

## LETTERS TO THE EDITOR

## Phacomatosis Pigmentokeratolica Complicated with Juvenile Onset Hypertension

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Sir,

The association of a speckled lentiginous naevus, an organoid naevus with sebaceous differentiation and skeletal and neurological anomalies, constitutes a specific syndrome that has been called phacomatosis pigmentokeratolica (1).

It has been hypothesized that the co-occurrence of the two different naevi reflects a so-called twin spot phenomenon (1–3). We herein describe an additional case with this rare condition, consisting of organoid epidermal naevus, speckled lentiginous naevus, microphthalmia, kyphoscoliosis, arachnoid cyst, solid tumours at the spinal roots and, in particular, juvenile hypertension.

## CASE REPORT

An 18-year-old Japanese man presented with verrucous plaques on his head, which had been noted at birth and became verrucous at puberty. His left eye was enucleated because of microphthalmia in his infancy. He had been treated for juvenile hypertension since the age of 15. There was no family history of consanguinity or birth defects. Postnatal development was normal with no evidence of seizures. Physical examination revealed band-like brown hyperkeratotic plaques on his left temporoparietal area extending to the cheek (Fig. 1a). A large hyperpigmented macule surrounded by small freckles was noted on his back and buttock. Within the brown macule two sets of V-shaped dark-brown verrucous plaque and melanocytic naevi up to 2 cm in diameter were observed (Fig. 1b). On the left scapula, there was a slate-blue macule clinically diagnosed as blue naevus. Roentgenographic studies showed kyphoscoliosis. Computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen revealed dumb-bell-shaped solid tumours involving the spinal roots between Th11 and L4, which were suspected as being of neural origin. At the level of the hilus renalis, solid tumours were contiguous to bilateral renal arteries (Fig. 2). Renal angiography demonstrated a stenosis of the left renal artery, strongly suspected as the cause of renovascular hypertension. Percutaneous transluminal renal angioplasty failed to release the stenosis. He still continues antihypertensive medication. MRI of the head revealed an arachnoid cyst in the left middle cranial fossa and a lipomatous tumour in the

left orbit. The result of an electroencephalogram was normal.

We performed surgical resections of several skin lesions. Histological studies of the verrucous plaques of the face showed hyperkeratosis and papillomatous hyperplasia of the epidermis. Numerous mature sebaceous glands were present in the upper dermis. The histological findings of the plaques of the head and back were almost the same as those of the face, being consistent with naevus sebaceous.

## DISCUSSION

The epidermal naevus syndromes include different diseases that have the common feature of mosaicism. Among these phenotypes, the Proteus, CHILD, naevus comedonicus, Becker naevus and Schimmelpenning syndromes have been delineated (2). Happle et al. (1) proposed phacomatosis pigmentokeratolica as the name for a distinct type of epidermal naevus syndrome associated with skeletal or neurological abnormalities. Happle explained this type of syndrome by the genetic mechanism of twin spotting (3). The syndrome is delineated by the presence of multiple organoid naevi with sebaceous differentiation, arranged according to Blaschko lines, along with a speckled lentiginous naevus arranged in a checkerboard pattern (4). In addition, hemiatrophy with muscular weakness of varying degrees and other neurological defects may be present, e.g. segmental dysaesthesia, hyperhidrosis, mild mental retardation, deafness, ptosis and strabismus (4–8).

For differential diagnosis, and Schimmelpenning syndrome may be considered. This syndrome is characterized by the presence of an organoid naevus showing sebaceous differentiation in association with ocular, cerebral and skeletal defects. In phacomatosis pigmentokeratolica, however, the other typical findings of Schimmelpenning syndrome, such as coloboma and lipodermoid of conjunctiva, have so far been absent (4). Only 18 cases of phacomatosis pigmentokeratolica have been reported up to date (1, 4–8). Ten were male and 8 were female. The age of patients ranged from 4 to 53 years (average 18 years). The extracutaneous findings of the reported patients included hemiatrophy, hyperhidrosis, dysaesthesia and scoliosis.

A distinctive feature of our patient was juvenile hypertension. Hypertension directly associated with

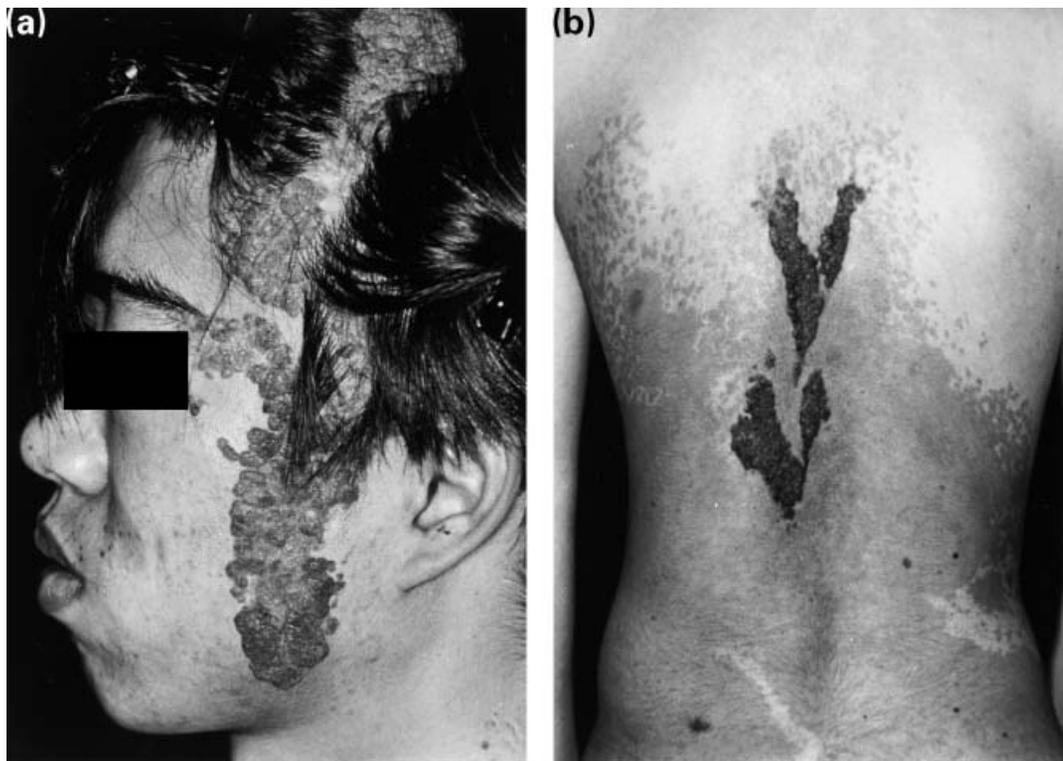


Fig. 1. (a) Band-like verrucous plaques involving the scalp and face. (b) Two sets of V-shaped verrucous plaques within a large hyperpigmented macule on the back.



Fig. 2. Magnetic resonance imaging showing solid tumours at bilateral hili renalis and spinal roots (arrows).

phacomatosis pigmentokeratolica and other epidermal naevus syndrome has never been reported. The findings of CT, MRI and renal angiography strongly suggest that in our patient hypertension may be due to the compression of renal arteries by tumours. The solid tumours are considered as benign neurogenic in origin because of their multiplicity and location at spinal roots as well as the hilus renalis.

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## Cutaneous Adenocarcinoma Metastases Associated with Swelling of the Neck and Cheeks

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Sir,

Cutaneous metastases occur in 0.7–10% of all patients with cancer (1). They may be the first sign of malignancy, especially in carcinoma of unknown primary origin, which accounts for 5–10% of all cancers (2). The types of skin metastases are varied but the most common clinical findings in skin metastases are clusters of discrete but firm, painless nodules (3, 4). We report here a patient with an unusual manifestation of cutaneous metastases presenting as bilaterally swollen neck and cheeks with indurated erythema. The primary site of the tumour could not be determined.

### CASE REPORT

A 66-year-old Japanese man consulted an otolaryngologist in May 2002, with a 1-month history of subcutaneous nodules in his submandibular region. The computed tomography (CT) findings suggested the diagnosis of inflammatory lymphadenitis. He was treated with antibiotics for 1 week, which resulted in no response. Five months later, his cheeks and neck suddenly became enlarged. A physical examination revealed bilaterally swollen neck and cheeks (Fig. 1a). Compared with a picture taken 2 years before, his looks had dramatically changed (Fig. 1b). The skin surface of his swollen neck and cheeks showed indurated erythema but without any inflammatory signs such as pain and heat. Within the lesion, there were three to four small firm nodules measuring up to 7 mm in diameter. A single nodule measuring 3 cm in diameter in his left pre-auricular region was also palpated. The first clinical diagnosis was of an infiltration of lymphoma cells and the differential diagnosis was granulomatous disease. A biopsy specimen of the lesion demonstrated a diffuse infiltration of atypical cells in the subcutaneous tissue and also in the dermis (Fig. 1c). There was no oedema in the dermis; the increase in the thickness of the dermis and the subcutaneous tissue were simply due to the infiltration of atypical cells. Some of these atypical cells had an apparently empty space in their cytoplasm and others together formed duct-like structures (Fig. 1d), suggesting a poorly differentiated adenocarcinoma. The atypical cells did not invade into the epidermis and did not have an obvious relationship with any skin appendages. The histological findings suggested a diagnosis of metastatic carcinoma to the skin. Superficial lymphatic vessels were not dilated and not

plugged with atypical cells, and there was no fibrotic stroma – findings incompatible with the diagnosis of inflammatory metastatic carcinoma or en cuirasse metastatic carcinoma.

Immunohistochemical studies showed that the tumour cells stained with cytokeratin 7 and carcinoembryonic antigen. Immunoreactivity for cytokeratin 20, prostate-specific antigen and cancer antigen 19-9 were negative. These results verified that the atypical cells were of adenocarcinoma origin. Periodic acid-Schiff (PAS) and Alcian blue stains revealed that the tumour cell cytoplasm was negative for mucin. A repeated CT showed that the skin and subcutaneous tissues of both sides of the neck and cheeks were now about five times thicker than previously (Fig. 2a, b). The bilateral sternocleidomastoid and latissimus dorsi muscles had also undergone thickening (Fig. 2b). The cervical, mediastinal and axillary lymph nodes were also swollen (Fig. 2c). Bone scintigraphy showed multiple metastatic lesions in the thoracic spine and the ribs; nevertheless

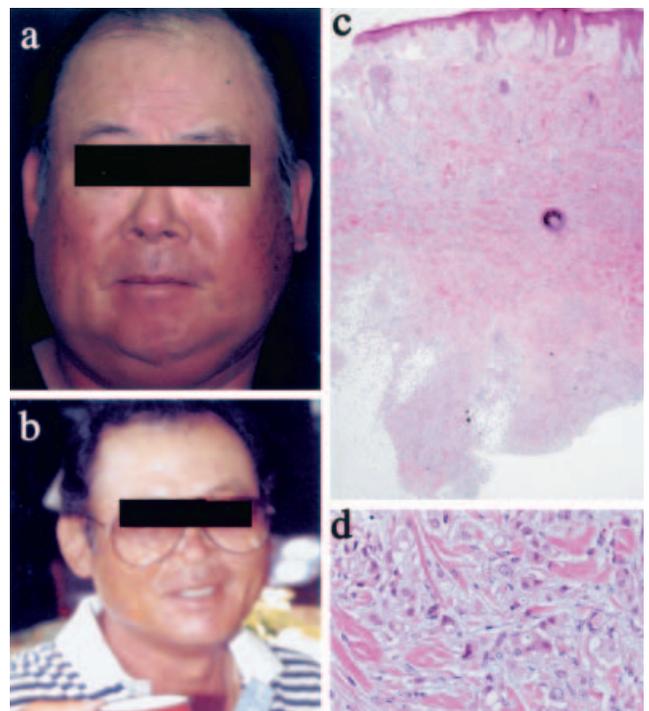


Fig. 1. (a) Clinical manifestations, highlighting the patient's bilaterally swollen neck and cheek with indurated erythema. (b) The same patient 2 years before the development of disease. (c) Diffuse infiltration of atypical cells in the dermis and subcutaneous tissue in a biopsy specimen of a nodule (H&E  $\times 2.5$ ). (d) Atypical cells show empty spaces in their cytoplasm and form duct-like structures ( $\times 200$ ).

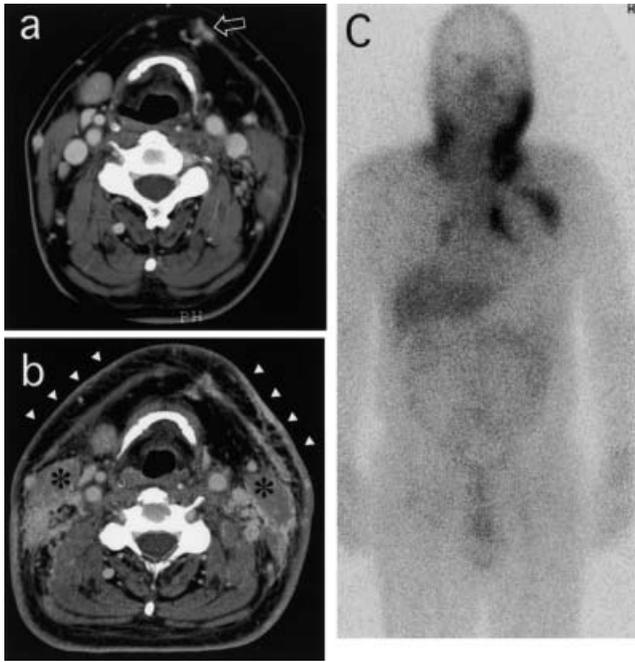


Fig. 2. Computed tomography showing (a) subcutaneous nodules in the submandibular triangle (arrow) in May 2002 and (b) thickened skin and subcutaneous tissue (arrowheads) and sternocleidomastoid muscles (asterisks) in September 2002. Gallium scintigraphy (c) showed spots of cervical, mediastinal and axillary lymph nodes.

we could not find any obvious primary origin. Diagnosis was therefore metastatic adenocarcinoma of an unknown primary origin. The patient received a chemotherapy treatment of paclitaxel, which resulted in a partial response.

## DISCUSSION

Cancer metastases to the skin are usually associated with a known identifiable primary disease. The most common primary sites are from the breast in women, and the lung and colon in both sexes, reflecting typical cancer demographics (5). In spite of improved imaging procedures and immunohistochemical analyses, the primary site of cancer can still not be determined in 5–10% of all cancer patients (2). In a retrospective study of 4020 patients with metastatic cancer, a primary

site was not found in 271 cases (7.3%) and cutaneous metastases were noted in 20 cases (7.4%) (6). The major histological findings were adenocarcinomas and the most frequent sites of the metastases were the lower limbs, neck and abdomen. They were mostly clinically described as nodules (in 15 of 20 cases), which was the most common clinical presentation of all cutaneous metastases from any cancer. Indurated ulcers in two cases and indurated plaques in one were also reported but not described in detail (6). Our case did not show any superficial lymphatic vessels plugged with atypical cells or fibrotic stroma characteristic of either an inflammatory metastatic carcinoma or en cuirasse metastatic carcinoma. To the best of our knowledge, the unusual manifestation of bilaterally swollen neck and cheeks with indurated erythema has not been reported previously in metastases from unknown origin.

In general, patients with metastatic carcinoma of unknown primary site have a poor prognosis (2, 6). However, a few subsets of treatable patients have been identified (7). In nearly half of all patients with cancer of an unknown origin, the skin metastases were the first sign of disease (6).

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## Dermatomyositis Associated with Acute Myeloid Leukaemia: A Paraneoplastic Association or a Drug-Induced Phenomenon?

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Sir,

Dermatomyositis (DM) is a relatively rare disease of unknown aetiology characterized by an inflammatory condition involving primarily the skin and the striated muscle and its associated vessels. The relationship of DM and neoplastic disease in adult patients was first reported in 1916 by Stertz and Kankeleit. Carcinomas are the most common malignancies found and parallel those observed in the general population: tumours of the lung, breast, uterus, ovary, prostate and gastrointestinal tract. Association with haematological disorders is highly uncommon and the presence of leukaemias in conjunction with DM is extremely rare.

We report here a patient affected by a severe and treatment-resistant DM who, 8 years after receiving multiple immunosuppressants, developed a myelodysplastic syndrome that subsequently transformed into acute myeloid leukaemia.

### CASE REPORT

In 1991, a 56-year-old man was admitted to our hospital with periorbital oedema and heliotrope erythema, and erythematous rash over the dorsum of his hands and trunk that had appeared 3 months before. He also complained of progressive diffuse muscle weakness and myalgia.

Initial laboratory examination showed high levels of serum creatine kinase (1077 IU/l; normal range <80 IU/l), serum transaminases (AST 92 IU/l, ALT 52 IU/l; normal ranges <40 IU/l), aldolase (32 IU/l; normal value <3.1 IU/l) and lactic dehydrogenase (778 IU/l; normal range 120–240 IU/l). Mild but persistent haematological abnormalities were also present at diagnosis (leukocytes 3800/ $\mu$ l, neutrophils 2200/ $\mu$ l and lymphocytes 730/ $\mu$ l). Serum antinuclear autoantibodies were absent. No evidence of antibodies to extractable nuclear antigen (ENA) or to anti-aminoacyl-transfer-RNA-synthetase (Jo-1) was found. Skin and muscle biopsies and electromyogram findings confirmed the diagnosis of DM. A search for possible malignancies was carried out with negative results in the initial investigations.

The patient was first treated with oral prednisone at a dose of 1 mg/kg per day for 3 months, but azathioprine and chloroquine (100 and 150 mg/day, respectively) were added to the regimen due to unresponsiveness of severe cutaneous lesions. As no improvement was observed, the regimen was subsequently changed to oral prednisone and oral cyclosporine (2.5–3 mg/kg daily).

High-dose intravenous immunoglobulin therapy was also attempted, due to severe treatment-resistant DM. Nine cycles were administered 4 days per month at a monthly dose of 2 g. Cyclophosphamide treatment was initiated when immunoglobulin was ineffective, and it was administered over 2 years, always in combination with oral prednisone ranging between 0.5 and 1 mg/kg. Despite the combined therapy, it was not possible to taper off the corticoids and the patient even required different adjuvant treatments on several occasions due to the presence of life-threatening flare-ups and multiple complications.

Ever since the initial diagnosis the patient presented persistently high serum enzyme values, and haematological abnormalities in peripheral blood, including relapsing episodes of severe thrombopenia, anaemia with anisocytosis requiring blood transfusions, eosinophilia and pancytopenia. Periodic complementary studies, including bone marrow analyses, were performed to rule out solid or haematological malignancies over this time. As no malignancies were found, the haematological alterations were considered to be drug-induced. A monoclonal  $\kappa$ -type gammopathy of undetermined significance was the only feature found during this period.

In 1999, while still on cyclophosphamide and prednisone, the patient presented a severe DM exacerbation with erythroderma, and was admitted to our hospital with high fever and malaise. Severe pancytopenia was detected. Finally, a myelodysplastic syndrome, refractory anaemia with excess of blast type (RAEB), was confirmed after repeated bone marrow aspirations and biopsies. Eight months later the RAEB transformed into an acute myeloid leukaemia (AML). The karyotype showed a deletion involving chromosome 7.

The patient received induction chemotherapy with idarubicine, cytarabine and etoposide. Complete response of both DM and AML was observed and the patient remained in remission for a whole year. He then presented a new erythrodermic flare-up of the DM coinciding with a recurrence of AML and died of acute, massive pulmonary bleeding at the age of 66.

### DISCUSSION

As patients with DM are often treated with immunosuppressive and even cytostatic agents over many years, it has been suggested that these drugs may heighten the risk of developing cancer, especially haematological disorders (1–3).

Myelodysplastic syndromes (MDS) are myeloid

clonal haemopathies where up to 30% of patients develop a secondary acute leukaemia (usually AML) within 6 months of diagnosis. Cytogenetic abnormalities are common in MDS, and define specific subsets of the disease (4). MDS can be subclassified as primary and secondary or therapy-related MDS. Primary MDS is diagnosed as *de novo* disease while secondary MDS corresponds to cases arising in patients who have previously received leukaemogenic chemotherapy and/or irradiation. The number of cases in this latter category is increasing: examples are therapy-related MDS secondary to alkylating agents or secondary to DNA topoisomerase II inhibitors.

Only seven cases of leukaemia have been reported in relation to DM. Two of them were paediatric cases with acute lymphoid leukaemia (5, 6). Two others were adults with Philadelphia chromosome positive chronic myelogenous leukaemia, who developed DM subsequently (7, 8). The three remaining cases were adult patients with DM who subsequently developed an AML. The first case was a 38-year-old man who developed an acute granulocytic leukaemia 11 months after diagnosis of DM which was resistant to treatment (9). The second was a 30-year-old man who had DM associated with metastatic seminoma. Four years after surgical excision and chemotherapy, he developed an acute promyelocytic leukaemia (10). The authors discussed the most likely causes of this association, ruling out a therapy-related leukaemia, as no alkylating agents had been used, and no cytogenetic abnormalities were present. The third case was a 62-year-old man with DM, who developed an AML 3 months after diagnosis (11). In this case the authors noted that the DM was probably associated with the AML, as haematological abnormalities were already present at initial evaluation and AML may be aleukaemic initially. No alkylating drugs were administered, and the diagnoses were almost coincidental.

Our patient had received several immunosuppressive agents, among them cyclophosphamide and azathioprine. Both drugs have been associated with MDS development, with monosomy 7 abnormality being described as one of the most frequent chromosomal abnormalities. Thus, prolonged use of azathioprine treatment for autoimmune diseases has been involved in the development of myelodysplasia and subsequent AML with a characteristic association in the karyotypic analysis (12, 13).

In conclusion, we report a case of adult DM who

died due to a neoplasia directly related to DM. Although a therapy-related leukaemia seems to be the most likely cause in our case, some events may suggest a paraneoplastic association, especially as haematological abnormalities and a monoclonal gammopathy were present from the onset of the disease.

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## Necrotizing Sialometaplasia: A Case Report

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Sir,

Necrotizing sialometaplasia is a benign, self-limiting, reactive, inflammatory process affecting the major and minor salivary glands throughout the upper aerodigestive tract (1). The aetiology is unknown. It was first described in 1973 by Abrams et al. (2), and is a relatively rare condition. In a recent publication by Fowler & Brannon (3), reviewing all cases previously published in English language medical literature, a total number of 184 cases were described. Because of the rareness and localization of the disease, it is a rather unknown condition among dermatologists. Most cases have been reported in the otorhinolaryngic literature; however, it is also an important disease for dermatologists to recognize.

Necrotizing sialometaplasia can be confused clinically and histologically with malignancy (4), but it is a self-limiting disease and only conservative treatment is necessary. We here present a case of bilateral necrotizing sialometaplasia in a woman.

### CASE REPORT

A 22-year-old woman experienced abrupt onset of swelling and pain of the hard palate. Within 3–4 days two ulcers developed, proceeding over the next 2 weeks to two crater-like lesions. No fever was present. In the 6 months before onset of her oral symptoms she had had a weight loss of approximately 12 kg. She denied having any eating disorders and attributed stress as the cause of her weight loss.

The patient was a student at the school of dentistry. A few days before the onset of symptoms she was the

subject in practical demonstration of a routine clinical oral examination. She was a non-smoker.

Two weeks after onset of symptoms the patient was referred to the Department of Dermatology. At physiological examination the hard palate presented with two symmetrically deep ulcers (Fig. 1a); the ulcers were 1 × 1 cm and 1 × 1.5 cm in size. Weak bilateral adenitis was present at the angulus mandibulae. No affection of the remaining mouth, genitalia or skin was seen. HIV, hepatitis, Epstein–Barr virus, cytomegalovirus, syphilis and antinuclear antibody screens were negative. Cultures from the ulcers were normal. X-ray of the chest and ultrasound examination of the abdomen were normal.

A biopsy specimen from the palate ulcer revealed the diagnosis necrotizing sialometaplasia (Fig. 2).

The patient was treated conservatively with the non-steroidal anti-inflammatory fluid benzydamine (Andolex<sup>®</sup>, 3M Pharma) five times a day and obtained spontaneous recovery within 5 weeks (Fig. 1b). Furthermore, she was referred to a psychologist because of a possible eating disorder.

### DISCUSSION

Necrotizing sialometaplasia is a rare disease. Among the 184 cases reviewed by Fowler & Brannon (3) in the year 2000 the average age was 45.9 years. The male:female ratio was 1.9:1; 58% occurred on the hard palate but only 12% occurred bilaterally (3). Most cases presented with deep ulcers, with a lesion size from 0.7 to 5.0 cm, but non-ulcerated swelling was also seen. The duration of the disorders ranged from 4 days to 3

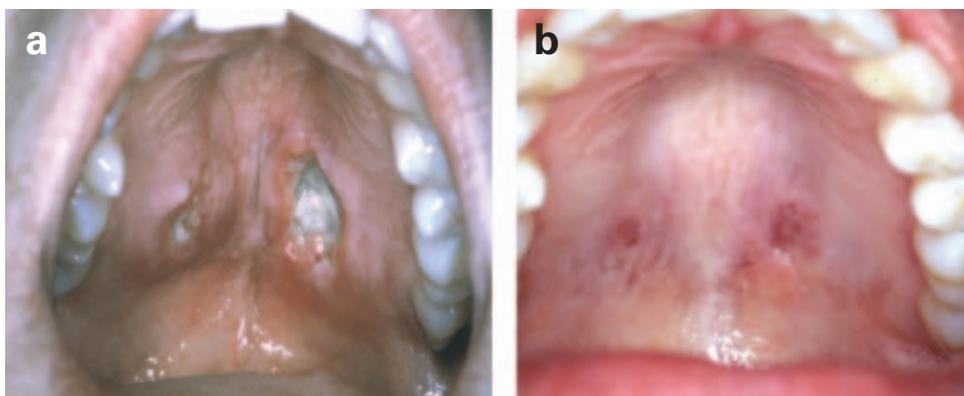


Fig. 1. (a) Necrotizing sialometaplasia of the hard palate 2 weeks after onset of symptoms. (b) Spontaneous recovery 7 weeks after onset of symptoms.

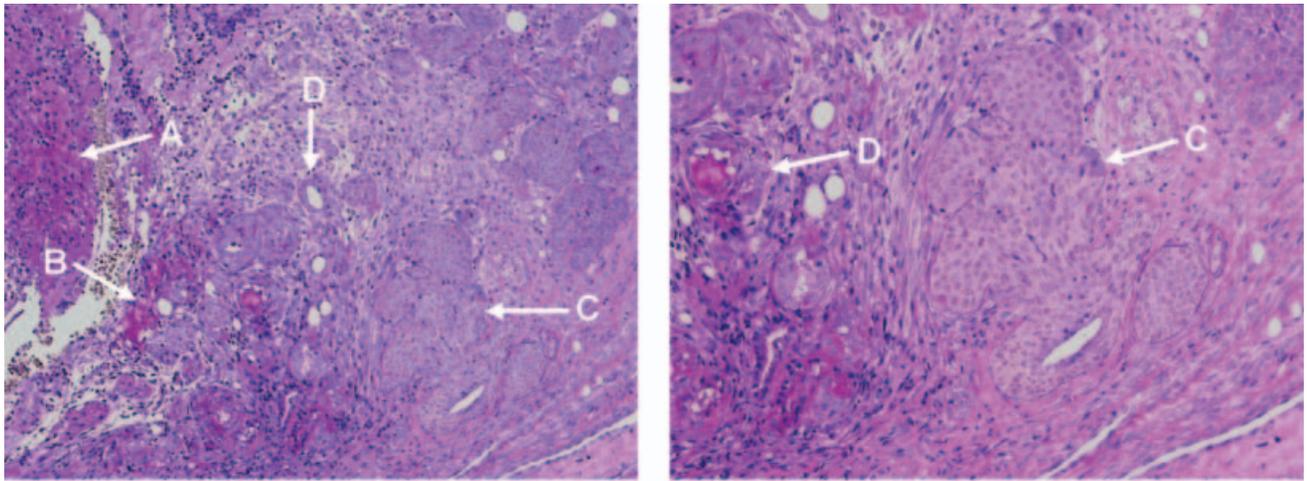


Fig. 2. Biopsy from the hard plate with necrotizing sialometaplasia (PAS staining) showing (left) necrosis (arrow A), and extravasation of mucus (B), and (left and right) squamous metaplasia of ducts and acini (C) and remnant of intact glandular structures (D).

months. Seventy-one of the 184 cases were smokers. Recently, bone involvement has been described (5).

The pathogenesis is most often ischaemia of the salivary gland leading to necrosis and ulceration followed by a spontaneous recovery. Necrotizing sialometaplasia has been produced in rats by ligating the blood vessels supplying the submandibular and sublingual glands (6). Traumatic injury such as dental instrumentation has been described as a possible initiating event (3), but local mucosal trauma in patients suffering from bulimia and chronic self-induced vomiting have also been described as possible aetiological factors (7, 8).

Our patient presented two possible triggering factors for necrotizing sialometaplasia. Firstly, she had participated in practical demonstrations at the school of dentistry a few days before the onset of symptoms. Secondly, she suffered from a possible eating disorder although she denied that possibility. Eating disorders should always be considered as a pathogenic factor in younger patients with necrotizing sialometaplasia.

Histologically, necrotizing sialometaplasia may simulate squamous cell carcinoma or mucoepidermoid carcinoma. It is recognized by the presence of squamous metaplasia of ducts and acini of seromucinous glands accompanied by necrosis, sometimes with ulceration (Fig. 2). Demonstration of intact lobular architecture is very important in the differential diagnosis (9, 10).

Necrotizing sialometaplasia often evolves very aggressively in the first few weeks to months and may therefore be mistaken for a malignant disease. In several cases patients have been treated with unnecessary surgery ranging from conservative excision to total maxillectomy (1). Because necrotizing sialometaplasia

is a benign and self-limiting disease which only requires conservative treatment it is important to recognize this disease before more aggressive and often disabling treatment regimes are carried out.

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## Homozygous Palmoplantar Keratoderma Type Bothnia Improved by Erythromycin: A Case Report

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Sir,

Hereditary palmoplantar keratodermas (PPKs) are a clinically and genetically heterogeneous group of mostly rare disorders with the unifying trait of hyperkeratosis on palms and soles. In northern Sweden diffuse palmoplantar keratoderma is more frequent than in other parts of the world with a reported prevalence of 0.3–0.6% among school children (1, 2). The overwhelming majority of PPK cases in Sweden are attributed to the autosomal dominant PPK type Bothnia (PPKB) (3) with only a few identified cases of autosomal recessive PPK (4). Furthermore, the first two cases of epidermolytic PPK in Sweden have only recently been described (5), even though this is the predominant variant of PPK worldwide.

All PPKB patients examined genetically share the same haplotype for the disease region on chromosome 12q1, indicative of a common genetic origin of this disorder. However, the actual PPKB mutation has not yet been identified, although a large number of candidate genes have been scrutinized for mutations. Due to the high frequency of PPKB in northern Sweden there are families where both parents are affected by PPKB, but so far no report has been presented of a more severe clinical presentation of PPK in children from such families. Here we report on the first case of PPKB shown to be homozygous for the disease region on chromosome 12q1. This homozygous patient was more severely affected than other PPKB patients examined (3), nevertheless she showed a discernible long-term improvement after a course of erythromycin treatment.

### CASE REPORT

An 18-year-old woman was referred to our department for evaluation of distressing PPK. Thickening of palmar skin was first observed at the age of 4 and upon water exposure a white spongy appearance was evident on palms and soles. At the age of 12 there was a marked deterioration, the skin changes became more conspicuous with striking hyperkeratosis appearing also on the dorsal aspects of finger and toe joints. Subsequently, distal onycholysis appeared on some toenails and anti-fungal treatment with terbinafine orally at 0.25 g daily was prescribed for 3 months. The nail condition improved but there was no amelioration of the skin. The patient was extremely unhappy with her condition and to avoid exposure of her hands she withdrew from other people. On examination the patient showed a more prominent PPK than usually seen in PPKB with a thin erythematous rim surrounding the hyperkeratotic skin (Fig. 1a, b). Hyperkeratosis was also present on the dorsal aspects of toe and finger joints. However, no additional skin changes were detected.

The mother, father and sister of the proband also showed signs of PPKB, although their skin alterations were less prominent. On account of our previous observations in PPKB patients, erythromycin 0.5 g twice daily for 1 month was prescribed to the proband. The treatment resulted in an obvious improvement with thinner and softer skin and a less conspicuous phenotype. However, 3–4 months after erythromycin treatment the patient experienced a relapse. The patient has received a few more courses of erythromycin, the interval between them has varied from 4 months up to more than 1 year. Each course has led to improvement followed by some relapse (Fig. 1c, d), but the skin condition has never deteriorated to the pre-treatment state. As a result of her improved condition the patient is now more outgoing and less apprehensive about the appearance of her hands.

Histopathological examination of punch biopsies from the proximal-ulnar site of palmar skin of the patient and her father showed orthohyperkeratosis without signs of epidermolytic hyperkeratosis or fungal infections. After informed consent blood samples were obtained from the proband and her family, genomic DNA was extracted and microsatellite analysis was performed according to standard procedures. The family members were genotyped with DNA markers covering the PPKB locus region on chromosome 12q1 and haplotypes were constructed. Haplotype analysis of the proband revealed a homozygous domain of approximately 5 Mb, whereas the affected relatives of the proband were heterozygous for the PPKB region (Fig. 2).

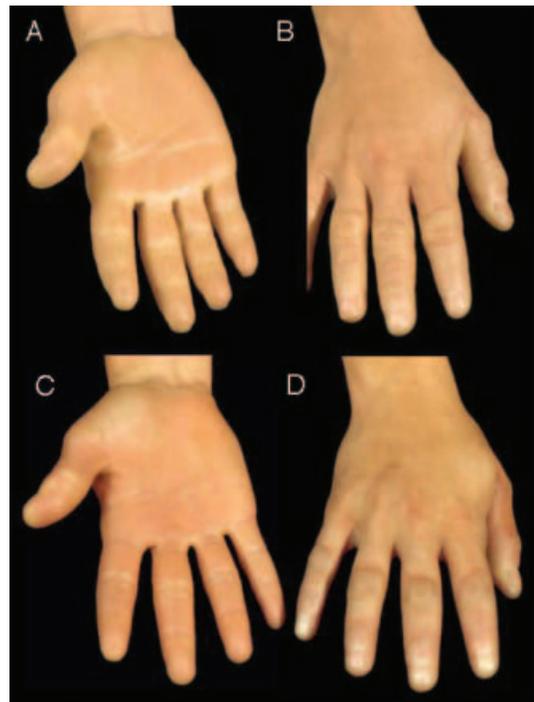


Fig. 1. Appearance of the right hand of the patient before the first (a, b), and 4 months after the second (c, d) erythromycin treatment.

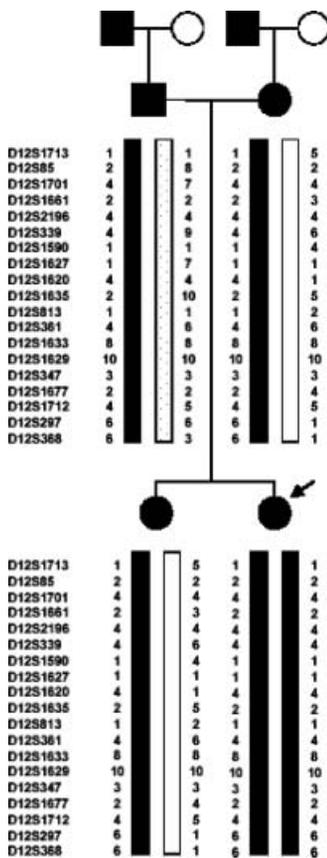


Fig. 2. Pedigree of the family of the homozygous palmoplantar keratoderma type Bothnia (PPKB) patient. Haplotypes of the PPKB region on chromosome 12q1 are given with the markers in centromeric to telomeric order (<http://genome.ucsc.edu>).

## DISCUSSION

In this report we describe the first case of a PPKB patient genetically shown to be homozygous for the PPKB chromosomal region. In a disorder with strict dominant inheritance, homozygous and heterozygous individuals should not differ in clinical expression. However, there are several examples of partly dominant diseases where the homozygotes are more severely affected than individuals carrying only one disease allele (6). In order to establish whether the more severe phenotype is due to the homozygous state of the disease locus or to other factors it will be necessary to examine more patients homozygous for PPKB.

There is no known curative treatment for PPKB. Although anti-mycotic treatment, especially when given orally, often results in improvement this is usually temporary. Some patients consider moisturizing agents useful, whereas topically applied retinoic acid has been tried without benefit (7). Systemic retinoid treatment has been dissatisfying, as the patients experienced that the skin became too sensitive and unsuitable for manual work. Surprisingly, several patients with PPKB have reported improvement after 10–30 days on oral erythromycin given for infectious diseases or the keratoderma (Lundström, unpublished observation). In particular, the white, spongy appearance of the palmoplantar skin after immersion in water became less pronounced but thinning and softening of the skin

have also been reported by the patients. Usually the improvement lasts for months to years.

As PPKB is not an infectious disease it is reasonable to assume that some mechanism other than the antibiotic effect of erythromycin is responsible for the observed improvement. Apart from the antimicrobial potency, a range of antibiotics including the macrolide erythromycin has been shown to modify host functions, especially those related to immunomodulation and anti-inflammatory effect (8, 9). However, there are no data supporting PPKB as an immunological disorder and the patients do not show any obvious signs of inflammation, as long as they do not contract fungal infections.

Another effect ascribed to some macrolide antibiotics is antiproliferation (10, 11). However, in PPKB such a mode of action seems unlikely as there is no evidence for hyperproliferation in PPKB, which is regarded as a retention hyperkeratosis (12). Thus, the mechanisms responsible for the observed improvement after erythromycin treatment remain obscure.

A controlled clinical trial needs to be done to confirm the beneficial effect of erythromycin on PPKB patients.

## ACKNOWLEDGEMENTS

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## Presence of *Demodex* in Follicular Hyperkeratotic Spicules on the Face. A Casual Association?

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Sir,

Follicular hyperkeratotic spicules (FHS) are a rare cutaneous disorder characterized by the presence of follicular, keratotic, horny spicules, mainly on the face. They have been described as idiopathic and associated with a variety of conditions including chronic renal failure, Crohn's disease and malignant diseases. They should be differentiated from the pseudohyperkeratotic spicules of the face, which correspond to cryoprecipitates in association with a monoclonal gammopathy (1), and pityriasis folliculorum, which associates the follicular plugging with a diffuse facial erythema and burning or itching sensations (2). The pathogenesis of FHS is unknown. Recently, it has been suggested that *Demodex* mites might play a role in the aetiology of these lesions, although this fact remains controversial (3).

### CASE REPORT

We describe here a 76-year-old woman diagnosed with hypertension, diabetes mellitus and polycythaemia rubra vera treated with oral hydroxyurea from February 1999 until October 2001. She was admitted to our department with a 2-year history of multiple asymptomatic follicular hyperkeratotic spicules on her face that had appeared in November 2001. No treatment had been applied. She did not have atopic history, photosensitivity or any systemic symptoms. She washed her face daily with water and denied using make-up, creams or oils. Examination revealed multiple spicules with a horny appearance in the follicular openings of the face, particularly on the frontal and temporal regions, cheeks, chin and ears (Fig. 1). No erythema or telangiectasia was observed. No lymphadenopathy was present. Microscopic examination of four biopsies from the spicules demonstrated follicular hyperkeratotic plugs with *Demodex* mites occupying the follicular infundibula in all of them (Fig. 2). A mild lymphocytic cell infiltrate around each follicular infundibulum was observed. A biopsy from apparently healthy skin on the temporal region showed similar

histopathological changes although slightly less pronounced. Laboratory investigations disclosed a mild thrombocytosis and hyperglycaemia. Serum and urine immunoelectrophoresis were normal. Autoantibody screen showed positive ANA (titre 1:160) and

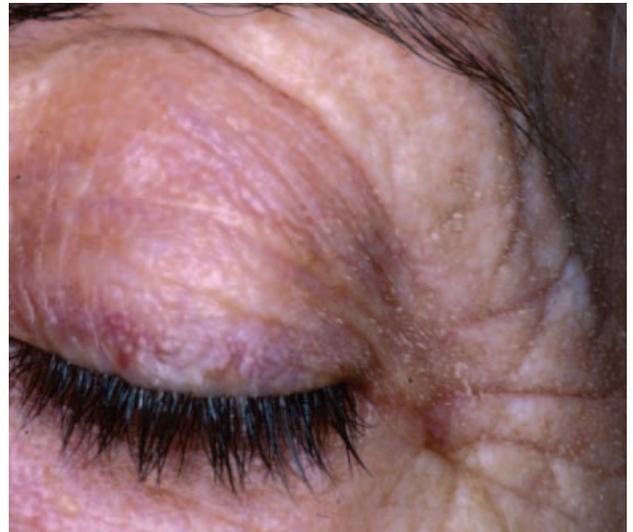


Fig. 1. Spicules with horny appearance in the follicular openings.

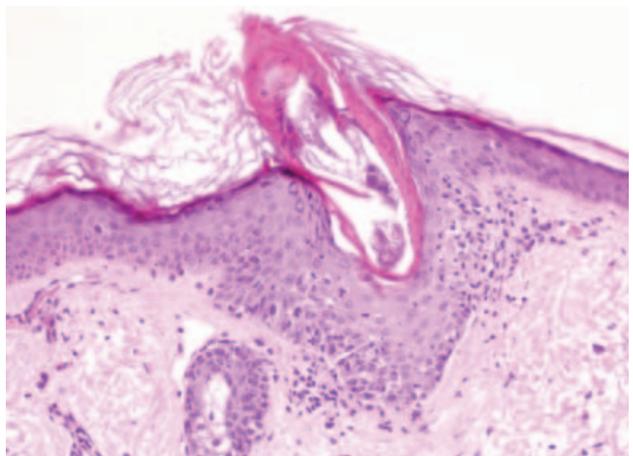


Fig. 2. Follicular hyperkeratotic plugs with *Demodex* mites.

anti-DNA<sub>n</sub> (1:160). Anti-SS-A/Ro, SS-B/La, Sm, nRNP, Jo-1, cryoglobulin and cold agglutinins were negative. She was treated with 5% permethrin cream for 15 days without improvement. Subsequent therapy with topical 0.75% metronidazole cream and oral metronidazole (250 mg/12 h for 10 days) showed no beneficial effects, with persistence of skin lesions.

## DISCUSSION

Fariña et al. (3) reported a patient who had follicular spicules on the face associated with the presence of large numbers of *Demodex* mites. They suggested a pathogenic role for the mites supported by the response of the lesions to topical therapy with permethrin, a known antiparasitic agent, and proposed spinulosis of the face to be included as a demodicidosis. Our patient has many similarities to the patient described by Fariña et al. She also had spicules on the face and *Demodex* within the follicular infundibula. Our patient, just like theirs, even had a polycythaemia vera treated with hydroxyurea, a matter that, except for the possible induction of

parasitic proliferation secondary to immunosuppression, seems not to be related to the cutaneous lesions. However, a biopsy from a close area of apparently healthy skin without spicules also disclosed a heavy presence of mites. Furthermore, treatment with permethrin and metronidazole showed no improvement of the lesions. These facts plus the presence of *Demodex* as an incidental finding in 10% of skin biopsy specimens (4) make us doubtful about the exact role of the mites in the genesis of the spicules.

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## Coexistence of Congenital Linear Punctate Keratoderma and Nevus Depigmentosus with Lentigines: A Case of Twin Spotting?

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Sir,

Punctate keratoderma is an autosomal dominant variant of palmoplantar keratoderma with variable penetrance (1). It usually develops at 12–30 years of age with multiple tiny punctate keratoses over the entire palmoplantar surfaces, beginning mostly from the lateral edge of the digits. Congenital linear punctate keratoderma along Blaschko's line and its association with nevus depigmentosus has never been described. The coexistence of lentigines within nevus depigmentosus is also rare (2). Herein, we describe a patient with congenital linear punctate keratoderma and localized nevus depigmentosus with multiple lentigines of his right palm and forearm since birth.

## CASE REPORT

A 43-year-old man had a streak of tiny asymptomatic hyperkeratotic papules and several variously sized off-white hypopigmented macules and patches along the right palm and forearm since birth. Some brown macules near the hypopigmented lesions were also present. He had no psychomotor or musculoskeletal

abnormalities. There was no family history of similar cutaneous findings or tuberous sclerosis. Physical examination revealed multiple 1–3-mm hyperkeratotic papules in a linear array at the ulnar aspect of right palm and forearm along the Blaschko lines (Fig. 1a). There were also a streak of off-white hypopigmented macules and patches at the right forearm near the antecubital fossa. Some medium to dark brown hyperpigmented macules, measuring 1–5 mm in diameter and irregular in outline, were found near the hypopigmented lesions (Fig. 1b).

Histopathological examination of the punctate keratotic papules from the right palm showed cone-shaped hyperkeratoses invaginating into the dermis (Fig. 2). There was no parakeratosis, acantholysis, or cornoid lamellae in the epidermis. Acrosyringium and squamous syringometaplasia of the eccrine glands were not observed in the immediate vicinity of these lesions. The hypopigmented macules demonstrated a normal melanocyte count and a decreased melanin content within the keratinocytes of the basal layer. The hyperpigmented macules showed an elongated rete ridge pattern and basal hyperpigmentation.

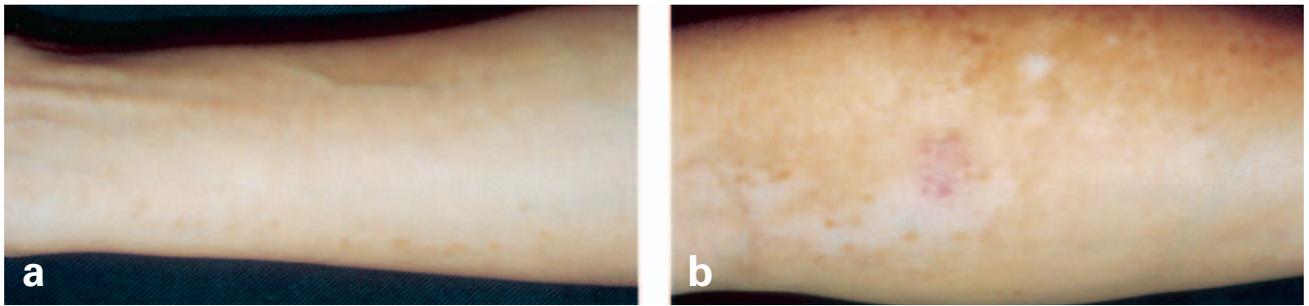


Fig. 1. Multiple 0.1–0.3-cm hyperkeratotic papules in a linear array on the ulnar aspect of the right forearm along the lines of Blaschko (a). Several off-white hypopigmented macules and patches on the right forearm near the antecubital fossa (b). The dark brown hyperpigmented lesions measuring 1–5 mm in diameter were confined to the hypopigmented area with irregular outline.

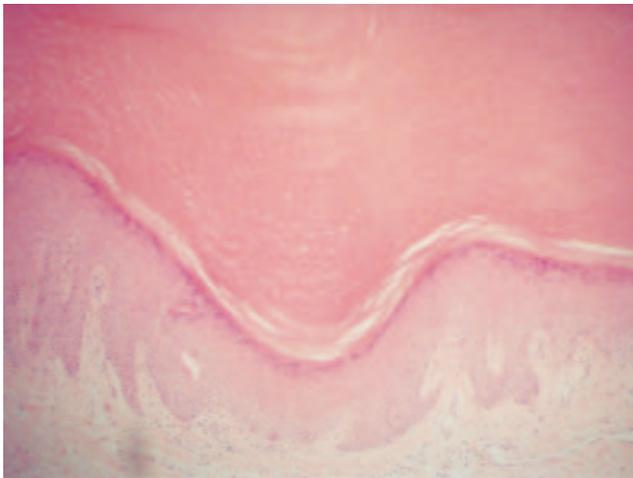


Fig. 2. Cone-shaped hyperkeratoses invaginating into the dermis (biopsy from the right palm). There was no parakeratosis, acantholysis or cornoid lamellae in the epidermis (H&E; original magnification  $\times 200$ ).

## DISCUSSION

The initial diagnosis of these hyperkeratotic papules in our patient was porokeratotic eccrine ostial and dermal duct nevus, but the pathological findings did not reveal any cornoid lamellae on serial sections. Arsenical keratosis was not likely because of negative exposure history. As for the lentiginosities near the hypopigmented lesions, only two previous patients have been reported to develop multiple lentiginosities within nevus depigmentosus (2). The development of lentiginosities to nevus depigmentosus is similar to repigmentation observed within the achromic patches of piebaldism (3).

The association between keratosis and hypo- or hyperpigmentation has been described in three English reports. Boss et al. (4) described a case of palmoplantar punctate keratosis with speckled hyperpigmentation. However, our case differs clinically by the linear arrangement and lack of blistering. Cole (5) and Vignale et al. (6) described patients from a family with disseminated hypopigmented macules on the trunk and limbs with punctate keratosis of the palms and

soles, but our case differs clinically by its localized linear distribution and the presence of lentiginosities.

When considering the coexistence of hypo- and hyperpigmentation with linear punctate keratoderma, the most important differential diagnosis is phacomatosis pigmentokeratotic, characterized by an organoid nevus sebaceous differentiation and a speckled-lentiginous nevus, or other association anomalies. The concept of 'twin spotting', which refers to paired patches of mutant tissue that differ from each other and from the background tissue, was proposed to explain the phenomenon of phacomatosis pigmentovascularis and phacomatosis pigmentokeratotic (7, 8). Congenital hyper- and hypopigmented macules in cutis tricolor as well as paired melanotic and achromic macules occurring in phacomatosis pigmentovascularis had been observed previously and were thought to be unusual examples of twin spotting (9, 10). We consider the congenital lentiginous hyperpigmentation with nevus depigmentosus and linear punctate keratoderma in our patient to be a further example of the twin spotting phenomenon.

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## Eczema Infantum and its Prognosis

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Sir,

Eczematous lesions observed in infants are predominantly considered as atopic dermatitis (AD), seborrhoeic dermatitis (SD), intertrigo, napkin dermatitis or scabies. In contrast, contact dermatitis is rarely seen in early childhood. The clinical appearance of these skin disorders is often non-specific and variable, and an exact diagnosis may be quite difficult.

AD is one of the most common skin diseases of childhood. Onset occurs in 60% of children during the first year of life, and in 85% within the first 5 years (1). The disease is characterized by intense pruritus, generalized dry skin, erythema, and later on by visible flexural dermatitis (1). However, there is a variable individual course (2, 3) and the diagnostic criteria as described by Hanifin & Rajka (3), and Archer & Hanifin (4) may sometimes not be met in very young children.

SD, commonly included in the differential diagnosis of AD, appears mostly within the first 3–18 months after birth (2). It is characterized by an inflammatory skin reaction and yellowish, oily scales especially on the head. In contrast to AD, SD does not affect the well-being of the infant, shows less pruritus and lacks a positive family history for atopy. Some authors have shown a progression of SD in early childhood to AD among 15% of their patients (5). Distinction between these diseases, however, represents a problem in early age (6, 7). Age at onset is not helpful in differentiating SD and AD, as both are common within the first 2–3 months of life.

Both intertrigo and napkin dermatitis show a characteristic body site distribution. Scabies leading to eczema may sometimes be difficult to distinguish from AD (8). The history and the presence of additional symptoms helps to distinguish AD from complex conditions like Wiskott-Aldrich syndrome or ichthyosiform syndromes like Comèl-Netherton syndrome (9).

The term *eczema infantum* has long been used to describe all kinds of eczema observed in early age, when a definite diagnosis is uncertain. The aim of this survey

was to study what happens among infants, when re-evaluated after a diagnosis of eczema infantum was given at first visit.

## PATIENTS AND METHODS

The charts of all patients up to 3 years of age presenting to our department with eczema between 1991 and 1997 were reviewed. After applying common diagnostic criteria for diagnosis of AD (3, 4), SD, and other forms of well recognized eczematous diseases in early childhood, 49 children (29 boys, 20 girls, median age 7 months, range 2–38 months), had a diagnosis of eczema infantum. A follow-up visit of these patients was performed after 4.5 years on average. Each patient was seen by the same dermatologist who assessed a detailed history and physical examination. We established two different groups: children with persisting or recurrent eczema that fulfilled the criteria of AD (3, 4), and children without any signs of skin alteration for the last 4 months. By means of a questionnaire, possible predisposing factors for AD were studied including positive atopic history, living conditions (10), number of siblings, presence of pets at home, breastfeeding, smoking habits at home (parents or others), adverse reactions to food and vaccination status.

Statistical analysis was done using a standard software package (SPSS V.9.0; SPSS GmbH, Munich, Germany). Continuous variables are presented with their medians and comparisons were made by using the U-test (Wilcoxon, Mann and Whitney). Rates and proportions were compared by mean of Fisher's exact test.

## RESULTS

At follow-up, 23 (47%) of the children with eczema infantum showed persistent eczematous symptoms (9 girls, 14 boys; ratio 1:1.6). All cases could be classified as AD according to the aforementioned criteria and were assigned to group 1. Nine (18%) of the children had no symptoms at follow-up but the parents reported recurrent eczema compatible with a diagnosis of AD and these children were also classified in group 1. The remaining 17 children (35%; 8 girls, 9 boys; ratio 1:1.12) had been free of eczema for at least the last 4 months (group 2). Table I shows demographic and anamnestic data of the patients.

The onset of eczema was slightly earlier in group 1,

Table 1. History, demographic and environmental characteristics of the patients in group 1 (atopic dermatitis at the time of follow-up) and group 2 (disappearance of eczema at the time of follow-up)

Parameter	Group 1 (n=32)	Group 2 (n=17)
Gender (M/F)	21/11	8/9
Median age of onset of eczema (range)	2 months (0.2–12.0)	3 months (0.2–11.0)
Family history		
atopic dermatitis (%)	16 (50)	6 (35)
allergic rhinitis (%)	15 (47)	4 (24)
asthma (%)	13 (41)	2 (12)
Patient's history		
allergic rhinitis (%)	9 (28)	3 (18)
age at onset	4.6 years	8 years
asthma (%)	7 (22)	1 (6)
age of onset	4.9 years	6 years
First-born children (%)	15 (48)	3 (17)*
At least one older sibling (%)	9 (28)	9 (53)*
Place of residence		
rural (%)	11 (34)	11 (65)
urban (%)	21 (66)	6 (35)*
Keeping pets		
no (%)	28 (88)	16 (94)
yes (%)	4 (13)	1 (6)
Smoking at home		
no (%)	23 (72)	12 (71)
yes (%)	9 (28)	5 (29)
Breastfeeding		
no (%)	8 (28)	6 (38)
≥6 months (%)	13 (45)	4 (25)

\* $p < 0.05$ .

with a median of 2 months as compared with 3 months for group 2. The clinical appearance of eczema was similar in both groups, mainly represented by diffuse erythematous rashes with mild scaling. However, children in group 2 with absence of eczema at re-evaluation were more likely to have involvement of the diaper area ( $p < 0.05$ ) and axillae ( $p < 0.05$ ), but had never had eczema on wrists, ankles, back of the hands, neck, earlobe or anterior chest like patients in group 1. Facial involvement was common in both groups (52–53% in group 2). Parents in group 1 reported a much higher incidence of pruritus in their children (58% vs 12% in group 2;  $p < 0.01$ ).

A positive family history for atopic diseases was more frequent in group 1 vs group 2: 50% vs 35% for AD, 47% vs 24% for allergic rhinitis, and 41% vs 12% for asthma ( $p < 0.05$ ). At the time of re-examination there was a higher percentage of children in group 1 who had developed allergic rhinitis and asthma as compared with group 2 (29% vs 18%, 23% vs 6%, respectively;  $p > 0.05$ ). Adverse reactions to food were similarly reported in both groups (29% vs 30%).

Children in group 1 were significantly more often first-born children (48% vs 17%;  $p < 0.05$ ) and 66% of patients in group 1 grew up in an urban area as compared with 35% of

children in group 2 ( $p < 0.05$ ). In both groups, only a minority of families kept pets (13% vs 6%;  $p > 0.05$ ). The smoking habits at home (parents and others) and vaccination status (tuberculosis, measles, mumps, rubella, *Haemophilus influenzae b*) of the children were similar in both groups. Exclusive breastfeeding was performed for a longer period of time in group 1 (median 5.0 months) than in group 2 (median 2.0 months). Also, more mothers in group 1 had breastfed their children for at least 6 months (45% vs 25%).

## DISCUSSION

Two-thirds of our patients first diagnosed with eczema infantum had developed AD at follow-up. In these cases, eczema infantum indeed appeared to be an early, yet non-specific manifestation of AD.

At the time of the follow-up, one-third of the children did not show eczema any more. In these infants the aetiology of eczema remains unknown without a further classification. The diagnosis eczema infantum can be used as a working diagnosis to describe eczema of unknown origin in infants until the course of the disease allows a definite diagnosis such as AD.

The follow-up examination revealed that the children with AD (persistent and recurrent; group 1) expressed multiple skin alterations accompanied by pruritus, erosions and excoriations. On their first visit children in group 2 had skin changes in areas not normally affected by infantile AD, e.g. in the area covered by the diaper or the axillae. The morphological skin changes with white pityriasisiform scales on erythema argue against the diagnosis of SD, as well as the body site distribution.

Our environmental and lifestyle findings are in line with the hygiene hypothesis (10–12). In group 2 with disappearance of eczema infantum at follow-up, there were significantly more children with one or more older siblings than in group 1. In addition, significantly more children in group 2 grew up in a rural area. However, the predictive value of these factors needs further evaluation.

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## Leukaemia Cutis Developing in a Pressure Ulcer

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Sir,

Leukaemia cutis is an infiltration of systemic leukaemia to the skin. Cutaneous manifestations may be concomitant with or precede the diagnosis of systemic leukaemia, suggesting that a precise diagnosis of leukaemia cutis may facilitate the subsequent therapeutic schedule. In general, leukaemia cutis has no specific predisposition in terms of the site of involvement (1). On the other hand, there are reports of cutaneous infiltrations in skin scars (2, 3). We report a case of leukaemia cutis that occurred in a pressure ulcer without any other cutaneous involvement.

### CASE REPORT

In February 1998, a 10-year-old boy developed cough associated with pancytopenia, i.e. white blood cell count  $1200/\text{mm}^3$ , haemoglobin 5.1 g/dl and platelet count  $17\,000/\text{mm}^3$ . Results of his bone marrow biopsy showed hypocellularity with multinuclear erythrocytes, micromegakaryocytes and hypogranular neutrophils compatible with the diagnosis of myelodysplastic syndrome (MDS). In September 1998, he developed high grade fever and leukocytosis with a white blood cell count of  $9900/\text{mm}^3$ , including 28% blast cells. Bone marrow aspiration revealed hypocellularity of which 34.4% of the cells consisted of myeloblasts and monoblasts. In the immunohistochemical examination, the blast cells were positive for CD11b, CD13, CD33, CD34 and HLA-DR. We made a diagnosis of transformation from MDS to acute myelomonocytic leukaemia. The patient received chemotherapy composed of cytarabine, mercaptopurine, vincristine and prednisolone. During the therapy, he developed respiratory failure and disseminated intravascular coagulation syndrome, and his immobility resulted in a pressure ulcer on his right heel in October 1998. The ulcer was covered with blackish necrotic material that reached the subcutis. We removed this thick necrosis surgically to prevent secondary infections. One month after debridement, a granuloma-like nodule suddenly

appeared within the ulcer, and gradually increased in size. It exhibited a 2-cm diameter, scarlet, dome-shaped granulomatous lesion covered with haemorrhaged blood (Fig. 1). The peripheral blood showed no blast cells at this time.

Suspecting the possibility of pyogenic granuloma, we performed skin biopsy. The biopsy specimen revealed a dense mononuclear cell infiltration in the epidermal defect. The infiltrating cells were characterized by large atypical nuclei, each with a narrow pale eosinophilic cytoplasm. Immunohistochemistry examination demonstrated that the infiltrating cells were negative for CD3, L26 and CD68, while they were partially positive for leukocyte common antigen, neutrophilic elastase and esterase. Although he was treated with a different chemotherapeutic regimen, he died in March 1999.

### DISCUSSION

Leukaemia cutis is relatively uncommon, reported in 3.1% of patients with all types of leukaemia (4). Among



Fig. 1. A 2-cm diameter, scarlet, dome-shaped granulomatous lesion covered with haemorrhaged blood on the patient's right heel.

them, both acute monocytic leukaemia and acute myelomonocytic leukaemia have a higher incidence of leukaemia cutis, reported to be 33% and 13–18%, respectively (4). Usually, cutaneous involvement occurs late in the disease during periods of uncontrolled leukaemia. However, it is not rare for leukaemia cutis to occur preceding the diagnosis of systemic leukaemia in acute monocytic leukaemia and acute myelomonocytic leukaemia (1, 5–8). In addition, recurrence of a cutaneous manifestation sometimes precedes that of the blood condition during the therapy. In our case, peripheral blood examination did not show the presence of blast cells at the time of the diagnosis of leukaemia cutis. These characteristics of leukaemia cutis suggest that careful cutaneous examination is important for making the diagnosis and determining an early relapse of leukaemia.

In our case, it is of note that the cutaneous infiltration appeared at the site of a pressure sore showing epidermal necrosis on the right heel. At first, the skin ulcer was not accompanied by any tumour, but later a haemorrhagic nodule developed there, and the histological changes were compatible with those of leukaemia cutis. In fact, we first suspected the possibility that a leukaemic infiltration might have directly produced the skin ulcer irrespective of the pressure sore. However, at the time of debridement the tissue damage reached to the subcutis at the skin ulcer without any macroscopic sign implying a leukaemic infiltration. Thus, we concluded that the cutaneous manifestation resulted from leukaemia cells attracted to the pressure ulcer rather than from those cells appearing initially in the skin. In general, leukaemia cutis involves multiple locations of the skin with no specific predilection in terms of the site of involvement (1). However, leukaemia cutis has been described to

have a predilection for scars, including those resulting from surgery, trauma, burns, excoriation, herpes simplex and herpes zoster (2, 3). In such cases, the production of chemical mediators has been proposed to act as an attractant for leukaemic cells to the skin scars. Monocytic leukaemia cells are unique populations prone to respond to such mediators from the skin. In the present case, it is likely that the cutaneous wound released abundant mediators such as IL-1, GM-CSF, FGF and TGF- $\beta$  that contributed to the recruitment of leukaemic cells from the peripheral blood.

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## An Atypical Presentation of Lymphomatoid Papulosis

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Sir,

Lymphomatoid papulosis (LP) is a chronic lymphoproliferative skin disorder characterized by a benign clinical course, yet histologic features of a malignant lymphoid infiltrate (1). However, in 10–20% of cases and even more it can precede, coexist with or follow malignant lymphoma (2, 3). We present here a unique clinical manifestation with the appearance of deep, punched out ulcers resembling a crater. To our knowledge, this is the first published case of such a manifestation.

## CASE REPORT

A 35-year-old man presented with a 5-month history of a widespread eruption of erythematous ulcerated papules and plaques. The patient denied systemic fever, loss of weight or night sweats. He was treated with topical and systemic antibiotics without any improvement. Except for hypothyroidism after thyroidectomy, which was treated for 20 years with thyroxin, he was healthy.

Examination of his skin revealed erythematous

papules and plaques (up to 5 cm in diameter), some with pink-brown scales, some with an ulcerated centre covered with a brown-black crust over his trunk and limbs. Circular ulcers with a diameter of 1–4 cm, a depth of 2 cm with annular erythematous borders and a depressed necrotic centre, covered with a brown-black crust were notable on his chin, left cheek and left lateral eyelid (Fig. 1).

Laboratory tests for mycobacteria, fungi, leishmaniasis, HIV, and syphilis were all negative or within the normal limits. Three punch skin biopsies revealed a mononuclear, band-like and deep, mostly interstitial infiltrate of lymphocytes, some small and some atypical, with exocytosis of lymphocytes to the epidermis. Only few eosinophils and neutrophils were present. The horny layer was densely packed with focal parakeratosis. Vacuolar degeneration in the basal layer and mild spongiosis were noted in the epidermis. Immunohistochemical stains were positive for CD3, negative for CD30 and only weakly positive for CD20. Based on these results a diagnosis of LP type B and C was made. T-cell receptor gene re-arrangement, done on a skin biopsy specimen, was positive for V $\gamma$ 2G10.

A biopsy of an enlarged inguinal lymph node was compatible with dermatopathic adenopathy. Imaging modalities showed no evidence of malignancy. The patient was started on phototherapy (ultraviolet B, three times a week) and over a period of a few weeks a marked regression of his eruption occurred, with the development of depressed scars in his facial lesions. The patient was advised to be followed up by a haematologist due to his lymphadenopathy.

## DISCUSSION

LP is characterized clinically by recurrent erythematous papular or nodular lesions which occur classically on the trunk and extremities, but have also been noted on the palms, soles, face, scalp and anogenital area. Lesions tend to appear in crops, grow rapidly within days to weeks and develop ulcerated necrotic centres. Spontaneous healing occurs with the development of fine atrophic hyperpigmented or hypopigmented circular scars (4, 5).

Histologically there is an infiltrate of atypical lymphocytes. Three major histologic types have been described, designated as A, B and C. Type A is characterized by a wedge-shaped infiltrate of pleomorphic histiocyte-like cells, resembling Reed-Sternberg cells. These cells express one or more T-cell antigens as well as lymphoid activation antigen CD30 and are embedded in a dense inflammatory background. Type B is composed of smaller CD30



Fig. 1. The facial ulcers following spontaneous shedding of the central crust, showing a crater-like appearance.

negative lymphocytes with cerebriform nuclei showing epidermotropism, classically resembling mycosis fungoides. In type C there are large monotonous atypical cells, positive for CD30 as in type A, but without the inflammatory background (2).

Necrotic ulcers usually develop in the centre of the papules or nodules of LP, yet our patient exhibited a unique clinical manifestation. His facial lesions evolved into deep ulcerated craters with a punched-out appearance. These bizarre-looking lesions expanded the differential diagnosis; however, the typical clinical morphology of the eruption on the trunk and limbs and the histopathology confirmed the diagnosis of LP.

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## Skin Necrosis after Injection of PEG-Interferon $\alpha 2b$ in an HCV-infected Patient

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Sir,

Skin necrosis is a rare complication following subcutaneous injection of interferon (INF)  $\alpha 2a$ ,  $\alpha 2b$  or  $\beta 1b$ . Pegylated interferon (PEG-INF) is a new formulation of recombinant human INF conjugated with polyethylene glycol which increases the half-life of INF, allowing patients to receive weekly injections. We report the case of a hepatitis C virus (HCV)-infected patient without human immunodeficiency virus (HIV) who developed aseptic skin necrosis following an injection of PEG-INF.

### CASE REPORT

A 50-year-old man with chronic HCV infection (genotype 1b, a high viral load of 1,200,000 UI/ml, and liver biopsy yielding a Knodell's score of 11) had been followed in the department since May 2001. The patient smoked and took no medications. Combination treatment with PEG-INF  $\alpha 2b$  (1.5  $\mu\text{g}/\text{kg}$  once weekly) associated with ribavirin (1000 mg daily) was initiated. After 9 months of treatment without complications, he developed a painful, erythematous, indurated skin lesion at the injection site on his right arm. The lesion progressed over a period of several days, forming a deep, necrotic ulcer, 6  $\times$  4 cm in diameter, with fever and severe pain (Fig. 1). Punch biopsies of the lesion showed a leucocytoclastic vasculitis and epidermal necrosis. Coagulation function tests including various tests for antiphospholipid antibodies, deficiencies in protein C, protein S or antithrombin III, activated



Fig. 1. Indurated and necrotic skin lesion at the injection site on the right arm.

protein C resistance, factor V Q506 mutation and prothrombin 20210G/A were all normal or negative.

With local treatment and systemic antibiotics the lesion healed slowly in 3 months. The subcutaneous injections of PEG-INF were pursued without dose adjustment at other injection sites; no further complications were noted.

### DISCUSSION

Skin reactions due to unmodified alpha-interferon represent 5–12% of all adverse effects, including alopecia, exacerbation of herpes labialis and autoimmune skin disorders, and rare, but well known, injection site skin ulceration.

Local skin reactions at PEG-INF injection sites occur more frequently than those with unmodified interferon, i.e. 58% for PEG-INF  $\alpha 2b$  versus 36% for INF  $\alpha 2b$  (1), and 31% with PEG-INF  $\alpha 2a$  versus 14% with INF  $\alpha 2a$  (2). Despite the thousands of patients treated with PEG-INF worldwide, only two cases of skin necrosis have been reported previously, and concerned non-HCV-infected patients. The first case involved a patient with a melanoma who received very high doses (6  $\mu\text{g}/\text{kg}$  of PEG-INF  $\alpha 2b$  once weekly) (3). The other case occurred in an HIV-infected patient who received 1.5  $\mu\text{g}/\text{kg}$  of PEG-INF  $\alpha 2b$  once weekly in a prospective pilot study to treat his HIV infection (4).

The pathogenesis of PEG-INF-induced skin necrosis is still unknown. Several hypotheses have been proposed for unmodified INF: intra-arteriolar injection, coumarin-like necrosis, procoagulant activity of INF combined with inherited prothrombotic states, and Arthus' phenomenon (5). In addition, the specific pharmacological properties of PEG-INF, especially its high local concentration level, may account for the increased risk of skin reactions. One would expect the rate of skin necrosis to be increased, but fortunately, in practice, it seems to remain a rare adverse effect. Furthermore, as observed with unmodified INF, PEG-INF injections can be repeated at other sites without further complications.

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