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Alpha Fetoprotein: Tumor Marker in Gynaecology

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Abstract

Ovarian carcinoma is the fifth most common cause of cancer death. It is the second most common gynecologic malignancy in developed countries and the third most common gynecological cancer. There are several intrinsic problems that render ovarian cancer screening difficult. An optimal screening test has high sensitivity, specificity, patient acceptance. The three screening techniques available for ovarian malignancy are: Pelvic examination, Tumor Marker, TVS. Tumor markers are used to screen for or diagnose malignancies, determine prognosis or monitor therapy. Alpha Fetoprotein is tumour marker for Embryonal Carcinoma, Yolk Sac tumour, Immature Teratoma, Sertoli-Leydigs cell tumour. The concept of preventive oncology has been developed to approach cancer problem at various points in evolution with goal of reducing cancer suffering and death.

Keywords: Ovarian Cancer; Alpha Fetoprotein; Germ cell tumours; Tumour Markers; Cancer Screening.

Introduction

'To cure was the voice of the past,
to prevent is the divine whisper of today'

Ovarian carcinoma is the fifth most common cause of cancer death. It is the second most common gynecologic malignancy in developed countries and the third most common gynecologic malignancy in developing countries. It is the most lethal gynecological cancer. The high mortality associated with ovarian cancer is largely due to inability to detect the disease early and lack of effective therapeutics for recurrence.[1] Ovarian cancers have vague symptoms such as abdominal discomfort or bloating, and therefore the majority of the cases present at an advanced stage. A late diagnosis may be a major contributing factor in the overall poor prognosis. Screening of ovarian cancer will ensure early diagnosis of the disease and overall outcome.[2] The common theme of the treatment modalities in ovarian cancer is loss of reproductive function, often with castration and associated morbidity and mortality. These treatments can be financially, emotionally and sexually threatening. The concept of preventive oncology has been developed to approach the cancer problem at various points in evolution with the overall goal of reducing cancer suffering and death.[3]

Difficulties with Ovarian Cancer Screening

There are several intrinsic problems that render ovarian cancer screening difficult. Unlike cervical cancer, ovarian cancer appears to be a heterogeneous group in which there is no well-defined precursor lesion and the rate of disease progression can be highly variable. This contributes to the difficulty of finding an effective screening test that can detect early disease and hence improve survival. Furthermore, unlike in cervical cancer screening in which a positive smear can be further investigated by colposcopy and biopsy, and precursor lesions, such as cervical intraepithelial neoplasia, can be treated by a minor procedure such as a large loop excision of the transformation zone, a positive test for ovarian screening would lead to surgical intervention, e.g. Diagnostic laparoscopy and

bilateral salpingo-oophorectomy, with its potential surgical complications. This further adds to the importance of finding a highly specific test.[2]

An optimal screening test has high sensitivity, specificity, patient acceptance and is easy to perform. The three screening techniques available for ovarian malignancy are:

- Pelvic examination
- Tumor Marker
- Vaginal ultrasound

But these screening tests do not actually diagnose ovarian cancer but only suggest its presence; laparotomy is required for definitive diagnosis.[4] Physicians evaluating women with these symptoms must be aware of the possibility of the ovarian pathology causing these symptoms. However, some evidence suggests that the screening tests using these symptoms is not as sensitive or specific as necessary, especially in those with early stage disease.[5]

Tumour markers are substances detected in blood and body fluids of individuals who harbour a malignancy. These substances are either produced by the tumour itself or are produced by the normal tissues in response to the malignancy. Tumour markers are not specific to malignancies but may also be seen in other benign conditions.

Tumour markers are used to:

- Screening
- Diagnosis of malignancy
- Determine prognosis
- Monitoring therapy

Acid phosphatase was the first tumour marker used for metastatic prostate cancer and was described by Gutman and Gutman in 1938. Various substances may be used as tumour markers. They include tumour antigens, enzymes, hormones, oncogenes and other substances. Tumour antigens include CEA, AFP and HCG which are oncofetal being produced during normal embryological development and also by neoplastic cells.[6]

Table 1: Tumor Markers.[7]

- Human Chorionic Gonadotropin (HCG)
- Alpha Feto Protein (AFP)
- Cancer Antigen 125(CA-125)
- Carcino Embryonic Antigen (CEA)
- Inhibin A /Inhibin B
- Lactate dehydrogenase (LDH)
- Placental Alkaline Phosphatase (PALP)
- Squamous Cell Carcinoma Antigen (SCCA)
- CA 15-3 (HER -2 neu, OVX 1,OVX 2)
- Lipid Associated Sialic Acid (LSA)
- NB/70 K
- Tag 72

Human alpha-fetoprotein (AFP), whose existence was identified in 1956 in two separate laboratories during electrophoretic experiments is the homologue of a serum protein found in all mammalian species during embryonic development. Scientists have found biochemical and immunological similarities between fetal development and neoplastic cells.[8] Alfa-fetoprotein is a normal fetal serum glycoprotein containing 3–4% carbohydrate moieties which is produced by the liver, yolk sac, and gastrointestinal tract. It is a major component of foetal plasma. It is used as a marker for hepatocellular carcinoma and germ cell tumours (Non seminoma) which contain embryonal or endodermal sinus elements where it is associated with levels greater than 500 ng/ml. It is also elevated in normal pregnancy and benign liver disease such as hepatitis and cirrhosis. Sometimes it may be elevated in pancreatic cancers, gastric cancers, colonic cancers and bronchogenic cancers.[5] Alpha-fetoprotein level is elevated in the serum in almost all cases of endodermal sinus tumor.[1]

Table 2: Concentration of AFP in Serum.[8]

First 2 months of life	400 ng/ml
6 months	30 ng/ml
1–2 years of age	<15 ng/ml
Childhood and adult life	3–15ng/ml

Table 3: Characteristics and Clinical significance of Alpha-fetoprotein.[9]

Tumor Marker	Size	Half-Life	Normal Range	Tumor type
Alpha Feto Protein (AFP)	70,000 daltons	5–7 days	<40µg/l	• Embryonal carcinoma • Yolk sac tumor • Immature Teratoma • Sertoli-Leydigs cell tumor (rare)

During development, AFP is expressed and synthesized sequentially by cells of the yolksac, and fetal liver and gastrointestinal tract. In adults, the AFP gene is silenced by methylation processes and AFP reappears only in instances of hepatic damage/regeneration and in solid tumors such as hepatomas and germ cell cancers.[10]

AFP is the prototype of oncofetal markers. Emphasis is given to the usefulness of elevated serum AFP levels in the diagnosis and management tumors of germ cell origin. AFP from a large pool of adult human serum by immune adsorbent

techniques. A variety of immunological techniques for the detection and quantitation of AFP have been utilized which vary greatly in their sensitivity.[11]

Table 4: Elevated Levels of AFP.[12]

- Germ cell tumours containing elements of yolk sac or endodermal sinus components
- Mixed germ cell tumours
- Pure tumors of extraembryonic origin derived from yolk sac
- Carcinoma GI tract, Pancreas
- Retinoblastoma
- Malignant melanoma
- Non Malignant Conditions
  - Cystic fibrosis
  - Turner Syndrome
  - Hereditary Tyrosinemia
  - Ataxia telangiectasia.

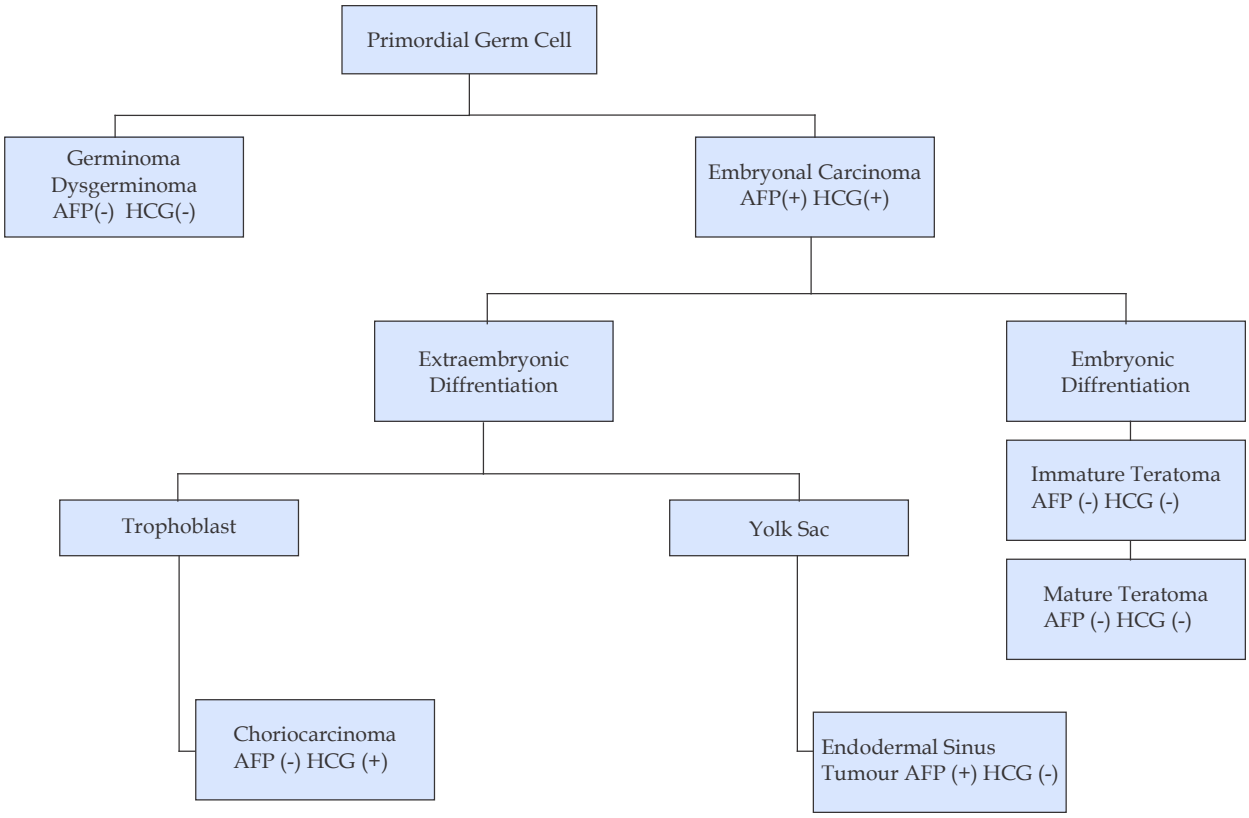
Discussion

Currently, ACOG recommends that the best way to detect ovarian cancer is to have a high index of suspicion. Most women with ovarian cancer are symptomatic, yet go undiagnosed for many months. Serological markers provide a means of monitoring tumor activity at many stages of disease-diagnosis, therapy and relapse. It is important that they are used appropriately and their significance is understood.

Physiological Properties of AFP

- It is the form off etalalbumin which may be involved in immune regulation during pregnancy.
- AFP exerts an immuno suppressive effect on antibody synthesis. AFP induces the formation of highly efficient suppressor T cells with capacity to inhibit helper T cells, but with no effect on B cells responding to thymus independent antigens. AFP suppresses the mitogenic response of human lymphocytes to phytornitogens, antihuman thymocyte antiserum and mixed lymphocyte culture.
- AFP maintains the fetus as an allograft in a genetically incom- patible environment. Administration of anti-AFP antisera to pregnant mice and rabbits has been abortogenic. AFP at the maternal/fetal interface might initiate rejection of the fetus through a cell-mediated immune reaction.
- AFP has a much lower estrogen binding ability. AFP could influence cell growth.[14]

In understanding the significance of elevated



AFP levels in patients with germ cell tumors of ovary, testes or extragonadal primary sites the classification of such tumor's according to Teilum is of the most important as it emphasizes the role of the yolk sac or endodermal sinus component of such tumor's in relationship to synthesis of AFP.

- Elevations of serum AFP levels are not seen in conjuction with pure seminomas of the testes or dysgerminomas of the ovary.
- In the mixed germ cell tumours(Embryonal cell carcinomas), elevations of both AFP and the β-chain of human chorionic gonadotropin (HCG) may be seen singly or together. In those instances where serum AFP levels are elevated, careful histopathological examination of the tumor will usually revel yolk sac elements where as HCG elevations corresponds to syncytotropho blastic tumor elements.
- In pure tumor's of extraembryonic origin derived from yolk sac elements AFP elevations are always present and HCG is absent.
- In teratoblastomas AFP and HCG are usually absent.

When such tumor's are suspected, serum monitoring of both AFP and HCG begin prior to surgery. The complete disappearance of elevated AFP levels, with an exponential fall of five to six day half-life, is good indication of complete extirpation of such malignancies. In surgically unrecectable or metastatic disease, by combination chemotherapy, long term serial follow up of both AFP and HCG serum levels can be undertaken.

In both surgically and medically treated patients, the reappearance of elevated serum of either AFP or HCG almost certainly heralds a clinical relapse, and appropriate diagnostic and therapeutic measures should be instituted. Chemotherapeutic intervention may be started while the tumor mass is small and more easily eradicated.[15]

Counselling: The challenges in cancer prevention for primary care health professionals are to apply effectively and efficiently the technologies preventing disease occurrence and progression. The opportunity for providing preventive services in medical care would require consideration of economical, organizational, and conceptual barriers. Although women have a range of practical , effective measures available to reduce their risk of these cancers, few are aware of them . Without this information women cannot make fully informed decisions about their health.[3]

Recent Advances

- Donaldson and co-workers reported that plasma level of AFP were elevated in patients with gynaecologic malignancies which includes the patients with ovarian epithelial tumor as well as those with invasive carcinoma of cervix and endometrium.
- Kurmana and co-workers have suggested that differential AFP and HCG production may be used as a reliable criteria to differentiate ovarian endodermal sinus tumors from embryonal cell carcinomas.[16]

Conclusion

The concept of preventive oncology has been developed to approach the cancer problem at various points in evolution with the goal of reducing cancer suffering and death. Finding proper screening strategy for ovarian cancer is challenging. Biomarkers like AFP provide more effective screening tests. Combination of biochemical markers and TVS is the commonest screening strategy. Detection and measurement of serum AFP level is found useful in the diagnosis, prognosis and follow up of patients with germ cell tumor. Prevention of gynecologic cancer is a neglected area of woman's health care. Investments in prevention will lower the costs of diagnosis and treatment of these diseases . Health care providers and the media – must advice women of these opportunities. Without this information, women cannot make truly informed decisions about their health.

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