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Poikiloderma with neutropenia: An alternate presentation with dyspigmentation and novel *USB1* mutation

Malina Yamashita Peterson BS[1] | Brooke Hanson MD[2] | Ingrid Polcari MD[2,3]

[1]University of Minnesota Medical School, Minneapolis, Minnesota, USA

[2]Department of Dermatology, University of Minnesota, Minneapolis, Minnesota, USA

[3]Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota, USA

Correspondence
Malina Yamashita Peterson, Department of Dermatology MMC 98, 420 Delaware Street S.E., Minneapolis, MN 55414, USA.
Email: pete9929@umn.edu

Abstract

Two siblings presented with sun sensitivity and progressive dyspigmentation. A diagnosis of xeroderma pigmentosum was initially favored due to *XPC* mutations, although variants were not clearly diagnostic. However, new moderate neutropenia and homozygous suspected pathogenic variants in *USB1* led to diagnosis of poikiloderma with neutropenia. This case highlights the importance of reevaluation of diagnosis due to significant phenotypic overlap in congenital disorders of photosensitivity with poikiloderma or dyspigmentation.

KEYWORDS
mutation, neutropenia/diagnosis, neutropenia/genetics, skin abnormalities/diagnosis, skin abnormalities/genetics

Two siblings, a 1-year-old boy and 5-year-old girl from Ethiopia, presented with sun sensitivity and progressive dyspigmentation. Sun sensitivity consisted of skin which burns easily without blistering in the brother and with subsequent blistering in the sister. The brother had normal pigmentation at birth, while his sister had a hypopigmented patch on her wrist. Progressive dyspigmentation started at 6 months of

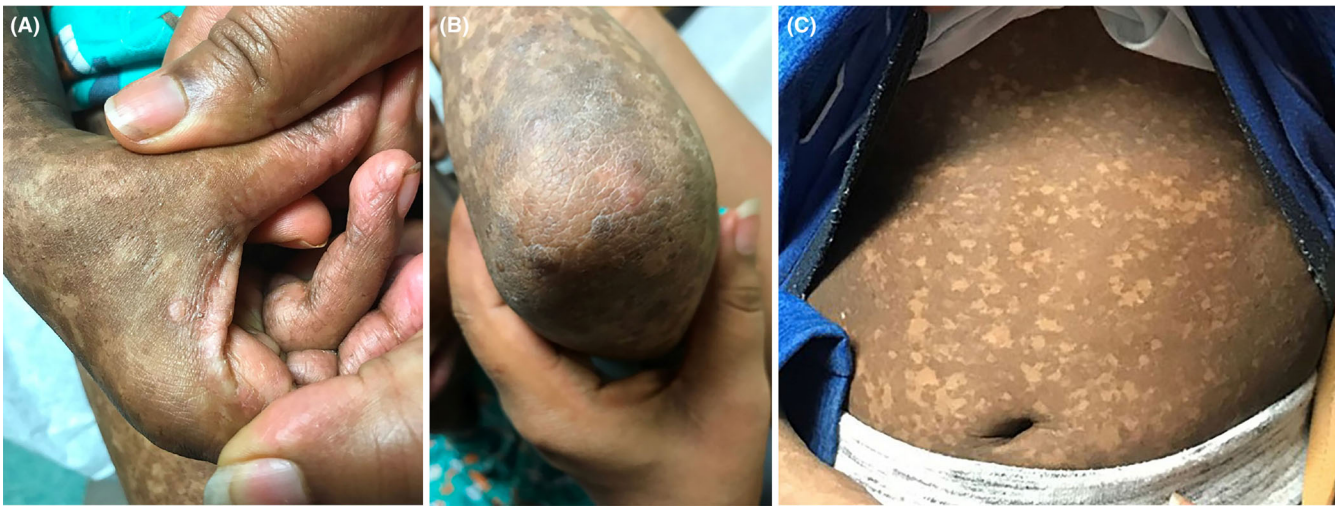

FIGURE 1 Male patient has diffuse macular hyper- and hypopigmentation on sun-exposed areas including the dorsal hand (A) and elbow (B) and sun-protected areas including the abdomen (C)

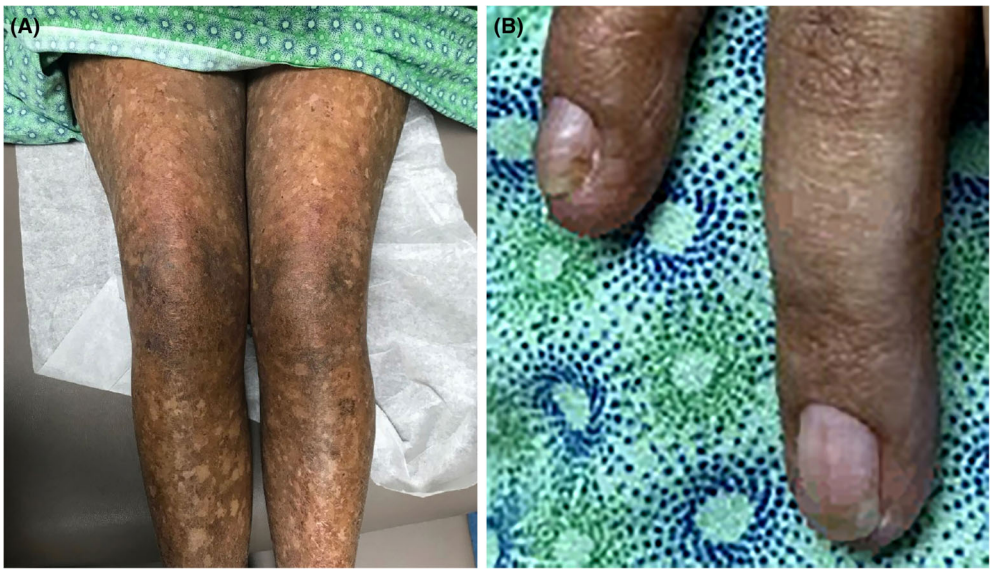

FIGURE 2 Female patient has diffuse generalized macular hyper- and hypopigmentation including her lower extremities (2A) and thickened nails with slightly raised nail beds (2B)

age for the brother and at 1 year of age for the sister. Dyspigmentation was reported to start on the extremities, but later became generalized. Past medical history included two episodes of pneumonia in the sister. Family history was notable for another sister with pigmentary changes who died at 8 months from pneumonia. Parents are from the same rural insular town in Ethiopia and may be distantly related.

On physical examination, they both had striking diffuse areas of macular hyper- and hypopigmentation most concentrated on sun-exposed areas including the face, upper chest, upper back and distal extremities (Figures 1A,B and 2A). Lesser changes were noted on the axilla, abdomen and genitals (Figure 1C). The nails showed hyperkeratosis and slightly raised nail beds (Figure 2B).

Xeroderma pigmentosum (XP) was initially suspected due to reported photosensitivity and focused genetic workup for XP revealed two heterozygous variants of uncertain significance in *XPC* and one heterozygous variant of uncertain significance in *ERCC5* (c.2203G > A). The variants in *XPC* included an unreported variant (c.1780C > T/p.Pro594Ser) and a neutral variant (c.2061G > A/p.Pro687Pro). Genetic testing for other XP variants and Cockayne syndrome (CS) was unremarkable. Although these variants were not clearly diagnostic, the diagnosis of xeroderma pigmentosum (XP) was initially favored due to skin findings and the *XPC* mutation.

The siblings were followed closely for 8 years and it was noted that there was an absence of skin malignancies despite imperfect adherence to strict sun avoidance. Over time, short stature, mildly flattened foreheads, short noses, gingival hyperpigmentation, numerous dental caries, and dystrophic nails were noted in both patients. The brother had ambulation difficulties causing frequent falls starting at age 3. Workup for fatigue in the sister led to detection of chronic moderate neutropenia with an absolute neutrophil count of 500–600/μl in the sister and 800–1000/μl in the brother.

The XP diagnosis was reconsidered and a congenital neutropenic panel revealed that both siblings had homozygous variants in *USB1* (NM_02598.3; exon 6, c.682C > T; p.Gln228*. Chr 16:

TABLE 1 Major criteria, minor criteria, and other findings associated with poikiloderma with neutropenia and a comparison of our reported patients

	Female patient	Male patient
Major criteria		
Poikiloderma	−	−
Persistent neutropenia	+	+
Recurrent infections	+	−
Palmoplantar keratoderma	−	−
Pachyonychia	+	+
Photosensitivity	+	+
Minor criteria		
Hepatosplenomegaly	−	−
Non-descended or retractile testicles	−	−
Milia	−	−
Verrucous lesions	−	−
Atrophic scars	−	−
Dental caries	+	+
Lacrimal duct obstruction	−	−
Growth retardation	+	+
Elevated lactate dehydrogenase	−	−
Transient thrombocytopenia	−	−
Transient leukopenia	+	+
Elevated ferritin	+	NA
Interface dermatitis	NA	NA
Other reported findings		
Calcinosis cutis	−	−
Facial dysmorphism	+	+
Skeletal defect	−	−

Note: + = present, − = absent, NA = not assessed. To fulfill diagnostic criteria described by Arnold et al, patient must meet at least four major and two minor criteria or three major and four minor criteria.

TABLE 2 Differential diagnosis for poikiloderma with neutropenia

Disorder	Gene(s)	MOI	Distinctive clinical findings
Bloom syndrome	*BLM*	AR	Poikiloderma on face most prominent in malar distribution, narrow face, short stature, growth retardation, early development of malignancy
Cockayne syndrome	*ERCC6*, *ERCC8*	AR	Mottled dyspigmentation, photosensitivity, cachectic dwarfism, microcephaly, cognitive dysfunction, peripheral neuropathy, retinal dystrophy, cataracts, sensorineural deafness
Dyskeratosis congenita	*ACD*, *CTC1*, *DKC1*, *NHP2*, *NOP10*, *PARN*, *RTEL1*, *TERC*, *TERT*, *TINF2*, *WRAP53*	XL, AD, AR	Poikiloderma on neck and upper chest, oral leukoplakia, nail dystrophy, bone marrow failure, pulmonary fibrosis
ELANE-related neutropenia	*ELANE*	AD	Poikiloderma is absent, congenital neutropenia, cyclic neutropenia, recurrent infections, oropharyngeal inflammation
Kindler syndrome	*FERMT1*	AR	Generalized poikiloderma starting at 2–3 years of age, trauma induced blistering, photosensitivity, skin atrophy, pseudosyndactyly
Hereditary fibrosing poikiloderma with tendon contractures, myopathy, and pulmonary fibrosis (POIKTMP)	*FAM111B*	AD	Poikiloderma in sun exposed areas starting at 6 months, muscle contractures, myopathy, pulmonary fibrosis, alopecia, lymphedema
Hereditary sclerosing poikiloderma	—	AD	Generalized poikiloderma most prominent in flexures starting at 2–3 years of age, linear sclerotic and hyperkeratotic lesions in axillary, antecubital, and popliteal fossa, palmoplantar sclerosis, finger clubbing, cardiac valvular calcification
Poikiloderma with neutropenia	*USB1*	AR	Post-inflammatory poikiloderma in infancy, congenital chronic moderate neutropenia, recurrent upper respiratory infections, palmoplantar hyperkeratosis, bronchiectasis, subungual hyperkeratosis, myelodysplastic syndrome, nail dystrophy, short stature
Rothmund-Thomson syndrome type I	*ANAPC1*	AR	Facial erythema and bullae at 3–6 months, post-inflammatory poikiloderma, short stature, loss of eyelashes or eyebrows, juvenile cataracts, skeletal abnormalities
Rothmund-Thomson syndrome type II	*RECQL4*	AR	Facial erythema and bullae at 3–6 months, post-inflammatory poikiloderma, short stature, loss of eyelashes or eyebrows, juvenile cataracts, skeletal abnormalities, osteosarcoma
Xeroderma pigmentosum	*ERCC2-5*, *DDB2*, *POLH*, *XPA*, *XPC*	AR	Poikiloderma in sun exposed areas, photosensitivity, skin malignancy

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; MOI, method of inheritance; XL, X-linked.

g.58052948G > T). This mutation was previously unreported, but suspected to be pathogenic. The mother was heterozygous for this variant in *USB1*, while the father declined genetic testing.

The condition associated with this mutation is poikiloderma with neutropenia (PN), a rare autosomal recessive disorder of *USB1*, which is involved in RNA splicing.[1] This may be an alternate presentation of PN because although the patients have extensive dyspigmentation, they do not meet criteria for poikiloderma given the absence of telangiectasias and skin atrophy. Another hypothesis for the lack of poikiloderma in these patients could be increased sun avoidance behavior by the family due to the original suspected diagnosis of XP. Specifically, the children stayed indoors during the day, did not participate in outdoor recreational activities, and utilized sunscreen, but did not wear face shields despite having these provided to them. However, intentional sun avoidance did not commence until age 1 in brother and age 5 in sister.

The sister had an additional mutation in *CSF3R* (NM_000760.3, exon 4B, g.160C > T; p.His54Tyr, Chr 1: g.36941179G > A). While *CSF3R* is associated with autosomal recessive severe congenital neutropenia, this heterozygous mutation has not previously been reported and is a variant of uncertain significance.[2] Given the novelty of the sister's *CSF3R* mutation, bone marrow biopsy is planned to evaluate for bone marrow failure.

PN was first reported in 1991 among 14 people in the Navajo Native American tribe in the United States of America.[3] PN is characterized by post-inflammatory poikiloderma, chronic neutropenia, and recurrent sinopulmonary infections. At age 15 days to 18 months, skin findings present with eczematous red papules and plaques that start on the extremities and spread to the face, neck, and trunk.[4] The red papules are replaced by dry mottled hypopigmentation and hyperpigmentation, telangiectasias, and atrophy, also known as poikiloderma.

In 2010, Arnold et al created clinical diagnostic criteria for PN (Table 1).[4] Major diagnostic criteria include poikiloderma, persistent neutropenia, recurrent infections, palmoplantar keratoderma, pachyonychia, and photosensitivity. Minor criteria include, but are not limited to, hepatosplenomegaly, dental caries, lacrimal duct obstruction, and growth retardation. Other reported clinical features include calcinosis cutis, facial dysmorphisms such as saddle nose, prominent forehead, micrognathia, and midfacial hypoplasia, and skeletal defects such as widened femoral metaphysis, delayed skeletal maturation, and osteopenia.[5–7] While early reports of PN do not mention photosensitivity, more recent cases have reported photosensitivity with development of poikiloderma in sun exposed areas[4,8] and blistering when exposed to sunlight.[9]

Based on case reports, PN is thought to be linked to acute myeloid leukemia[10,11] and myelodysplasia.[9,11–15] Early development of squamous cell carcinoma has been also been reported in three patients, specifically at age 14 in two patients.[11,16,17]

Differential diagnosis for PN includes but is not limited to XP, CS, dyskeratosis congenita and Rothmund–Thomson Syndrome (Table 2). These cases highlight the importance of reevaluation of the diagnosis and additional genetic testing as clinical findings evolve.

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None.

CONFLICT OF INTEREST

No conflict of interest.

CONSENT STATEMENT

No consent statements.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Malina Yamashita Peterson https://orcid.org/0000-0002-0270-2941

Ingrid Polcari https://orcid.org/0000-0002-7871-1836

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