Trophoblastic Neoplasia

Its Basic and Clinical Aspects

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Preface

Of the malignant neoplasia growing in females, carcinoma such as uterine or breast carcinoma, sarcoma, chorionepithelioma or some others, the latter is of the worst prognosis in that it has a remarkable tendency to give rise to metastasization not only in external visible parts, mostly vagina or vulva, but also very often extensively in any of the inaccessible internal organs whatsoever of the body.

And yet it seems that, unlike in case of the uterine carcinoma in which every possible means of campaign against it using, for example, popular periodicals, movies, "paper dramas" or even special clinic cars are being mobilized, it is a matter of far lesser concern than carcinoma of the uterus to the people in general, or sometimes even to medical specialists so that the postoperative control of patients with hydatidiform mole, for example, medical measures indispensable for preventing them from being stricken by the development of chorionepithelioma because of the former's prominently high incidence as a pregnancy preceding the latter, is often neglected not only by the patients themselves but also sometimes even by the attending doctors, and as a result the outcome of hydatidiform mole is being obliged to get exceedingly worsened.

Such circumstances are to be profoundly regretted from viewpoint of the welfare of mankind so that it should firmly be born in mind that it is a very important task entrusted to doctors as a whole to heighten, with the sufficient knowledge of its tragic nature in view, more and more the concern of the people in general over its seriousness so as to assure them of the perfection in prophylaxis, early diagnosis and treatment of that most dreadful disease in this world.

It was just to meet such demand that a monograph entitled "Hydatidiform Mole and Chorionepithelioma" was published by the author in February, 1956, and that, in accordance with the proposal made by the author, the then Professor of Obstetrics and Gynecology, University of Tokyo School of Medicine, and President, Japan Society of Obstetrics and Gynecology, and with an immediate view to conducting nationwide investigations into the natural history of the neoplasia concerned, a scientific research committee named the Chorionic Tumor Committee was inaugurated within the Society in March, 1956, with all the members of the Board of Directors as Committee members and some of the Society members as extraordinary Committee members.

It is now just fifteen years since then, during the duration of time of which the basic as well as the clinical knowledge of the trophoblastic neoplasia has remarkably been broadened, and its dark and gloomy aspects have now notably been brightened, thanks to the vigorous scientific activities centering around the Chorionic Tumor Committee evidenced, for instance, in the sponsorship by the Committee of the nationwide investigations into

its natural history, the annual trophoblastic neoplasia symposia, or the standardization of its definition, classification and diagnostic criteria, and also demonstrated in a number of national research grants-in-aid of various kinds to some of the Committee members, or the participation in the international symposium on the chemotherapy of the trophoblastic neoplasia, and finally also in taking part in the similar international joint chemotherapy studies likewise by some of them.

The present monograph partly commemorating the 15th anniversary of the founding of the Chorionic Tumor Committee is aimed at, as a revised and somewhat enlarged edition of the initial one, having its readers well informed in part of such scientific activities of the Committee as those mentioned previously, and also in part of the marked progress in the basic as well as the clinical knowledge of trophoblastic neoplasia at home and abroad during a decade and more in the past.

Though modest in size with much left untouched, the author will feel more than happy should the present little monograph play a role of something like the foundation-stone on which more details of the knowledge of the trophoblastic neoplasia will be piled up to its perfection so that it could be of some aid to the extermination of this most fatally malignant disease out of the earth.

Acknowledgement

The author is indebted to members of the Japan Society of Obstetrics and Gynecology, those of the latter's Chorionic Tumor Committee in particular, for their painstaking activities, in collaboration with the Committee, in the nationwide yearly investigations into the natural history of trophoblastic neoplasia ever since the Committee was inaugurated in 1956.

Grateful acknowledgement is made to Dr. HOWARD C. TAYLOR, Professor Emeritus, College of Physicians and Surgeons, Columbia University, New York, for his kind review as well as recommendation of the manuscript of this monograph to the Williams & Wilkins Company in Baltimore in connection with, a prerequisite to its publishing in Japan, the distribution of the book in the United States, without whose good offices it would'nt have been able to see the light.

Words of the sincere appreciation are conveyed to Mr. IZUMI HASEGAWA, Editor-in-Chief, the Igaku Shoin Ltd., Tokyo, for his cordiality in giving, at the request of the author, the latter's manuscript an opportunity to take shape of a book as it is.

Thanks are also tendered to a number of researchers for their generosity in allowing the author to cite valuable figures and tables which appeared in their past works.

For scores of slides of the specimens as well as chromosome figures appearing in this book the author owes much to Dr. NOBORU TANAKA, Chief, Central Laboratory, and Miss TAMIKO SHINOHARA, laboratory technichian, the Japanese Red Cross Central Hospital, Tokyo, respectively.

Lastly, the author would like to thank Mrs. TAKAKO ISHIGURO, Mrs. MASAKO MUKAI and Mrs. MASAKO WATANABE who troubled themselves to co-operate with him in typewriting the manuscript for its publication.

February 2, 1971, with his 73rd birthday just around the corner,

Author

Contents

GENERAL CONCEPT

Chapter I

Definition, classification or nomenclature of trophoblastic neoplasia

I. Definition of trophoblastic neoplasia

Chorionic or trophoblastic neoplasia are the fetal tumors or new growths consisting of syncytial and LANGHANS' cells of fetal ectodermal origin, trophoblastic epitherial cells or trophoblasts, syncytiotrophoblasts (syncytial cells) and cytotrophoblasts (LANGHANS' cells), as they are collectively called, microscopically in a state either of an abnormal (in cases of hydatidiform mole and destructive mole) or an atypical (in case of chorionepithelioma) proliferation, the findings which diagnostically are not absolutely necessary, particularly in case of hydatidiform mole, as will be stated later (p. 150).

The term "chorionic or trophoblastic neoplasia" has its origin in the agreement reached at the Conference on the Chemotherapy of Choriocarcinoma which was held in Baguio City, Philippines, from January 18th to 20th, 1965, under the auspices of the International Union Against Cancer, Union International Contre le Cancer (UICC).

II. Classification or nomenclature of trophoblastic neoplasia

Historically the classification or nomenclature of trophoblastic neoplasia has undergone scores of changes up to now, its original one dating back to the proposal by MARCHAND in 1895.

1. *Classification by MARCHAND (1895)*
   1) Blasenmole, mola hydatidosa s. hydatidiformis
   2) destruierende Blasenmole
   3) Malignes Chorionepitheliom, Chorionepithelioma malignum
      i) Of a typical form: One with the ratio of number of syncytial cells to that of LANGHANS' cells orderly almost similar to that in normal villi in an early stage of pregnancy.
      ii) Of an atypical form: One with the ratio of number of syncytial cells to that of LANGHANS' cells out of order in a greater part of the tumor.

2. *Classification by EWING[1] (1910)*
   1) Syncytial endometritis (abbreviated to SE), chorial or chorionic invasion
   2) Chorioadenoma destruens (=destruierende Mole by MARCHAND)
   3) Choriocarcinoma (=malignes Chorionepitheliom by MARCHAND)

It is to be noted that in this classification hydatidiform mole is excluded, presumably because, as pointed out by EWING, it is not to be regarded as a kind of tumors, while SE is included in the category of neoplasia. However, this is not the case with the classification in Japan in accordance with the agreement reached at the Chorionic Tumor Committee meeting, Japan Society of Obstetrics and Gynecology, for one thing in line with the classification made by MARCHAND as well as NOVAK in case of hydatidiform mole, and for another for fear of the possibility of being mistaken for an inflammatory disease in case of SE, as will be mentioned anew later (pp. 13—14).

3. Classification by MEYER[2] (1927)

This classification is just the same as the one by MARCHAND mentioned previously except for three subdivisions added to malignes Chorionepitheliom of an atypical form, as given below:

Malignes Chorionepitheliom of atypical form

1) One with the numerical predominancy of LANGHANS' cells
2) One likewise with the numerical predominancy of syncytial cells
3) One with the distribution of both of trophoblasts quite out of the physiological order, each invading the myometrium and, unlike sporadically in case of normal pregnancy, forming a lot of collective cellular masses in it. In case a primary lesion is lacking in endometrium, physiological site of nidation of fertilized ovum, it is to be regarded as having been lost in sight as a result of the degeneration or the curettage previously done. Anyhow, malignes Chorionepitheliom of group (3) has a trend to grow infiltratively rather than tumorously without, however, necessarily assuming the attitude of particularly marked malignancy.

4. Classification by HERTIG and MANSELL[3] (1956)

Adding "chorionepithelioma in situ" to the classification by EWING, HERTIG and MANSELL classified chorionic malignancy, as was collectively called by them, into the following four subdivisions:

1) SE
2) Chorioadenoma destruens
3) Choriocarcinoma
4) Chorionepithelioma in situ

By chorionepithelioma in situ here is, with negative "chorionic villi" or "well-formed villous pattern" and only positive small masses of atypical hyperplastic trophoblasts in microscopical endometrial findings following the normal or molar delivery, meant such a kind of trophoblastic neoplasia as will promise no development of chorionepithelioma in the future in the light of the results of the statistical investigations, the term "in situ" having nothing to do with that used in case of "carcinoma in situ".

5. Classification by NOVAK (1958)

1) hydatidiform mole

2) malignant hydatidiform mole (=Chorioadenoma destruens)
3) chorionepithelioma (=choriocarcinoma)
4) SE (or syncytioma)

6. *Classification in Japan (1964)*
This will be specified later (pp. 13—14)

7. *Classification proposed at the conference on the chemotherapy of choriocarcinoma held in Baguio City, Philippines, in 1965*

Trophoblastic neoplasia
I.
1. Gestational
2. Nongestational
II. Clinical diagnosis
1. Non-metastatic
2. Metastatic
III. Morphological diagnosis
1. Hydatidiform mole
1) Non-invasive
2) Invasive
2. Choriocarcinoma (? chorionic carcinoma)
3. Uncertain

N. B.
"Syncytial endometritis" not regarded as a neoplasia

Chapter II

Development of the studies on trophoblastic neoplasia in Japan

Although the studies on trophoblastic neoplasia in Japan date back as early as even to 1940 or beyond, they were mostly those sporadically by individual researchers or clinicians without any cooperation with others so that, inspite of its extremely intensive malignancy even surpassing that of carcinoma, it was not too much to say that no grave concern was brought about as to its fatality both from the individual as well as social point of view. The inauguration of the Chorionepithelioma Committee (later Chorionic Tumor Committee), Japan Society of Obstetrics and Gynecology, on March 31, 1956, however, has given rise to a tremendous progress both in its clinical and basic researches, a series of which will be specified one after another in the following paragraphs.

I. Inauguration of the Chorionepithelioma Committee and its activities

A. INAUGURATION OF THE CHORIONEPITHELIOMA COMMITTEE

Because of the importance of the studies of chorionepithelioma, proposal was made on June 18, 1955, as to the establishment of the Chorionepithelioma Committee by the author, concurrently the then Professor of Obstetrics and Gynecology, University of Tokyo School of Medicine, President, the Japan Society of Obstetrics and Gynecology, and Chairman, Malignant Chorionepithelioma Research Team to be referred to later, at the preliminary session of the Board of Directors, the 8th Annual Meeting of the Japan Society of Obstetrics and Gynecology, with all the members of the Board of Directors as ex-officio Committee members and some of the Society members as extraordinary Committee members at the request of the President. The proposal was unanimously accepted, and in accordance with Article 18 of the Society regulations, the Chorionepithelioma Committee (abbreviated to Committee) was formally inaugurated on March 31, 1956, following its announcement at the meeting of the Board of Trustees, and at the General Assembly as well, of the Annual Meeting, the Japan Society of Obstetrics and Gynecology.

The organization of the Committee is as follows:

Chairman: President TOSHIO HASEGAWA
Ex-officio Committee members: MUNI IIDA, MASAOMI ISHIKAWA, TOSHIEI IWATSU, GENICHI OGAWA, MICHITAKA KAKU, TADASU SHINODA, SEI NAKAJIMA, EINOSUKE NAKAYAMA, TAIJUN NISHIZUKA, TOSHIO HASEGAWA, TOYOICHI HIROSE, KIYOSHI MURAKAMI, HIDEO YAGI, RYUKICHI MIBAYASHI

Members of the Board of Directors were not only subject to reelection every two years but also were increased in number thereafter so that they were 67 in all including 41 extraordinary Committee members on May 20, 1966, as will be listed below:

Chairman: TOSHIO HASEGAWA
Ex-officio Committee members: SHOJI MATSUDA, SHOSHI KUJIMA, YOSHIMARO HATA, SHOJI IWAI, MINORU UMEZAWA, CHIAKI SAWASAKI, KAZUNARI HIGUCHI, KICHISUKE FUJII, KYUSHIRO FUJII, TAKASHI KOBAYASHI, SHIGEMITSU MIZUNO, FUMIO AKASU, NAOTAKA ISHIZUKA, KINSABURO WATANABE, YOSHIO ASHIDAKA, YASUO UEDA, AKI KOJIMA, TOSHIO NISHIMURA, HAYAMI FUJIMORI, AKI TABUCHI, TARO FUJIU, HARUO ADACHI, MICHITAKA KAKU, KOHACHIRO KOGA, YASUSHI MITANI, MICHIAKI MIYAHARA
Extraordinary Committee members: SUSUMU IZUCHI, MASAO IGARASHI, HIROSHI IWAYA, HAJIME UCHIDA, NOBUHIDE KAWAI, HIROSHI KAWAKAMI, TAKURO KOBAYASHI, KAN SAITO, SHOSHI JIMI, REIGI SHIOJIMA, SHOJI SHINTANI, MASAKUNI SUZUKI, MASAKATSU SUZUMURA, HIROSHI SEKI, HIROAKI SOMA, YUKICHI TAKAMIZAWA, ICHIRO TAKI, SHOSHICHI TAKEUCHI, TETSUYA NAKAYAMA, MISAO NATSUME, GENICHI NOZUE, YUKIO NOTAKE, MOTOYUKI HAYASHI, YASUNORI FUKUI, TORU FUKUDA, YUKIO FUJIWARA, HIROSHI FURUYA, TSUTOMU HOSOKAWA, KAZUMASA MASUBUCHI, SEIICHI MATSUMOTO, YUZO MISONOO, HIDEO MIYAKE, JUNJI MIZUNO, HAJIME MUROOKA, TAKESHI MORI, FUMIO YAMADA, YUKIMASA WATANABE, KIHEI ICHINOE, TSUTOMU FUKUSHIMA, KAZUO MAEDA.

B. ACTIVITIES OF THE CHORIONEPITHELIOMA COMMITTEE

The Committee has since its inauguration energetically exerted itself to fulfil its mission and has attained a great deal of achievements, some of which will be shown here in detail.

1. Nationwide investigations into the natural history of trophoblastic neoplasia

These investigations have been carried out twice so far by arranging and putting in order answers to questionnaires in two forms (one in regard to hydatidiform mole and molar rests and the other to destructive mole and chorionepithelioma, as shown in Tables 1—2), which had previously been sent to, and, unlike those in the first investigation, having been duly filled in, back from the participating doctors mainly working at the Government-run or private university or college hospitals and major official medical facilities such as national, prefectural, municipal or Red Cross hospitals throughout the country.

The 1st investigation: Materials concerned were hydatidiform mole in 476 cases and (62 diagnostically uncertain cases excluded) chorionepithelioma in 398 cases collected from 128 hospitals during the three years from January 1st, 1955, to December 31st, 1957, and the results of the investigation based

Table 1. Blank to be filled up in regard

Date of filling up:
Name of doctor in charge:
Name of hospital:
Address of hospital:

Patient:
Name:
Address:

(A) Pregnancy or birth in the past						
Total number of pregnancies						
Kind of preg.	Term	Abortion		Hydatid mole	Ectopic preg.	Others
	Preg.	Spontaneous	Artificial			
Number						
Date of birth 1 2 3 4 5						
Month of preg. at birth 1 2 3 4 5						

(B) Hydatidiform mole			
Before birth		At birth	
Date of diagnosis made		Date of birth	
Menstruation	Cycle: regular, irregular every days Duration: for days The last menst.: /for days unknown Menarch: years old Menopause: years old	Month of pregnancy	th month, unknown
		Amount of ut. hemorrhage	cc. Measured Estimated
		Kind of mole	Total, Partial, Dead (missed molar abortion)
Atypical ut. hemorrhage	+++ ++ + ± −	Mode of birth	1. Spontaneous followed by curettage none 2. D & C 3. Hysterectomy Subtotal hysterectomy total hysterectomy 4. Others
Uterus: Size	oversized, normal, unduly small		
Uterus: Enlargement	rapid, normal, suspended, unknown		
Hysterosalpingogram (HSG)	Rough sketch	Ovariectomy	+ Bilateral Right side, Left side −
Urinary HCG titer	Method of determination: Units:	Rough sketch of removed specimens	
Symptoms or procedures which determined diagnosis	Ut. oversized, Rapid enlargement of ut. HSG, HCG titer	Operation on metastases	Technic Rough sketch
Metastases	Thorax (Rough sketch) (Roentgenogram) + −	Luteal cyst	Bilateral + Right side Left side; Size (diameter): right side: left side: −
	Vagina + Vulva −		
	Others + Locality (Brain symptoms, hematuria, etc.) −		
Luteal cyst	+ Bilateral Right side Left side; Size (diameter): right: left:	Histological findings	Rate of syncytial cells to Langhans cells: Syn. cells dominant; Langh. cells dominant; Balanced
	−		Proliferation of trophoblasts: Exophytic; Endophytic (intrastromal); None
Clinical symptoms	Hyperemesis +++ ++ + ± −		Invasion: Myometrial; Vascular; None
	Abdominal pain +++ ++ + ± −		Polymorphia of cells: + −
	Edema +++ ++ + ± −		Nuclear: Atypia + −
	Albuminuria +++ ++ + ± −		Karyokinesis + −
	Blood pressure /		Myometrial vascular hypetrophia: Artery −, Slight High, Obliterated
	Fever (Over 38°C) + −		Vein −, Slight High, Obliterated
	Others		
Chemotherapy (incl. sex steroid therapy)	Name of drug, total dose, etc.	Size of vesicles (to be measured floated on saline)	Diameter: mm − mm Average: mm
Radiotherapy	Kind, total dose, etc.		
Side effects			
Remarks		Remarks	

to Hydatidiform mole and Molar rests

Occupation of patient: family:

Estimated financial condition of patient: extremely rich / considerably rich / middle class / considerably poor / extermely poor

Age:

* Long-term result		
	First year	alive, dead
	Second year	alive, dead
	Third year	alive, dead
	Over forth year	alive, dead

(C) After birth (including molar rests)

Menstruated after birth?	Yes No First menst. after birth / for days							
Ut. hemorrhage	Days after evacuation							
	Mode in graphs							
Uterus	Days after evacuation							
	Size							
	Consistence							
Hysterosalpingogram	Rough sketch							
Urinary HCG titer	Days after evacuation							
	Units							
Curettage	Number of curettages done	2	3	4	5			
	Days after evacuation							
	Findings of removed specimens							
Metastases	Thorax (Roentgenogram)	+ −	Date of discovery	Rough sketch	Clinical course	Improved No change Worsened Others		
	Vagina Vulva	+ −	Date of discovery		Clinical course	Improved No change Worsened Others		
	Others (Brain symptoms, hematuria, etc.	+ −	Date of discovery	Locality	Clinical course	Improved No change Worsened Others		
Changes in luteal cyst								
Clinical course	Hyperemesis	+ + +	+ +	+	± −	Clinical course	Improved, No change, Worsened, Others	
	Abdominal pain	+ + +	+ +	+	± −		Improved, No change, Worsened, Others	
	Edema	+ + +	+ +	+	± −		Improved, No change, Worsened, Others	
	Albuminuria	+ + +	+ +	+	± −		Improved, No change, Worsened, Others	
	Blood pressure						Improved, No change, Worsened, Others	
	Others							
Chemotherapy (incl. sex steroid therapy)						Name of drug, total dose, etc.		
Radiotherapy	Kind, total dose, etc.							
Side effects								
Remarks								

Long-term prognosis

Followed by a pregnancy?
Yes No
Remarks on new pregnancy

Abortion
spontaneous before 4. month / after 5. month
artificial
Hydatid mole
Term preg.
Others

Friedman test turned negative days after evacuation

If prophylactically hysterectomy done following evacuation:

1. Date of operation:
2. Technics:
Uterus Subtotal hysterectomy / Total hysterectomy
Ovary Bilateral ovariectomy / right side ovariectomy / left side ovariectomy / None
3. Rough sketch of removed specimens
4. Histological diagnosis
Examiner's name and position
5. Outline of postoperative course:

* This column is not to be filled up by co-operating doctors.