Pregnancy-Associated Hyperkeratosis of the Nipple

A Report of 25 Cases

H. William Higgins, MD; Jennifer Jenkins, MD, MPH; Thomas D. Horn, MD, MBA; George Kroumpouzos, MD, PhD

Importance: Reported physiologic nipple changes in pregnancy do not include hyperkeratosis and are expected to resolve or improve post partum. Hyperkeratosis of the nipple and/or areola can develop in the context of inflammatory diseases (such as atopic dermatitis), in acanthosis nigricans, as an extension of epidermal nevus, after estrogen treatment, and/or in nevoid hyperkeratosis of the nipple and areola. We performed a clinicopathologic analysis of cases of pregnancy-associated nipple hyperkeratosis.

Observations: Twenty-five cases of pregnancy-associated nipple hyperkeratosis identified during a 5-year period (January 1, 2007, through December 31, 2012) are reported. The lesions were bilateral and involved predominantly the top of the nipple. Lesions were symptomatic in 17 patients (68%), causing tenderness or discomfort, pruritus, sensitivity to touch, and/or discomfort with breastfeeding. Nine patients (36%) experienced symptomatic aggravation only during pregnancy or breastfeeding. The lesions persisted post partum in 22 patients (88%). Histopathologic features were conspicuous orthokeratotic hyperkeratosis, with papillomatosis and acanthosis being mild or absent.

Conclusions and Relevance: Pregnancy-associated hyperkeratosis of the nipple can be symptomatic and persist post partum. It may represent a physiologic change of pregnancy. The characteristic clinicopathologic features of this disorder allow differentiation from nevoid hyperkeratosis of the nipple and areola. We suggest that this distinctive clinicopathologic entity be called pregnancy-associated hyperkeratosis of the nipple.


P HYSIOLOGIC CHANGES OF THE nipple and areola during pregnancy include enlargement, hyperpigmentation, secondary areolae, erectile nipples, prominence of veins, striae, and enlargement of the Montgomery glands or tubercles (hypertrophied sebaceous glands). In addition, benign tumors, such as seborrheic keratoses, skin tags, and warts, can develop on the nipple during gestation. Furthermore, the nipple can be affected in pregnancy by diseases, such as atopic dermatitis, and other conditions associated with hyperkeratosis of the nipple and areola (HNA), such as acanthosis nigricans, ichthyosis, and Darier disease. The idiopathic form of HNA is reported as nevoid HNA. More than 70 cases of HNA have been reported. Although HNA can worsen, become bilateral in pregnancy, or both, onset during or immediately after pregnancy has been only exceptionally reported. It has been postulated that endocrine factors may be involved in the etiopathogenesis of HNA because the lesions worsen in pregnancy and have been associated with estrogen therapy.

In this case series we describe 25 patients with pregnancy-related hyperkeratosis of the nipple. We discuss the distinctive clinicopathologic features, differentiation from other entities (such as HNA), postpartum prognosis, and treatment.

Clinical and histopathologic data were obtained from a medical record review of cases that were seen during a 5-year period (January 1, 2007, through December 31, 2012) in a dermatology clinic of a health system. Documentation included photography of lesions; medical, family, and ob-
stric history; postpartum course; and treatment. Patients’ response to treatment was rated by the physician as none (absence of any improvement), mild (minimal improvement), moderate (satisfactory response), and complete (resolution of lesions). Nine patients underwent histopathologic examination of the lesions. The study was determined to be exempt from institutional review board review by the Harvard Pilgrim Health Care Human Studies Committee.

### REPORT OF CASES

Twenty-five patients, aged 23 to 42 years, presented with hyperkeratosis of the nipple in association with pregnancy (Table). Twenty patients (80%) developed the lesions in the second or third trimester and 3 patients (12%) in the first trimester. In the remaining 2 patients, the lesions were noticed by the physician post partum, but pa-

### Table. Clinical Findings of the Study Patients

<table>
<thead>
<tr>
<th>Patient No./Ape, y/a</th>
<th>Involvementb</th>
<th>Dermatologic Findings</th>
<th>Symptoms</th>
<th>Affected/Total Pregnancies</th>
<th>Postpartum Duration and Course, yc</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/38</td>
<td>Focal</td>
<td>Focally warty, pink or yellow, fissured papules</td>
<td>Sensitive to touch</td>
<td>3/3</td>
<td>9</td>
<td>12% Ammonium lactate cream (MDR)</td>
</tr>
<tr>
<td>2/34</td>
<td>Focal</td>
<td>Focal, warty, pink or yellow papules</td>
<td>No</td>
<td>2/2</td>
<td>6</td>
<td>Emollients (MR)</td>
</tr>
<tr>
<td>3/32</td>
<td>Diffuse</td>
<td>Mildly hyperkeratotic, focally warty, fissured, infiltrated papules</td>
<td>Tenderness or discomfort</td>
<td>4/4</td>
<td>14</td>
<td>Low-potency topical steroids (MR)</td>
</tr>
<tr>
<td>4/31</td>
<td>Diffuse</td>
<td>Mildly warty, minute papules</td>
<td>Sensitive to touch</td>
<td>2/2</td>
<td>10</td>
<td>Emollients (MR)</td>
</tr>
<tr>
<td>5/29</td>
<td>Focal, areola less affected</td>
<td>Mildly hyperkeratotic, yellow papules</td>
<td>Mildly pruritic</td>
<td>2/2</td>
<td>2</td>
<td>0.025% Tretinoin cream after second pregnancy (MDR)</td>
</tr>
<tr>
<td>6/33</td>
<td>Diffuse</td>
<td>Moderately hyperkeratotic, yellow, confluent, fissured papules</td>
<td>Pain during breastfeeding</td>
<td>2/2 (1 twin)</td>
<td>12</td>
<td>Low-potency topical steroids (MR)</td>
</tr>
<tr>
<td>7/29</td>
<td>Focal; R&gt;L</td>
<td>Moderately hyperkeratotic, yellow, inflammatory papules</td>
<td>Mild tenderness or discomfort</td>
<td>3/3 (1 twin)</td>
<td>25</td>
<td>12% Ammonium lactate cream after last pregnancy (MDR)</td>
</tr>
<tr>
<td>8/31</td>
<td>Diffuse</td>
<td>Mildly hyperkeratotic, tan papules</td>
<td>No</td>
<td>3/3</td>
<td>Improved after breastfeeding</td>
<td>None</td>
</tr>
<tr>
<td>9/35</td>
<td>Diffuse; areola less affected</td>
<td>Moderately hyperkeratotic, yellow, inflammatory papules</td>
<td>Mildly pruritic</td>
<td>2/2</td>
<td>Improved prior to breastfeeding</td>
<td>None</td>
</tr>
<tr>
<td>10/31</td>
<td>Diffuse</td>
<td>Warty, pink or yellow papules</td>
<td>Tenderness or discomfort during breastfeeding</td>
<td>1/1</td>
<td>24</td>
<td>None</td>
</tr>
<tr>
<td>11/32</td>
<td>Diffuse</td>
<td>Mildly warty tan papules</td>
<td>No</td>
<td>1/1</td>
<td>1</td>
<td>Spontaneous pp improvement</td>
</tr>
<tr>
<td>12/29</td>
<td>Diffuse</td>
<td>Mildly warty, pink to yellow papules</td>
<td>Tenderness or discomfort in pregnancy</td>
<td>1/1 (twin)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>13/32</td>
<td>Diffuse; R&gt;L</td>
<td>Moderately hyperkeratotic, yellow, confluent, fissured papules</td>
<td>Tenderness or discomfort, breastfeeding difficulties</td>
<td>2/2</td>
<td>Spontaneous pp improvement</td>
<td></td>
</tr>
<tr>
<td>14/29</td>
<td>Diffuse</td>
<td>Mildly warty, tan papules</td>
<td>No</td>
<td>3/3 (1 twin)</td>
<td>9</td>
<td>None</td>
</tr>
<tr>
<td>15/30</td>
<td>Diffuse</td>
<td>Moderately hyperkeratotic, yellow papules</td>
<td>Mild tenderness or discomfort with breastfeeding</td>
<td>3/8 (3 full term)</td>
<td>13 y; worse with each full-term pregnancy</td>
<td>None</td>
</tr>
<tr>
<td>16/31</td>
<td>Focal, well demarcated</td>
<td>Warty, yellow papules</td>
<td>Mild tenderness or discomfort during breastfeeding</td>
<td>1/2 (1 full term)</td>
<td>4 y; worse with full-term pregnancy (did not breastfeed)</td>
<td>0.025% Tretinoin cream (MR)</td>
</tr>
<tr>
<td>17/23</td>
<td>Focal, well demarcated</td>
<td>Warty, yellow papules</td>
<td>Mild tenderness or discomfort in pregnancy</td>
<td>1/1</td>
<td>10</td>
<td>Emollients (MR)</td>
</tr>
<tr>
<td>18/37</td>
<td>Focal</td>
<td>Moderately hyperkeratotic, yellow papules</td>
<td>Tenderness or discomfort during breastfeeding of first child</td>
<td>2/2</td>
<td>5</td>
<td>Emollients (MR)</td>
</tr>
<tr>
<td>19/24</td>
<td>Focal</td>
<td>Moderately hyperkeratotic, yellow papules</td>
<td>No</td>
<td>3/3</td>
<td>17</td>
<td>None</td>
</tr>
<tr>
<td>20/34</td>
<td>Focal</td>
<td>Moderately hyperkeratotic, tan, confluent papules</td>
<td>No</td>
<td>2/2</td>
<td>10</td>
<td>None</td>
</tr>
<tr>
<td>21/42</td>
<td>Focal</td>
<td>Focally hyperkeratotic, tan papules</td>
<td>Tenderness or discomfort during breastfeeding</td>
<td>1/2; lesions in 2nd pregnancy</td>
<td>2</td>
<td>Lanolin-based emollient (NR)</td>
</tr>
<tr>
<td>22/25</td>
<td>Focal</td>
<td>Mildly hyperkeratotic, yellow papules</td>
<td>Tenderness or discomfort during breastfeeding</td>
<td>3/3</td>
<td>17</td>
<td>Lanolin-based emollient (NR)</td>
</tr>
<tr>
<td>23/36</td>
<td>Focal; R&gt;L</td>
<td>Mildly hyperkeratotic, tan papules</td>
<td>No</td>
<td>1/1</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>24/22</td>
<td>Focal</td>
<td>Warty, yellow papules</td>
<td>No</td>
<td>1/1</td>
<td>8</td>
<td>None</td>
</tr>
<tr>
<td>25/31</td>
<td>Focal; L&gt;R</td>
<td>Mildly hyperkeratotic, yellow papules</td>
<td>Sensitive to touch</td>
<td>2/3 (2 full term)</td>
<td>16</td>
<td>12% Ammonium lactate cream (MDR)</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; MDR, moderate response; MR, mild response; NR, no response; pp, postpartum.

aAge of patient at presentation.
bSymmetric, unless otherwise noted.
cPersisted post partum, unless otherwise noted.
tients had noticed their onset in the third trimester. All cases showed bilateral, predominantly symmetric involvement (Figure 1A). Fourteen cases (56%) involved only focally the top of the nipple (Figure 1B), whereas the rest involved the entire top (Figure 1C). The lesions were yellow (Figure 1A-C) to tan or mildly pigmented (Figure 1D), hyperkeratotic, and/or warty papules. Occasionally, desquamation of the areas (Figure 1E), mild erythema (Figure 1C), or both was seen. Lesions were symptomatic in 17 patients (68%): 10 patients reported mild tenderness or discomfort post partum, 3 had sensitivity to touch, and 2 had tenderness or discomfort in pregnancy. Eight patients (32%) reported tenderness, and 1 patient (4%) reported improvement with breastfeeding (Table). The lesions persisted post partum in 22 patients (88%). Persistence of lesions was not associated with any medications. The lesions were unremitting between pregnancies in 16 of 18 patients (89%) and worse with each full-term pregnancy in 3 of the 18 patients (17%) (Table). Two patients had a history of atopic dermatitis, and another had a history of psoriasis, but there were no signs of active disease during pregnancy. There was a family history of psoriasis in 1 patient.

The most typical histopathologic feature was prominent orthokeratotic hyperkeratosis (Figure 2A and B), which was often massive (Figure 2A). Epidermal hyperplasia was absent, and papillomatosis was mild or absent; of note, mild papillomatosis is a normal finding in this anatomical area. Typical histopathologic features of HNA, such as ramifying epidermal hyperplasia with marked elongation of rete ridges (Figure 2C), were absent. No histopathologic features of inflammatory dermatoses, such as atopic dermatitis or psoriasis, were seen.

We present a series of 25 patients with pregnancy-associated hyperkeratosis of the nipple. All patients were diagnosed as having nipple hyperkeratosis during pregnancy or in the immediate postpartum period. To our knowledge, this is the largest series of patients with hyperkeratosis of the nipple. Most lesions were yellow to tan, hyperkeratotic, and/or warty papules. Most cases involved predominantly the top of the nipple and persisted post partum. Lesions were symptomatic in more than two-thirds of patients.

The differential diagnosis includes acanthosis nigricans; pregnancy-induced pseudoacanthotic changes; diseases that can affect the nipple and may worsen in pregnancy, such as atopic dermatitis; superimposed benign tumors, such as seborrheic keratoses, warts, and epidermal nevi; and HNA. Acanthosis nigricans has been associated with HNA, but features of acanthosis nigricans, such as hyperpigmentation of the areolar and periareolar areas, involvement of the neck, intertriginous areas, genital skin, and/or oral mucosa, were not seen in...
our patients. In addition, histopathologic features of acanthosis nigricans, such as prominent acanthosis, conspicuous papillomatosis, and suprapapillary epidermal thinning, were not observed in our series. Finally, our patients had no underlying endocrinopathy or malignant neoplasm that could have triggered acanthosis nigricans. Pseudocarcinomatous changes have been reported in pregnancy but did not involve the nipple and resolved post partum. The history, clinical course, and histopathologic findings exclude epidermal nevi and warts. Furthermore, the symmetric distribution, histopathologic findings, and absence of a significant number of seborrheic keratoses elsewhere make seborrheic keratoses unlikely.

Hyperkeratosis of the nipple and areola has been classified by Levy-Frankel into 3 types. Type 1 is an extension of epidermal nevus. Type 2 is associated with other dermatoses, such as acanthosis nigricans, atopic dermatitis, ichthyosis, Darier disease, or lymphoma. Type 3 is the isolated nevoid variant (nevoid HNA). Several authors have challenged the designation nevoid for HNA type 3 and suggest that idiopathic be used instead. Other authors disputed the inclusion of the type 1 variant into the spectrum of HNA. The onset of HNA is usually in the second or third decade of life. Our cases can be differentiated from HNA on the basis of several clinicopathologic features. First, HNA starts earlier in life (second to third decade) than our patients’ presentation and affects solely the nipple in only 17% of cases. Hyperkeratosis of the nipple and areola starts only exceptionally in pregnancy, and only 1 of 6 cases with onset in pregnancy involved exclusively the nipple. Second, HNA shows verrucous lesions that are hyperpigmented, confluent, and diffuse, reminiscent of a verrucous epidermal nevus. In comparison, our cases showed yellow to mildly tan, focal hyperkeratotic, or wart-like lesions. Third, histologic features that characterize HNA, such as ramifying epidermal hyperplasia with marked elongation of the rete ridges, basal layer hyperpigmentation, irregular filiform acanthosis, and occasional keratotic plugging, were not observed in our cases.

Regarding the etiology of this disorder, it may represent a physiologic change of pregnancy. This is supported by onset during pregnancy or in the immediate postpartum period and worsening with subsequent pregnancies, which suggest an effect of high estrogen levels during pregnancy. This view agrees with prior reports describing estrogen-induced hyperkeratosis of the nipple in males. Along the same lines, unilateral HNA associated with androgen insensitivity and estrogen replacement therapy in an individual with female phenotype has been reported. Furthermore, hyperkeratosis of the nipple has resulted from administration of diethylstilbestrol to guinea pigs for more than 20 days before term. Alternatively, this disorder may result from friction in women who develop breast enlargement during pregnancy and are somehow predisposed. Friction may also contribute to the chronicity of the lesions. Although one may suggest that our cases represent a forme fruste of HNA or overlap with HNA, the clinicopathologic features in our series differ from those of HNA.

Treatment was challenging in our series because emollients and topical medications provided only mild to moderate response. Petrolatum- and lanolin-based emollients were ineffective or only mildly effective, and low-potency topical steroids were mildly effective. A 12% ammonium lactate cream and a 12% lactic acid lotion were moderately effective. Two patients used a 0.025% tretinoin cream with mild or moderate improvement. Treatment modalities in HNA, such as a 6% salicylic acid gel and topical calcipotriol, should also be tried in this condition. The use of potent keratolytics, such as urea, under occlusion may be effective in the entity we present, but a prospective study is required to clarify their efficacy and whether they can be tolerated in this anatomical area without adverse effects, such as irritation. A short course of topical tretinoin has been effective in HNA, but significant irritation as an adverse effect and recurrence after cessation were reported. Isotretinoin gel was effective in another case. A sustained remission of HNA has been maintained with low-dose acitretin combined with calcipotriol. Surgical modalities, such as cryotherapy, shave excision, surgical removal, carbon dioxide laser, and radiofrequency ablation, have been used in unresponsive cases of HNA and might also find utility here. Symptomatic, recalcitrant lesions showed a complete response to curettage in 1 of our patients.

In conclusion, this series of patients represents a distinct clinicopathologic presentation of pregnancy-associated nipple hyperkeratosis. This disorder can be differentiated from HNA based on later onset in life, presentation during or immediately after pregnancy, more focal involvement of the nipple, and characteristic histopathologic features. In the authors’ experience, this entity is reasonably common, whereas onset of nevoid HNA in pregnancy has been only exceptionally reported. Because the lesions can be persistent and symptomatic, physicians should be familiar with pregnancy-associated hyperkeratosis of the nipple and able to counsel the patient appropriately on prognosis and treatment.

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Author Contributions: Dr Kroumpouzos had full access to all data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Jenkins, Horn, and Kroumpouzos. Acquisition of data: Jenkins, Horn, and Kroumpouzos. Analysis and interpretation of data: All authors. Drafting of the manuscript: Higgins and Kroumpouzos. Critical revision of the manuscript for important intellectual content: Jenkins, Horn, and Kroumpouzos. Administrative, technical, or material support: All authors. Study supervision: Kroumpouzos.
Conflict of Interest Disclosures: None reported.

REFERENCES


