# Correspondence

## GTP-cyclohydrolase I and vitiligo

Sir, We have read with great interest the report by Bandyopadhyay *et al*. entitled 'Vitiligo is not caused by mutations in GTP-cyclohydrolase I gene' in this Journal.[1] Previously, a relationship between GTP-CHI deficiency and vitiligo was suggested by De la Fuente-Femandez.[2] However, examination of the international database on tetrahydrobiopterin deficiencies and examination of more than 4000 patients with vitiligo failed to demonstrate any causative relationship between these two entities.[3] Unfortunately, the above authors missed this comment on this subject.[4] However, the analysis of the GTP-CHI in 25 patients with vitiligo confirmed the clinical data.

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## Multiple lentigines and testicular microlithiasis

Sir, The nosology of conditions characterized by the development of multiple lentigines has not been entirely clarified. Many of the lentiginosis syndromes are associated with extracutaneous manifestations. We report a case of multiple lentigines associated with testicular microlithiasis.

A 17-year-old school boy presented with marked lentigo formation involving his face, neck and the 'V' of the chest. The vermillion of his lips and ocular sclerae were also involved (Fig. 1). His mother stated that these had begun to appear shortly after birth and had gradually increased in number. His referral had been prompted by cosmetic concerns.

His general health was excellent and he had a type 1 skin (Boston classification). There was no family history of similar cutaneous changes and his sister has a normal complexion. There were no signs of any of the systemic abnormalities incorporated in the lentiginosis acronymn conditions (LEOPARD, NAME, LAMB)[1,2] and an ECG and ECHO cardiogram were normal. In view of his low tolerance to natural sunlight, xeroderma pigmentosum (classical and variant forms) were excluded by phototesting and by DNA excision studies.

Complaints of scrotal discomfort 2 years after his initial presentation resulted in ultrasonic examination of his testes which demonstrated multiple punctate, nonshadowing hyperechoic foci within the testicular parenchyma, typical of testicular microlithiasis (Fig. 2). This is an uncommon abnormality, usually an incidental finding, and the result of calcium deposits in the lumina of the seminiferous ducts. Microlithiasis appears to be associated with premalignant and malignant change of the testes.[3,4]

Genital abnormalities such as gonadal hypoplasia, hypospadias, cryptorchidism and absent ovaries have been reported

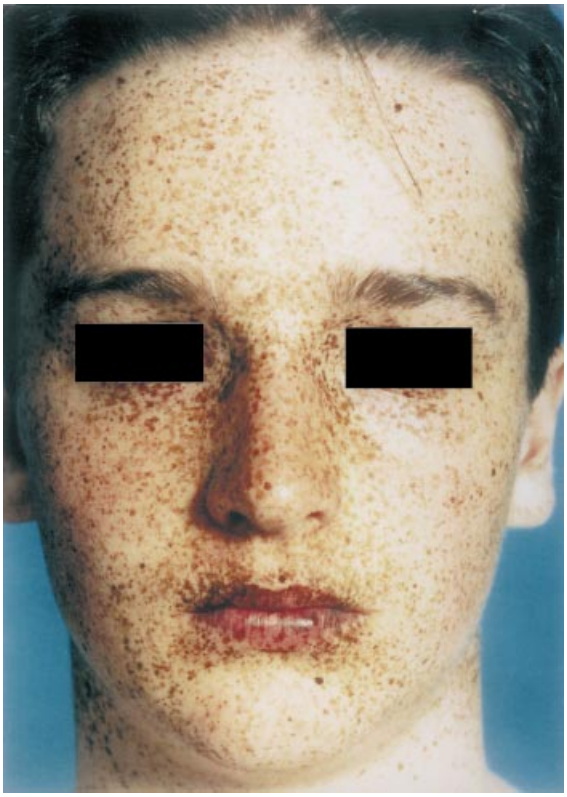

**Figure 1** multiple facial lentigines.

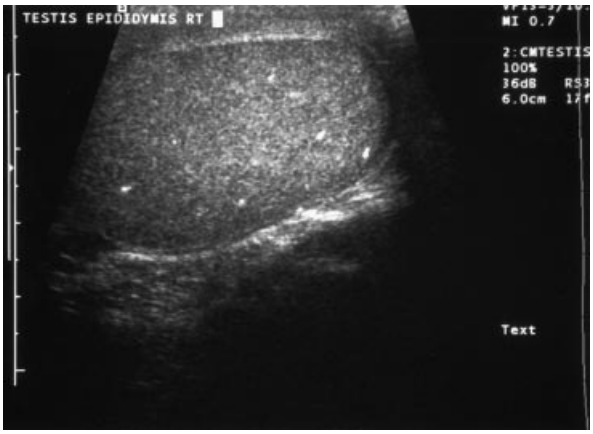


**Figure 2** Ultrasound of testis showing calciferous deposits of microlithiasis.

in association with multiple lentigines. The Carney complex has also been associated with Sertoli cell tumours.[5] Although a chance association cannot be excluded, this case suggests that testicular microlithiasis should be considered in the context of multiple lentigines.

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## Spontaneous regression of a tufted angioma

Sir, Tufted angioma is a rare, benign vascular tumour[1] which has been described under a variety of synonyms including progressive capillary haemangioma[2] and angioblastoma of Nakagawa.[3] The tufted angioma tends to grow progressively and treatment can be difficult. We report a case of spontaneous regression of this lesion.

A 2-month-old female child presented with a tender lesion below the left antecubital fossa that had been present since she was 3 weeks old. Examination revealed a 2 × 2.5 cm firm subcutaneous tender lump. The overlying skin had a bluish colouration with a more erythematous patch evident centrally (Fig. 1a). The remainder of the skin was normal. There was no other medical history of note and no family history of similar lesions. The lesion was biopsied. Histological examination showed lobulated aggregates of basophilic cells within the dermis (Fig. 2). These cells appeared vasoformative with canalization but showed a predominantly solid growth pattern. There was no cytological atypia and mitoses were inconspicuous. There were slit-like lymphovascular spaces at the periphery of the aggregates (Fig. 3). Immunocytochemistry demonstrated positivity with factor VIII-related antigen, Ulex europaeus agglutinin I and smooth muscle actin. In addition to these cellular aggregates there were single cells

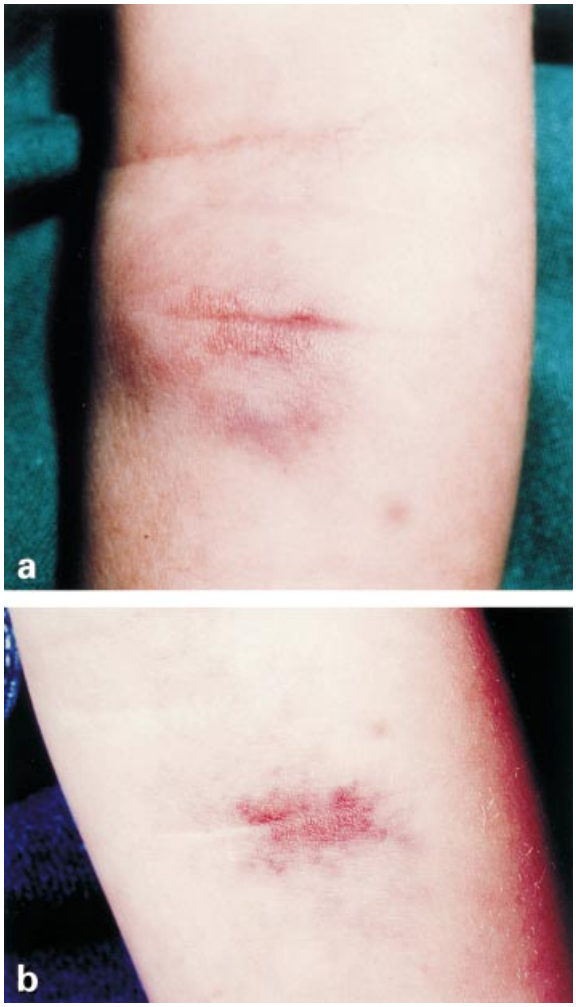


**Figure 1** (a) A swelling of bluish coloration is present below the left antecubital fossa at time of presentation. (b) A residual macular erythematous patch is evident at follow-up 2 years later.

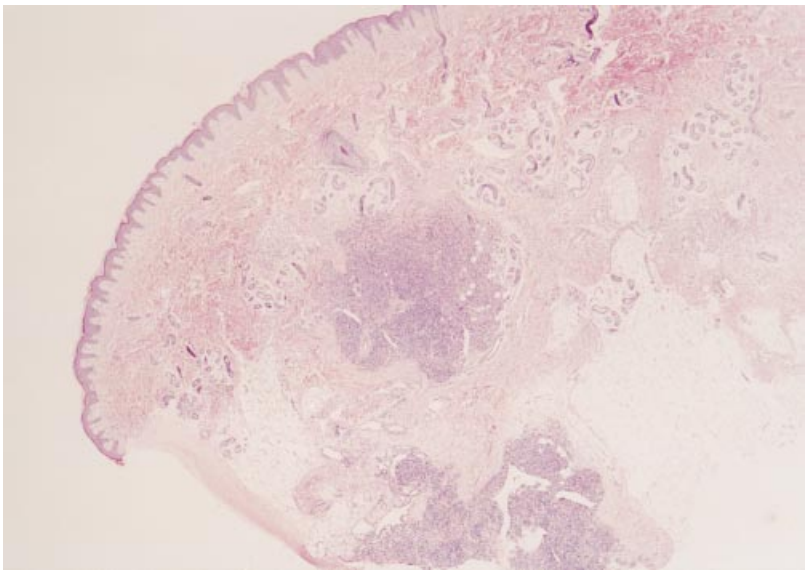

**Figure 2** Basophilic cellular aggregates within the dermis (haematoxylin & eosin × 40).

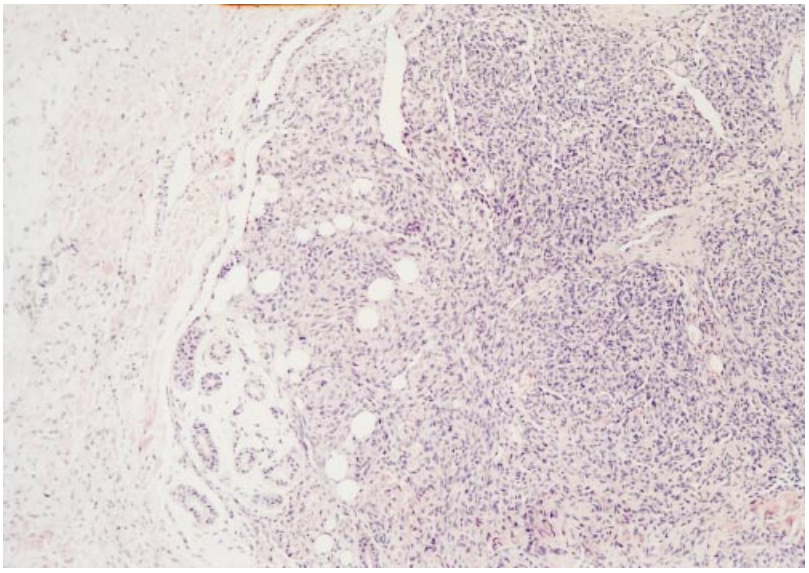

**Figure 3** Slit-like lymphovascular spaces within the cellular aggregates (haematoxylin & eosin × 100).

infiltrating through dermal collagen, surrounding skin adnexae and there were further dilated lymphovascular channels in the adjacent dermis.

The child was referred to the plastic surgery department for assessment of possible complete excision of the lesion. It was decided to observe the lesion. The lesion gradually regressed over a 14-month period and became nontender. The child is now 2 years old and the lesion is macular and is no longer tender or indurated (Fig. 1b).

The tufted angioma occurs mainly in early childhood and usually involves the trunk and neck. It typically presents as a solitary red or red–brown patch or plaque which is frequently indurated and tender. A variety of treatments have been used in the management of the tufted angioma with limited efficacy. These include excision, cryotherapy and radiotherapy,[1] pulsed dye laser,[4] topical and intralesional steroids,[5,6] high-dose systemic steroids,[7] and interferon-alpha.[8] Recurrences following surgical excision are common.[1,9]

Spontaneous regression of tufted angioma has been reported by several authors.[10–14] Miyamoto *et al.*[10] reported a 62-year-old woman with acquired tufted angioma who presented with a 1 year history of multiple nodules on the chest and neck. Many of these lesions regressed spontaneously over a 6 month period. Lam *et al.*[11] reported two children aged 3 months with tufted angiomata. One lesion was a 6 cm plaque, the other a 12 cm mass of angiomatous papules. The former regressed

over 3 years, the latter over 8 years. Jang *et al.*[12] reported a 2-month-old child with a tufted angioma on the abdomen since birth. This regressed over a 10-month period. Chu *et al.*[13] reported an eruptive vascular proliferation which histologically resembled tufted angioma, developed 10 days after liver transplantation and resolved spontaneously some weeks later. Recurrent acquired tufted angioma has been reported to develop during pregnancy and to regress spontaneously 6 months after delivery.[14]

The pathogenesis of the tufted angioma remains unclear and there is controversy whether it is due to a reactive or neoplastic process.[5] Elevated serum levels of oestrogen in pregnancy may be important in the development of vascular proliferations such as spider naevi, pyogenic granuloma and tufted angioma.[14] It has also been reported that there is an increase of oestrogen and progesterone receptors in the lesional skin of the unilateral nevoid telangiectatic syndrome.[15] We agree with the suggested management of tufted angioma that unless the lesion is symptomatic or cosmetically disfiguring, observation is the treatment of choice for lesions that are not amenable to surgical excision.[6]

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## Bullous pemphigoid and neurofibromatosis—a chance association requiring special vigilance

Sir, Bullous pemphigoid (BP) is an autoimmune blistering disorder characterized by pruritus, urticated erythema and large tense blisters. A variety of disorders have been associated with BP including pernicious anaemia, vitiligo, insulin-dependent diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis and multiple sclerosis.[1] We report a case of pemphigoid in a patient with neurofibromatosis type 1 (NF1), an association not described previously.

A 59-year-old woman presented with a 2-week history of blistering of the arms and legs. She was known to suffer from NF1 and had a previous history of cerebrovascular accident treated with aspirin. Examination showed urticated erythematous plaques on the trunk and limbs, some of which had tense blisters filled with serous fluid. There were no oral lesions and the face, scalp, palms and soles were uninvolved. She also had multiple cutaneous neurofibromas on the trunk and extremities, a few of which were in close proximity to the blisters (Fig. 1). Biopsy of a blister from the arm showed subepidermal separation with a moderate perivascular chronic inflammatory infiltrate in the dermis composed of lymphocytes and scattered eosinophils. Immunofluorescence revealed a linear deposition of C3 and IgM along the dermo-epidermal junction consistent with BP. Epidermolysis bullosa acquisita was excluded by antilaminin and type 4 collagen stains on split-skin preparations. The patient responded well to prednisolone 40 mg daily which was then gradually tapered; she is presently on 10 mg a day and has been in remission for the last 8 months. Extensive investigations showed no associated malignancy and in particular there was no evidence of central nervous system malignancy although interestingly, since the commencement of prednisolone, we have noted a marked increase in the number of neurofibromas (Fig. 2).

Even though the association between NF and BP may be coincidental, the mast cell plays a role in the pathogenesis of both conditions.[2] The proposed mechanism of blister formation in pemphigoid involves the activation of the complement cascade by the BP antigen–antibody complex that in turn activates mast cells. Degranulation of mast cells leads to a release of the inflammatory mediator eosinophil chemotactic factor. Subsequent infiltration by eosinophils and their degranulation is central in the development of the blister. In NF, Riccardi had suggested that local trauma induces mast cell accumulation and secretion of various cytokines which in the presence of the NF mutation, leads to the proliferation of Schwann cells, perineural cells, fibroblasts, vascular elements and further accumulation of mast cells, resulting in neurofibroma formation.[3]

Malignant transformation in NF1 patients occurs in excess

  

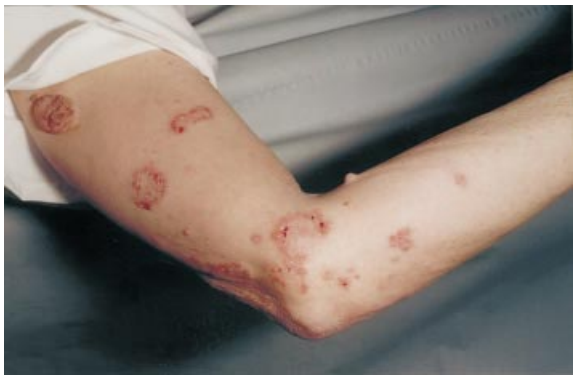

**Figure 1** Erythematous plaques and blisters with scanty neurofibromas.

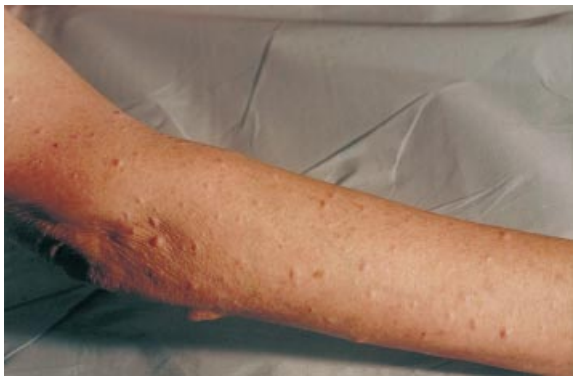

**Figure 2** Numerous small neurofibromas in the same area after commencement of prednisolone.

but the rates vary widely. A tendency to develop neurofibrosarcomas, Wilms' tumour, rhabdomyosarcoma and leukaemia has been noted.[4] No cutaneous or systemic malignancy has yet been found in our patient; however, the occurrence of new neurofibromas with prednisolone is a worrying finding that has not been reported previously. Neurofibromin, the gene product of the *NF-1* gene, is a GTPase-activating protein that acts by negatively regulating Ras proteins.[5] Similarly, glucocorticoids down-regulate the expression of the growth-associated gene *Ha-ras*[6] both potentially contributing to tumour development.

Thus BP, a condition potentially associated with malignancy[7] arising in a patient with neurofibromatosis, may compound this risk of malignancy, especially when combined with with the immunosuppressive effects of steroids. We speculate, therefore, that in this setting the chance of malignancy arising may be significantly higher than expected and close follow-up is warranted.

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## Staphylococcal fissure of the upper lip

Sir, It has previously been reported that persistence of fissuring of the lower lip can be caused by infection with *Staphylococcus aureus*.[1]

We have recently seen a patient in whom colonization with *S. aureus* has resulted in persistence of a fissure of the upper lip.

A 51-year-old male who was previously fit, presented with a 1-year history of a cracked area on the right side of the upper lip. This had started as chapping and general dryness at the time of an upper respiratory tract infection, but had become persistent and worsened to produce a deeper fissure. He had previously been seen by a surgical team. Conservative treatment with emolients had been unsuccessful and the area had therefore been excised completely. Histology showed a mixed inflammatory infiltrate, with colonies of bacteria on the skin surface. A month after excision the fissure recurred (Fig. 1). A swab was taken from this area, showing a heavy growth of *S. aureus.* Treatment with twice daily mupirocin ointment resulted in complete healing of the fissure within 2 weeks.

Staphylococcal infection has been implicated previously as a cause of prolonged median fissuring of the lower lip.[1] This is the first report of the same problem occurring in the upper lip. Chapping and minor fissuring of the lips are common, but are not normally persistent. Under normal circumstances one would certainly expect healing after surgical excision. With localization to the upper lip one should also consider possible nasal carriage of *Staphylococcus* as a reason for recurrence. Bacterial colonization should always be considered in cases of prolonged lip fissure and swabs taken for bacterial culture, both from the fissure and the nose. The absence of crusting or

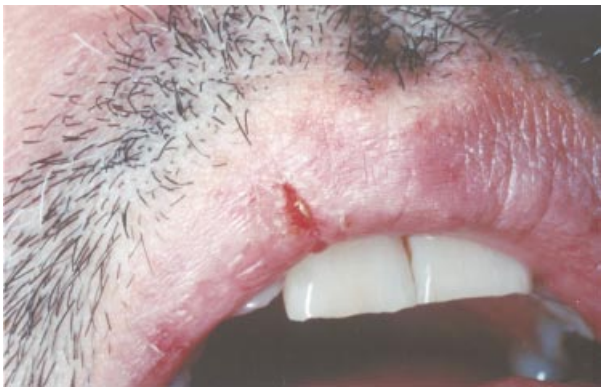

**Figure 1.** Reoccurance of fissure 1 month after excision.

exudate should not exclude this diagnosis. Treatment of this condition with topical antibiotics is quick, cheap and effective.

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## Treatment of pityriasis versicolor with a shampoo containing 1% bifonazole (Agispor$^{R}$ shampoo) in children

Sir, Pityriasis versicolor is a common, chronic superficial infection of the skin caused by *Malassezia furfur*. It is characterized by yellow to reddish brown or hypopigmented scaly patches on the upper trunk, neck and arms. Mild itching may be present. Pityriasis versicolor affects mostly children and young adults. In this open study we evaluated the clinical efficacy of bifonazole 1% shampoo (Agispor$^{R}$ shampoo, Agis, Israel), a new antifungal product, in children. Twenty-two children raging in age from 9 to 14 years, who were clinically diagnosed as suffering from mild to severe pityriasis versicolor, were treated with bifonazole 1% shampoo (Agispor$^{R}$ shampoo). Bifonazole 1% shampoo was applied for 3–5 min to the wet trunk and arms once a day for 3 weeks. The same physician evaluated all of the patients before treatment and at the end of the therapy. All patients treated with bifonazole 1% shampoo achieved clinical cure. The drug was well tolerated by the patients with very good compliance; no side-effects were reported. Several therapeutic modalities are used in the management of pityriasis versicolor including topical application of selenium sulphide shampoo and topical or systemic antifungal agents.[1] Topical application of bifonazole 1% cream or solution for 2 to 3 weeks is known to be effective in patients with pityriasis versicolor.[2–5] In the present study, daily use of Agispor$^{R}$ shampoo, a new antifungal product containing bifonazole 1%, for 3 weeks was found to be effective, safe and obviously friendly to use, in the treatment of mild to severe cases of pityriasis versicolor in children.

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