Pulse.

Easy

PATHOLOGY

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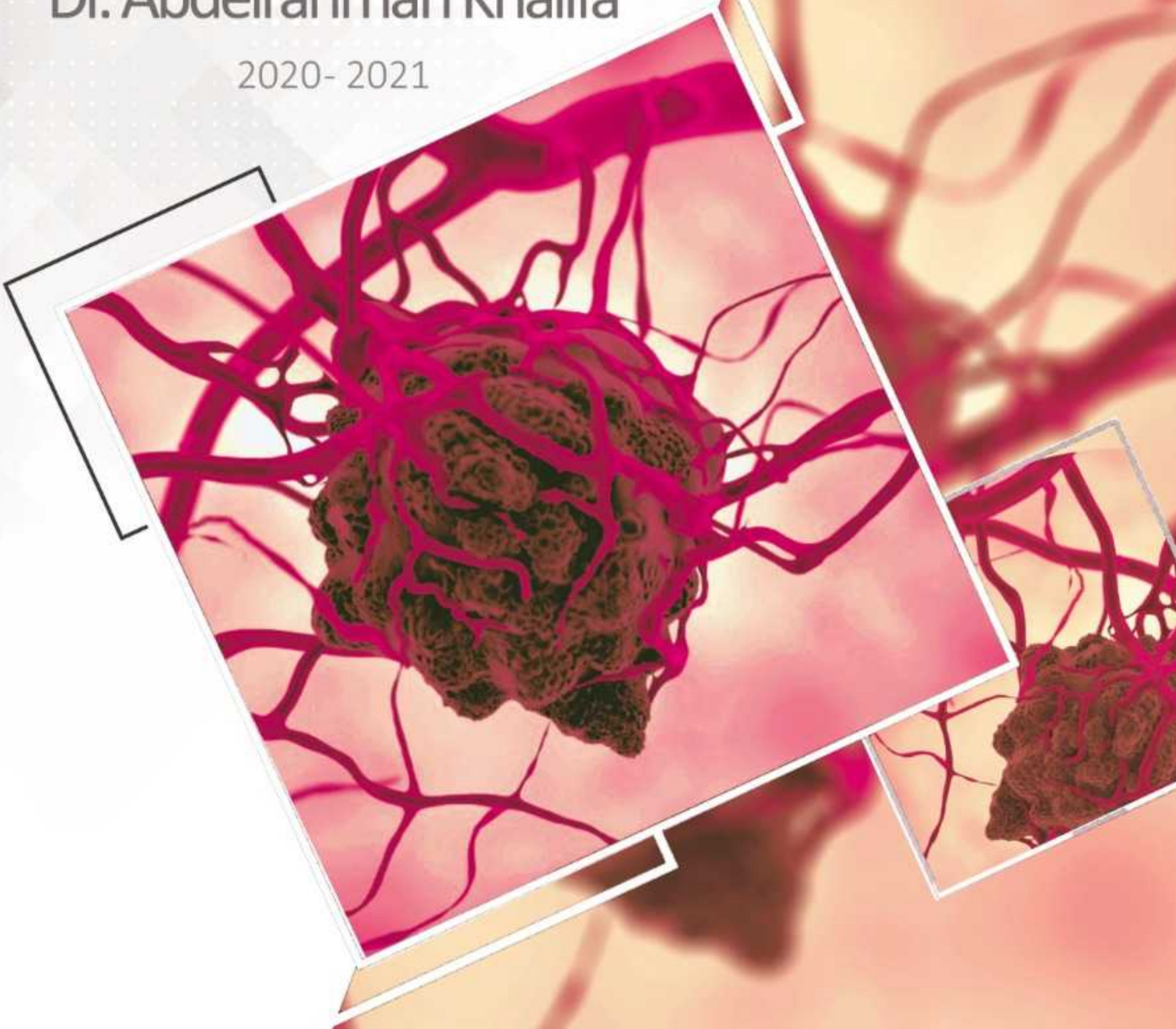
2020- 2021



Neoplasia

Part 2

www.easypathology.net

د/ عبدالرحمن خليفه

Easy Pathology

Epidemiology & PF

Incidence

- in ♀ →
  - Breast
  - then
  - lung
- in ♂ →
  - prostate
  - lung

cancer induced death is lowered by early detection

Geographic

65% risk

- Egypt & Africa → HCC
- USA → Breast

Age

more in old (55 - 75 years)

- multible mutations
- ↓↓ immunity

cancer death in children < 10 %

Familial

Herditery (Genetic)

- RB → ritinoplastoma
- APC → colon cancer
- BRCA → breast cancer
- P53 → multiple cancers
- NF → Neurofibroma
- Xerodermia Pigmintosa

Sex

In general ♀ > ♂

Cancers common in females:

- Breast
- Thyroid
- GB

Hormones

- Estrogen
  - Breast
  - Endometrium
- Androgen (anabolic)
  - Liver
- C. pills
  - Breast cancer
  - Liver adenoma

Pre neoplastic diseases (precancerous)

1) Regenerative cells  regenerative nodules of cirrhosis → HCC  Edge of Margoline ulcer → Sq. C. C.

2) Hyperplasia endometrial hyperplasia in ♀ → endometrial carcinoma

3) Dysplasia  bronchial dysplasia → Bronchogenic carcinoma

4) Inflammation 

atrophic gastritis & 

ulcerative colitis → Carcinoma

5) Metaplasia & Leukoplakia

6) Benign tumors  villus adenoma → carcinoma  Neurofibroma → sarcoma
(Van Recklinghausen disease)

7) Others undescended testis → Germ cell tumors 

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Molecular properties & Carcinogenesis

Tumor is Multistep, multifunctional, mutations of monoclonal cells to acquire new properties

Mutated genes regulating cancer

❶ ↑↑ Oncogenesis

Over expressed ↑↑

↓ produce

Oncoprotiens

↓

Autonomous growth (independent)

Types:
- ☑ GF
- ☑ GF receptor
- ☑ Signals transducers
- ☑ Nuclear factors

Autosomal Dominant inheritance

❷ ↓↓ tumor suppressor gene

Down regulation ↓↓

↓

Insensitivity to growth inhibition

e.g.
- ☑ Rb
- ☑ P53
- ☑ APC

Autosomal Recessive inheritance

❸ Apoptosis genes

Inhabited apoptosis genes

↓

Escape cell death

e.g.
- ☑ BCL2

Is mutated in 85% of cancers in follicular B-cell lymphoma

❹ DNA repair genes

Inhibited DNA repair

e.g.
- ☑ hereditary non-polyposis colorectal cancer (HNPCC)
- ☑ BRCA 1,2

In breast cancer 85% hereditary
- ☑ Xerodermia Pigmintosa

↓ UV

Skin cancer

❺ Aging avoided

Maintain active telomerase

↓

Maintain telomere length

↓

Overcome aging 95% of cancers

❻ Angiogenesis

 MQ  tumor

- ☑ VEGF
- ☑ bFGF

↓

++ angiogenesis

↓
- ☑ ↑ blood supply
- ☑ Endothelium secrete GF → tumor growth
- ☑ In P53 mutations → No thrombospondin 1 (anti-angiogenesis)

❼ Invasiveness & metastasis

By
- ☑ Matrix
- ☑ Vascular dissemination

❽ Progression

With time

↓

More accumulated materials

↓

Tumor become more aggressive

↓
- ☑ ↑ Size
- ☑ Necrosis
- ☑ Invasion
- ☑ Grade

❾ Micro RNA

Non coding RNA

↓

Act as suppressor or promotor of tumor

Oncogenesis

A gene whose product (Oncoprotiens) are associated with tumor formation

➢ Formation

Proto-oncogene (normal) —*mutation*→ Oncogene

Types of mutation:

1. Point mutation:  single base change e.g. RAS
2. Translocation: 
   e.g. (t9:22) → Philadelphia chromosome → CML (leukemia)
   (t8:14) → c-myc gene → Burkett's lymphoma
3. Amplification:  ↑ copies of sequence → ↑ mRNA → ↑ products → ↑ proliferation
   e.g. HER2/neu

➢ Types:

1. Growth factor GF:  e.g. PDGF in glioblastoma
   TGFα in Sarcoma
2. GF receptors  or 

   Mutated GF receptors → Direct stimulation without GFs

   Over expressed receptors → increased sensitivity too GFs

   e.g. EGF-r (HER2/nu) in 30% of cancer breast
3. Single transduction: active single pathway without GF or receptor

   e.g. RAS in  30% of human cancer
4. Neuclear transcription: DNA transcription & enter S phase

    e.g. MYC family: c-myc in Burkett's Lymphoma
5. Cell cycle regulatory proteins 

   in normal cell: Cyclins → ++ CDK → cell cycle progression

   e.g. some tumors produce Cyclin D as Manlle lymphoma

   Cyclin dependent kinase CDK4 as Melanoma

Tumor suppressors

Tumor suppressor genes are inhibited by

- Autosomal recessive loss of one copy then acquired loss of the other copy
- Sporadic cases: loss of both copies is acquired

Rb

- Control G1 to S check point
- If inhibited (e.g. HPV) → bypass check point

P53

يا نعيش عيشة فل
يا نموت احنا الكل

- In 70% of tumors → mutated
- In normal cells monitors stress (e.g. hypoxia) → activation DNA repair gene → In case of failure ☹ → activate Apoptosis gene → cell death
- e.g. P53 mutation by DNA virus proteins (HPV – HBV – EBV)

APC

- In 70% of sporadic cancer cases
- Normal: APC → inhibited B catenin
- In tumor ~~APC~~ inhibited or lost → activate B catenin (neuclear factor) →

Adenomatous polyposis coli → cancer colon
(hundreds of polyps)

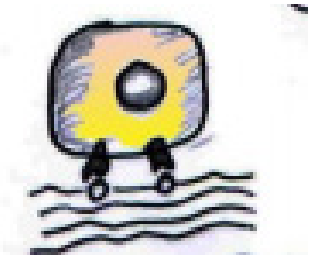
Multistep carcinogenesis

- APC mutation → hyperplasia of colon of hundreds of polyps (adenoma) → k-RAS mutation → advanced adenoma → P53 mutation → Carcinoma

Mechanism of invasion & metastasis

Matrix invasion

Detachment
Mutation of E-cadherin



Attachment to ECM
By specific receptors

Degradation of ECM
Secrete enzymes (MMPs, Cathepsin D)

Migration
Secrete cytokines → Autocrine motility activation

Vascular dissemination

Invasion of Blood vessel

Escape immunity
Attach to leukocytes & platelets

Embolism

Attach to endothelium
Organ Tropism (?)

Invasion & proliferation

Carcinogens

Factors inducing genetic abnormalities in cancer

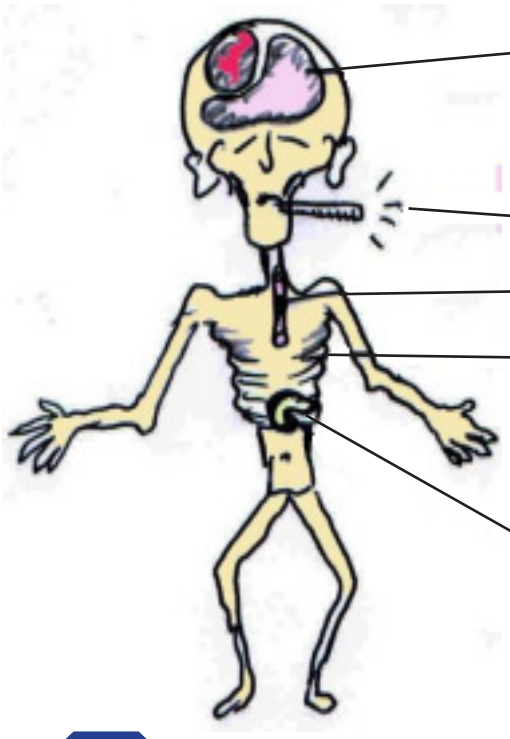
- **Chemicals** → Direct: - Alkylating agents (for ttt of cancer)
  Indirect: - P.C. hydrocarbons
  Smoking  , smoked fish , feul

- **Radiation**: UV, X-ray, radioactive substances → - Translocation
  - Mutation
  - Deletion
  e.g. Skin cancer , Thyroid , Leukemia , Angiosarcoma (SLTA)
- **Bacteria**: H. Pylori
  
  - Chronic inflammation → oxidative stress (F.R.) → gastric carcinoma
  - Mutations (oncogenes) → B-cell lymphoma (MALT)
- **Fungus**: Aspergillus Flavus → Aflatoxin → with help of HBV → HCC 
- **Parasite**: Shistozoma →  Tryptophan → Nitrosamine → ~~P53~~ → carcinoma

- **Viruses**

HTLV-1 (RNA)	HCV (RNA)	HPV (DNA)	EBV (DNA)	HHV8 (DNA)	HBV (DNA)
☑ Sexual trans. ☑ Milk ↓ 1% CDK ↑ & P53 ↓ ↓ Leukemia after 20y	• Similar to HBV ↓ HCC	Type 16, 18, 31 ↓ ☑ ↓ P53 → ↓ Bax ↓ ↓ apoptosis ☑ CDK & cyclin ☑ ↓ aging ↓ Carcinoma of Cervix Vagina Oral, anal	☑ ↑↑ MYC ☑ ↓ apoptosis ↓ B lymphoma Burkett's lymphoma Hodgkin lymphoma Nasopharyngeal carcinoma	With AIDS ↓ Kaposi sarcoma	☑ Chronic inflammation ↓ F.R. ☑ HBx protein (oncogene) signal transduction ☑ ↓ tumor suppressor genes ↓ HCC

Clinical effect



- **Compression:** e.g.
  pituitary adenoma → compress gland → ↓ function
  Leiomyoma → renal ischemia
  infarction , ulcer , hemorrhage
- **Fever:** cytokines e.g. H. lymphoma
- **Obstruction** of tubular organs
- **Cachexia:** loss of weight + weakness + Anemia
  - ↑ metabolism
  - TNF & IL1 → ↓ appetite , fatty acids
  - Muscle damaging factor
- **Hormonal secretion** e.g. adenoma, adenocarcinoma

مهم

- **paraneoplastic syndrome**
  - 10-15% of cancers
  - Symptoms not directly related to tumor or metastasis

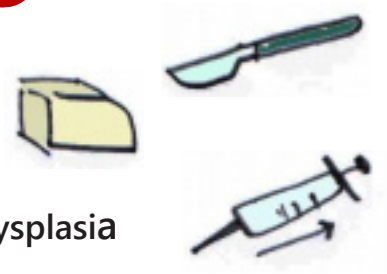
Sq.C.C. Lung → ACTH → Cushing; ADH; PTH related peptide → ↑ Ca+2

RCC → Erythropoietin → polycythemia

Pancreas, Prostatic → Thrombogenic factor

Carcinoid → serotonin , Bradykinin

Lab diagnosis of cancer



- **Excision biopsy:** surgical adequate specimen
- **Frozen section:** rapid technique
- **FNAC:** fine needle aspiration & cytology
  From palpable tumors
  - ☑ Fast
  - ☑ Used in cervix dysplasia
- **Immunohistochemistry (IHC):** Tumor products:
  - Diagnostic
  - Prognostic
  - Cytokeratin in Carcinoma
  - Vimentin in Sarcoma
  - LCA in Lymphoma
  - PSA in Prostate
  - Er & Pr in breast
  - HER2/neu in breast
- **Flow cytometry:** detect Ag for phenotyping (lymphoma)
- **Tumor markers:** detected in blood or tissue
  - ☑ PSA , CEA in colorectal & pancreatic cancers
  - ☑ αFP in HCC & yolk sac tumor
- **Molecular (DNA)** for hereditary cancers & diagnosis

Paraneoplastic syndromes associating cancers

Clinical syndrome	Cancer	Causal mechanism
Endocrinopathies - Cushing's syndrome	- Small cell carcinoma of lung, Pancreatic carcinoma	- ACTH or ACTH like substance
- Syndrome of inappropriate ADH secretion	- Small cell carcinoma of the lung	- ADH
- Hypercalcemia	- Squamous cell carcinoma of lung, breast & renal carcinoma	- Parathyroid hormone related protein (PTHrP)
- Carcinoid syndrome	- Bronchial carcinoid - Pancreatic carcinoma - Gastric carcinoma	- Serotonin, bradykinin
- Polycythemia	- Renal cell carcinoma	- Erythropoietin
Vascular & hematologic changes - Venous thrombosis (Trousseau phenomenon) - Non-bacterial thrombotic endocarditis	- Pancreatic carcinoma - Bronchogenic carcinoma - Metastatic adenocarcinoma	- Tumor products that activate clotting Hypercoagulability
Others - Nephrotic syndrome	- Various cancers	- Tumor antigens, immune complexes

Q14: Malignant epithelial cells would most likely show decreased expression of which of the following?

a) Tumour necrosis factor
b) E_cadherin
c) Vascular endothelial growth factor
d) Telomerase

Q15: Which of the following changes in cell behavior is the first step in the process of metastases?

a) Stimulation of angiogenesis
b) Circulating in blood or lymph vessels
c) Exit from circulation into a new tissue
d) Penetration of vascular or lymphatic vessels
e) Invasion of underlying basement membrane

Q16: A 55-year-old female had an 8 cm left breast mass diagnosed as high-grade invasive duct carcinoma. A chest CT scan revealed bilateral lung canon ball nodules. The presence of pulmonary nodules is most likely related to which of the following?

a) Proximity of breast carcinoma to lungs
b) Extensive lymphatic connection between breast and pleura
c) Expression of estrogen receptors in nuclei of breast carcinoma cells
d) Vascular pulmonary ligands that bind to adhesion molecules on carcinoma cells

Q17:Which of the following carcinogenic agents is the most important in skin cancer?

a) Aflatoxin
b) Vinyl chloride
c) Sunlight
d) Asbestos

Q18: Endometrial adenocarcinoma can be preceded by which of the following changes in endometrial tissue?

a) Atrophy
b) Hypertrophy
c) Metaplasia
d) Hyperplasia

Q19: The neoplastic cells most likely acquire a set of mutation that cause, which of the following changes in cell behavior?

a) Decreased cellular motility
b) Increased cell-cell adhesion
c) Increased susceptibility to apoptosis
d) Loss of cell cycle check point control

Q20: Compare to a normal adult somatic cells, cancer cells would most likely show high level of expression of which of the following proteins?

a) Desmin
b) Dystrophen
c) Cytochrome c
d) P selectin
e) Telomerase

Q21: A 65-year-old female had undergone total abdominal hysterectomy for uterine leiomyosarcoma. One year later a chest x-ray revealed a 4 cm nodule in her right lung. Ultra sound guided biopsy and histopathologic examination revealed a poorly differentiated sarcoma. The patient's medical history indicate that she had smoked cigarettes most of her adult life. Which of the following mechanisms best explain these findings?

a) Continued cigarettes smoking by the patient
b) Development of a second primary neoplasm
c) Inheritance of a defective RB gene
d) Metastases from an aggressive tumour sub-clone

Q22: A 55-year-old female complained of breast mass that surgically excised by modified radical mastectomy with axillary clearance and was diagnosed as invasive duct carcinoma T3 N1 M1. She had no family history of breast cancer. Which of the following molecular abnormality is most likely to be found in the carcinoma cells?

a) Amplification of EGFR2 (Her2) gene
b) Inactivation of one BRCA 1 gene copy
c) Deletion of one RB gene copy
d) Mutation of one p35 gene copy
e) Fusion of BCR and ABL genes

Q23: A 25-year-old female was diagnosed as having an invasive duct carcinoma. The patient's older sister was recently diagnosed with ovarian cancer and 3 years ago her maternal aunt had performed mastectomy for a diagnosis of invasive duct carcinoma. Which of the following mutated genes would most likely be present in this family?

a) BRCA 1
b) EGFR 1
c) RB
d) BCL2
e) RAS

Q24: A 58-year-old heavy smoker man presents to the emergency department with shortness of breath and haemoptysis. Chest x-ray demonstrates a large left central lung mass. The serum calcium is 13 mg/dl (normal 8.5 to 10.2). The metabolic abnormality described here is likely due to elaboration of which substance?

a) Erythropoietin
b) Antidiuretic hormone
c) Carcinoembryonic antigen
d) Parathyroid-related hormone
e) Adrenocorticotropic hormone-like substance

Q25: A 68-year-old man has a long history of prostate cancer that was metastatic at the time of diagnosis. Over the past 2 months, he has had significant weight loss, loss of appetite, and loss of energy. His current spectrum of conditions can be attributed to which of the following?

a) Interleukin-2
b) Fibroblast growth factor
c) Tumor necrosis factor alpha
d) Platelet-derived growth factor
e) Vascular endothelial growth factor

Q26: Which of the following neoplasm is most likely to arise following viral infection?

a) Retinoblastoma
b) Small cell carcinoma of the lung
c) Prostatic adenocarcinoma
d) Hepatic angiosarcoma
e) T cell leukemia

Q27: Which of the following is considered a risk factor for papillary thyroid carcinoma?

a) Repeated viral infection
b) Exposure to radiation
c) Blunt trauma from a fall
d) Exposure to arsenic compounds

Q28: Epstein Barr virus infection can increase the risk of which of the following neoplasms?

a) Kaposi sarcoma
b) Small cell carcinoma of the lung
c) Osteosarcoma
d) Nasopharyngeal carcinoma
e) Endometrial carcinoma