive mole

It invades locally but is not as aggressive as choriocarcinoma.
It retains hydropic villi which penetrates uterine wall causing rupture and probably hemorrhage. The epithelium is marked by hyperplasia and atypical changes.
Metastases does not occur although villi may embolise to distant organs or regress.

- Choriocarcinoma

This very aggressive tumor arises from the gestational chorionic epithelium or the potential cells in gonads or elsewhere. It appears as very hemorrhagic necrotic masses within uterus.
In contrast with the moles chronic villi are not formed but the tumor is purely epithelial composed of anaplastic cytotrophoblasts and synciotrophoblasts.
It appears before 20 years or after 40 years. In 50% of cases arise from complete hydatiform mole and 25% after abortion. In general the more abnormal the conception, the higher the risk.
It metastises to lungs, vagina, brain, liver and kidneys but not lympagenously.

50. IRRADIATION

Ionizing radiation 2 types:
1) Particulate radiation, e.g. Alpha particles, Betaparticles, neutrons +protons.

2) Electromagnetic waves, e.g. X-ray +gamma rays.

Modes of actions

1. Direct position action: Iomioaction of H_2O inside the cell + the formation of oxidizing agent as H_2O_2 which inactivate cellular enzyme.
2. Target action: Direct injury to a gere cr enzyme.

Radiation Injury of cells

1. Degeneration and necrosis.
2. Arrest of mitosis.
3. Fragmentation of the chromosomes.
4. Gere mutation: e.g. change its characters.
5. Mutation may lead to malignancy.

Radiosensitivity of cells

Embryonic immature + an differentiated cells are more susceptible to radiation injury than mature +differentiated cells. According to ratio sensitivity, tissues are differentiated to: i) Radiosensitive tissues include haemopoietic tissue, lymphoid tissue, intestinal epithelium + germ cells.

ii) Radioresponsive tissues, liver, pancreas + salivary glands, vascular endothelium, growing ends of bone, collagen elastic tissues.

iii) Radioresistant tissues include bones, skeletal muscles, nerve cells, lung, kidney + endocrine glands.

Radiation effects on different tissues.

1. Haemopoietic tissue: Anemia, granulocytopenia, thrombocytopenia.
2. Lymphoid tissue: Lymphopenia + atrophy of lymph nodes. Mutation if occurs causes leukemia.
3. Testis: arrested spermatogenesis.
4. Ovary: ↓ number of follocles.
5. Intestine: degeneration + necrosis of the mucosa.
6. Blood vessels: Inflammation to blood by thrombosis.
7. Skin: Acute or chronic radio-dermatitis. The epidermis undergoes atrophy + dermis shows dilated capillaries. Carcinoma may develop after years.
8. Kidney: Radiation nephritis ending in chronic renal failure.
9. Brain: Edema.

52. TERATOMAS, HAMARTOMAS

Teratomas

Neoplasms characterized by the presence of cells representing all 3 germ cell layers: ectoderm, mesoderm, endoderm.

Benign from: easily recognizable, may contain teeth and hair.

Malignant form: Less easily identifiable

Teratomas have a germ cell origin, they can occur most often in the glands, where germ cells are abundant.

In female: always xx

In male: 50% xx, 50% xy.

Ovarian teratomas: benign and cystic

In testis: Malignant and relatively solid.

Teratomas arise occasionally elsewhere in the body, usually in the midline sacro- coccygeal region.

Hamartomas

- Tumor – like lesions, the growth of which is coordinated with the individual
- lacks the autonomy of a true neoplasm
- always benign

- usually consists of 2 or more cell types normally found in the organ in which the lesion arises, e.g. hamartoma in lung consists of a mixture of cartilage and bronchial – type epithelium
- "moles" may also be considered as hamartomatous lesions

Clinical importance

1. Hamartomas may be mistaken for malignant neoplasms on a check X-ray for example
2. Hamartomas are sometimes associated with clinical syndromes, as, for example, in tuberose sclerosis.

Q. 86 PATHOLOGY OF THE ADRENAL GLANDS

PHYSIOLOGY

- Glucocorticoids (zona fasciculate) → inhibit protein synthesis
  → increase protein breakdown e.g. cortisol (hydrocortisone)
  → increase gluconeogenesis

- Mineralocorticoids (zona glomerulosal) → acts on the renal tabules to increase reabscription of Na^+, Ce^- e.g. aldosterone

Regulated by rennin – angiotensin system

-Sex steroids (zona retucularis) → production of sex steroids in the adrenal cortex is low compared with that in the gonads

HYPERFUNCTION

(a) Cushing's syndrome → excess of glucocorticoids due to

1. Exogenous administration of glucocorticoids: ->adrenocorticotropic hormone -> ACTH
   (Moon face, Hypertension, Central obesity, Osteoporosis, Factors, Tendency, to infections)
2. Exogenous administration of glucocorticoids
3. Excess ACTH secretion by adenohypophysis – Due to adenoma in adenohypophysis:

- Hypersecretion of ACTH by adenoma in corticotropl
- Bilateral hyperplasia of adrenal cortex

➔ CUSHING'S SYNDROME

4. Adrenal cortex neoplasms – may secrete cortisol, independently of ACTH control
5. Ectopic ACTH secretion – certain tumors may produce ACTH: Cat (small) cell carcinoma lungs, carcinoids, pancreatic islet cell tumors and renal adenocarcinomas (hypernephroma)

Hypofunction of Adrenal cortex

↓ of ACTH or anatomic lesion of the cortex.

Addishoms disease => ↑ a MSH

Addishoms is the primary adrenocorticoid insufficiency. In the secondary skin pigmentation is decreased cause lack of a –MSH + ACTH.

Addishoms may be caused by => autoimmune adrenalitis, tuberculour adrenalitis metastatic cancer

Morphology

- ➔ tuberculous + metastatic are classical
- ➔ autoiimune →glands are smaller , diffuse atrophy at all zones, infiltration of lymphocytes, macrophages + plasma calls.
- ⇨ Addisonial crisis => extreme weakness, tachycardia, diahrea, hypoglycer, hyponatremia, hyperkalemia, oliguria, fall in blood pressure.

⇨ In addisoms disease all the above + weight loss ↓ pubic hair (antrogen deficiency) loss of libido, muscle wasting, gastrointestinal infections.

(b) Hyperaldosteronism

1. Primary hyperaldosteronism (Conn Syndrome)

↑ secretion of aldosterone due to

➔ hyperplasia of zona glomerulosa

➔ adenoma of zona glumerulosa

⇨ retension of Na, H_2O -> hypertension

⇨ R loss -> muscular weakness, arrhythmias

2. Secondary hyperaldosteronism

By ↓ renal Glomerular perfusion, e.g. blood volume, rennin – angiotensin system stimulate aldosterone secretion from zona glomerulosa to correct this

(c) Hypersecretion of sex steroids due to

→ Cortical adenomas producing androgens

→ congenital enzyme defects

→ hyperplasia of renal cortex – by ↑ ACTH secretion

INSUFFICIENCY

CAUSES for PRIMARY INSUFFICIENCY:

1. Tuberculosis
2. autoimmune adrenalitis
3. amyloidosis
4. haemochromatosis
5. metastatic tumors
6. atrophy due to prolonged therapy

- ACUTE INSUFFICIENCY (Waterhouse – Fridenchen)

There is adrenal necrosis probably due to (DIC)

- CHRONIC INSUFFICIENCY (Addison's disease)

- Caseous necrosis of adrenal cortices due to TB.

- "Organ specific" autoimmune diseases e.g. pernicious anemia, thyroids, insulin – dependent diabetes mellitus & parathyroid failure.

**23. MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes are a group of clonal stems cell disorders characterized by ineffective Hematopoiesis and an increased risk of transformation to acute myelogenous leukemia.

The bone marrow is partly or wholly replaced by the clonal progeny of a mutant multipotent stem cell that retains the capacity to differentiate into red cells, granulocytes + platelets but in a manner that is both ineffective and disordered. The marrow is usually hypercellular or normocellular but peripheral blood shows pancytopenia.

Myelodysplastic syndrome arises in two distinct settings:

1. Idiopathic or primary, occurring mainly in patients older than 50.
2. Therapy-related, is a complication of previous myelosuppresive drug therapy or radiation therapy.

All forms can transform to AML (acute, myeloid, leukemia).

Pathogenesis: Is unknown. May arise out of a background of stem cell damage. Both types occurring often exposure to radiation.

Morphology: The most characteristic finding is disordered differentiation affecting all 3 lineages (erythroid, myeloid and megakaryotic).

* Erythroid:
1. Ringed sideroblats, erythroblasts with cron-laden mitochondria that are visible as perinuclear granules.
2. Megaloblastoid maturation.
3. Nuclear budding abnormalities
* Granulocytic:
1. Neutrophilis with decreased number of secondary granules, toxic granulation.
2. Neutrophilis with only two nuclear lobes.
* Megakaryotic: Megakaryocyte with single nuclear lobes or multiple separate nuclear.
*Peripheral blood: Platelets, macrocytes, monocytosis.
Clinical course:
Affects individuals older than 60, approximately half are asymptomatic. The course is dominated by symptoms stemming from cytopenias, thrombocytopenia.

Myelodysplastic syndrome is a disease that is associated with decreased production of blood cells. Blood cells are produced in bone marrow, but in case of this disease they do not mature normally. There are 3 major types of blood cells – red, white, platelets. Patients with M.S. can have ↓ production of one two or all types of blood cells.
In M.S. blood cells fail to mature normally, or even the cells that are produced do not function normally. The marrow eventually becomes filled with immature cells (blasts) + there is no room for the normal cells to grow and develop.
There are 5 types according to the number + appearance of blast cell in bone marrow.
1. Refractory anemia- less than 5% blast cells +abnormal red blood cell blasts.
2. Refract. anemia with ring siderblasts.
3. Refract. anemia with excess blasts. 5-20% blast cells +higher risk of changing into acute leukemia.
4. Refract. anemia with excess blasts in transformation.
5. Chronic myelomonocytic leukemia. Excess monocytes.

24. LYMPHOCYTIC LEUKEMIAS

Chronic lymphocytic leukemia (CLL)

These malignancies are characterized by proliferation of neoplastic lymphoid or hematopoietic cells that are more mature than those of the acute leukemias.

a. General considerations

1. CLL is characterized by proliferation of neoplastic lymphoid cells (almost always B cells) with widespread filtration of the bone marrow, peripheral blood, lymph nodes, spleen, liver and other organs.
2. Leukemic cells of CLL are less capable of differentiating into antibody-producing plasma cells.
3. CLL most often occurs in persons older than 60 years of age and frequently men.

b. Characteristics

1. The leukemic cells closely resemble normal mature peripheral blood lymphocytes and express surface immunoglobulin and pan-B-cell markers such as CD19 and CD20
2. The cells are susceptible to mechanical disruption and often appear on the peripheral blood smear as smudge cells
3. The peripheral WBC count varies from 50.000 µl to 200.000µl
4. Leukemic cells diffusely infiltrate the bone marrow.

c. Complication
1. Warm antibody autoimmune hemolytic anemia.
2. Hypogammaglobulinemia and increased susceptibility to bacterial infection.
d. Clinical features
1. The clinical course is usually described as cudolent, often with few symptoms.
2. Generalized lymphadenopathy + moderate hepatosplenomegaly.
3. Survival is 3-7 years.

ACUTE LYMPHOSYTIC LEUKEMIA
Overproduction +continuous multiplication of malignant +immature WBC (lymphoblasts) in bone marrow is a hematological malignancy. Can be fatal. Common in childhood. Weakness, fatigue, anemia, frequent fever, weight loss, bone/joint pain, enlarged lymph node, liver or spleen. There is lack of normal + healthy blood cells because they are crossed by malignant +immature leukocytes. genetic +environmental factors