Congenital Melanocytic Nevi With Placental Infiltration by Melanocytes

A Benign Condition That Mimics Metastatic Melanoma

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Background: Placental metastases from cutaneous malignant melanoma from both the mother and the fetus have been reported. The finding of benign-appearing melanocytes in the placenta in association with congenital melanocytic nevi (CMN) is more exceptional, with only 6 reports in the literature. Clinically, the finding of melanocytes in the placenta in this setting can be alarming and might erroneously lead to the diagnosis of metastatic melanoma.

Observations: Herein, we describe 3 additional patients with CMN with placental infiltration by melanocytes with a benign phenotype. In the results of immunoperoxidase stains, the melanocytic cells were positive for S-100 protein and HMB-45 in the 2 lesions available for study. Staining of placental vessels with Ulex europaeus agglutinin I (Vector Laboratories, Burlingame, Calif) failed to show intravascular melanocytes in the 1 lesion available for study. We report for the first time DNA diploidy in 2 lesions available for study, which were analyzed by DNA image cytometry. We describe the first patient with a relatively small, non-giant CMN.

Conclusions: We support the notion of the aberrant migration of melanocytes from the neural crest during fetal development as the most likely explanation of this phenomenon and note the similarity to the association of CMN and leptomeningeal melanocytosis. However, the precise histogenesis of this process remains uncertain. Most importantly, our data provide further evidence for the benign nature of this condition. Awareness of this entity is of vital importance in avoiding overdiagnosis of melanoma in this clinical setting.

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THE INFILTRATION of the placenta by aggregates of melanocytes in neonates with congenital melanocytic nevi (CMN) is rare. Other than the 3 patients we describe herein, only 6 other patients have been described. The nature of the placental deposits in 1 of our patients has been partially described in a prior report by Carroll et al. Prior observers contend that the cells in these cases are benign melanocytes. This entity must be distinguished from the placental infiltration of melanoma cells originating from maternal melanoma and fetal congenital melanoma.

Similar phenomena occurring in CMN may include cutaneous satellite nevi and leptomeningeal infiltration by melanocytes. In the latter condition, melanocytes may rest in the leptomeninges during migration from the neural crest. A simultaneous migration of cells giving rise to the CMN would explain the shared dermatomal distribution of the skin and leptomeningeal lesions. A similar mechanism may explain the migration of these cells to the placenta. It is also possible that this phenomenon could be explained by benign hematogeneous metastasis to the placenta.

Herein, we describe 3 additional patients and the DNA analysis of 2 lesions available for this study. Our data are combined with that from the literature to further characterize this unusual and potentially alarming entity.

REPORT OF CASES

CASE 1

A female infant with an uncomplicated term delivery was noted to have a 3.8 × 2.8-cm CMN involving the trunk, along with several scattered satellite lesions on the head, neck, and extremities. A biopsy specimen from a slightly raised area in the CMN was diagnosed as a CMN with architectural disorder and cytologic atypia following review by several dermatopathologists. The patient was evaluated by a computed tomographic scan of the chest and abdomen,
a magnetic resonance imaging scan of the head, and a bone scan; the results of these scans were interpreted as normal. The results of gross examination of the placenta showed normal parenchyma (643 g). The results of microscopic examination revealed the incidental finding of pigmented cells within chorionic villi. However, the possibility of metastatic melanoma was strongly considered. The patient is completely healthy at 4 years of age.

CASE 2

A stillborn female infant delivered near term to a healthy mother presented with the umbilical cord wrapped around the neck and thrombosis of 1 umbilical artery, confirmed in the results of microscopic examination. The only abnormality noted in the findings of an autopsy was a giant CMN on the upper back and shoulders; the results of microscopic examination of the lesion revealed a congenital compound nevus. The results of gross examination of the placenta revealed meconium staining but otherwise normal parenchyma (460 g). The results of microscopic examination of the placenta demonstrated changes of hemorrhagic endovasculitis, segmental villous fibrosis, and the incidental finding of pigmented cells within chorionic villi.

CASE 3

A female infant had a giant CMN on the trunk and scattered cutaneous satellite lesions at birth. The infant was otherwise healthy and the product of an uncomplicated term pregnancy. The results of gross examination of the placenta revealed no abnormality of the parenchyma (510 g). The results of microscopic examination showed the incidental finding of several foci of pigmented cells within chorionic villi. The patient is healthy at 8 months of age.

METHODS

HISTOLOGICAL CHARACTERISTICS OF PLACENTAL LESIONS

The microscopic sections of all 3 placentas were reviewed by 3 of the authors who are pathologists (R.A.B., B.S., and R.L.B.). The results of microscopic examination in patients 1 and 2 demonstrated only rare foci of melanocytes within placental villi, while the results in patient 3 demonstrated cell clusters focally present in villi of 15 of 22 histological sections. The results in all 3 patients demonstrated involvement by pigmented cells with similar morphologic characteristics (Figure 1 and Figure 2). The cells ranged from 7 to 21 µm in diameter and were heavily pigmented. Oval to reniform nuclei had pale, focally vesicular chromatin, occasional slight condensation of chromatin at the periphery, and 1 to 3 relatively small nucleoli. No mitoses or significant cytological atypia were seen in any of the patients.

No melanocytes were found within vessel walls or vascular lumina. Ulex europaeus agglutinin I staining was performed in patient 3 (the only case with material available for this study). Despite the highlighting of the vessels by the stain, melanocytes were not observed within vascular lumina.

The results of immunoperoxidase studies revealed the melanocytic cells to be positive for S-100 protein and HMB-45 in patients 1 and 3. (Neither the tissue block nor paraffin sections was available for immunostaining from patient 2.) Additionally, in patient 3, the cells were positive for vimentin. The pigment in patient 2 was positive for melanin using the Masson-Fontana ammoniacal silver stain. The results of the iron hematoxylin method were negative for hemosiderin.

DNA ANALYSIS

Material from patients 1 and 3 was available for DNA analysis. Sections from patients 1 and 3 were stained with the Feulgen stain and analyzed via image cytometry by methods previously described.13 Analysis of DNA content was performed using a cell analysis system (CAS 200 System, Cell Analysis System, Lombard, Ill) and computer software. Calibration was performed by measuring the DNA content of whole rat hepatocytes. The DNA content of the studied cells was derived from the total nuclear optical density and expressed as an absolute quantity. One hundred forty-six cells in patient 1 and 246 cells in patient 3 were measured, and DNA histograms were generated. A DNA range of 0.80 to 1.20 was classified as

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diploid, and the DNA histograms were interpreted according to the criteria of Auer et al.\(^4\)\(^7\)

The results in patient 1 demonstrated a diploid DNA population with a DNA index of 0.84. The results in patient 3 were more difficult to interpret but were also consistent with a diploid DNA pattern with an index of 0.92. However, the latter histogram also showed 3 single cells with hyperdiploid or aneuploid content. The latter results were attributed to the heavy pigment content in melanocytes.

**COMMENT**

Despite the relatively common occurrence of CMN (in as many as 1% of infants),\(^1\)^\(^5\)\(^6\) the finding of associated benign melanocytes in the placenta is exceedingly rare. Furthermore, we have not been able to find any reports of this occurrence in the absence of CMN. In our patient 1, a diagnosis of metastatic melanoma of the placenta was considered by the original pathologist and was a cause of some alarm among the investigating medical team. Additional details of this patient have been described previously.\(^5\) A review of the literature and further characterization of this process provide further support for a benign infiltration of the placenta by melanocytes in this setting and assist in its distinction from malignant melanoma.

Including the new patients described herein, there are a total of 9 patients described in the literature with melanoma.\(^5\) The affected neonates included blacks, whites, and an Asian. Of the infants, 6 were female and 3 were male. The results of examination of the skin revealed that all infants but 1 exhibited a giant nevus (≥20 cm in greatest dimension). Our patient 1 is the first described to have a relatively small CMN (3.8 cm). Interestingly, 7 of 9 patients demonstrated scattered small cutaneous pigmented lesions in association with the dominant skin lesion (ie, satellite nevi\(^10\)), raising the question of an association.

Skin biopsy specimens in 3 infants revealed a benign congenital compound nevus. A skin biopsy specimen from a fourth patient (our patient 1) demonstrated cytological atypia, and, following review by several experienced dermatopathologists, was diagnosed as an atypical congenital compound nevus, consistent with the finding that the lesion showed atypical histological features that were not diagnostic of malignant melanoma.

The results of gross examination of the placenta demonstrated pigmented foci visible in the placental tissue in only 1 patient.\(^4\) No other case reports have described similar pigmented lesions, and all were grossly unremarkable except for 2 patients whose results showed meconium staining.

The results of microscopic examination of the placentas in all cases revealed benign-appearing pigmented cells within chorionic villi. All observers have interpreted these as nevus cells except for Werner,\(^4\) who postulated that these cells were placental macrophages that had passively engulfed melanin granules (positive for melanin in the results of Masson-Fontana ammoniacal silver stain); however, later reviewers\(^4\) concluded that the descriptions and photographs provided are consistent with pigmented benign nevus cells. No observers except Jauniaux et al\(^5\) have reported nevus cells within vascular lumina. In our patients as in others, the nevus cells appear to be situated in villous stroma and are largely of the tertiary type. Despite staining of vessels by Ulex europaeus agglutinin I in 1 patient studied, we could not find nevus cells within chorionic vessels. No observer has reported the presence of these cells in the intervillous space, which are the maternal blood space and the reported site of maternal melanomas metastatic to the placenta.\(^8\)

The results of staining identified S-100 protein in the pigmented cells in 4 patients, HMB-45 in 3 patients, and vimentin in 1 patient. In 3 patients, the results of the Fontana-Masson ammoniacal silver stain have been positive for melanin.

In the only electron microscopic study of the placental nevus cells, Sotelo-Avila and colleagues\(^4\) report developing cytoplasmic melanosomes.

The length of clinical follow-up in these patients ranged from 8 months to 10 years. Additional follow-up of 9 years was provided for the patient described by Demian et al,\(^17\) in response to a challenge regarding the benign nature of the condition in a letter to the editor.\(^18\) The patient was alive and healthy at the age of 10 years. The patient described by Antaya et al\(^6\) is currently healthy at 5 years of age (Richard Antaya, MD, oral communication, March 1997). Despite the presence of melanocytic atypia in the CMN in our patient 1, this patient is also healthy at 4 years of age.

The cause of this phenomenon has been a matter of debate. In the initial case report, Holaday and Castrow\(^1\) proposed that “nevus cells are filtered from the fetal circulation” and thus are “metastases” of benign nevus cells from the skin lesions. Others\(^3\) have strongly argued in favor of a developmental anomaly whereby the same cells within the neuroectoderm that give rise to the CMN likewise migrate to the placenta in early development. The failure to find melanocytes within placental vessels in all but 1 of the patients described thus far (including our own) provides some evidence supporting a developmen-

### Table: Clinical Information of All Patients

<table>
<thead>
<tr>
<th>Source, (^\text{y})</th>
<th>Age of Mother, (\text{y})</th>
<th>Race</th>
<th>Sex</th>
<th>Giant Nevus</th>
<th>Satellite Nevus</th>
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<tr>
<td>Holaday and Castrow,(1) 1968</td>
<td>NS</td>
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<td>Demian et al,(3) 1974</td>
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<tr>
<td>Sotelo-Avila et al,(4) 1988</td>
<td>29</td>
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<td>Yes</td>
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<tr>
<td>Jauniaux et al,(5) 1993</td>
<td>28</td>
<td>White</td>
<td>Male</td>
<td>Yes</td>
<td>No</td>
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<td>Antaya et al,(6) 1995</td>
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<td>No</td>
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<tr>
<td>Patient 3‡</td>
<td>36</td>
<td>Asian</td>
<td>Female</td>
<td>Yes</td>
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</table>

*NS indicates not stated.
†Patients described in the current report.
‡Patients with CMN ≥20 cm.
tal rather than metastatic origin. The equally interesting occurrence of melanocytes in the shared dermatome of leptomeningeal melanocytosis and a CMN may be a similar phenomenon.\textsuperscript{12} We favor the theory of an analogous infiltration of melanocytes in the placenta during fetal development vs a hematogenous spread. However, as in the well-known and debated histogenesis of benign melanocytes in lymph nodes, the definite cause remains to be determined.

In summary, the occurrence of benign melanocytes in the placenta in association with a CMN is extremely rare. Including the patients described herein, there are a total of 9 patients described in the literature. A review of these patients indicates a newly reported association with satellite nevi. We also describe the only patient known to have a relatively small, nongiant CMN. Furthermore, we support the views of others suggesting that the cause of this entity relates to an abnormality of fetal development rather than from hematogenous spread. Irrespective of the debate as to the origin, a benign process is supported by the benign cytological appearance of melanocytes, the absence of melanocytes in the intervillous space (a finding in maternal metastatic melanoma), the lack of biologically aggressive disease in any of the infants to date, and the first evidence of a diploid DNA pattern in 2 of our patients. However, any conspicuous involvement of the intervillous space or cytological atypia in the melanocytic population warrants full consideration of malignant melanoma metastatic to the placenta and should include a thorough clinical evaluation of the mother and fetus for a primary melanoma. Equally important, awareness of the phenomenon of benign melanocytes in the placenta of a fetus with CMN can assist physicians in evaluating these infants and may prevent a hasty and erroneous diagnosis of melanoma arising in either the mother or especially the CMN of the infant.

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REFERENCES