Cameo

Well-differentiated squamous cell carcinoma of the penis associated with HPV type 33

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A 70-year-old Caucasian widower, who was a heavy smoker and negligent in his personal care, but apparently in good general condition, come to our attention in November 1994. He referred to the onset, about 5 months previously, of a genital ulcer. On clinical examination, an irregular, oval-shaped (3 cm × 2 cm) ulcer was observed that extended from the glans to the coronal sulcus (Fig. 1). The fundus of the lesion was reddish, the margins were prominent, and indurated. A palpable lymph node of 1 cm in diameter was present in the left inguinal region, while the other superficial nodes were clinically normal. The medical history and laboratory examinations were otherwise unremarkable.

Pathologic examination showed a well-differentiated squamous cell carcinoma, partly "*in situ*" (Fig. 2A) and partly infiltrating the deeper structures (Fig. 2B) with a maximal thickness of 0.6 cm. No Bowenoid-type differentiation was seen.

The carcinoma specimen, analyzed by flow cytometry, revealed the presence of one cellular diploid population.

The patient was transferred to the Urologic Clinic of our hospital where he underwent partial penectomy and bilateral inguinal lymphadenectomy. The pathologic report of these lymph nodes was negative for metastatic lesions.

At 1 year follow-up, the patient was negative for local cancer relapse and inguinal metastatic lesions at clinical examination.

A polymerase chain reaction (PCR) analysis was performed on DNA from the tumor specimen, using specific primers complementary to DNA sequences highly conserved among human papillomavirus (HPV) types 16, 18, 31, 33 and 56. The specimen was found to be positive for HPV type 33 DNA (Fig. 3).

Discussion

Penile carcinoma is an uncommon affection; in the USA and Europe, it accounts for 0.5% of all human tumors. Generally, it develops in patients over 60 years of age, and is favored by poor genital hygiene and chronic irritation in the coronal sulcus. It has been associated with chronic inflammatory dermatosis, scars, cigarette smoking, UV radiation, and human papillomavirus (HPV) infection.

So far, more than 77 distinct HPV types and 30 putative novel genotypes have been characterized.[1] Some, such as HPV 6, 11, and 42, have usually been associated with benign genital lesions, e.g. warts and acuminate condylomas, while others, particularly HPV 16, 18, 31, and 33, have been associated, especially in women, with the development of cancer.[2]

Today, it is generally accepted that one-third to one-half of the cases of infiltrating carcinoma of the penis are associated with HPV.[3] HPV types 16 and 18 are the most frequently associated with penile carcinoma, while other types have occasionally been found.[4]

Only a few epidemiologic studies have been carried out on squamous cell carcinoma of the male genitalia, probably because of the fairly low prevalence of this disease. In 1994, Chan *et al.*[5] reported that the prevalence of HPV types 16 and 18 associated with penile squamous cell carcinoma ranged, in the literature, from 0% to 67%. The authors observed that the reports considered did not subclassify the tumors histologically. They applied this classification to their cases, and pointed out that the subgroup of well-differentiated squamous cell carcinoma was not associated with HPV types 16 or 18. This observation may suggest the role of different HPV types in the pathogenesis of well-differentiated tumors.

HPV 33 is regarded as an HPV of intermediate oncogenic risk. Cell lines transfected with HPV 33 became immortal-

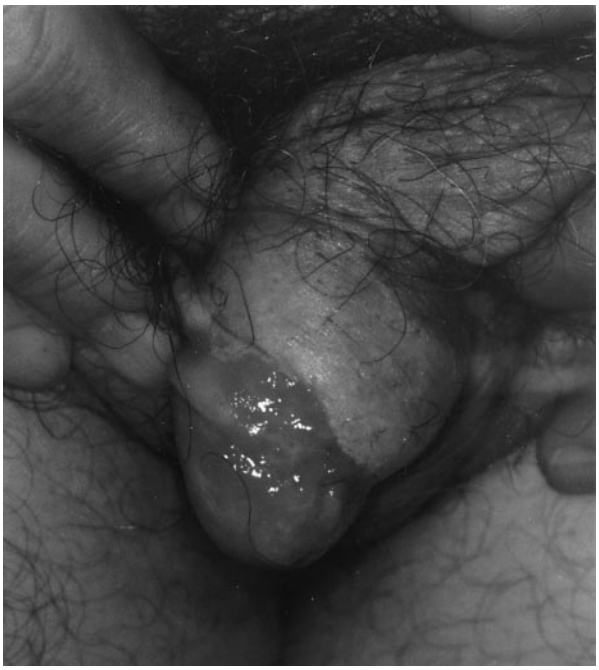

Figure 1 Wide painless ulceration on the glans extending to the coronal sulcus

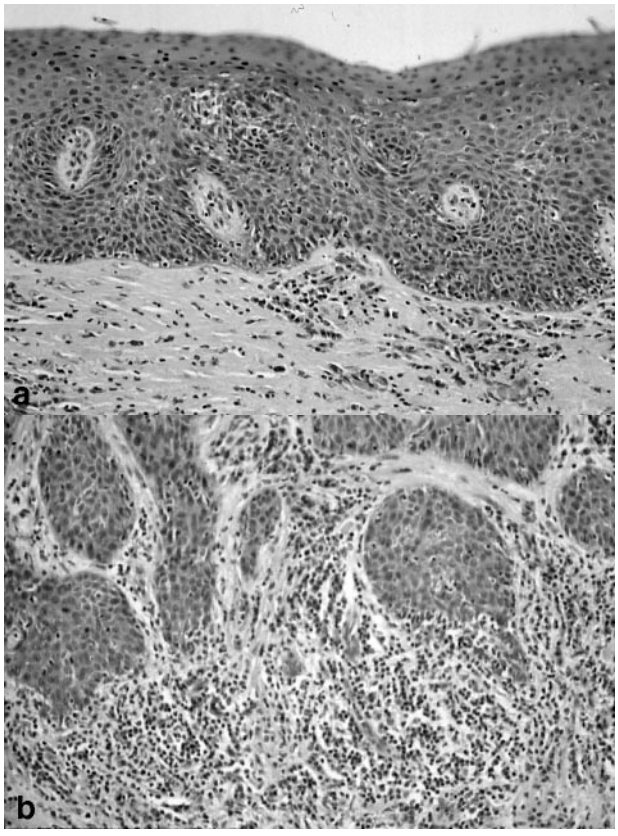

Figure 2 Well-differentiated squamocellular carcinoma: (a) partly "*in situ*"; (b) partly infiltrating the deeper structures

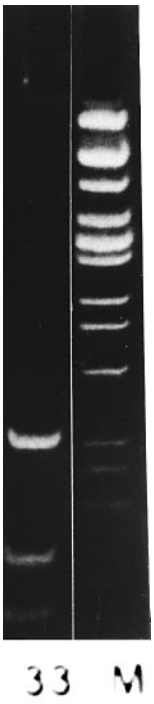

Figure 3 PCR results demonstrating the presence of HPV type 33 DNA in the tissue specimen

ized, and *in vitro* reconstituted epithelia with these cell lines acquired the characteristics of cervical intraepithelial neoplasia grade III lesions.[6] These phenomena cannot be strictly related to HPV 33 infection alone; more probably, a second event is necessary for the transformation into carcinomas.[1]

We believe that, in our case of well-differentiated squamous cell carcinoma, other cofactors, such as cigarette smoking and poor hygiene, could have contributed, together with HPV 33 infection, to the development of the tumor. Moreover, the follow-up after conservative surgery showed a benign course with no relapse; this observation was consistent with the positive prognostic factors for survival in our patient.[7] We wish to stress the importance of HPV subtype characterization and the early diagnosis and prognostic evaluation of pre-cancerous and cancerous lesions of the male genitalia.

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Cameo

Flexural purpura and Epstein–Barr virus infection

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A 38-year-old woman presented with flexural lesions of 4 days duration, accompanied by pruritus in her hands, arthralgia, sore throat, and a 38 °C fever. Examination revealed macular purpuric lesions with a tendency to be grouped into plaques that affected, in a selective way, the axillary folds (Fig. 1), the elbow flexures, and the inguinal (Fig. 2) and perianal areas. Inflammatory laterocervical and submandibular lymphadenopathy was noted.

Histopathologic examination showed a normal epidermis and a perivascular lymphocytic infiltrate in the papillar dermis, consisting of eosinophils and extravasated red cells. Vasculitis and other signs of vascular damage were not observed. A Congo red stain was negative.

Laboratory tests showed moderate lymphocytosis with 2% atypical lymphocytes and mild elevation of serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT). Coagulation studies, urinalysis, immunoglobulins, and serum electrophoresis were normal. Cryoglobulins were negative. Serology for cytomegalovirus (CMV), toxoplasma, rubella, and human parvovirus B19 showed findings of past infection. Serology for A, B and C hepatitis virus was negative. Mono-spot test was negative and the Epstein–Barr virus (EBV specific antibody response is shown in Table 1. The standard True-test was negative.

The clinical manifestation cleared spontaneously within 15 days.

Discussion

The Epstein–Barr virus (EBV) is a lymphotrophic human herpes virus with a biology similar to its homologs in the herpes family, because it infects humans through a primary infection and further reactivation.[1] Primary infection by EBV usually occurs during early childhood and is asymptomatic. In developed countries, its delay is frequently to later childhood, adolescence, or young adults, showing a more severe clinical presentation.[2] EBV reactivations have been associated with several diseases, such as hematologic neoplasia, nasopharyngeal carcinoma, and oral hairy leukoplakia.[3]

From the first clinical description of infectious mononucleosis in 1920, and its etiologic association with EBV in 1968, the recognized cutaneous manifestations of infection with this type of human herpes virus have increased.[4] Currently, we can classify them into three groups (Table 2): (1) dermatologic manifestations associated with primary infection, which may be expressed as infectious mononucleosis (IM) or Gianotti–Crosti syndrome; (2)

Table 1 Serologic evolution of EBV infection in our patient

		Sept 1995	Nov 1995	Mar 1996
Anti-VCA	IgG	+	+	+
	IgM	+	–	–
Anti-EBNA	IgG	–	+	+

VCA, viral capsid antigen; EBNA, EBV-determined nuclear antigen; IgG, immunoglobulin G; IgM, immunoglobulin M.

Table 2 Cutaneous manifestations of Epstein–Barr virus infection (modified from Baldari *et al.*[4])

(1) During the course of infectious mononucleosis (primary infection)
- Exanthem
- Exanthem induced by antibiotics
- Acute urticaria and cold urticaria
- Acrocyanosis
- Palmar dermatitis
- Erythema multiforme
- Erythema nodosum
- Erythema annulare centrifugum
- Pityriasis lichenoides
- Granuloma annulare-like eruption
- Lipschütz's ulcer
- Flexural purpura

Or Gianotti–Crosti syndrome (primary infection)

(2) Mucous manifestations
- Petechiae on the palate (primary infection or reactivation)
- Oral hairy leukoplakia (reactivation)

(3) Other associations with cutaneous involvement (reactivations)
- Hemophagocytic syndrome in childhood
- Bullous pemphigoid
- Cutaneous vasculitis
- Kawasaki-like disease
- Secondary Sjogren syndrome
- Pseudolymphoma, lymphoma, leukemia, and myelodysplastic syndrome with cutaneous involvement
- Histiocytic cytophagic panniculitis

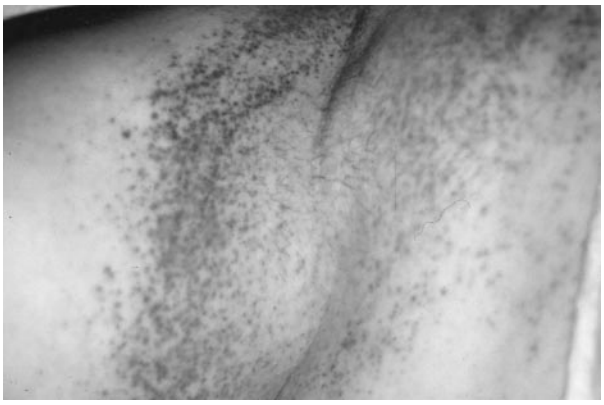

Figure 1 Purpuric papules on the axillary folds

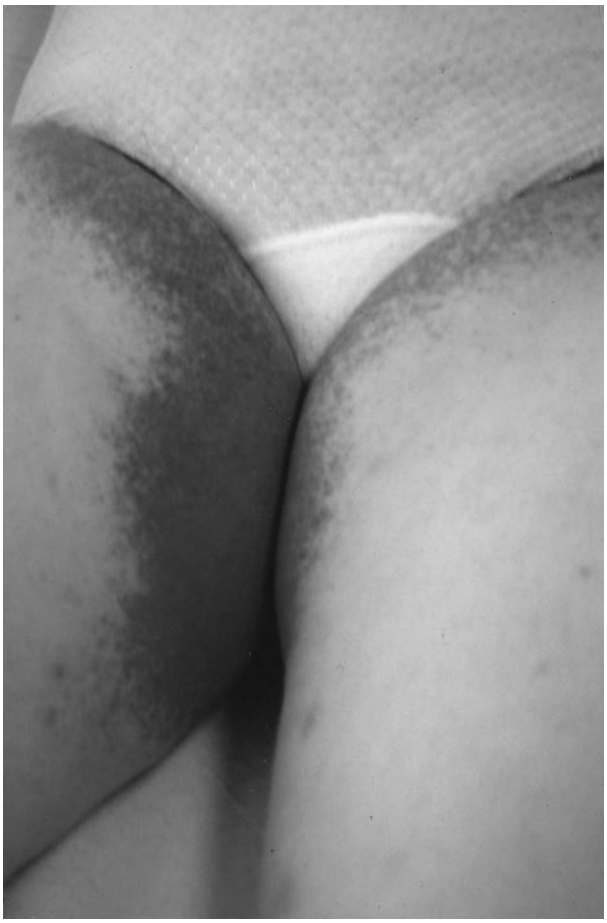

Figure 2 Lesions grouped into purpuric plaques on the inguinal folds

mucous manifestations; (3) features that usually appear during the course of hematologic neoplasia or in immunosuppressed patients.

The exanthems that appear during the primary infection are usually directly related to EBV, although some antibiotics may play an inductor role in their pathogenesis. A wide clinical morphology for these exanthems has been described, including morbilliform, roseolliform, rubelliform, urticarial, and rarely generalized purpuric eruptions.[5]

Several viral diseases, such as enteroviral infection, B- and C-type hepatitis, rubella, measles, human parvovirus B19, and EBV infection, may produce purpuric lesions,[6] but in no case with a distribution exclusively located on the folds.

Purpuric features associated with EBV infection, previously described, include morbilliform purpuric exanthem as IM manifestation,[7] cutaneous vasculitis as initial feature of myeloproliferative syndrome,[8] palatal petechiae in both primary infection and reactivation phases,[1] and disseminated small purpuric lesions in immunosuppressed patients.[9]

Our patient had a self-limiting process, characterized by a sore throat, fever, arthralgia, lymphadenopathy, and exanthem, which was clinically compatible with a virosis. We have discarded the main viral diseases that cause purpuric exanthem and other causes of purpura. The serologic findings clearly demonstrated a primary infection by EBV. Therefore, we believe that, in our case, the flexural purpura was an unusual manifestation of primary EBV infection.

To our knowledge, flexural purpura has not previously been reported in relation to EBV infection. Because EBV is so ubiquitous, the observation of a new manifestation of EBV infection might seem unusual. Nevertheless, because primary EBV infection is a self-limiting process, an adequate study is not made in most cases, and uncommon features may be overlooked.

Although more reports will be necessary to verify this atypical presentation, we believe that a primary EBV infection should be investigated in patients with flexural purpura.

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Cameo

Anhidrotic ectodermal dysplasia (Christ–Siemens–Touraine syndrome) presenting as a fever of unknown origin in an infant

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A 16-month-old boy (Fig. 1) was referred to the Department of Pediatrics, University Hospital of Hacettepe, in February 1997, suffering from recurrent fever and inability to sweat. His history revealed repeated otitis media and rhinitis, together with dry skin and heat intolerance. Lacrimation was also lacking. His parents were not relatives and both of them were healthy.

On physical examination, his weight was below the third percentile for length; the patient was irritable, but normal in view of mental development. His skin (Fig. 2) was smooth, dry, and pale. Subcutaneous fat was scanty and vessels were easily visualized. His nails, palms, and soles were normal, his scalp hair was sparse, fragile, and extremely blonde, and his eyebrows and eyelashes were lacking. His nose was saddled. Anodontia was present, and ortopantography revealed that only one canine at each side of the mandible and two canines at the upper jaw were present, and were conical in shape (Fig. 3). The ears were pointed and low set.

Discussion

Thurnam in 1848 described a most frequent, well-recognized form of anhidrotic ectodermal dysplasia (Table 1) known as the Christ–Siemens–Touraine syndrome.[1] It is characterized by hypotrichosis, hypodontia, and absence of eccrine sweating.[2] Pathogenetically, ectodermal dysplasia is hypothesized to be a developmental delay defect which prenatally affects the ectoderm and is inherited as an X-linked recessive trait.[3] A clinically identical autosomal recessive form has also been described.[4] Recurrent fevers, at times quite high, can be the presenting symptom, leading to unnecessary diagnostic tests. This diagnosis may go unrecognized in a patient presenting with a fever of no apparent origin if anhidrotic ectodermal dysplasia is not considered in differential diagnosis. The incidence of ectodermal dysplasia is unknown. The men : women ratio is 5 : 1.[5,6] Affected men demonstrate the characteristic signs of anhidrosis, resulting from the complete absence of eccrine sweat glands, as well as a partial deficiency of apocrine glands. Affected women are carriers without clinical abnormalities.[7] Diagnosis is confirmed by skin biopsy which, as in our case, reveals the absence of dermal appendages. Eyebrows are scanty or totally absent.

Table 1 Key features of anhidrotic ectodermal dysplasia

Soft, thin skin
Hypotrichosis
Hyperthermia from inadequate sweating
Dentition abnormalities: anodentia/hypodontia, small, conical or missing teeth
Small, saddle-shaped nose
Fine, dry, sparse hair, eyebrows
Small, pointed, low set ears
Dystrophic nails
Chronic rhinorrhea
Increased periorbital pigmentation

Figure 1 Photograph of case at 16 months

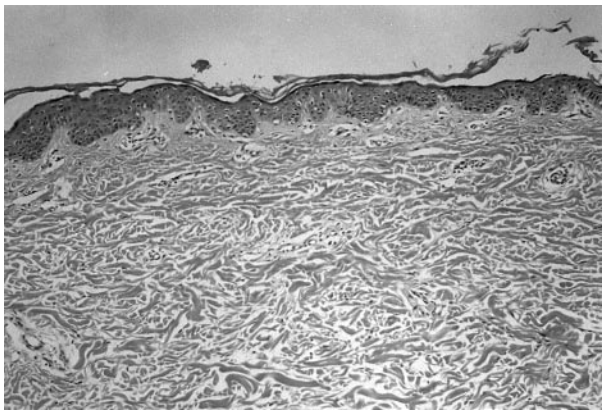

Figure 2 Absence of dermal appendages is confirmatory (hematoxylin and eosin; original magnification, × 100)

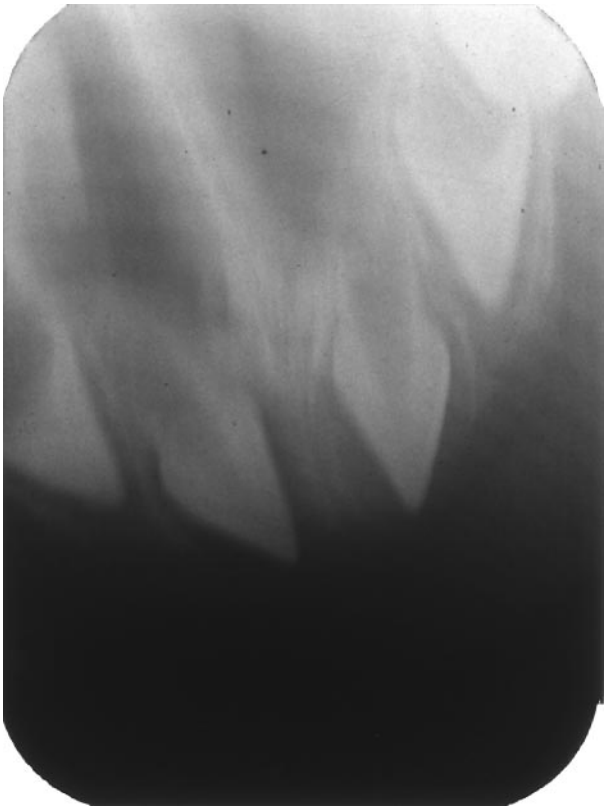

Figure 3 Abnormal dentition is a frequent finding at X-ray

Periorbital pigmentation, a feature not observed in our case, may present at birth.

Conjunctivitis may present from the lack of lacrimation and eyelashes, as in this situation. The patient may be severely photophobic. Our case demonstrated the abnormalities of low set and pointed ears. In addition, he had a typical low nasal bridge producing a saddle-shaped nose. Chronic rhinitis is typically present, as in our case. Scalp

hair is scanty, fine, and fragile, and at times completely absent. The body hair is sparse. Despite the fact that the parents may have darkly pigmented hair, the hair color is blond. The skin is soft, shiny, thin, and wrinkled. The subcutaneous fat layer is severely thinned, allowing easy visualization of the subdermal vessels. Dentition is usually delayed. Abnormalities vary from anodontia to hypodontia with only one or two normally shaped teeth.[8] X-Rays revealed that our patient had only a few abnormally shaped teeth. Mental development is most often normal, but subthreshold cerebral dysrhythmia and mental retardation have been reported.[5,6] The electroencephalogram was normal in our case.

Abnormalities of the gonads and skeletal system may occur, although in our case laboratory and radiologic evaluation revealed no such defects.[9] The deficiency or absence of buccal glands in the oral mucosa induces a susceptibility to infection. A lack of protective secretions of the oral, nasopharyngeal, and upper respiratory mucosa tends to induce frequent and sometimes chronic pharyngitis, bronchitis, rhinitis, and otitis media. Paradoxically, watery rhinorrhea may occur because of a lack of respiratory mucus.

Conclusions

The consideration of the diagnosis of anhidrotic ectodermal dysplasia is critical when evaluating a child presenting with a fever of unknown origin. The mitigation of fever using methods such as cold compresses is critical in the newborn and infant to prevent fluid and electrolyte disturbance, central nervous system damage, and possible demise from hyperthermia. Corrective dental measures are the only therapy available.[10] Once the diagnosis is made, the physician should refer the parents and, when the afflicted individual becomes a young adult, the patient for genetic counseling.

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Cameo

Kwashiorkor/zinc deficiency overlap following partial gastrectomy

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A 48-year-old African–American woman presented with an eruption on her thighs, buttocks, and upper extremities of approximately 2 months duration. She also complained of diarrhea, poor appetite, weakness, and pain around her mouth and eyes. Her medical history was significant for a gastrojejunostomy and stomach stapling for morbid obesity at the age of 32. The procedures resulted in a 500 lb weight loss over several years (from 600 lb to 106 lb). Her course was complicated by multiple bouts of diarrhea, inanition, and coma.

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Physical examination demonstrated sharply demarcated plaques of dusky erythema, with superficial desquamation and a "cracked enamel" appearance, over the upper extremities, buttocks, and extending to the lateral aspects of the thighs (Fig. 1). Erythema and crusting were noted at the corners of her mouth, and a few small crusts were apparent over the medial aspect of the left upper lid margin. No intraoral, periungual, or perianal abnormalities were noted. No hair abnormalities were appreciated.

Initial laboratory data included a complete blood count (CBC), chemistry profile, and levels of magnesium, vitamin B12, folic acid, total iron, glucagon and zinc. Abnormal laboratory values included total serum protein 5.5 g/dL (normal, 6.0–8.2 g/dL), albumin 2.2 g/dL (normal 3.5–5.0 g/dL), and serum zinc 30 μg/dL (normal, 60–130 μg/dL).

A biopsy from the left hip (Fig. 2) revealed dense parakeratotic scale with an irregularly acanthotic epidermis. Foci of minimal spongiosis were noted. Superficially, the keratinocytes were large and pale. Within the dermis, papillary dermal edema, scattered extravasated erythrocytes, and a superficial, perivascular, mononuclear infiltrate were noted.

Discussion

Kwashiorkor is a form of protein–energy malnutrition where the caloric intake remains adequate in the face of prolonged protein deficiency. It is most frequently diagnosed in the pediatric population, when malnourishment causes a 20% to 40% decrease in expected body weight with edema or hypoproteinemia. Classic cutaneous manifestations include hypopigmentation and dry fissured areas with an "enamel paint" appearance over locations under pressure or with increased moisture.[1] These areas appear hyperpigmented in dark skin and red–purple in fair skin. The lesions tend to extend peripherally, eventually coalescing into widespread erosions with a waxy, "flaky paint" appearance.[2]

There is a predilection for lesions to appear on limbs and buttocks. Secondary colonization with *Candida albicans* or bacterial infection may occur.[3] Mucous membrane involvement, such as cheilitis and angular stomatitis, can be seen in advanced disease. The hair may be sparse and dry. A reddish tinge can be appreciated in patients with dark hair. Intermittent episodes of insufficient protein intake can cause bands of alternating light and dark hair known as the "flag sign".[4] The nails may appear thin and soft.[5] Central nervous system effects include irritability and apathy.

Total and partial gastrectomies have been performed for various purposes, such as gastric carcinoma, gastric ulcers, gastric angiomas, and weight control. The occurrence of

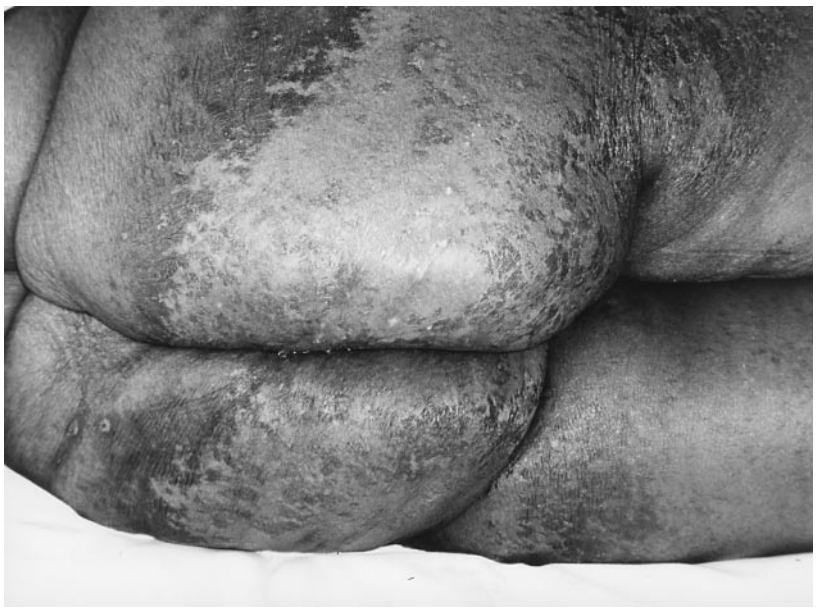

Figure 1 Sharply demarcated, dusky red plaques with superficial desquamation in a "cracked enamel" configuration

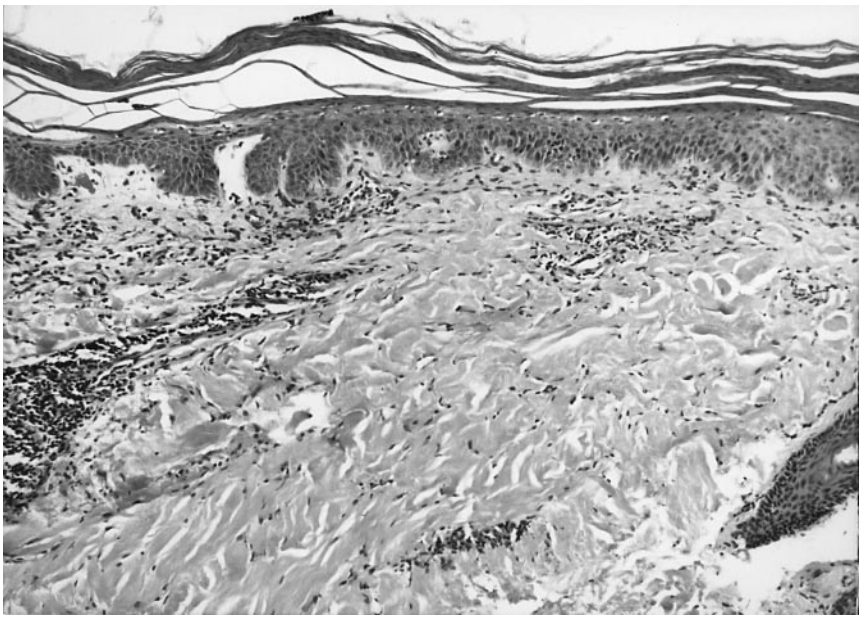

Figure 2 A biopsy showing dense parakeratotic scale with an irregularly acanthotic, minimally spongiotic epidermis. Keratinocytes appear large and pale. Papillary dermal edema, scattered extravasated erythrocytes and a superficial, perivascular, mononuclear infiltrate can be seen

malnutrition in long-term survivors of total or partial gastrectomy has been well documented.[6,7] Several investigators have noted a striking similarity of kwashiorkor to zinc deficiency.[3,8] Ulceration, edema, stunting, and wasting have been observed in patients with low plasma zinc concentrations. Diarrhea, hair fragility, and dyspigmentation, as well as an increased susceptibility to infection, are also common features to both protein–energy malnutrition and zinc deficiency.[9] The classic findings in kwashiorkor resemble those of acrodermatitis enteropathica. Golden *et al.*[10] reported a statistically significant response of kwashiorkor skin lesions to the topical application of zinc sulfate. They also concluded that, "low plasma zinc concentrations previously found in malnourished children with skin sores reflected actual zinc deficiency, and not a spurious association caused by lowering of plasma zinc binding sites or redistribution of zinc within the body." The precise mechanisms by which zinc deficiency may be associated with protein–energy malnutrition remained to be defined.

Only a few reports exist of combined protein and zinc deficiency in adults. In 1976 and 1978, Weismann *et al.*[11,12] described two parallel cases of zinc deficiency associated with chronic alcoholism, cirrhosis, pancreatitis and Billroth II gastric resection. Low albumin levels were also noted. The negative zinc balance was attributed to chronic alcoholism and cirrhosis. The patients' skin improved rapidly after oral zinc sulfate therapy, although relapses were common. Another case from Weissman *et al.*[11] displayed zinc deficiency in a 28-year-old woman secondary to a small-intestine bypass operation for obesity. She similarly responded to zinc sulfate therapy; however, follow-up was not obtained. In 1977, a similar kwashiorkor-like syndrome was reported in a 6-week-old male infant who underwent a necrotic bowel resection, although zinc levels were not investigated.[2] In 1979, a kwashiorkor-like zinc deficiency syndrome was reported in a 26-year-old woman with anorexia nervosa.[3] She improved shortly after receiving oral zinc sulfate and intravenous human albumin. This case brought into question the true etiology of the skin changes seen in classic Kwashiorkor, including hypoproteinemia and/or hypozincemia.

Our patient suffered a prolonged hospital course complicated by diarrhea, dehydration, and sepsis. Her skin lesions improved within 1 week after receiving total parenteral nutrition with zinc sulfate supplementation. One month after initiation of therapy, her skin showed diffuse postinflammatory hyperpigmentation without erythema or crusting. She is currently awaiting surgical evaluation for a potentially curative bypass reversal. Several methods of treatment for kwashiorkor-like illness following gastrectomy have been reported. Kumei *et al.*[13] have shown that elemental diets improve the overall condition of such patients. A report by Kadowaki *et al.*[14] detailed a reconstructive intestinal procedure providing the relief of symptoms over an 8-year follow-up period to a woman with secondary kwashiorkor due to total gastrectomy.

Our case is the first documented kwashiorkor/zinc deficiency overlap following partial gastrectomy for obesity. While other nutritional deficiencies (i.e. essential fatty acids, other vitamins) certainly could have contributed to our patient's clinical presentation, they were, unfortunately, not measured. The cases reported by Weissman *et al.*[11,12] showed some similarities to our patient. The patients with

combined zinc and protein deficiencies in the setting of chronic alcoholism, cirrhosis, and chronic pancreatitis after gastric resection showed a probable mixed etiology. The authors attributed these deficits to malabsorption and poor nutrition from chronic alcoholism, cirrhosis, and pancreatitis. Because our case was not complicated by other variables, such as alcoholism and its sequelae, we can hypothesize that the clinical presentation was at least partly due to a kwashiorkor/zinc deficiency overlap following gastrectomy.

This report should serve to make physicians more aware of the existence of multiple nutritional deficiencies in post-gastrectomy patients, and the need to determine both zinc and protein levels if suspicious skin lesions appear.

Acknowledgments

Dr Robert Gerard referred this patient to us and provided clinical and laboratory data. Dr Roy L. Stern provided photographs and a review.

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Cameo

Cutaneous bronchogenic cysts

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Case 1 A 13-year-old girl had a swelling and draining sinus on the suprasternal notch which had been present since infancy. The lesion had previously been treated with many methods, but none had been successful. Clinically, there was a mobile cystic mass (3 cm × 2 cm) on the suprasternal notch, together with a sinus mea with a small amount of mucoid secretion (Fig. 1).

Although a mediastinal mass was seen in the chest X-ray, ultrasound (US) and magnetic resonance (MR) examination demonstrated that the lesion was a hyperplastic thymus. No other abnormalities were found in the general physical and laboratory examination of the patient.

The skin lesion was excised under local anesthesia. There was no evidence of extension or connections to other structures or to deep tissues. The postoperative course was uneventful and the patient has been free from recurrence.

Microscopic examination of the punch biopsy specimen performed on the cutaneous cyst revealed skin structures and adjacent cystic space lined by ciliated pseudostratified columnar epithelium (Fig. 2). The cyst epithelium contained many goblet cells intermingled with ciliated columnar cells (Fig. 3). In the connective tissue surrounding the cystic cavity, smooth muscle, cartilage, or thyroid tissue could not be identified. Based on these histologic features, a diagnosis of bronchogenic cyst was made. Excisional biopsy followed, and pathologic examination of the specimen confirmed the diagnosis.

Case 2 A 14-year-old boy had a draining sinus on the suprasternal notch which had been present since 3 months of age. Drainage had been applied to this lesion 6 months previously, as it was thought to be an infection. On close examination, a mobile cystic mass (1.5 cm $\times$ 2.5 cm) and a sinus mea were present on the suprasternal notch. Physical and laboratory examination revealed no other abnormalities.

Total surgical excision of this skin lesion was performed under local anesthesia. During the operation, a small amount of clear mucoid fluid was obtained from the cyst by lateral compression; however, no evidence of extension or connections to other structures or to deep tissues was present. The postoperative course was uneventful. The histologic features of the second case were similar to the first.

Discussion

Cutaneous bronchogenic cysts (CBCs) are extremely rare congenital anomalies; about 50 cases have been described in the literature. In most cases, the lesions are noted shortly after birth or in early childhood and present as a swelling or draining sinus. The cysts are usually observed near the suprasternal notch or manibrum sterni; they can also be found in the neck, chin, base of the tongue, shoulder, and scapular region.[1–5]

The origin and pathogenesis of CBCs are difficult to explain. Cutaneous bronchogenic cysts are thought to arise from congenital anomalous development of the tracheobronchial buds from the primitive foregut origin. Another explanation is that a preformed cyst of the thoracic cavity may be pinched off and then migrate to the cutaneous tissues of the neck during the development of the tracheobronchial tree. Support for this theory of displacement is offered by two cases reported by Fraga *et al.*, in which a cord-like connection arched from the extrathoracic cyst around the suprasternal notch towards the mediastinum.[1–3]

Clinically, most patients have an asymptomatic soft mass or draining sinus tract in the extrathoracic area noted in infancy or childhood. The cyst predominates in boys over girls by a ratio of almost 4 : 1.[2]

Although mucoepidermoid carcinoma arising from bronchogenic cyst has been reported to be quite rare, it emphasizes the importance of total surgical excision.[6–8]

The differential diagnosis includes cutaneous ciliated cysts, thyroglossal duct cysts, branchial cysts, and teratoma. Thyroglossal duct cysts are usually located on the midline of the neck in the region of the hyoid bone; histologically, they may be lined ciliated epithelium; they lack goblet cells. Thyroid follicles are often observed in the surrounding connective tissues of thyroglossal duct cysts. Branchial cysts are usually found on the lateral surface of the neck, and histologically are characterized by prominent lymphoid tissues. Ciliated cystic lesions in male patients are distinguished from some of the ciliated cysts found in female patients from a consideration of the location e.g. vulvar cysts of urogenital sinus origin, cutaneous endometriosis, and cutaneous ciliated cysts occuring on the lower extremities.[6,9–11]

In our two cases, CBCs are located on the midline of the suprasternal notch. Swelling and drainage were observed from the cysts periodically. Histologically, the cysts were lined by ciliated pseudostratified columnar epithelial cells

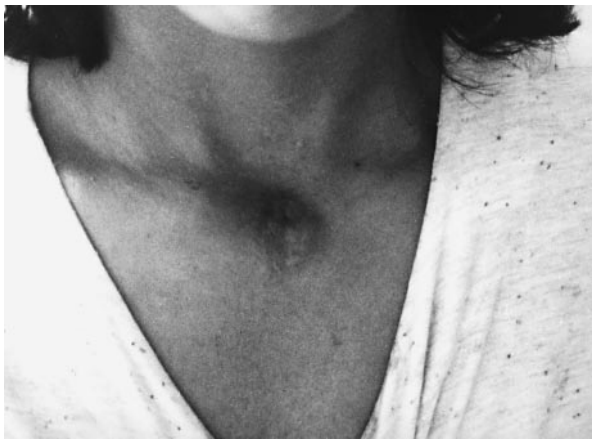

Figure 1 Case 1: a swelling and draining sinus on the suprasternal notch

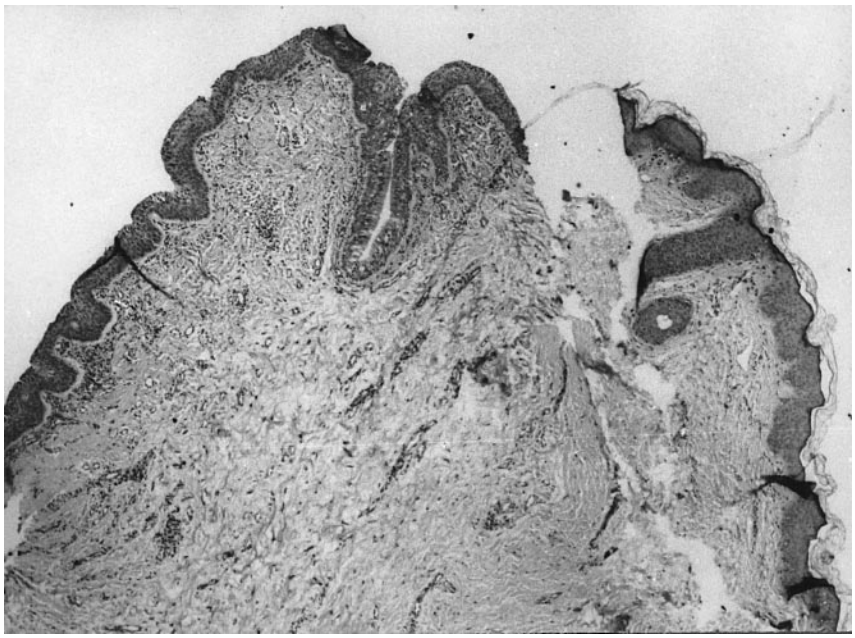

Figure 2 Adjacent to skin surface on the right, cystic structure lined by columnar epithelium (hematoxylin and eosin, × 40)

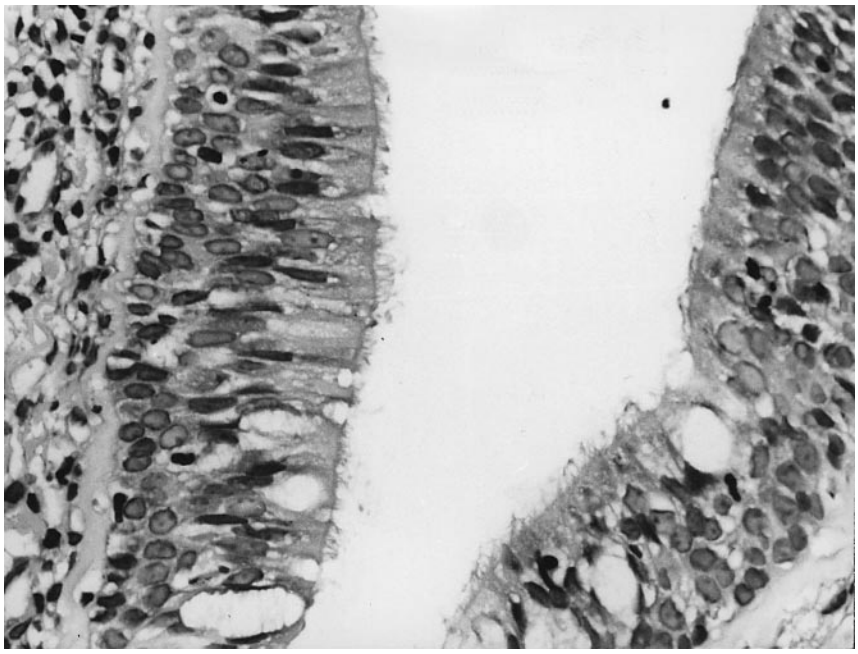

Figure 3 High magnification of an infolding of the inner lining of the cyst epithelium showing ciliated columnar cells and intermingled goblet cells (hemetoxylin and eosin, × 400)

interspersed with goblet cells; thyroid tissues could not be identified. Based on these histologic features, the diagnosis of CBC was made. No other complications in the postoperative follow-up were seen.

The duration and location of the cyst and sinus are important considerations in making an accurate preoperative diagnosis of CBC. For the dermatologist, CBC must be considered in the differential diagnosis of cysts on the neck. Awareness of this lesion by surgeons in the differential diagnosis of masses or sinuses presenting in the suprasternal region may prevent the incomplete excision of components, which can extend deep into the site of origin. The possibility of extension into the mediastinum should be eliminated by evaluation of the chest X-ray and, if necessary, by magnetic resonance (MR). These assist in planning the operative approach. The lesion should be excised totally to eliminate the possibility of recurrence.

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Clinical trial

Short-term itraconazole versus terbinafine in the treatment of tinea pedis or manus

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A total of 304 patients with a clinical diagnosis of palmar-type tinea pedis or manus and a positive mycologic examination were recruited into this double-blind, randomized, multicenter, phase III study. Patients were randomized to receive either oral itraconazole 200 mg twice daily (in the morning and evening) for 7 days, followed by placebo for 7 days ($n = 153$), or placebo in the morning and oral terbinafine 250 mg in the evening for 14 days ($n = 151$).

At the first visit and 1, 2, and 6 weeks after the start of the study, signs and symptoms were assessed clinically, and scales were taken for mycologic assessments (microscopy and culture). At weeks 1, 2, and 6, the effectiveness of therapy was evaluated globally and given a rating of healed (absence of signs and symptoms), marked improvement ($\geqslant$ 50% clinical improvement), considerable residual lesions ($<$ 50% clinical improvement), no change, or worsened. The primary efficacy parameter was the mycologic cure rate at the follow-up end-point (week 6).

The tolerability of the study medications was assessed at weeks 1 and 2. Adverse events were recorded at weeks 1, 2, and 6. Routine hematologic and biochemical tests were performed at the start of the study and after 1 week of treatment.

No significant differences were seen in the baseline patient characteristics between the two groups. The rate of mycologic cure (negative microscopy and culture test result) was 79% in the itraconazole group and 80% in the terbinafine group at the follow-up end-point. The analysis of the 90% confidence interval for the difference between the treatment groups (–7.1, 5.4) and the outcome of the Blackwelder test (for two one-sided tests, $P = 0.013$ and $P = 0.029$) showed the two treatments to be equivalent.

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The following investigators participated in the study: J. Decroix (Belgium); A. Aenstoots, J. Dinu, D. Krausch, X. Kuehn, E. Morgenstern, D. Petzoldt, M. Schnicke, X. Schramm, R. Stadler, I. Tausch, J. Teichmann, T Walther, W. Wehrmann, H. Wetz, X. Wokalck (Germany); E. Panconesi, M. Papini (Italy); E. Baran, Z. Gwiezdzinski, T. Kotodziej, S. Urbanowski, M. Ziarkiewicz (Poland); C. Keyzer, G. Levy, Y. Omar, D. Presbury, W. Sinclair, J. Van Heerden, S. Voget, R. Weiss (South Africa); A. Del Palacio, A. Tuneu (Spain).

The results of the global evaluations of the efficacy in the two treatment groups are shown in Table 1. The rate of clinical response (healed or markedly improved) was 93% in the itraconazole group and 91% in the terbinafine group at the follow-up end-point. The analysis of the 90% confidence interval for the difference between the two groups (–2.5, 5.7) and the outcome of the Blackwelder test (for two one-sided tests, $P = 0.004$ and $P < 0.001$) showed the two treatments to be equivalent. The severity of the clinical signs and symptoms decreased from the baseline to the treatment end-point and from the treatment end-point to the follow-up end-point in both groups.

At the double-blind treatment period end-point (week 2), the tolerability of the study medication was rated as very good or good in more than 97% of patients. During treatment, 21 of 153 patients (14%) in the itraconazole group and 28 of 151 patients (19%) in the terbinafine group reported adverse events. During follow-up, one patient in the itraconazole group and two in the terbinafine group reported adverse events. The most frequent events were headache, abdominal pain, nausea, vomiting, and hypertriglyceridemia.

Two patients in the itraconazole group and four in the terbinafine group withdrew because of adverse events. Severe adverse events were reported by one patient in the itraconazole group and five in the terbinafine group. Serious adverse events were reported by two patients in the terbinafine group, although these were probably not drug related. No clinically relevant changes in laboratory variables were observed.

Discussion

Pharmacokinetic studies have shown that the triazole antifungal agent itraconazole has a high affinity for the stratum corneum and can persist in this tissue for up to 4 weeks after the discontinuation of therapy (100 mg/day for 4 weeks).[1,2] This pharmacokinetic profile has led to the development of short itraconazole treatment courses, such as 400 mg/day for 7 days and 100 mg/day for 15 or 30 days, which have been shown to be effective in the treatment of dermatophyte infections of the skin (J. Schuller, personal communication).[3]

The therapeutic effect, tolerability, and safety of a short-term itraconazole schedule (200 mg twice daily for 7 days) was compared in the present study with those of a standard recommended treatment, terbinafine 250 mg once daily for 14 days, in patients with tinea pedis or manus. The results showed that, at the follow-up end-point, both mycologic cure rates and clinical response rates were statistically equivalent in the two treatment groups. The cure rates were similar to those reported previously with terbinafine 250 mg/day for 2–6 weeks[4] or itraconazole 100 mg/day for 4 weeks,[5,6] and were consistent with the results of a preliminary clinical trial of itraconazole 200 mg twice daily for 1 week.[7]

Overall, both trial medications were well tolerated, with the incidences of adverse events within the ranges of previous values for terbinafine[4,8] and itraconazole.[3,5,9]

The short treatment schedule of itraconazole 400 mg/day for 7 days has the advantages of reducing the time during which the patient is at risk of experiencing side-effects and of being generally more convenient for the

Table 1 Global evaluation of efficacy

	Patients (%)			
	End-point of treatment		End-point of follow-up	
	Itraconazole ($n = 151$)	Terbinafine ($n = 150$)	Itraconazole ($n = 143$)	Terbinafine ($n = 140$)
Healed	13	11	58	54
Markedly improved	61	55	35	37
Considerable residual lesions	20	27	6	5
No change	6	7	1	4
Worse	0	0	0	0

patient than long-term schedules, thus improving the likelihood that the patient will complete the full course of treatment.

Conclusions

The results of this trial showed that itraconazole 400 mg/day for 7 days and terbinafine 250 mg/day for 14 days are equally effective in the treatment of tinea pedis or tinea manus. Itraconazole and terbinafine were equally well tolerated by patients. Itraconazole had a slightly better safety record in terms of severe or serious adverse events; however, the overall number of patients with severe or serious adverse events was too small to confirm or refute this statistically. The treatment regimen of itraconazole 400 mg/day for 7 days can be recommended for patients with tinea pedis or tinea manus.

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Clinical trial

Clobetasol propionate emollient 0.05% in the treatment of atopic dermatitis

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A 4-week, double-blind, randomized clinical trial, comparing the efficacy and safety of clobetasol propionate emollient cream 0.05% and its vehicle, was conducted at four private dermatology clinics in 81 non-hospitalized patients (≥ 12 years old) with moderate-to-severe atopic dermatitis covering 2% or more of their body surface. All patients had at least one lesion 2 cm or more in diameter. Three signs/symptoms of target lesions (erythema, pruritus, and induration/papulation) were scored by investigators on a scale of 0–3 (in 0.5-point increments; 0 = absent, 1 = mild, 2 = moderate, and 3 = severe); the total of the three scores had to be ≥ 6 for patients to qualify for study entry. Patients were excluded if they were immunocompromised, pregnant, or nursing; had skin atrophy, telangiectasia or striae in skin areas to be treated; or had received topical treatments for atopic dermatitis within 1 week prestudy, intramuscular triamcinolone within 6 weeks prestudy, or long-term systemic corticosteroid usage within 6 months prestudy.

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Patients were randomized in a 1 : 1 ratio to receive either clobetasol propionate emollient 0.05% twice daily (n = 41), or the emollient vehicle twice daily (n = 40), for 4 weeks. A fingertip unit, equaling approximately 0.5 g in males and 0.43 g in females (enough to cover approximately 2% of the body), was used to measure and apply a thin film of study drug to the affected areas.

The efficacy was evaluated by investigators and patients on days 4, 8, 15, and 29 after initiation of therapy, and 2 weeks after the end of treatment (day 43). Investigators performed a physician's gross assessment based on the percentage improvement of the target lesion. They also rated changes from baseline in mean severity scores for six individual signs/symptoms (erythema, pruritus, induration/papulation, lichenification, erosion/oozing/crusting, and scaling/dryness) and for total signs/symptoms according to the severity scoring system described above. Patients rated their response to treatment as excellent, good, fair, poor, or worse. Laboratory assessments were made on days 15, 29, and (if necessary) day 43.

Results

Eighty-one patients were initially enrolled into the study (41 treated with clobetasol propionate and 40 with vehicle). There were no significant differences between the treatment groups in any of the demographic parameters or baseline medical history, physical examination results, location of the atopic dermatitis lesions, or concurrent drugs or illnesses. Thirty-seven patients (90%) in the clobetasol group and 24 (60%) of the vehicle group completed all 43 days of the study. No withdrawals in the clobetasol group were for treatment failure, whereas 10 patients (25%) in the vehicle group withdrew for this reason.

Clobetasol propionate emollient produced significantly ($P \leq 0.006$) greater improvement than the vehicle by day 4 with respect to total severity scores (Fig. 1) and scores for erythema, pruritus, induration/papulation, and scaling/dryness, and by day 8 with respect to severity scores for lichenification and erosion/oozing/crusting. This significantly greater improvement than the vehicle was maintained for all individual and total symptom/sign scores throughout the rest of the treatment period, and during the 2 weeks post-treatment, except at day 43 for erosion/oozing/crusting. Physician gross assessment ratings (Fig. 2a) and patient self-assessment ratings (Fig. 2b) for clobetasol propionate were superior ($P < 0.006$ and $P < 0.002$, respectively) by day 4 to those of the vehicle, and remained so during the rest of the treatment and post-treatment periods. More clobetasol-treated patients were assessed as good, excellent, or cleared at both day 29 (82% vs. 29%) and day 43 (78% vs. 33%) in the physician's gross assessment ratings and as good or excellent at day 29 (84% vs. 29%) and day 43 (78% vs. 42%) in the patient self-assessments.

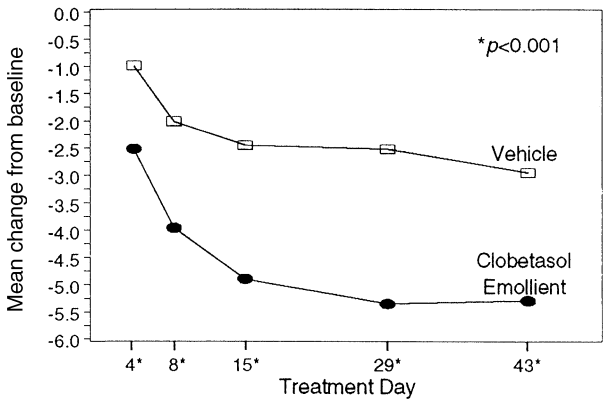

Figure 1 Investigator-rated changes in mean severity scores for total signs/symptoms. *Evaluation times when clobetasol emollient group had significantly lower scores than the vehicle group.

Clobetasol propionate emollient and vehicle were equally well tolerated, with only mild drug-related adverse events noted in one clobetasol-treated patient (pruritus, burning/stinging) and in two vehicle-treated patients (skin atrophy, pruritus). No skin atrophy was observed in the clobetasol emollient group. No significant differences between treatment groups were noted in the number of patients who experienced a 50% decrease or more in serum cortisol concentrations (15% with clobetasol propionate vs. 11% with vehicle, P = 0.737). Three (8%) of the patients treated with clobetasol propionate had serum cortisol concentrations decreased below the lower limit of the normal range (5–18 μg/dL) during the study compared with none in the vehicle group (P = 0.240). Two of these three patients had baseline cortisol concentrations at the low end of the normal range (5 and 7 μg/dL, respectively) and one used 240 g of study drug during the 4-week

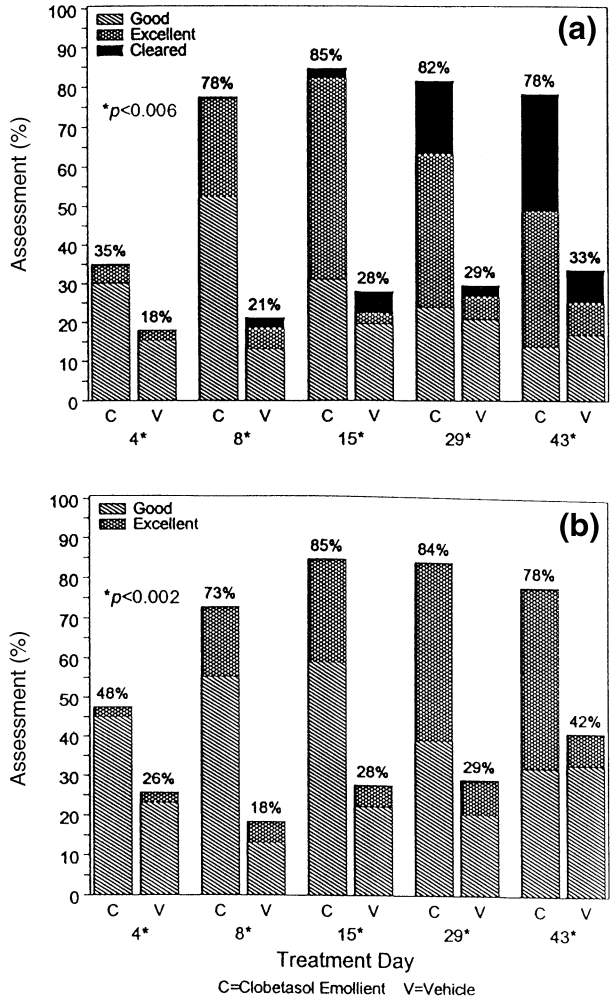

Figure 2 Physician's gross assessment (a) and patient's self-assessment (b) of target lesion response; C, clobetasol emollient; V, vehicle; *evaluation times when clobetasol emollient group had significantly lower scores than the vehicle group.

treatment period instead of just 200 g as defined by the protocol. Serum cortisol concentrations returned to normal by day 29 in two patients (despite the continuation of treatment), and by day 43 in the third patient. The decreases in cortisol concentrations were considered too small to be clinically significant.

Discussion

The results of this study demonstrate that clobetasol propionate emollient 0.05%, applied twice daily for 4 weeks, is effective and well tolerated in the treatment of moderate-to-severe atopic dermatitis. The improvement observed at the end of the first 2 weeks of treatment is not only safely sustained during the subsequent 2 weeks and 2 post-treatment weeks, but may actually progress, as confirmed in all physician and patient ratings. Unlike other formulations of high-potency topical corticosteroids administered for longer than 2 weeks,[1] the emollient formulation of clobetasol propionate, administered continuously for 4 weeks, appears unlikely to cause skin atrophy or clinically significant hypothalamus–pituitary–adrenal (HPA)-axis suppression.

Only one patient (2.5%) developed subnormal plasma cortisol concentrations (< 5 μg/dL) after receiving the total dose of 200 g prescribed by the protocol. In an earlier study evaluating clobetasol emollient over a 2-week treatment period, one of 52 (2%) patients with eczema likewise developed subnormal cortisol concentrations.[2] Two-week clinical trials supporting the New Drug Applications for the ointment, cream, gel, or scalp solution indicated that subnormal serum cortisol concentrations occur with a 4–15% incidence.[2] Thus, HPA-axis suppression with a 4-week regimen of clobetasol propionate emollient 0.05% may be less likely, or certainly no more frequent, than such suppression occurring with other topical clobetasol propionate formulations used for 2 weeks.

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