and GVHD-associated leucoderma. Vitiligo developing within 3 months of allogeneic BMT, in the absence of concomitant GVHD, has been reported from an HLA-matched related donor who had extensive vitiligo. In this case the vitiligo may have been acquired through the transfer of donor immunity.

No information regarding vitiligo in the bone marrow donors is available for our patients. Drug-induced hypopigmentation has been described with topical agents such as hydroquinones and diphenycyprone and systemic agents including phenobarbitol, afloqualone and sulphamide. However, our patients had not been exposed to any of these. Depigmentation and leucotrichia have been reported following PUVA treatment for mycosis fungoides (MF), localized to the area of the pre-existing MF lesions. Biopsies with S100 staining in these cases demonstrated the total absence of melanocytes, with no evidence of MF, and it was suggested that the phototherapy may have activated a cell-mediated immunity leading to destruction of the melanocytes. Prior to the onset of leucoderma and leucotrichia both our patients had PUVA treatment which may have contributed to their development by increasing the susceptibility of the melanocytes to immune-mediated destruction.

Leucoderma associated with GVHD has been reported in a 14-year-old boy who had undergone allogeneic BMT for severe aplastic anaemia. The patient developed acute GVHD with skin, gastrointestinal tract and liver involvement at day 21 post-BMT which was successfully treated with methylprednisolone and ciclosporin. He later developed chronic lichenoid GVHD, then hypopigmentation with greying hair and eyelashes evolving into total leucoderma. Skin biopsies were stained with dihydroxyphenylalanine (DOPA), which showed an absence of labelling in the epidermis, indicating a loss of melanocytes. However, there was DOPA-positive cellular debris (melanin) within dermal phagocytes. In addition, the patient’s serum demonstrated elevated cytotoxic activity against two melanocyte cell lines, suggesting the presence of antimelanocyte antibodies. These results suggest that in this patient the depigmentation occurred as a result of a specific immune response against the melanocytes triggered by the GVHD. Another case report describes a 14-year-old white boy who developed total leucoderma arising from chronic GVHD very acutely over the course of 2 weeks. The authors believe that this may be an example of T cell-mediated vitiligo which has been described in the context of antigen-specific immunotherapy for melanoma.

We propose that our patients, who developed leucoderma and leucotrichia in the context of GVHD, also have immune-mediated melanocyte destruction.

References

Key words: graft-versus-host disease, leucoderma, leucotrichia, purnel plus ultraviolet A

Conflicts of interest: none declared.

Acral papular neuromatosis: an early manifestation of Cowden syndrome

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Sir, Cowden syndrome (CS) is an autosomal dominant genodermatosis characterized by the presence of multiple cutaneous and extracutaneous hamartomas and a high risk of thyroid and breast cancers. It is caused by PTEN gene germline mutations, and it has recently been included within the concept of ‘PTEN hamartoma-tumour syndrome’ (PHTS), together with Bannayan–Riley–Ruvalcaba syndrome. Mucocutaneous signs are present in > 90% of patients in their twenties and > 99% in their thirties. Some of the manifestations are considered as pathognomonic features of CS, such as multiple facial trichilemmomas, papillomatous papules, mucosal lesions and acral keratoses, whereas sclerotic fibroma and lipomas are considered as minor criteria. Although mucocutaneous nevi are not included within the diagnostic criteria, a recent report suggests that cutaneous neviomas might be more specific for CS than other cutaneous signs used for the diagnostic criteria.
A 6-year-old girl with noncontributory medical and family history presented with a 4-year history of a persistent papular eruption which progressively developed on the dorsal and lateral aspects of both hands. Multiple minute, translucent, dome-shaped papules, 0.1–4 mm in diameter and occasionally painful, were observed on the back and sides of the thumb and index and middle fingers of both hands (Fig. 1). Physical examination was otherwise unremarkable. Histopathological and immunohistochemical features were diagnostic for cutaneous neuroma (Fig. 2).

Laboratory investigations including serum calcium and phosphate levels, thyroid function tests and serum calcitonin, and 24-h urinary 5-hydroxyindoleacetic acid, vanillylmandelic acid and catecholamines were within normal limits. Ophthalmological examination did not reveal corneal nerve hypertrophy and audiometric tests were normal. Cerebral magnetic resonance imaging and spine X-ray showed no abnormalities.

Subsequently, routine examinations revealed that her mother and maternal grandfather had mucocutaneous lesions characteristic of CS. Histopathological examination confirmed this clinical suspicion.

Initially, mutation analyses were performed in order to exclude diseases associated with benign cutaneous nerve tumours, specifically multiple endocrine neoplasia 2b syndrome (MEN2b) and neurofibromatosis type 2 (NF2). We failed to show any mutations in the RET proto-oncogene or the NF2 gene. Genetic study for CS was undertaken only after observing the clinical and histopathological features of our patient’s maternal relatives. The same germline heterozygous mutation of the PTEN gene was identified in our patient and her mother (487–491delA; K164X) (Fig. 3).

Our patient was followed closely for more than 10 years. After this period, she started to develop isolated papillomatous mucosal lesions, fulfilling criteria for CS. In her mother, additional investigations disclosed a diffuse thyroid hyperplasia and a fibrocystic disease of the breast. Other studies did not show any abnormality. The patient’s grandfather did not consent to be studied, and no further investigations were performed.

Classically, the main disorder to be considered when encountering multiple mucocutaneous neuromas is MEN2b.7 MEN2b is a rare autosomal dominant disorder characterized by the association of medullary thyroid carcinoma, pheochromocytoma, mucosal neuromas and marfanoid phenotype. Mucosal neuromas are the most consistent and distinctive feature (100% of patients) and are present at birth or appear

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**Fig 1.** Multiple minute, translucent papules distributed bilaterally on the back and sides of the index and middle fingers.

**Fig 2.** Histopathological and immunohistochemical examinations were consistent with neuromas, expressing S100 and neurofilament proteins. (a) Haematoxylin and eosin (original magnification × 20); (b) S100 (original magnification × 10); and (c) neurofilament proteins (original magnification × 10).

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during early childhood. Cutaneous neuromas have rarely been described. Recently, a case of multiple cutaneous neuromas together with macular amyloidosis and medullary thyroid carcinoma has been described in a patient with a mutation in the RET proto-oncogene.

Some cases of idiopathic mucocutaneous neuromatosis have been described in the literature. In some of them, genetic analysis failed to show RET proto-oncogene mutations, ruling out MEN2b. However, additional genetic analyses were not performed.

The differential diagnosis of multiple cutaneous nerve sheath tumours should include the group of neurofibromatoses, specifically NF2. Although cutaneous neurilemmomas are seen in up to half of patients with NF2, they are generally a fairly minor component of the disorder. The importance of NF2 lies in the increased risk for the development of intracranial tumours. Some cases of multiple idiopathic cutaneous neurilemmomas, without any other sign of NF2, have been reported. However, as the locus of idiopathic neurilemmomatosis seems to lie within the NF2 gene, it has been postulated that both diseases probably correspond to a single disorder.

Schaffer et al. have recently described mucocutaneous neurofibromatosis as the initial skin manifestation of PHTS. The authors described a 5-year-old boy with macrocephaly and prominent cornal nerves, who progressively developed mucosal and acral neuromas. A genetic analysis of the PTEN tumour suppressor gene revealed a novel heterozygous germline mutation.

In contrast to this case, our patient presented early-onset multiple acral papular neuromas. To our knowledge, this unique clinical form of presentation has not been previously reported. The diagnosis of CS was suspected only after a careful clinical examination of the mother and maternal grandfather, and was confirmed only after performing PTEN gene mutation analysis.

Our observation supports the view that mucocutaneous neurofibromatosis can represent an early manifestation of CS and could provide an early clue to the diagnosis of CS.