Dermatology

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Cryotherapy as a Precipitant Factor in Focal and Segmental Dystonia

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Key Words
Cryotherapy • Dystonia, focal and segmental

An increasing number of reports has drawn attention to the importance of trauma as a cause or precipitant of pain and movement disorders [1]. In 1888, Gowers [2] suggested that movement disorders can be produced not only by central but also by peripheral trauma and this concept is now becoming more accepted. Focal and segmental dystonia (FSD) is a peripherally induced dystonia caused by an injury to a nerve or nerve root. The location rather than the nature of the injury seems to determine the type of induced movements. The nature of the injury can vary, i.e. cutaneous or eyelid surgery, dental procedure and so on. Besides associated pain, which has been described in nearly all cases of posttraumatic dystonia, patients present dystonic movements.

We report the case of a patient affected by FSD of the lumbar region and legs whose causalgia and dystonia were precipitated by cryotherapy for multiple actinic keratoses of the face.

A 62-year-old woman had undergone cryotherapy treatment for multiple small actinic keratoses of her face from 1990 to 1992 with no side effects. In 1992, the diagnosis of FSD was made after orthopaedic manipulation on the lumbar rachis; the patient felt a very strong pain in this region and a sensation of 'electric shock' spread all over her lower limbs and feet. Since then, any trauma in any region of her body induced a strong pain in her lumbar region and dystonic movements of her toes. Moreover, the patient continuously has a burning sensation in her legs and feet so that she no longer wears stockings even in winter. A therapy with lorazepam and triazolam was of only little benefit to her neurological symptoms. In 1995 cryotherapy for actinic keratoses was again performed on the face, and after a few hours pain appeared in her lumbar region and dystonic movements developed in her toes. Lorazepam induced little effect. Cryotherapy was repeated in 1996, but it caused such strong pain in the face and in her lumbar region as well as movements of the toes in spite of lorazepam that it was discontinued. Treatment with either topical 5-fluorouracil or retinoic acid was considered but was then ruled out because the strong irritation induced by these drugs was thought to be able to precipitate the causalgia. Therefore, topical retinaldehyde (RAL) 0.05% was chosen as a medical therapy of the actinic keratoses. The cream was applied once a day and was well tolerated; 3 years after the beginning of treatment, the patient is still applying the cream without trouble and her keratoses are well controlled.

Causalgia and dystonia are usually triggered by peripheral injuries but may occur spontaneously in some cases. The injury is often trivial and does not cause overt peripheral nerve lesions. In a series of 18 patients [3] the mean age of presentation was 28.5 years and women were more affected. None had a family history of dystonia. The mechanism of dystonia following peripheral trauma is unknown but may relate to reorganization of central synaptic connections, possibly in the spinal cord [4].

RAL, a natural metabolite of vitamin A, is the immediate precursor of retinoic acid isomers, the retinoid nuclear receptor ligands. 0.05% topical RAL is well tolerated by the human skin; it improves chronic solar damage and is effective in treating actinic keratoses [5]. Recent studies indicate that its long-term use is safe [6]. The very low irritance profile of topical RAL allowed us to treat actinic keratosis in our patient affected by causalgia and dystonia which was triggered by minimal peripheral injuries. We believe that the knowledge of neurological diseases such as FSD is important for dermatologists owing to the number of cutaneous surgical procedures they perform.

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Partial Response of Severe Alopecia areata to Cyclosporine A

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Key Words
Alopecia areata • Cyclosporine A • Anagen hair

Alopecia areata (AA) is a chronic cutaneous disease in which an autoimmune origin has been demonstrated. Peribulbar, inflammatory infiltrates are mainly composed by T4 lymphocytes, macrophages and Langerhans cells [1]. Autoantibodies directed to specific hair follicle antigens have also been demonstrated [2].

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Table 1. Patient data

Patient No.	Sex	Age years	Grade of affection	Duration of AA years	Type of hair response, months			Hair regrowth		Associations and adverse reactions
					vellus	intermediate	terminal	percent	time months	
1	M	35	AAT	2	1	2	3	70	8	asthenia
2	F	18	AAU	12	2	–	–	0	8	
3	M	18	AAU	7	1	2	3	70	4	
4	F	35	AAU	23	2	–	–	0	4	atopy
5	F	34	PAA (80%)	24	1	3	4	90	12	gingival hyperplasia and residual diastema
6	M	51	AAU	22	–	–	–	0	4	
7	M	18	PAA (50%)	1	–	–	–	0	4	
8	F	33	AAU	4	3	5	8	95	10	total loss 2 months after the treatment had been stopped
9	F	24	AAU	6	2	–	–	0	4	
10	F	18	AAT	3	2	4	6	80	8	atopy
11	M	22	AAU	8	1	3	4	75	11	
12	F	39	PAA (70%)	8	2	–	–	0	6	
13	M	31	PAA (60%)	4	2	–	–	0	4	
14	M	24	PAA (50%)	16	2	4	6	75	7	
15	F	33	AAU	8	–	–	–	0	1	severe hypertension

M = Male; F = female; AAT = AA totalis; AAU = AA universalis; PAA = patchy AA.

In some patients AA can be very extensive: patchy AA affecting more than 50% of the scalp, AA totalis and AA universalis. In these cases most patients do not respond to standard treatment and suffer from severe social disabilities and psychiatric disturbances. Oral steroids and topical sensitizers are the main therapeutic options in these patients but sometimes fail to achieve any response.

Cyclosporine A (CsA) is a specific inhibitor of T4 lymphocyte activation and therefore may be useful in treating patients with AA [3]. This drug has been reported to not only clear immune cells from the hair follicles but also to alter the balance of regulatory lymphocytes. On the other hand, the well-known hypertrichotic side effect of CsA has been suggested to be due to prolongation of the anagen phase of the hair cycle [4]. CsA has been reported to restore hair growth in the DEBR rat model for AA [5], and some trials recommend its use in combination with oral steroids [6, 7]. On the other hand, AA has been described in renal or liver transplant recipients on high doses of CsA [8–10], and CsA failed to restore hair growth after 3 months in a case of severe AA [11]. Large studies on severe AA treated with CsA alone are lacking.

In the present study, we treated 15 cases of severe AA with CsA (table 1): 8 patients with AA universalis, 2 patients with AA totalis and 5 patients with patchy AA involving more than 50% of the scalp. There were 7 males and 8 females between the ages of 18 and 51 years (mean 28.8 years). AA had started between 1 and 24 years prior to treatment (mean 9.8 years). None of the patients suffered from thyroid disease.

CsA was started at a dose of 5 mg/kg/day, and the dose was adjusted at every follow-up to achieve a therapeutic blood level between 100 and 350 ng/ml of CsA. The average dose was 150 mg twice a day for 6–12 months.

One patient (case No. 15) discontinued the treatment due to hypertension. In 12 of the other 14 patients, vellus hair appeared in 1–3 months. Seven of these patients (50% of the series) developed intermediate hair at 2–5 months of the treatment and terminal hair after 3–8 months. Two of them (cases 5 and 8) achieved a complete hair regrowth. Case No. 5 was a 34-year-old white woman, who still maintains her regrowth 4 years after finishing treatment with CsA. She developed gingival hyperplasia with residual diastema. Case 8 was a 33-year-old white female who lost her hair 2 months after treatment had been stopped. Five other patients obtained a cosmetically acceptable response with regrowth of 70% of the hair. The other 7 patients did not show any regrowth after 4 months of therapy. Except for cases 5 and 15, side effects were minimal (asthenia or hypertrichosis).

We could not find in our series any factor (sex, age, type of AA or disease duration) that could be correlated with responsiveness to CsA. A good response to this treatment was seen as early as 1–4 months, so CsA was discontinued if there was no response after 4 months. In any case, treatment with CsA for more than 6 months is not recommended. Since the natural evolution of severe cases of AA (AA totalis, AA universalis and patchy AA affecting more than 50% of the scalp) is chronic and usually does not regress spontaneously, as was observed in our series (mean duration of the disease before treatment 9.8 years), we believe that a partial regrowth in 50% of the cases is significant. CsA can be an alternative treatment for cases of severe AA not responding to other therapies. Further studies with larger numbers of patients comparing CsA with placebo need to be done in order to clarify the role of this drug in the management of severe AA.

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Subcorneal Pustular Dermatosis (Sneddon-Wilkinson Disease) in a Patient with Multiple Sclerosis

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Key Words
Sneddon-Wilkinson disease • Subcorneal pustular dermatosis • Multiple sclerosis

Subcorneal pustular dermatosis (SPD) was first described in 1956 by Sneddon and Wilkinson [1]. It is a chronic benign relapsing vesiculopustular disorder which generally involves the trunk, characterized by subcorneal blisters filled with polymorphonuclear leukocytes. IgA monoclonal gammopathy [2] and rheumatoid arthritis [3] are diseases significantly associated with SPD. To our knowledge this is the first report on SPD occurring in a patient with multiple sclerosis (MS).

A 26-year-old woman had a 9-year history of MS. The clinical course followed the relapsing/remitting pattern. Due to the short duration between her first two flares, oral therapy with azathioprine was initiated. Under this regimen clinical symptoms improved and remained stable.

At presentation in 1996, the patient had had a 1-year history of a pustular rash starting at the abdomen. In addition, she reported on intermittent slightly pruritic episodes. Administration of topical antiseptics and glucocorticoids did not result in the clearance of lesions.

Physical examination displayed flaccid pustules mostly on erythematous bases, located mainly in the groin, on the lower abdomen, chest and lower extremities (fig. 1). Erosions with scaly margins followed rupture of pustules. When lesions cleared, a brown, slight hyperpigmentation remained. Microbiological cultures were sterile.

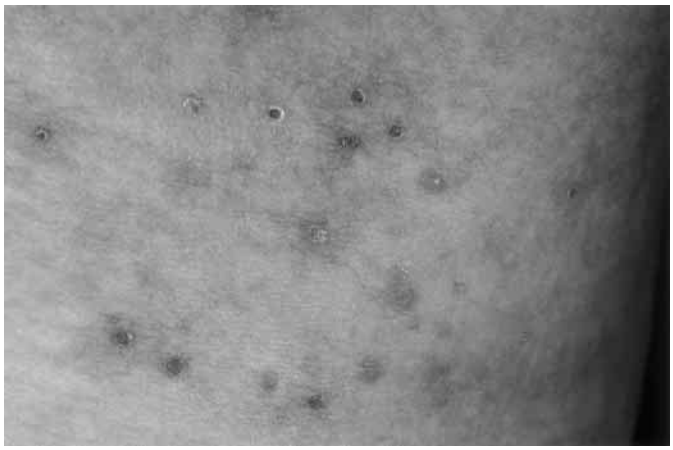

Fig. 1. Flaccid pustules on erythematous bases in the groin region.

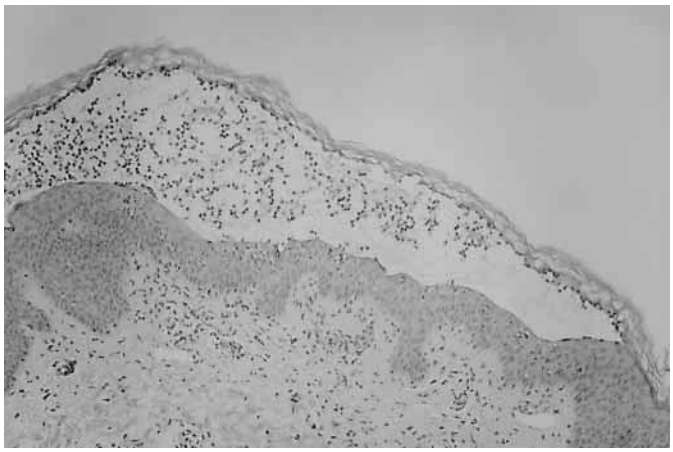

Fig. 2. Subcorneal blister filled with neutrophilic polymorphonuclear leukocytes. Hematoxylin-eosin stain. Original magnification ×30.

Histopathological examination showed a subcorneal blister filled with polymorphonuclear leukocytes (fig. 2). A perivascular infiltrate of neutrophils was noted. Direct and indirect immunofluorescence studies were negative.

Differential white cell count showed 80.5% neutrophils and 14.1% lymphocytes with a total white cell count of 9.0×10^9/l. The erythrocyte sedimentation rate was 28 mm. Biochemical analyses were unremarkable. Screening for rheumatoid factor and antinuclear antibody was negative. Immunoelectrophoresis and immunofixation were not performed.

The patient was treated with dapsone (50 mg/day). The skin lesions cleared within 4 weeks and only slight hyperpigmentation persisted. When dapsone was discontinued, she developed again typical lesions of SPD after a period of 6 weeks. Under dapsone, the patient obtained complete relief.

This case report shows the outcome of two distinct diseases, whether coincidental or based on a common pathogenetic background is unclear. SPD associated with MS has not been reported yet. Some reasons suggest that the association may not be coincidental.

SPD is repeatedly reported in proven or putative autoimmune diseases like lupus erythematosus [4], rheumatoid arthritis [3], hyperthyroidism [5] or Crohn's disease [6], while MS is seen in rheumatoid arthritis, myasthenia gravis and rarely bullous diseases [7, 8]. Furthermore, MS itself fulfills, at least partially, the criteria of an autoimmune disease.

The mean onset of SPD and MS differs. In SPD it is the fifth decade, whereas the first manifestations of MS often occur in the third decade [9].

Despite some associations between SPD and other diseases, the pathogenesis of SPD is still unclear. It was suggested that the hyperactivation of neutrophils in the skin is at least partly due to excessive production of TNF-α [10]. Occasional reports of IgA dysregulation in SPD may point to a disturbance in chemotaxis of leukocytes because of IgA's functional role as a chemoattractant agent [11]. Nevertheless, beside these aspects, the pathogenesis of SPD remains unclear.

In MS, autoimmune activated T cells specific for myelin components or other locally expressed autoantigens play a key role [12]. After local stimulation they produce a wide range of cytokines and inflammatory mediators inducing and recruiting additional inflammatory cells. Production of ANAs in up to 30% of all cases reflects systemic immune abnormalities, which may account for a possible pathogenetic link to SPD [13].

Dedication

This case report is dedicated to Prof. H.-J. Vogt, Department of Dermatology and Allergy Biederstein, Technical University of Munich.

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Alkaptonuria

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Key Words
Alkaptonuria • Phenylalanine • Tyrosine • Ochronosis • Homogentisic acid

Sir Archibald Garrod [1] was one of the pioneers in the study of alkaptonuria, an extremely rare autosomal recessive deficiency of homogentisic acid oxidase (HGAO), an enzyme normally produced by liver and kidneys that plays a key role in the degradation pathway of phenylalanine and tyrosine. A deficiency of HGAO induces homogentisic aciduria, ochronosis and arthritis [2, 3]. Homogentisic acid (HGA), an intermediate metabolite of this process, accumulates in collagenous tissue because it is not converted to maleylacetoacetic acid. The consequence of HGA accumulation is the blue-black pigmentation of connective tissue called ochronosis. Ochronosis is not limited to alkaptonuria and can be caused by several exogenous substances such as hydroquinone, phenol, resorcinol, antimalarials, tetracyclines, phenothiazine, amiodarone, heavy metals and chemotherapeutic agents [4, 5]. The genetic mutation responsible for HGAO deficiency has recently been located on chromosome 3q [6].

A 72-year-old woman was seen in our Institute for a 30-year history of progressive blue-black pigmentation of her sclerae, helix and antihelix. The patient denied the use of antimalarials or phenolic intermediates. She reported that, for as long as she could remember, her urine had turned dark after exposure to air. The family history was not contributory. Physical examination at that time revealed blue-black pigmentation on the sclerae (Osler's sign; fig. 1) [7], as well as on the helix and antihelix (fig. 2). In addition to external pigmentation of the ears, the otorhinolaryngological examination revealed that the tympanic membranes and even the cerumen were bluish black.

Radiological examination showed diffuse osteopenia, narrowing and calcification of dorsal and lumbar disk spaces, arthropathic phenomena involving the sacroiliac joint and the pubic symphysis and narrowing of the tibiofemoral articular space. A diffuse presence of marginal osteophytes, a subluxation of some metatarsophalangeal joints and luxation of the second right metatarsophalangeal joint were also revealed. The rest of the physical examination, including cardiac consultation, was unremarkable. A complete blood cell count and serum chemistry profile were normal.

A skin punch biopsy specimen was obtained from the ear helix. Histology revealed an ochraceous pigmentation of elastic fibers typical of ochronosis and degeneration of collagenous fibers (hematoxylin-eosin stain). No other cutaneous findings were noted. The qualitative presence of homogentisic acid in the urine was determined by gas

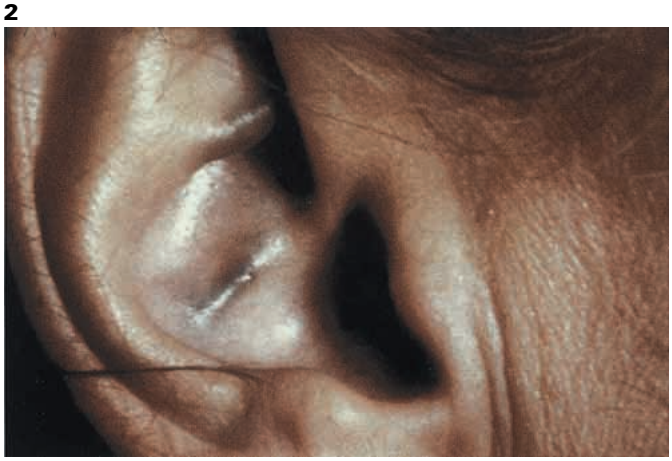

Fig. 1. Blue-black pigmentation on the sclerae (Osler's sign).
Fig. 2. Blue-black pigmentation on the helix and antihelix.

chromatography-mass sspectrometry and high-performance liquid chromatography. On the basis of clinical and laboratory findings the diagnosis of alkaptonuria was made.

The patient has been followed in our clinic for almost 4 years. She has recently undergone a total left hip replacement, which resulted in a satisfactory outcome, but is otherwise in good health.

Alkaptonuria is a raare (1:1,000,000) autosomal recessive disease affecting the metabolic pathway of tyrosine and phenylalanine. This metabolic defect, essentially consisting of an impaired production of HGAO in the liver and kidneys, leads to accumulation of HGA, which is partially excreted in urine and accumulated in collagenous tissues. Alkaptonuria is generally asymptomatic in childhood, the only sign being the darkening of urine after air exposure. With age, the blue-black cutaneous discoloration appears, especially involving external ears, sclerae and air-exposed cutaneous sites. HGA accumulates in connective tissues where it is oxidized to benzoquinone acetic acid which destabilizes collagen fibers producing their degeneration for loss of periodicity and in the end their total replacement. This is probably carried out through an inhibition of lysine hydroxylase, whose role it is to provide critical sites for cross-linkage between collagen fibers. This product of HGA oxidation is thus the real cause of collagen fiber degeneration [8, 9].

Although the real mechanism of the onset of arthritis is not well understood, oxidation products and chronic microtrauma certainly play a key role in the development of ochronotic arthritis which mainly affects the large weight-bearing joints, which are more subject to trauma [10–12].

Because of its proven antioxidant acitivity, ascorbic acid was employed at high doses in patients affected by alkaptonuria. Although this therapy proved ineffective in patients with a long-standing arthritis, the reduction of the urinary excretion of benzoquinone acetic acid leads us to hypothesize that early vitamin C administration could reduce or even prevent the onset of arthropathy [13].

We report this case because alkaptonuria is very rare and many affected patients are treated by physicians who may not realize the causal relationship between this metabolic disorder and the patient's arthritis. If this happens, as it did in our case, patients spend their life trying therapies which not only prove ineffective in most cases but are sometimes even harmful. Today computerized gas chromatography-mass spectrometry and high-performance liquid chromatography offer new low-cost and noninvasive diagnostic tools which can guarantee the patient an early and certain diagnosis [14, 15].

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Progressive Cribriform and Zosteriform Hyperpigmentation: The Late-Onset Feature of Linear and Whorled Nevoid Hypermelanosis Associated with Congenital Neurological, Skeletal and Cutaneous Anomalies

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Key Words
Blaschko's lines • Mental retardation • Nevus spilus • Polythelia

The term 'linear and whorled nevoid hypermelanosis' (LWNH) was first introduced in the literature by Kalter et al. [1] in 1988. It defines a congenital or perinatal condition characterized by macules arranged in a linear and whorled pattern along Blaschko's lines, not preceded by inflammatory events or palpable lesions, and without histological presence of incontinentia pigmenti or melanophagia [1].

The same clinical entity has been described with other names still in use: zebra-like hyperpigmentation or reticulate hyperpigmentation [2, 3].

In 1978, Rower et al. [4] first described segmentary forms with onset during adolescence, which they called progressive cribriform and zosteriform hyperpigmentation (PCZH).

Recently, the term LWNH has been used to encompass a wide spectrum of clinical entities, ranging from the one described by Kalter et al. to the segmentary and delayed form of Rower et al., for which there is a tendency to use the term PCZH [5].

We present a 15-year-old male born at full term from nonconsanguineous parents, following a normal pregnancy. His birth weight was 3,600 g.

The patient showed a good general condition, generalized muscle hypotrophy, kyphoscoliosis, bilateral pes varus and normocephaly. The psychological assessment disclosed moderate mental retardation as well as affective and relational behavioral impairment. The dermatological examination revealed 4 supernumerary nipples (2 on each side of the thorax) and asymmetric reticulate punctiform hyperpigmentation in the thoraco abdominal region (fig. 1), the hips and the trunk, especially on the left side. The lateral region of the ankles and the internal surface of the right thigh were also involved. The macules, which had developed approximately 3 years prior to our examination, were distributed along Blaschko's lines. A congenital nevus spilus with a diameter of approximately 4 cm is also present on the anterior surface of the left thigh (fig. 1). A biopsy, obtained from reticulate hyperpigmented skin, showed moderate melanic pigmentation of the basal layer, without pigmentary incontinence. A blood workup, kidney and urinary tract ultrasound, cerebral CT scan, karyotype and fragile-X (FMR1) gene study were normal.

The clinical, histopathological and cytogenetic aspects of our patient allowed us to exclude the macular conditions which can be mostly confused with LWNH: incontinentia pigmenti, hypomelanosis of Ito and cutaneous mosaicism [6].

We think that our patient, affected by PCZH or reticulate hyperpigmentation, should be classified more appropriately in the late-onset group, although the lesions are not 'zosteriform'. In agreement with Quecedo et al. [5], we believe that a wide spectrum of the disease exists between the diffuse congenital or perinatal forms of Kalter et al. [1] and the acquired and segmental forms of Rower et al. [4]. Our patient presents clear analogies with the one described by Bjorngren and Holst in 1990 [7]. In both cases, the dermatosis became evident during adolescence, and the nevus spilus was present at birth. The presence of nevus spilus is reported by Iijima et al. [3] in a brother and in the mother of their first patient. Bjorngren and Holst go as far as interpreting this presence as part of a syndromic picture [7].

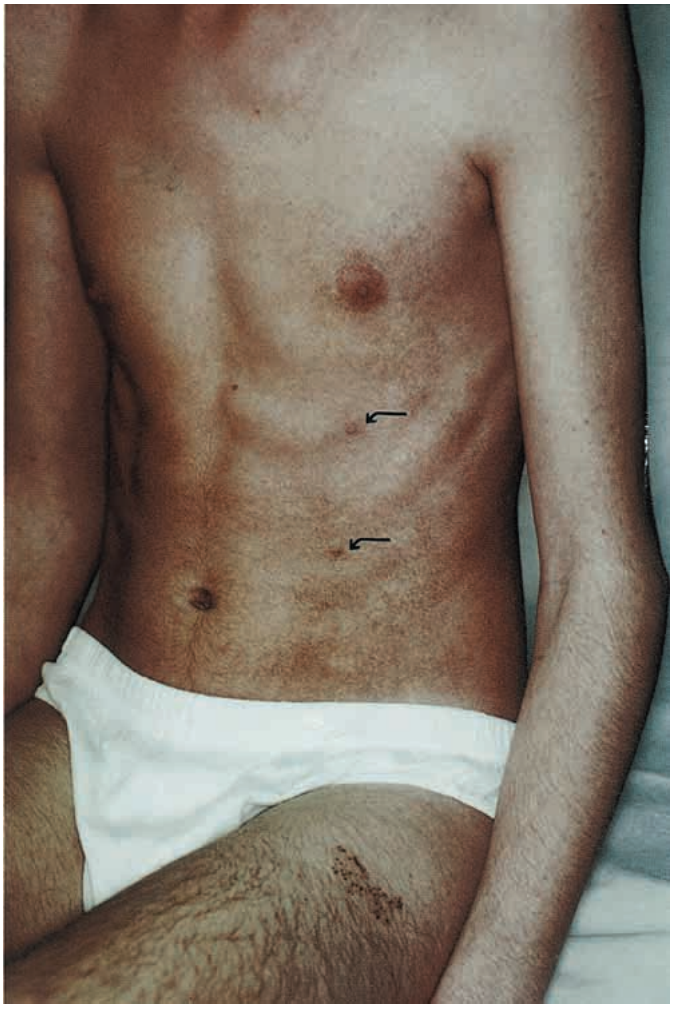

Fig. 1. Progressive cribriform and zosteriform hyperpigmentation on the trunk. Nevus spilus and 2 of the 4 accessory nipples are detectable (arrows).

In 1976, Griffiths [8], while describing 7 cases of Kitamura's reticulate acropigmentation, a condition similar to LWNH and PCZH, reported in patient No. 7 the concomitance of nevus spilus. We may therefore consider as association the presence of nevus spilus and reticulate hyperpigmentation.

Furthermore our patient presents with polythelia, and its significance remains to be interpreted when associated with kidney and urinary tract malformations, and neoplasia [9–11]. The incidence of such an association has variably been considered by many authors. In their

recent paper on accessory mammary tissues, Urbani and Betti [12] report a value of 7.53% in association with kidney and urinary tract malformation, and they report also on what is known regarding the association between accessory mammary tissue and other organ anomalies [13].

Our patient could be the first case of PCZH associated with polythelia; however, this is probably occasional. More important is the fact that although the association of PCZH with mental retardation has already been reported in the past, it occurred only in congenital cases of LWNH [2, 14–17].

We think that it will be worthwhile to investigate in the future the significance of these associations.

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Nevoid Hyperkeratosis of the Areola in Men: Response to Cryotherapy

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Key Words
Nevoid hyperkeratosis · Areola · Men

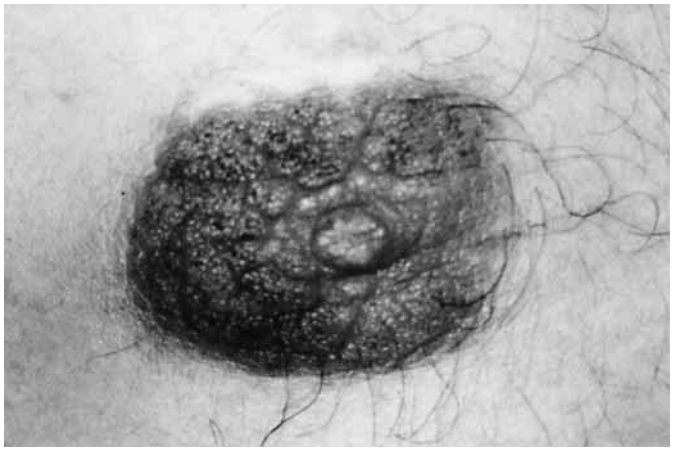
Hyperkeratosis of the nipple and areola is a rare dermatologic disorder characterized by asymptomatic, hyperpigmented and verrucous hyperkeratosis. Histologic changes resemble either a papillomatous epidermal nevus or acanthosis nigricans. It has been separated into three types: hyperkeratosis due to the extension of an epidermal nevus to the nipple and areola, hyperkeratosis associated with other underlying dermatoses and the nevoid form, in which the verrucous changes are confined to the areola. This last form is usually bilateral and occurs more often in young women and in men under estrogen treatment, suggesting a hormonal influence. The condition is usually refractory to topical steroids, keratolytics and retinoids. Six cases of nevoid hyperkeratosis of the areola have been reported in men. We report 3 additional cases with no underlying endocrinopathy or estrogen treatment. The lesions were unilateral in 2 of them. Interestingly, cryotherapy produced good cosmetic results in 2 of the patients.

Report of Cases

Case 1. A 41-year-old man presented with a 1-year history of progressive thickening and hyperpigmentation of both areolae (fig. 1). He was otherwise in good health. He gave no personal or family history of ichthyosis, epidermal nevi or acanthosis nigaricans. There was no history of hormonal therapy. Histologic examination of the lesion showed hyperkeratosis, acanthosis and papillomatosis. Therapy with 40% urea was started in his left areola and cryotherapy in his right areola. The right areola had a better response, so 3 cryotherapy treatments (of 20 s each) were given in both areolae. A satisfactory cosmetic result was obtained.

Case 2. A 24-year-old man presented with a painless change of color and texture of his left areola. The lesions had started 2 years previously. He gave no personal or family history of epidermal nevi, ichthyosis or acanthosis nigricans. Physical examination revealed a hyperpigmented, verrucous left areola. His right areola showed no alterations. Histopathologic examination showed hyperkeratosis, papillomatosis, acanthosis, and lymphocytic infiltration in the papillary dermis (fig. 2), consistent with a diagnosis of nevoid hyperkeratosis. The lesions did not respond to 6 months of daily application of 40% urea; however, cryotherapy produced a satisfactory result, so 5 further cryotherapy treatments (of 20 s each) were given.

Case 3. A 71-year-old man presented with a seborrheic keratosis on his trunk. The patient had a medical history of benign prostatic hypertrophy. Physical examination revealed, besides the seborrheic keratosis, that his left areola showed a thickened and pigmented verrucous appearance that was unremarkable for the patient. He had no evidence of ichthyosis, acanthosis nigricans or Darier's disese. Differential diagnosis at the time of presentation was seborrheic keratosis versus nevoid hyperkeratosis. Biopsy of the left areola revealed hyperkeratosis, acanthosis and papillomatosis. The changes were consistent with nevoid hyperkeratosis. The lesions were asymptomatic. The patient refused any treatment.



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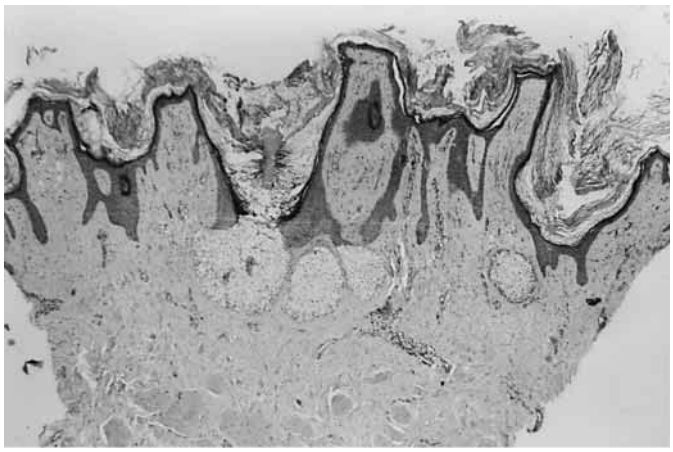

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Fig. 1. Verrucous thickening and hyperpigmentation of the right areola in patient 1.
Fig. 2. Hyperkeratosis, papillomatosis and lymphocytic infiltration in the papillary dermis of the left areola in patient 2.

Discussion

Nevoid hyperkeratosis of the nipple and areola is a rare benign condition. Levy-Franchel [1] classified this condition into three categories. The first type is hyperkeratosis of the nipple and areola as an extension of an epidermal nevus; this type is usually unilateral and occurs in both sexes. The second type is hyperkeratosis of the nipple and areola associated with ichthyosis, acanthosis nigricans, Darier's disese or lymphoma. It is usually bilateral and appears in both sexes. The third type is the nevoid form; this type is usually bilateral, symmetric and occurs mainly in woman in the second or third decade of life. This form is rare in men, with only 6 cases reported to date. In 1978 Schwartz [2] and in 1980 Mold and Jegasothy [3] reported each the case of a man with prostatic adenocarcinoma treated with diethylstilbestrol who developed bilateral hyperkeratosis of their nipples and areolae. A possible endocrinopathy or a history of estrogen therapy was postulated as the cause of their hyperkeratosis. However, Dupré et al. [4], Kuhlman et al. [5] and English and Coots [6] reported the cases of some men with nevoid hyperkeratosis that were not associated with hormonal therapies or other underlying abnormalities. Therefore, nevoid hyperkeratosis of the nipple and areola in men could be classified into two subtypes, the first affecting men receiving estrogen therapy and the second occurring in men with no underlying endocrinopathy or synthetic estrogenic drug treatment.

Histologic changes of the nevoid hyperkeratosis of the areola may resemble either a papillomatous epidermal nevus or acanthosis nigricans showing hyperkeratosis, acanthosis and papillomatosis [7, 8].

Response to topical steroids [9], keratolytics [5, 9] and retinoids [10, 11] has been reported as variable. Vestey and Bunney [12] reported cosmetically satisfactory results with cryotherapy applied in five sessions. Surgical excision [4, 7] of the areolae may be performed if the patient is greatly disturbed by the cosmetic appearance.

We report 3 cases of nevoid hyperkeratosis of the areola in men with no evidence of hormonal therapies or other underlying abnormalities. Our cases are different from those reported previously in two aspects: the first is that the lesions were unilateral in 2 patients; the second is that our patients who were treated had a better response to cryotherapy than to keratolytics.

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Acyclovir Can Abort Rejection of Punch Grafts in Herpes-simplex-Induced Lip Leucoderma

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Key Words
Acyclovir • Herpes simplex • Leucoderma

Lip leucoderma due to recurrent herpes labialis is not uncommon. Medical management hardly ever yields any satisfactory result [1]. Consequently, different surgical modalities [2] have been tried to correct these defects. Of these, punch grafting is a very commonly undertaken procedure. We have found that such grafts can be rejected. In 3 patients after punch grafting, erythema and small vesicles appeared in and around the grafted site followed by rejection [3].

Whether prophylactic acyclovir can help such cases or not was the aim of the present study. Ten women and 3 men were studied with different doses of acyclovir before transplantation (table 1).

Table 1. Different dose schedules of acyclovir before punch grafting

Group	Dose	Time before operation	Patients n	Result
1	200 mg × 5	6 months	5	no vesicles, 3 pigmented
2	800 mg × 2	10 days	5	no vesicles, 3 pigmented
3	200 mg × 5	6–9 days	3	vesicles + erythema; none pigmented

Group 1 and group 2 had a favourable outcome. In group 1, all the patients had a history of herpes labialis, recurring frequently compared to other groups. Hence patients in this group were treated with acyclovir during several months before grafting.

As shown in table 1, this study demonstrates that oral acyclovir for 10 days at a dose of 800 mg twice daily prior to punch grafting in herpes-simplex-induced lip leucoderma is an effective prophylaxis against the rejection of the grafts.

Two types of degeneration of the epidermis occur in herpes simplex infection, i.e. ballooning and reticular changes. Ballooning degeneration causes marked swelling of the epidermal cells and loss of intercellular bridges leading to acantholysis. Since it causes dissolution of the lower epidermis, it takes part in the rejection of the graft. Reticular degeneration represents a process in which the epidermal cells become greatly distended by intracellular oedema, as a result of which many of the cell walls burst. Reticular degeneration occurs mainly at the periphery of the viral vesicles which might be further adding to the process of rejection of the graft by formation of perigraft vesicles. These degenerative processes disturb the graft not only at the bed but also all around the graft by breaking its attachment to the surrounding tissues.

The observation of vesicle formation with rejection of punch grafts probably points towards a phenomenon of reactivation of herpes simplex infection incited by trauma of the grafting procedure. Oral acyclovir, when given in an adequate dose and period, was found to abort the process.

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