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Ibrahim Hassan Galadari, MD, PhD, FRCP

*Dhabi, United Arab Emirates*
EDITORIAL

Contemporary American Dermatology: Continuing Medical Education I

W. Clark Lambert, MD, PhD; Lawrence Charles Parish, MD, MD (Hon)

“The time has come,” the Walrus said, “to talk of many things: of [CME, and MOC, and recertification,] and kings.”*

Lewis Carroll, “The Walrus and the Carpenter,” Through the Looking-Glass, and What Alice Found There

Continuing medical education (CME) continues to be among the buzzwords of the 21st century. Physicians are subject to penalties for not completing a specified number of hours of CME in a calendar year. Medical societies continue to thrive on providing CME programs, while medical schools have deans whose sole responsibilities are CME programs.

DEFINITIONS

The American Medical Association defines CME in the following terms: "A physician's continuing professional development is critical to keeping up with advances in medicine and with changes in the delivery of care."

Harvard Medical School's CME Web site states: “Our continuing education mission is to optimize patient care. To this end, our programs are designed to provide the most up-to-date information and strategies for physicians and allied health professionals.”

On their Web site, the Johns Hopkins School of Medicine offers a slightly different approach: “We strive to provide exemplary educational activities, which teach evidence-based practices and identify new and emerging health care needs and opportunities from research through delivery of care so that, through education, we can significantly improve health.”

If the definition were stated more succinctly, it might read: Physicians have an obligation to stay continually abreast of advancements in their respective fields.

PURPOSE AND MEANS

CME “credits” can be obtained in any number of ways, from attending a meeting to reading a journal. There have been annual meetings, international congresses, and specific courses offered by societies, schools, hospitals, and independent organizations. There are journals, books, and even independent supplements purporting to provide educational information.

Why then an editorial on the subject? CME is not something new but something that has been an integral part of medicine. Even when American medical schools consisted of a 3-year ungraded curriculum, there were spring and fall courses to supplement the curriculum and to permit practitioners to learn about recent advancements. The postgraduate schools and polyclinics developed out of this need.

As medicine evolved in the 20th century in the United States, organized postgraduate training in residencies and then examinations to measure competency emerged. A physician became “board certified” in one and/or another specialty, with the certification generally awarded for life, following the passing of a thorough examination and, in some specialties, a designated number of years of practice beyond residency. More recently, more has been required. Initially, CME was sufficient, but not so long ago, “maintenance of certification (MOC)” and now “recertification” have become the norm, with initial board certification awarded on a time-limited basis. Recertification has itself been expanded to include not just periodically taking a rigorous, proctored examination, but also maintaining a list of other activities, such as the monitoring of office records.

THE DOWNSIDE

With this progress came rules and regulations and new accrediting and regulatory bodies. State boards of medicine began to demand a certain number of CME hours to maintain licensure. With each political wind, they added new requirements,

*With apologies to Lewis Carroll.
such as safety and quality (whatever these should mean). Forget that medicine is a broad specialty, and many physicians do not provide hospital care or practice general medicine. We wonder whether these legislators take recurring examination themselves, before they are permitted to write laws or pass them.

Each of the activities described above has itself become formalized, with presenters of talks at CME-approved events, for example, required to present “goals and objectives,” often requiring extensive information on why and how each topic was presented and to have a disinterested party present to evaluate the event. Then, the presenter is required to document how the success or failure of each aspect of the presentation was measured, and these results have to be presented to an accrediting agency. All of these regulatory activities have laudable goals; they are ostensibly designed to help the physician and protect the public, and each one, individually, may arguably do so. This, in turn, fuels and justifies further calls for increased regulation1; however, we believe that, collectively, these regulatory measures have become counterproductive. For the physician, keeping up and helping other physicians keep up have become ways of life. The tail is now wagging the dog!

Stricter and more stringent rules have permitted offices of CME to develop. Because they are now able to exert more authority, the bureaucrats running these departments have become more powerful. With this, new regulations and charges have emerged, and the entire process is expanding and redoubling on itself, creating an absurd atmosphere. We are leaving Lewis Carroll behind and are progressing to the world of George Orwell.

THE DOWNSIDE MAGNIFIED

Imagine organizing an international meeting and being directed to pay for an associate dean and a secretary to attend the congress to ensure that the program was appropriate. What happens if the speaker diverges from his or her abstract or the presentation is a somnolent affair? Should the audience be punished even more by the unnecessary charges?

Consider a journal contribution that disseminates questionable information. The author is an alleged authority, and the peer reviewers agreed with his or her ideas. The participant must swallow the dribble completely, for fear of not passing the recertification examination thrust upon him or her. Alternatively, the information may be correct but irrelevant to the physician, who has subspecialized within his or her specialty; he or she must learn it anyway, taking time from learning what is actually relevant and which may help his or her patients to satisfy certification/recertification requirements.

THE LAST STRAW

All of this is occurring in an environment in which the United States is educating and training far too few physicians to meet our needs, not just in primary care specialties, but in other ones as well.2 These regulatory burdens are stressing an already overburdened system. We are also draining other, less developed countries of physicians sorely needed at home.3 Surely, these absurd physician shortages should be addressed before additional regulation is added, even to the extent that it is justified.

REFERENCES

The incidence of dermatologic conditions in the pediatric age group presents a pattern that often differs from that in adults; this is important for epidemiologic studies and population-based analysis. This clinical study was carried out in children up to age 14 in the western part of India. Dermatologic conditions were tabulated based on the etiology, incidence, age, and sex distribution, as well as seasonal variations, and the results were analyzed. There were a total of 390 boys and 310 girls. The majority of skin conditions in newborns are transient. The most common dermatoses found were of infectious etiology (38.43%) in which impetigo (11.13%) and pyoderma (8.9%) were the most common. In infectious etiology, incidence of scabies was 5.32%. Viral warts were the most common viral infections followed by molluscum contagiosum. Incidence of eczema, atopic dermatitis, and sweat gland disorders were 6.64%, 0.83%, and 8.86%, respectively. The study shows various unique features of tropical pediatric dermatology in a developing country, such as high frequency of infections and infectious, nutritional, and environmentally associated disorders. Many of these dermatoses can be controlled by proper environmental sanitation, improving nutrition, awareness among parents and children, and preventing overcrowding. (SKINmed. 2010; 8:136–142)
physical examination including skin and necessary tests such as Gram’s stain, potassium hydroxide examination, Tzanck test, hematology and biochemistry analysis, urine analysis, Wood’s lamp examination, diascopy, purified protein derivative (tuberculin), chest x-ray, skin biopsy, and other investigations as needed. The diseases were tabulated based on the etiology, incidence, age distribution, sex distribution, and seasonal variations and results were analyzed. We did not include patients who had more than one dermatological condition.

RESULTS
In all age groups, there were a total of 390 boys (55.71%) and 310 girls (44.29%) in the study, with a boy to girl ratio of 1.2:0.8. There were 56 (8.00%) boys and 42 (6.01%) girls in the neonate group and 334 (47.71%) boys and 268 (38.28%) girls in the >1 month to 14 years old group (Table I). The dermatologic conditions vary according to age, climate, nutrition, hygiene, socioeconomic class, and heredity (Table II–Table VII). The majority of the skin conditions in the newborn group were transient (physiological) and constituted 73.47%. The most common dermatoses found were of infectious etiology (Table VI), which was 38.43% of the study population. Impetigo and pyoderma were the most common infectious diseases and comprised 11.13% and 8.97%, respectively. The incidence of scabies and pediculosis capitis were 5.32% and 0.5%, respectively. Viral warts are the most common of all viral infections followed by molluscum contagiosum, and viral infection was most common in the 11- to 14-year age group (Table VII). In the hot and humid climate of Ahmedabad, sweat

<table>
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<th>Age Group</th>
<th>Boys, No. (%)</th>
<th>Girls, No. (%)</th>
<th>Total, No. (%)</th>
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<tr>
<td>&lt;1 Month (neonates)</td>
<td>56 (8.00)</td>
<td>42 (6.01)</td>
<td>98 (14.01)</td>
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<td>&gt;1 Month to 14 years</td>
<td>334 (47.71)</td>
<td>268 (38.28)</td>
<td>602 (85.99)</td>
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<td>390 (55.71)</td>
<td>310 (44.29)</td>
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<tr>
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<td>36.74 (36)</td>
<td>4.31 (26)</td>
<td>8.86 (62)</td>
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<td>8.16</td>
</tr>
<tr>
<td>Parasitic</td>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>Allergic disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug eruption</td>
<td>3</td>
<td>3.06</td>
</tr>
</tbody>
</table>
gland disorders (milia, miliaria, and erythema toxicum) were common and we observed 8.86% in our study. Also, sweat gland disorders are more often observed in neonates (36.74%) than in older children (4.31%) (Table III). The percentage of congenital pigmentary disorders in neonates was 10.57% (Table II). Mongolian spots was the most common pigmentary disorder in the neonate group, followed by congenital melanocytic nevus. In the present study, the incidence of eczema was 6.64% and atopic dermatitis was 0.99%. We also observed that eczema was more common in the 6- to 14-year age group (school age group) (Table VII).

Papular urticaria (insect bite reaction) was found in 6.27%, while nutritional disorders were found in about 6.3%. Among the papulosquamous disorders, lichen planus was observed in 2.16% and psoriasis in 0.99%. In the present study, herpes zoster (0.33%), tinea capitis (0.17%), and generalized pruritus (0.17%) were found in children infected with human immunodeficiency virus. Other miscellaneous disorders found were alopecia areata (1.50%), allergic drug reactions (1.33%), vesicobullous disorders (0.99%), collagen disorders (0.99%), nail disorders (0.66%), pruritus (0.66%), geographic tongue (0.17%), syringoma (0.17%), acneform eruption (0.17%), and erythroderma verrucous variable (0.17%). Bacterial infections and sweat gland disorders (miliaria) peak in summer months (April to June) while parasitic infections and eczema were observed more in fall months (October through December) (Table VI). Pityriasis alba was also more common in the summer and fall seasons.

**DISCUSSION**

The various dermatologic conditions vary according to age, geographic location, climate, nutrition, hygiene, socioeconomic class, and heredity. The majority of skin conditions in newborns are transient (physiological) and constituted 73.47%, which is similar to studies done by Nobby and Chakrabarty (69%), Baruah and colleagues (93%), and Kulkarni and Singh (72%). In our study, older children had more incidence of skin conditions than younger children, which is similar to a study done in Turkey \(P<.001\). The most common dermatoses found were infectious disorders, which were found in 38.43% of the study population (Table II). In their study, Dogra and Kumar found only 11.4% of disorders of infectious etiology; however, various other authors in India have reported that disorders of infectious and infestations etiology contributed to 35.6% to 85.2%. We found 5.81% of infestations etiology, similar to the 5% found by Dogra and Kumar. In all these studies, whether institution-based or community-based, infection was the main etiological agent for pediatric dermatoses. Impetigo and pyoderma were the most common infections in our study and comprised 11.13% and 8.97%, respectively. In most of the studies, including one conducted in rural Pakistan, researchers found that pyoderma and impetigo were the most common infections. Poor hygiene, lack of awareness, overcrowding, poverty, and high prevalence of biting flies appeared to be underlying causes for the largest number of cases of pyoderma and impetigo.

We found the incidence of scabies to be 5.32%, compared with the incidence rate found in other reports that range from 5.1% to 22.4%. We found 5.81% of infestations etiology, similar to the 5% found by Dogra and Kumar. In all these studies, whether institution-based or community-based, infection was the main etiological agent for pediatric dermatoses. Impetigo and pyoderma were the most common infections in our study and comprised 11.13% and 8.97%, respectively. In most of the studies, including one conducted in rural Pakistan, researchers found that pyoderma and impetigo were the most common infections. Poor hygiene, lack of awareness, overcrowding, poverty, and high prevalence of biting flies appeared to be underlying causes for the largest number of cases of pyoderma and impetigo.

### Table IV. Pattern of Various Dermatoses in the >1-Month Age Group

<table>
<thead>
<tr>
<th>Dermatoses</th>
<th>No. of Cases</th>
<th>Percentage (n=602)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sweat gland disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miliaria</td>
<td>26</td>
<td>4.31</td>
</tr>
<tr>
<td><strong>Pigmentary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital melanocytic nevus</td>
<td>27</td>
<td>4.49</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>19</td>
<td>3.16</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>14</td>
<td>2.33</td>
</tr>
<tr>
<td>Post-inflammatory hyperpigmentation and hypopigmentation</td>
<td>5</td>
<td>0.83</td>
</tr>
<tr>
<td>Xeroderma pigmentosum</td>
<td>2</td>
<td>0.33</td>
</tr>
<tr>
<td>Mongolian spots</td>
<td>1</td>
<td>0.17</td>
</tr>
<tr>
<td>Lentigines</td>
<td>1</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Dermatitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>40</td>
<td>6.64</td>
</tr>
<tr>
<td>Pityriasis alba</td>
<td>30</td>
<td>4.98</td>
</tr>
<tr>
<td>Papular urticaria</td>
<td>26</td>
<td>4.31</td>
</tr>
<tr>
<td>Seborrheic dermatitis</td>
<td>11</td>
<td>1.82</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>6</td>
<td>0.99</td>
</tr>
<tr>
<td>Lichenoid dermatitis</td>
<td>6</td>
<td>0.99</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>4</td>
<td>0.66</td>
</tr>
<tr>
<td>Perianal dermatitis</td>
<td>4</td>
<td>0.66</td>
</tr>
<tr>
<td>Pompompholyx</td>
<td>2</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Infectious disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial</td>
<td>145</td>
<td>24.90</td>
</tr>
<tr>
<td>Parasitic</td>
<td>35</td>
<td>5.81</td>
</tr>
<tr>
<td>Fungal</td>
<td>47</td>
<td>7.81</td>
</tr>
<tr>
<td>Viral</td>
<td>33</td>
<td>5.48</td>
</tr>
</tbody>
</table>
overseas studies have different infestation rates, such as 19% in Israel, 33.7% in Australia, 50% in Brazil, and 81.5% in Argentina.29–32 The low incidence of pediculosis capitis in our study may be due to more awareness of hair care and easy availability of over-the-counter products for pediculosis capitis in the urban area. Viral warts are common in children and prevalence increases in childhood, with its peak in adolescence, and declines in the second decade of life.6,33 In this study, viral warts were the most common of all viral infections, followed by molluscum contagiosum; the 11- to 14-year age group had more incidence than the rest of the study group (Table VII), which is similar to findings observed in other studies.6,33 These observations are also supported by studies in Turkey and Switzerland and recently in Taiwan and Nigeria, where the higher incidence of warts in children was also found.19,34–36 Surprisingly, the incidence of fungal infection was 7.81% in our study, which was mainly observed in the older age group. Low incidence may be related to newspaper and television advertisements of antifungal products, maturation of sweat glands, and easy availability of over-the-counter products in the urban area. A recently published study also mentioned that dermatophyte infections are declining among new-patient outpatient visits.36

In the hot and humid climate of Ahmedabad, incidence of sweat gland disorders (milia, miliaria, and erythema toxicum) was more common and observed as 8.86%. Another study, however, found the incidence of sweat gland disorders to be between 30% and 40%.37 Incidence of congenital pigmentary disorders (Mongolian spots, hemangioma, melanocytic nevus, sebaceous nevus, and xeroderma pigmentosum) in all age groups in our study was 10.57%, which is much lower than that found by Cordova38 (80%) and Baruah and colleagues (78.40%).17 Their studies mainly related to newborn inpatients, however, while our study mainly refers to outpatients. This may be a reason for the low incidence of pigmentary disorders in our study. Congenital melanocytic nevus was found in 5.51%, while a study done in Hong Kong found 3.6%.39 Incidence of vitiligo in the >1-month age group was 3.16%, similar to the 2.9% observation of Negi and colleagues,21 but higher than that observed in Taiwan (0.09%),35 and lower than that observed in China (20%).40

In the present study, the incidence of eczema was 6.64%, which is similar to Dogra and Kumar (5.2%)40 and Johnson and colleagues (4.66%).41 Other western studies, however, ranged their incidence of eczema from 18% to 34%.10,11 Atopic dermatitis (0.83%) was very low when compared with other studies performed in developed countries, where they found rates ranging from 3% to 28%.35,46–49 Low frequency of atopic dermatitis and eczema may be related to climate, dietary habits, genetics, or other unknown factors. The incidence of papular urticaria in our study was 0.83%, which is similar to Karthikeyan and colleagues (5.27%)34 and Sharma and colleagues (7.5%). Other overseas studies, however, found lower incidences such as 3.3% to 3.6% in Nigeria and 2.3% in Thailand.27,36,50–52 Higher incidence can be explained by the higher prevalence of flea bites and wearing scanty clothes in the hot climatic conditions of Ahmedabad. Nutritional disorders were found in about 6.3% of children, which was less than the 17.5% found in a study by Negi and associates.21 This difference may exist because the study by Negi and associates21 was done in a rural area while our study center was in an urban area. Pityriasis alba was observed more in the 1- to 10-year old age group. The higher incidence may be because of the growth period in children, irregular and inadequate food habit, worm infestation, and in some cases socioeconomic factors. Among the

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. of Patients (n=602)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impetigo</td>
<td>67</td>
<td>11.13</td>
</tr>
<tr>
<td>Pyoderma</td>
<td>54</td>
<td>8.97</td>
</tr>
<tr>
<td>Furuncle</td>
<td>21</td>
<td>3.49</td>
</tr>
<tr>
<td>Mycobacterium</td>
<td>2</td>
<td>0.33</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>1</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Parasitic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scabies</td>
<td>32</td>
<td>5.32</td>
</tr>
<tr>
<td>Pediculosis</td>
<td>3</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinea</td>
<td>33</td>
<td>5.48</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>14</td>
<td>2.33</td>
</tr>
<tr>
<td><strong>Viral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warts</td>
<td>9</td>
<td>1.50</td>
</tr>
<tr>
<td>Molluscum contagiosum</td>
<td>8</td>
<td>1.33</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>8</td>
<td>1.33</td>
</tr>
<tr>
<td>Measles</td>
<td>4</td>
<td>0.66</td>
</tr>
<tr>
<td>Chicken pox</td>
<td>2</td>
<td>0.33</td>
</tr>
<tr>
<td>Herpes virus</td>
<td>2</td>
<td>0.33</td>
</tr>
</tbody>
</table>
Papulosquamous disorders, lichen planus was observed in 2.16%, which is similar to Samman (2%)\(^5\) and Handa and Sahoo (2%),\(^5\) while Kumar and colleagues\(^5\) and Luis-Montoya and colleagues\(^5\) found higher incidences of about 11.2% and 10.2%, respectively. Psoriasis (0.99%) was the second most common papulosquamous disorder after lichen planus in our study which is similar to the findings of Rao and associates (2.4%).\(^2\) Seasonal variations in dermatologic disorders in our study were comparable with those noticed by other investigators.\(^1\)–\(^3\) In our study (Table VI) we found that bacterial infections and sweat gland disorders (miliaria) peaked in the summer months of the hot and humid climate (April to June), while parasitic infections and eczema were more often present in the fall months (October to December). Higher incidence of bacterial infections can be explained by higher prevalence of insect bites in the summer. We did not find the incidence of any specific dermatoses to occur more during January to March or July to September.

### CONCLUSIONS

Seven hundred pediatric patients were examined, 55.71% were boys and 44.29% were girls. Patients in the neonate group constituted 14%, while patients >1 month of age constituted 86% of the total number of patients examined. Physiological skin conditions were more common in the neonate group, while infections and infestations were more common in the older age group. Sweat gland disorders were more common after the infectious etiology, which was also more common in neonates, along with pigmentary disorders. Infection and dermatitis were more common in the older age group. In the category of infectious disease, pyoderma and impetigo were more common. Bacterial infections and sweat gland disorders (miliaria) peak during the summer months, while parasitic infections and eczema occurred more often in the fall months. Pityriasis alba was more common in the summer and fall seasons. Our study shows various unique features of tropical pediatric dermatology such as high frequency of infections and infectious disorders, nutritional disorders, and environmentally associated disorders such as miliaria and papular urticaria. We would like to highlight the fact that many of these dermatoses can be controlled by proper environmental sanitation; improving nutrition; educating parents, children, and society; improvements in living standards; and personal hygiene.

### REFERENCES


---

### Table VI. Seasonal Distributions of Various Dermatoses in the >1-Month Age Group

<table>
<thead>
<tr>
<th>Month</th>
<th>Bacterial, No. (%)</th>
<th>Parasitic, No. (%)</th>
<th>Miliaria, No. (%)</th>
<th>Eczema, No. (%)</th>
<th>Pityriasis Alba, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>January to March</td>
<td>12 (8.27)</td>
<td>2 (5.71)</td>
<td>-</td>
<td>4 (10.00)</td>
<td>5 (16.66)</td>
</tr>
<tr>
<td>April to June</td>
<td>68 (46.89)</td>
<td>9 (25.71)</td>
<td>23 (88.46)</td>
<td>7 (17.50)</td>
<td>9 (30.00)</td>
</tr>
<tr>
<td>July to September</td>
<td>25 (17.24)</td>
<td>5 (14.28)</td>
<td>-</td>
<td>5 (12.50)</td>
<td>4 (13.33)</td>
</tr>
<tr>
<td>October to December</td>
<td>40 (27.58)</td>
<td>19 (54.28)</td>
<td>3 (11.53)</td>
<td>24 (60.00)</td>
<td>12 (40.00)</td>
</tr>
<tr>
<td>Total</td>
<td>145 (100)</td>
<td>35 (100)</td>
<td>26 (100)</td>
<td>40 (100)</td>
<td>30 (100)</td>
</tr>
</tbody>
</table>

### Table VII. Common Dermatoses Among Different Age Groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dermatosis</th>
<th>Percentage as per Age Group (No.)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 Month (n=98)</td>
<td>Mongolian spots</td>
<td>25.51 (25)</td>
</tr>
<tr>
<td>1 Month to 1 year</td>
<td>Milia</td>
<td>20.41 (20)</td>
</tr>
<tr>
<td>1 Year to 5 years</td>
<td>Intertigo</td>
<td>12.28 (14)</td>
</tr>
<tr>
<td>6 Years to 10 years</td>
<td>Hemangioma</td>
<td>11.40 (13)</td>
</tr>
<tr>
<td>11 Years to 14 years</td>
<td>Melanocytic nevus</td>
<td>8.77 (10)</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>37.21 (83)</td>
<td></td>
</tr>
<tr>
<td>Miliaria</td>
<td>8.07 (18)</td>
<td></td>
</tr>
<tr>
<td>Papular urticaria</td>
<td>6.27 (14)</td>
<td></td>
</tr>
<tr>
<td>Pityriasis alba</td>
<td>5.82 (13)</td>
<td></td>
</tr>
<tr>
<td>Fungal infections</td>
<td>10.00 (18)</td>
<td></td>
</tr>
<tr>
<td>Pityriasis alba</td>
<td>6.11 (11)</td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>6.11 (11)</td>
<td></td>
</tr>
<tr>
<td>Viral infections</td>
<td>10.58 (9)</td>
<td></td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>9.41 (8)</td>
<td></td>
</tr>
<tr>
<td>Vitiligo</td>
<td>9.41 (8)</td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>8.23 (7)</td>
<td></td>
</tr>
</tbody>
</table>

*Total number of common dermatoses for that age group. Total number of cases in that age group may be different.

---

papulosquamous disorders; lichen planus was observed in 2.16%, which is similar to Samman (2%)\(^5\) and Handa and Sahoo (2%),\(^5\) while Kumar and colleagues\(^5\) and Luis-Montoya and colleagues\(^5\) found higher incidences of about 11.2% and 10.2%, respectively. Psoriasis (0.99%) was the second most common papulosquamous disorder after lichen planus in our study which is similar to the findings of Rao and associates (2.4%).\(^2\) Seasonal variations in dermatologic disorders in our study were comparable with those noticed by other investigators.\(^1\)–\(^3\) In our study (Table VI) we


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Pemphigus Vulgaris (PV) is a severe, potentially life-threatening autoimmune blistering disease of the skin and mucous membranes associated with autoantibodies against the cadherin-type adhesion molecules desmoglein (Dsg)3 and Dsg1. The binding of immunoglobulin (Ig)G antibodies to Dsg on epidermal keratinocytes leads to intraepithelial blister formation. It is a well recognized fact that PV more frequently affects middle-aged women, including those in their childbearing years. The disease may occur for the first time or flare during pregnancy or immediately after delivery. The association of PV with pregnancy, although very rare, raises numerous questions with regard to its clinical manifestation, management, and prognosis for both the mother and child. Maternal pemphigus autoantibodies are able to cross the placenta, thereby causing neonatal pemphigus in 30% to 45% of the cases, the latter being a transient condition with good prognosis after antibodies are metabolized.

The influence of pregnancy on the evolution of PV has been a matter of debate for decades. Since the description of “acantholytic bullous eruption in the newborn infant of a pemphigus mother” in 1975, almost 50 well documented cases of PV associated with pregnancy have been reported in the literature, adding to earlier existing data. In contrast to a common former belief that women with PV should avoid pregnancy due to high risk of detrimental outcomes to both the mother and the fetus, newer data demonstrate that advances in the treatment of pemphigus and the management of pregnant women with this disease have improved the prognosis for mother and child.

We report 2 more cases of PV and pregnancy, which, while differing from each other in time of occurrence and clinical course, had similar favorable outcomes.

**CASE REPORTS**

**Case 1**

A 27-year-old Caucasian primiparous woman was admitted to the Department of Dermatology, Sofia Faculty of Medicine for a severe vesiculobullous eruption affecting the face, neck, trunk, and extremities (Figure 1) that had occurred 1 week after delivery of a healthy, term-appropriate-for-gestational-age boy. She described an episode of similar but milder eruption, the onset of which coincided with a delayed menstrual cycle and a positive pregnancy test. Subsequent gynecological consultation confirmed an intrauterine pregnancy with a probable period of conception about 2 weeks before the onset of the first blisters. The patient was given a diagnosis of PV at a different institution based on the histology results that revealed suprabasal bulla with acantholysis, spongiosis, and sparse mixed perivascular inflammatory infiltrate in the upper dermis. At that time, oral methylprednisolone 12 mg/d had been administered and was sufficient to control the disease at a stable dose throughout the whole pregnancy. At admission to our department, the diagnosis of PV was confirmed based on histological assessment and positive direct immunofluorescence (DIF) on perilesional skin (Figure 2). High titers (1:640) of circulating IgG antiepithelial cell surface antibodies were detected by indirect immunofluorescence (IIF) on human esophagus substrate. The disease was successfully controlled with 80 mg/d methylprednisolone, subsequently tapered to a maintenance oral dose of 8 mg/d. Oral azathioprine 100 mg/d was initially added but was discontinued in 5 days due to nausea and vomiting. During the next 3-year follow-up the mother’s disease remained stable and her child was in good health.
CASE 2
A 24-year-old Caucasian woman presented to our department due to vesiculobullous eruption initially spread next to a free autologous skin graft following a thermal burn in the area of the right breast. Later lesions disseminated to the abdomen, back, and extremities (Figure 3). The diagnosis of PV was confirmed through histological examination, positive DIF on perilesional skin, and positive IgG antiepithelial cell surface antibodies at a titer of 1:320 by IIF on human esophagus. Methylprednisolone 60 mg/d and azathioprine 100 mg/d led to clinical remission followed by gradual tapering of methylprednisolone to a maintenance dose of 4 mg/d. Since the onset of her disease the patient was regularly assessed with regard to clinical and laboratory data and therapeutic monitoring. During the whole observation period she did not experience severe flare ups and demonstrated negative IIF or low titers of pemphigus antibodies (up to 1:20). Three years after the beginning of PV and nearly 1 year prior to a planned pregnancy, azathioprine was discontinued and the patient remained disease free. She conceived at the age of 28. The dose of methylprednisolone was raised to 16 mg/d at the first month of gestation and was kept unchanged throughout the pregnancy in order to prevent possible exacerbations. After an uneventful pregnancy during which the patient remained clinically healthy, she gave birth through Cesarean section to a healthy, appropriate-for-gestational-age boy. Forty days after delivery, methylprednisolone was tapered again to 8 mg/d. During the next 2 years of follow-up, both the mother and her child remained disease-free.

DISCUSSION
The prevalence of PV in women and its possible occurrence in childbearing age oblige the specialist to take into account disease and therapy effects on conception, pregnancy, and the period of after delivery.\(^1,9\)

Various autoimmune disorders, such as systemic sclerosis, rheumatoid arthritis, Crohn’s disease, insulin-dependant diabetes mellitus, chronic active hepatitis, etc., are associated with impairment of fertility. In a retrospective study, 8 of 9 patients suffering from PV failed to conceive. Four patients had luteal phase defects, 4 had follicle stimulating hormone defects, and antisperm antibodies were detected in 2 patients. None of the 8 patients conceived even after discontinuation of their therapy (corticosteroids, azathioprine, or cyclophosphamide). Only one became pregnant, but during full remission.\(^10\) In contrast to these data, a recent report described a pemphigus patient who conceived during the active phase of severe PV, which required high doses of prednisone, thus implying that active disease is not necessarily associated with infertility.\(^11\) Nevertheless, it is advised that conception coincide with a period of clinical remission and low titers of pemphigus antibodies, as was the case with our patient 2.\(^12\) In addition, literature data analysis showed that PV was diagnosed before conception in more than half of the reported cases of PV in pregnancy.

This raises the question, how should the dermatosis be treated safely and efficiently whenever a pregnancy is planned? No prospective, controlled studies exist to evaluate the efficacy and safety of PV management before conception. The conclusions are mainly drawn from case reports. It is proposed that every attempt should be made to taper or discontinue any immunosuppressive...
agent, including prednisone which should be reduced to the lowest effective dose. On the other hand, a sufficient control of the disease is required before conception as it is expected that pregnancy can aggravate preexisting PV as it does in other autoimmune diseases (eg, myasthenia gravis, lupus erythematosus). Most authors believe that adverse pregnancy outcome is more closely related to poor control of maternal disease and high titers of pemphigus antibodies than to particular medication. Corticosteroids remain the first-choice treatment for PV if low doses are sufficient to control the disease, but when high doses are required steroid-sparing immunosuppressive agents may be added to therapy. Azathioprine is the most common adjuvant therapy in PV although its use during conception and early pregnancy has not been evaluated systematically within the field of dermatology. It is widely accepted that azathioprine (US Food and Drug Administration [FDA] pregnancy category D) increases human fetal risk, and therefore, should be avoided in pregnancy. Having this in mind, in our second patient it was discontinued a year before the planned conception which did not result in exacerbation of the disease. In 2 formerly reported cases, on the contrary, azathioprine was used in the preconception period in a dose regimen of 15 mg/d and 75 mg/d, respectively. Both pregnancies were generally uneventful without signs of fetal teratogenicity. The lower dosage of azathioprine was related to transient neonatal pemphigus lesions that resolved within 3 weeks postpartum, while the 75 mg/d regimen resulted in the delivery of a healthy newborn. Other therapeutic modalities, such as mycophenolate mofetil, cyclophosphamide, methotrexate, cyclosporine A, dapsone, intravenous immunoglobulins, rituximab, or plasmapheresis, remain to be proven safe and efficient in the preconception period in PV patients.

It is of interest to the clinician to investigate what is the effect of pregnancy on the course and manifestations of PV. Current information on the association of pemphigus and pregnancy is based on 38 reports and 49 pregnancies. Age at onset of PV in mothers ranged from 18 to 42 years (mean, 30 years) and there was no correlation with the number of pregnancies. PV appeared de novo during pregnancy in 18 patients and our first case adds to this number. In the rest of cases, the disease preceded the pregnancy, this period ranging from 2 months to 8 years (mean, 4 years). Clinical records available for 40 patients demonstrated the following distribution: 25% of the patients presented with mucosal lesions, 45% showed both mucosal and cutaneous involvement, while in 30% only skin was affected. Gingival erosions were reported as the first and/or only manifestation of PV during pregnancy. Seven patients had no active disease during pregnancy. Our second case should be included in that group. Exacerbation of PV was observed in 11 of 49 patients, occurring during the second trimester in 2 cases, and postpartum in 5 patients. Similarly to other autoimmune diseases, such as systemic lupus erythematosus, myasthenia gravis, etc., aggravation of PV should be expected during pregnancy. The first and second trimester, as well as the postpartum period, are the critical time points. Difficulty in controlling disease flare-up has been reported during the period of conception and early pregnancy, as was observed in our first clinical case. Improvement or remission of PV during the third trimester of pregnancy was related to the elevated endogenous corticosteroid production by the chorion, and consequent immunosuppression. Postpartum flare-up of PV is also likely to appear, as in our case, so attention and close follow-up of patients at that period is recommended.

Two of the most important questions that arise with regard to the association of pemphigus and pregnancy are the possible influence of the disease on the intrauterine fetal development, and that of pregnancy prognosis. PV during pregnancy showed various outcomes ranging from stillbirth, retardation of the intrauterine growth, premature delivery, transient neonatal pemphigus, or delivery of a healthy neonate completely free of skin disease, as in our clinical observations. The reported perinatal mortality rate was 12% (6 of 49 cases) although there were not enough cases for representative statistics. Of these, there were 5 stillbirths and 1 newborn who died 2 days postpartum due to meconium aspiration syndrome. Of the 5 intrauterine deaths, one was related to umbilical cord prolapse, one
to placental dysfunction, and one to cytomegalovirus pneumonitis. In the other 2 cases the reason remained unknown. All 5 stillbirths occurred in mothers with severe active disease, and azathioprine was administered in 2 of the cases. Despite these observations and the impression that poor pregnancy prognosis is related to severe PV, there is no clear evidence in the literature that PV plays a causative role in fetal death, as in several reports mothers with severe active disease gave birth to completely healthy neonates. The exact mortality causes could not be strictly identified, although intrauterine growth retardation, placental insufficiency, immune suppression, infections, and adverse drug reactions have been suspected. 

Premature deliveries were mainly related to high doses of systemic corticosteroid treatment. Other authors do not find consistent association between maternal treatment regimen and fetal outcome. Twenty newborns of 44 reported live births presented with transient pemphigus lesions, which resolved within 4 weeks postpartum with or without treatment. Clinical manifestation of PV in the neonate is a result of transplacental transmission of maternally derived IgG pemphigus antibodies. A correlation between the maternal disease severity, antibody titers, and the development of neonatal pemphigus seemed probable. However, mothers with severe disease gave birth to healthy newborns, and infants with neonatal pemphigus were born by asymptomatic mothers.

On the other hand, mothers without active disease most commonly deliver healthy children, although some reports contradict this assumption. A probable explanation is the different sensitivity of fetal skin to the maternally derived antibodies. These data lead to the conclusion that clinical presentation or antibody titers in the mother cannot be predictive for the development of pemphigus in the neonate, but parents and pediatricians should be aware of the possible occurrence of neonatal lesions.

More often neonatal pemphigus presented with skin lesions (12 out of 20 cases) and this did not always correlate to the clinical manifestation in the mother. Isolated cutaneous involvement in the child was observed even in mucosal dominant PV in the mother. Only rarely, mucocutaneous lesions in the newborn were reported. This was explained by the different tissue distribution of Dsg1 and Dsg3 in the adult and neonatal skin.

Healthy, full-term, and completely free of skin lesions neonates were reported in 4 women with milder PV, but the same pregnancy outcome has been observed in mothers with severe, active disease. There is no consensus on the choice of delivery type in PV mothers. Vaginal birth can result in worsening and spreading of the pemphigus lesions in the mother. On the other hand, systemic steroid therapy delays and complicates the healing of the Cesarean section. Despite that caveat, in an analysis of 4 cases of PV, all the patients underwent Cesarean section at their own request, and none demonstrated impaired wound healing. The method of choice should be individualized in each patient in accordance with the medical indications and the patient’s preferences. Whenever there are PV lesions in the genital mucosa, Cesarean section is advisable.

The management of PV during pregnancy is similar to that in the nonpregnant woman, however there is no doubt that the control of the disease during pregnancy is a challenge for both dermatologists and obstetricians. Systemic steroids are widely accepted as first-choice treatment of PV with or without pregnancy. Prednisone and/or its equivalents are usually administered in doses varying from 5 to 300 mg/d for several weeks with subsequent tapering to a maintenance dose. Although corticosteroids, mainly prednisone, have been established as safe during pregnancy with no increase of congenital malformations, high dosage may increase fetal risk for low birth weight, prematurity, infection, and adrenal insufficiency. Preterm premature rupture of membranes and preterm delivery may be the result of aggressive steroid therapy during pregnancy. Some authors recommend introducing systemic steroid therapy after the twelfth week of gestation to avoid possible teratogenic effects of high doses administered in early pregnancy.

Azathioprine was coadministered with the steroid treatment during pregnancy in 5 cases, with doses ranging from 15 to 150 mg/d. In one case the child was healthy, in 2 cases the infants presented with self-limiting pemphigus lesions, and 2 stillbirths were reported. In each of these cases, the mother’s condition was severe, which was considered a possible independent risk factor for neonatal PV or fetal death. In most reports, the use of azathioprine during pregnancy is not recommended. Recent data suggest that azathioprine could be a reasonable treatment in pregnant patients who require steroid-sparing agents for serious medical conditions.

Dapsone (200 mg/d) was used in one case in combination with prednisone. Fetal death at 33 weeks of gestation was attributed to placental insufficiency due to the steroid use. Dapsone (US FDA pregnancy category C) can be used for its antiinflammatory effect in PV and pregnancy and it was even suggested that dapsone 100 mg/d should be preferred to prednisone. Regarding treatment of PV during breastfeeding, only prednisone and azathioprine were approved for use in nursing mothers by the American Academy of Pediatrics. Dapsone is also considered compatible with breastfeeding due to its minimal excretion in breast milk.

Cyclosporine A (US FDA pregnancy category C) was reported to be the safest corticosteroid-sparing agent in pregnancy, but was considered...
less effective in the treatment of PV than other therapies.\textsuperscript{15,19} On the contrary, in another review of the literature it was characterized as strongly contraindicated in pregnancy in pemphigus patients.\textsuperscript{3}

Mycophenolate mofetil, cyclophosphamide, and methotrexate are strongly discouraged and contraindicated in pregnancy because of their immunosuppressive and teratogenic effect.\textsuperscript{15,17}

There are still no reports on the use of intravenous immunoglobulins for PV during pregnancy but they may be necessary in some patients to achieve clinical control of the disease.\textsuperscript{3}

Plasmapheresis was reported to be a successful alternative to immunosuppressive therapy in pregnant PV patients.\textsuperscript{40,41} It was regarded as a useful way to decrease fetal risk that may be associated with high-dose maternal medication, but it is still considered an experimental procedure in PV and should be restricted to severe corticosteroid-resistant cases.\textsuperscript{11,12}

Other therapeutic modalities include topical corticosteroid therapy,\textsuperscript{27} intrallesional triamcinolone acetonide application,\textsuperscript{9} or no treatment.\textsuperscript{18}

CONCLUSIONS

Despite the lack of systemic controlled studies there is growing evidence on the association between pemphigus and pregnancy. Still, many practical approaches with regard to clinical and therapeutic monitoring of PV during pregnancy remain controversial. Whenever this association occurs, every attempt should be made by clinicians, dermatologists, obstetricians, pediatricians, and parents to lead such a pregnancy to a favorable outcome.

Possible aggravation of PV postpartum requires special attention during the period after delivery as well. We believe that a careful, individualized approach based on personal experience, published data, and patients’ choices, is the most appropriate strategy.

REFERENCES

27. Chowdhury MM, Natarajan S. Neonatal pemphigus vulgaris associated with mild oral pemphigus vulgaris in the mother during


**ABSTRACT**

Only a few corticosteroids for topical use have been proven safe and effective in pediatric populations down to 3 months of age. The authors examined the systemic safety (adrenal suppression potential) of topically applied hydrocortisone butyrate 0.1% cream (proprietary lipid rich cream vehicle) in the treatment of moderate to severe atopic dermatitis in pediatric patients aged 3 months to 6 years and 12 years to 18 years. An open-label hypothalamic-pituitary-adrenal axis suppression study was conducted wherein the sole treatment was 0.1% proprietary lipid rich cream vehicle. A total of 65 patients with moderate to severe atopic dermatitis and body surface area involvement of at least 25% were included in the treatment phase of the study based on the requirement that these patients had normal baseline cortisol and hypothalamic-pituitary-adrenal system function. All signs and symptoms of atopic dermatitis showed progressive improvement beginning with day 8 through the day 29 evaluation. Pruritus showed the greatest improvement, with a decrease in grade of 1.3 at day 8, and continued to show improvement at day 29, with a decrease of 1.8 from baseline. The percent body surface area affected at baseline averaged 40.5%, and it decreased significantly to a mean of 6.5% at day 29. Only 5 (8%) of the 63 patients showed laboratory evidence of adrenal suppression at the end of the treatment evaluation. None of these ever demonstrated any clinical signs or symptoms of adrenal suppression. This study adds hydrocortisone butyrate 0.1% cream, to the short list of corticosteroids that have been proven effective and safe by the cosyntropin suppression test in children 3 months and older with widespread atopic dermatitis. (SKINmed. 2010;8:150–154)
has been established that 0.25 mg of cosyntropin will maximally stimulate the adrenal cortex and to the same extent as 25 units of natural ACTH, producing a maximal secretion of 17-OH corticosteroids, 17-ketosteroids, and/or 17-ketogenic steroids. Because of its rapid effect on the adrenal cortex, it may be used to perform a 30-minute test of adrenal function (plasma cortisol response) as an office or outpatient procedure.10

TRIAL DESIGN
To examine the potential for systemic toxicity for HCB, an open-label hypothalamic-pituitary-adrenal (HPA) axis suppression study was conducted. There was no comparator-control group for this study; the sole treatment was HCB 0.1% cream. The study was designed to maximally challenge the response of the adrenal gland to cosyntropin stimulation after 4 weeks of treatment 3 times daily with HCB 0.1% cream in a pediatric population aged 3 months to older than 6 years and 12 years to older than 18 years with moderate to severe AD affecting at least 25% of the body surface area (BSA). Thrice-daily dosing was included in this study design to maximally challenge these patients with respect to adrenal axis function.

STUDY POPULATION
Sixty-nine patients were enrolled into the study, 65 of whom were included in the treatment phase of the study based on the requirement that these patients had normal baseline cortisol and HPA system function and did not have any clinically significant out-of-range baseline laboratory test results.

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS
The average age of the 65 treated patients was 6.31 years. Thirty-six (55%) were boys. The average BSA affected was 40.53%. Forty-eight patients (74%) had moderate disease (Physician's Global Assessment score [PGA]=3) and 17 patients (26%) had severe disease (PGA=4). The majority of patients had moderate to severe erythema (55 patients, 84%), induration/papulation (57 patients, 87%), excoriations (36 patients, 55%), lichenification (45 patients, 69%), scaling (35 patients, 54%), pruritus (53 patients, 82%), and no or mild oozing/crusting (44 patients, 68%).

CLINICAL DIAGNOSTIC CRITERIA
The 3 major diagnostic criteria for entry into the study included the following: patients had to have a clinical diagnosis of stable, moderate to severe AD defined by criteria per Hanifin & Rajka2,11–13; the severity of AD according to PGA scale had to be 3 or 4 (Table I); and there had to be a minimum percent surface area involvement of at least 25% BSA.

TREATMENT
The intent-to-treat population for safety evaluation consisted of 23 patients 3 months to older than 2 years, 22 patients 2 to older than 6 years, and 20 patients 12 to older than 18 years, diagnosed with moderate to severe AD affecting a minimum of 25% BSA. Eligible patients were treated with HCB 0.1% cream 3 times daily for up to 4 weeks, depending on improvement of the condition. A patient who completed 4 weeks of treatment was expected to apply 84 applications of study medication. If a patient was clear at the day 8, 15, or 22 evaluation, they completed the study at that point and were expected to have applied 21, 42, or 63 applications of study medication, respectively. If a patient prematurely discontinued from the study, the number of expected applications was based on the number of dosing days the patient participated in the study.

Although the protocol did not identify a minimum number of study medication applications for a patient to be considered compliant with the dosing regimen, the data were reviewed to ensure that patients used study medication appropriately. A standard of 75% compliance was used to determine dosing compliance. One patient applied study medication <75% of the expected doses, which was 3 times daily for up to 4 weeks. This patient was 73.8% compliant and applied 62 applications of study medication while completing the study.

Table I. Physician's Global Assessment Score and Description

<table>
<thead>
<tr>
<th>Score</th>
<th>Category</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>Clear</td>
<td>No inflammatory signs of atopic dermatitis.</td>
</tr>
<tr>
<td>1</td>
<td>Almost clear</td>
<td>Faint, barely detectable erythema and/or trace residual induration/papulation in limited areas; neither excoriation nor oozing/crusting are present.</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>Light pink erythema and slightly perceptible induration/papulation; excoriation, if present, is mild.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Dull red, clearly distinguishable erythema and clearly perceptible induration/papulation but not extensive; excoriation or oozing/crusting, if present, are mild to moderate.</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>Deep/dark red erythema and marked and extensive induration/papulation; excoriation and oozing/crusting are present.</td>
</tr>
</tbody>
</table>
Efficacy

At baseline, patients were required to have an overall disease severity of moderate or severe. Forty-eight of 65 patients (74%) were enrolled into the study with moderate severity and 17 of 65 patients (26%) were enrolled with severe disease. Administration of the study drug resulted in immediate efficacy, as noted by the day 8 evaluations in which 12 of 64 patients (19%) were almost clear, 31 of 64 patients (48%) were mild, 19 of 64 patients (30%) were moderate, and 2 of 64 patients (3%) were severe. By the day 29 evaluation, 24 of 64 patients (38%) were clear, 28 of 64 patients (44%) were almost clear, 11 of 64 patients (17%) were mild, and 1 of 64 patients (2%) was moderate (Table II).

All signs and symptoms showed progressive improvement beginning with day 8 through the day 29 evaluation. At day 8, the mean erythema score decreased by 0.8 and continued to decrease to 1.4 grades less than baseline at day 29. Induration/papulation showed similar efficacy with a mean decrease of 0.8 at day 8 down to 1.5 grades less than baseline at day 29. The mean excoriation score decreased by a grade of 0.9 at day 8 and continued to decrease to 1.5 grades less than baseline at day 29. The mean lichenification score decreased by 0.6 at day 8 and continued to decrease to 1.2 grades less than baseline at day 29. Pruritus showed the greatest improvement with a decrease in grade of 1.3 at day 8, which continued to show improvement at day 29 with a decrease of 1.8 from baseline. The percent BSA affected at baseline averaged 40.5%, which significantly decreased to a mean of 6.5% at day 29.

Safety

Cosyntrpin stimulation testing is an established surrogate measure for system toxicity of topical corticosteroids. The definition for suppressed response in this study was a poststimulation plasma cortisol level £18 μg/dL on day 29.

The cosyntropin stimulation test (CST) was scheduled at the screening and final visit (day 29). This evaluation was performed between 7 AM and 9 AM, with the poststimulation blood draw being completed by 9 AM. Cosyntrpin was intravenously administered following blood sampling for baseline serum cortisol evaluation and followed by a second blood draw for serum cortisol evaluation exactly 30 minutes later. A patient was considered to have evidence of adrenal suppression if the serum cortisol level 30 minutes after cosyntropin administration was £18 μg/dL.

If there was evidence of adrenal suppression from the CST at the posttreatment assessment, this was to be considered an adverse event. For suppressed patients, the posttreatment CST testing was performed every 4 weeks until axis function was documented as returning to normal. At the end of the study, 5 of the 63 patients (8%) showed laboratory evidence of adrenal suppression at the end of treatment evaluation. None of these patients ever demonstrated any clinical signs or symptoms of adrenal suppression. The average prestimulation cortisol level at baseline was 14.32 μg/dL compared with 13.89 μg/dL at end of treatment, for an average difference of 0.45 μg/dL. The average poststimulation cortisol level at baseline was 26.90 μg/dL compared with 24.90 μg/dL at end of treatment, for an average difference of 2.03 μg/dL (Table III).

The CST retesting for 4 of the 5 patients with suppressed responses, with follow-up testing 28 to 65 days after end of treatment, was >18 μg/dL (ie, nonsuppressed). The other patient was lost to follow-up. None of the patients with abnormal serum cortisol values showed any clinical signs and symptoms of adrenal suppression.

Assessment of Adverse Effects

Adverse events were reported in 19 of the 65 patients (29%) entered into the treatment phase. The most common adverse

<table>
<thead>
<tr>
<th>Table II. Summary of Efficacy: Physician’s Global Assessment Score</th>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>Clear</td>
</tr>
<tr>
<td>Almost clear</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>Completely clear</td>
</tr>
<tr>
<td>Not reported</td>
</tr>
</tbody>
</table>
events reported during the treatment phase included upper respiratory infection (4 of 65 patients, 6%) and pyrexia (3 of 65 patients, 5%), which were all mild in severity and considered not related to study medication. All other adverse events reported during the treatment phase were reported by 3% of patients or less, were mild to moderate in severity, and the majority was considered not related to study medication. There were 6 events considered by the investigator to be related to study medication. The majority of these events were related to the 5 patients that had laboratory evidence of adrenal suppression (day 29) that, per protocol, were to be documented as adverse events (Table IV).

There were no serious adverse events reported during the study and no patients prematurely discontinued due to adverse events.

**DISCUSSION**

The efficacy of topical corticosteroids in AD is unquestionable. Their systemic safety in pediatric populations by means of cosyntropin stimulation testing to assess for adrenal suppression has been evaluated for only a few; particularly down to 3 months of age.

A PubMed search allowed us to find studies where fluocinolone acetonide 0.01% in peanut oil showed no adrenal suppression in 24 infants as young as 3 months of age treated with twice-daily applications for 4 weeks. Among 34 children aged 6 months to 6 years who applied a desonide hydrogel 0.05% twice daily, only 1 (3%) patient developed adrenal suppression at the 4-week evaluation. A fluticasone propionate lotion 0.05% did not cause adrenal suppression in 44 patients aged 3 to 71 months who applied the preparation twice daily for 4 weeks. The same corticosteroid at the same concentration of 0.05% in a cream formulation caused adrenal suppression in 2 (4.7%) of 43 children 3 months of age and older who applied it twice daily for 3 to 4 weeks.

In the daily practice of dermatology, the need for comfort in prescribing topical corticosteroids to pediatric patients often arises. Studies that support the safety of a particular corticosteroid preparation allow mitigating corticosteroid phobia by parents, concerns by physicians, and medicolegal risks related to their use.

**CONCLUSIONS**

This study adds another topical corticosteroid preparation, HCB 0.1%, a proprietary lipid rich cream vehicle, to the short list of corticosteroids that have been proven safe by the gold standard to evaluate for systemic toxicity, the CST for adrenal suppression, in children 3 months and older.
REFERENCES


Table IV. Summary of Adverse Events (N=65)

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Events reported</th>
<th>No. of Patients Reporting ≥1 Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events reported</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>No. of patients reporting ≥1 event</td>
<td>19 (29%)</td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>35 (100%)</td>
<td></td>
</tr>
<tr>
<td>Severity of event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>32 (91%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3 (9%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Relationship to study drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unassessable</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Not related</td>
<td>29 (83%)</td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>2 (6%)</td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td>3 (9%)</td>
<td></td>
</tr>
<tr>
<td>Certain</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>System organ class/preferred term</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>10 (5%)</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4 (6%)</td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Folliculitis</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Otitis media</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (2%)</td>
<td></td>
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<tr>
<td>Pustular eruption</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Viral infection</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>5 (8%)</td>
<td></td>
</tr>
<tr>
<td>Adrenal suppression</td>
<td>5 (8%)</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>4 (6%)</td>
<td></td>
</tr>
<tr>
<td>Application site irritation</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (5%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

Table IV. Summary of Adverse Events (N=65)
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providing a global spectrum of skin care
In 1982, Riccardi described 8 subtypes of neurofibromatosis. Classic neurofibromatosis (also referred to as both von Recklinghausen neurofibromatosis and neurofibromatosis type I) is the most common subtype, comprising 90% of the cases of neurofibromatosis, with an estimated incidence of 1 in 3000 people. Segmental neurofibromatosis, previously referred to as neurofibromatosis type V and now designated as segmental neurofibromatosis type I, is an uncommon subtype with an estimated incidence of 1 in 38,000 people. In contrast, however, to neurofibromatosis type I, in which syndrome-associated internal malignancy may develop, cancer has not usually been considered to be prominent in patients with segmental neurofibromatosis.

Segmental neurofibromatosis was originally described by Gam mel in 1931. Later, Crowe and colleagues in 1956, observed 4 more patients with café-au-lait macules and neurofibromas limited to one sector of the body. These patients had no systemic involvement and no family history. They called this syndrome sectorial neurofibromatosis, and proposed that it may be due to a later development of a somatic mutation of the neurofibromatosis type I gene, resulting in a localized form of disease.

Miller and Sparkes, in 1977, renamed this disease as segmental neurofibromatosis. In 1982, Riccardi included this variant as neurofibromatosis type V in his classification of the neurofibromatoses. He defined segmental neurofibromatosis as the presence of café-au-lait macules and neurofibromas limited to one region of the body, without crossing of the midline, and not associated with a family history of neurofibromatosis.

In 1987, Roth and colleagues further expanded the description of segmental neurofibromatosis into 4 subtypes to include individuals that did not meet Riccardi’s strict criteria, such as patients with bilateral segmental neurofibromatosis, and patients with a positive family history. Most recently, in 2000, Tinschert and associates confirmed what Crowe and colleagues proposed half a century earlier: that segmental neurofibromatosis is a variant of neurofibromatosis type I. This has led to the general acceptance of this syndrome being referred to as segmental neurofibromatosis type I.

CANCER IN NEUROFIBROMATOSIS TYPE I PATIENTS

Neurofibromatosis type I is associated with malignancy. According to the American Society of Clinical Oncology, the overall lifetime risk of developing cancer in patients with neurofibromatosis type I is 7%, about twice the risk of that seen in the general population. Children with neurofibromatosis type I also have a 200-fold relative risk of developing juvenile chronic myelogenous leukemia.

The most common associated malignancy in neurofibromatosis type I patients is malignant peripheral nerve sheath tumor which has a lifetime risk of 5% in these patients, which is nearly 4000 times greater than the general population.
times the rate seen in the general population.\textsuperscript{8,17} Other neurofibromatosis type I-associated malignancies include carcinoid tumors, lymphomas, medullary carcinoma of the thyroid, meningiomas, optic gliomas, pheochromocytoma, rhabdomyosarcoma, and Wilms tumor.\textsuperscript{8,18–20} Lymphomas associated with neurofibromatosis type I are uncommon and have mostly been non-Hodgkin. To the best of our knowledge, there has only been one report of a patient with neurofibromatosis type I and Hodgkin lymphoma.\textsuperscript{18}

**CANCER IN SEGMENTAL NEUROFIBROMATOSIS PATIENTS**

Ten individuals with segmental neurofibromatosis and cancer have been reported (Table).\textsuperscript{17,21–28} The most common malignancy associated with segmental neurofibromatosis was malignant peripheral nerve sheath tumor. This is the same tumor that is most frequently seen in patients with neurofibromatosis type I. Painful, recurrent, and/or rapidly growing neurofibromas prompted the detection of malignant peripheral nerve sheath tumors in several of the neurofibromatosis type I patients with this cancer. In contrast, only 1 of 3 patients with segmental neurofibromatosis had painful and recurrent tumors (case 1).

Malignant melanoma was the second most common cancer in patients with segmental neurofibromatosis. With the exception of malignant peripheral nerve sheath tumor and malignant melanoma, tumors of neural crest origin that have been previously associated with neurofibromatosis type I such as astrocytomas, carcinoid tumors, glioblastomas, meningiomas, neuroblastomas, and optic nerve gliomas, were not observed in patients with segmental neurofibromatosis. The other reported malignancies were of non-neural crest origin, including breast cancer, colon cancer, gastric cancer, lung cancer, and lymphoma.

Malignancy was found to be more common in women (6 women as compared to 4 men). Eight patients had segmental neurofibromatosis localized to the left side (cases 2–8 and 10). One patient had right-sided involvement (case 1) and 1 patient had bilateral involvement (case 9). The most common associated cutaneous findings in patients with segmental neurofibromatosis and malignancy were painless neurofibromas (cases 2–4, 9, and 10) and café-au-lait macules (cases 5, 6, and 8–10) which were each observed in 50% of the patients.

The diagnosis of segmental neurofibromatosis preceded the discovery of cancer in at least 5 patients. Three patients were reported to have segmental neurofibromatosis develop after their malignancy was detected (cases 3–5). Some authors have proposed that the occurrence of segmental neurofibromatosis following the onset of malignancy was related to the tumor treatment-associated lymphedema,\textsuperscript{21} whereas others have suggested that the finding of segmental neurofibromatosis should prompt the clinician to look for an underlying concurrent malignancy.\textsuperscript{27}

Whether the development of these malignancies is related to underlying segmental neurofibromatosis or is coincidental remains to be determined.

Previously, segmental neurofibromatosis has usually not been considered to be associated with malignancy. However, based on the previously reported frequency of patients with upper extremity segmental neurofibromatosis (18.2%),\textsuperscript{7} and the recent review of 34 of these individuals in the literature,\textsuperscript{28} it would imply that there are approximately 187 patients with segmental neurofibromatosis.\textsuperscript{9} The incidence of cancer in patients with segmental neurofibromatosis can then be calculated to be 5.3% (10/187). This incidence for developing malignancy in segmental neurofibromatosis patients approaches the observed 7% lifetime risk for cancer in neurofibromatosis type I patients.\textsuperscript{15}

**CONCLUSIONS**

Ten patients with segmental neurofibromatosis were found to have a systemic malignancy. Malignancy was more common in women and more frequently observed in patients with segmental neurofibromatosis involving the left side. The most common tumor in patients with segmental neurofibromatosis was the same as that observed in neurofibromatosis type I: malignant peripheral nerve sheath tumor. With the exception of malignant peripheral nerve sheath tumor and malignant melanoma, all of the other cancers were of non-neural crest origin. The incidence of malignancy in segmental neurofibromatosis patients approaches the observed risk for cancer in that of patients with classical neurofibromatosis type I. A conservative approach, therefore, for the management of individuals with segmental neurofibromatosis is to monitor these patients for the possible development of malignancy.
### Table. Segmental Neurofibromatosis and Malignancy

<table>
<thead>
<tr>
<th>Case</th>
<th>Age of Onset (y) of SN/Malignancy</th>
<th>Gender</th>
<th>Site of SN</th>
<th>Cutaneous Involvement</th>
<th>Other Systemic Involvement</th>
<th>Malignancy</th>
<th>Family History</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40/43 F</td>
<td>Right lower extremity</td>
<td>Neurofibroma&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
<td>Malignant peripheral nerve sheath tumor</td>
<td>–</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>41/48 F</td>
<td>Left buttock</td>
<td>Neurofibroma&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
<td>Malignant peripheral nerve sheath tumor</td>
<td>–</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>47/44 F</td>
<td>Left arm</td>
<td>Neurofibroma&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
<td>Breast cancer</td>
<td>–</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>66/64 F</td>
<td>Left pubis</td>
<td>Neurofibroma&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
<td>Malignant peripheral nerve sheath tumor</td>
<td>–</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>72g/72 F</td>
<td>Left trunk, lower extremity</td>
<td>Café au lait macule</td>
<td>–</td>
<td>Lung cancer</td>
<td>–</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>NS/71 F</td>
<td>Left lower extremity</td>
<td>Café au lait macule</td>
<td>–</td>
<td>Malignant melanoma</td>
<td>–</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>16/48 M</td>
<td>Left neck</td>
<td>Large congenital nevus, neurofibroma&lt;sup&gt;a&lt;/sup&gt;, plexiform, neurofibroma&lt;sup&gt;a&lt;/sup&gt;, schwannoma</td>
<td>+&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Malignant melanoma</td>
<td>–</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>21/61 M</td>
<td>Left trunk</td>
<td>Axillary freckling, café au lait macule, neurofibroma&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
<td>Colon cancer</td>
<td>–</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>60/61 M</td>
<td>Bilateral trunk</td>
<td>Café au lait macule, neurofibroma&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
<td>Gastric carcinoma</td>
<td>–</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>NS/32 M</td>
<td>Left forearm, hand</td>
<td>Café au lait macule, neurofibroma&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
<td>Hodgkin lymphoma</td>
<td>–</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Race of the patient was defined in 1 patient: case 8 = Korean. <sup>b</sup>The neurofibromas were ‘painful, ‘painless, or ‘without description of symptoms. <sup>c</sup>Some of the neurofibromas recurred in the same area after excision. <sup>d</sup>The diagnosis of SN occurred 3 months after the patient's diagnosis of lung cancer. <sup>e</sup>Other systemic involvement was reported in 1 patient: case 7 = multiple osseous abnormalities including congenital fusion of the cervical spine, marked kyphosis, and scoliosis. Abbreviations: +, present; –, absent; F, female; M, male; NS, not stated; SN, segmental neurofibromatosis.

### REFERENCES

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Acanthosis nigricans (AN) is a common dermatologic abnormality seen in numerous endocrine disorders as well as malignancies. It was first described by Pollitzer and Janovsky in 1890. AN is more common in dark-skinned persons. Higher rates of incidence have also been reported in certain groups such as Native Americans.

AN is mostly seen in individuals with underlying diabetes mellitus. In a recent study, nearly 36% of patients with newly diagnosed diabetes had AN. Obese individuals are also at an increased risk for developing AN. In a recent study, researchers reported that 39% of their study population of obese children had AN. AN may also appear as a paraneoplastic syndrome (malignant AN). Malignant AN is usually seen in gastrointestinal adenocarcinomas such as primary malignant lesions of the gallbladder and gastric lymphomas. The lesions may also appear in individuals with no apparent identifiable underlying cause. In fact, most cases of AN are idiopathic.

Genetic causes of AN have also been identified. These include Crouzon syndrome and Berardinelli Seip syndrome (congenital generalized lipodystrophy). In Crouzon syndrome, the transmission is autosomal dominant (caused by mutation of the fibroblast growth factor receptor 3 gene), while in Berardinelli Seip syndrome, the transmission is autosomal recessive (caused by mutation of the 1-acylglycerol-3-phosphate O-acyltransferase 2 gene).

Iatrogenic AN usually occurs secondary to the use of hormonal therapies such as birth control pills for contraception or growth hormones and human chorionic gonadotropins. In addition, AN has also been reported secondary to the use of highly active antiretroviral therapy medications such as amprenavir and even vitamins such as nicotinic acid. AN may also be seen in other endocrine disorders such as Cushing syndrome and acromegaly. Another rare but important cause of AN is nonalcoholic steatohepatitis. Researchers have also reported AN in a pregnant woman without any underlying glucose intolerance or gestational diabetes. Pathologically, the lesions of AN occur secondary to elevated levels of serum insulin, resulting in the activation of insulin-like growth factor-1 receptors of epidermal keratinocytes and fibroblasts. Interestingly, investigators reported an increased expression of fibroblast growth factor 3 in certain individuals with malignancy associated AN.

**DIAGNOSIS**

AN tends to affect the skin folds, flexural areas, and the intertriginous areas. The neck and axillary regions are most commonly affected, although lesions may appear almost anywhere on the body (Figure 1). Lesions have even been described on the nipples, perineum, groin, and extensor surfaces of the legs. Researchers have also described AN of the conjunctiva in a patient with underlying bronchial squamous cell carcinoma.

In general, the lesions appear as dark-brown, thickened plaques (Figure 2). These hyperpigmented plaques generally tend to be velvety on touch. Lesions of AN may occur alone or may develop in other skin lesions such as hyperkeratosis of the nipple and areola (HNA type 2). Researchers have also described the case of a patient with coexisting AN and confluent reticulated papillomatosis. Verrucous AN may also occur. These lesions tend to affect the eyelids, lips, and buccal mucosa. Rarely, the lesions may have a nevoid appearance. These nevoid lesions usually appear at birth or puberty and may appear as unilateral lesions or midline umbilical lesions.

The dermatologist should always inquire about any familial history of diabetes or AN. In fact, in a recent study, a prevalence...
of 17% in African individuals with type II diabetes mellitus was reported.\textsuperscript{23} Presence of AN in obese individuals usually points toward hyperinsulinemia and peripheral insulin resistance.\textsuperscript{24,25} Investigators\textsuperscript{26} have reported that children with AN are almost 4 times more likely to have hyperinsulinemia compared with children without AN. Presence of AN alone may also indicate increased risk of type 2 diabetes mellitus. In a recent study, Kong and co-authors\textsuperscript{27} reported that the prevalence ratio for type 2 diabetes in patients with AN was 1.97. In another recent study, researchers\textsuperscript{1} showed that patients with AN usually require a higher dosage of insulin compared with diabetic patients without AN (82.3 units/d vs 50.2 units/d). Clearly, AN has significant diagnostic and prognostic value.

Any healthy patient diagnosed with AN without an underlying explanation should also be investigated for any occult malignancy. The gastrointestinal system should be particularly focused on and appropriate tests should be performed if deemed necessary. For instance, investigators\textsuperscript{28} recently described the case of a patient with AN and hepatic metastasis secondary to an occult underlying primary malignant lesion. Patients with gastrointestinal neoplasms may also present with other paraneoplastic dermatoses such as tylosis and cutaneous papillomatosis. Rarely, multiple paraneoplastic dermatoses may be present in the same patient. Researchers\textsuperscript{29} recently reported the case of a patient with malignant AN who had the sign of Leser-Trelat as well as tripe palms. AN has also been reported with other adenocarcinomas, including those of the testes and prostate in men and the breast and uterine parametrium in women. A detailed medication history should also be taken to rule out any iatrogenic cause such as steroids, palifermin, or triazinate. Acanthosis nigricans can be associated with other features such as hypodontia and cutis gyrata as in patients with Beare-Stevenson syndrome.\textsuperscript{30}

Biopsy of the lesions may be performed to confirm the diagnosis. Histology reveals hypertrophy and hyperplasia of the epidermis and papillary dermis accompanied by hyperkeratosis and acanthosis. Typically, there is an increase in extracellular matrix, resulting in papillary extensions into the dermis. Typically, no melanocytic hyperplasia or hyperpigmentation is seen.

Further evaluation should include fasting blood glucose and thyroid function tests. In addition, a complete blood cell count and serum chemistries should be performed. Patients with AN are more likely to have the metabolic syndrome.\textsuperscript{31,32} In a recent study, 75% of patients with AN had the metabolic syndrome; hence, lipid panels should also be routinely performed in all patients with AN.\textsuperscript{33} In a recent study in Asian women, investigators\textsuperscript{34} confirmed a strong association between AN and polycystic ovarian disease; therefore, obese women with AN should also have quantitative follicle-stimulating hormone and luteinizing hormone assays performed to rule out polycystic ovarian disease.\textsuperscript{35} Incidentally, estrogen and its corresponding receptors have recently been shown to play a role in the evolution of skin tags.\textsuperscript{36}

**TREATMENT**

There is no specific treatment for AN. The treatment plan focuses on management of the underlying disorder. This usually results in partial or complete regression of the AN. Researchers\textsuperscript{37} recently showed that regression of AN correlates with the disappearance of anti-insulin receptor antibodies in patients with diabetes. They demonstrated that the achievement of euglycemia in diabetic patients is accompanied by marked regression of AN. Similarly, malignant AN usually improves after the underlying malignancy is treated. The prognostic response to treatment is, however, not significant in certain cases such as individuals with truncation mutations of Tre-2, BUB2, CDC16,
1 domain family members 4 (TBC1D4). Researchers have also shown that patients presenting with AN secondary to underlying congenital adrenal hyperplasia show symptomatic resolution of the skin lesions after effective treatment of the adrenal hyperplasia. Similarly, investigators have reported dramatic improvements of AN lesions in patients with congenital generalized lipodystrophy following leptin replacement therapy. This clearly demonstrates the need to address and treat the underlying etiology in all patients with AN.

The management of obesity-associated AN primarily involves behavioral modifications, particularly increased exercise and rigorous dietary control. In addition, oral metformin may be potentially used as a potent treatment agent with considerable significant response. It acts by increasing the sensitivity of the peripheral insulin receptors. Investigators have reported that patients taking metformin therapy show significant improvements of their AN lesions compared with those taking placebo alone; however, some other researchers have reported no significant changes with metformin therapy. Oral octreotide has also been used with moderate success. It acts by decreasing insulin secretion. Topical application of 0.1% tretinoin cream can be tried to lighten the lesion. In addition, combinations of tretinoin cream with 12% ammonium lactate cream have also been successfully used. Topical calcipotriol ointments have also been effective in treating AN. Edema of the axillae using a long-pulsed (5-msec) alexandrite laser. Dermatol Surg. 2004;30:1158–1160.

Systemic therapy that primarily relies on isotretinoin or acitretin may be tried if the patient fails to respond to topical therapy. Ozdemir and researchers recently reported remarkable success of the treatment with topical calcipotriol ointment of a 26-year-old obese woman with bilateral AN of the nipples. Calcinotriol binds to vitamin D3 receptors in the keratinocytes, thus decreasing their proliferation.

CONCLUSIONS

AN is a skin disorder that is difficult to treat. It should be explained to patients that complete resolution of the AN may never occur. As new developments in dermatology emerge, we may one day have a better treatment, but, for now, the management of AN should clearly focus on the management of the underlying disorder.

REFERENCES


SELF-TEST REVIEW QUESTIONS

W. Clark Lambert, MD, PhD, Editor

Instructions: For each of the following numbered questions, choose the single most appropriate lettered response.

1) Acanthosis nigricans is mostly seen in individuals with:
   a. Addison's disease
   b. Cushing's syndrome
   c. diabetes mellitus
   d. hypothyroidism
   e. thyrotoxicosis

2) Lesions of acanthosis nigricans have been described in (on) the:
   a. conjunctiva
   b. extensor surfaces of the legs
   c. groin
   d. nipple
   e. perineum
   f. All of these are correct
   g. None of these is correct

3) Verrucous acanthosis nigricans tends to occur on the:
   a. buccal mucosa
   b. eyelids
   c. lips
   d. All of the above are correct
   e. None of the above is correct

4) The most common malignancies associated with acanthosis nigricans are:
   a. adrenal cancers
   b. gastrointestinal carcinomas
   c. metastatic hepatic cancers
   d. metastatic renal cancers
   e. thyroid cancers

5) Which of the following statements regarding acanthosis nigricans is correct?
   a. In patients with diabetes mellitus, regression of acanthosis nigricans correlates with appearance of anti-insulin receptor antibodies.
   b. Patients with acanthosis nigricans are more likely to have the metabolic syndrome.
   c. Oral metformin counteracts acanthosis nigricans by decreasing insulin secretion.
   d. Oral octreotide counteracts acanthosis nigricans by increasing the sensitivity of peripheral insulin receptors.
   e. All of the above are correct.
   f. None of the above is correct.
Worldwide economic, social, and medical standards for teledermatology have not been established. There are almost 8 million doctors in the world, and the ratio of physicians to population by country vary from 1 to 440 per 100,000 people.\(^1\) For instance, the United Kingdom has a ratio of 164 physicians for every 100,000 people, but the doctor-to-population ratio for Rwanda is only 1.1 physicians per 100,000 people.\(^2\) Rural/urban physician distribution is a crucial issue in many undeveloped and developing countries. If physicians were distributed according to population around the world, there would be 124 physicians to every 100,000 people. There are currently 57 countries with critical shortage, equivalent to a global deficit of 2.4 million doctors.\(^2\) Africa has 25% of the world’s disease burden, 13.8% of the world’s population, but only 1.3% of the world’s health workforce.\(^3\)

The ideal ratio of dermatologist to population has been estimated to be 1:50,000.\(^4\) In the aspect of dermatology, The International Foundation for Dermatology estimates that 3 billion people living in more than 100 countries where skin diseases and sexually transmitted diseases are common and on the increase lack basic care for their skin diseases.\(^5\)

Teledermatology is a technique in medicine that uses modern communication technologies to transfer medical information and services.\(^6\) The World Health Organization (WHO) defines the term teledermatology as:

> The delivery of healthcare services, where distance is a critical factor, by all healthcare professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of healthcare providers, all in the interests of advancing the health of individuals and their communities.\(^7\)

Teledermatology could reduce waiting time, treatment costs, and the number of follow-up visits and it is a particularly promising technology for undeveloped and developing countries.\(^8,9\) Still, there are no standard international guidelines for all teledermatology applications.

Teledermatology is an application of teledermatology that evaluates patients via the latest digital and informative technology.\(^6,10\) It is the most exciting and fast-developing part of teledermatology by means of the advances in digital technology.\(^9,11\) Telemedicine basically uses telecommunication technologies to transfer images of lesions with the demographic and clinical data of the patient. A specialist or consultant evaluates the patient and makes the diagnosis.

**TELEDERMATOLOGY METHODS**

Teledermatology can be performed in two methods: store-and-forward teledermatology (SAFT) and real-time videoconferencing. Each method has its advantages and disadvantages (Table).
Diagnostic agreement between SAFT and conventional face-to-face examination ranges from 65% to 93% in various studies.\textsuperscript{13–15}

**REAL-TIME VIDEOCONFERENCEING SYSTEM**

The real-time videoconferencing system needs a broadband connection and synchronous video and audio streaming services to allow a live, interactive consultation. Simultaneous evaluation can minimize information gaps, but may increase the cost of the teledermatology application.\textsuperscript{7,16} Diagnostic accuracy agreement ranges from 59% to 80% between real-time teledermatology and face-to-face evaluation.\textsuperscript{17–21}

**HISTORY OF TELEMEDICINE AND TELEDERMATOLOGY**

Telemedicine was first used in 1959 in Nebraska. The Nebraska Psychiatric Institute began using a closed-circuit television system between the institute itself and Norfolk State Hospital, about 112 miles away, in 1964.\textsuperscript{22} The name of this study was the Nebraska Project.\textsuperscript{23} The aim of the project was the transmission of motion visuals for psychiatric and neurologic evaluation of patients.\textsuperscript{24} The system was used for 6 years to provide consultation and education.\textsuperscript{25}

The Space Technology Applied to Rural Papago Advanced Health Care (STARPAHC) Project\textsuperscript{26} demonstrates another significant early endeavor of telemedicine. The project was started in the late 1950s by the National Aeronautics and Space Administration (NASA) for telemedical help for people living in remote locations with little or no medical services, such as those in Arizona’s Papago Indian Reservation.\textsuperscript{25} The other main purpose of the project was to develop a system to provide medical service to astronauts in space by using audio and visual telecommunication.\textsuperscript{23,27} The project successfully provided medical care to remote sites on the Papago Indian Reservation for 20 years.\textsuperscript{28}

In 1967, an interactive television link was established between a medical station at Boston’s Logan International Airport and Massachusetts General Hospital, miles away within the city of Boston. Physicians at the hospital provided telediagnostic care to the patients at the airport 24 hours a day by using the telemedicine link. After the success of this program, telesychiatric services provided by the hospital were expanded to schools and the courts.\textsuperscript{29}

There were 15 teledermatology sites receiving federal funding in the United States in the 1970s.\textsuperscript{30} NASA started to use satellite video consultations to improve the quality of rural health care in Alaska in 1971. Five installed ground stations of the trial had two-way audio but only one-way video.\textsuperscript{31} Simultaneous video transmission and evaluation was not available. At the end of this trial it was determined that the unique capabilities of the video transmission may play a critical role in 5% to 10% of the cases selected for video presentation.\textsuperscript{32} In 1972, The Health Care Technology Division of the US Department of Health, Education and Welfare (HEW) funded 7 teledermatology research and demonstration projects such as Dartmouth Medical School’s Impact Project and Massachusetts’ Cambridge Hospital Project.

The North-West Telemedicine Project was started in 1984 in Australia to pilot-test a government satellite communications network (the Q-Network). The aim of the successful project was to provide health care to people in 5 remote regions of the Gulf of Carpentaria.\textsuperscript{22} In 1989, after a catastrophic earthquake that hit the Soviet Republic of Armenia, NASA conducted the first international telemedicine project, Space Bridge. One-way video and audio transmission systems were used between a medical center in Yerevan, Armenia, and 4 medical centers in the United States. This program was later extended to Ufa, the capital of the Republic of Bashkortostan in Russia.\textsuperscript{31}

Since teledermatology applications were first started, teledermatology has become a crucial component of many telemedicine networks. The term teledermatology was first used by Perednia and Brown in 1995. They reported the results of the teledermatology project in the remote rural areas of Oregon where dermatologic care was supplied by only 2 dermatologists.\textsuperscript{10} The

<table>
<thead>
<tr>
<th><strong>STORE-AND-FORWARD TELEDERMATOLOGY</strong></th>
<th><strong>VIDEOCONFERENCEING SYSTEM</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Synchronized evaluation is not necessary</td>
<td>Interactive consultation</td>
</tr>
<tr>
<td>Inexpensive but effective way for diagnosis and treatment</td>
<td>Expensive</td>
</tr>
<tr>
<td>Often unable to accept information directly from the patient</td>
<td>Enables 3-way discussion between general practitioner, patient, and the consultant dermatologist</td>
</tr>
<tr>
<td>High picture quality</td>
<td>Poorer picture quality but streaming</td>
</tr>
<tr>
<td>Simple computer systems and dial-up connection are sufficient</td>
<td>Requires faster (broadband) Internet connection</td>
</tr>
<tr>
<td>Good method for the patient triage</td>
<td>Effective method for general practitioner treatment</td>
</tr>
</tbody>
</table>
authors reported that the installation of a teledermatology system dramatically increases the number of patients referred for specialist evaluation. Even while the number of in-person visits to specialists fell and although there was no statistical diagnostic difference between dermatologist and primary care providers, a significant difference in treatment modalities was found.

In 1997, three independent teledermatology programs to provide dermatologic care to 3 traditionally underserved populations of the United States, Pacific Islanders, migrant farm workers, and prison inmates were described in one report. Teledermatology was found to be a useful technology to provide dermatologic support to remote or underserved communities. In the same year, researchers reported that teledermatology was an effective way of dermatology consultation in new patients referred from rural communities. In addition, experts reported a high diagnostic concordance rate (95%) between a simple videocferencing method using a digital camera and face-to-face evaluation, which correctly diagnosed 95 of 100 patients.

Investigators reported high diagnostic concordance (77.2%) between face-to-face examination and teledermatologic evaluation in 1998. In January 1998, the first telemedicine link for the British Defense Medical Services was set up between the British military hospital in Sipovo, Bosnia, and the Royal Hospital Haslar, the main tri-service hospital in the United Kingdom. In the same year, telemedicine technology was used at sea in Sweden from an aircraft in the United Kingdom, and from a moving ambulance in Greece.

In 1999, researchers reported a diagnostic concordance of 91% between face-to-face examination and teledermatologic evaluation of 66 pigmented skin lesions. One year later, in 2000, the same authors found an average of 85% correct concordance of the evaluation in a subset of 43 cutaneous pigmented skin lesions sent by e-mail to 11 colleagues with different degrees of experience in a subset of 43 cutaneous pigmented skin lesions. In 2003, dermatoscopic images of 108 melanocytic and nonmelanocytic lesions were evaluated via the Internet by 40 experienced dermatoscopists for the consensus meeting performed to describe diagnostic criteria and pattern analyses for benign and malignant skin tumors. In 2006, investigators evaluated teledermatscopy as a triage system for pigmented lesions in a pilot study that included 219 pigmented skin lesions. One year later, researchers stated that mobile teledermatology with cellular phones is an easy, applicable, and efficient way for melanoma screening.

Teledermatology is a developing field and a relatively new branch of telemedicine. Advances in telecommunication and visual digital systems make teledermatology an area with potential to apply telemedicine resources. Teledermatology is a proven-useful technology to provide dermatologic care in places where there is no dermatologist. It may reduce waiting time for patients with limited access to medical care and improve survival in patients with malignant skin tumors by means of providing swift diagnosis and early excision of the lesion. Physicians should be aware of the techniques of teledermatology and encouraged to perform new studies to develop this technology.

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Analysis of the history of melanoma shows a dramatic increase in the lifetime risk of melanoma in recent years. In 1996, the lifetime risk of contracting melanoma was 1:87, significantly greater than the risk of 1:1500 in the 1930s.1 Some have speculated that this rapid increase in the development of melanoma results from increased life expectancy, whereas others attribute this to increased levels of ultraviolet radiation in the atmosphere due to destruction of the ozone layer.2

Melanoma is a malignant tumor of melanocytes found predominantly in the skin, but also the gastrointestinal tract and eyes. Although melanoma of the skin is one of the rarest types of skin cancer, it causes the majority of skin cancer–related deaths. Once the cancer has metastasized, the survival rate is often measured in months rather than years. This is due to the fact that melanoma is able to cloak itself from the body's immune system, leaving it to grow relatively unchallenged. Based on information retrieved from the National Cancer Institute's (NCI's) Surveillance Epidemiology and End Results (SEER) Cancer Statistics Review, it has been estimated that 59,940 persons (specifically 33,910 men and 26,030 women) were diagnosed with melanoma and 8110 men and women died of melanoma of the skin in the year 2007.3

This paper examines the development of the concept of melanoma in the 19th century to better understand the origins of this disease and how the medical community has realized its significance, ultimately leading to it becoming widely studied and researched.

THE ORIGINS OF MELANOMA

Although melanoma is not a new disease, evidence for its occurrence in the past is still rather scarce. Nine Peruvian Inca mummies that were studied in the 1960s showed apparent signs of melanoma. René Théophile Hyacinthe Laennec, the inventor of the stethoscope, first described melanoma as a disease entity. William Norris, an English general practitioner, gave the first English language report of this disease. There are many other physicians from France, England, and the United States who had an active role in the discovery of melanoma.

THE 19TH CENTURY AS THE AGE OF DISCOVERY

Discoveries of Melanoma in France: 19th Century

French physician René Théophile Hyacinthe Laënnec (February 17, 1781–August 13, 1826) first described melanoma as a disease entity. He is also considered to be the first to recognize that melanotic lesions were different from the black tuberculosis granulomas or carbon deposits commonly found in the lungs. In describing these tumors, Laënnec coined the term melanose, which means “black” in Greek.3

Jean Cruveilhier, a French pathologist, anatomist, and physician, wrote several important works on pathologic anatomy. Between 1829 and 1842 he published an atlas of pathology, Anatomie Pathologique du Corps Humain (“Pathological Anatomy of the Human Body”), which included the original descriptions of melanoma of the hand, foot, and vulva, and metastatic melanoma of the heart and bowels.6
DISCOVERIES OF MELANOMA IN ENGLAND: 19TH CENTURY

In 1820, William Norris, an English general practitioner from Stourbridge, United Kingdom, presented the first English language report of melanoma. In retrospect, Norris published what he called “the first genuine good case of melanoma,” although his original term was fungoid disease. In this case, a changing and increasing tumor resulted from degradation of blood. Oliver Pemberton (1858) detailed the characteristics and sites of metastases, early pathologic studies, and the earliest descriptions with statistics on prognosis. He studied 60 cases of melanoma and made the first report of malignant melanoma deposit on a woman’s leg. On the basis of this single autopsy of a patient who had died of disseminated malignant melanoma, he suggested the removal of 2 inches of subcutaneous tissue down to the level of muscle fascia along with a radical removal of lymph nodes. His work, published in The Lancet in 1907, set the rules for the surgical management of malignant melanoma for 50 years. While the first case of cutaneous malignant melanoma ever treated was by John Hunter in 1787, the first logical approach to surgical therapy was not investigated until 1905. William Handley, a research fellow at Middlesex Hospital, London, spent 2 years researching the metastatic dissemination of breast cancer. In 1905, he began to analyze the lymphatic spread of a secondary melanoma deposit on a woman’s leg. On the basis of this one case of metastatic melanoma, he suggested the removal of 2 inches of subcutaneous tissue down to the level of muscle fascia along with a radical removal of lymph nodes. His work, published in The Lancet in 1907, set the rules for the surgical management of malignant melanoma for 50 years.

In 1908, Handley delivered the famous Hunterian Lectures on malignant melanoma to the Royal College of Surgeons of England. He acknowledged that he never treated a case of primary malignant melanoma and based all his recommendations on a single autopsy of a patient who had died of disseminated melanoma. Nevertheless, his recommendations became the standard of treatment for most of the 20th century. Handley suggested excising a 1-inch circumference of skin and a 2-inch margin of subcutaneous tissue around the melanoma. That recommendation was later expanded to 5 centimeters, and even 15...
centimeters in select cases. Several investigators supported this trend by reporting premalignant changes in the skin within several centimeters of the primary lesion. 

**Discoveries of Melanoma in the United States: 19th Century**

In 1840, Samuel Cooper was the first person to formally acknowledge that advanced melanoma is untreatable. He stated that the “…only chance for benefit depends upon the early removal of the disease…” This situation currently remains largely unchanged.

Besides Cruveilhier’s descriptions of melanoma in his pathology text, there were other early reports of melanoma in the United States. Isaac Parrish in 1837 and Montgomery in 1844 described melanoma of the foot. The report by Parrish is the first case report of melanoma in North America. The book on the melanoma of the foot by Montgomery included a rare case of melanoma in a black patient. Furthermore, in 1837, John Warren reviewed several cases of melanoma in his book on tumors.

The identification and treatment of melanoma has come a long way from the initial discoveries in the 19th century. Although the medical community has made great leaps, there is still much we do not know about these cancerous lesions. Melanoma is currently a hot topic of research, and because of the dramatic increase in its rate of development, investigations will persist until a treatment is devised that can lead to a better recovery, a decent prognosis, and a higher survival rate.

**REFERENCES**

On September 11, 2009, the US Food and Drug Administration (FDA) approved telavancin (Vibativ; Theravance, Inc, San Francisco, CA, and Astellas Pharma US, Inc, Deerfield, IL) for the treatment of complicated skin and skin structure infections (cSSSIs) caused by methicillin-resistant *Staphylococcus aureus*, methicillin-sensitive *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, and vancomycin-susceptible *Enterococcus faecalis*. Telavancin, a lipoglycopeptide derivative of vancomycin, has a 2-fold mechanism of action: (1) it inhibits polymerization and cross-linking of peptidoglycans during bacterial cell wall synthesis, and (2) it alters cell membrane permeability by disrupting the membrane potential. It is currently approved for intravenous infusion at a dosage of 10 mg/kg over 60 minutes every 24 hours, although it is recommended that the dosage be decreased to 7.5 mg/kg every 24 hours and 10 mg/kg every 48 hours in patients with a creatinine clearance of 30 to 50 mL/min and 10 to 29 mL/min, respectively.

The efficacy of telavancin was initially examined in 2 randomized, double-blind, active-controlled phase II trials (FAST I and FAST II studies), which demonstrated that intravenous administration of telavancin was as effective as standard therapy for the treatment of cSSSIs. Ultimately, its approval by the FDA was based on 2 parallel, randomized, double-blind phase III clinical trials (the Assessment of Telavancin in Skin and Skin Structure Infections [ATLAS] I and ATLAS II studies). In these large-scale studies spanning 21 countries, a total of 1867 adult patients were randomized to 2 treatment groups: 10 mg/kg of telavancin administered intravenously every 24 hours or 1 g of vancomycin administered intravenously every 12 hours. Of those patients, 1410 were considered to be clinically evaluable. The types of infections treated most commonly were major abscesses, deep cellulitis, infected wounds, infected ulcers, and infected burns. After 1 to 2 weeks of the last administered dose, 88% and 87% of the patients had successful responses to telavancin and vancomycin, respectively (95% confidence interval for the difference, –2.1 to 4.6). Among 579 patients infected with methicillin-resistant *Staphylococcus aureus*, 91% of patients in the telavancin group and 86% of patients in the vancomycin group were effectively treated (95% confidence interval for the difference, –1.1 to 9.3). Overall, the study demonstrated a comparable efficacy and tolerability profile to vancomycin for the treatment of cSSSIs caused by Gram-positive bacteria.

Adverse effects of telavancin include taste disturbances, nausea, and vomiting. Furthermore, it is classified as a category C drug, stemming from developmental toxicology studies that demonstrated a decrease in fetal weight and a low incidence of limb defects in rats treated with telavancin. There have also been reported incidences of reversible renal dysfunction and prolonged corrected QT interval, although no major cardiovascular events or arrhythmias have been reported. Given these findings, clinicians are advised to perform a pregnancy test and monitor renal function during treatment with telavancin.

The mounting epidemic of antibiotic-resistant cSSSIs has prompted clinical investigations for the development and approval of telavancin, a novel antibiotic with a substantial efficacy and tolerability profile. The superiority of telavancin over traditional antibiotics stems from its rapid, concentration-dependent bactericidal activity, as well as a 2-fold mechanism of action that helps curb the development of resistance. It also has considerable economic practicality compared with the use of vancomycin, owing primarily to its once-daily dosing and a lack of need for monitoring its serum concentrations. There is a lack of evidence purporting its clinical effectiveness over vancomycin, however, which has been a mainstay of treatment options for cSSSIs and is associated with substantially less renal toxicity.

Therefore, although telavancin may hold promise as a timely supplemental to current treatment options for cSSSIs amidst their growing incidence, further clinical investigations should be implemented to explore its efficacy against vancomycin-resistant bacteria.
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A 28-year-old pregnant (week 27 of gestation) patient came for routine follow-up examination of recurrent condylomata acuminata. Examination of the outer anogenital area with a clear and powerful light detected no lesions suspicious for condyloma. She did, however, have a verrucose lesion on her nipple that was removed and histologically diagnosed as condyloma acuminatum. She was instructed not to breastfeed her baby.

**DISCUSSION**

The issue of extragenital human papillomavirus (HPV), eg, in oral mucosa and breast, is not new, but most of the relevant studies focus on a possible etiologic link between HPV and breast cancer. Since 1992, 11 of 15 published studies that searched HPV DNA in breast carcinomas by polymerase chain reaction observed the presence of HPV DNA genes in breast tumors at a prevalence of 12% to 86%. Normal breast tissue controls were available for 4 of these studies, and HPV sequences were identified in only 1 of 89 controls (1.1%). Neither the patients nor the controls were tested for the presence of genital HPV and so these studies cannot provide any indication about the rates of transmission of HPV from the genital area to the breast. Furthermore, all but one study examined breast tissue and not the skin of the mamilla.

The issue of transmission of HPV from parent to child has been poorly investigated. Most of the studies on transmission have focused on genital HPV, while the role of extragenital HPV (oral and breast) has been neglected. There is enough evidence today that perinatal transmission of genital HPV from mothers to infants does occur. The mechanisms of HPV transmission between parents and children are of great interest but remain poorly understood.

**BREASTFEEDING AND RISK OF HPV TRANSMISSION**

We are aware of only one very recent study that addressed this issue. The investigators tested HPV by polymerase chain reaction in 223 milk samples 3 days postpartum, and HPV DNA was detected in 10 (4.0%) of the samples, of which 9 were positive for HPV-16. HPV carriage of the milk was not related to the genital or oral HPV DNA status of the mother. Rather, it was significantly correlated with the oral HPV carriage of the spouse at months 6 and 12 after childbirth, but not at the time of delivery. The researchers made every effort to avoid contamination of the milk from the mother's hands and skin surrounding the nipple. This approach is obviously correct if the aim is to analyze the milk, but it does not allow an examination of the real risk of contamination involved in the entire breastfeeding process, eg, the possibility of acquiring the virus from the nipple and areolar tissues. There is some evidence today (we are aware of only one study) of the occurrence of HPV in nipple and areolar tissues, and it is assumed that the HPV reached the milk from these tissues in a retrograde manner. Consequently, we might assume that the transfer of HPV from the skin of the nipple is possible even if the milk itself is not infected. Furthermore, the length of time the baby's oral mucosa is in contact with the skin is many times longer than it is with the milk, thus increasing the risk of virus transmission from the skin to the baby's oral mucosa.

**THE BOTTOM LINE**

We are not aware of any investigations of the rate of breast HPV infection among women with genital or oral HPV infection. Transmission of viral particles from the mother's nipple and areola or her milk to the baby's oral cavity is certainly a very plausible possibility. Taken together, we conclude that until more information on the subject is available, in spite of the important health benefits, it would be wise to err on the side of caution and recommend that HPV-positive mothers refrain from breastfeeding.

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VINTAGE LABEL

Courtesy of BuyEnlarge, Philadelphia, PA
Docetaxel is a taxane chemotherapeutic agent approved for a wide variety of neoplastic conditions, including breast cancer, non–small-cell lung cancer, head and neck cancers, and androgen-independent metastatic prostate cancer. Common side effects of docetaxel therapy vary according to treatment schedules and most commonly include myelosuppression when dosed every 3 weeks, and malaise, fatigue, excessive tearing, and skin and nail changes with weekly treatment. Skin changes classically include erythematous macular and papular eruptions with desquamation, nonpruritic erythema, and the hand-foot syndrome, occurring in as many as 50% to 70% of patients. Docetaxel-induced nail changes are also very common, occurring in up to 44% of patients and include paronychia, onycholysis, subungual hemorrhage, subungual abscess, nail pigmentation, splinter hemorrhages, nail bed purpura, Beau's lines, and nail bed pigmentation. One nail change that has yet to be reported in the literature, however, is blue lunulae. Here we describe a case of a patient with blue lunulae developing in the context of docetaxel therapy for treatment of adenocarcinoma of the prostate.

DISCUSSION

Acquired blue lunulae are commonly induced by systemic medications, with zidovudine being perhaps the most frequent causative agent. Combination chemotherapies have also been shown to cause this reaction, with different combinations of cyclophosphamide, vincristine, doxorubicin, dacarbazine, 5-fluorouracil, vinblastine, dactinomycin, and bleomycin being implicated. Additional causes of blue lunulae include the intentional or inadvertent ingestion of silver-containing products (argyria), hemoglobin M disease, Wilson’s disease, hereditary acrolabial telangiectasia, and the medication phenolphthalein purgative.

To our knowledge, this bluish lunulae discoloration in a patient being treated with docetaxel is unique and has yet to be reported in the literature. Accordingly, we present this case so that physicians can recognize this finding as a potential, harmless reaction to docetaxel therapy and avoid unnecessary tests and referrals. As seen in this case, this discoloration is not a precursor to the more severe and often painful nail changes associated with docetaxel therapy and should not prompt a change to a different dosing schedule or chemotherapeutic agent, which could lead to therapeutic failure.


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**Figure.** Clinical presentation of blue lunulae resulting from docetaxel therapy. The patient's bilateral thumbs reveal a bluish discoloration of the lunulae (A). A return to normal nail bed coloration after discontinuing docetaxel therapy (B).

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Submitted by Douglas D. Altchek, MD, New York, NY
Spinal dysraphism refers to incomplete fusion of midline structures of the embryonal dorsal median region that may affect any combination of somatic ectoderm, neuroectoderm, or mesoderm. Since both skin and nervous tissue are of ectodermal origin, anomalies of these tissues may simultaneously occur.1 Faun tail nevus is an abnormal lumbar hypertrichosis represented by tufts of coarse terminal hair, several inches in length that usually manifests as a lozenge or triangular patch in the lumbosacral area and may overlie an occult spinal abnormality.2,3 A midline cutaneous posterior anomaly is often a clue for an underlying occult spinal dysraphism. The cutaneous signs of spinal dysraphism are seen in 50% of cases of occult spinal dysraphism.4 Other studies have documented an even higher prevalence of cutaneous lesions up to 76% (43%–95%).5 The cutaneous lesions that should raise a higher degree of suspicion include hypertrichosis, dimples, aplasia cutis, lipoma, hemangioma, dermoid cyst or sinus, acrochordons, aplasia cutis, lipoma, hemangioma, dermoid cyst or sinus, acrochordons, true tail, pseudo-tail, and congenital scarring. Lesions with a low index of suspicion include telangiectasia, capillary malformations (port wine stain), hyperpigmentation, hypopigmentation, melanocytic nevi, connective tissue nevus, hypertrophic skin, hamartomas, teratoma, and neurofibroma.1 Sacral hypertrichosis (faun tail nevus) is the most common skin lesion evident at birth, as was seen in our patient. Hairy patches are most frequently associated with tethered cord and diastematomyelia.4 Our patient had a hairy patch in association with diastematomyelia.

Abnormal lumbar hypertrichosis may present as a “faun tail” or “silky down.” Silky down is represented by tufts of hair with the texture of fine, soft, nonterminal, or lanugo hair. A faun tail is a wide, often triangular or lozenge-shaped patch of coarse hair, usually several inches long. Faun tail is a rare entity. Mild hypertrichosis on the back, including the lumbar area, is a common finding in certain ethnic groups, such as persons found in the Middle East. It is usually not sharply circumscribed and is never as long or thick as in the case described herein.

The term spinal dysraphism encompasses many congenital abnormalities, including dermal sinuses, dermoid cysts, diastematomyelia, fibrous bands, filum terminale, intraspinal lipomas, lipomyelomeningoceles, and myelomeningoceles. Among them, diastematomyelia presents as an embryologic defect that is characterized by the division of the spinal cord or cauda equina into two separate portions.2,3

CASE STUDY

A Rare Cutaneous Marker of Spinal Dysraphism
Muhterem Polat, MD;1 Fazli Polat, MD;2 Pinar ÖztAŞ, MD;1 Canan Kaya, MD;1 Nuran Alli, MD1

A 10-year-old girl who was admitted to the urology department with complaints of urinary incontinence was referred to our dermatology outpatient clinic because of a congenital, circumscribed, hypertrichotic area on the lumbosacral region. Cutaneous examination revealed a circumscribed area of coarse, dark terminal hair measuring 25×15 cm overlying the lumbosacral area with normal underlying skin (Figure 1). There were erythematous macular lesions on the superior of the hairy area. The lesion had been present since birth, and no other family member had similar lesions. Her history revealed back pain and a long history of urinary incontinence. On neurologic examination, no motor weakness or sensory changes were observed. Babinski reflex was positive on the left. Magnetic resonance imaging (MRI) findings included diastematomyelia between T12 and L1 levels and slight flattening of lumbar lordosis (Figure 2). A diagnosis of faun tail with underlying spinal dysraphism was made. There was also urinary incontinence as late sequelae of spinal dysraphism.

Figure 1. Tufts of coarse terminal hair in the lumbosacral area.
Faun tail is very rare, and it is not only an aesthetic problem, because its presence may be one of the cutaneous stigmata of occult spinal dysraphism like other midline posterior cutaneous anomalies.\textsuperscript{1,7–11} Although both the cutaneous and neurologic lesions are usually asymptomatic until the child is older, a delay in diagnosis may result in neurologic, urologic, and orthopedic complications. This emphasizes the need for increased awareness of these cutaneous signs. Patients with well-localized paraspinal hypertrichosis must undergo neurologic and radiologic assessment to exclude spinal abnormalities. Our patient had been to various first-step health care clinics for the complaint of urinary incontinence, but no neurologic or radiologic assessment was performed, and she was advised to see a child psychiatrist. The patient was referred to our outpatient clinic by a urologist for the hypertrichotic area on the lumbosacral area. MRI was performed and diastematomyelia was detected. Early diagnosis of spinal dysraphism is important, because spinal correction can prevent irreversible neurologic damage. When neurologic deterioration starts, complete recovery may not be guaranteed, and if the cases remain untouched, sensorimotor deficits and bladder and bowel dysfunction may occur.\textsuperscript{5,11} In our patient, urinary incontinence occurred as late sequelae of spinal dysraphism.

Surgical intervention should be early after entire neural axis screening by MRI.\textsuperscript{5} In occult spinal dysraphism, neurosurgical treatment methods differ from patient to patient. Laminectomy of the lumbar and lumbo-sacral spine with excision of intraspinal lipoma, excision of bony or cartilaginous spur in diastematomyelia, and detethering of the conus medullaris and cauda equina can be successful.\textsuperscript{12} Significant improvements can be achieved with a judiciously timed division of the spinal tethered cord.\textsuperscript{13} There are studies showing that tethered cord release is beneficial in terms of clinical and urodynamic outcomes.\textsuperscript{13} In one study,\textsuperscript{6} the most common postoperative complications were pseudomeningocele, wound infection, and meningitis.

CONCLUSIONS

Dermatologists should be familiar with faun tail as it can easily be overlooked by physicians other than dermatologists. We think that the recognition of the cutaneous stigmata of spinal dysraphism may decrease the long-term morbidity of this condition. The aim of this article is to draw attention to faun tail and to emphasize the responsibility of physicians in the early recognition of lumbar paraspinal skin lesions so that appropriate early treatment may be given for underlying anomalies before irreversible sequelae develop.

REFERENCES


**WAX MOULAGE**


Courtesy of Michael Geiges, MD
CASE STUDY

Werner Syndrome in an Iranian Family

Zahra Hallaji, MD; Massumeh Barzegari, MD; Katrin Kiavash, MD

A 49-year-old man was first seen in our department for the evaluation of scleroderma-like skin changes and a nonhealing ulcer on his leg from 2 years before referral. His medical history was of long duration. His growth was stunted at the age of 12. At 21 years of age, the patient noted graying of the scalp hair, most prominent on his temples, and the process was progressively completed by the age of 23. At the same age, atrophy and thinning of the skin and loss of subcutaneous fat resulted in a tense, shining, and adherent appearance of his skin, most obvious on his face and extremities. Soon after, he developed a high-pitched, hoarse voice. He had undergone bilateral cataract surgery at the age of 30. Around the age of 46, he developed a unilateral nonhealing chronic leg ulcer (Figure 1). He had separated from his wife because of infertility. He was the first offspring of his second-degree healthy relative parents. The other 3 siblings had similar signs and symptoms. Our patient gave the history of premature graying of the hair of his younger brother at the age of 18 and his 2 younger sisters at the age of 12 and 16. His brother had recently received diagnoses of bilateral cataract and diabetes mellitus. All of the siblings had ceased growth from early adolescence. On physical examination, our patient’s weight was 48 kg and his height was 150 cm. He had normal intelligence. He was speaking with a high-pitched and childish voice. He had a bird-like appearance with a beak-shaped nose. Mottled and diffuse pigmentation and poikiloderma appearance was conspicuous on his neck (Figure 2). The entire skin was smooth, shiny, and scleroderma-like, and a marked decrease in the subcutaneous fat was noted over the extremities. A deep cutaneous ulcer was evident on his slightly leg. Digital ulcers were not found, and radial and dorsalis pedis pulses were palpable. Clinodactyly of the toes were conspicuous. His nails were dystrophic and he had used dentures from the age of 20. On examination of the external genitalia, his testes were smaller than normal. In the biopsy taken from the leg ulcer, there were no signs of malignancy. There were no signs of osteomyelitis on x-ray. Biopsy of the normal skin revealed atrophic epidermis and thick dermis with hyalinization of the collagen fibers and absence of pilosebaceous structures (Figure 3). The patient’s scalp hair was thin and sparse and there were few axillary and pubic hairs. His fasting plasma glucose level was normal.

Werner syndrome, or adult progeria, is a rare inherited disorder in which the aging process is accelerated.1 Patients show normal growth in childhood that usually arrests at puberty. It is followed by balding and premature graying of hair, scleroderma-like skin changes, poikiloderma, atrophy, and cataracts in the late 20s to 30s.2 Other features include muscle wasting, especially in the extremities, giving rise to spindle-shaped legs, chronic leg ulcer, hypogonadism and impotence, high-pitched voice, osteoporosis, premature arteriosclerosis, diabetes mellitus, and increased rate of malignancy, especially fibrosarcoma.3 Our patient’s history was compatible with Werner syndrome, and many features of this syndrome were also found in his siblings.

Werner syndrome occurs worldwide, but 75% of patients are Japanese.4 Few cases have been reported from the Middle East.5 Werner syndrome is an autosomal-recessive disorder that belongs to the category of human premature aging disorders.6 Disorders such as Rothmund-Thomson syndrome, progeria, Cockayne syndrome, xeroderma pigmentosum, and Hutchinson-Gilford progeria belong to this disease category.7 Werner syndrome is caused by a mutation in the RecQ-type DNA helicase gene (WRN gene), which was identified in 1996.8 It appears that the syndrome is the result of complete loss of the WRN gene product, which is required for genomic stability.9 Consanguinity of our patient’s parents and occurrence of the same disease in his siblings point to an autosomal-recessive pattern of inheritance; unfortunately, genetic analysis was not available.

Since Werner’s original report in 1904,10 several authors have attempted to define more accurate diagnostic criteria of the Werner syndrome to be distinguished from other premature aging syndromes. Thannhauser presented a list of principal features for accurate diagnosis of this syndrome in 1945.11 According to diagnostic criteria from the Werner Syndrome International Registry, Werner syndrome can be diagnosed as definite, probable, or possible based on number of positive cardinal and further signs and symptoms.12 Cardinal signs and symptoms include: (1) bilateral cataract; (2) characteristic dermatologic pathology (tight skin, atrophic skin, pigmen-tary alterations, ulceration, hyperkeratosis, regional subcutaneous atrophy) and characteristic facies (“bird” facies); (3) short stature; (4) parental consangunuity (3rd cousin or greater) or affected sibling; (5) premature graying and/or thinning of scalp hair; and (6) positive 24-hour urinary hyaluronic acid test (when available). Further signs and symptoms include: diabetes mellitus; hypogonadism (secondary sexual underdevelopment, diminished fertility, testicular or ovarian...
atrophy); osteoporosis; osteosclerosis of distal phalanges of fingers and/or toes (x-ray diagnosis); soft tissue calcification; evidence of premature atherosclerosis (eg, history of myocardial infarction); mesenchymal neoplasms, rare neoplasms, or multiple neoplasms; voice changes (high-pitched, squeaky, or hoarse voice); positive 24-hour urinary hyaluronic acid test (when available); and flat feet.12 Since our patient had all of the cardinal features (except for a positive result of 24-hour urinary hyaluronic acid test, which was not available) and two further features (hypogonadism and voice changes), diagnostic group assignment of our patient is “definite.”

Our patient was referred to our clinic because of his leg ulcer. Unusual ulcers are a feature of Werner syndrome but they are not always recognized as being a part of this syndrome.13 In this case, the clinical feature led us to suspect Werner syndrome rather than a simple ulcer. Correct diagnosis is important since these patients must be followed for possible occurrence of malignancies. Study of patients with Werner syndrome may also help in understanding the process of aging.7

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HISTORICAL DIAGNOSIS & TREATMENT
Diagnosis and treatments have advanced over the past century. This feature depicts conditions from a collection of stereoptic cards published in 1910 by The Stereoscopic Skin Clinic, by Dr S. I. Rainforth.
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Laboratory studies revealed normal complete blood cell count and lactate dehydrogenase values. Computed tomography scans of his chest, abdomen, and pelvis confirmed the bilateral inguinal lymphadenopathy, but were otherwise unremarkable. Skin histopathology showed an atypical lymphocytic infiltrate involving the full thickness of the dermis and extending into the subcutis (Figure 2). While focal epidermotropism was present, folliculotropism was more prominent. Admixed with the lymphocytes were numerous histiocytic multinucleated giant cells, consistent with granulomatous mycosis fungoides (MF). In immunoperoxidase-stained sections, most of the lymphocytes stained positive for leukocyte common antigen. The majority of lymphocytes were CD3 positive. No organisms were identified in either acid fast– or periodic acid Schiff–stained sections. Skin tissue culture results were negative. Biopsy of an enlarged inguinal lymph node also revealed histopathologic features of granulomatous MF, with partial effacement of the normal nodal architecture. Flow cytometric immunophenotyping of both the skin and lymph node samples revealed an aberrant clonal population of lymphoid cells expressing CD2, CD3, CD4, and CD5 and partial CD45 and CD25. The cells failed to express CD7. Peripheral blood flow cytometric analysis showed no aberrant clone. Blood, skin, and lymph node analysis for T-cell receptor (gamma chain) gene rearrangements (TCRγ) by polymerase chain reaction (PCR) were negative. Bone marrow histology, flow cytometry, and molecular analysis showed no evidence of involvement.

Based on these results, the patient was diagnosed with cutaneous T-cell lymphoma (CTCL), granulomatous MF variant, stage IVA (T3, N3, M0, B0). Therapy with subcutaneous interferon α (2b) at 4 million units 3 times per week and acitretin 25 mg daily was initiated. The ulcerated lesions were irradiated with electron beam. The patient’s lesions responded well to radiotherapy (left ankle [21.5 Gy], right posterior thigh [33 Gy], and right flank [33 Gy]) (Figure 3A and 3B). He has been maintained on acitretin and interferon α, with resolution of his systemic symptoms and lymphadenopathy, minimal skin findings, and no evidence of disease progression for 30 months.

DISCUSSION

CTCLs are a heterogeneous group of primary cutaneous lymphomas characterized by malignant, skin-homing abnormal T-cell clones. MF, the most common type of CTCL, is frequently difficult to diagnose. This is due to the wide variation in clinical manifestations,1 and also to the heterogeneity of histopathologic findings. In addition, assays for the detection of monoclonality in the cutaneous infiltrate, although useful adjuncts, are occasionally inconclusive or negative, particularly in the early stages of disease.

Granulomatous MF is a rare variant of MF originally described in 1970.2 Since that time there have been only a few dozen cases of granulomatous MF published in the English literature.3–5 Granulomatous MF is distinct from granulomatous slack skin, as the latter condition has a distinctive clinical presentation characterized by multiple, pendulous, and lax skin folds. In addition, it has been suggested that elastolysis is a prominent histopathologic feature of granulomatous slack skin, but it is less of a characteristic feature in granulomatous MF.6 The two conditions have significant histological overlap, however,6,7 and they likely represent different forms of the same disease.

According to previously published reports, patients with granulomatous MF may present with a variety of skin lesions, similar to that of classic MF. These include localized or widespread patches, papules, plaques, and tumors. Ulcerations, erythroderma, and ichthyotic and poikilodermatous lesions have also rarely been reported.3,4,8

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Apart from granuloma formation, no other histological features are unique to granulomatous MF as compared with other forms of MF. The presence of granulomas in cutaneous infiltrates of MF is a rare phenomenon and was once ascribed as a favorable prognosis. It has since been acknowledged, however, that the granulomatous response in MF is not necessarily protective, nor is it of clear prognostic relevance. In fact, there are rare reports of granulomatous MF characterized by progression to visceral involvement and subsequent death. In a recent review from Europe of 15 patients with granulomatous MF, the overall prognosis appeared to be less favorable than those with classic MF.

In the case of our patient, the presence of granulomas in the infiltrate prompted a thorough investigation in search of microbial pathogens, particularly in light of his extensive travel history. When presented with granulomatous infiltrates, tissue cultures should be performed, since they are generally more sensitive than direct tissue examination (even with special stains), for pathogens such as deep fungi. Even if the histology is supportive of granulomatous MF, examination for infectious agents is critical, as patients with lymphoid malignancies often manifest immune dysregulation predisposing them to infection.

An interesting and notable feature in our patient was the absence of a detectable clone by PCR analysis for TCRγ chain gene rearrangements in both the skin and the lymph node. The reason for this is unclear. It is possible that the particular rearrangement occurring in our patient was not detectable by the molecular assay used in our laboratory. Published studies using PCR suggest the range of detection of a clonal (TCRγ) rearrangement from involved skin of patients with CTCL is 74% to 90%.

CONCLUSIONS
Prognosis of patients with granulomatous MF, as with other subtypes of CTCL, depends on overall stage of disease. No...
particular therapeutic regimen has been shown to be superior for patients with the granulomatous variant, and the optimum therapeutic approach remains to be determined. Previously reported effective therapies include retinoids, interferon, chemotherapy, and radiation. Because treatment with a combination of modalities seems to offer benefit over any single agent in advanced cases of MF, we employed skin-directed therapy (radiation) along with systemic immunomodulatory agents acitretin and interferon α. With this approach, our patient reported herein with stage IVA disease has remained alive and well for 30 months without evidence of disease progression.

REFERENCES

In ancient times, henna was used to treat psoriasis, eczema, and even ringworm because of its mild anti-inflammatory effect. The flowers, pulverized leaves, fruit, and bark were all used as a remedy. The ancient Egyptians identified 7 types of henna and used henna even before mummification. Because of the sweet smell of the henna flowers, the distilled water made from them was applied into cosmetics in the Orient. The powdered leaves have been used all over the world for dying hair, nails, and skin.

There are only a few reports concerning allergic reactions due to pure henna. Sensitization to henna is common in hairdressers. The typical symptoms consist of sneezing, runny nose, cough, and shortness of breath, with a lack of skin reactions.

The mixtures applied to the skin for creation of temporary tattoos do not contain only henna. The painting with pure henna gives a red color. The henna paste used by “henna artists” contains natural henna and different coloring agents to darken the color. The following ingredients might be found in henna paste: PPD, coffee, black tea, lemon juice, eucalyptus, clove, mustard oil, and fenugreek seeds.

PPD is in the “top 10” of the most frequent contact allergens. A skin eruption is the major outbreak of allergic reactions to PPD. The molecular mechanism behind the recognition of PPD by the immune system has not been fully elucidated. According to classic studies, such small molecules need to form reactive metabolites, which, in turn, may lead to the formation of immunogenic hapten-protein conjugates and are then presented to the immune system. PPD may be oxidized to benzoquinone diimine, which, in turn, may form the trinuclear dye called Bandrowski’s base. Researchers reported that Bandrowski’s base is responsible for the common allergic reactions of PPD.

CASE STUDY
Contact Dermatitis Due to Temporary Henna Tattoos
Jana Kazandjieva, MD; Maria Balabanova, MD; Kamelia Kircheva, MD; Nikolai Tsankov, MD

Case 1: A 19-year-old woman presented with an allergic contact dermatitis on her back. Skin lesions developed exactly where a henna tattoo had been applied 3 days earlier. She noticed that the henna artist placed some kind of occlusive dressing on her back for 30 minutes. The artist explained that this is made to keep the tattoo on her skin. During the first 2 days after the application, the patient experienced severe pruritus in the tattooed area. One day later, multiple small vesicles developed within the tattoo design (Figure 1). The eruption was palpable. The skin lesions had risen, sparing the unpainted areas. The histologic investigation revealed spongiosis in the epidermis with dense lymphohistiocytic infiltrates in the dermis (Figure 2). Epicutaneous tests were positive for henna paste and paraphenylene diamine (PPD). Epicutaneous test results with henna powder was negative, confirming the lack of allergy to henna. Treatment with topical steroids (class IV) resulted in gradual improvement, with resolution in several weeks.

Case 2: During a holiday on the coast of the Black Sea, a 14-year-old boy applied on his back a nonpermanent henna tattoo in the shape of a dragon (Figure 3). His mother noticed that the henna artist used a syringe to apply the henna mixture. Two days later an acute erythematous and edematous pruritic eruption developed where the skin paint was originally applied. The skin lesions improved after treatment with local corticosteroids, but a residual postinflammatory hyperpigmentation remained, tracing the tattoo design occurring in the form of a dragon. Patch tests were performed with the European Standard Series and commercial and natural henna. The patient revealed positive reactions (3+) to PPD 1%, but not to henna.

Figure 1. Case 1: Contact dermatitis 1 week after application of a henna tattoo.
PPD is the most widely used agent in hair dye formulae. This compound is also used as a photographic developing agent and as an intermediate in the manufacture of azo dyes, antioxidants, and accelerators for rubber vulcanization.

Patch testing of our patients showed a strongly positive response to PPD. PPD is added to henna paste to speed up the process (to minutes) and intensify the color of the dye.6 The risk of allergic reaction to PPD escalates due to a lack of a neutralizing agent, long duration of skin contact, and high concentration of the allergen.

More than 100 cases of contact dermatitis due to temporary tattoos have been reported.8 In all cases, PPD was confirmed to be the key factor for the development of allergic contact dermatitis. In the present 2 cases, there are some special features: the use of a syringe and an occlusive dressing by the henna tattooist. According to our previous investigations,1,9 the occlusive dressing used enhanced the penetration and thus could explain the short incubation period and severity of the allergic reaction. In the second case, the syringe needle penetrated the stratum corneum and this way the antigen was directly presented in the Langerhans cells. Because of this, the upper layer of the skin was bypassed and a very short incubation period was observed (only 2 days).

Persons with known reactions to PPD or cross-reacting allergens with a para-positioned amino group in the benzene ring should be cautious of temporary tattoo application.10 This fact is especially important for such substances as sulfonamides, para-amino benzoic acid, sulfonylureas, dapsone, azo dyes, and benzocaine.8

REFERENCES

Locoid Lipocream® Cream, 0.1% Rx Only
(hydrocortisone butyrate 0.1% cream)
For Topical Use Only

BRIEF SUMMARY

INDICATIONS AND USAGE
Locoid Lipocream is a topical corticosteroid indicated for: relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in adults and the treatment of mild to moderate atopic dermatitis in patients 3 months to 18 years of age.

WARNINGS AND PRECAUTIONS
Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression may occur, with the potential for glucocorticosteroid insufficiency. Consider periodic evaluations for HPA axis suppression if Locoid Lipocream is applied to large surface areas or used under occlusion. If HPA axis suppression is noted, reduce the application frequency, discontinue use, or switch to a lower potency corticosteroid.

Systemic effects of topical corticosteroids may also include manifestations of Cushing's syndrome, hyperglycemia, and glucosuria. Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface-to-body-mass ratios. Initiate appropriate therapy if concomitant skin infections develop. Discontinue use if irritation develops.

ADVERSE REACTIONS
The most common adverse reactions (>1%) are HPA axis suppression and application site reactions. The following additional local adverse reactions have been reported infrequently with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions included: irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, miliaria and telangiectasia.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Systemic corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women. Therefore, Locoid Lipocream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Please refer to full prescribing information for detailed information regarding systemic embryofetal development studies.

Nursing Mothers
Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Locoid Lipocream is administered to a nursing woman.

Pediatric Use
Safety and efficacy in pediatric patients below 3 months of age have not been established. Because of higher skin surface-to-body-mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. They are therefore also at a greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment.

Eighty-six (86) pediatric subjects (5 months to less than 18 years of age) with moderate to severe atopic dermatitis affecting at least 25% of body surface area (BSA) treated with Locoid Lipocream three times daily for up to 4 weeks were assessed for HPA axis suppression. The disease severity (moderate to severe atopic dermatitis) and the dosing regimen (3 times daily) for which Locoid Lipocream is indicated. Five of the 82 evaluable subjects (6.1%) demonstrated laboratory evidence of suppression, where the sole criterion for defining HPA axis suppression was a serum cortisol level of less than or equal to 18 micrograms per deciliter after cosyntropin stimulation. Suppressed subjects ranged in age from 5 months to 16 years and, at the time of enrollment, had 25% to 95% BSA involvement. These subjects were seen at doses of 0.7x maximum human dose (MTHD). Mild effects on maternal animals, such as reduced food consumption and a subsequent reduction in body weight gain, were seen at doses of 0.6 mg/kg/day (0.2x MTHD).

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from freezing. Keep out of the reach of children.

Manufactured for: Triax Pharmaceuticals, LLC
Crandon WI 54822

Marketed and Distributed By:
Triax Pharmaceuticals, LLC
Crandon NJ 07016

By: Ferndale Laboratories, Inc.
Ferndale MI 48022

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1318301
Rev 11/09
Now younger eczema patients have something to smile about

Now approved for use in children down to 3 months of age

Locoid Lipocream®
(hydrocortisone butyrate 0.1%) Cream

The power of an ointment with the elegance of a cream

Locoid Lipocream is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, including the treatment of mild to moderate atopic dermatitis in patients 3 months of age and older.

Safety and effectiveness in pediatric patients below 3 months of age have not been established.

Reversible HPA axis suppression may occur, with the potential for corticosteroid insufficiency. Consider periodic evaluations for HPA axis suppression if applied to large surface areas or used under occlusion. Systemic effects of topical corticosteroids may also include manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria. Pediatric patients may be more susceptible to systemic toxicity due to their large skin surface-to-body-mass ratios. Initiate appropriate therapy if concomitant skin infection develops. Discontinue use if irritation develops. Please see full Prescribing Information on adjacent page.

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