chorion Epithelioma
[CHORIOCARCINOMA]

ESSAY

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BY

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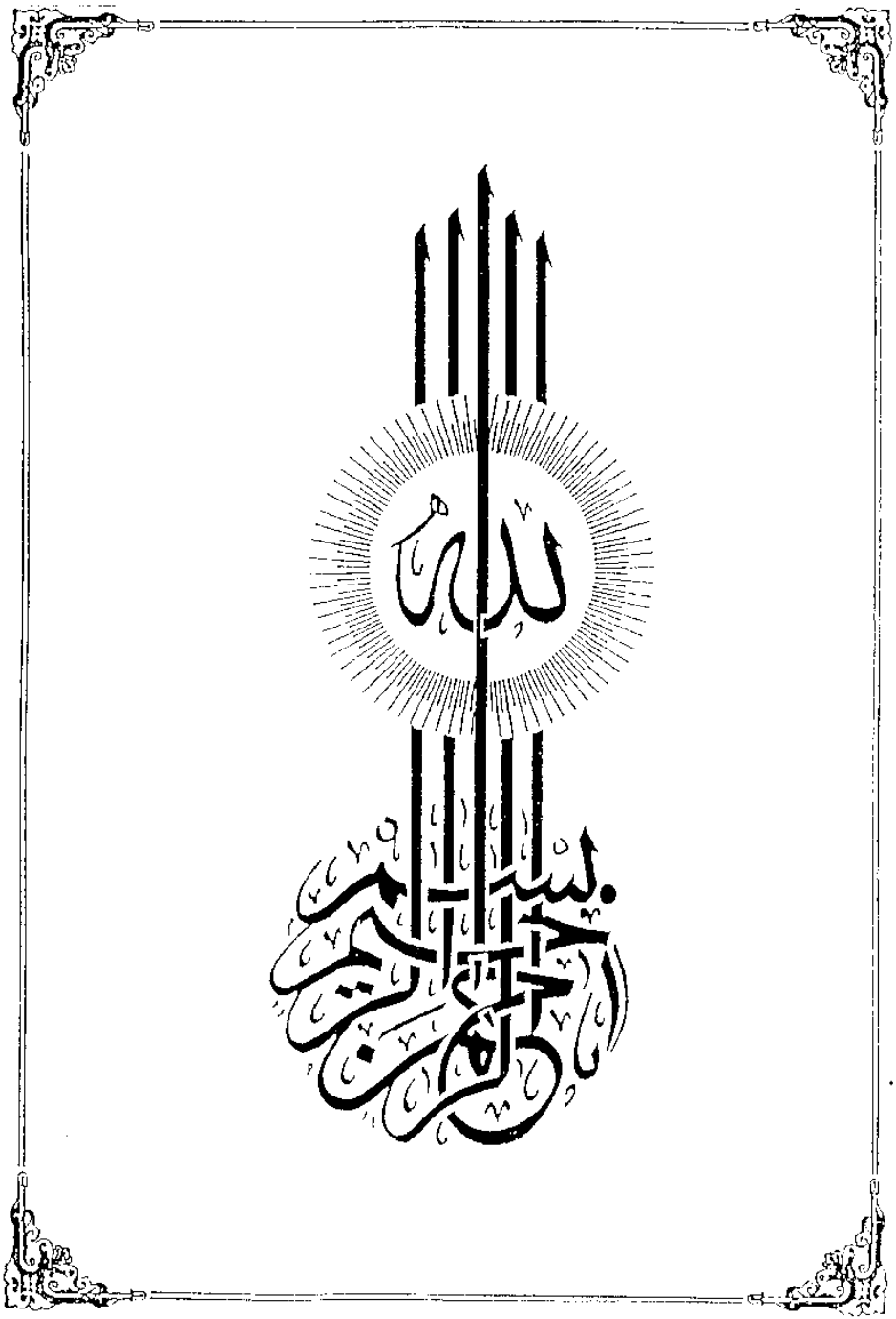

Contents

Introduction

Malignant trophoblastic disease can exist in two forms,namely in a non-metastatic form; invasive mole, or in a metastatic form; choriocarcinoma.The distinction between the two conditions is somewhat artificial because both are treated with chemotherapy and monitored by the levels of that reliable tumor marker; human chorionic gonadotropin (Whitfield, 1984) .

Choriocarcinoma is most frequently seen following hydatidiform mole.Lurain et al.1982, reported that 46% of cases were seen following hydatidiform mole, 28% were seen following term pregnancy, and 24% following an abortion .

Choriocarcinoma is a tumor not of the uterus,but of the embryonic chorion; the uterus is only secondary involved through local invasion of the tumor (Ramsy, 1983) .

Choriocarcinoma is a malignant neoplasm composed entirely of active chorionic epithelium which is avillous,necrotic and hemorrhagic (Ramsy , 1983) .

The incidence of choriocarcinoma is difficult to establish with certainty but has been estimated as lying between 1 :10000 and 1:70000 pregnancies in the West and between 1:250 and 1:6000 pregnancies in Asia(Buckley,1984).

Our interest in this subject stems from the fact that choriocarcinoma is an absolutely curable disease and so throughout this study we shall emphasize the significance of early and definite diagnosis of this tumor aiming to halt its menace.

Definition

Choriocarcinoma is a very highly malignant tumor of gestational trophoblastic disease(G.T.D) which is unique amongst human neoplasms. It retains certain characteristics of normal placenta such as invasive tendencies and ability to make a polypeptide hormone human chorionic gonadotropin [H.C.G] and its sensitivity to chemotherapy . Since methotrexate was first used to treat G.T.D. in 1956 these properties have combined to allow it to become one of the curable human malignancies [Jones and Jones.1981]. However: gestational choriocarcinoma is always related to pregnancy events thus differs basically from non gestational choriocarcinoma of the ovary or the testis (Jones and Jones. 1981).

In the past , the vast majority of patients who developed metastatic choriocarcinoma were dead within one year despite hysterectomy, x-ray therapy and attempts at surgical removal of metastatic foci. on the other hand patient with locally invasive mole or choriocarcinoma treated early with hysterectomy generally survived (Donald.1970).

This poor prognosis for metastatic disease has now dramatically reversed by the use of anti-tumor drugs singly or combined with surgical treatment(Donald,1970).

ETIOLOGY

The etiology of malignant trophoblastic neoplasia is unknown. Several factors that may affect ovigenesis , spermatogenesis and the fertilized ovum have been considered important in the development of trophoblastic neoplasia. Among them injury , endocrine deficiencies, infection (eg. unidentified virus disease, toxoplasmosis), inadequate nutrition or dietary carcinogens (socioeconomic status, fungus, contamination of foodstuffs), climatic and racial factors (higher incidence in some parts of the world than others), chromosomal aberrations (the majority of moles are genetically female), immunological deficiencies (consanguinity), and the paternal blood groups (highest risk of occurrence when one parent is group A and the other group o) have all been announced. Circumstantial and, in some instances, suggestive epidemiologic and experimental evidence has been provided no etiologic factors have been firmly established, however (Holland et al., 1987)

The mechanism by which choriocarcinoma survives as a graft in an immunologically hostile environment seems likely to be similar to that which allows the normal trophoblast to resist maternal rejection (Billington and Bell, 1983; Head et al., 1987).

Studies of the association of HLA antigens (human lymphocytic antigens) with gestational trophoblastic disease have yielded conflicting results, but overall there is little evidence to support the theory that choriocarcinoma is more likely to develop when there is histo-compatibility between the conceptus and the mother (Brewer et al., 1978; Lawler, 1976).

There is no correlation between disease incidence and the presence of specific HLA antigens. The presence of HLA incompatibility between choriocarcinoma and their male partners has no effect on cure or duration of therapy required to achieve remission.

Therefore, HLA specificity does not appear to have a major influence on the etiology of trophoblastic tumor or on their response to treatment (Philip et al, 1987).

Complete hydatidiform mole are beleived to be as a result of androgenesis ,i.e., the development of an ovum under the influence of a spermatozoon nucleus with the original nucleus of the ovum being either absent or inactivated. Theoretically, this may occur in two ways. First, nondivision at the second meiotic division could result in a diploid sperm for fertilization. Alternatively, a haploid sperm could cause fertilization and subsequently duplicate its chromosomes after meiotic division (John et al, 1982).

Staging and Classification

In the past,the classification of trophoblastic diseases was based upon pathological examination of excised tissue . Specimens consisted of tissue removed at curettage,hysterectomy,or at surgical excision . Specimens were then classified as hydatidiform mole,invasive mole,or choriocarcinoma (Nathan et al., 1990) . In 1973 Hammond et al.suggested a new categorization for GTD . This new classification treats GTD as a spectrum of neoplasia and allows identification of high- risk factors in this disease process.By so doing,one is able to individualize therapy and thereby treat a specific patient more appropriately (Creasman and Disaia, 1993) .

Classification of GTD (Hammond, 1973) :

1. Non metastatic disease:no evidence of disease outside the uterus.
2. Metastatic disease:any disease outside the uterus.

A. Good prognosis metastatic disease

* Short duration (last pregnancy < 4 months)
* Low pretreatment HCG titer(< 100,000 IU/24 hr or <40,000 mIU/ml)
* No metastasis to brain or liver
* No significant prior chemotherapy

B. Poor prognosis metastatic disease

* Long duration (last pregnancy> 4 months)
* High pretreatment HCG titer (>100,000 IU/24 hr or > 40,000 mIU/ ml).
* Brain or liver metastasis
* Significant prior chemotherapy
* Term pregnancy

There have been several suggested modifications or staging proposals.In 1976 Bagshawe suggested the use of a prognostic scoring system instead of a staging system.The World Health Organization(WHO) has adopted a modification of Bagshawe's scoring system(Creasman and Disia,1993).

WHO scoring system (Creasman & Disaia, 1993) :

Prognostic factors	score			
	0	1	2	4
Age	<39	>39		
Antecedent pregnancy	HM	Abortion	Term	
Months from last pregnancy	4	4 to 6	7 to 12	12
HCG(IU/L)	10^3	10^3-10^4	10^4-10^5	10^5
ABO(femalexmale)		OxA AxO	B AB	
Largest tumor (cm)		3 to 5	5	
Site of metastases		Spleen Kidney	GI Liver	Brain
Number of metastases		1 to 4	4 to 8	8
Prior chemotherapy			Single drug	2 or more drugs

* HM = hydatidiform mole
* The total score for a patient is obtained by adding the individual scores for each prognostic factor.
* Total score : < 4 low risk , 5 - 7 : middle risk , > 8 high risk

The International Federation of Gynecologists and Obstetricians(FIGO) has adopted a staging system based on anatomic criteria.This system is similar to the staging systems used for reporting other gynecologic malignancies(Goldstein et al,1984).Although survival correlated very well with the FIGO classification.there were patients with significant subsets of prognostic factors not specifically identified with this simplified method.In 1991, FIGO revised the staging to combine prognostic factors with anatomical staging . Only two prognostic factors(HCG>100,000mIU/ml and duration of the disease longer than 6 months from termination of the antecedent pregnancy) were inclueded based on recommendations of many investigators (Creasman and Disaia, 1993) .

FIGO staging for trophoblastic tumors (Creasman & Disia, 1993) :

Stage I : Disease confined to the uterus .

- Stage Ia Disease confined to the uterus with no risk factors .
- Stage Ib Disease confined to the uterus with one risk factor .
- Stage Ic Disease confined to the uterus with two risk factors .

Stage II : GTT extends outside the uterus but is limited to the genital stuctures(adenxa,vagina,broad ligament) .

- Stage IIa GTT involving genital structures without risk factors.
- Stage IIb GTT extends outside the uterus but limited to the genital structures with one risk factor .
- Stage IIc GTT extends outside the uterus but limited to the genital structures with two risk factors .

Stage III : GTT extends to the lungs with or without known genital tract involvement .

- Stage IIIa GTT extends to the lungs with or without genital

tract involvement and with no risk factors .

Stage IIIb GTT extends to the lungs with or without genital tract involvement and with one risk factor .

Stage IIIc GTT extends to the lungs with or without genital involvement and has two risk factors

Satge IV : All other metastatic sites .

Stage IVa All other metastatic sites without risk factors .

Stage IVb All other metastatic sites with one risk factor .

Stage IVc All other metastatic sites with two risk factors .

An anatomic staging system for GTT was adopted at a meeting of the International Society for the study of trophoblastic neoplasms in October 1979 at University of Hong Kong (Kistner, 1986) .

Stage	
I	confined to uterine corpus
II	metastases to pelvis and vagina
III	metatases to lung
IV	distant metastases

This staging system will hopefully enable the objective comparison of data among various centers.

Stage I includes all patients with persistently elevated HCG levels and tumor confined to uterine corpus.

Stage II comprises all patients with tumor outside of the uterus but localised to the vagina and / or pelvis.

Stage III includes all patients with pulmonary metastases with or without uterine , vaginal, or pelvic involvement. Precise morphologic diagnosis is not easily obtained in stage III without open thoracotomy. However, we do not advocate performing thoracotomy in these patients merely to obtain information concerning the histologic pattern. We therefore base our histologic diagnosis on the known morphology as determined by reviewing the previous pathologic findings, endometrial curettings and antecedent pregnancy.

Stage IV patients have far advanced disease with involvement of the brain, liver, kidneys or gastrointestinal tract. Patients with stage IV disease are in the highest risk category because they are the most likely to be resistant to chemotherapy. Stage IV tumors generally have the histologic pattern of choriocarcinoma and more commonely follow a non molar pregnancy (Kistner,1986).

PATHOLOGY

Choriocarcinoma is a tumor not of the uterus but of the embryonic chorion, the uterus is only secondary involved through the local invasion of the tumor (Ramsy,1983).

The chief feature of choriocarcinoma is invasion of the uterine wall by trophoblastic cells, with destruction of the uterine tissue accompanied by necrosis and hemorrhage with absence of chorionic villi due to trophoblastic growth in columns and masses which obliterate the original villus pattern, though it must be noted that their presence does not negate a diagnosis of subendometrial choriocarcinoma .About 50% of cases follow hydatidiform mole and invasive moles, 25% follow abortion and 22.5% follow full term pregnancy (Ramsy,1983) .

Gross Features :

Choriocarcinoma presents as a circumscribed single or multiple hemorrhagic necrotic masses in the uterine wall and within the uterine cavity, rarely it forms a diffusely infiltrating lesion. The neoplasm may infiltrate the wall of the uterus beneath an intact epithelium, which may lead to an erroneous benign diagnosis based on curettage specimen (Ramsy,1983).

As the disease advanced the surface may show ulceration and necrosis . The tumor is dark red or purple and ragged or friable, if it involves the endometrium bleeding, sloughing and infection of the surface usually occurs early. Masses of tissue burried in the myometrium may extend outward, appearing on the uterus as dark irregular nodules that eventually penetrate the peritoneum (Pritchard et al., 1985).

Microscopic Features

Islands of proliferating trophoblasts invade the wall of the uterus, parauterine

tissues and blood vessels . Extensive hemorrhage and necrosis of myometrium and infiltrating polymorphs are quite characteristics.It is most unlikely to see the intact chorionic villi, the neoplastic syncytial and cytotrophoblastic cells are mixed together in a plexiform pattern. Atypical and abnormal mitotic figures are frequent. However, the trophoblastic cells may lack evidence of anaplasia. The diagnosis of choriocarcinoma can not be established in curettage specimens, unless one can identify necrotic muscle, hemorrhage and lack of villus pattern associated with marked cellular atypia and proliferation (Ramsy .1983). Hyperchromatism with numerous large, heavily stained and perhaps multiple nuclei is frequently seen but may be found also in the benign hydatidiform mole or even normal trophoblast. Cell changes are of less importance in diagnosis than the growth pattern of the tumor , for trophoblast itself is undifferentiated and active in its appearance (Novak and Woodruff, 1979).

Early Choriocarcinoma :

An exception to the usual form of malignant chorionic disease is exemplified by two cases reported by Brewer and Gerbie ,1966 which added to two other cases, brings to four the number of certain early trophoblastic lesions . Those occurred in patients with a non molar pregnancy who has small lesions located in a normal placenta, with a living fetus. Despite hysterectomy , death occurred because of metastatic choriocarcinoma (Novak, 1979).

In such cases chorionic villi, are present as a vascular supply but the usual necrosis and hemorrhage found in the most carcinomatous choriomas are absent. No villi are found in the metastatic lesion, perhaps because it is the proliferating trophoblast rather than the placental villus that is prone to erode into a vascular sinus. As the disease progresses there is invasion of villous stroma by trophoblast and ultimate loss of the villous structure . these are exceptions to the usual histologic pattern of choriocarcinoma,but the cases reported are usually early