

Transplacental metastasis of malignant melanoma.

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Summary

Malignant metastasising tumors of the pregnant woman usually do not metastasise to the fetus. Although melanoma is not the most frequent malignant tumor in pregnancy, the cases of fetal metastatic melanoma are more frequent as compared with all the other malignant tumors. Five cases of the relevant literature are reviewed and the pathogenetic mechanisms of this exceptional experiment of the nature are discussed.

Key words

Fetal malignant melanoma, melanoma in pregnancy, transplacental metastasis.

In the placentally transmitted melanoma (PTM) the primary tumor, which is present in the mother, crossing the placental barrier, is responsible for metastases in the fetus. From a theoretical point of view, also the contrary is possible, namely that a primary melanoma of the fetus, overcoming the placental filter, metastasises in the maternal tissues. Until now only a primary melanoma of the fetus responsible for placental metastases has been shown (16).

PTM is exceptional due to physical factors, namely related to the presence of the rightly called placental barrier, and to immunological factors. In fact, fetus and mother are two different organisms and the metastases of a tumor leaved from each one of them represent for the other one a homotransplantations. Due to this reason, such a metastasis can take root only in presence of an immunological tolerance.

The placental barrier

The maternal blood in the placenta is discharged into a lake, the intervillous space, into

which project the villi, which are lined by fetal trophoblast. The latter consists of an outer layer of syncytiotrophoblast and an inner cytotrophoblast layer of Langhans. In the villi there are the capillary vessels of the fetus. Therefore, the fetal and maternal circulations are separated by trophoblast, the connective tissue of the villi and the capillary wall. Pressure in the fetal capillary exceeds that of the intervillous space and this pressure gradient may influence tumor cell migration. All physicians know the physiological exchanges between maternal and fetal blood of liquids, gas, electrolytes, sugar and proteins. On the other hand, the discussion is open whether or not tumor cells can pass from the maternal blood to the fetal one and viceversa. Besides the different results reported in the relevant literature and discussed by Potter and Schoeneman (14), there are the real, although exceptional, metastases in the fetus coming from a metastatic maternal melanoma. The passage of tumor cells is anyway exceptional. This is clinically shown by the imbalance between the high number of metastasising tumors of the pregnant mother and the much smaller number of fetal

metastases: It is also histologically shown by the preferential presence of the tumor cells of maternal origin in the intervillous space, namely in the maternal blood, than in the fetal villi. Tumor cells can penetrate the capillaries inside the villi thanks to the partial destruction of the villi due to the tumoral growth. Alternatively, tumor cells could theoretically enter the fetal capillaries during the latter phase of labor concomitant with placental separation (6, 14, 19). Once penetrated within the fetal circulation, the first site of fetal metastasis are the hepatic capillaries, where the tumor cells arrive with the umbilical veins (6, 10). The tumor cells can jump over the liver through the venous duct and give the first metastases to the lung (8) and then in the other organs.

The immunological factors

As above mentioned, the maternal tumor should theoretically be rejected by the fetal immune system, unless it arrives in the fetus before such system becomes immunocompetent. There are data "pro and contra" the role of these immunological factors. The data supporting the role of the immunological factors are numerous and summarized by Stephenson et Al. (19). There are antimelanoma antibodies, there are cases of melanoma healed or improved after administration of antimelanoma antibodies produced in the rabbit or after blood transfusion from subjects recovered and finally after cross transplantation between subjects affected by melanoma. Even the spontaneous regression of a melanoma transmitted to the fetus through the placenta (4, 1) favors the hypothesis of a role played by the immune factors. This is why some Authors tried to induce an immune response in newborns affected by metastases of maternal melanoma, injecting an extract of the tumor itself after irradiation (6) or maternal tissues, hypothesizing the presence in the latter of mutual antigens with melanoma (2).

There are also data talking against the role of the immune factors. The newborns stimulated with tumoral antigens did not improve. Moreover, the findings of an immune inflamma-

tion similar to those ones observed in case of rejection lack in the placenta affected by metastases. Finally, in case of choriocarcinoma, a placental tumor of fetal origin, metastases are hardly found in the fetus, whereas surprisingly metastases are more easily found in the mother (14).

Prevalence of placental melanoma

Although the exact prevalence of PTM cannot be established, this topic is interesting because melanoma is the most frequent metastasising tumor to the fetus among the other malignant tumors of the pregnant woman.

The first reason of difficulty in establishing the exact prevalence of PMT is the not well defined border between benign and malignant (13). From this point of view, the diagnostic difficulties in PTT are largely lower than those ones encountered in establishing the malignancy of a mass arising on a congenital melanocytic nevus or on the normal skin, but they do exist. This is why many Authors include in the series of malignant melanoma only the cases with metastases in the skin, lymph nodes or other organs (17). However, even this apparently selective criterion is sometimes not enough. In fact, the presence of placental metastases due to a giant congenital melanocytic nevus of the fetus without any sign of melanoma was reported. Therefore, not even the presence of metastases at distance can be considered a clue to the diagnosis of melanoma.

Another difficulty is that nobody is able to collect a large series of cases, given the extreme rarity of this disorder. Only putting together the cases of several Authors a series of cases can be collected. Doing so, only five or six cases can be collected in the last century. These cases are heterogeneous both because observed by specialists of different disciplines such as pediatricians, obstetricians, dermatologists and pathologists and because observed in different periods of time with various criteria of evaluation. Moreover another difficulty in reviewing the literature is that sometimes the same case is reported more times by the same Author or by

different Authors. Among the five cases of PTM three cases were reported two times by different Authors, particularly case n. 3 of table 1 by Weber in 1930 and by Holland 19 years later, the case n. 4 by Aronson and by Cavell in the same year and the case n. 6 by Dargeon in 1950 and by Lerman in 1969. This is why Potter and Schoeneman (14) in their important report concerning the metastases of malignant tumors of the pregnant woman metastasising to the placenta and fetus presented as separate cases that one reported independently by Aronson and by Cavell.

These Authors (14) try to establish the frequency of the passage of a malignant tumor from the mother to the fetus. They establish that of 11,087 pregnant women observed in a period of 7 years in 2 hospitals of New York, 11 are affected by malignant tumors, excluding carcinomas in situ and basal cell carcinoma, thus with a prevalence of 1 case every 1,008 pregnant women. As in the States 61,359,844 neonates were born in the period 1950-64, the Authors conclude that in this period 60,872 women are simultaneously pregnant and affected by a malignancy. The Authors examined then all the cases of metastases of maternal tumors to the fetus and placenta in the American literature of the same period and found 7 cases of placental metastases, two of which with metastases even to the fetus. Therefore, the fetus has 1 possibility out of 30,000 of receiving a metastasis by the mother with a malignancy.

The same Authors examined also the whole American literature of any time and found 24 cases (23 when eliminating the case of metastatic melanoma repeated 2 times) of maternal tumor metastasising to the product of conception, particularly melanoma in 11 cases (10 eliminating the case reported 2 times) mammary carcinoma in 4 cases, carcinoma of the stomach and lung respectively in 2 cases, lymphosarcoma, sarcoma, carcinoma of the adrenal gland, of the ovary and ethmoid in 1 case. The placenta is always affected in the 18 cases, in which it is examined and reported. On the other hand, the fetus is interested by metastases in only 8 cases (7 when eliminating the repeated case). Of these 7 cases, 6 are of melanoma and 1 of lymphosar-

coma. Therefore, 6/7 newborns with placentally transmitted metastases have metastases of melanoma, namely 6/10 newborns of mothers with melanoma versus only 1/13 newborn of mothers with other malignancies. The other 4 newborns of mothers with melanoma are free of metastases, only their placenta being affected. Melanoma has another sad primacy, being the malignancy more frequently metastasising to the fetus. This finding is more significant when taking into account that melanoma with its 93 cases (14) is not the most frequent malignancy of the pregnant woman, being surpassed in frequency by mammary carcinoma (298 cases), carcinoma of the cervix (294), leukemia (174) and lymphoma (119). None of these malignancies is able to metastasise to the fetus.

According to Trozak et Al. (21) only 3 cases of PTM are proven, namely that one of Weber-Holland (10, 22), that one of Dargeon et Al. (6) and finally that one of Brodsky et Al. (2).

Of the other cases included in our series, the case of Aronson-Cavell refers to a 27-year-old woman died 4 days after delivery, in whom post-mortem examination unveils multiple metastases of melanoma. Her placenta, which presents scars and infarcts, is not microscopically examined. Her baby girl presents multiple skin, lung and hyle nodules at the age of 2.5 months. The biopsy of a skin nodule shows an undifferentiated, non pigmented nodule compatible with the diagnosis of metastatic melanoma. Her clinical course is characterized by a progressive decrease in size of the nodules till their complete regression. A second skin biopsy performed during this regressive phase shows necrotic phenomena with residua of melanic pigment. The baby girl recovers and does not present any problem in the two subsequent years. The transmission of her tumor through the placenta cannot be demonstrated because the placenta is not microscopically examined. However, it is difficult to accept that between the malignant tumor responsible for death of the mother and the spontaneously healing tumor of the baby girl there is not any relationship.

The spontaneous regression of malignant melanoma is well known. According to Stephenson et Al. (19) melanoma represents 1%

TABLE 1: placentally transmitted melanoma.

Author, year	Age, sex	Site	Predisposing factors	Mother outcome	Placental metastases	Villi invasion	Ulceration	Extension	Follow-up months	Treatment	Outcome
Gottrohn, 1940	5 months	liver	placental transmission	/	not researched	not researched	/	/	6	/	D
Weber, 1930; Holland, 1949	8 months M	liver, subcutan., pleura, lymph nodes	placental transmission	exitus 3 months after delivery	yes	yes	/	/	10	/	D
Aronsson, 1963; Cavel, 1963	2,5 ms, F	multiple skin, lung	placental transmission	exitus 4 days after delivery	scars, no histological finding	not researched	/	multiple metastases	24	spontaneously regressed	A
Brodsky, 1964	11 days, M	diffuse metastases	placental transmission	exitus 17 days after delivery	yes	yes	/	diffuse metastases	37 days after diagnosis	skin graft from mother and grandmother	D
Dargeon, 1950; Lerman, 1969	7 months M	liver mastoideal lymph nodes	placental transmission	exitus 4 days after delivery	not researched	not researched	/	/	4 months after diagnosis	antitumoral vaccine	D

LEGENDA: M = males; F = females; D = died; A = alive; mms = months

of all malignancies, whereas the cases of spontaneously regressing melanoma represent 14% of all spontaneously regressing malignancies.

Also the Gottron' case starts with a mother affected by metastatic melanoma, who gives birth to an apparently healthy baby. Surprisingly enough, the newborn presents melanic pigment in the urine disappearing when the child is formula-fed, to reappear when the child is breast-fed. The maternal milk presents melanic pigment. When aged 5 months, the child presents a liver nodule, which is clinically diagnosed as metastatic melanoma and is responsible for the child death.

The Holland's report does not talk about pigmentation, but about anaplastic carcinoma.

The Friedreich's case (8) of 1866 is not included in this series. However, it has a historical value, being the first report of metastases to the fetus of a maternal malignancy. The mother, which has a visceral anaplastic, pigmented tumor, dies 9 days after the delivery due to diffuse metastases. The newborn presents at birth a subcutaneous nodule on the left knee, which is microscopically pigmented and anaplastic like the maternal tumor, and dies 6 days after birth. In this case the diagnosis of maternal melanoma metastasising to the fetus is not proven. However, the presence of a pigmented tumor, lethal for the mother and baby, given the literature data saying that melanoma is the only pigmented tumor with a clinical course like that, makes the diagnosis of malignant melanoma of the mother metastasising to the fetus highly probable even in this first case.

Placental metastases with exclusive involvement of the mother or the fetus

We would like to discuss now the placental metastases of maternal melanoma without involvement of the fetus and the placental metastases of fetal melanoma without involvement of the mother.

There are 5 documented cases of placental metastases with healthy fetus deriving from mother with metastatic melanoma (3, 7, 15, 18, 19). The child is healthy, except for the Byrd's

case, who dies due to other reasons and does not present fetal metastases. The chorial villi do not exhibit metastases in the cases of Byrd, Reynolds and Fredman, whereas metastatic cells are shown in the chorial villi in the cases of Stephenson and Sokol. In the case of Stephenson a transfusion from newborn to mother is tried unsuccessfully.

There are 3 cases of fetal melanoma -a same case was reported by 2 different Authors, namely Campbell and Schneidermann- with mother free of disease. Two of them arise on congenital nevus (16, 20) and one on healthy skin. In one case (16) there are placental metastases, without invasion of the intervillous space belonging to the maternal circulation. In one case (5) the placenta is not mentioned and in another case (20) the placenta does not present metastases, not even on microscopic examination.

In the Holaday's case biologically benign nevus cells are shown in the chorial villi of a newborn with a giant congenital melanocytic nevus.

Markus (12) reported a case of melanotic sarcoma of the mother, who gives birth to a baby by transvaginal hysterotomy. Mother and baby die the day after. Post-mortem examination of the mother shows metastases of melanotic sarcoma in the ovary, pericardium, lymph nodes, bronchi, liver, peritoneum, brain and skin. A carcinoma of the bladder with metastases in the liver and peritoneum is also shown. Melanotic nodules are shown in the placenta and melanotic cells in the intervillous spaces and villi. Post-mortem examination of the baby does not show any tumor.

In conclusion, the metastatic melanoma of the pregnant woman giving metastases to the fetus is an experiment of the nature, which testifies with its exceptionality the efficacy of the physical and immunological defence system of the fetus. Although effective, this mechanism is more vulnerable for melanoma as compared with other more frequent malignancies of the pregnant woman, such as mammary and cervix carcinoma, leukemia and lymphoma. In spite of their relative frequency, the latter are not able to metastasise to the fetus.

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