FEMALE GENITAL

HYDATIDIFORM MOLE

+

CHORIOCARCINOMA

TUMORS OF FEMALE GEN. ORGANS

part I.

TUMORS OF THE FEMALE SEX ORGANS

Part 1

HYDATIDIFORM MOLE AND CHORIOCARCINOMA

Arthur T. Hertig, M. D.

and

Hazel Mansell, M. B., B. S.

ARMED FORCES INSTITUTE OF PATHOLOGY

ATLAS OF TUMOR PATHOLOGY

Section IX—Fascicle 33

TUMORS OF THE FEMALE SEX ORGANS

Part 1

HYDATIDIFORM MOLE AND CHORIOCARCINOMA

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Arthur T. Hertig.
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HYDATIDIFORM MOLE AND CHORIOCARCINOMA

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Plate I

A. A chorioadenoma destruens nine weeks following a hydatidiform mole. The single hemorrhagic cavity in the upper left portion of the fundus is typical of this locally invasive lesion. The cavity contained an invasive hydatidiform villus not seen in the picture. (Such invasive villi may be seen, however, in figures 51 to 54 and 63.) In the left parametrium an arrow points to a metastasis composed of neoplastic trophoblast. This is an atypical but occasional feature of chorioadenoma destruens. In spite of such a metastasis the patient was known to be alive and well more than six years postoperatively. Note the lack of theca-lutein cysts in the ovaries. (Courtesy of Dr. Harry Finkel, Boston, Mass.) B. L. I. H.* S–46–1417; A. F. I. P. Acc. No. 218754–473.

B. A typical choriocarcinoma of the uterus which was diagnosed by curettage and confirmed by hysterectomy four months following a normal pregnancy. The patient died one year postoperatively with widespread metastases. Note the solid but variegated appearance of the tumor. Although the ovaries contain small follicular cysts they have not reached the enormous size attained in some cases of hydatidiform mole and choriocarcinoma (fig. 13). (Courtesy of Dr. Earl Clark, Providence, R.I.) S–46–1832, Rhode Island Hospital, Providence, R. I. B. L. I. H. S–46–531; A. F. I. P. Acc. No. 218754–475.

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HYDATIDIFORM MOLE AND CHORIOCARCINOMA

HYDATIDIFORM MOLE AND CHORIOCARCINOMA OF THE UTERUS

INTRODUCTION

The syndromes of hydatidiform mole and choriocarcinoma, though clinically and pathologically essentially different, are usually discussed together because the former often precedes the latter. Thus it is that when the uncommon condition of hydatidiform mole is followed on occasion by the rare, fatal choriocarcinoma, these two conditions are reflexly linked together in the physician's mind. It matters little that the vast majority of patients with hydatidiform mole survive, many subsequently to become normally pregnant, or that at least half the choriocarcinomas are preceded by other forms of pregnancy; the initial villous "degeneration" and subsequent malignancy are still regarded as a single entity by many doctors.

Trophoblast even in its most benign form shows to a profound degree the attributes of invasion, endothelial response, intravascular permeation, and ultimate transport of such epithelium to the lungs. It is not surprising, therefore, that a hydatidiform mole should, on occasion, realize the full clinical potential of trophoblastic malignancy; for it, of all forms of pregnancy, remains nearest to the state of placental development when all trophoblast possesses most fully those criteria of malignancy exhibited ordinarily only by cancer. Trophoblast, therefore, should serve as an excellent tool with which to study the problems of invasion, and of metastasis in general. Why should the early trophoblast of the 7-day ovum invade rapidly and progressively while its more mature derivative usually comes to rest within a millimeter or two of the myometrium? Why should trophoblast be transported to the lungs but only that of the choriocarcinoma be capable of sustained growth? If we knew the answers to these two simple questions, the phenomena of invasion and metastasis—the two fundamental factors which make cancer differ from normal tissue—would be understood vastly better than they are now.

Pathogenesis of Hydatidiform Mole

A hydatidiform mole results from the progressive accumulation of fluid within the connective tissue spaces of the chorionic villi of the pathologic ovum—the conceptus in which the embryo is absent or dies during the third to fifth week of development, a period which coincides with the time when the fetal and chorionic circulations are anatomically complete and begin to func-

tion. Thus, deprived of a functioning fetal circulation, although still nourished maternally and thereby possessing a functioning trophoblast, the immature villi containing loose mesenchymal tissue swell segmentally to form multiple isolated cysts. These grapelike bodies, now simulating the previllous ovum, exhibit various degrees of trophoblastic activity ranging from the normal through stages of hyperplasia, undifferentiation, to apparent neoplasia. The isolated villous segment thereby acquires to a variable extent the invasiveness of the early ovum. It is upon this thesis that the pathologic and clinical manifestations of this uncommon but important entity can best be explained.

Supporting evidence for this thesis of the pathogenesis of hydatidiform swelling, namely the presence of a functioning maternal circulation and the absence of a fetal one, may be seen in the normal developing placenta. Hydatidiform villi are frequently seen at the junction of the chorion frondosum and the chorion laeve of a normally developing placenta (fig. 4). Moreover, as placentas mature, small to large foci of true hydatidiform swelling occur on rare occasions. This is probably associated with the fact that as older villi continue to grow, their newer branches possess immature trophoblast, loose mesenchymal stroma, and discontinuous vascular primordia (Hertig, 1935). Hydatidiform swelling in these newer villous branches could result from the failure of such vascular primordia to reunite with the parent vascular system from which they were originally derived. This fact may, therefore, explain the rare presence of marked hydatidiform swelling of significant portions of the placenta associated with a normally developed fetus. Three such cases have been observed by the senior author in 22 years.

Therefore, wherever it occurs, hydatidiform swelling of chorionic villi appears to depend on a continuing maternal circulation, an actively functioning trophoblast, but a nonfunctioning fetal circulation with consequent disappearance of villous vessels from a loose-textured immature mesenchymal type of connective tissue.

A hydatidiform mole is in no sense a true neoplasm, although its trophoblast is normally capable of invasion and vascular transport and may on occasion give rise to choriocarcinoma, which is a true neoplasm.

Spontaneous abortion occurs in approximately 10 percent of all pregnancies, and approximately one half of such abortuses are pathologic or blighted ova (fig. 5). The chorionic villi show early hydatidiform swelling in two thirds of such abnormal pregnancies (figs. 6, 7) and in lesser numbers of abortuses containing fetuses. Hence, between 3 and 4 percent of all pregnancies are potential hydatidiform moles, but they fortunately terminate as abortions before this potentiality is realized. In contrast, the mature form of this condition, a true hydatidiform mole (figs. 10, 11), occurs only once in approximately 2,000 pregnancies, or an incidence of 0.05 percent.

Potential hydatidiform moles tend to abort during the eleventh week, whereas true hydatidiform moles usually are delivered during the eighteenth week of gestation. Thus the classic mole, in which hydatidiform swelling of the villi has increased from microscopic to macroscopic size, can be described as a missed abortion of a pathologic ovum. The absence of a functioning fetal (and hence chorionic) circulation is presumably the factor which allows the products of trophoblastic secretion or imbibition or both to accumulate in the still viable villi.

Chemical studies in our laboratory by McKay et al. on the fluid aspirated from living molar villi show that it is of interstitial type and essentially similar in its composition to other environmental fluids such as ascitic and edema fluid and that of the normal tendon. Moreover, water is retained within the molar villi against the force of a higher osmotic pressure exerted by the surrounding maternal serum. Other evidence of activity by molar trophoblast is shown by the relatively high concentration of amino acids within the molar fluid as compared with that of the surrounding maternal serum.

As would be expected, transitional forms in the genesis of hydatidiform mole (figs. 8, 9), representing varying degrees of hydatidiform swelling, are also found between the eleventh and eighteenth weeks of gestation. These early and intermediate stages in the formation of hydatidiform mole show little alteration of trophoblastic histology or pattern. For this reason their clinical course is apparently that of a spontaneous abortion rather than of a hydatidiform mole. It is possible, however, that choriocarcinoma following abortion may arise from such a transitional hydatidiform mole, the true nature of which was not recognized clinically or pathologically.

The morphologic sequence of events leading to formation of a hydatidiform mole is seen in figures 1 to 13. Details of this process have been published by Hertig and Edmonds.

Histogenesis of Trophoblast—Its Relationship to Hydatidiform Mole and Choriocarcinoma

The earliest known stages of trophoblastic development are found in specimens of the eighth to tenth days of development. The trophoblast of the 7½-day specimen is solid and composed of primitive syncytiotrophoblast and cytotrophoblast (fig. 14).

In the 9-day specimen, the primitive syncytiotrophoblast is more abundant, tending to peripheral arrangement, and is becoming vacuolated. The primitive cytotrophoblast, now tending to surround the chorionic cavity, is beginning to form small masses which are destined to be the primordial villi (fig. 15).

The trophoblast of the twelfth and thirteenth days of development, now about to form villi, shows coalescence of the syncytiotrophoblastic vacuoles to form the future intervillous space. The cytotrophoblastic masses are rapidly grow-

ing peripherally and are beginning to penetrate the syncytiotrophoblast (figs. 16, 17).

The trophoblast of the fourteenth to the sixteenth days of development, now forming early villi, is composed of irregular cytotrophoblastic columns extending from the chorionic membrane to the floor of the developing placenta. The cytotrophoblast of these primordial villi is covered by syncytiotrophoblast, which in turn lines the intervillous space. The latter, thus completed by coalescence of syncytiotrophoblastic vacuoles, now contains increasing amounts of maternal blood (figs. 18, 19).

The trophoblast of the potentially malignant hydatidiform mole (figs. 23–42) more or less recapitulates the normal stages of the trophoblastic development of the 7-day to 12-day ova as seen in figures 14–17.

Many moles, on the other hand, possess trophoblast of very low, if any, malignant potential (figs. 20, 21) and resemble therefore the villi of the first trimester of pregnancy (fig. 22). The trophoblastic pattern of choriocarcinoma (figs. 57, 58), however, resembles that of the early villous ovum of the fourteenth day (figs. 18, 19).

It is, moreover, apparent that there is considerable difference between the solid and vacuolated trophoblast of the normal previllous ovum and the columnar pattern of that in the early villous stage. A similar difference also exists between the trophoblast of potentially malignant moles (no matter how atypical they may be) and the very occasional choriocarcinoma that may result therefrom. Stated differently and in a more practical manner, the trophoblast of even the most potentially malignant moles never, in the authors' experience, looks quite like the trophoblast of the choriocarcinoma which may follow it (figs. 39–42). Unless this fact is clearly realized by pathologists and clinicians alike, uteri will be removed unnecessarily.

Why any mole should become locally invasive or truly malignant is unknown, but the general resemblance of the individual molar villus to the implanting ovum is often striking. Hence it is not surprising that molar villi possessing such primitive trophoblast should, on occasion, invade maternal tissue. On the other hand, why the very occasional mole becomes truly malignant and kills by metastases from choriocarcinoma is no more clear than the etiology of any cancer.

While it is impossible to determine from examination of the mole whether or not it will become truly malignant, yet the more potentially malignant it looks, the greater the statistical chance of malignant sequelae, namely local invasion (chorioadenoma destruens) or true malignancy (choriocarcinoma). (See table II.)

For further details of trophoblastic development during implantation and early villous formation, the reader is referred to the papers of Hertig and Rock, and Heuser, Rock, and Hertig.

Classification (Grouping) of Hydatidiform Moles

The original histopathologic classification of hydatidiform mole (figs. 20–42) proposed by Hertig and Sheldon in their clinicopathologic correlation of 200 cases, based on an objective examination of the mole itself but without reference to the patient's curettings, uterus, or clinical history, is given in table I.

Table I*

HYDATIDIFORM MOLE CLASSIFICATION

Group	Name	Histologic criteria	Number of cases	Number of malignancies
I	Benign	None to slight hyperplasia of the trophoblast.	22	0
II	Probably benign	Slight to moderate hyperplasia.	30	2
III	Possibly benign	Hyperplasia with slight anaplasia.	33	4
IV	Possibly malignant	Moderate anaplasia with hyperplasia.	59	10
V	Probably malignant	Marked anaplasia with hyperplasia.	39	20
VI	Malignant	Exuberant trophoblastic growth (variable mitotic activity) with marked anaplasia and often evidence of endometrial invasion.	17	17
	Total.....	.....	200	53

*This is table I in Hertig, A. T., and Sheldon, W. H. Hydatidiform mole—a pathologico-clinical correlation of 200 cases. Am. J. Obst. & Gynec., 53: 1–36, 1947.

When the endometrium or uteri from these 200 cases were examined and the clinical histories evaluated, 53 cases were found which lay within the whole spectrum of morphologic or clinical chorionic malignancy. The distribution of these 53 choriomas with respect to the histologic grouping of the associated mole is given in table II.

It is thus apparent from both tables that there is a general but by no means specific correlation between the apparent morphologic malignancy of the mole and its effect upon the patient or her uterus. Furthermore, not all of these so-called choriomas are of equal clinical malignancy, as shown in table III.

Table II*

GRADES OF 53 UTERINE CHORIONIC MALIGNANCIES DISTRIBUTED ACCORDING TO MOLAR GROUPS IN 200 CASES OF HYDATIDIFORM MOLE

	I	II	III	IV	V	VI	Total cases	Percent
Chorionepithelioma in situ	0	..	..	1	1	5	7	3.5
Syncytial endometritis	0	..	1	1	3	4	9	4.5
Chorioadenoma destruens	0	2	3	8	13	6	32	16.0
Choriocarcinoma	0	..	..	..	3	2	5	2.5
Total chorionic malignancies	0	2	4	10	20	17	53	26.5
Cases in each molar group	22	30	33	59	39	17	200	100.0

*This is table II in Hertig, A. T., and Sheldon, W. H. Hydatidiform mole—a pathologico-clinical correlation of 200 cases. Am. J. Obst. & Gynec., 53:1–36, 1947.

Table III*

FOLLOW-UP DATA ON CHORIONIC MALIGNANCIES

Grade	Cases	Subsequently pregnant	Living and well		No data	Died	Percent cured	Remarks
			with uterus	without uterus				
Chorionepithelioma in situ	7	2	2	3	0	0	100	No deaths
Syncytial endometritis	9	0	2	6	0	1	89	1 death, sepsis
Chorioadenoma destruens	32	0	0	27	4	1	97	1 death, sepsis
Choriocarcinoma	5	0	0	0	0	5	0	5 deaths, choriocarcinoma
Total	53	2	4	36	4	7	86.6	

*This is table IV, slightly modified, in Hertig, A. T., and Sheldon, W. H. Hydatidiform mole—a pathologico-clinical correlation of 200 cases. Am. J. Obst. & Gynec., 53:1–36, 1947.

CHORIOMAS

Chorionepithelioma in Situ (figs. 43, 44, 46, 47)

This is a term introduced by Hertig and Sheldon to describe a small discrete mass of superficially invasive, apparently malignant trophoblast without villi found in uterine curettings associated with any type of pregnancy but usually with a hydatidiform mole. That this may not be the early stage of a true choriocarcinoma is suggested by the facts that (*a*) it is not morphologically identical with the typical plexiform pattern exhibited by choriocarcinoma (figs. 57, 58), and (*b*) none of these cases was followed by fatal choriocarcinoma. Indeed, of the four patients who retained their uteri, two became normally pregnant subsequent to the molar gestation (table III), the other two were well from four to five and one-half years later, while the three who underwent hysterectomy were alive and well from one and one-half to a little more than three years later.

Irrespective of whether this lesion is or is not the incipient form of choriocarcinoma, it does not resemble the trophoblast usually seen in cases of retained secundines following pregnancy. Moreover, it was associated largely with "malignant" moles (group VI), although two cases were associated with moles of groups IV and V.

Syncytial Endometritis

Syncytial endometritis (fig. 45) is also of doubtful significance with respect to its malignant potential. It has usually been regarded in standard classifications as an atypical chorionepithelioma or one of very low grade malignancy. Pathologists now generally agree, and the authors concur, that this histopathologic picture is merely an accentuation of the morphology of the placental site. Endometrium and myometrium are infiltrated by trophoblastic cells with variable degrees of inflammation. That this lesion is benign is apparent from clinical followup of these cases (table III), a specific case from which is illustrated in figure 45. Of significance is the fact that the patient was alive and well four years after curettage, the only treatment she received for her molar pregnancy. Possibly choriocarcinoma may arise from such placental site trophoblast, although definite proof is lacking. It must be emphasized from a purely practical standpoint that syncytial endometritis is sometimes morphologically similar to choriocarcinoma. Indeed, the normal cells of the postpartum placental site often appear abnormal to those unfamiliar with its morphology (figs. 48–50). It deserves more study by the general pathologist. Misdiagnosed cases of syncytial endometritis, since they are clinically benign, probably contribute to the number of so-called cured cases of chorionepithelioma. At any rate, it may be significant that the number of our cases of syncytial endometritis increased in proportion to the undifferentiation of the molar trophoblast that preceded them (table II).

Chorioadenoma Destruens

Chorioadenoma destruens (Ewing) is the lesion produced when one or more molar villi and associated trophoblast invade the myometrium or its blood ves-

sels or both (figs. 51–54). That these invasive moles are clinically benign is attested to by the fact that, of the 32 cases in Hertig and Sheldon's series, the only death was due to diffuse peritonitis following hysterectomy (table III). In spite of the usually benign outcome of chorioadenoma destruens, clinically evident metastases may occur. In such rare instances, the uterine lesion shows morphologic evidence of choriocarcinoma as well as invading villi.

All groups of moles with the exception of the histologically benign group I of Hertig and Sheldon's series (figs. 20–22) are potentially able to invade the uterine musculature. This invasive potential is, in general, correlated with the degree of hyperplasia, anaplasia, and apparent neoplasia (table II). It would not be surprising, however, if even a benign hydatidiform mole should on occasion become locally invasive, in view of the ability of normal trophoblast to invade myometrium in cases of placenta accreta (fig. 48), increta, or percreta (Irving and Hertig).

Choriocarcinoma

Choriocarcinoma (Ewing), in contrast to all other forms of chorioma, is usually fatal (figs. 55–62, pl. I–B). Such was the case in all five of the patients recorded in table III. The tumor is composed of pure trophoblast (figs. 55–58) and exhibits a characteristic plexiform pattern (figs. 40, 42, 57, 58). This pathognomonic feature is due to anastomosing cords of cytotrophoblast covered by syncytiotrophoblast. The latter also form the lining of blood-filled spaces which are analogous to the primitive intervillous space of the 14-day ovum (figs. 18, 19).

While choriocarcinoma may follow any form of pregnancy, approximately one half of these rare tumors are the result of hydatidiform moles. Even though it is not possible to foretell with absolute accuracy whether or not an individual mole will be followed by choriocarcinoma, it is significant that all of Hertig and Sheldon's cases were associated with those moles diagnosed microscopically as either probably malignant (group V) or definitely malignant (group VI). This suggests that the original histopathologic criteria used by these authors in classifying hydatidiform moles were too finely drawn. For all practical purposes moles of groups V and VI are obviously not significantly different, since three choriocarcinomas followed the "probably malignant" variety while two followed those designated as "malignant" (table II).

Therefore, this histopathologic classification of hydatidiform moles with respect to their apparent potential of malignancy might be simplified as in table IV.

The authors, however, continue to use their original classification for teaching purposes, since there are morphologic differences between the various groups. It is obvious that the clinical significance of such morphologic variants is not yet fully understood.

Table IV

SUGGESTED NEW CLASSIFICATION OF HYDATIDIFORM MOLES

New grade	New name	Old group	Old name
1	Apparently benign	Group I.....	Benign.
2	Potentially malignant	Group II.....	Probably benign.
		Group III.....	Possibly benign.
		Group IV.....	Possibly malignant.
3	Apparently malignant	Group V.....	Probably malignant.
		Group VI.....	Malignant.

THE ROLE OF THE PATHOLOGIST IN THE EVALUATION OF HYDATIDIFORM MOLE

There is no certain method of diagnosing a hydatidiform mole except by the recovery of the characteristic vesicles. Even though sooner or later these pathologic pregnancies will terminate spontaneously, rarely does the patient pass these vesicles prior to the delivery of the entire specimen. Hence the diagnosis, though suspected on clinical grounds (bleeding, disproportionately enlarged uterus, abnormally high chorionic gonadotrophic hormone titers, enlarged cystic ovaries, and absence of fetal skeleton and fetal heart tones), rests upon gross examination of the specimen.

In order to evaluate fully the morphologic malignant potential of any hydatidiform mole, tissue from at least 8 to 10 different areas of the specimen must be taken for microscopic section. Clusters of villi, not merely individual vesicles, must therefore be selected. This is necessary because within the molar mass the most atypical trophoblast often lies between the vesicles or on the surface of blood clot. Hence sections of the blood clot are important in the evaluation of a mole.

It is most important to section all the associated endometrial curettings, preferably at several levels. This tissue should be submitted with the mole but in a separate container. Too often the surgeon neglects to submit them at all, let alone keep them separate from the main specimen. Aside from the obvious therapeutic value of a curettage, the curettings give the pathologist the best opportunity to evaluate the prognosis. This is due to the fact that the placental site trophoblast is not only within maternal issue but is usually morphologically less differentiated than the trophoblast of the mole itself.

Even though there is a good general correlation between the microscopic appearance of a hydatidiform mole (and its associated curettings) and the clinical outcome of the patient in a large series of cases (tables I and II), it is impor-