CASE REPORT
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Metastatic melanoma and pregnancy

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ABSTRACT

Pregnancy after complete treatment of metastatic melanoma is an extremely rare event. We presented a case of a skin melanoma patient with lung and liver metastases who was treated by combined immunochemotherapy for the period of two years. A year and a half after the successful treatment, which resulted a complete remission of metastatic lesions she got pregnant and delivered a healthy baby girl.

KEY WORDS: *Melanoma; Neoplasm Metastasis; Pregnancy; Antinoplastic Agents*

INTRODUCTION

Cutaneous melanoma is known to have the capacity to metastasize to virtually any organ. Most frequent are metastatic lesions in liver (54%) and lung (58%). Metastatic melanoma has very limited responsiveness to chemo- or immunotherapy (1). Response rate is less than 20%, and the median overall survival for stage IV is 4 to 12 months (depending on invaded organs). Combined immunochemotherapy has showed some activity in metastatic melanoma, but it has not been possible yet to define standard therapy, which should be the most beneficial. The rationale for combining cytostatics with interferon for treatment of melanoma is based on the assumption of their different antitumor mechanisms (2-4).

The estimated incidence of melanoma complicating pregnancy ranged from 0.1 to 2.8 per 1,000 pregnancies, although data from this population have not been systematically ascertained (4). Despite the fact that melanoma is not the most common cancer in pregnancy, it is most likely that it will metastasize to the placenta and fetus. Melanoma incidence rates are increasing dramatically, and melanoma is now a major cause of cancer death in women of childbearing age. To facilitate appropriate patient education, clinical and histologic evaluation, physicians should be familiar with the data regarding fetal complications in a pregnant woman with melanoma. Most published discussions regarding management and treatment of metastatic melanoma in pregnancy have focused on the mother, with no analysis of fetal management published to date (5).

Pathologists should carefully examine the placentas of women with known or suspected metastatic melanoma, grossly and histologically. With placental involvement, fetal risk of melanoma metastasis is approximately 22%. Neonates delivered with concomitant placental involvement should be considered a high-risk population. The risk-benefit ratio of adjuvant treatment for a potentially affected infant should be carefully weighed.

Placental involvement of maternal cancer has been defined as gross or microscopic evidence of maternal cancer within any section of the placenta. Fetal metastasis has been defined as metastasis of maternal cancer developing in the fetus, with no evidence of primary tumor originating in the fetus. Since the first case report in 1866, only 87 patient cases of placental or fetal metastasis have been reported. It is important to note that the number of patient cases reported in the literature is increasing, with more than 20% of the patient cases being reported in the last decade (6,7).

CASE PRESENTATION

A 38-year-old woman was admitted to the Institute of Oncology in January 2001; after routine check up she was completely asymptomatic but standard radiography of chest showed suspicious infiltration on right side of lung and ultrasound of liver showed metastasis in right lobe. She had Karnofsky performance of 100.

Her medical history showed pigmented skin lesion of right arm, which was radically excised on February 14, 1997. The histopathological examination disclosed a superficial spreading melanoma, measuring 3.2mm of thickness (Breslow V), Clark invasion II. She was classified in stage II A (UICC/AJCC) of melanoma and regularly followed up till January 2001. Visceral evaluation by CT scan showed bilateral multiple metastases of lung (from 2.5cm to 0.5cm) and revealed two metastases in right lobe of liver (approximate diameter 4cm) (Figure 1).

The laboratorial exams were within normal ranges. After the disease progression (stage IV), the patient was submitted to immunochemotherapy. She received 12 cycles of combined chemotherapy: dacarbazine (250mg/m≤ IV, day 1-3)+cisplatin (25mg/m≤ IV, day 1-3) every 4 weeks + interferon alpha (6 MU, SC, 3x weekly, in TD 180 MU, and 3 MU, SC, 3x weekly, in TD 180 MU). First complete evaluation by CT scan was performed after four cycles of chemotherapy, and showed partial regression of all metastatic lesions. We decided to continue with same therapy, which resulted in further regression of metastatic lesions, what was confirmed by CT scan (Figure 2).

Concerning toxic and side effects (leukopenia, polineuropathy, nausea, vomiting, gastritis, hypertension, headache, mild flu like symptoms) as well as excellent result of therapy, we continued with single agent therapy with dacarbazine (four cycles more). As complete remission was achieved in June 2002 we continue with frequent checkups. Last CT scan was done in May 2003 and confirmed complete remission (Figure 3).

Planning maternity, in spite of all warnings for possible complications either her or fetus/infant, she got pregnant in December 2003. In the course of pregnancy all examinations that are available in our country were performed regularly. Delivery was normal, on

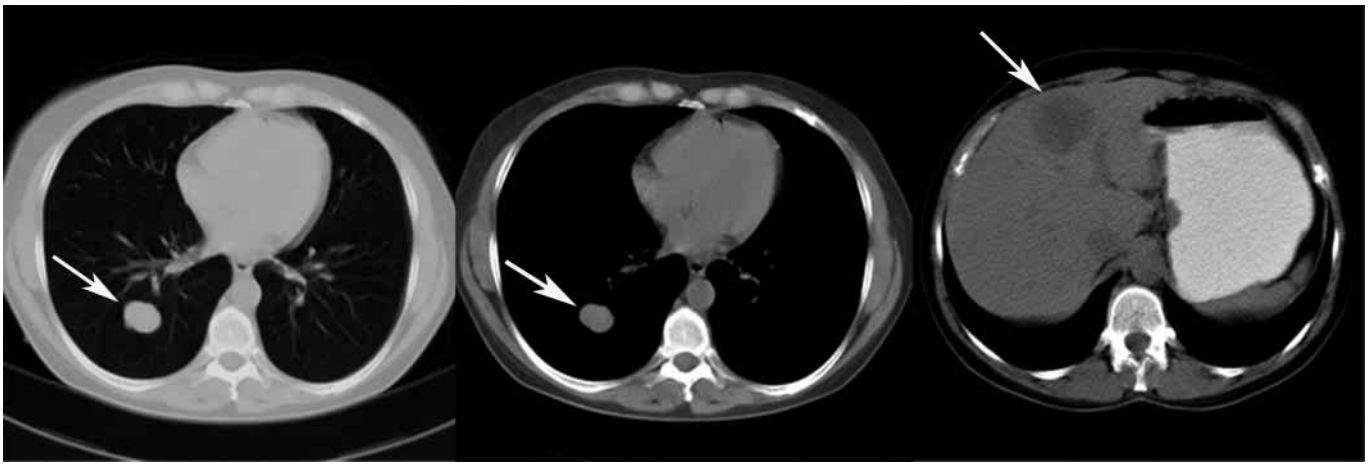

Figure 1. Patient s CT findings before therapy 2001. Lung metastases are clearly evident in both lung and mediastinal window)arrows) as well as

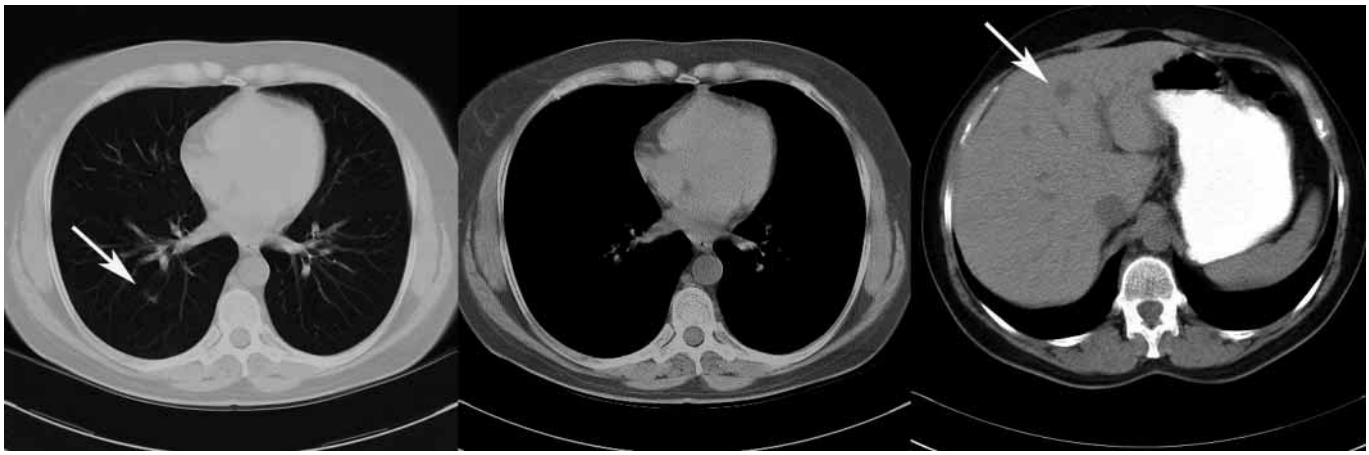

Figure 2. CT findings after one year of immunochemotherapy (2002) - an almost complete response of lung and liver metastasis

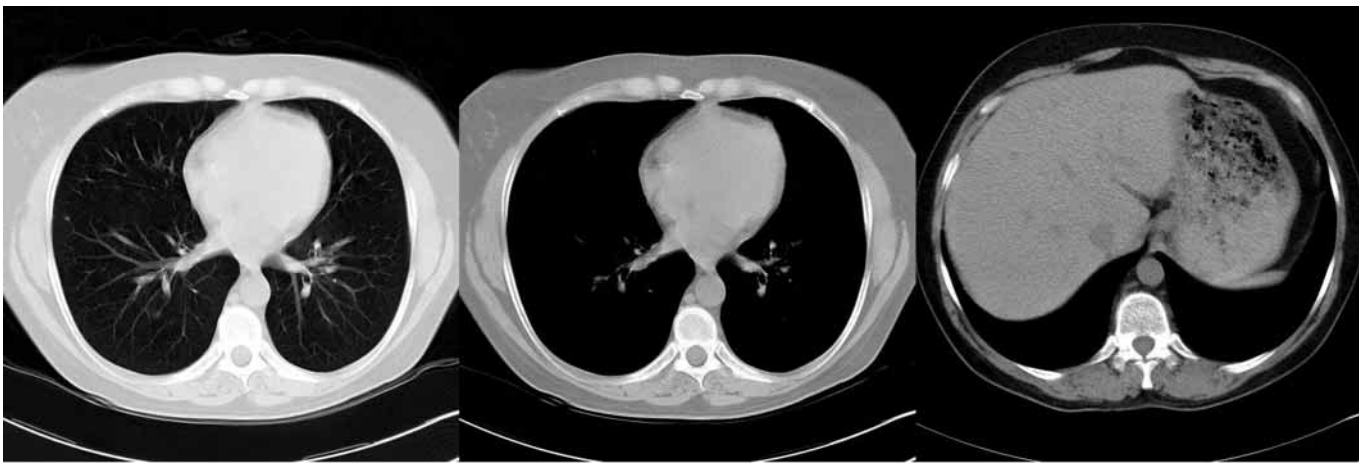

Figure 3. CT scans of the same patient after two years (year 2003) showing complete remission of lung and liver metastasis

time-gestational age of 36 weeks (in August 2004), microscopic placental examination gave normal histopathological findings and baby girl was Apgar score 9. Her last checkup (laboratory findings, radiography of lung, ultrasound of liver) in October 2004 showed normal results.

DISCUSSION

Melanoma is the cancer most commonly found to involve the placenta and fetus, accounting for 27 of 87 (31%) patient cases published to date. Advances in cytogenetic tumor analysis using cellular DNA markers that permit discrimination between maternal and fetal cells now make it possible to establish the maternal origin of the tumor more conclusively. The most common sites of presentation included the liver and subcutaneous tissue (8,9). During the period from 1918 to 2002, there were 27 patients with melanoma reported to involve the placenta or fetus. Microscopic evaluation was performed in 24 of 27 patients, and placental involvement was documented in all 24 patients. Six of the 27 reports indicated fetal metastasis, but three reports did not document corresponding placental involvement.

Previously published reviews focused on assessing the risk of maternal-fetal transmission of melanoma and calculated an approximate 25% mortality risk to babies born to mothers with placental involvement. Infants developing clinical evidence of maternally derived

metastases have an exceptionally poor prognosis, with death typically occurring within 3 months of diagnosis. Thus, neonates delivered with concomitant placental involvement but without clinical evidence of disease should be considered a high-risk population. Adjuvant treatment of infants born to women with placental metastasis of melanoma has not been reported (10,11).

In the past, physicians were only alerted to the occurrence of transplacental metastasis when gross placental involvement or clinically evident fetal metastases were present.

Even when examined microscopically, metastatic deposits within the placenta may be difficult to localize, given its enormous blood supply. Multiple placental sections may be necessary to document the true extent of placental invasion. Fetal metastasis requires two components: maternal tumor invasion of fetal tissues and fetal inability to eliminate metastatic cells. Placental or fetal vessel invasion may be necessary, but not sufficient, for fetal metastasis.

Other maternal factors that have been reported to indicate an unfavorable fetal or infant outcome include maternal age less than 30 years, primiparity, disease onset more than 3 years before current pregnancy, nodal metastasis before pregnancy, more than three sites of metastatic foci during the third trimester, primary site of the leg, and maternal death within 1 month of birth. However, data from the literature do not support any of these factors (12,13).

Previously reported fetal factors indicating an unfavorable fetal or infant outcome include birth at greater than 36 weeks and male sex. Gestational age at birth did not seem to influence risk of fetal transmission of melanoma. However, male infants seem to be at higher risk than females for developing metastasis of any maternal cancer. Males comprised 80% of all infants with metastasis of melanoma and 75% with metastasis of all cancers. Although long-term survival cannot be determined for patients for whom follow-up was limited, the only infant to survive without therapy was female, indicating that sex may influence survival.

The tendency of melanoma to metastasize to the fetus relative to other tumor types is intriguing, but poorly understood. As part of the metastatic model recently proposed by Hanahan and Weinberg, it is clear that metastatic cells must alter their expression of numerous genes, including proteases, cellular adhesion molecules, and integrins before they are able to invade and establish themselves in an alternative tissue environment. Because melanoma is overrepresented in the number of placental metastases that occur during pregnancy, there must be some unique or dominant feature within melanoma cells relative to other malignancies that allows this process to occur. An additional consideration is the fact that the placenta is a site of production for many growth factors and is exceptionally vascular. In fact, angiogenic factors produced by the placenta, including placental growth factor, hepatocyte growth factor, and vascular endothelial growth factor, have also been shown to be released by, and to influence the growth of, melanoma cells in culture. It is also possible that placental growth factors or shared endothelial adhesion molecules encourage adhesion, survival, and invasion of melanoma cells. This relative affinity of melanoma for placental metastasis, growth, and invasion may account for the increased risk of fetal metastasis (14-16).

An inadequate fetal immune response has also been suspected in the pathophysiology of transplacental spread. In infants who present with metastases, immunologic tolerance seems to have been induced. Tolerance may be induced by exposure to tumor antigens at a time when the developing immune system is not yet capable of responding. T- and B-cell responses in the fetus are thought to develop around weeks 7 to 10 and 14 to 20, respectively, and many of the incidences of fetal metastasis occurred in women who had metastatic disease before that date. Thus, metastatic cells may localize to the fetus early enough to be considered self by the developing immune system. However, the timing of maternal metastasis of melanoma does not seem to differ in placental versus fetal metastasis (17,18).

The ability of the fetus to clear maternal metastatic cells seems to play a role in melanoma as well. Given the risk of metastasis to the fetus, it is recommended that the placentas of all women with suspected metastatic melanoma during pregnancy should be closely evaluated by gross and microscopic examination. Immunohistochemical staining for melanoma antigens should be performed on histological sections, using S-100, HMB-45, or other appropriate markers. Research tests that may be of value include examination of cord blood buffy coat for the presence of tumor cells using immunohistochemical staining or reverse transcriptase polymerase chain reaction. Research evaluation to establish the maternal origin of the tumor (including karyotyping, cytogenetics, and HLA typing of the mother, infant, and tumors) may also be useful (19,20).

If the neonate does not present with metastases at birth, recommendation is periodic evaluation for development of melanoma for at least 24 months postpartum coinciding with routine well-child checks. Evaluation should include a baseline chest x-ray and liver enzymes, including lactate dehydrogenase, which may be repeated every 6 months. Other studies may be included on the basis of clinical suspicion.

Because of its rarity, studies regarding melanoma treatment are lacking in infants. At this point, there is insufficient information to make a definitive recommendation about adjuvant therapy for infants at risk for maternal melanoma metastases (21, 22).

CONCLUSION

Morbidity for the fetus in patients with placental disease is unclear. Pregnant women with metastatic melanoma often had complicated clinical courses, but infants without fetal metastasis did well. Prematurity is a common complication of infants born with placental metastasis of melanoma, with a mean gestational age of 34 weeks, but the mortality rate secondary to prematurity was low. Follow-up should be long-term. Because congenital and infantile melanomas are so rare, there are no existing standardized guidelines for observation or therapy. Recommendations for follow-up include skin inspection, abdominal ultrasound, and screening for melanogens in the infant's urine.

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