Neonatal Giant Congenital Nevi With Proliferative Nodules

A Clinicopathologic Study and Literature Review of Neonatal Melanoma

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Background: Review of the literature reveals that congenital malignant melanoma is an exceptionally rare occurrence and has a generally poor prognosis when it does occur. However, benign proliferative melanocytic lesions are known to occur within giant congenital nevi (GCN). This entity is not well recognized and can be confused clinically and histologically with malignant change.

Observations: We report 2 cases of GCN in neonates demonstrating benign proliferating nodules present at birth. An initial diagnosis of malignant melanoma was assumed in both cases. Careful histologic analysis, however, revealed these lesions to be benign, as did long-term follow-up of 3.5 years, with both patients remaining well with no evidence of melanoma. Review of the literature suggests that there are 2 clinical patterns of these benign nodules arising within GCNs: small (<1 cm) and large (>1 cm) dermal nodules with varying histologic patterns that we have attempted to categorize.

Conclusions: Our cases illustrate the difficulty in accurate diagnosis of melanocytic lesions in the neonate. We recommend caution in making a diagnosis of malignant melanoma and highlight the possibility that benign lesions can be mistaken for melanoma in this age group. We encourage the acquisition of fixed histologic specimens for accurate diagnosis of melanocytic lesions.

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Neonatal malignant melanoma is extremely rare, with fewer than 20 cases reported in the literature,1-16 and can occur within a preexisting giant congenital nevus (GCN), de novo, or as metastases from the mother.13 There are only 8 reported cases of neonatal malignant melanoma arising from a GCN6,7,11-13 and 1 from a smaller preexisting nevus.16 Surprisingly, death occurred in only 3 patients,1,13,16 and 5 were reported to be alive from 4 months to 10 years later. It seems possible, if not likely, therefore, that some of these cases were in fact benign and mistakenly diagnosed as malignant melanoma.

Neonatal melanoma arising de novo (ie, from apparently normal skin with no evidence of a preexisting nevus) has been reported in 6 cases, with variable outcomes.5,7,10 Melanoma can also arise as placental metastases from maternal lesions; such an event, although exceptional, is easier to diagnose and invariably rapidly fatal.1-3

Dermatologists are generally aware of the potential complications of GCN, including neurocutaneous melanosis17 and malignant transformation. Malignant change, however, is exceptional in neonates. By contrast, benign lesions arising within GCNs are common and clinically or histologically may mimic malignant transformation.

The diagnostic criteria for and classifications of benign lesions arising within GCNs are variable in the literature and therefore somewhat confusing. Careful review of our own cases and published material shows that 2 clinical patterns (small dermal nodules of <1 cm and large dermal nodules of >1 cm) and 2 histologic patterns (“proliferation nodules” and tumorous or hamartomatous lesions) can be distinguished. We have reviewed the literature and attempted to reassess the clinical and histologic nature of benign nodules associated with GCNs, incorporating our own cases as illustrative examples.

We describe 2 children born with dermal nodules arising within a GCN. In both cases, the ulcerated nodules were considered to represent malignant change, and 1 child was initially diagnosed as having malignant melanoma on the basis of fresh frozen section evaluation. Further analy-
sis of fixed histologic sections and clinical follow-up confirmed the benign nature of the lesions in both cases—the children are both well after 3.5 years of follow-up with no evidence of metastases.

REPORT OF CASES

CASE 1

A firstborn baby girl was delivered by emergency cesarean section because of suspected placental hemorrhage. At delivery, it was evident that the bleeding arose from an ulcerated, pedunculated nodule (40 × 40 mm) within a 120 ×120-mm hairy pigmented GCN affecting the scalp (Figure 1). Also arising within the nevus was a smaller pink fleshy nodule measuring 10 × 10 mm in front of the larger lesion. The nevus itself was well demarcated and distributed over the left forehead, eyebrow, and extending to the vertex. There were numerous scattered deeply pigmented lesions of various sizes elsewhere on her body. She appeared otherwise healthy with no evidence of lymphadenopathy or organomegaly. There were no suspicious maternal lesions, and the placenta was normal.

Clinically, it was considered likely that these findings represented a malignant melanoma arising within a GCN, with the scattered lesions elsewhere representing cutaneous metastases. She was found to be anemic due to the hemorrhage and required a blood transfusion. Other laboratory investigations were normal. An urgent magnetic resonance imaging scan performed under sedation showed no evidence of neural involvement. Subsequently, urgent shave biopsies of both nodules were performed under general anesthesia on her fourth day of life. The specimens were formalin fixed and sent for urgent histologic analysis.

Gross examination revealed a deep shave biopsy specimen of a melanocytic lesion with a central hemorrhagic ulcerated nodule. The surrounding flat area was 2.5 mm thick and had intact epidermis. On sectioning, junctional melanocytic activity was not found. The melanocytes were densely packed and uniform in nature (Figure 2). Occasional cells had fine nucleoli. Nuclear pleomorphism was not seen. Rare normal mitoses were identified (<1 per 50 high-power field). No maturation was seen until an abrupt change in cellularity at the base (Figure 3), where individual melanocytes infiltrated collagen in a benign fashion. Both nodules demonstrated similar changes. A diagnosis of a proliferation nodule within the background of a benign intradermal congenital melanocytic nevus was made. There was no histologic evidence of melanoma.

Three and a half years later, this child remained well, with no evidence of malignancy. The nevus was covered with thick dark hair except for a pink hairless area at the shave site of the larger lesion, which took months to heal. Partial nevus excision is planned in the near future.

Figure 1. Clinical appearance of the ulcerated nodule within the scalp giant congenital nevus of patient 1.

Figure 2. Histologic specimen of the large ulcerated nodule from patient 1 (hematoxylin-eosin). A, Low-power view (original magnification ×40); B, high-power view (original magnification ×400) showing uniformity of melanocytes.
CASE 2

Following a normal delivery, a firstborn baby girl was found to have an extensive congenital pigmented nevus of the bathing-trunk variety extending onto the genitalia and scalp (Figure 4). There were several small (<1-cm) and large (>1-cm) pigmented fleshy dermal nodules arising within this lesion, predominantly over the genital and periumbilical regions. The largest dermal nodule near the umbilicus was ulcerated, clinically raising the concern of malignancy. She also had several smaller pigmented nevi elsewhere on the body. There was no lymphadenopathy or organomegaly. There were no maternal lesions evident, and the placenta was normal. A magnetic resonance imaging scan showed no evidence of neural involvement.

On the second day of life, biopsy specimens of 4 of the largest dermal nodules were taken, and fresh frozen sections were performed on the ulcerated lesion near the umbilicus. The frozen section showed nuclear pleomorphism and high numbers of mitotic figures, which led to an initial diagnosis of malignant melanoma. As a result, the child received chemotherapy in the form of vincristine, Adriamycin, and cyclophosphamide.

Subsequently, however, and after several further opinions had been obtained, the formalin-fixed tissue specimens were thought to demonstrate a benign lesion. Examination of formalin-fixed tissue showed a large proliferative lesion of variable cellularity composed of moderately pleomorphic cells rich in mitoses (>10 per high-power field). These mitoses were normal in configuration. Areas of hypercellularity blended imperceptibly with the less cellular areas in the surrounding nevus (Figure 5). No junctional component was noted. Little necrosis was evident within the biopsy specimen. Although the degree of pleomorphism and mitotic activity was very disturbing, the features were judged to represent a benign proliferative lesion arising within a congenital nevus. To date the child remains well at 3.5 years with no evidence of metastases.

COMMENT

We have described 2 cases of GCN in a neonate where a diagnosis of malignant transformation was posited because of the presence of ulcerated nodules. Histologic findings from these cases varied considerably, prompting a review of the subject.

Congenital nevi occur in approximately 1% of newborns. Giant congenital nevi, defined as greater than 20 cm in diameter, occur in 1 in 20000 live births, and the even larger bathing-trunk variety occur in 1 in 500000 live births. Giant congenital nevi are usually disfiguring and have a malignant potential. The lifetime risk for development of malignant melanoma in GCN has been variably estimated at between 4% and 42%, considerably higher than that of the normal population. Only 2% of all melanomas occur in patients younger than 20 years, and even fewer (0.3%-0.4%) occur prepubertally. Up to half of malignant melanomas occurring in patients younger than 20 years are thought to occur within GCNs, and the risk of malignant transformation is thought to be greatest within the first 10 years of life. However, the true incidence of congenital malignant melanoma is unknown, and from our review of the available literature, it appears that some of the cases described as “neonatal melanoma” may have been mistakenly interpreted as malignant lesions.

Neonatal malignant melanoma is extremely rare (Table). Excluding melanoma arising from maternal malignant melanoma via placental metastases (because this does not present a diagnostic dilemma), there are just 15 reported cases of neonatal malignant melanoma. Nine neonatal melanomas developed within a GCN or preexisting nevus; there was evidence of metastases or local spread in 4 of these patients, 3 of whom subsequently died. The other 6 cases arose de novo (ie, on apparently normal...
skin), and 3 of these proved fatal. We have not included cases where the diagnosis of melanoma was not made or where the lesion was not documented within the first month of life.\footnote{7}

Malignant melanoma is a notoriously difficult diagnostic problem in children, especially neonates, because clinical indicators such as changes in color, size, shape, rapid growth rate, nodularity, and even ulceration may occur in benignly evolving GCNs. Many histologic features accepted as evidence of malignancy in an adult may also be present in benign lesions in infants (eg, mitotic activity, nuclear pleomorphism, and pagetoid melanocytic proliferation).\footnote{17} It is particularly important to recognize that the morphologic findings of melanocytic lesions cannot be confidently interpreted on frozen tissue sections, so this method should be used with extreme caution in the diagnosis of pigmented lesions.\footnote{21}

Herein we describe lesions within GCNs that, although clinically alarming, proved via histologic analysis and clinical behavior to be benign. The clinical picture of these lesions is represented by 2 patterns: (1) GCNs often exhibit clinically small dermal nodules (<1 cm in diameter). These are often apparent at birth but can arise throughout life, with most developing in childhood.\footnote{22} They vary in color from pale to very dark brown and usually have an intact epidermis. (2) Large dermal nodules (>1 cm in diameter) are less frequent. They may grow rapidly initially, occasionally ulcerate, and are often deeply pigmented. If left untreated, they usually become smaller and softer and do not exhibit a malignant phenotype.\footnote{12,22-25}

Within these 2 clinical patterns, the histologic appearances may vary. The larger dermal nodules may contain various cell types owing to the embryonic development of melanocytes from the neural crest.\footnote{17} The range of histologic appearances include the following:

Benign “Proliferative” or Expansile Nodules. This term describes the histologic appearance of highly cellular foci or nodules of atypical melanocytes. This is a microscopic diagnosis, but the appearance generally correlates with the smaller dermal nodules.

Two types of proliferative nodules have been described: (1) atypical epithelioid melanocytic cells with infrequent mitoses blending imperceptibly with the underlying nevus and showing evidence of maturation, as described by Elder and Murphy,\footnote{20}; and (2) sharply demarcated “nodules” of large epithelioid cells with abundant cytoplasm and no mitoses present within the papillary or mid-dermis, as described by Collina et al.\footnote{27} Within both types of nodule there is little or no necrosis, few if any mitoses, and no atypical junctional component.

Tumoral Dermal Nodules and Subcutaneous Nodules. These may be composed of monomorphous, epithelioid, and spindle or small melanocytes and may show neural or, more rarely, mesenchymal differentiation. In addition, hamartomatous elements may be present, including adipose cells and cartilage.\footnote{17} One type described by Mancianti et al\footnote{12} has been termed a “nodular proliferative neurocristic hamartoma” and is composed of more than 1 cell type. These nodules may exhibit variable cytologic atypia but, again, all usually blend in with the underlying nevus cells and show little or no necrosis. Normal mitotic figures may be present and are sometimes numerous, reflecting this benign rapid growth.\footnote{23}

Malignancy was suspected clinically in both of our patients because they presented with ulcerated dermal nodules arising within a GCN. In 1 case this suspicion was supported by the erroneous interpretation of fresh frozen sections as showing evidence of malignancy. Subsequent careful histologic assessment, however, determined that in both cases the lesions were benign.

However, the histologic findings of the nodules in the 2 cases were strikingly different, which illustrates the wide spectrum of changes that may be seen in benign pigmented lesions in the neonate. The first case, although clinically a large ulcerated nodular lesion, histologically was quite unremarkable, showing features consistent with a benign congenital nevus only and a benign proliferative nodule composed of monomorphous nevus cells. The second case is thought to represent a large dermal “tumoral” nodule arising within a GCN. In general, malignant melanoma arising within a congenital nevus is sharply demarcated rather than blending imperceptibly with the adjacent nevus as was the case in this lesion. Previous reports have recognized the presence of similar benign nodules within GCNs that behave in a nonaggressive manner.\footnote{12,23,25} Despite their clinically alarming appearance, in time these nodules may reduce in size, become softer,\footnote{24,25} even regress completely, and the histologic features become less worrisome.

Drawing on our own experience and the excellent prognosis of many of the reported cases, we believe that some previously reported cases of neonatal malignant melanoma were probably not truly malignant at all. Man-
ciani et al\textsuperscript{12} studied the in vitro behavior of cell lines sampled from tumors in 2 neonates diagnosed as having congenital malignant melanoma. Cultures of cell lines from the tumors failed to demonstrate a malignant phenotype in growth characteristics, karyotype, or cell proliferation markers, and both infants survived with no evidence of metastatic lesions. Carrol et al\textsuperscript{24} also reported a case of a neonate with a congenital nevus that contained

<table>
<thead>
<tr>
<th>Source</th>
<th>Maternal Disease</th>
<th>Gestational Age</th>
<th>Sex</th>
<th>Age at Diagnosis</th>
<th>Site of Lesion</th>
<th>Metastatic Disease</th>
<th>Outcome</th>
<th>Histology</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Oldhoff and Koudstaal,\textsuperscript{6} 1968</td>
<td>No</td>
<td>No data</td>
<td>M</td>
<td>At birth</td>
<td>Right thigh</td>
<td>No</td>
<td>Alive at 10 y</td>
<td>Papillomatous tumor, pleomorphic cells, mitotic activity, diagnosis: malignant melanoma</td>
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<td>Stromberg,\textsuperscript{7} 1979</td>
<td>No data</td>
<td>No data</td>
<td>M</td>
<td>At birth</td>
<td>Temple</td>
<td>Extension through dura</td>
<td>Alive at 6 mo</td>
<td>Foci of malignant melanoma in GCN Malignant melanoma with GCN</td>
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<tr>
<td>Campbell et al,\textsuperscript{11} 1987</td>
<td>No 33 wk</td>
<td>M</td>
<td>In utero, hydrocephalus</td>
<td>Mass over spine</td>
<td>Lungs, liver, and spleen</td>
<td>Died at 17 min</td>
<td>Malignant melanoma (tumor nodule)</td>
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<td></td>
</tr>
<tr>
<td>Narayasingh and Busby,\textsuperscript{3} 1986</td>
<td>No 35 wk</td>
<td>M</td>
<td>At birth</td>
<td>Extensive over back containing tumor nodules; multiple satellite lesions</td>
<td>Liver</td>
<td>Died at 6 wk</td>
<td>Malignant melanoma</td>
<td>Skin grafts and lymphocyte injection</td>
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</tr>
<tr>
<td>Mancianti et al,\textsuperscript{12} 1990</td>
<td>No data</td>
<td>No data</td>
<td>No data 8 wk</td>
<td>Right thigh</td>
<td>No</td>
<td>Alive at 41 mo</td>
<td>Dermal tumor blending with base of nevus</td>
<td></td>
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<td>Mancianti et al,\textsuperscript{12} 1990</td>
<td>No data</td>
<td>No data</td>
<td>No data 3 wk</td>
<td>Bathing-trunk nevus with nodules</td>
<td>No</td>
<td>Alive at 18 mo</td>
<td>Neural type of tumor with cells blending with nevus</td>
<td></td>
<td></td>
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<tr>
<td>Baeder et al,\textsuperscript{13} 1992</td>
<td>No Term</td>
<td>F</td>
<td>At birth</td>
<td>Thoracolumbar and gluteal</td>
<td>No</td>
<td>Alive at 4 mo</td>
<td>Focal areas of malignant melanoma within GCN</td>
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<tr>
<td>Ishii et al,\textsuperscript{15} 1991</td>
<td>No 37 wk (twin)</td>
<td>M</td>
<td>Present at birth, diagnosed 40 d</td>
<td>Left thigh</td>
<td>Lung, bone, liver, and skin</td>
<td>Died at 18 mo</td>
<td>Malignant melanoma in nevus</td>
<td>Excision and chemotherapy</td>
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<tr>
<td>Koyama et al,\textsuperscript{14} 1996</td>
<td>No 39 wk</td>
<td>F</td>
<td>At birth</td>
<td>Scalp with nodules</td>
<td>No</td>
<td>No data</td>
<td>Melanocytic lesion with rhabdomyogenic differentiation</td>
<td>Excision</td>
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<tr>
<td>Coe,\textsuperscript{4} 1925</td>
<td>No Term</td>
<td>F</td>
<td>Present at birth, diagnosed 8 wk</td>
<td>Head</td>
<td>Neck, abdomen</td>
<td>Died at 5 mo</td>
<td>No data</td>
<td>No data</td>
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<tr>
<td>Sweet and Connerty,\textsuperscript{5} 1941</td>
<td>No Term</td>
<td>M</td>
<td>Present at birth, diagnosed 7 d</td>
<td>Buttocks</td>
<td>Generalized</td>
<td>Died at 17 d</td>
<td>Widespread malignant melanoma</td>
<td>No data</td>
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<td>Stromberg,\textsuperscript{7} 1979</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>Present at birth, diagnosed 5 mo</td>
<td>Mastoid process</td>
<td>2 Nodes</td>
<td>Alive at 18 y</td>
<td>Malignant melanoma Wide excision and lymph node dissection 12 courses of chemotherapy and removal of 6 lesions</td>
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<tr>
<td>Hayes and Green,\textsuperscript{8} 1984</td>
<td>No Term</td>
<td>M</td>
<td>At birth</td>
<td>Disseminated tumor</td>
<td>Groin nodes and hepatosplenomegaly</td>
<td>Alive at 5 y 10 mo</td>
<td>Malignant melanoma</td>
<td>No data</td>
<td></td>
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<tr>
<td>Prose et al,\textsuperscript{9} 1987</td>
<td>No NS</td>
<td>F</td>
<td>6 wk</td>
<td>Abdomen</td>
<td>No</td>
<td>Alive at 1 y</td>
<td>Malignant melanoma sheets and nests of pleomorphic cells</td>
<td>Excision</td>
<td></td>
</tr>
<tr>
<td>Song et al,\textsuperscript{10} 1990</td>
<td>No 29 wk</td>
<td>M</td>
<td>At birth</td>
<td>Occiput</td>
<td>No</td>
<td>Died at 2 h</td>
<td>Solid pigmented lesion with large monomorphic cells and no metastases</td>
<td>None</td>
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<tr>
<td>Holland,\textsuperscript{1} 1949</td>
<td>Yes Term</td>
<td>M</td>
<td>8 mo</td>
<td>Generalized subcutaneous nodules</td>
<td>Yes, hepatosplenomegaly</td>
<td>Died at 10 mo</td>
<td>NS</td>
<td>No data</td>
<td></td>
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<tr>
<td>Gottron et al,\textsuperscript{5} 1941</td>
<td>Yes Term</td>
<td>No data</td>
<td>5 mo</td>
<td>Left upper quadrant</td>
<td>No data</td>
<td>Died</td>
<td>No data</td>
<td>No data</td>
<td></td>
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<tr>
<td>Dargeon et al,\textsuperscript{2} 1950</td>
<td>Yes Preterm</td>
<td>M</td>
<td>9 mo</td>
<td>Preauricular</td>
<td>Yes</td>
<td>Died at 11 mo</td>
<td>Malignant melanoma</td>
<td>No data</td>
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<td>Brodsky et al,\textsuperscript{3} 1985</td>
<td>Yes 38 wk</td>
<td>M</td>
<td>11 d</td>
<td>Cord blood showed malignant cells; multiple lesions on chest wall</td>
<td>Multiple metastases and hepatomegaly</td>
<td>Died at 7 wk</td>
<td>Widespread malignant melanoma</td>
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</tbody>
</table>

Abbreviations: GCN, giant congenital nevus; NS, not specified.

*See Campbell et al.\textsuperscript{11}
nodules, widespread satellitosis, and even placental deposits with no evidence of metastases at 10 months. Such lesions may represent the extreme end of a wide spectrum of changes seen in melanocytic lesions.

We believe that both of our cases represent benign large dermal nodules within GCNs that clinically, and in 1 case histologically, resembled malignant melanoma. Histologically, case 1 represented a benign proliferation nodule composed of monomorphic epithelioid melanocytes, and case 2 is an example of a large benign mitotically active tumoral dermal nodule. The importance of correctly diagnosing these lesions is self-evident: misdiagnosis may lead to unnecessary treatment and anxiety.

Accurate diagnosis of melanocytic lesions requires careful histologic examination using fixed tissue rather than frozen sections, which do not show the architecture of melanocytes as well. Mitotic activity in pigmented nevi in a newborn can be a normal feature, and the high number of mitoses present in case 2 is thought to reflect the rapid proliferative nature of the lesion rather than malignant transformation. In contrast, case 1 demonstrated alarming clinical features but histologically exhibited a much more benign appearance.

Neither child demonstrated any signs of malignancy at 3.5 years’ follow-up. From our own experience and literature review we find that although lesions can appear alarming, one must exercise extreme caution in making a diagnosis of malignant melanoma in a healthy neonate. We therefore recommend rapid initial physical assessment, magnetic resonance imaging identification of possible neural involvement, and early and expert histologic analysis of fixed tissue.

In summary, 2 neonates presented with nodular lesions within a GCN that were clinically suspected to be due to malignant transformation. In both cases, careful histologic evaluation showed the nodules to be benign, and 3.5 years later showed no signs of progression. Benign nodules within GCNs are frequently seen, and malignant transformation is exceptionally rare in the neonate. Two clinical patterns are recognized (large and small nodules), but histologic patterns vary considerably. Formalin-fixed tissue is necessary for accurate diagnosis.

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