Brief Report

The Role of Genetic Testing in Hereditary Poikiloderma: A Case Report

Sarah El-Heis, MBBS[1,2] and Keith M. Godfrey, BM, PhD, FRCP[1,2]

Case Report and Hospital Course

This 4-year-old girl who was born at 33 weeks to non-consanguineous parents from Afghanistan presented at the age of 24 months with mottled hypo- and hyperpigmentation. She was otherwise well, growing, and achieving her developmental milestones. Nucleotide excision repair studies and histology ruled out xeroderma pigmentosum; skin biopsy showed an epidermis with focal areas of slight atrophy and flattening, focal very mild hyperkeratosis, basal pigmentation consistent with pigmented skin, a slightly thickened papillary dermis, and dermal melanophages together with pigmentary incontinence (Figure 1a-c). No significant inflammatory infiltrate of the papillary dermis, elastosis, or parakeratosis was evident.

In the following months, the pigmentary changes became more widespread involving the limbs and included the palms and soles and the trunk to a lesser extent (Figure 2a and b). There was evidence of poikiloderma as skin atrophy and telangiectasia were noted. Thickening of the toenails developed. There was no lymphadenopathy or hepatosplenomegaly. Blood counts showed noncyclic neutropenia (neutrophil count 0.3×10^9/L); however, this was not associated with recurrent infections. A connective tissue disease screen was negative and immunoglobulin concentrations were unremarkable.

The clinical features of poikiloderma and nail changes with neutropenia suggested Clericuzio-type poikiloderma with neutropenia (PN) syndrome. Genetic testing through whole exosome and direct Sanger sequencing identified a novel homozygous missense mutation c.623A>G, p.His208Arg in the USB1 gene. The telomere length was normal. With molecular genetic testing confirming the diagnosis of PN, genetic counselling was offered and pediatric monitoring of growth and development, hematological surveillance for dysmyelopoiesis, and dermatological surveillance for malignancy were instigated.

Diagnosis

Clericuzio-type poikiloderma with neutropenia syndrome.

Discussion and Conclusion

PN is a rare autosomal recessive inherited genodermatosis, described first in Navajo Indians by Clericuzio in 1991.[1] The clinical features of PN include poikiloderma, nail abnormalities, and noncyclic neutropenia. Skin changes in the first year of life are described as eczematous or a papular erythematous rash evolving into poikiloderma, with telangiectasia and skin atrophy having a marked acral distribution.[2] Nail changes described are primarily pachyonychia, tending to affect the toenails.[2] Growth retardation, lacrimal duct obstruction, and palmoplantar hyperkeratosis are generally accepted findings. Skeletal defects, dental caries, facial dysmorphism, hepatosplenomegaly, and photosensitivity have also been described.[3,4] Patients may be predisposed to recurrent infections, particularly of the respiratory tract, due to noncyclic neutropenia and neutrophil functional defects.[2] Neutropenia and myelodysplasia arise due to bone marrow alterations, with a risk of leukemic transformation reported to occur before the second decade of life.[2] Furthermore, cutaneous squamous cell carcinoma has been reported in 2 cases.[5,6]

The known causative mutations are mainly biallelic truncating mutations in USB1 (formerly known as
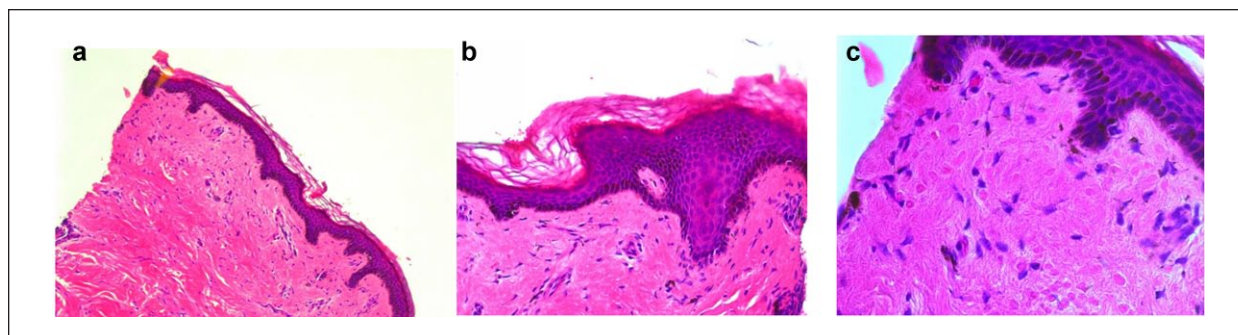
[1]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK
[2]University Hospital Southampton NHS Foundation Trust, Southampton, UK

Corresponding Author:
Keith M. Godfrey, MRC Lifecourse Epidemiology Unit (University of Southampton), Southampton General Hospital, Mailpoint 95, Southampton SO16 6YD, UK.
Email: kmg@mrc.soton.ac.uk

Figure 1. Histology of skin demonstrating (a) focal areas of epidermal atrophy and flattening with the loss of the ridges (×10 magnification), (b) mild focal hyperkeratosis (×20 magnification), and (c) basal pigmentation consistent with pigmented skin. Thickened papillary dermis, dermal melanophages with pigmentary incontinence (×40 magnification).

Figure 2. Poikilodermatous changes affecting (a) the upper limb and (b) lower limbs including the soles of the feet.

C16orf57), a gene located at 16q21 encoding for a protein that is crucial for U6snRNA (small nucleolar RNA) processing and stability.[7] U6snRNA has a vital role in RNA splicing and functions as a 3′-5′ exoribonuclease that removes both adenosine and uridine residues from the 3′-end of U6 snRNA.[7] To date there have been 40 reported cases and 19 disease causing mutations. The variants reported in USB1 are predicted to be loss of function (splicing, nonsense, or frame shift).[8] The current patient has been reported by Walne et al in a recent case series that describes whole exome and direct Sanger sequencing used to identify casual genetic variants in a subset of patients with a clinical diagnosis of dyskeratosis congenita (DC) or with overlapping features.[9] The missense variant identified in our patient affects pHis208, a crucial residue, which is in 1 of the 2 highly conserved H-x-S motifs shown to mediate the 3′-5′ exoribonuclease activity of U6 snRNA in vitro,[7] and therefore thought to be disease causing.

Little is known about USB1 mutations in acquired myelodysplastic syndrome, although mutations in the splicesome machinery are recognized in leukemogenesis.[10] The defective USB1 gene affects myeloid hemostasis and

neutrophil maturation and reports of myelodysplastic syndrome and acute myeloid leukemia support the classification of PN as a bone marrow failure syndrome with a predisposition to malignancies.[10] In cases where hematopoietic stem cell transplantation may be required, molecular genetic studies can aid in the selection of healthy sibling donors, highlighting the value of these studies in planning management.

Hereditary poikilodermas such as xeroderma pigmentosum (XP), Rothmund-Thomson syndrome (RTS), and DC can be phenotypically similar to PN, but result from different gene mutations. Photodistribution of the poikiloderma is a feature of XP and RTS, the diagnosis of which can be confirmed by nucleotide excision repair studies and identification of RECQL4 gene mutations, respectively. DC can result from a number of various gene mutations encoding for products essential for telomere maintenance. A short telomere length below the first centile is considered to be diagnostic for DC[11]; in PN, however, telomere length is not known to be affected.

Identification of all the coding regions in a gene by whole exome sequencing has been instrumental in determining casual gene mutations in variants of disease, and

can be particularly helpful in conditions with considerable phenotypic overlap, such as those described above. This case illustrates the value of targeted molecular studies of USB1 mutations and telomere length in confirming a clinical diagnosis of PN, enabling selection of further tests and management. Pediatric involvement in monitoring growth and development, hematological monitoring of neutrophil count and evidence of myelodysplastic syndrome or acute myeloid leukemia, and dermatological surveillance for skin malignancies are crucial. The involvement of a clinical geneticist can provide further insights into the family history and offer genetic counselling. Specific guidelines on management and follow-up of PN do not exist and while the risks associated with the condition are not fully understood, it is recognized that a multidisciplinary approach to management is needed.

Author Contributions

SE: Contributed to interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
KMG: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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