Tumour Markers: -

• Definition: -
  – A tumour marker is a biochemical indicator selectively produced by the neoplastic tissue and released into blood and detected in blood or in other body fluids.

• It may be used to: -
  – Detect the presence of a tumour
  – Monitor the progress of disease
  – Monitor the response to treatment

• They cannot be constructed as primary modalities for diagnosis of tumours
Tumour Markers: -

- Types of Tumour markers
  - Cell surface antigens.
  - Cytoplasmic proteins.
  - Enzymes.
  - Hormone.

- Criteria of an Ideal Tumour Marker: -
  - Specific
  - Sensitive
  - The method of assay must be cheap & easy
Tumour Markers: - Classification

• Class 1: -
  – Antigens unique to a neoplasm not shared by other tumours of same histological type.

• Class 2: -
  – Antigens expressed by many or most tumours of a specific histological type and of other histological type,
  – But not expressed by normal adult tissue.

• Class 3: -
  – Antigens expressed by both cancer and normal adult tissue.
Tumour Antigens: -

• With Malignant Transformation Of A Benign Tumour Some Modifications may Occur In The Tumour Antigens.
  – Expression of new tumour antigen.
  – Increase / decrease in expression of present tumour antigen.
  – Micro anatomic changes in distribution of cellular antigens.
  – Alteration in biochemical nature of antigens like glycosylation of glycolipid and glycoprotein antigens.
Nature Of Tumour Antigens: -

• Oncofetal antigens →
  – Alpha Feto Protein
  – CEA
  – Pancreatic Oncofoetal Antigen

• Proteins →
  – Casein – By breast carcinoma
  – Ferritin- Leukaemia

• Enzymes→
  – Creatinekinase – Prostate tumour
  – Alkaline Phosphatase – Lungs tumour
  – Acid Phosphatase – Prostate tumour
Nature Of Tumour Antigens: -

4. Receptors ➔
   - Oestrogen, Progesterone, Androgen

5. Polyamines ➔
   - Spermine, Spermidine, Putridine – leukemia, lymphoma, colorectal CA

6. Cell Markers ➔
   - T cell marker, B cell marker-lymphoma

7. Ectopic Hormones ➔
   - HCG, GH, Erythropoetin, Renin, GnRh, HPL
Gynaecological Tumour Markers

1. Human Chorionic Gonadotrophin (HCG)
2. Alfa Feto Protein (AFP)
3. Cancer Antigen-125 (CA125)
4. CA 19-9
5. Carcino Embryonic Antigen (CEA)
6. Placental Alkaline Phosphatase (PLAP)
7. Squamous Cell Carcinoma Antigen (SCCA)
8. CA15-3, (Also known as HER-2neu, OVX1, OVX2).
Gynaecological Tumour Markers

9. Macrophage Colony Stimulating Factor (MCSF)
10. Tumour Associated Trypsin Inhibitor (TATS)
11. Galactosyl Transferase Associated with Tumour (GAT)
12. Alfa Amylase
13. Lactate Dehydrogenase (LDH)
14. Tumour Associated Glycoprotein-72 (TAG-72)
15. Estrogens, Progesterone, Androgen
HCG: -

- Selectively produced by syncytiotrophoblast, normal titre 20 to 30 mIU /ml,
- A glycoprotein having molecular weight 36,000 to 40,000, half life 32 to 37 hours
- It has two fractions alpha and beta.
- There is immunological and biological similarity between alpha fraction and pituitary gonadotrophins.
- So beta fraction of HCG is specific which is measured by immunological & biological methods, RIA and enzyme immunoassay.
HCG: -

- Can be detected in pregnancy one day after implantation, 8 days after ovulation and 9 days after LH surge.
- Concentration rises exponentially until 9 to 10 weeks of gestation with a doubling time of 1.3 to 2 days.
- Reaches its peak of around 105 IU/ml after 60 to 90 days of gestation.
- It decreases from this peak level to a plateau value of 10,000 to 20,000 IU/ml, which is maintained for the remainder of the pregnancy.
- \( \beta \text{HCG} \) level comes to nonpregnant level of less than 5mU/ml, 21 to 24 days after delivery.
HCG: -

• The HCG doubling time can differentiate between viable intrauterine pregnancy from ectopic pregnancy.
• A 66% rise in the HCG level over 48 hours represents the lower limit of normal value of viable intrauterine pregnancy but
  – in 15% of cases of viable intrauterine pregnancy, rise of HCG may be less than 66% in 48 hours
  – in 15% cases of ectopic pregnancy rise of HCG may be more than 66% in 48 hours
• It is also produced by some ovarian epithelial tumours
HCG: - in Hydatidiform Mole

• Hydatidiform mole is very much suggestive if:-
  – urine in dilution of 1 in 200 to 1 in 500 is positive for HCG beyond 100 days of gestation.
  – If HCG in urine in 24 hours is around 0.3 to 3 million IU during similar period of amenorrhoea.

• Molar pregnancy patients are more prone to develop Choriocarcinoma: -
  – If excreting HCG > 100,000 IU/ in urine in 24 hours
  – If serum level of HCG is > 40,000 mIU/ml.
HCG: - in Choriocarcinoma

- A single tumour cell produces HCG around $5 \times 10^{-5}$ to $5 \times 10^{-4}$ IU/24 hours.
- If a patient excretes 106 IU of HCG in 24 hours, it indicates presence of $10^{11}$ viable tumour cells.
- Normally with functioning gonads a woman excretes HCG less than 4 IU in 24 hours.
- During methotrexate, treatment
  - Serum level of HCG is measured at weekly intervals and
  - The HCG regression curve serves as an indicator to determine the need for second course of chemotherapy.
HCG: - in Choriocarcinoma

• A second course of chemotherapy is to be administer under the following conditions: -
  – If HCG level plateaus for more than 3 consecutive weeks or begins to rise again
  – If the HCG level doesn’t declined by one log with in 18 days of the completion of first course of treatment.

• During second course of chemotherapy,
  – The dose of methotrexate is kept unaltered if the patient’s response to the first course of chemotherapy is adequate.
  – If response is inadequate the dose of methotrexate is increased from 1mg/kg body wt. to 1.5mg/kg body wt.
HCG: - in Choriocarcinoma

- An adequate response is, when serum level of HCG falls by one log.
- If the response to two consecutive courses of chemotherapy is inadequate the patient is considered resistant to methotrexate-folic acid and then Actinomycin-D is given.
- Subsequently the response to Actinomycin-D is estimated by measuring serum HCG level.
- If the patient is resistant to Actinomycin-D then combination chemotherapy is indicated.
HCG: - in Choriocarcinoma

• False +ve test for serum and urinary HCG can occur
  – When a patient is taking drugs like phenothiazines, antidepressants & antiepileptics,
  – In proteinuria / protinemia, menopause, pelvic TB associated with amenorrhoea.
Alfa Feto Protein:

- A major foetal serum protein, resembles albumin.
- AFP exists in a number of isoforms which can be separated by their differential binding to lectins.
- Physiologically AFP is produced by
  - The yolk sac of human foetus more than 4 weeks old and
  - Later by liver & GI tract.
- AFP attains peak values i.e. 4mg/ml at 34 weeks of gestation.
Alfa Feto Protein:

- Measurement of maternal serum and amniotic fluid levels play an important role in the screening for
  - Foetal neural tube defects
  - Chromosomal abnormalities including Down’s Syndrome.
- Most measurements are done at 16 weeks of gestation.
- Raised maternal serum AFP levels are not specific for neural tube defects.
- Must be used in combination with other modalities such as USG, amniotic fluid AFP and acetylcholine esterase.
Alfa Feto Protein:

- Many fetal conditions are associated with abnormal maternal serum AFP levels.
  - Elevated:
    - NTD, GI obstruction, Liver necrosis, Abdominal wall defects (Omphalocele, Gastrochisis), Sacrococcygeal tumour, Cystic hygroma, IUGR, multiple pregnancies, renal anomalies.
  - Low:
    - Chromosomal trisomies (Down’s syndrome), Gestational trophoblastic disease, IUD, placental defects, GA underestimated, Foetal distress, Hydrops Foetalis, TOF, Cyclopia.
Alfa Feto Protein:-

• After birth AFP usually falls, within 8 to 12 months of delivery to a very low conc. of 10mcg/ml and persists at this low level throughout life.
• Unexplained and persistent elevation of AFP in nonpregnant state should be screened, as it may be due to-
  – Hepatocellular Ca, germ cell tumour, hereditary persistence of AFP, viral hepatitis and cirrhosis.
• In addition to its role in prenatal diagnosis, it is also widely used in the diagnosis, therapeutic monitoring and follow up of patients in germ cell tumours.
### Germ Cell Tumours Producing AFP and HCG:

<table>
<thead>
<tr>
<th></th>
<th>AFP</th>
<th>HCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dysgerminoma</td>
<td>--</td>
<td>+/-</td>
</tr>
<tr>
<td>2. Endodermal Sinus tumour / yolk sac tumour</td>
<td>+</td>
<td>--</td>
</tr>
<tr>
<td>3. Immature tetratoma</td>
<td>+/-</td>
<td>--</td>
</tr>
<tr>
<td>4. Mixed germ cell tumour</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>5. Choreocarcinoma</td>
<td>--</td>
<td>+</td>
</tr>
<tr>
<td>6. Embryonal CA</td>
<td>--</td>
<td>+</td>
</tr>
</tbody>
</table>
CA-125: -

• A mullerian differentiated antigen identified by a monoclonal antibody OC 125.
• It is a mucin like glycoprotein having molecular wt >200 KDA.
• It is expressed by
  – 80% of nonmucinous ovarian tumours including serous, endometroid, & clear cell & undifferentiated ovarian tumours
  – Endometriosis
• The cut off level of CA-125 is 35 u/ml.
• It is detected in serum by RIA.
• It is useful as a marker for Ovarian tumours and Endometriosis
CA-125: -

• It can also be positive in
  – 0.2% of healthy blood donors and 1% of normal healthy women and 5% Benign gynaecological disorder like endometriosis & PID.
  – 16% of woman in 1st trimester of pregnancy
  – 25% of non gynaecological conditions like cancers of GI tract and breast cancer.
  – High levels of CA-125 is detected also in advanced cases of Adenocarcinoma of CX, endometrium & fallopian tube.
CA-125: - in Ovarian Cancer

• It is useful for the screening for ovarian cancer, along with bimanual examination & USG, in high risk groups like-
  – Family history of breast, ovarian, endometrial cancer
  – History of removal of benign ovarian and breast tumour.
  – Postmenopausal palpable ovary.
  – Woman workers in asbestos industries.

• Sensitivity –
  – It can detect Ca.Ovary in 50% of Stage I and in 60% in Stage II.
  – Its specificity increases if it is combined with USG or is measured over a period of time
CA-125: - in Ovarian Cancer

• The predictive value of a +ve test is 100% and indicates presence of tumour tissue
  – because when the level of ca125 was >35u/ml, disease was always detected during second look surgery.
• The predictive value of a -ve test is only 56% and does not exclude the presence of tumour
  – because when the level of ca125 was <35u/ml, disease was still detected in 44% during second look surgery.
• Persistently high levels of CA125 after treatment with cycles of chemotherapy indicates presence of resistant clones of tumour tissue.
CA-125: - in Endometriosis

• In minimal to mild endometriosis serum CA125 level is normal but in moderate to severe endometriosis the level rises.
  – In normal person with out endometriosis level is: - 8 to 22 u/ml (non-menstrual phase)
  – In minimal to mild endometriosis level is: - 14 to 31 u/ml (non-menstrual phase)
  – In moderate to severe endometriosis level is: - 13 to 95 u/ml (non-menstrual phase)
• The specificity in endometriosis is about 80%
• The sensitivity is around 66%.
• If the ratio during menstrual phase to follicular phase is more then 1.5, then it is a better sensitive marker.
CA-19-9: -

- Carbohydrate determinant 19-9.
- Mainly expressed by colonic CA.
- Also expressed by the most mucinous ovarian tumours.
- It can also be expressed by a significant proportion of serous and other non-mucinous ovarian tumours.
- Used in combination of CA125 for clinical monitoring.
CEA:

- It is a glycoprotein of mol.wt 200kda.
- Though it is a tumour marker for GI cancers, it is also expressed by
  - malignant mucinous tumor (100%),
  - 100% cases of atypical hyperplasia of endometrium,
  - 60% cases of endometrial Ca,
  - 50-80% cases of squamous cell of Cx,
  - 75-100% cases of adenocarcinoma of Cx.
- It is also produced in pneumonia, hypothyroidism and pancreatic tumours.
PLAP: -

- Placental Alkaline Phosphatase, normally produced by the placenta.
- Also expressed by Serous and Endometroid tumours of Ovary as well as by the germ cell tumour, Dysgerminoma.
### Tumour Markers Produced by Epithelial Ovarian Tumours

<table>
<thead>
<tr>
<th>TUMOUR</th>
<th>PERCENT OF TUMOURS PRODUCING MARKERS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CA125</td>
</tr>
<tr>
<td>SEROUS: -</td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>80</td>
</tr>
<tr>
<td>Borderline</td>
<td>100</td>
</tr>
<tr>
<td>Malignant</td>
<td>100</td>
</tr>
<tr>
<td>MUCINOUS: -</td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>0</td>
</tr>
<tr>
<td>Borderline</td>
<td>12.5</td>
</tr>
<tr>
<td>Malignant</td>
<td>16</td>
</tr>
<tr>
<td>ENDOMETROID CA</td>
<td>66</td>
</tr>
<tr>
<td>CLEAR CELL CA</td>
<td>75</td>
</tr>
<tr>
<td>UNDIFFERENTIATED</td>
<td>82</td>
</tr>
<tr>
<td>MIXED MULLERIAN tumour</td>
<td>80</td>
</tr>
</tbody>
</table>
SCCA: -

• It is a sub-fraction of the glycoprotein TA-4 which can be demonstrated by immunohistochemical methods.
• Produced mainly by Sq.Cell Ca. of Cx, Vagina & Vulva
• Used as a marker for monitoring Sq. cell and Adenosquamous cell Ca.
• Raised levels are also seen in Sq.cell Ca of head, neck, lung, oesophagus and anal canal.
• Levels become highest if there is metastasis.
CA 15-3: -

- It is a circulating breast cancer associated antigen identified by two distinct monoclonal antibodies.
- It is present in a variety of adenocarcinomas of breast, colon, lung, ovary, pancreas.
- It is a sensitive and specific marker for monitoring the clinical course of patients in breast cancer.
- Raised CA15-3 levels are also seen in:
  - chronic hepatitis, liver cirrhosis, sarcoidosis, TB, SLE.
MCSF: -

- It stimulates growth of monocytes
- Supports survival of macrophages
- Enhances antibody dependant cellular cytotoxicity
- Encourages production of cytokines
- It is a tumour marker for –
  - Epithelial Ovarian Tumours
  - Alongwith CA125 helps in the early diagnosis of epithelial Ovarian Tumours with high sensitivity
  - Level also increased in Myelodysplastic Syndrome, Neutropaenia, Infection, PIH & Eclampsia
TATS: -

- This peptides has been found in veins, serum, and cyst fluids of mucinous Ca.
- It compliments CA125 as clinical monitors for serous Ca.
GAT: -

- It is used to differentiate ovarian tumour from endometriosis with CA125
Alpha Amylase: -

• Demonstrated by serous and endometroid tumours.
Lactate Dehydrogenase (LDH)

- An enzyme normally produced by hepatic cells
- Also produced by
  - Ovarian Germ Cell Tumour
  - Cutaneous Melanoma
  - Pleural Mesothelioma
  - Lung Cancer
  - Testicular Germ Cell Tumour
Conclusion: -

• A large number of tumour markers have been found to be associated with gynecological malignancies.
• However most of them have low & variable specificity.
• The methods of their detection and estimation are difficult, costly and not widely available.
• To be of practical use, these problems associated with tumour markers need to be solved
THANK YOU