CLASSIFICATION AND TRANSITIONS IN CHORIONIC TUMORS

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Attempts at classification of tumors arising from the placenta started with Marchand who first recognized the chorionic rather than the maternal origin of the tumor we now know as choriocarcinoma. He divided chorionic tumors into: (a) typical — which consisted of the actively growing and metastasizing tumors and (2) atypical — which consisted of the less active tumors composed mainly of giant cells (3,11). Ewing introduced the term chorioma to designate a tumor arising from the cells of the chorion (4). The classification by Ewing in 1910 into choriocarcinoma, chorioadenoma destruens, and syncytioma has gained the greatest popularity and has persisted to the present with slight modification. Other terms have been used to signify the same entities: chorion-epithelioma which Marchand originally gave for choriocarcinoma; invasive mole, destructive mole, penetrating mole, malignant mole and metastasizing mole for chorioadenoma destruens; and syncytial endometritis for syncytioma. Hydatidiform mole, because of its obvious close relationship to the other choriomas, has since been added to this group of tumors. In 1947 Hertig and Sheldon subdivided the ordinary hydatidiform mole into six groups for purposes of prognostication which later was reduced to 3 grades (6, 7). This grading depended on the degree of hyperplasia, anaplasia, and neoplasia of the tumor. More recently, Sutomo in 1956 proposed the term villous choriocarcinoma to designate the invasive variants of mole and non-villous choriocarcinoma to those showing no villous patterns, including the syncytioma and the typical choriocarcinoma (18). These are aside from the ordinary hydatidiform mole. Obviously, these classifications were intended to correlate the clinical manifestations with the pathologic findings in order to reduce the confusion that these tumors have created in the clinician as

well as the pathologist. The confusion is the result of many variable and inexplicable outcomes encountered very frequently in these tumors.

Our purpose is mainly to give emphasis to certain observations on the progression or regression of this group of tumors that may account for their apparent clinical unpredictability. Only by knowing these possible pathways of transition can one fully understand why these tumors behave in such an enigmatic manner. The key to the enigma lies in the different pathways that trophoblasts may follow, depending on factors not yet fully understood and probably residing not only in the cells themselves but also in the environment of the host tissues.

It is definitely established that choriomas, as implied in the name given by Ewing, arise from the chorion of the product of conception. In this sense choriomas must all be derived from the developing fertilized ovum. The tumor cells in these neoplasms arise from one of the earliest cells that differentiate in the developing embryo: the trophoblasts. It is theoretically possible that the fertiltized ovum will, from the very start, give rise only to primitive malignant trophoblasts without producing the embryonic cells of the inner cell mass from which the future embryo finally develops. Because of the lapse of time that precedes choriomas and the relatively short period within which trophoblasts and the inner cell mass differentiate in the early 4-day-old fertilized ovum (9), it is more likely that almost always they arise from already well-formed trophoblasts that have become malignant.

Comparatively speaking, the histological appearance of choriocarcinoma mimics very closely the pattern of the trophoblasts in the early previllous developing ovum (7, 9). It is also of interest that the destructiveness of the trophoblasts at this early age of pregnancy simulates very closely the destructiveness of choriocarcinoma (13). In short, choriocarcinoma can be classed as a tumor whose pattern assumes the most immature form of differentiation considering that it reduplicates cells the maturity of which is only a few days old (12-15 days). It can be said that the morphologic aspects of this tumor repeats the earliest stages of embryogenesis. From this point of view, it is also theoretically possible that occasionally

rare villous formation may occur depending upon the degree of differentiation or undifferentiation the malignant trophoblasts may follow. These villi are, of course, aside from those that may remain from the original pregnancy, abortion, or hydatidiform mole. While in most instances, therefore, villi may be regarded as tending to support a diagnosis other than choriocarcinoma, in rare cases where there is overwhelming trophoblastic activity and anaplasia, one or two villi need not necessarily rule out the possibility of choriocarcinoma.

It is generally agreed that choriocarcinoma follows a mole, an abortion or a term pregnancy all of which represent an end product of conception. An exception to this general rule is, however, pertinent. The germ cell of either male or female or any pluripotential cell that has the potentiality of giving rise to teratogenous growths may also be capable of trophoblastic differentiation. In this way, therefore, teratogenous growths may give rise to choriocarcinoma not necessarily resulting directly from a product of conception. This genesis explains the rare cases of choriocarcinoma found in male or pre-pubertal females usually of gonadal origin, as well as still rarer choriocarcinomas of extrauterine, extragonadal, and usually of midline origin. Other than these exceptions, therefore, all choriocarcinomas must arise from trophoblastic cells which ultimately must be regarded as sequential to conception.

It is to be assumed that choriocarcinoma following a term pregnancy or an abortion arises from trophoblasts that have somehow gained a nidus in the uterus and have failed to be expelled with the rest of the placental elements. Initial manifestations in such instances are primarily in the uterus although occasionally the primary focus in the uterus may remain small and undetected clinically while the metastases manifest themselves more prominently in whatever organ they may be located. In such instances, the genital manifestations are absent or nil so that the clinician is often confused or even misled in his diagnosis.

Not infrequently one encounters benign trophoblastic deportation to the lungs in pregnant woman (3, 10, 13, 20). This should be regarded as a consequence of the unusual invasive capacity of trophoblasts including invasion of the uterine sinuses,

even in normal pregnancies. From these sinuses the trophoblasts, no doubt, can easily be transported to the lungs where they are filtered. These must, however, be regarded as mere mechanical benign deportations and not as true metastases. The chances of molar trophoblasts to be transported to the lungs are similar, if not greater, because of a neoplastic aspect present in the hydatidiform moles. If perchance these transported trophoblasts cells remain viable and are somehow activated into malignant growth, then they can give rise to a choriocarcinoma manifesting itself initially in the lungs. This possibility may also explain certain choriocarcinomas without any apparent primary lesions in the uterus (13, 19).

The fact that the majority of choriocarcinomas follow hydatidiform moles suggests the presence of a factor or factors in moles, not sufficiently present in pregnancies terminating either as term deliveries or as abortions that predispose to the development of this highly malignant and fatal tumor. Hertig and Edmonds in their classic study of the genesis of hydatidiform mole concluded that moles usually resulted from either a failure or a defective development of the embryo resulting in nondevelopment of the fetal circulation in the presence of an intact maternal circulation and functioning trophoblasts (8). This apparently explains the degenerative aspects of moles but does not satisfactorily explain the proliferative aspects of moles bordering neoplasm or actually neoplastic in character. Opinions as to the possible explanation of this phenomenon may be postulated, but the final explanation will probably await the perennial problem of what is the ultimate cause of neoplasm. It is this neoplastic tendency, prominently noted in moles and not found in the other types of pregnancy, which undoubtedly predisposes to the development of choriocarcinoma. The malignant potentiality of the trophoblasts in moles obviously is greater than that seen in either abortions or in term deliveries which ordinarily manifests proliferative activity within bounds of what is regarded as normal in contrast to the varying degrees of proliferation, anaplasia, and neoplasia observed in moles. The neoplastic nature of moles contributing to their malignant potentiality is further supported by the general correlation between morphologic variation and clinical malignancy as attested by the studies of various authors (6, 7, 10).

The term "invasive" mole should be used to designate a mole that has shown invasion of the structures beyond the ordinary confines of trophoblastic invasion in a normal pregnancy. Invasion of any structure by direct contiguity beyond these limits in the uterus serves to differentiate an "invasive" mole from a "metastasizing" mole which should show molar elements transported to other organs or structures not showing any direct contiguity with the original uterine molar mass. These two types of mole can be rightfully classed under the more encompassing term "malignant" hydatidiform mole. It is admitted that the term "malignant" in this instance is a "modified" form of malignancy because the true malignant nature of the "metastasizing" and invasive moles as implied in the terms used to qualify them, is not in the true sense of malignancy as their clinical outcomes are not always predictable in spite of their "metastasizing" or invasive tendencies. The term "malignant" mole, therefore, is used more to distinguish these variants of mole from the ordinary noninvasive and nonmetastasizing mole rather than imply a dark prognostic significance as is usual for truly malignant tumors. To the moles that show neither invasion nor "metastasis" the term "benign" mole is assigned in contradistinction to the "malignant" ones as already described. Because of their different behavior simulating malignancy, "malignant" moles have to be designated under a different category that will make them distinguishable from their more benign counterparts. In view of these distinguishing characteristics, therefore, we have divided hydatidiform moles into 2 big categories: the ordinary "benign" mole which is limited to the endometrial cavity and the "malignant" mole which, in turn, may be subdivided into the "invasive" and "metastasizing" varieties. The term "benign" as used in this sense, however, does not necessarily eliminate the potentiality of these types of hydatidiform moles to precede choriocarcinoma as is generally agreed. These moles can vary morphologically from the very innocuous to the very hyperplastic and anaplastic patterns. Distinguishing these types of mole from the evacuated molar material and curettings would naturally also follow the general correlation between morphologic variation and clinical malignancy as stated earlier.

The invasive property of trophoblastic tissue is apparently accentuated in the invasive mole as defined above. Invasion is a property ordinarily ascribed to malignant tumors, but because the prognosis in these instances is not necessarily dark due to the usually localized nature of the invasion, it is doubtful if classification under the truly malignant tumors is warranted. On the other hand, there is no doubt that if the invasion is extensive it can lead to perforation of the uterus, widespread infection and hemoperitoneum which may be fatal in outcome. The invasive potentiality of a mole, like its potentiality to precede choriocarcinoma, can be correlated with its morphologic variation. On the premise that any trophoblasts when activated can give rise to choriocarcinoma, it is not presumptuous to assume that invasive moles can also precede choriocarcinoma if and when the factor or factors responsible for malignant transformation are present.

The metastasizing mole apparently exhibits a feature of greater malignancy than the invasive mole. In this variant of mole the metastatic lesions may be found in any part of the body but more prominently in the lungs and vagina (1, 15, 17, 18). There are 2 possible ways by which villi may get into the lungs or to any other distant organ not in contiguity with the original mole in the uterus. The villi may be carried by the blood stream to these organs or they may develop within these organs by a process of differentiation of trophoblasts that have been carried to these sites. In the latter instance the villi are formed "in situ" in the organs where the differentiating trophoblasts have lodged. In invasive moles, the possibility that trophoblasts with their accompanying villi may invade sinuses and from there be transported to the lungs is great. The transported structures, if capable of autonomous growth, may persist and thus can now be called a metastasizing mole. A metastasizing mole may, therefore, coexist with an invasive mole. If on the other hand, these structures are not capable of autonomous growth, then they undergo degeneration (see later discussion of syncytioma) and finally disappear. The extent, size, as well as the location of the dissemination will obviously determine the prognosis in these instances. In a case reported by Delfs (2), the metastases are in relatively unimportant structures and this apparently led to an extended course. If on the

other hand, these are located in strategic positions as the brain, they can no doubt be rapidly fatal. One would expect also that multiple lesions in the lungs though benign morphologically may give rise to massive bleeding. This type of mole, therefore, though morphologically benign, is clinically malignant. It may be likened to the well-differentiated carcinoma of the thyroid which morphologically is indistinguishable from the normal such that it was previously designated as a "lateral aberrant thyroid." The good morphologic differentiation may be indicative of its slow growth as observed clinically. The over-all evaluation of the metastasizing mole appears to indicate predominantly malignant features rather than benign ones but a categorical statement to this effect has to await further studies on this unusual tumor. A malignant transformation into frank choriocarcinoma is not beyond reasonable bounds in this instance where cells composing the tumor are even more capable of autonomous growth. It should be emphasized, however, that the transported trophoblasts do not always remain viable in their secondary sites of deposition and therefore the criteria for metastasis are not always satisfied (1). True metastasis calls for transportation of tumor cells to a distant site, followed by growth of these cells in this secondary site.

Syncytioma or syncytial endometritis has been of even more controversial nature. The true neoplastic nature of this tumor has been questioned (3, 7, 13) so that the designation syncytial endometritis has been applied especially when the inflammatory response is very prominent. Ewing believed, to which the author concurs, that the trophoblasts found in this lesion are actually regressing rather than progressing (3, 4). The lesion appears to be an accentuation of the invasive property of the placental site giant cells which normally may be found as deep as the myometrium especially at the site of implantation of the original placenta (7). Because of its close relationship to trophoblastic tumors, however, in spite of its doubtful neoplastic nature, this lesion should rightfully belong to this class of tumors.

The placental giant cells have been regarded as individual trophoblasts that have broken off from the original trophoblastic shell and have wandered into the decidual or myometrial layers (3, 4, 7, 13, 14). Ordinarily this is of no consequence

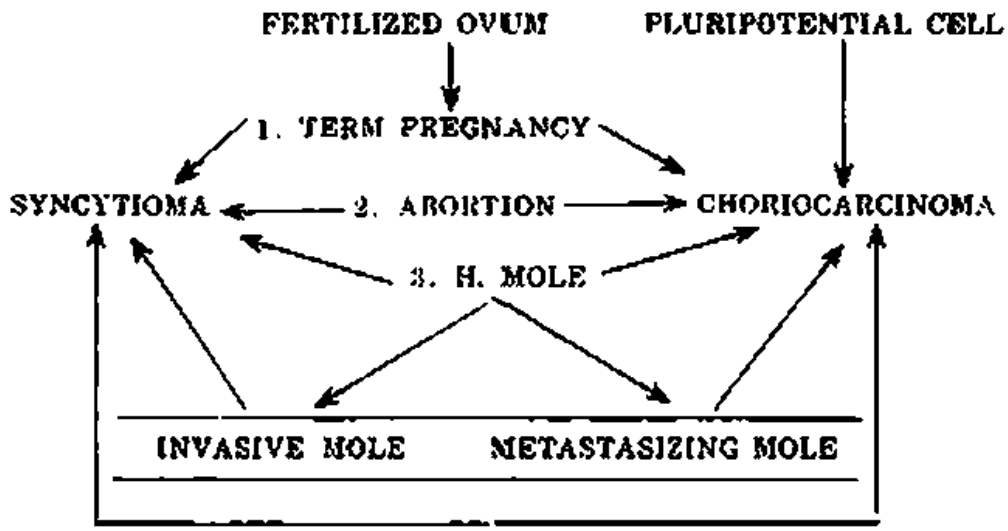
but when several of these cells are left in the placental site, they apparently prevent the normal healing of the denuded endometrial cavity and induce considerable hemorrhage. These effects may be attributed to the retention of vasodilating and anti-coagulating substances, enzymes, and other factors usually found in trophoblasts (9, 21). Recently histochemical studies seem to indicate that these cells are of cytotrophoblastic origin (12). The inflammatory cells incident to the presence of these cells, which normally should have undergone spontaneous regression, appear to be a reaction to the lesion and vary considerably in quantity. The symptoms and even the pathologic changes that may be produced by this lesion may closely simulate choriocarcinoma.

Since these cells are derived from trophoblasts, it is not improper to deduce that they may create the same lesion wherever trophoblasts may be transported. While, heretofore, syncytioma has been described only in the uterus, there are indications that its location is not limited to this organ (1,5). Wherever trophoblasts are transported, a syncytioma may also develop (1). This type of lesion is, however, more frequently seen when the transported trophoblasts have a greater malignant potentiality as in the higher grades of mole described by Hertig and Mansell than when they come from an ordinary pregnancy. The cells in this category produce much less injury to the host tissue than metastasizing mole and certainly are not malignant like choriocarcinoma. When found in the uterus, this lesion may regress spontaneously or may subside after a curettage, not necessitating a more radical procedure as a hysterectomy. In the same token, lesions produced elsewhere in the body are similarly more innocuous and may disappear spontaneously. The symptoms manifested and the outcome produced will no doubt depend on the location, size, and number of lesions present. Since these are viable trophoblasts, although possibly undergoing regressive changes, the theoretical possibility that they may still possess malignant potentialities cannot be completely ruled out. This possibility has, up to the present, not been substantiated. For want of a more appropriate name, "extra-uterine" syncytioma is proposed for this type of extra-uterine lesion whose genesis is similar to that of

its uterine counterpart. Obviously, the name syncytial endometritis cannot be applied to a lesion outside the endometrial confines.

Frequently, densities in the lungs are seen radiologically after an ordinary benign or an invasive mole (16). These lesions that regress spontaneously are probably extra-uterine syncytiomas. It is, however, conceded that even well developed choriocarcinoma, for unknown reasons, may undergo spontaneous regression. It has been noted that such regressing choriocarcinomatous foci may produce changes morphologically similar to those of extra-uterine syncytioma (1).

In view of the foregoing discussion, the following diagram to illustrate the development and transitions in choriomas is presented: Invasive mole and metastasizing mole are blocked to indicate that both may give rise to either syncytioma or choriocarcinoma.



The following modified classification of chorionic tumors is also proposed:

CHORIONIC TUMORS

A. Hydatidiform mole

1. Benign hydatidiform mole
2. Malignant hydatidiform mole

a. Invasive mole (chorioadenoma destruens)

b. Metastasizing mole

B. Choriocarcinoma

C. Syncytioma

1. Uterine syncytioma (syncytial endometritis)

2. Extra-uterine syncytioma

Since tumors need not necessarily include only neoplastic conditions, there can be no objection to this classification even when syncytioma and hydatidiform mole may be claimed to be not truly neoplastic in nature. In both conditions tumoral lesions are produced.

SUMMARY

The enigmatic manner with which chorionic tumors behave has been conceded by most clinicians and pathologists. This uncertainty in the behavior of these tumors has created some confusion in the original classification by Ewing into choriocarcinoma, chorioadenoma destruens, and syncytioma. Without deviating considerably from this original and classic classification, a better understanding of these tumors can be obtained by a study of the possible pathways of transition that trophoblasts may follow depending on factors not yet fully understood.

The genesis of choriocarcinoma from trophoblasts and pluripotential cells of the body explains choriocarcinoma after a mole, abortion, or a term pregnancy and teratogenous choriocarcinoma. The very great similarity between this tumor and early pregnancy is stressed. The possibility of potentiality malignant trophoblasts to be deported via the blood stream to other organs and there developing extra-uterine choriocarcinoma is explained. The fact that majority of choriocarcinomas follow hydatidiform mole suggests that there is a neoplastic aspect of mole not found in term pregnancy or abortions.

Three varieties of mole are postulated. These are the ordinary "benign" mole which is limited to the uterine cavity, the "invasive" mole which invades by contiguity structures adjacent to the uterine cavity (chorioadenoma destruens), and the

"metastasizing" mole which shows distant "metastasis" of villous structures. The latter two may be considered as "malignant" moles. Again it is conceded that great difficulty is encountered in differentiating these three from each other on the basis of histological examination of the evacuated molar material. Most often diagnosis can be made only after the entire uterus is removed or a biopsy of the lesion outside the uterus is made. In none of these instances, however, is the prognosis usually dark as in choriocarcinoma, although it appears to be a little worse in the order that they are mentioned above. Any-one of these three may also precede choriocarcinoma. The modified meanings of "metastasis" and "malignant" as used in this terminology is explained.

Syncytioma is definitely tumorous in that it is a space occupying lesion but not definitely neoplastic. In fact, it is probably regressive in nature. The lesion appears to be an accentuation of the invasive property of placental site giant cells which are derived from the trophoblasts. More and more cases have been encountered by the author proving that these cells may be seen not only in the myometrium but also in any site where trophoblasts may be transported. Therefore, aside from the uterine syncytioma (syncytial endometritis), the category of extra-uterine syncytioma is proposed. The usual spontaneous regression of these latter lesions may explain densities in the lungs, heretofore considered as choriocarcinomatous, that spontaneously regress. While seemingly benign histologically, they may be fatal depending on their number, size, and location.

A diagram illustrating the origin and transition of chorionic tumors is presented. A new, modified classification of these tumors is proposed.

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