MALIGNANCY AND TUMOUR MARKERS (WITH CASE STUDY)

BY

DR. OMAR J KATWAN

CLINICAL BIOCHEMIST

Introduction.

Tumours may secrete a wide range of substances into blood, including hormones, enzymes and tumour antigens, which are collectively referred to as tumour markers. Tumour marker measurements can contribute to patient management in a number of ways

When interpreting the results of serum tumour markers it is essential to remember the following:

- Concentrations within the reference range do not exclude malignancy.
- A rise in concentration within the reference range should raise the suspicion of tumour recurrence in previously diagnosed patients.
- Non-malignant conditions may increase the concentration of some tumour markers.

Table 17.2 Malignant disease where tumour markers are used in clinical practice.

Malignancy	Marker	Follow-up	Diagnosis	Prognosis with other factors	Screening
Breast	CA 15.3	*Yes	No	No	No
Choriocarcinoma	hCG	Yes	Yes	Yes	Yes
Colorectal	CEA	Yes	No	Yes	No
Germ cell	hCG	Yes	Yes	Yes	No
Germ cell	AFP	Yes	Yes	Yes	No
Hepatocellular carcinoma	AFP	Yes	Yes	Yes	**Yes
Myeloma	Paraprotein	Yes	Yes	Yes	No
Ovarian	CA-125	Yes	Yes	Yes	Yes
Pancreatic	CA 19-9	Yes	Yes	Yes	No
Prostatic	PSA	Yes	Yes	Yes	No
Thyroid, medullary	Calcitonin	Yes	Yes	Yes	***Yes
Thyroid, follicular, papillary	Thyroglobulin	Yes	No	No	No

*Only when disease cannot be evaluated by other means.
**Subjects at high risk, e.g. chronic hepatitis B and C or cirrhosis.
***Screening relatives of diagnosed patients.

Table 17.1 Uses for tumour marker measurements.

1. *Monitoring treatment and detecting recurrence of disease* These are their most useful roles.
2. *Diagnosis* Tumour markers provide an aid to diagnosis, but only when used in conjunction with clinical and radiological evidence. Not all patients with a malignancy may exhibit increased concentrations of the tumour marker. Tumour marker concentrations may also be increased in clinical conditions not associated with malignancy.
3. *Screening* With a few exceptions (Table 17.2), tumour markers are of little value in screening for asymptomatic disease, but in some specific instances may be used to screen high-risk groups.
4. *Prognosis* Tumour markers can only be used for prognosis on the few occasions when the plasma concentration correlates with tumour mass (Table 17.2).

Commonly used tumour markers.

Carcinoembryonic antigen (CEA).

CEA is a high molecular weight glycoprotein and its measurement remains the most widely used marker as an aid to prognosis, surveillance and monitoring in patients with colorectal cancer. CEA levels should return to normal post-operatively following successful surgical resection. Failure to do so suggests residual or metastatic disease. Serial monitoring with CEA can detect recurrent disease with a sensitivity

Of approximately 80% and specificity of approximately 70%, and Provides an average lead- time of about 5 months. Patients monitored Frequently with CEA have an improved 5-year survival rate, and CEA testing is often carried out every 2–3 months for at least 3 years after the Initial diagnosis. Monitoring the response to chemotherapy using CEA is also desirable, with measurements being taken every 2–3 months of active treatment. It should be remembered that CEA is also increased in a variety of non-GI malignancies (including breast, lung and haematological cancers), as well as in non-malignant conditions.

Table 17.3 Examples of nonmalignant conditions that may cause increases in serum tumour markers.

CA-125
- Liver disease
- Pancreatitis
- Acute urinary retention
- Rheumatoid arthritis
- Renal failure
- Colitis
- Congestive heart failure
- Cystic fibrosis
- Diabetes
- Diverticulitis
- Endometriosis
- Irritable bowel syndrome (IBS)
- Menstruation
- Ascites
- Peritoneal inflammation
- Respiratory disease
- Lupus
- Pregnancy Surgery

CEA
- Liver disease
- Renal failure
- Colitis
- IBS
- Respiratory disease
- Smoking

PSA
- Prostatitis
- Benign prostatic disease
- Urinary tract infection
- Digital rectal examination

AFP
- Hepatitis
- Liver repair/regeneration
- Pregnancy
- Physiological in neonates/infants

CA-125.

CA-125 is a high molecular weight glycoprotein that has a well-defined role in the screening and monitoring of ovarian carcinoma. Serum CA-125 is elevated when there is vascular invasion, tissue destruction and inflammation associated with malignancy.

It is increased in over 90% of women with advanced ovarian cancer disease and in 40% of patients with advanced intra-abdominal malignancy. However, serum CA-125 can also be increased during menstruation and pregnancy and in other nonmalignant conditions

If the CA-125 concentration is >35 kU/L, ultrasound of the pelvis and abdomen should be performed and the 'risk of malignancy index' (RMI) calculated. Patients who have a score >250 should be referred for specialist investigation.

Important points:

- In stage 1 ovarian cancer, CA-125 is only elevated in 50% of cases.
- A result within the reference range should never be used to exclude ovarian cancer.
- There are many causes of a raised CA-125 other than malignancy, particularly in pre-menopausal women.
- The likelihood of a raised CA-125 being caused by an ovarian malignancy increases with age.
- CA-125 is a relatively reliable marker of response to treatment and disease progression.

Case Study 1.

Mrs PA, 32 years old, presented to her GP complaining of feeling bloated after eating; this had been going on for a couple of months. Her mother had died of ovarian cancer. Examination found no evidence of an abdominal or pelvic mass.
The CA-125 was found to be 45IU/L (reference range <35IU/L).

An ultrasound of the abdomen and pelvis was carried out and found to be entirely normal. What should be done now?
Comment: Given the normal ultrasound and age of the patient, ovarian malignancy is unlikely despite the increased CA-125. Further clinical assessment and investigations should be carried out and any alternative diagnosis considered. It may be worth repeating the CA-125, ensuring the sample is not taken during menstruation. This case illustrates the problem of screening using CA-125, i.e. abnormal CA-125 levels may be found in many women who do not have ovarian cancer (Table 17.3).

Prostate-specific antigen (PSA).

PSA is a glycoprotein used as a tumour marker to aid diagnosis and to monitor patients with prostatic cancer. PSA is detectable in the serum of healthy men and the concentration rises with age; thus age-related reference ranges are useful (Table 17.5). Most PSA circulates in plasma bound to α_1-antichymotrypsin, but a small fraction circulates unbound to any protein (free PSA). Patients with prostatic cancer appear to have a higher ratio between bound and free PSA than patients with benign hypertrophy, PSA is also increased in a number of non-malignant conditions (Table 17.3).

Important points:

- Approximately 50% of men with prostatic cancer who have a PSA between 4 and 10µg/L will have disease out with the prostate capsule.
- Approximately 15% of patients diagnosed with prostatic malignancy will have a PSA between 3 and 4µg/L
- Bone metastases are unlikely in patients with a PSA below 4µg/L.

Table 17.5 Age-specific PSA reference ranges.

Age (years)	PSA reference range (µg/L)
<50	≤2.5
50–60	≤3.0
60–70	≤4.0
≥70	≤5.0

Case Study 2.

A 73-year-old man presented to his doctor, complaining of back pain and increasing problems with passing urine. The following results from chemical tests were obtained:

Serum	Result	Reference range
Prostate-specific antigen	70	<5 µg/L
Albumin	38	35–50 g/L
ALP activity	200	40–125 U/L
ALT activity	35	10–50 U/L
Bilirubin total	10	2–21 µmol/L
GGT activity	35	10–55 U/L

What is the likely diagnosis?

Comments: The man is likely to have metastatic prostatic cancer. Although there is overlap in the levels of PSA seen in men with benign prostatic hypertrophy and those with prostatic cancer, the high levels of PSA found in this patient are usually seen only in patients with metastatic disease.

The elevated ALP in the presence of normal GGT and other liver function tests also suggests metastatic spread to bone.

Examination of the prostate per rectum disclosed an enlarged and hard prostate, and tissue obtained during a transurethral resection demonstrated the presence of tumour.

α-Foetoprotein (AFP).

Patients with cirrhosis, haemochromatosis and persistent infection with hepatitis B and C are at high risk of developing hepatocellular carcinoma. Measurement of serum AFP on a regular basis (every 6–12 months) appears to be of value to allow early detection of tumour. Serum AFP is increased in many patients with cirrhosis, but a concentration in excess of 400 kU/L is almost diagnostic of malignancy; those with a concentration greater than 40 kU/L require close investigation. In such circumstances serum AFP is of value both for monitoring response to treatment and potential recurrence.

Case Study 3.

A 50-year-old male lecturer presented to his doctor, complaining of tiredness, abdominal discomfort and poor appetite. He had worked in Africa in the past, where he had contracted hepatitis B and had become a carrier. On examination, he was jaundiced and his liver was enlarged. Urine was positive for both bilirubin and urobilinogen. The following results were found:

Serum	Result	Reference range
Albumin	34	35–50 g/L
ALP activity	420	40–125 U/L
ALT	146	10–50 U/L
Bilirubin total	60	2–21 μmol/L
GGT activity	164	10–55 U/L
AFP	3130	5 kU/L

What is the likely diagnosis?

Comments: The patient has a primary hepatocellular carcinoma. This is a relatively uncommon malignancy in the developed world, but common in China, South-East Asia and parts of Africa as a result of the high incidence of hepatitis B in these regions. Chronic carriers of the virus have an increased risk of developing the malignancy. The liver function tests show a mixed pattern of cholestasis, probably arising from the tumour, and hepatitis, arising from the chronic hepatitis. The very high concentration of AFP is highly suggestive of hepatocellular carcinoma, but levels of up to ~500kU/L can be found in some patients with non-malignant hepatobiliary disease.

Human chorionic gonadotrophin (hCG).

Patients presenting with a lump in the testes or malignancy of unknown origin should have hCG measured alongside AFP. The presence of hCG denotes the presence of trophoblastic tissue. When hCG testing is combined with that for AFP, approximately 75% of patients with non-seminomatous germ-cell tumours demonstrate elevated tumour marker levels. A small proportion of patients with seminomas (or dysgerminomas) will also secrete hCG as a tumour product; such tumours do not secrete AFP. Due to the existence of multiple forms of hCG in serum (intact, free β-subunit, nicked and hperglycosylated), it is important that the laboratory hCG assay used for oncological purposes detects all possible forms of hCG.

CA 19-9.

Measurement of CA 19-9 is primarily indicated in the post-operative monitoring of patients with pancreatic tumours, although values can also be increased in patients with colorectal or other GI malignancies. However, the usefulness of CA 19-9 is limited by the fact that there are few effective treatments available for the disease.

CA 15-3 and HER2/neu.

CA 15-3 is a mucin glycoprotein of use in monitoring patients with breast cancer. Measurement of CA 15-3 provides prognostic information, and serial monitoring has the potential to detect recurrent disease and evaluate response to treatment. The marker may become more important when more effective treatments are developed to treat metastatic disease.

HER2/neu is a 185-kDa cell surface receptor protein which is a member of the epidermal growth factor receptor family. It is expressed in small amounts on the plasma membrane of normal cells. The protein appears to be involved in the growth and spread of breast cancer cells, and about 25% of patients have a high concentration of the protein. The presence of HER2/neu suggests an aggressive tumour and appears to provide a prognostic indicator. Patients with HER2/neu-positive tumours respond to treatment with monoclonal antibody therapy directed to the HER2/neu protein.

Inhibin A and B.

Inhibin is a 32-kDa glycoprotein produced by the granulosa cells of the ovary and Sertoli cells of the testis. The primary use of inhibin measurements is for monitoring recurrence post-operatively in patients with granulosa or Sertoli-cell tumours. The concentration of inhibin in women varies markedly depending on the stage of the menstrual cycle and whether or not the patient is post-menopausal. Interpretation is therefore also dependent on whether unilateral or bilateral oophorectomy is performed.

Thyroglobulin.

Patients with papillary or follicular thyroid cancer are usually treated by total thyroidectomy followed by ablative doses of radioiodine. Thyroxine is then prescribed at doses that suppress TSH to concentrations of <0.01mU/L with a view to impairing the growth of any residual tumour. In patients with low-grade disease, complete suppression of TSH may not be required. Many of these tumours synthesise and secrete thyroglobulin, and the measurement of serum thyroglobulin is of value in monitoring progression of the disease and in assessing response to treatment. Measurement of thyroglobulin has no role in the diagnosis of thyroid cancer because elevated concentrations are found in many thyroid disorders other than malignancy. In patients who have been treated with total thyroidectomy and ^{131}I ablation, a serum thyroglobulin is usually undetectable. The finding of a detectable thyroglobulin is suggestive of residual or recurrent tumour, but could also indicate persistence of a remnant of normal thyroid tissue. The sensitivity of serum thyroglobulin measurements for detecting recurrence is enhanced by an elevated TSH concentration. Therefore, serum thyroglobulin should preferably be measured when the serum TSH is >30mU/L; this can be achieved by either withdrawal of T4 or administering recombinant TSH. However, the introduction of high-sensitivity automated thyroglobulin assays that can measure thyroglobulin to <0.1µg/L obviates the need for performing a recombinant TSH stimulation test in many circumstances.

Case Study 4.

A 54-year-old female shop assistant presented to the endocrine clinic for annual follow-up. She had been diagnosed 9 years earlier with a small focal papillary carcinoma of the thyroid that had been treated by partial thyroidectomy with no radioiodine ablation. She was taking thyroxine and had remained well with no evidence of recurrent disease. At annual follow-up the following results were found:

Serum	Result	Reference range
TSH	4.0	0.2–4.5 mU/L
FT4	13	9–21 pmol/L
Thyroglobulin	5	µg/L

(Anti-thyroglobulin antibodies were negative.)

How would you interpret these results?

Comments: The patient has been taking inadequate doses of thyroxine. The aim of T4 therapy in patients with papillary carcinoma of the thyroid is to suppress TSH to undetectable concentrations; this has not been achieved in this patient. Compliance should be verified and the need for an increase in T4 dose ascertained.

In patients who have undergone total thyroidectomy and in whom TSH is <0.01mU/L, thyroglobulin should be undetectable. This patient has residual thyroid tissue (she only has had a partial thyroidectomy) and she has detectable circulating TSH that will stimulate thyroglobulin production from the thyroid remnant. It is thus impossible to determine from these results if the thyroglobulin is originating from the thyroid remnant or a recurrent tumour. Thyroglobulin was later found to be undetectable when the patient's TSH was <0.01mU/L and no further action was required other than continued annual follow-up.

Calcitonin.

Medullary thyroid cancer (MTC) arises from the parafollicular, calcitonin-producing cells (C cells) of the thyroid gland, and accounts for about 10% of thyroid cancers. Sporadic cases account for 80% of all cases of MTC; a familial form of the disease occurs in conjunction with a syndrome known as multiple endocrine neoplasia (MEN).

Plasma calcitonin is often greatly increased in patients with MTC, but plasma calcium is usually normal. Raised plasma calcitonin may occur in other conditions, including Hashimoto thyroiditis, chronic renal failure and diseases associated with transformed neuroendocrine cells (e.g. carcinoid tumours and phaeochromocytoma).