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Squamous cell carcinoma in a child with Clericuzio-type poikiloderma with neutropenia

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MADAM, Poikiloderma with neutropenia (PN) is a rare disorder attributed to mutations in the *USBI* gene,^{1,2} with many similarities to other hereditary poikilodermas (HP).³ The risks ascribed to this condition are yet to be fully elucidated.

We report the case of a patient with PN who developed a squamous cell carcinoma (SCC) of the toe at an early age, and we include studies demonstrating abnormal neutrophil function.

Our patient developed pigmented, reticulate skin lesions with atrophic change and telangiectasia on the arms, legs, face and trunk⁴ from the age of 3 months. Additional features include pachonychia of the toenails, occasional mouth ulcers and plantar keratoderma. Distinctive facies were noted: a saddle nose, flat nasal bridge, flared nostrils and prominent forehead with some mid-face hypoplasia (Fig. S1; see Supporting Information).

She was initially on the 25th centile for height and weight; however, this fell after her third year to her current stature below the 2nd centile for height and weight. Ophthalmology reviews have shown no abnormality. There is no history of photosensitivity, noting that the family lives in Cyprus. However, the patient has taken great care to avoid sun exposure, using high factor sun protection cream and covered shoes whenever outside.

The initial diagnosis was considered to be Rothmund–Thomson syndrome; however, she had a normal karyotype and no evidence of a *RECQL4* mutation.³ A persistent neutropenia became apparent from the age of 3 years. This was asso-

ciated with frequent admissions for infections requiring intravenous antibiotics, and necessitating the initiation of granulocyte colony stimulating factor (G-CSF) at 5 years. A diagnosis of PN was made and genetically proven.⁵ Direct sequencing shows the patient to be homozygous for a *USBI* gene mutation. Mutation analysis revealed a point mutation 541C>T, protein Gln181X. The patient's asymptomatic parents are heterozygous for this mutation.

Her haemoglobin and platelet counts have remained low/normal to low since first recorded at 2 years. Neutrophils have remained very low, in the absence of G-CSF support. Recently she has relied on antibiotic prophylaxis, with G-CSF for breakthrough infections only.

She presented at 13 years with a nonhealing skin lesion on the right fourth toe (Fig S1; see Supporting Information). This was treated at an outside hospital as an infection, by debridement and repeat dressings, but with no improvement. She was subsequently evaluated at our institution 16 months after onset. Examination revealed the toe to be swollen and purple with no adjacent spread. Biopsy revealed it to be a SCC (Fig. 1). The fourth toe was amputated and healed well; 3 months postsurgery she has recovered completely.

This patient had been referred to in the literature^{4,5} prior to the development of the SCC.

Histology showed an acanthotic epidermis with hypergranulosis and compact hyperkeratosis (Fig. 1). A longitudinal section through the junction of the ulcerated area demonstrated an invasive well-differentiated SCC, with adjacent basal atypia that was completely excised by at least 4 mm.

Neutrophil function studies have been performed twice. Phagocytosis of *Escherichia coli* and shedding of L-selectin in response to lipopolysaccharide or phorbol 12-myristate 13-acetate (PMA) were normal. On both occasions patient neutrophils produced a significantly lowered respiratory burst when stimulated with PMA (8% of the median response in

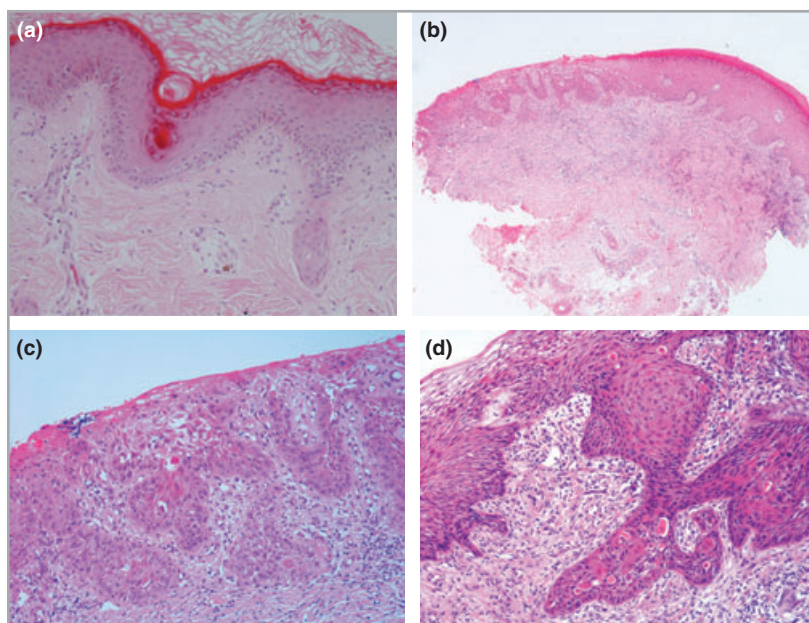


Fig 1. Photomicrographs demonstrating (a) background skin with hyperkeratosis and acanthosis, (b) skin immediately adjacent to an area of invasive squamous cell carcinoma seen on low power, which on higher power (c,d) shows typical invasive features well differentiated from infiltrating nests of tumour and marked dyskeratosis.

Table 1 Neutrophil function testing

Function	Patient value	Normal range
L-selectin (CD62L) shedding		
Fold decrease in L-selectin (mfi)		
Response to LPS	4.4	2.6–10.6
Response to PMA	4.6	2.3–10.2
Fold increase in CD11b (mfi)		
Response to LPS	2.1	2.2–7.0
Response to PMA	2.2	2.3–8.4
Phagocytosis		
% Granulocytes engulfing <i>Escherichia coli</i>		
5 min	94.9	87.6–96.4
10 min	98.3	94.2–99.2
Respiratory burst		
DHR conversion to rhodamine 123 (mfi)		
Response to <i>E. Coli</i>	58	28–122
Response to PMA	36	211–663

L-selectin shedding was assessed using an in-house assay. Phagocytosis and respiratory burst were assessed using the Phagotest and Phagoburst kits, respectively (both Glycotope, Berlin, Germany). Normal ranges were established by testing healthy controls (L-selectin shedding, $n = 23$; phagocytosis, $n = 13$; respiratory burst, $n = 19$) and expressed as the mean \pm SD. mfi, median fluorescence intensity; LPS, lipopolysaccharide; PMA, phorbol 12-myristate 13-acetate; DHR, dihydrorhodamine 123.

healthy donors) but a normal response to *E. coli* as assessed by oxidation of dihydrorhodamine 123 (Table 1).

We report the case of a patient with PN who developed a SCC of the toe at an early age. PN is an autosomal recessive condition linked to the USB1 gene.^{2,6,7} Mutations of the USB1-gene have an association with cancer; acute myeloid leukaemia has been described twice, and one patient developed a SCC on the left hand, which was successfully excised.⁸ A variable but noncyclical neutropenia is common to most patients,⁴ though debate remains over the haematological pathology. Erythroid and megakaryocytic lineages are often marginally depressed, but the striking feature is severe neutropenia.⁸

A distinctive facies is predominant in those affected with PN, of which the major features are saddle nose, prominent forehead and midface hypoplasia,^{1,2,6,9} which is not a feature of other HP. The clinically diagnostic triad of poikiloderma, neutropenia and characteristic facies, though a possibility, requires further cases in order to be established.

Defective neutrophil function has been reported in PN,^{6,7} with reduced respiratory burst and/or bacterial killing with or without impaired chemotaxis in the context of normal phagocytosis. Our testing has confirmed normal phagocytic ability in the neutrophils of our patient. Oxidative burst was normal in response to *E. coli* but severely impaired in response to PMA, an intracellular activator of protein kinase C (PKC), which is required for assembly of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. The neutrophils of this patient are not impaired in their ability to shed L-selectin, and upregulate CD11b in response to stimulation with lipopolysac-

charide, which to our knowledge has not been previously reported. We do not know whether the USB1 gene product affects PKC activation or the assembly of NADPH oxidase; either could explain the abnormal oxidative burst. The exact function of USB1 remains elusive, though a role in RNA biogenesis is proposed given its homology to prokaryotic RNA 3'-5' ligases.¹⁰ One function of USB1 may be to regulate signalling pathways in haematopoietic cells.^{1,11,12}

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Supporting Information

Additional Supporting Information may be found in the online version of the article:

Fig S1. Left: Characteristic facies showing midface hypoplasia; also note poikiloderma with prominent pigmentary changes. Right: Preoperative image of the nonhealing ulcer of the right fourth toe.

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The British Medical Journal and prescribing of minocycline for acne

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MADAM, Walsh and Creamer,¹ in their commentary on a French report of the adverse effects of minocycline used for acne,² note the apparent influence of the British Medical Journal (BMJ) on prescribing. They state that BMJ guidance in 2002 recommended minocycline as a first-line treatment for acne; despite a Cochrane review the next year that failed to find any reliable evidence favouring minocycline, it 'was not until 2006 and again in 2007 and 2009 that the [British Medical] journal published guidance concurring with the recommendations of the Cochrane Review of 2003; it was around this time that prescribing rates of minocycline began to fall'.

In fact a much more significant fall in minocycline prescribing had already occurred in the U.K., between 1995 and 2002, and is also apparent in the French data. Following a BMJ report in January 1996 of rare but serious adverse effects,³ and our accompanying editorial,⁴ U.K. prescription

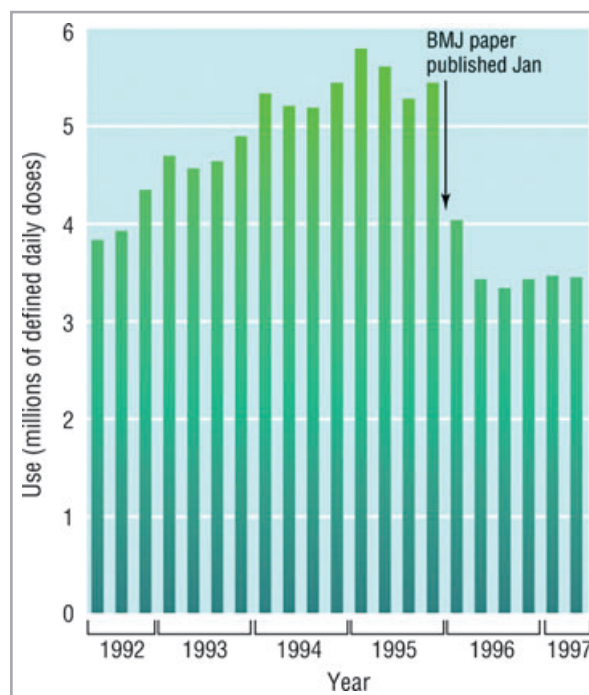


Fig 1. Millions of defined daily doses of minocycline prescribed in England and Wales by 3-month period between 1992 and 1997. Reproduced from Ferguson et al. (1998),⁵ copyright 1998, with permission from BMJ Publishing Group Ltd.

numbers had fallen to 70% by the end of the first quarter of 1996, and in the following quarter to 62% of the prior values, and remained at that level for at least the 15 months of observation⁵ (Fig. 1).

We agree that the BMJ is a powerful modifier of prescribing habits. The switch to newer drugs for which there are fewer pharmacovigilance data is a concern, as their potential harms are necessarily less well delineated. What we said 15 years ago is still true: (oxy)tetracycline is generally effective, probably safer, and certainly cheaper than minocycline – and perhaps than these newer agents.

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