LETTERS

Psoriasis and Brooke–Spiegler syndrome with multiple malignancies

To the Editor

A coincidence of cylindroma and trichoepithelioma was described first by Friboes in 1912. The disease was named Brooke–Spiegler syndrome or familial autosomal dominant cylindromatosis (MacKusick catalogue, 123850, 313100; OMIM numbers 123850, 132700, 313100 and 605041).[1,2]

A 72-year old Caucasian man was referred to our dermatology department because of a relapse of his long-standing psoriasis, which had been treated repeatedly by the modified Ingram scheme. He had a history of multiple cylindromas and spiradenomas of the scalp and trunk. Trichoepitheliomas on the face, shoulder and trunk were surgically removed. In 1996 a malignant cylindroma of the scalp was operated on. In the same year multifocally growing basal cell adenocarcinomas of both parotid glands were diagnosed and treated by combined surgery and radiotherapy.

On examination, he presented with large disseminated erythematosquamous plaques, Fitzpatrick skin type II–III. On the trunk, multiple skin-coloured to reddish papules and nodules were found. Small yellowish papules were seen in the nasolabial fold and retroauricular. An exophytic nodule (3 cm diameter) on the right flank was removed by surgery. Histological examination revealed a cystic skin tumour with adnexal differentiation. We found atypical enlarged cells with prominent nuclei, partially irregular nuclear shapes and increased ductal proliferation. Focally, there was a squamous differentiation with infiltrative growth into the hyalinized and sclerotic connective tissue (fig. 1). The diagnosis of spiradenoma with malignant transformation was made. We investigated p53 expression using pronase-digested specimen. The tumour expressed p53 as shown in fig. 2. Chest X-ray and ultrasound investigation of the abdomen and lymph nodes did not provide any evidence of metastatic spread.

The combination of cylindroma(s) with trichoepithelioma(s) is characteristic for the Brooke–Spiegler syndrome. Less often, spiradenomas develop.[1,2] Malignant transformation of sweat gland tumours of skin is rare. We found only 31 cases of malignant cylindroma[2–5] and 16 cases of malignant spiradenoma[2,6–8] reported in the literature. To the best of our knowledge, malignant transformation of a spiradenoma has not been reported before in Brooke–Spiegler syndrome.

The involvement of the parotid gland has occasionally been observed.[2] Basal cell adenomas are the most frequent parotid tumours in association with Brooke–Spiegler syndrome, but adenocarcinomas may also develop as in the present case.

The occurrence of several malignancies in the same patient is remarkable. Based on investigative studies in skin adnexal tumours and parotid gland tumours, p53 overexpression occurs in about two-thirds of specimens.[9,10] It was assumed that UV light may play a role in the development of sweat gland carcinomas.[9] Indeed, the present patient was repeatedly exposed to UV irradiation because of his coincident psoriasis. On the other hand, we have demonstrated that the tumour expressed p53 (fig. 2). UV-therapy of psoriasis may be considered a risk factor for malignant transformation of adnexal skin tumours in Brooke–Spiegler syndrome.

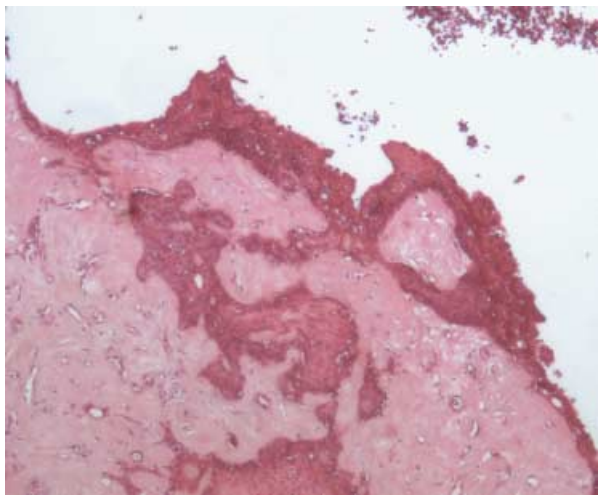


fig. 1 Histopathology of malignant spiradenoma: focally squamous differentiation with infiltrative growth into the hyalinized and sclerotic connective tissue (haematoxylin–eosin stain).

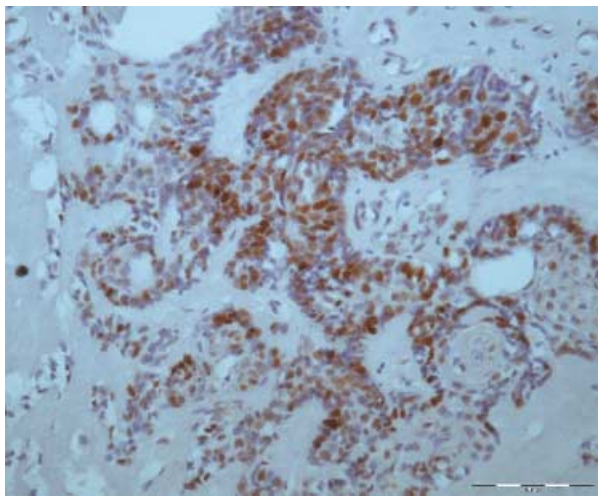


fig. 2 p53 expression in malignant spiradenoma (immunoperoxidase staining).

E Köstler,*† J Schönlebe,‡ T Mentzel,§ G Haroske,‡ U Wollina†

*†Department of Dermatology and ‡Institute of Pathology 'Georg Schmorl', Hospital Dresden-Friedrichstadt 41, 01067 Dresden, Germany, and §Dermatopathology Laboratory Hügel-Kutzner-Rütten-Mentzel-Hantschke, Friedrichshafen, Germany. *Corresponding author, tel. +49 351 480 1210; fax +49 351 480 1219; E-mail: Koestler-Er@khdf.de*

References

1 Friboes W. *Beitrag zur Klinik und Histopathologie der gutartigen Hautepitheliome*. S. Karger-Verlag, Berlin, 1912.
2 Kleine-Natrop HE. Simultaneous generalization of benign basalioma of both Spiegler and Brooke types. *Arch Klin Exp Dermatol* 1959; **209**: 45–55.
3 Volter C, Baier G, Schwager K *et al.* Cylindrocarcinoma in a patient with Brooke-Spiegler syndrome. *Laryngorhinootologie* 2002; **81**: 243–246.
4 Durani BK, Kurzen H, Jaeckel A *et al.* Malignant transformation of multiple dermal cylindromas. *Br J Dermatol* 2001; **145**: 653–656.
5 Pizinger K, Michal M. Malignant cylindroma in Brooke–Spiegler syndrome. *Dermatology* 2000; **201**: 255–257.
6 McKee PH, Fletcher CD, Stavrino P, Pambakian H. Carcinosarcoma arising in eccrine spiradenoma. *Am J Dermatopathol* 1990; **12**: 335–343.
7 Grouls V, Iwaszkiewicz J, Berndt R. Malignes ekkrines Spiradenom. *Z Hautkr* 1991; **66**: 892–895.
8 Meriggi F, Tagliabo R, Morone G *et al.* The potential malignancy of eccrine spiradenoma. *Ital J Surg Sci* 1989; **19**: 265–268.
9 Biernat W, Peraud A, Wozniak L, Ohgaki H. P53 mutations in sweat gland carcinomas. *Int J Cancer* 1998; **76**: 317–320.
10 Mutoh H, Nagata H, Ohno K *et al.* Analysis of the p53 gene in parotid gland cancers: a relatively high frequency of mutations in low-grade mucoepidermoid carcinomas. *Int J Oncol* 2001; **18**: 781–786.

DOI: 10.1111/j.1468-3083.2005.01037.x

Cutaneous necrosis during paroxysmal nocturnal haemoglobinuria: role of parvovirus B19?

To the Editor

We report the case of a 70-year-old woman hospitalized in January 2001 for the treatment of diffuse cutaneous necrosis. She had a past history of myelodysplastic syndrome since 1988, treated with prednisone and transfusions of red blood cells.

Twenty-four hours earlier, she had presented with a pseudo-influenza syndrome followed by necrosis of the ear lobes (fig. 1) and necrotic plaques involving the whole of the tegument, and 39.6 °C fever.

Laboratory analyses revealed anaemia (haemoglobin was 7 g/dL) and a platelet count of 30 g/L. The Coombs' test was negative. The remainder of the analysis eliminated disseminated intravascular coagulation, cryoglobulinaemia and a primary antiphospholipid antibody syndrome. Cold agglutinin titre was also negative.

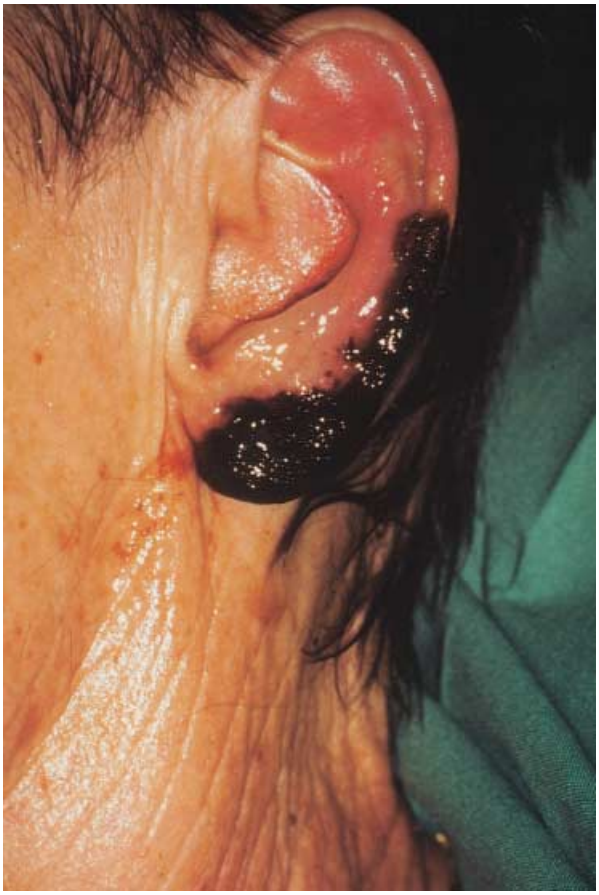


fig. 1 Necrosis of the ear lobes in a 70-year-old woman hospitalized for the treatment of diffuse cutaneous necrosis.

Bacteriological cultures and virus serologies remain negative except for parvovirus B19. Indeed, serology for parvovirus B9 showed acute infection (parvovirus B19 IgM was positive, whereas parvovirus B19 IgG was initially negative and later became positive) and there was presence of viral DNA on polymerase chain reaction (PCR) in serum.

Cutaneous histology revealed thrombosis of the capillaries of the superficial and median dermis with thrombotic and necrotic vascularitis and vascular deposits of A, M and C3 immunoglobulin under direct immunofluorescence.

Corticosteroid therapy was initiated at the dose of 1 mg/kg, the patient's fever disappeared, the skin lesions improved and, despite the loss of the ear lobes, the patient's general state improved.

In June 2001, 6 months later, the patient was again hospitalized because of haemolytic anaemia (haemoglobin was 6 g/dL, reticulocytes were 273 g/L), there was lowered haptoglobin and increased lactic dehydrogenase levels at 8180 IU/L (normal

210–400 IU/L). For the first time during her blood disease, she had haemoglobinuria. There was no new cutaneous lesions. The acid haemolysis test (Ham–Dacie test), not performed before, was positive and there was a deficiency of proteins attached to the cell membrane by a phosphatidylinositol link (CD55 and CD59), measured by flow cytometry, which confirmed the diagnosis of paroxysmal nocturnal haemoglobinuria (PNH), 13 years after pancytopenia had first been demonstrated.

Cutaneous lesions during PNH are known, but rare, and are manifested by petechias, leg ulcers and haemorrhagic bullae becoming necrotic and predominantly involving the soles of the feet, the toes, the tip of the nose and the ears.[1] Corticosteroids appear to be the treatment of choice for such lesions.[2] Skin histology showing thrombosis of the dermal vessels, reveals the thrombotic tendency of these patients, in whom venous, peripheral or central thromboses are the principal complications. The pathogenesis is uncertain, but the increase in platelet aggregability during this disease could be one explanation.[3]

The infections are described as inducing attacks in PNH.[4] In our case, a parvovirus B19 primo-infection appears to have been at the origin of the haemolysis.

In adults, symptomatic parvovirus B19 primo-infection may include an influenzae-like syndrome concomitant to various cutaneous signs, such as classical 'gloves and socks' purpura or other types of vasculitis giving an image of necrosing leucocytoclastic vascularitis[5] on cutaneous histology, but without thrombosis.

With regard to haematology, this is responsible for acute episodes or erythroblastopenia in patients suffering from corpuscle haemolysis[6] as is the case in our patient.

This study is interesting as it suggests a relationship between parvovirus B19 and the occurrence of haemolytic attack in PNH, and in the development of cutaneous necrosis during this disease. We propose that parvovirus B19 serology be conducted when confronted with cutaneous necrosis in patients suffering from PNH, as this was never done in the observations reported earlier.

C Cholez,† JL Schmutz,*† C Hulin,‡ JY Hesse,† A Barbaud†

†Departments of Dermatology and ‡Hematology, Centre Hospitalier Universitaire, 36, quai de la bataille, Nancy 54000, France.
**Corresponding author, tel. +33 (0)3 83 85 24 65; fax +33(0)3 83 85 24 12; E-mail: jl.schmutz@chu-nancy.fr*

References

1 Rietschel RL, Lewis CW, Simmons RA *et al.* Skin lesions in paroxysmal nocturnal hemoglobinuria. *Arch Dermatol* 1978; **114**: 560–563.
2 Issaragrisil S, Piankijagum A, Tang-Naitrisorana Y. Corticosteroids therapy in paroxysmal nocturnal hemoglobinuria. *Am J Hematol* 1987; **25**: 77–83.
3 Peytremann R, Rhodes RS, Hartmann RC. Thrombosis in paroxysmal nocturnal hemoglobinuria (PNH) with particular reference to progressive, diffuse hepatic venous thrombosis. *Ser Haematol* 1972; **5**: 115–136.
4 Manchester RC. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria. *Ann Intern Med* 1945; **23**: 935–944.
5 Levesque H, Marie I. Infection and vascular purpura. *J Mal Vasc* 1999; **24**: 177–182.
6 Harris JW. Parvovirus B19 for the hematologist. *Am J Hematol* 1992; **39**: 119–130.

DOI: 10.1111/j.1468-3083.2005.01061.x

Sweet's syndrome and polycythaemia vera

To the Editor

Sweet's syndrome (SS) is thought to be a hypersensitivity reaction characterized by the sudden onset of tender, dark red or purple, raised skin plaques that usually occur on the face, neck, chest and limbs, accompanied by fever, malaise and neutrophilic leucocytosis.[1] The disease may be linked to haematological cancers such as acute myelomonocytic leukaemia.[2,3] We report an uncommon case of SS associated with polycythaemia vera (PV). A 63-year-old female complained of a 2-week history of fever (38.5 °C), malaise, anorexia and weight loss, as well as a skin rash located on her upper back and legs. Her medical history included three outbreaks of SS in the past 14 years (in 1989, 1991 and 1999), all of them diagnosed in our department, that responded to treatment with oral corticosteroids, malignancy having been ruled out. Skin examination showed a symmetrical asymptomatic eruption of reddish blue, firm and confluent papules and plaques of varying size on her upper back (fig. 1) and firm red nodules on her legs, particularly on the ankles and pretibial aspects. No lymphadenopathy or splenomegaly was found in a physical examination. The laboratory findings revealed a white blood cell count of $12.6 \times 10^3/\mu L$ with 73%

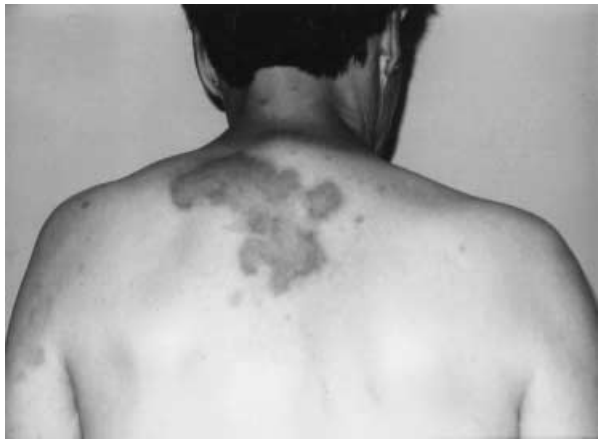


fig. 1 Reddish blue, firm and confluent papules and plaques of varying size affecting the dorsal back.

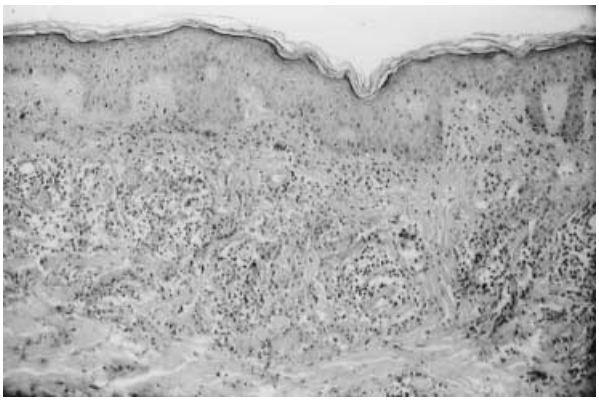


fig. 2 Normal epidermis, intense neutrophilic infiltrate in the upper and middermis and leucocytoclasis (haematoxylin–eosin stain; original magnification × 100).

segmented forms. Her haemoglobin concentration was 17.8 g/dL (haematocrit 52.8%), total red blood cell volume 38.9 mL/kg, and thrombocyte count $47.6 \times 10^4/\mu L$. The erythrocyte sedimentation rate was 1 mm/h. Bone marrow examination showed triline age hyperplasia. An abdominal ultrasonogram revealed homogeneous splenomegaly. A chest X-ray was normal. Histopathological examination of skin biopsy specimens of the back and leg showed an intense papillary and middermal infiltrate of polymorphonuclear leucocytes with leucocytoclasis, but vasculitic changes were absent (fig. 2). After a diagnosis of PV and SS, the patient was treated with prednisone, 30 mg/day, tapering at 10 days, and healing occurred without scarring within 4 weeks. The haematological disease was treated later with oral hydroxyurea, 500 mg/day. At the 2-year follow-up, no evidence of leukaemic conversion was found.

A variety of conditions have been clearly linked to SS including malignancies in about 20% of published cases,[4,5] most commonly haematological cancers, and particularly acute myeloblastic leukaemia.[3,4] In cases associated with underlying malignancy, males are affected as frequently as females, fever is usually but not invariably present, while neutrophilia may be absent. These cases may also have anaemia, cytopenias, more severe cutaneous manifestation, oral mucous membrane participation and extracutaneous involvement.[2–5] To the best of our knowledge, six cases of SS associated with PV have been reported so far.[5–10] In five cases, PV preceded the onset of SS by many years. In the sixth patient, as in ours, the cutaneous lesions occurred intermittently for years (range 4–13 years) prior to the onset of the haematological disorder.[7] Progression to myelofibrosis was reported in two cases[6,7] and an acute myelogenous blast crisis occurred in one patient,[9] whereas in three patients[5,8,10] no progression or transformation to more aggressive stages took place. Furukuwa *et al.*[8] suggest that the association of SS and PV may be analogous to that of pyoderma gangrenosum and PV. Therefore, patients with SS or pyoderma gangrenosum and PV should be carefully followed up, as the disorder may be related to myeloid transformation or frank leukaemia.[5,7–8] Association of neutrophilic dermatosis and PV seems to worsen the prognosis of the last one. We report a new case of SS heralding the onset of PV. The appearance of skin lesions typical of SS should prompt investigation for underlying malignancy, particularly haematological, and patients with an established myeloproliferative disorder should be carefully followed up in order to rule out a leukaemic conversion.

M Gómez Vázquez,* D Sánchez-Aguilar, C Peteiro, J Toribio

*Departamento de Dermatología, Facultad de Medicina, C/San Francisco, s/n, 15872 Santiago de Compostela, Spain. *Corresponding author, fax +34 981547094; E-mail: mejaime@usc.es*

References

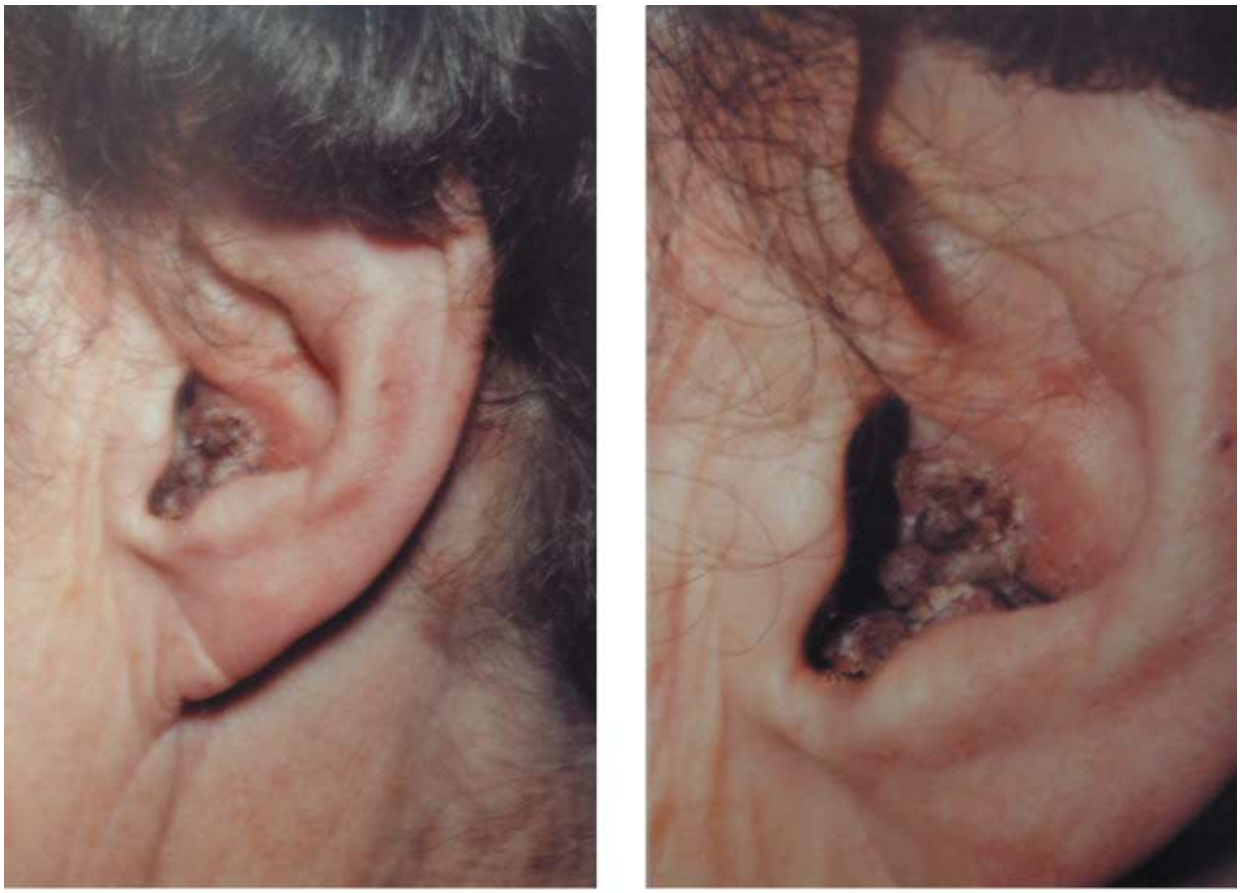
1 Sweet RD. An acute febrile neutrophilic dermatosis. *Br J Dermatol* 1964; **76**: 349–356.
2 Cohen PhR, Talpaz M, Kurzrock R. Malignancy associated Sweet's syndrome: review of the world literature. *J Clin Oncol* 1988; **6**: 1887–1897.
3 Sharma PK, Schwartz RA, Janniger CK *et al.* Sweet's syndrome with acute leukemia. *Cutis* 1991; **47**: 249–252.
4 Cooper PH, Innes DJ, Greer KE. Acute febrile neutrophilic dermatosis (Sweet's syndrome) and myeloproliferative disorders. *Cancer* 1983; **51**: 1518–1526.
5 Wong GAE, Guerin DM, Parslew R. Sweet's syndrome and polycythaemia rubra vera. *Clin Exp Dermatol* 2000; **25**: 296–298.
6 Singh M, Kaur S. Sweet's syndrome and polycythaemia vera. *Br Med J* 1985; **291**: 1542.
7 Grob JJ, Mege JL, Prax AM, Bonerandi JJ. Disseminated pustular dermatosis in polycythaemia vera. *J Am Acad Dermatol* 1988; **18**: 1212–1218.
8 Furukawa T, Takahashi M, Shimada H *et al.* Polycythaemia vera with Sweet's syndrome. *Clin Lab Haematol* 1989; **11**: 67–70.
9 Horan MP, Redmond J, Gehle D *et al.* Postpolycythemic myeloid metaplasia, Sweet's syndrome and acute myeloid leukemia. *J Am Acad Dermatol* 1987; **16**: 458–462.
10 Cox NH, Leggat H. Sweet's syndrome associated with polycythaemia rubra vera. *J Am Acad Dermatol* 1990; **23**: 1171–1172.

DOI: 10.1111/j.1468-3083.2005.01091.x

An unusual presentation of a common skin pathology at an uncommon site

To the Editor

An 81-year-old female was referred by her general practitioner to the plastic surgery outpatient clinic with a 5-month history of a growth in the left ear. The growth had been



a b

fig. 1 (a) Growth within the concha of left ear. (b) Magnification showing its pigmented, raised, papular appearance.

increasing in size for the past 2 months and was a cause of concern for the patient. There was no past medical or family history of note, and there had been no previous surgery around the left auricular area. On examination, there was an area of skin measuring 2×2.5 cm within the left concha with multiple papular, nodular and pigmented lesions extending into the external auditory meatus. This growth was of skin origin and freely mobile over the underlying cartilage (fig. 1). There were no palpable regional lymph nodes. An incisional biopsy was carried out, the results of which were inconclusive. A decision was made to perform an excisional biopsy of the lesion with split skin graft to cover the defect. This was in view of the short history and the diagnostic difficulty in excluding underlying skin malignancy. Histopathological examination showed features of irritated seborrhoeic keratosis with no evidence of malignancy.

Different types of benign and malignant neoplasms are known to originate from the skin. Benign tumours can originate from the epidermis, hair follicles, sebaceous glands and sweat glands. Examples include seborrhoeic keratosis, keratoacanthoma, adenomas and papillomas among others. Clinically, benign tumours are either slow growing or static, whereas malignant tumours of the skin usually increase in size with time and have a tendency to invade surrounding tissues. Common skin cancers include basal and squamous cell carcinomas, malignant melanoma, adnexal tumours and Kaposi's sarcoma. A number of premalignant conditions of the skin are also known to undergo malignant change if left untreated, such as solar keratosis and Bowen's disease.

Seborrhoeic keratosis is one of the most common benign neoplasms of the skin in adults. However, it rarely occurs on the ear. Many factors have been suggested in the aetiology of this disease, such as ultraviolet light exposure, human papillomavirus infection, hereditary factors, action of oestrogen and other sex hormones.[1] The majority of clinically diagnosed seborrhoeic keratoses are left untreated.

However, when diagnosis is in doubt material should be taken for histological examination. Current methods include shave biopsy and sharp curettage. In the above patient excision biopsy was performed to exclude underlying skin malignancy such as basal cell carcinoma, squamous cell carcinoma, etc. and to obtain a histopathological diagnosis as this lesion had a short history of rapid growth at an atypical site. Such a presentation is not typical for a seborrhoeic keratosis as these are usually slow growing and more common on areas of the skin exposed to sun.

Clinically apparent seborrhoeic keratoses are known to mimic skin neoplasms[1,2] and the possibility of an association between the two cannot be ruled out.[1] Indeed there have been reports of malignant transformation occurring in seborrhoeic keratosis.[3,4] Previous reports of auricular seborrhoeic keratoses have described functional and diagnostic problems.[5–7] Our patient had an unusual presentation of a fast-growing, atypical-looking lesion of the concha of the ear. An inconclusive incisional biopsy necessitated the need for an excision biopsy, which to our surprise showed seborrhoeic keratosis. Seborrhoeic keratosis of the concha of the ear is very rare and it is thus advised that full excision biopsy of conchal lesions should be performed if an incisional biopsy is inconclusive.

A Tahir,* DS Murray

*West Midlands Regional Plastic Surgery Unit, Selly Oak Hospital, Birmingham, UK. *Corresponding author, 72 Arosa Drive, Harborne, Birmingham, UK, BI7 0SE, tel. +121 4275642; fax ; E-mail: doctahir@doctors.org.uk*

References

1 Rigopoulos D, Rallis E, Toumbis-Ioannou E. Seborrhoeic keratosis or occult malignant neoplasm of the skin? *Eur Acad Derm Venereol* 2002; **16**(2): 168–170.

2 Izikson L, Sober AJ, Mihm MC. Prevalence of melanoma clinically resembling seborrhoeic keratosis. *Arch Dermatol* 2002; **138**: 1562–1566.

3 Akasaka T, Kon S. Two cases of basal cell carcinoma arising in seborrhoeic keratosis. *J Dermatol* 1997; **24**(5): 322–327.

4 Yap WM, Tan PH, Ong BH. Malignancy arising in seborrhoeic keratosis: a report of two cases. *Ann Acad Med Singapore* 1997; **26**(2): 235–237.

5 Kobayashi M, Suga Y, Nishimura K, Ogawa H. A patient with seborrhoeic keratosis which caused impaired hearing by closure of the external auditory meatus. *Int J Dermatol* 2000; **39**: 550–559.

6 Kyrmizakis DE, Vrentzos EE, Papadakis C. Seborrhoeic keratosis of the auricle: report of an unusual case. *Ear Nose Throat J* 2002; **81**(2): 107–109.

7 Konishi E, Nakashima Y, Manabe T, Mazaki T, Wade Y. Irritated seborrhoeic keratosis of the external ear canal. *Pathol Int* 2003; **53**(9): 622–626.

DOI: 10.1111/j.1468-3083.2004.01111.x

Neurofibromatosis associated with psoriasis

To the Editor

Psoriasis and neurofibromatosis are both disorders that probably have a strong genetic basis. Neurofibromatosis is an autosomal dominantly inherited syndrome (except for type 5) manifested by developmental changes in the nervous system, bones and skin.[1] It has an incidence of 1 : 3000–5000 and is seen among all racial groups. The exact pathogenesis of the highly variable features is not understood.[2] Psoriasis is a common, chronic and recurrent inflammatory disease of the skin. The cause of psoriasis is still unknown. It is apparent that heredity is of significance in some cases. Although genetic transmission has not been clearly delineated.[3]

A 20-year-old woman with neurofibromatosis who developed psoriasis bilaterally on the extremities presented to our outpatient clinic (Department of Dermatology, Faculty of Medicine, Dicle University, Diyarbakir, Turkey) for treatment. She had suffered from psoriasis vulgaris for the last 13 years. She had also noted the onset of skin nodules and café-au-lait macules when she was 10 years old. No other family members had a history of neurofibromatosis. Her family history revealed that her brothers, age 10 and 27 years, had psoriasis.

Dermatological examination revealed multiple cutaneous neurofibromas and café-au-lait macules on the extremities, face and trunk, a giant pigmented hairy naevi on the trunk (figs 1 and 2),

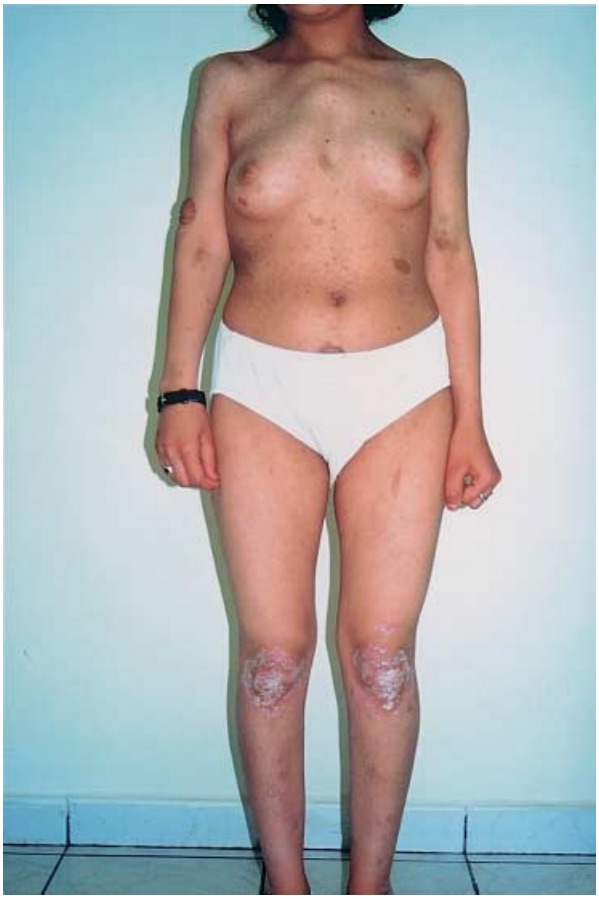


fig. 1 Multiple café-au-lait macules, cutaneous neurofibromas on the front of body and bilateral psoriatic plaques on the knees.

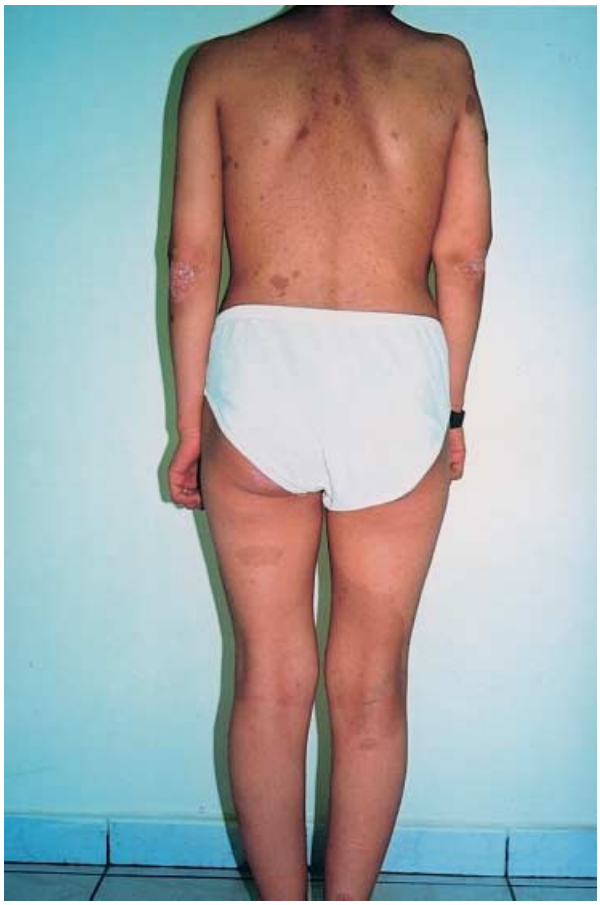


fig. 2 Multiple café-au-lait macules, cutaneous neurofibromas on the back of body and bilateral psoriatic plaques on the elbows.

common efelid on the face and the freckles in the left axillary area. Bilateral Lisch nodules were seen on ophthalmic examination. The psoriatic plaques were especially present bilaterally on the knees and elbows (figs 1 and 2). She had pectus carinatus on the chest. Histopathological examination of the psoriatic lesion demonstrated the characteristic histological findings: hyperkeratosis with parakeratosis, neutrophilic infiltrates forming microabscesses into epidermis and dermal papillomatosis. A biopsy specimen from a cutaneous nodule demonstrated the characteristic histopathological findings of a cutaneous neurofibroma.

Routine laboratory and endocrinological investigations were normal. Electroencephalography, abdominal ultrasonography, magnetic resonance imaging (cranial) and X-ray of the head showed no significant alteration. Topical calcipotriol 0.05% ointment therapy for psoriatic lesions was begun twice daily, and excellent improvement was obtained after 4 weeks.

Neurofibromatosis is a relatively common autosomal dominant trait. A typical case is characterized by the presence of multiple café-au-lait spots and soft fibrous tumours arising from nerve sheaths that usually develop during childhood or adolescence. Aside from typical cases, this disease has a variable expression.[4] Several types have been described (types 1–7).[1]

Psoriasis and neurofibromatosis are both disorders that probably have a strong genetic basis.[5] The two disorders also include the characteristic skin lesions. As it rare to see patients having both disorders, a lack of direct relationship between these two diseases has been suggested.[5] In the past, there were three reported cases in which neurofibromatosis and psoriasis coexisted. In 1985, Roenigk and Manick[5] reported a 57-year-old man with neurofibromatosis type 1 and psoriasis. In 1990, Nishimura and Hori[4] reported a 58-year-old man with psoriasis vulgaris. In the patient, neurofibromas had developed during psoralen + ultraviolet A treatment. In 1999, Çelebi *et al*.[6] reported a 7-year-old boy with neurofibromatosis who developed scalp psoriasis.

Our patient is a 20-year-old girl with neurofibromatosis and psoriasis vulgaris. According to Riccardi's[7] classification, our patient demonstrated neurofibromatosis type 1. No other family members had a history of neurofibromatosis. Her brothers, age 10 and 27, both had psoriasis. We would expect this combination to occur again in her family.

Most likely, this combination of psoriasis and neurofibromatosis represents a chance event. The absence of reported cases suggests that a direct relationship between these two diseases is unlikely. Other reports of this combination would be of interest and could be expected statistically.

M Arica,†* SA Erdal‡

*†Department of Dermatology, Faculty of Medicine, Dicle University, Diyarbakýr, Turkey, ‡City Hospital, Diyarbakýr, Turkey. *Corresponding author, Mustafa Arica, Dicle University Faculty of Medicine, Department of Dermatology, 21280 Diyarbakir, Turkey, tel. +90 4122488001/4221; fax +90 4122488440; E-mail: mustafa2arica3@yahoo.co.uk*

References

1 Odom RB, James WD, Berger TG. Some genodermatoses and acquired syndromes. In: *Andrew's Disease of the Skin*, 9th edn. WB Saunders, Philadelphia, 2000: 682–732.
2 Braun-Falco O, Plewig G, Wolff HH, Burgdorf WHC. Malformations and genetic disorders. In: *Dermatology*, 2nd, completely revised edn. Springer-Verlag, Berlin, 2000: 833–854.
3 Odom RB, James WD, Berger TG. Seborrheic dermatitis, psoriasis, recalcitrant palmoplantar eruptions, pustular dermatitis and erythroderma. In: *Andrew's Disease of the Skin*, 9th edn. WB Saunders, Philadelphia, 2000: 214–253.
4 Nishimura M, Hori Y. Late-onset neurofibromatosis developed in a patient with psoriasis vulgaris during PUVA treatment. *Arch Dermatol* 1990; **126**: 541–542.
5 Roenigk RK, Manick KP. Neurofibromatosis and psoriasis. *Cutis* 1995; **35**: 479–480.
6 Çelebi S, Kýlýç Sþ, Okan M. Psoriasis in a patient with neurofibromatosis. *Turk J Pediatr* 1999; **41**: 545–549.

7 Riccardi VM. Von Recklinghausen's neurofibromatosis. *N Engl J Med* 1987; **305**: 1617–1627.

DOI: 10.1111/j.1468-3083.2005.01113.x

Acute depression from isotretinoin. Another case

To the Editor

Psychological side-effects due to isotretinoin therapy have been previously described, with particular emphasis on depression and consequent suicide.[1,2] Recent reports[1–4] confirm ongoing interest in this matter, which still remains controversial.

A 16-year-old male teenager was referred in January 2001 because of severe acne, which had been worsening over the last 3–4 months. The patient, a high school student and basketball player, did not show any embarrassment about his unaesthetic appearance, whereas his mother seemed to be particularly anxious and worried. Systemic treatment with isotretinoin, 0.75 mg/kg per day, was started. Five weeks later, the patient appeared to be fretful and beginning to complain about his acne. Moreover, his mother reported an increased irritability and a loss of concentration at school.

In the next 2 weeks, the situation came to a head. The mother returned to our consultation saying that her son was terribly depressed, often crying and frequently arguing with his parents. The patient was immediately examined, and the presence of pyogenic granuloma-like lesions on the cheeks confirmed that there was no improvement in the acne; in addition, typical features of major depression,[5] including mood disturbances and behaviour changes, were clearly detectable. Finally, the treatment was discontinued and both mother and son were advised that psychotic symptoms quickly disappear after discontinuing the isotretinoin. Unfortunately, contact with them was lost after this episode.

Although several studies supported by Hoffmann-La Roche have provided no evidence of a correlation between isotretinoin therapy and psychiatric symptoms[6–8] various cases of depression and a few cases of suicide or attempted suicide have been reported over the last 15 years.[1,3] I believe that the number of reports of acute depression due to isotretinoin therapy are widely underestimated. Many physicians, in fact, avoid a priori the use of isotretinoin in a subset of patients considered predisposed to developing depression. Furthermore, some patients under isotretinoin do not complete the treatment successfully, on account of the appearance of hyperlipidaemia, myalgia or other side-effects that may have preceded the psychiatric symptoms.

In conclusion, before the therapy the patient had no complaints about the acne and no detectable psychiatric disorders, but his mother was extremely concerned, and had decided to consult a dermatologist and to start the therapy. It is quite likely that he was probably susceptible to developing depression, and that his mother's anxiety in association with the isotretinoin therapy had increased the depressive symptoms.

M La Placa*

Department of Clinical and Experimental Medicine, Dermatology Section, University of Bologna, Bologna, Italy.
**Corresponding author, Department of Clinical and Experimental Medicine, Dermatology Section, University of Bologna, Via Massarenti, 1, 40138 Bologna, Italy, tel. +39 051 341820; fax + 39 051 302744; E-mail: dermolap@med.unibo.it*

References

1 Hull PR, D'Arcy C. Isotretinoin use and subsequent depression and suicide: presenting the evidence. *Am J Clin Dermatol* 2003; **4**: 493–505.
2 Bremner JD. Does isotretinoin cause depression and suicide? *Psychopharmacol Bull* 2003; **37**: 64–78.
3 O'Connell KA, Wilkin JK, Pitts M. Isotretinoin (Accutane) and serious psychiatric adverse events. *J Am Acad Dermatol* 2003; **48**: 306–308.
4 Chu A, Cunliffe WJ. The inter-relationship between isotretinoin/acne and depression. *J Eur Acad Dermatol Venereol* 2003; **17**: 619.
5 Gupta MA. Incidence of psychiatric disorders in dermatological patients. *J Eur Acad Dermatol Venereol* 2003; **17**: 624–626.
6 Jacobs DG, Deutsch N, Brewer M. Suicide, depression, and isotretinoin: is there a causal link? *J Am Acad Dermatol* 2001; **45**: S168–S175.
7 Wysowski DK, Pitts M, Beitz J. An analysis of reports of depression and suicide in patients treated with isotretinoin. *J Am Acad Dermatol* 2001; **45**: 515–519.
8 Jick SS, Kremers HM, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression, psychotic symptoms, suicide, and attempted suicide. *Arch Dermatol* 2000; **136**: 1231–1236.

DOI: 10.1111/j.1468-3083.2004.01120.x

Are we starting to induce skin cancer in order to avoid topical steroids?

To the Editor

For the last couple of years topical tacrolimus has started to be popular in treating atopic eczema. Its use has not been restricted to specialists only but also extended to other specialities and to general practitioners. It is stated by the manufacturer in the pamphlet enclosed with the ointment that

> Exposure of the skin to sunlight should be minimized and the use of ultraviolet (UV) light from a solarium, therapy with UVB or UVA in combination with psoralens (PUVA) should be avoided during use of Protopic ointment. Physicians should advise patients on appropriate sun protection methods, such as minimization of the time in the sun, use of a sunscreen product and covering of the skin with appropriate clothing.[1]

However, the main site currently treated with it is the face and more seriously in children. To the best of our knowledge there still many doctors who do not emphasize this risk to parents before prescribing it to children. On the contrary, many parents continue to expose their children to sunlight to add its 'beneficial' effect to that of topical tacrolimus.[2]

Moreover, the manufacturer stated in the same pamphlet that

> In a photocarcinogenicity study, albino hairless mice were chronically treated with tacrolimus ointment and UV radiation. Animals treated with tacrolimus ointment showed a statistically significant reduction in time to skin tumour (squamous cell carcinoma) development and an increase in the number of tumours. It is unclear whether the effect of tacrolimus is due to systemic immunosuppression or a local effect. The relevance of these findings for man is unknown.

However, the first author investigated this issue and proved that topical tacrolimus did not only statistically increase the number of tumours produced on the skin of CD-1 mice within 14 weeks[3,4] (figs 1 and 2), but it also significantly decreased the CD4/CD8 ratio in axillary and inguinal lymph nodes.[2–4] This feature was associated with unexpectedly higher tacrolimus concentration in the same lymph nodes 6 weeks after application despite the fact its serum concentration was 50–100-fold lower than when the drug is systemically administered[2] (Table 1). Homey *et al.* also found that topical tacrolimus affects local immunity through decreasing the CD25 expression on CD4+ cells in the local draining lymph nodes.[5]

The main reason for using topical tacrolimus so extensively is that parents do not wish to use topical steroids especially on the face of their children for a prolonged period in fear of developing irreversible steroid damage. However, it is well known that weak steroids could be used safely for a longer period. We wonder whether it is worth it to use an ointment that can induce skin cancer on children's faces just to avoid topical steroids in a non-fatal condition such as atopic eczema.

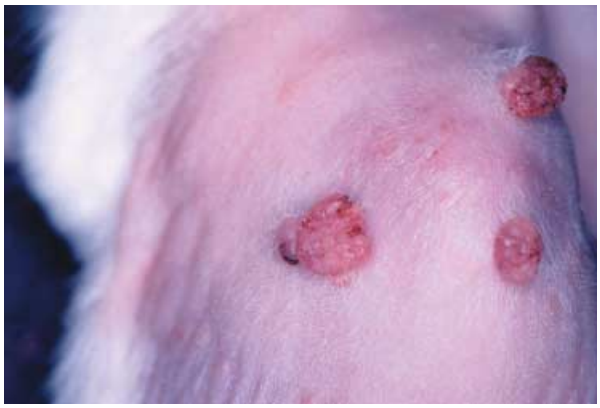


fig. 1 Squamous cell carcinoma that developed by week 15 in a mouse treated with DMBA + tacrolimus without 12-O-tetradecanoylphorbol-13-acetate (TPA).

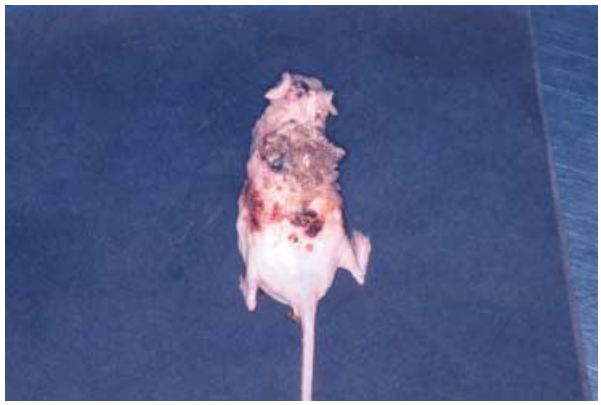


fig. 2 Squamous cell carcinoma *in situ* (Bowen's disease) or solar (actinic) keratosis that developed by week 31 in ultraviolet light (UVL) irradiated-mouse simultaneously applied with topical tacrolimus.

Table 1 Concentration of tacrolimus in inguinal and axillary lymph nodes after application of topical and systemic tacrolimus (performed in our laboratory, Niwa Institute for Immunology)

	Duration after application (weeks)			
How to apply	**3**	**4**	**6**	**9**
Oral uptake (0.3 μg daily)	5.9	5.6	5.3	5.3
Topical application (20 mg daily)	6.1	5.8	6.3	5.4

Tacrolimus concentration is expressed as ng per weight of minched lymph tissues.

On the other hand, we do not wish to lose the use of such an effective therapy. To this end, we would like to make some suggestions. We recommend:

- The manufacturer should emphasize the risks in children more clearly.
- The use of topical tacrolimus should be restricted to specialists only.
- The face and other exposed areas should be covered properly by a suitable sun block whenever it is prescribed for these areas, otherwise, the ointment should not be applied on these areas.
- Do more extensive research to indicate the maximum safe period that we can use it for.
- At the moment we feel that it should not be used for more than 12 weeks and to cover the areas treated with sun blocks for the whole period of use and may be for a further 4 weeks.
- We do not know whether it would be safe to repeat the treatment after the 12-week period or not, so we would not recommend such practice until more information is available.

Y Niwa,†* I Nasr‡

*†Niwa Institute for Immunology, Tosashimizu, Japan, ‡Royal Berkshire Hospital, Reading, UK. *Corresponding author, Niwa Institute for Immunology & Tosashimizu Hospital, 4-4 Asahimachi, Tosashimizu, Kochi 787-0303, Japan, tel. +81(0)880 82 2511; fax +81(0)880 82 4915; E-mail: yniwa@lime.ocn.ne.jp*

References

1 Fujisawa Limited. Protopic 0.1% ointment: information leaflet. Emc.vhn.net URL: http://emc.vhn.net/eMC/assets/c/html/DisplayDoc.asp?DocumentId=8816

2 Niwa Y. Topical tacrolimus potentiates carcinogenesis in mouse skin and reduces the lymph node CD4/CD8 ratio. *Jpn J Allergol* 2003; **52**: 333 (Abstr.) (in Japanese).

3 Niwa Y, Terashima T, Sumi H. Topical tacrolimus accelerates tumor formation and carcinogenesis in mouse skin. *J Invest Dermatol* 2002; **119**: 749 (Abstr.).

4 Niwa Y, Terashima T, Sumi H. Topical application of the immunosuppressant tacrolimus accelerates carcinogenesis in mouse skin. *Br J Dermatol* 2003; **149**: 960–967.

5 Homey B, Assmann T, Vohr HW *et al.* Topical FK506 suppresses cytokine and costimulatory molecule expression in epidermal and local draining lymph node cells during primary skin immune responses. *J Immunol* 1998; **160**: 5331–5340.

DOI: 10.1111/j.1468-3083.2004.01123.x

Effects of ultraviolet irradiation on mediator release from basophils and mast cells

To the Editor

We read with interest the manuscript by Monfrecola *et al*. about the inhibiting and enhancing effects of ultraviolet (UV) A irradiation on histamine release from human basophils.[1] The discussion gives a general overview about the human basophil structure and physiology as well as interesting calculations about circulating basophils as targets for natural or artificial UVA irradiation; however, important information on the effects of UV irradiation on mediator release from basophils and mast cells is not considered. Early studies on natural sunlight effects upon mast cell degranulation were published decades ago followed by many studies on this topic. Experiments with rat mast cells in the presence of photosen-sitizers (e.g. protoporphyrin, acridine, pyrene, benoxaprofen, chlorpromazine, chlortetracycline, 8-methoxypsoralen) showed a dual effect (reduced mediator release at low UV doses, enhanced release at high UV doses).[2] A photo-basophil-histamine-release test was introduced in 1987 by Przybilla *et al*. demonstrating phototoxicity of non-steroidal anti-inflammatory drugs.[3] In addition, inhibiting effects of UVA irradiation in this test have been reported by our group using UVA doses up to 100 J/cm^2.[4] Also, we defined the action spectrum of this effect with enriched basophils (29% purity) showing inhibitory effects with UVA1 irradiation, but not with UVB irradiation.[5] Furthermore, not only anti-IgE, but also calcium-ionophore, FMLP, C5a in basophils and compound 48/80, calcium-ionophore, substance P and concanavalin A in mast cells were used as stimuli. More data exist about the cell membrane as a possible target structure for UVA-induced effects and other possible mechanisms,[5] e.g. increase in intracellular Ca^+ levels or involvement of reactive oxygen species.[6]

Besides *in vitro* measurements, several *in vivo* experiments have shown inhibitory effects of UV irradiation on allergen, anti-IgE, codeine phosphate or substance 48/80 induced weal and flare reactions and itch in human skin as well as on substance 48/80 and concanavalin A induced ear swelling in mice underlining similar mechanisms *in vivo*.[7,8]

We agree with the authors that studies on the differential effects of UV irradiation on basophils and mast cells may add useful information on pro- or anti-inflammatory effects of UV on human health.

B Eberlein-König,* J Ring

*Division 'Environmental Dermatology and Allergology' GSF/TUM, Neuherberg-Munich, Department of Dermatology and Allergy Biederstein, Technical University Munich, Germany, *Corresponding author, Klinik und Poliklinik für Dermatologie und Allergologie am Biederstein, Technische Universität München, Biedersteiner Str. 29, 80802 München, tel. +49 89 4140 3324; fax +49 89 4140 3526; E-mail: eberlein-koenig@lrz.tu-muenchen.de*

References

1 Monfrecola G, de Paulis A, Prizio E *et al. In vitro* effects of ultraviolet A on histamine release from human basophils. *J Eur Acad Dermatol Venereol* 2003; **17**: 646–651.

2 Gendimenico GJ, Kochevar IE. Degranulation of mast cells and inhibition of the response to secretory agents by phototoxic compounds and ultraviolet radiation. *Toxicol Appl Pharmacol* 1984; **76**: 374–382.

3 Przybilla B, Schwab-Przybilla U, Ruzicka T, Ring J. Phototoxicity of non-steroidal anti-inflammatory drugs demonstrated in vitro by a photo-basophil-histamine-release test. *Photodermatology* 1987; **4**: 73–78.

4 Ring J, Przybilla B, Eberlein B. Ultraviolet A inhibits histamine release from human peripheral leukocytes. *Int Arch Allergy Appl Immunol* 1989; **88**: 136–138.

5 Krönauer C, Eberlein-König B, Ring J, Behrendt H. Influence of UVB, UVA and UVA1 irradiation on histamine release from human basophils and mast cells in vitro in the presence and absence of antioxidants. *Photochem Photobiol* 2003; **77**: 531–534.

6 Amano H, Kurosawa M, Miyachi Y. Inhibition of substance-P-induced histamine release from rat peritoneal mast cells by 8-methoxypsoralen plus long-wave ultraviolet light irradiation: decreased intracellular calcium as possible mechanism. *Int Arch Allergy Immunol* 1998; **115**: 55–60.

7 Fjellner B, Hägermark Ö. Influence of ultraviolet light on itch and flare reactions in human skin induced by histamine and the histamine liberator compound 48/80. *Acta Derm Venereol* 1982; **62**: 137–140.

8 Vocks E, Stander K, Rakoski J, Ring J. Suppression of immediate-type hypersensitivity elicitation in the skin prick test by ultraviolet B irradiation. *Photodermatol Photoimmunol Photomed* 1999; **15**: 236–240.

DOI: 10.1111/j.1468-3083.2004.01126.x

Grover's disease (transient acantholytic dermatosis) associated with atopy

To the Editor

Grover's disease (transient acantholytic dermatosis) is a non-immune acantholytic dermatosis, clinically characterized by pruritic papules and vesicles, mainly distributed on the trunk, that affects mostly adult males over 50 years old. In some cases it has been reported in association with other systemic diseases.

We report a case of Grover's disease in association with atopy in a woman who was under 50 years old.

A 36-year-old woman was referred to the Department of Biomedical and Surgical Sciences, Section of Dermatology and Venereology (Verona University, Italy) in April 2002 after experiencing onset of itchy papulovesicles and erosive lesions in the abdominal region. These lesions were reported to have been present for a month and had appeared spontaneously or after minimal trauma. The patient reported that analogous lesions had appeared on the trunk and abdominal region 6 months earlier and then spontaneously receded, except for the persistence of hyperpigmentation.

Clinical examination revealed papulovesicles and erosive plaques in the abdominal region, large from 3 to 20 cm (fig. 1).

Laboratory findings showed an atopic state, as demonstrated by high levels of immunoglobulin E (627 KU/L), high levels of eosinophilic cationic protein (31 μg/L) and RAST was positive to some of the following: *Poa pratensis* > 100 kU/L; *Cynodon dactilon* 31.3 kU/L; *Parietaria officinalis* 12 kU/L; *Artemisia vulgaris* 6.3 kU/L; *Ambrosia elatior* 6.16 kU/L; *Betulla* 5.68 kU/L; *Olivo* 5.58 kU/L. Other laboratory examinations were normal.

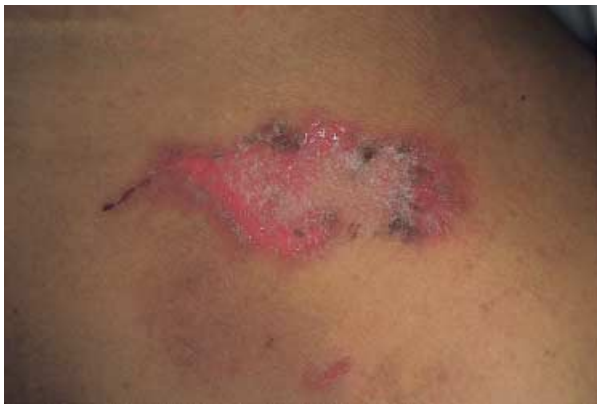


fig. 1 Papulovesicles and erosive plaques in the abdominal region with hyperpigmentation in the resolution area.

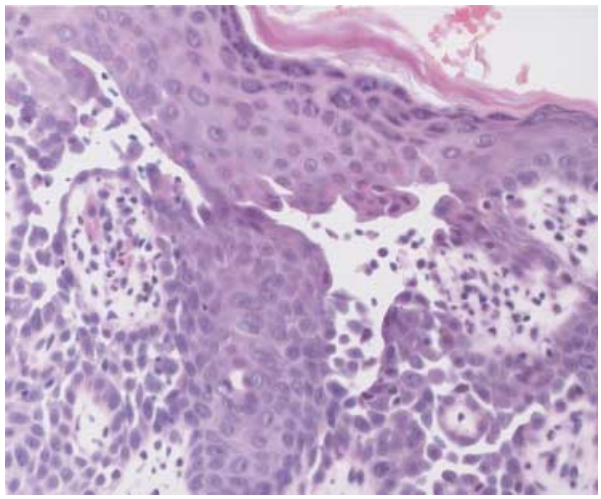


fig. 2 Focal acantholysis in the spinosum layer, associated to dyskeratosis, parakeratosis and neutrophilic exocytosis with micropustules (haematoxylin and eosin, original magnification × 25).

A biopsy specimen was taken from the abdominal cutaneous lesion. It revealed focal acantholysis in the spinosum layer, associated with dyskeratosis, parakeratosis and neutrophilic exocytosis with micropustules; in the dermis, under the dermoepidermal junction and around the superficial and the deep vascular plexus, there was a lymphohistiocytic infiltrate with melanophages and neutrophilic granulocytes (fig. 2). Direct immunofluorescence was negative.

Topical treatment with steroids and antibiotics led to clinical resolution in 15–20 days, except for the persistence of pigmentary lesions. After 6 and 12 months of follow-up the patient reported occasional onset of papulovesicles and erosive lesions, which remitted after application of topical steroids. Grover's disease is a non-immune acantholytic disease, clinically characterized by pruritic papules and papulovesicles, mainly distributed on the trunk, occurring mostly in males, over 50 year old.

Histologically, the hallmark of the disease is focal acantholysis in the epidermis, at a suprabasal or subcorneal level. Focal acantholysis may present, in the same specimen, different forms such as pemphigus-like, Hailey–Hailey disease-like, Darier's disease-like, and spongiotic. In the classical form of Grover's disease, cutaneous adnexa are not affected. Spongiosis, dyskeratosis and hypergranulosis also may be seen. A dermal inflammatory infiltrate, with lymphocytes, histiocytes and eosinophils is often reported, and direct immunofluorescence is negative.[1]

The aetiology and pathogenesis of Grover's disease is unknown. Triggering factors have been identified in sweat, fever, heat and sunlight. Some reports have hypothesized causation by poral

occlusion of damaged eccrine in intraepidermal ducts, with spillage of sweat contents and focal acantholysis;[2] otherwise, acantholysis is often not associated with the eccrine duct outflow tract.[2] In our case, for example, acrosyringium was histologically intact. In Grover's disease, different studies have shown the primary damage in the proteins of the desmosomal attachment plaque, such as desmoplakin I and II and plakoglobin;[3] these proteins, in fact, were seen dissolved and diffused into the acantholytic cells.[4]

Grover's disease has been reported in association with other diseases. Davis *et al.* found a prevalence of association with malignant diseases in 25% of patients; neoplasms were both solid and haematological.[5,6] Other sporadic associations include human immunodeficiency virus infections,[5] chronic renal failure and haemodialysis.[7] In some cases an association with cutaneous diseases has been found, even if it is not clear if the association is casual. Grover's disease, in fact, has been reported to occur with scabies,[8] pyoderma gangrenosum, asteatotic eczema and allergic contact dermatitis.[9]

To the best of our knowledge, we have found one study in the literature in which Grover's disease is associated with atopic dermatitis, and a Koebner phenomenon is postulated as the pathogenetic mechanism.[9]

We presented this case for the onset of Grover's disease in a woman under 50 years old, and in association with an asymptomatic atopic state; moreover, the onset of lesions was both posttraumatic and spontaneous. We may hypothesize, however, that the skin of our patient was more sensitive to irritative or traumatic stimuli.

P Rosina,†* G Melzani,† M Marcelli,† W Zakaria,† C Colato,‡ A Barba†

*†Department of Biomedical and Surgical Sciences, Section of Dermatology and Venereology, ‡Department of Pathologic Anatomy, Verona University, Italy. *Corresponding author: Dipartimento di Scienze Biomediche e Chirurgiche, Sezione di Dermatologia e Venereologia, Università di Verona, P.le Stefani, 1, 37126 Verona, Italy, tel. +039 45 8072547; fax +039 45 8300521; E-mail: paolo.rosina@univr.it*

References

1 Heenan PS, Quirk CS. Transient acantholytic dermatosis (Grover's disease). In: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF *et al.*, eds. *Dermatology in General Medicine*, 3rd edn. McGraw-Hill, New York, 1987: 526–529.

2 Antley CM, Carrington PR, Mrak RE, Smoller BR. Grover's disease (transient acantholytic dermatosis): relationship of acantholysis to acrosyringia. *J Cutan Pathol* 1998; **25**: 545–549.

3 Hashimoto K, Fujiwara K, Tada J *et al.* Desmosomal dissolution in Grover's disease, Hailey-Hailey's disease and Darier's disease. *J Cutan Pathol* 1995; **22**: 488–501.

4 Hashimoto K, Fujiwara K, Harada M *et al.* Junctional proteins of keratinocytes in Grover's disease, Hailey-Hailey's disease and Darier's disease. *J Dermatol* 1995; **22**: 159–170.

5 Davis MD, Dinneen AM, Landa N, Gibson LE. Grover's disease: clinicopathologic review of 72 cases. *Mayo Clin Proc* 1999; **74**: 229–234.

6 Rockley PF, Bergfeld WF, Tomecki KJ, Brydon JK. Myelodysplastic syndrome and transient acantholytic dermatosis. *Cleve Clin J Med* 1990; **57**: 575–577.

7 Casanova JM, Pujol RM, Taberner R *et al.* Grover's disease in patients with chronic renal failure receiving hemodialysis: clinicopathologic review of 4 cases. *J Am Acad Dermatol* 1999; **41**: 1029–1033.

8 Kaddu S, Mullegger RR, Kerl H. Grover's disease associated with *Sarcoptes scabiei*. *Dermatology* 2001; **202**: 252–254.

9 Grover RW, Rosenbaum R. The association of transient acantholytic dermatosis with other skin diseases. *J Am Acad Dermatol* 1984; **11**: 253–256.

DOI: 10.1111/j.1468-3083.2004.01129.x

Spitz naevus: a proposal for management

To the Editor

Spitz naevus is a clinical entity with clinical ambiguity that makes the diagnosis and management of the patient difficult. Much more is still to be learnt about its evolution, modifications seen clinically and by dermoscopy. Today, when a diagnosis of Spitz naevus is made, the most common therapy is surgery.

We believe dermoscopy is a very useful method in the study of Spitz naevi in order to understand its evolution, which until now was unknown, and subsequently this will lead to better management. We present our experience in the management of Spitz naevi with a proposal of guidelines to differentiate Spitz naevi to be asported and others to follow-up.

We report two cases of pigmented Spitz naevi that showed morphological changes during the period of dermoscopic follow-up.

Patient 1 is a 3-year-old boy with a pigmented, brownish black papule (2.5 mm) on left knee. On dermoscopic evaluation a globular pattern with brownish, black and light brownish globules and a grey–blue pigmentation in the central area can be recognized (fig. 1). During the second evaluation, a year later, dermoscopic features were characterized by large brownish globules with a reduction of the central grey–blue pigmentation (fig. 2). At the third evaluation, 4 years later, clinically, the lesion appeared as a pink reddish papule, and dermoscopic features showed a reduction of globules and multiple fibrotic areas (fig. 3).

Patient 2 is an 11-year-old boy with a pigmented, black, very small lesion (1.2 mm) on the right knee. Initially, dermoscopic features were characterized by a globular pattern, associated with a homogeneous central black area (fig. 4). At the second evaluation 6 years later, the lesion was clinically smaller in size. Dermoscopic features showed only a light brown reticular pattern with a peripheral area that was more pigmented (fig. 5).

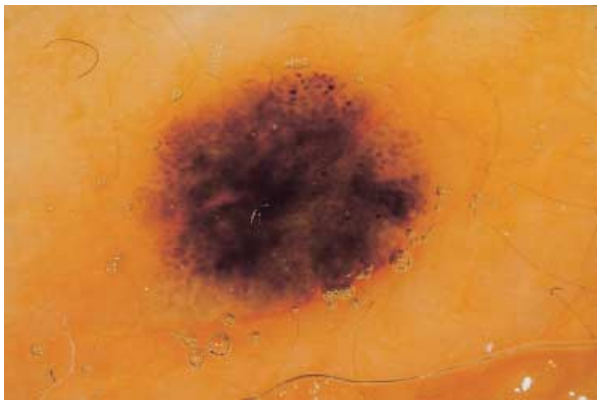


fig. 1 Patient 1: dermoscopic evaluation at 3 years old: globular pattern with brownish black and light brownish globules, and a grey–blue pigmentation in the central area.

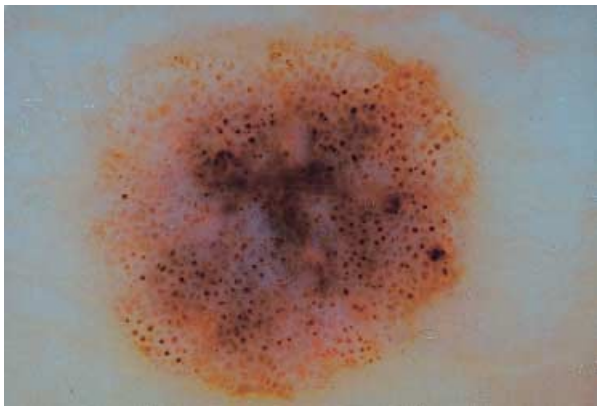


fig. 2 Patient 1: dermoscopic evaluation at 4 years old: large brownish globular with a reduction of central grey–blue pigmentation.

fig. 3 Patient 1: dermoscopic evaluation at 7 years old: reduction of globules and multiple fibrotic areas.

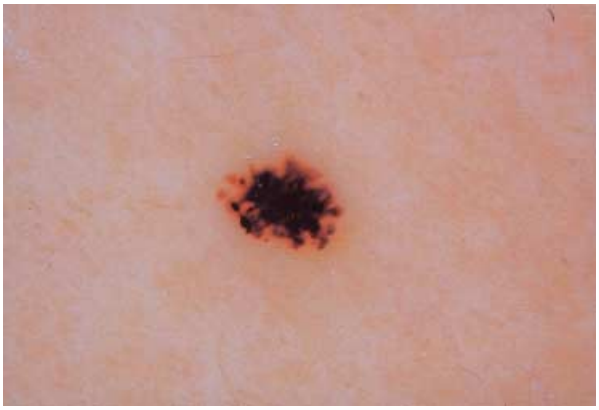


fig. 4 Patient 2: dermoscopic evaluation at 11 years old: globular pattern, associated with homogeneous central black area.

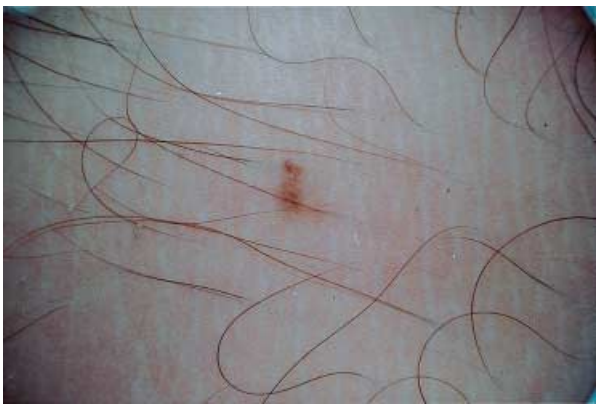


fig. 5 Patient 2: dermoscopic evaluation at 17 years old: light brown reticular pattern with a peripheral area more pigmented.

We would like to emphasize the uncertainty and difficulty in the diagnosis and correct management of Spitz naevi. There is no consensus about the benign nature of Spitz naevi, but their natural history is not fully understood and the histopathological differentiation is often as difficult as the management.[1]

We are agreement with Kreusch *et al.*[2] and Pizzichetta *et al.*[3] in that there are various possible dermoscopic appearances of Spitz naevi during their evolutionary phases, and are not always in a globular or starburst pattern.

There are two extremes of management: Spitz naevus can be always periodically controlled, or should be always excised. In a recent article about the management of Spitz naevi, 93% of dermatologists consulted recommended biopsies of 'suspected' Spitz naevus.[4]

In future we should hypothesize a dermoscopic follow-up for Spitz naevi:

1 In children under 12 years follow-up every 6 months for the first 2 or 3 years and then just once a year.
2 In children 12 years aged and over (i) follow-up every year for lesions with typical clinical and dermoscopic features, and (ii) surgical removal of all Spitz naevi with atypical clinical and dermoscopic features.

B Brunetti,* M Nino, E Sammarco, M Scalvenzi

*Department of Dermatology, Univesity 'Federico II' of Naples, Italy, Via S. Pansini, 5, 80131, Naples, Italy. *Corresponding author, Department of Dermatology, Univesity 'Federico II' of Naples, Italy, Via S. Pansini, 5, 80131, Naples, Italy, tel. +39 0817462412; fax +39 0817462442; E-mail: cldermat@unina.it*

References

1 Argenziano G, Scalvenzi M, Staibano S *et al.* Dermatoscopic pitfalls in differentiating pigmented Spitz naevi from cutaneous melanomas. *Br J Dermatol* 1999; **14**: 788–793.

2 Kreusch J, Rassner G. Standardized epiluminescent microscopy for differentiating melanocytic and non-melanocytic pigment nevi. *Hautarzt* 1991; **42**: 77–83.

3 Pizzichetta MA, Argenziano G, Grandi G *et al.* Morphologic changes of a pigmented Spitz nevus assessed by dermoscopy. *J Am Acad Dermatol* 2002; **47**: 137–139.

4 Gelbard SN, Tripp JM, Marghoob AA *et al.* Management of Spitz nevi: a survey of dermatologists in the United States. *J Am Acad Dermatol* 2002; **47**: 224–230.

DOI: 10.1111/j.1468-3083.2004.01137.x

Topical immunotherapy with diphencyprone in the treatment of extensive and/or long-lasting alopecia areata

To the Editor

Alopecia areata (AA) is a common disease characterized by the sudden and complete loss of hairs in a localized area of the body. Diphencyprone (diphenylcyclopropenone, DPCP), which had been known as a potent contact allergen since 1972, was first reported as an effective treatment in AA in 1983.[1] DPCP has since been used extensively as contact sensitizer for AA.[2–4] Although the mechanism of action of DPCP has not been clearly defined, it has been proposed this immunogen recruits a different T-cell subpopulation to the treated area, which in turn enhances the clearance of the putative follicular antigen.[5] Reported response rates of DPCP are highly variable, ranging from 4% to 85%.[6] A recent evidence-based review on the treatment of AA concluded that immunotherapy with contact sensitizers is the only approach that has proven effectiveness.[7]

This study was conducted to assess the efficacy of DPCP in the treatment of AA, and to identify patient and treatment factors related to therapeutic success. The study was approved by the Institutional Review Board of the Center for Research and Training in Skin Diseases and Leprosy. Fifty-six consenting patients with chronic and/or extensive AA were selected. The criteria for inclusion were the presence of extensive AA (loss of more than 25% of scalp hair) and/or chronic AA (no hair regrowth in more than a year). Grading of the disease was done by AA investigational assessment guidelines.[8] Table 1 shows the characteristics of the study population. The preparation and application of DPCP were similar to previous studies.[2–4] The overall duration of therapy was 4–48 months (mean ± SD, 12.7 ± 9.2 months).

Table 1 Characteristics of study population

Mean age (years)	23.8 ± 11.5
Male/female ratio	14/33
Mean age at onset of AA (years)	16.5 ± 8.9
Mean duration of current episode (years)	2.3 ± 2.0
Grade of AA* (%)	
S1	6 (12.8)
S2	6 (12.8)
S3	6 (12.8)
S4	12 (25.6)
S5	17 (35.9)
Nail involvement (%)	26 (55.3)
Stress as the trigger (%)	22 (46.8)
Personal history of autoimmune disease (%)	14 (29.8)
Family history of autoimmune disease (%)	34 (72.2)

*The grading was based on alopecia areata (AA) investigational assessment guidelines.[8]

At least 3 months after the initiation of the treatment, we evaluated the patients based on their clinical response to treatment. Hair regrowth was assessed according to the grading system proposed by MacDonald Hull and Norris and grades of 3 and 4 were considered as 'response to treatment'.[4]

Nine patients of 56 were treated for less than 3 months (and excluded from analysis) due to lack of efficacy ($n = 4$), changing their residence ($n = 3$), occurrence of side-effects (blister, $n = 1$), and complete improvement of AA ($n = 1$). Response to treatment was observed in 51.1% of the remaining patients (24 of 47). Duration of treatment was related to grade of response (fig. 1). Other variables, including gender, age, grade of AA (scalp, body or nail), age at onset of AA, total duration of AA,

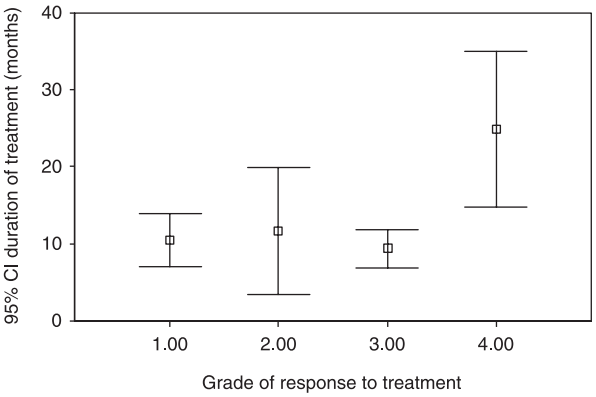


fig. 1 Duration of treatment in each grade of response ($P < 0.001$).

duration of the current episode of AA, and personal or family history of autoimmune diseases were not associated with response to treatment.

In those patients who responded, the duration of treatment to response achievement ranged between 2 and 30 months (mean ± SD, 9.8 ± 7.2 months), and was not related to grade of AA. Among these patients, five patients showed evidence of relapse.

The response rate in this study seems to be similar to studies reported by Wiseman *et al.* (50%),[5] and van der Steen *et al.* (50.4%).[2] However, response rates to DPCP ranging from 4 to 85% have been reported.[6] Presence of nail abnormalities, the extent of alopecia, the duration of alopecia, age at onset of AA, personal history of atopy have been considered as prognostic factors in some previous studies,[2,5,6,9,10] but we did not find such relations. Possible explanations for this high degree of inconsistency are the number of patients in the trials, variability in immunotherapy protocols, treatment duration, follow-up periods, and different methodological or reporting factors, especially lack of a uniform definition for 'response'. Any interpretation of the efficacy of topical immunotherapy is further limited by the fact that AA may clear by chance during a course of treatment.

A Firooz,†* N Bouzari,† F Mojtahed,† H Pazoki-Toroudi,‡ M Nassiri-Kashani,† M Davoudi,§ Y Dowlati†

*†Center for Research & Training in Skin Diseases & Leprosy, Tehran University of Medical Sciences, 79 Taleghani Avenue, Tehran, I.R. Iran, ‡Department of Physiology, Iran University of Medical Sciences, Hemmat Highway, Tehran, I.R. Iran, §Department of Dermatology, Baghiat-Allah University of Medical Sciences, Molla-Sadra Avenue, Tehran, I.R. Iran. *Corresponding author, 79 Taleghani Avenue, Tehran 14166, I.R. Iran, tel/fax (98 21)8978190; E-mail: firozali@sina.tums.ac.ir*

References

1 Happle R, Hausen BJ, Wiesner-Menzel L. Diphencyprone in the treatment of alopecia areata. *Acta Derm Venereol* 1983; **63**: 49–52.

2 van der Steen PH, van Baar HM, Perret CM, Happle R. Treatment of alopecia areata with Diphencyprone. *J Am Acad Dermatol* 1991; **24**: 253–257.

3 Hull SM, Cunliffe WJ. Successful treatment of alopecia areata using the contact allergen Diphencyprone. *Br J Dermatol* 1991; **124**: 212–213.

4 Macdonald Hull S, Norris JF. Diphencyprone in the treatment of long-standing alopecia areata. *Br J Dermatol* 1988; **119**: 367–374.

5 Wiseman MC, Shapiro J, MacDonald N, Lui H. Predictive model for immunotherapy of alopecia areata with diphencyprone. *Arch Dermatol* 2001; **137**: 1063–1068.

6 Cotellessa C, Peris K, Caracciolo E *et al.* The use of topical diphenylcyclopropenone for the treatment of extensive alopecia areata. *J Am Acad Dermatol* 2001; **44**: 73–76.

7 Freyschmidt-Paul P, Happle R, McElwee KJ, Hoffmann R. Alopecia areata: Treatment of today and tomorrow. *J Invest Dermatol Symp Proc* 2003; **8**: 12–17.

8 Olsen E, Hordinsky M, McDonald-Hull S *et al.* Alopecia areata investigational assessment guidelines. *J Am Acad Dermatol* 1999; **40**: 242–246.

9 Weise K, Kretzschmar L, John SM, Hamm H. Topical immunotherapy in alopecia areata. *Dermatology* 1996; **192**: 129–133.

10 Schuttelaar MLA, Hamstra JJ, Plinck EPB *et al.* Alopecia areata in children: treatment with diphencyprone. *Br J Dermatol* 1996; **135**: 581–585.

DOI: 10.1111/j.1468-3083.2004.01138.x

Incontinentia pigmenti: a case with an unusual course

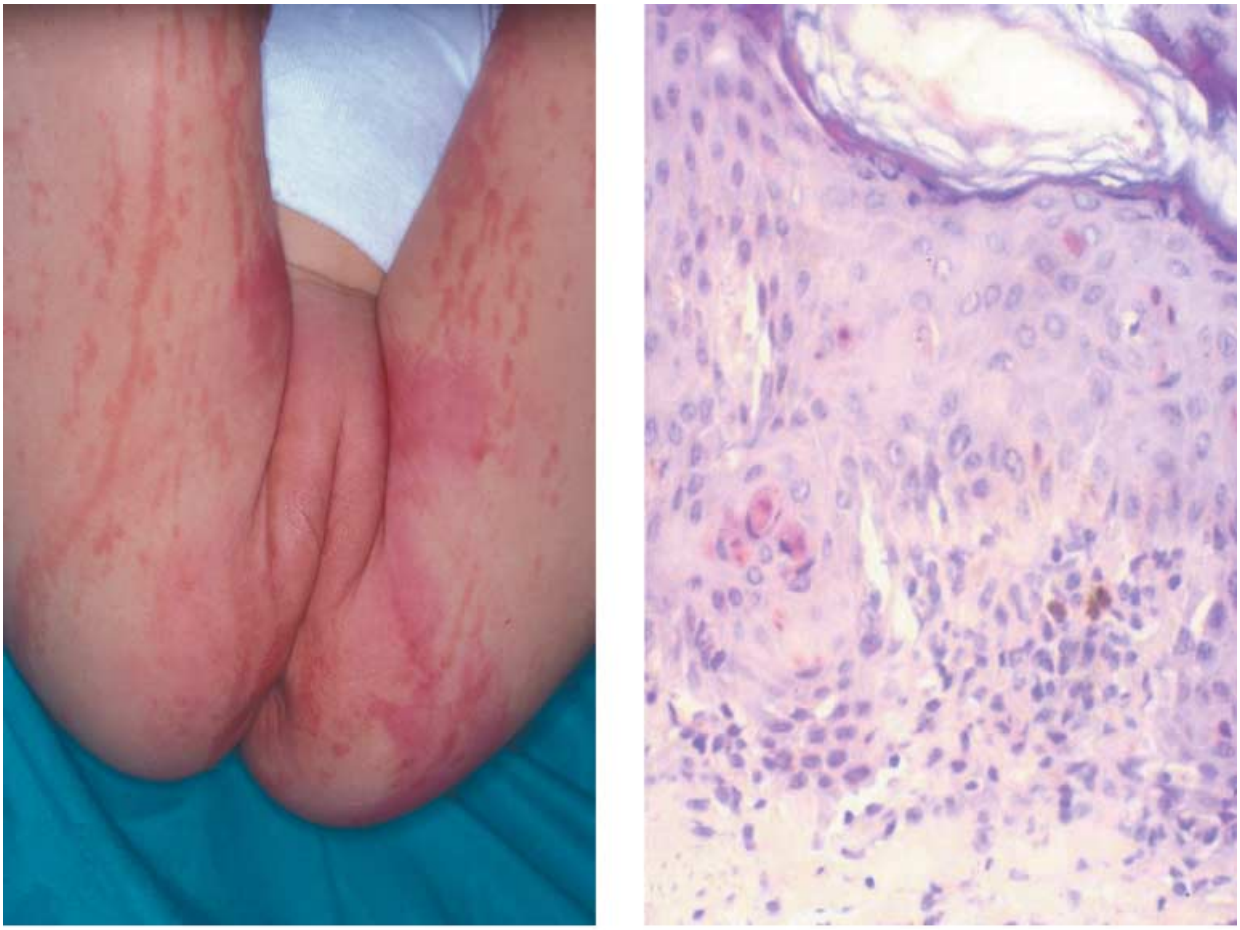
To the Editor

An 18-month-old girl presented with a 14-month history of several recurrent erythematous, papular lesions with a linear pattern. Typical vesicular lesions were not found. The lesions affected extremities, and particularly the legs (fig. 1a). Each recurrence was triggered by viral infections, either gastrointestinal or rhinopharyngeal, always accompanied with fever. The inflammatory lesions cleared in 45 days, leaving a discrete hyperpigmentation. The mother declared that this phenomenon reappeared in the same location each time her daughter had a feverish infection. There were no lesions at birth. She had partial anodontia (missing two upper incisors) and deformity of two teeth, the same as her mother, but there were no signs of associated malformations concerning the eyes or the central nervous system. The mother had been born with erythematous papules and vesicles on both arms and legs, and a clinical diagnosis of incontinentia pigmenti (IP) had been made.

The diagnosis of IP was suggested by a familial history of IP, the linear pattern of the lesions and their hyperpigmented evolution. The diagnosis was confirmed by histological examination of a skin biopsy specimen from a lesion on the thigh, which showed epidermal acanthosis with numerous dyskeratotic cells and focal ballooning of basal keratinocytes (fig. 1b). The upper dermis showed lymphocytic and histiocytic inflammatory infiltrates, both interstitial and perivascular. In addition, foci of pigmentary incontinence, with numerous subepidermal melanophages were also present.

The patient was followed for 2 years and no similar flares were observed.

Our patient had IP according to diagnostic criteria defined by Landy and Donnai.[1] Classically, the skin lesions may occur at birth, with four successive stages: erythema, then vesicles and pustules (stage 1); verrucous lesions (stage 2); linear hyperpigmentation (stage 3); and pallor and scarring (stage 4). It is not necessary for all stages to occur, and sometimes a number of



a b

fig. 1 (a) Erythematous and papular lesions showing a linear distribution on the buttocks and legs. (b) Several dyskeratotic cells as focal pigmentary incontinence, with melanophages, on the right (haematoxylin and eosin, original magnification × 100).

stages overlap.[1,2] They follow a linear pattern along the lines of Blaschko, reflecting the somatic mosaicism due to the X chromosome random inactivation in female patients.

Our case has some peculiar features relating to the cutaneous course of IP. First, the delay in onset of the inflammatory stage. The inflammatory skin changes of IP are usually present at birth or develop within the first weeks. In only a few cases it has been noted after the first 2 months. In a review of 310 cases of IP, Carney[2] found that, in 90% of cases, the eruption began within 2 weeks of birth, and in 96.4% of cases, eruptions began before the patient was 6 weeks old. He found only eight patients in whom, as in our case, the disease appeared between 6 and 52 weeks. Second, the recurrent inflammatory skin manifestations along the hyperpigmented areas in combination with a feverish infection is unusual. Until now, only a few cases of late recurrences have been reported[3–10] (Table 1). In most cases the recurrence was preceded by fever and/or a viral infection, and only one case appeared after laser treatment. No resurgence of extracutaneous involvement was experienced in any of these cutaneous exacerbations.

The mechanisms of these cutaneous reactivations still remain unknown. The gene for IP has recently been identified in 85% of cases, NEMO/IKKγ (Xq28), which encodes a regulatory component of the IκB kinase complex, and whose alteration is implicated in susceptibility to cellular apoptosis in response to tumour necrosis factor-α.[10] The mechanism of incontinence of melanin in the skin might be the result of apoptosis of the IKKγ-deficient cells. In a recent report Bodak *et al.*[10] suggested the possibility that this phenomenon of recurrence could be explained by the persistence of some residual IKKγ-deficient cells, and that some triggering factors, such as fever or infections, provoke new flares of skin lesions, until the mutated cells are completely eliminated. We agree with other authors that this atypical presentation of IP, as in our case, is probably a more common phenomenon, which may be mis/underdiagnosed; a statement that should be tested in the future.

Table 1 Review of the clinicopathological characteristics of recurrent episodes of IP in the literature

Cases	Skin lesions at birth	Associate alterations	Number and age of recurrence (month or year)	Predisposing factors	Clinical Stage of recurrence	Pathological stage of recurrence
Barnes[3] 1978	No	Teeth	Several episodes between 2 m and 18 y	_	1	2
Bessems[4] 1988	Yes	Teeth/alopecia	3 episodes 2 y; 11 y; 20 y	_	1-2-3	2
Sahn[5] 1994	Yes	Teeth	Several episodes between 1 m and 12 m	_	1	1
Pfau[6] 1995	Yes	No	Several episodes between 1 m and 7 y	Infection/fever	1–2	2
De Argila[7] 1996	No	SNC (white substance)	Several episodes between 2 m and 18 m	_	1	1
Nagasse[8] 1997	Yes	No	1 episode 3 y	Ruby laser	1	1
Van Leeuwen[9] 2000	Yes	No	1 episode 8 m	_	1	_
Bodak[10]						
N1 2003	Yes	Retinal vasculopathy	Several episodes between 9 m and 18 m	Infection	1	_
N2 2003	Yes	No	Several episodes between 9 m and 12 m	Fever	2	_
N3 2003	No	No	1 episode 7 m	Fever	1–2	2
N4 2003	Yes	Convulsions	6 episodes between 4 m and 11 m	Infection/not fever	1	_
N5 2003	Yes	No	Several episodes between 6 m and 7 y	Fever	1	_
Our case	No	Teeth	4 episodes between 4 m and 18 m	Infection/fever	1–2	2

B Llombart,†* L Garcia,† C Monteagudo,‡ JM Martín,† V Alonso,† I Pinazo,† L Calduch,† E Jordá†

*Departments of †Dermatology and ‡Pathology, Hospital Clinico Universitario, Valencia, Spain. *Corresponding author, Servicio de Dermatología, Hospital Clínico Universitario, Avenida Blasco Ibáñez 17, 46010, Valencia, España, fax 0039 963862646; E-mail: beatriz.llombart@uv.es*

References

1 Landy SJ, Donnai D. Incontinentia pigmenti (Bloch–Sulzberger syndrome). *J Med Genet* 1993; **30**: 53–59.
2 Carney RG. Incontinentia pigmenti: a world statistical analysis. *Arch Dermatol* 1976; **112**: 535–542.
3 Barnes CM. Incontinentia pigmenti: a report of a case with persistent activity into adult life. *Cutis* 1978; **22**: 621–624.
4 Bessems PJM, Jagtman BE, Van de Staak WJB, Hulsmans RFH, Croughs KJM. Progressive persistent hyperkeratotic lesions in incontinentia pigmenti. *Arch Dermatol* 1988; **124**: 29–30.
5 Sahn EE, Davidson LS. Incontinentia pigmenti: three cases with unusual features. *J Am Acad Dermatol* 1994; **31**(5 Part 2): 852–857.
6 Pfau A, Landthaler M. Recurrent inflammation in incontinentia pigmenti of a seven-year-old child. *Dermatology* 1995; **191**: 161–163.
7 De Argila D, Rivera R, Guerra A, Iglesias L. Incontinentia pigmenti: a case with an unusual course. *Pediatr Dermatol* 1996; **13**(5): 434–435.
8 Nagase T, Takanashi M, Takada H, Ohmori K. Extensive vesiculobullous eruption following limited ruby laser treatment for incontinentia pigmenti: a case report. *Australas J Dermatol* 1997; **38**: 155–157.
9 Van Leeuwen RL, Wintzen M, van Praag MCG. Incontinentia pigmenti: an extensive second episode of a 'first-stage' vesiculobullous eruption. *Pediatr Dermatol* 2000; **17**: 70.
10 Bodak N, Hadj-Rabia S, Hamel-Teillac D, de Prost Y, Bodemer C. Late recurrence of inflammatory first-stage lesions in incontinentia pigmenti. *Arch Dermatol* 2003; **139**: 201–204.

DOI: 10.1111/j.1468-3083.2004.01141.x

Diffuse cutaneous eruption due to interferon alfa and ribavirin treatment of chronic hepatitis C

To the Editor

Interferon alfa and ribavirin combination, a selected treatment option for chronic hepatitis C, has been reported to cause various cutaneous changes.[1] We present such a case who developed a diffuse, pruritic eruption.

A 56-year-old man was first seen because of a pruritic eruption of 1 week's duration, which had started at the extremities and had progressed to include his entire body. Examination revealed erythematous and mildly oedematous 1–20 cm wide plaques with no sharp borders. Lesions showed a tendency to coalesce and were most prominent in the lower extremities and the torso. A few plaques in the gluteal region and upper extremity also had erosions and excoriations (fig. 1). The patient had been diagnosed with hepatitis C 10 months prior to his cutaneous complaints and had been started on ribavirin + interferon alfa therapy 10 weeks ago. Laboratory work-up was normal except for anaemia and leucopenia, which had emerged during antiviral therapy and was accepted as an expected side-effect. Hepatitis C virus RNA, which had been positive before therapy, was negative this time. A lesional biopsy showed mild psoriasiform hyperplasia and a mixed inflammatory reaction consisting of perivascular eosinophils and lymphocytes. Immunofluorescent examination showed only scattered and

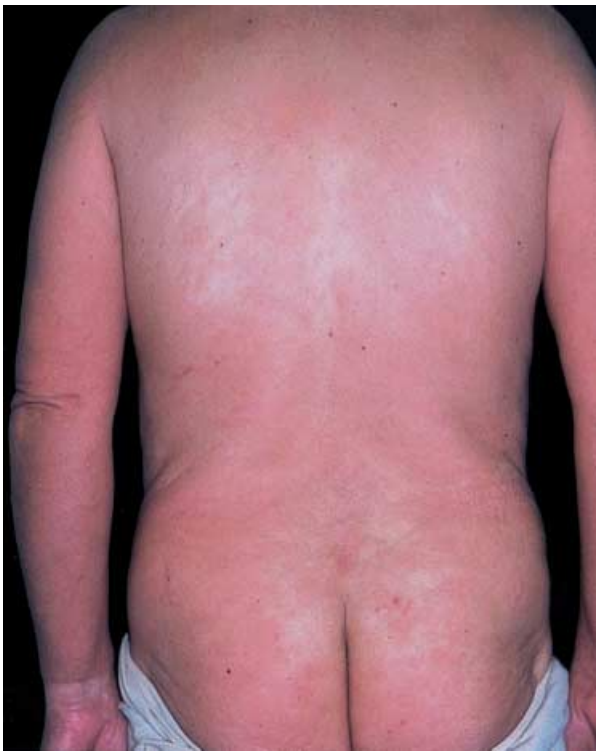


fig. 1 Erythematous and mildly oedematous plaques with no sharp borders and a tendency to coalesce most prominently in the lower extremities and the torso.

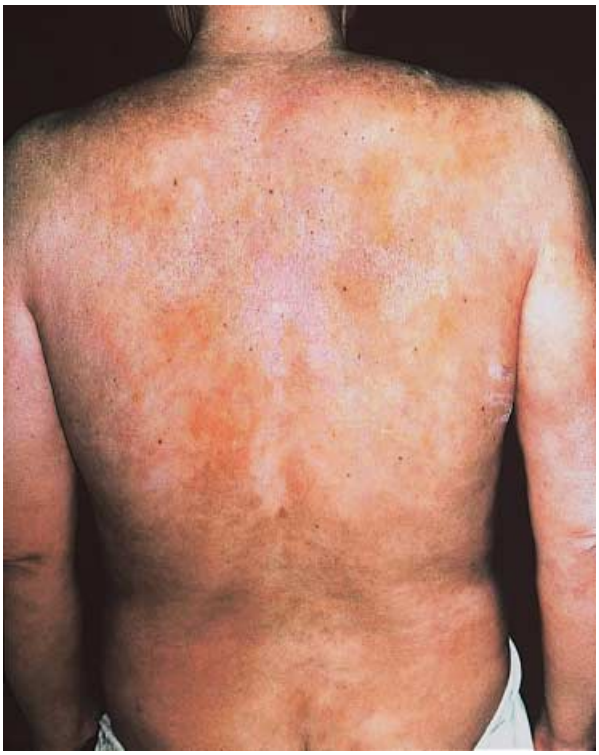


fig. 2 Regression of lesions into diffuse hyperpigmentation and fine desquamation.

perivascular fibrinogen. Patch testing with the standard series revealed no positive reactions. He was started on antihistamines and a topical corticosteroid. Two weeks later, there was no regression and facial involvement was more prominent. A repeat biopsy showed hyperkeratosis, marked acanthosis, focal spongiosis, exocytosis and dermal oedema with a moderate mononuclear inflammatory infiltrate. Topical treatment was switched to a more potent corticosteroid and a second antihistamine. Then the patient was seen at bi-weekly intervals but did not show any improvement except for less pruritus until the end of the second month of the eruption. At this time, which was the 18th week of antiviral therapy, there was an intermission of hepatitis C treatment due to nose bleeds. Interferon alfa was stopped for 1 week and ribavirin for 3 weeks. Rapid regression of the plaques into diffuse hyperpigmentation and fine desquamation was observed during this interval, especially after cessation of ribavirin (fig. 2). Fifteen days after restarting ribavirin therapy the patient was seen again for mild pruritus and similar plaques, mainly on the lower half of the body. From then he was followed with the same topical treatment for 10 weeks until these lesions also regressed by hyperpigmentation.

Among reported cutaneous side-effects of ribavirin and interferon alfa combination therapy are alopecia, herpes, lichen planus, photoallergic eczema, hyperpigmentation, erythema and/or induration at the injection site and a transient generalized rash.[1–4] The most extensive series with diffuse inflammatory lesions has been reported by Dereure *et al.*, who in 20 patients observed eczema-like skin lesions mainly on the extremities and sometimes associated with photosensitivity. Initial appearance was between the second and fourth months; histopathology revealed a perivascular lymphocytic infiltrate and skin testing was not informative.[5] Our patient's clinical history, morphology and distribution of lesions were similar to the ones reported by Dereure *et al.* In contrast to another report on patients with a diffuse eruption following administration of only interferon alfa, our patient's cutaneous changes appeared later and took longer than 2 weeks to disappear.[6] Rapid regression of lesions following intermission of antiviral treatment coupled with the relapse when medication was restarted served as a challenge test in our patient. The fact that hepatitis C virus RNA, positive before therapy, was negative all throughout the eruption also helps us incriminate the interferon alfa and ribavirin combination and not hepatitis C virus as the culprit that caused the cutaneous symptoms.

E Şavk,*† G Uslu,† AÖ Karaoğlu‡ N Şendur,† G Karaman†

Departments of †Dermatology and ‡Gastroenterology, Faculty of Medicine, Adnan Menderes University, Aydýn, Turkey.

**Corresponding author, tel. +90 256 2120020; fax +90 256 2146495; E-mail: ekin.bozkurt@excite.com*

References

1 Sparsa A, Loustaud-Ratti V, Liozon E *et al.* Cutaneous reactions or necrosis from interferon alpha: Can interferon be reintroduced after healing? Six case reports. *Rev Med Intern* 2000; **21**(9): 756–763.

2 Dalekos GN, Christodoulou D, Kistis KG *et al.* A prospective evaluation of dermatological side-effects during alpha-interferon therapy for chronic viral hepatitis. *Eur J Gastroenterol Hepatol* 1998; **10**(11): 933–939.

3 Willems M, Munte K, Vrolijk JM *et al.* Hyperpigmentation during interferon-alpha therapy for chronic hepatitis C virus infection. *Br J Dermatol* 2003; **149**(2): 390–394.

4 Stryjek-Kaminska D, Ochsendorf F, Roder C *et al.* Photoallergic skin reaction to ribavirin. *Am J Gastroenterol* 1999; **94**(6): 1686–1688.

5 Dereure O, Raison-Peyron N, Larrey D *et al.* Diffuse inflammatory lesions in patients treated with interferon alfa and ribavirin for hepatitis C: a series of 20 patients. *Br J Dermatol* 2002; **147**(6): 1142–1146.

6 Toyofuku K, Imayama S, Yasumoto S *et al.* Clinical and immunohistochemical studies of skin eruptions: relationship to administration of interferon-alpha. *J Dermatol* 1994; **21**(10): 732–737.

DOI: 10.1111/j.1468-3083.2004.01143.x

Has *Helicobacter pylori* eradication therapy any effect on severity of rosacea symptoms?

To the Editor

Rosacea is a relatively common cutaneous vascular disorder with a wide spectrum of clinical manifestations. Genetic disposition, gastrointestinal disturbances, *Demodex folliculorum* mites, hypertension and psychogenic factors have been attributed as causes of this disease, but the aetiology still remains to be identified.

The role of *Helicobacter pylori* in rosacea has been an area of interest after the presentation of a higher prevalence of *H. pylori* infection in patients with rosacea than in the general Italian population by Rebora *et al.*[1] in 1994. Then, the possible aetiological role of *H. pylori* in rosacea has been investigated in several clinical trials.[2–5] Taking into consideration the contradictory results on rosacea and the infection of *H. pylori*, we undertook a study in which we investigated the prevalence of *H. pylori* in rosacea and the effect of eradication therapy for *H. pylori* infection on the severity of the rosacea symptoms. Our study population consisted of 39 patients with clinically and histologically proven rosacea. The severity of the disease was staged based on the criteria which was described by Plewing and Jansen[6] Following the diagnosis and staging of the disease, presence/absence of *H. pylori* infection was investigated by ^{14}C urea breath in our nuclear medicine department. The Heliprobe urea breath test (Heliprobe, Noster System AB, Stockholm, Sweden), a recently introduced dry system, was used as the ^{14}C urea breath test following 6 h fasting. Rosacea patients with *H. pylori* infection were assigned to the treatment group and were given a triple regimen consisting of amoxicillin 1000 mg (two times a day), clarithromycin 500 mg (two times a day) and lansoprazole 30 mg (two times a day), orally for 2 weeks. During the time of *H. pylori* eradication therapy, no other treatment for rosacea was given. At the end of treatment (at the final clinical follow-up) each patient underwent a follow-up ^{14}C urea breath test to reveal whether the infection was successfully eradicated or not. The clinical evaluation was done three times for each patient: at baseline (day 0: the time of diagnosis), at the end of therapy (day 14) and at the final clinical follow-up (day 60). All measurements were done by the same dermatologist using the same staging criteria and the efficacy measurement of *H. pylori* eradication therapy was made comparing the findings of baseline and final (60th day) clinical evaluation. Follow-up clinical evaluations were labelled as 'partial remission' (decrease in the stage compared with basal evaluation), 'no change'(remaining in the same stage compared with basal evaluation) and 'total remission' (disappearing of symptoms). The distribution of rosacea staging and *H. pylori* positivity at presentation are summarized in Table 1. Comparison of basal and final clinical evaluation (60th day) revealed that 13 of 20 (65%) patients in whom *H. pylori* was successfully eradicated, had no change and seven of 20 (35%) had some improvement in the severity of symptoms. Three of four patients (75%) with persistent *H. pylori* positivity following the eradication therapy had no change, while one of four (25%) had partial remission in the severity of rosacea symptoms (Table 2). In terms of partial remission, there was no statistically significant difference between the patients who had *H. pylori* at the end of the treatment and who were eradicated. (Table 2, Fisher's Exact Test, $P = 0.593$). Twenty-six of 39 (66.6%) rosacea patients had *H. pylori* infection and the remaining 13 (33.4%) were negative for the organism. It was shown by ^{14}C urea breath test that in 20 of 24 patients (83.3%) *H. pylori* infection was successfully eradicated. Among those 20 patients, only less than half of the patients (seven of 20; 35%) had some clinical improvement in rosacea symptoms and the majority of patients (13 of 20; 65%) had no change in the severity of the disease in spite of the fact that *H. pylori* was successfully eradicated. The above findings led us to think that there is no clear beneficial effect of *H. pylori* eradication on rosacea symptoms in concordance with the results of the studies by Herr and You[4] and Bamford *et al.*[5] There have been contradictory reports regarding the question of whether prevalence of *H. pylori* infection is higher than non-rosacea patients. In this presented study consisting of 39 rosacea patients we found the prevalence of *H. pylori* infection to be 66.6% using ^{14}C urea breath test. We did not have our own control group for comparison, but the prevalence of *H. pylori* infection in non-rosacea patients in our hospital has been previously reported to be 60% using the ^{13}C urea breath test, which is very similar to patients with rosacea in our study.[7] Therefore, it can be thought that the prevalence of *H. pylori* is similar to those of non-rosacea patients in our population, which is disconcordant with the other studies.[1,8,9]

Table 1 Characteristics of 39 rosacea patients

Patient no.	Age, sex	Result of ^{14}C urea breath test	Clinical staging of rosacea: Baseline (day 0)	First evaluation (day 14)	Final evaluation (day 60)	*H. pylori* eradication therapy†
1	58, M	+	3	1	1	Successful
2	53, M	+	2	1	1	Successful
3	40, F	+	2	1	1	Failed
4	51, M	+	2	1	1	Successful
5	55, M	+	2	1	1	Successful
6	49, F	+	1	0	0	Successful
7	44, F	+	2	1	1	Successful
8	53, F	+	2	2	2	Successful
9	61, F	+	2	1	2	Successful
10	49, F	+	2	2	2	Successful
11	48, M	+	2	1	2	Failed
12	43, F	+	2	1	2	Failed
13	49, F	+	2	1	2	Successful
14	62, M	+	2	2	2	Successful
15	45, F	+	3	3	3	Successful
16	63, F	+	3	1	3	Successful
17	44, F	+	2	2	2	Successful
18	39, M	+	3	1	3	Successful
19	57, F	+	2	2	2	Successful
20	48, F	+	2	2	2	Failed
21	52, F	+	2	2	2	Successful
22	46, M	+	1	1	1	Successful
23	34, F	+	2	1	2	Successful
24	40, M	+	2	1	1	Successful
25*	50, F	+	2			Not done
26*	50, M	+	2			Not done
27	43, F	−	1			Not done
28	44, F	−	3			Not done
29	40, F	−	1			Not done
30	55, F	−	2			Not done
31	55, M	−	2			Not done
32	20, F	−	2			Not done
33	33, M	−	2			Not done
34	62, F	−	3			Not done
35	65, M	−	2			Not done
36	41, F	−	2			Not done
37	66, F	−	1			Not done
38	54, M	−	3			Not done
39	45, M	−	2			Not done

*The patients refusing the eradication therapy for *H. pylori*.
†Determined by ^{14}C urea breath test.

Lack of control group is the limitation of our study. But it can be concluded that improvement in rosacea following eradication therapy for *H. pylori* seems unlikely to be due to eradication of *H. pylori*.

Table 2 Improvement of rosacea symptoms after *H. pylori* eradication

Result of ^{14}C urea breath test	Partial remission	No change	Total remission	Total
H. pylori+	1	3	0	4
H. pylori–	7	13	0	20
Total	8	16	0	24

$P = 0.593$, > 0.05. Fisher's Exact Test.

GK Gedik,†* A Karaduman,‡ B Sivri,§ B Caner†

*Departments of †Nuclear Medicine, ‡Dermatology and §Gastroenterology, 06100, Sihhiye, Ankara, Turkey. *Corresponding author, tel. +90 312 3051336; fax +90 312 3093508; E-mail: goncak@hacettepe.edu.tr*

References

1 Rebora A, Drago F, Picciotto A. *Helicobacter pylori* in patients with rosacea. *Am J Gastroenterol* 1994; **89**: 1603–1604.

2 Szlachcic A, Sliwowski Z, Karczewska E *et al. Helicobacter pylori* and its eradication in rosacea. *J Physiol Pharmacol* 1999; **50**: 777–786.

3 Utaş S, Özbakır Ö, Turasan A *et al. Helicobacter pylori* eradication treatment reduces the severity of rosacea. *J Am Acad Dermatol* 1999; **40**: 433–435.

4 Herr H, You CH. Relationship between *Helicobacter pylori* and rosacea: it may be a myth. *J Korean Med Sci* 2000; **15**: 551–554.

5 Bamford JT, Tilden RL, Blankush RN *et al.* Effect of treatment of *Helicobacter pylori* infection on rosacea. *Arch Dermatol* 1999; **135**: 659–663.

6 Plewing G, Jansen T. Rosacea. In: Freedberg IM, Eisen AZ, Wolff K *et al.*, editors. *Dermatology in General Medicine*, 5th edn. McGraw-Hill, Philadelphia 1999: 785–794.

7 Balaban Y, Özarslan E, Ercis S *et al.* Hacettepe Üniversitesi Erişkin Hasta Grubunda Gaitada Helikobakter Antijen Testinin Helicobakter Kültürü ve Üre-Nefes Testi ile Karsilastirilmasi. *Turkish J Gastroenterol* 2001; **12** (Suppl. 1): 78.

8 Gürer MA, Erel A, Erbaş D *et al.* The seroprevalence of *Helicobacter pylori* and nitric oxide in acne rosacea. *Int J Dermatol* 2002; **41**: 768–770.

9 Powell FC, Daw MA, Duguid C. Positive *Helicobacter pylori* serology in rosacea patients. *Irish J Med Sci* 1992; **161** (Suppl.): 75 (Abstr.).

DOI: 10.1111/j.1468-3083.2005.01144.x