CASE REPORT
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Clericuzio-type Poikiloderma with Neutropenia Syndrome in a Turkish Family: a Three Report of Siblings with Mutation in the *C16orf57* gene

Turkan Patiroglu and H. Haluk Akar

Department of Pediatric Immunology, Erciyes University School of Medicine, Kayseri, Turkey

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ABSTRACT

Clericuzio-type poikiloderma with neutropenia (PN) is characterized by poikiloderma, non-cyclic neutropenia, recurrent sinopulmonary infections, pachyonychia, and palmo-plantar hyperkeratosis. Mutations in the *C16orf57* gene, which is located on chromosome 16q13, have been identified as the cause of PN. PN was first described by Clericuzio in Navajo Indians. Herein, we reported the clinical presentations and laboratory investigations of PN in three siblings from Turkey.

The older siblings presented with typical cutaneous poikiloderma, plantar keratoderma, pachyonychia of toenails, and recurrent upper respiratory infections. As the most affected patient, in addition to classic manifestations, the youngest sibling had recurrent pneumonia, hepatosplenomegaly, dental caries, failure to thrive, and hand malformation.

Genetic study revealed a homozygous mutation (c.531delA) in the *C16orf57* gene in siblings.

With the presented study, we aimed to draw attention to PN which can be a predisposing factor to malignancies.

Keywords: *C16orf57* gene; Poikiloderma with neutropenia syndrome; Siblings

INTRODUCTION

Poikiloderma is a chronic skin disorder characterized by telangiectatic lesions, dyspigmentation, and epidermal atrophy. Many types of genodermatosis such as Rothmund-Thomson syndrome (RTS), Bloom syndrome (BS), xeroderma pigmentosum (XP), dyskeratosis congenital (DC), and Kindler syndrome (KS) show poikilodermatous skin manifestations.

The autosomal recessive disorder Clericuzio-type poikiloderma with neutropenia (PN) was first described in Navajo Indians by Clericuzio.[1] PN is characterized by pachonychia, poikiloderma, recurrent infections, neutropenia, neutrophil dysfunction, and significant predisposition to cancer such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). PN is caused by mutations in the *C16orf57* gene which encodes USB1 protein. This gene is highly expressed in myeloid lineage. USB1 is a specific 3'-5' exoribonuclease essential for the processing and stability of U6 snRNA which have a crucial role in RNA splicing.[2-3] Thus, the mutation of *C16orf57* gene

Corresponding Author: H. Haluk Akar, MD;
Department of Pediatric Immunology, School of Medicine, Erciyes University, Kayseri, Turkey. Tel: (+90 352) 2076 666/ 25300, Fax: (+90 352) 4375 825, E-mail: himmetakar@gmail.com

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impairs cell growth. The arrest of bone marrow maturation with persistent neutropenia is the main neutrophil defect that can start in infancy or later. In the English medical literature to date, almost 38 PN patients have been reported with 19 different mutations in the *C16orf57* gene.[2] In this report, we describe the clinicopathologic features of three siblings with PN from Turkey. The aim of this article was to draw attention to this rare form of genodermatosis.

CLINICAL REPORTS

Three siblings, two females (Patients A and C) and one male (Patient B), were presented in this study. The siblings were born as term newborns, with absence of perinatal problems and all growth parameters were in the normal range. At birth, none of the presented patients showed skin changes or dysmorphic signs. The youngest one (Patient A) was the most severe patient. was the most affected patient. There was third degree consanguinity between the parents. The family history was negative for immunodeficiencies, neutropenia, and malignancies. Also, the mother had two abortions in her first and third pregnancies (Figure 1).

Patient A

She was a 6-year-old girl. During her first month of life, the child had elevated liver enzymes and hepatosplenomegaly, and she had been evaluated as having myelomonocytic leukemia. Bone marrow aspiration was performed 4 times in that period, and leukemia had been excluded. The cutaneous manifestations began at 4 months of age as a rash involving primarily the extensor surface of lower extremities. She had failure to thrive since infancy, but no delay was observed in her psychomotor development. The patient was referred to the Department of Pediatric Immunology at the age of 5 years with recurrent otitis, aphthous stomatitis, and skin lesions. Initial physical examinations revealed failure to thrive [weight: 14 kg (<3p), height: 98 cm (<3p)], generalized poikiloderma on the trunk, extremities and face, midface hypoplasia, mild frontal bossing, mild prognathism, widely spaced eyes, small nose with depressed nasal bridge, and 2-3 cm hepatosplenomegaly below the costal margin (Figure 2a). Hepatosplenomegaly was confirmed with abdominal ultrasonography. Palmo-plantarhyperkeratosis was observed with pachyonychia (Fig.2b, c). She had photosensitivity with sunexposure. Her laboratory investigations

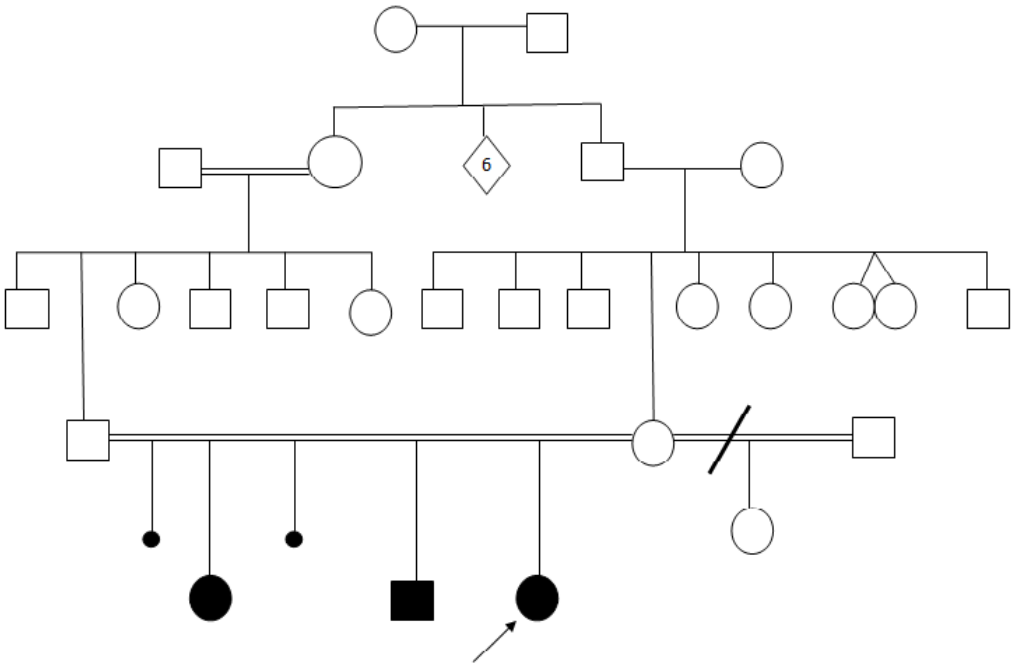

Figure 1. Pedigree

showed leukopenia (2500-3020/mm^3) with neutropenia (130-550/mm^3) and increased lactate dehydrogenase (LDH: 654 u/l, normal range: 135-214u/l).

Creatine phosphokinase (CPK), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), immunoglobulins (IgA, IgM, IgG, IgE), complement factors (C3 and C4), vitamin B12, folate, lymphocyte count, and lymphocyte subsets were normal. The peripheral blood smear was completely normal. Also, neutrophil function test with dihydrorhodamine (DHR) and sweat chloride test were normal. There were no bone abnormalities with skeletal X-rays. The bone age was appropriate for chronological age. The ophthalmologic examination was normal for cataract. Bone marrow smears (BMS) revealed 10% myelodysplastic changes and abnormal neutrophil maturation with an increased number of immature cells. Genetic test revealed a homozygous mutation (c.531delA) in the *C16orf57* gene. Also, the same mutation was detected as heterozygous in parents. Hematopoietic stem cell transplantation (HSCT) was planned for patient.

Patient B

He was an 8-year old boy. The skin manifestations appeared at 2 years of age with a rash involving primarily the face and lower extremities evolving into classic poikiloderma. During the first years of life, he experienced recurrent upper respiratory infections. At the age of 7 years, he was first visited at our clinic. Physical examination showed poikiloderma on the face, extremities and trunk, pachyonychia, and mild midface hypoplasia, normal growth [(weight: 22 kg (50p), height: 121 cm (50-75p)], normal mental and cognitive development (Figures 3a, b). His ophthalmologic exam was normal for cataract. His laboratory findings revealed leukopenia (2990/mm^3) with neutropenia (980/mm^3). Hepatic functions, CPK, LDH, C3, C4, immunoglobulins, lymphocyte count, lymphocyte subsets, and viral serology were normal. There were no bone abnormalities with skeletal X-rays. BMS showed abnormal maturation of neutrophil and increased numbers of immature cells. Also, the same mutation was detected in this sibling (c.531delA).

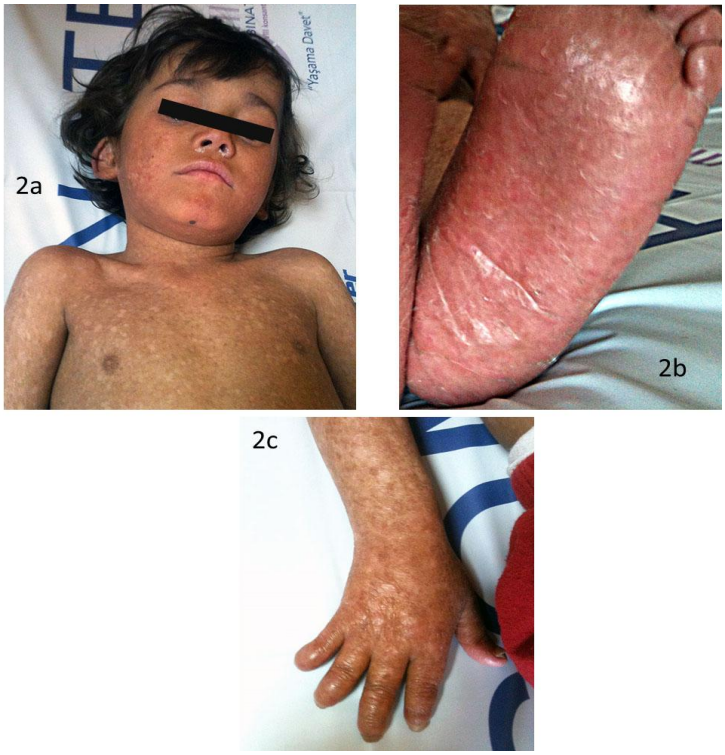

Figure 2. Patient A, Note midfacial hypoplasia, the pattern of poikiloderma (2a), plantar hyperkeratosis (2b), pachyonychia, and hand malformation (2c).

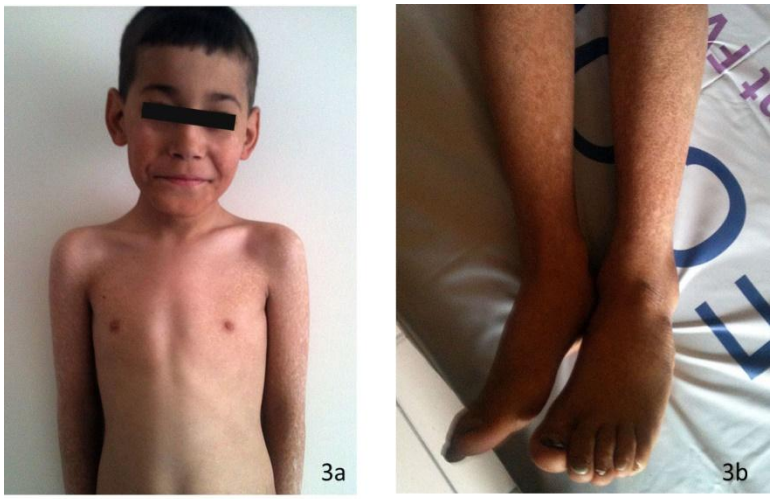

Figure 3. Patient B, Note midfacial hypoplasia (3a), the pattern of poikiloderma, pachyonychia (3b).

Patient C

She was a 14 year-old girl. At the age of 13 years, she came for the first time to our clinic with other siblings. We learned from the medical history that she experienced recurrent upper respiratory infections in her first years of life. Physical examination showed poikiloderma, mild facial hypoplasia, mild retromicrognathia, hypermobile fingers with ‘‘beak of swan’’ appearance and normal growth [weight: 42 kg (25-50p), height: 147 cm (25p)], normal mental and cognitive development (Fig. 4a,b,c). Leukopenia (3390/mm^3) with neutropenia was found (1120/mm^3) at the time of presentation. The routine laboratory investigations showed normal biochemistry including CPK and LDH. The levels of immunoglobulins, C3, and C4 were normal. BMS showed abnormal maturation of neutrophil and increased numbers of immature cells. Her ophthalmologic examination was normal as in others. Also, the same mutation (c.531delA) was identified in this sibling.

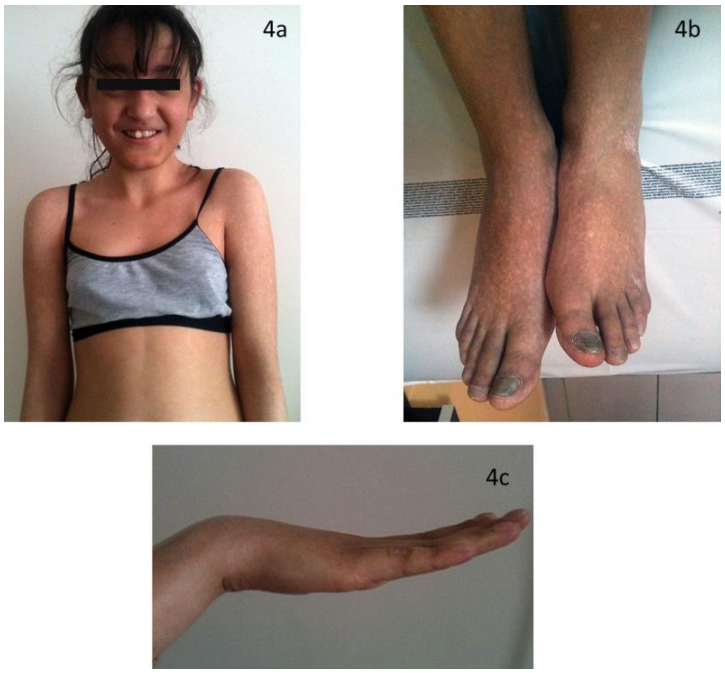

Figure 4. Patient C, Note midfacial hypoplasia (4a), the pattern of poikiloderma, pachyonychia (4b), and hypermobile fingers (4c).

DISCUSSION

In the PN patients, chronic cutaneous changes start from the distal extremities, as irregular eczematous eruptions developing in the first year of life and progressively evolving into poikiloderma, and spread centripetally to the trunk and face. Photosensitivity has been reported as a clinical manifestation in some PN patient in the medical literature. In the presented siblings, just the patient A had photosensitivity.[4-5] Most PN patients exhibit recurrent pulmonary infections in the first years of life, skin problems and abnormalities in the annexes such as pachyonychia, palmo-plantar hyperkeratosis, teeth abnormalities including decay and eruption delay, saddle-short nose, prominent forehead, micrognathia, midfacial hypoplasia, craniofacial dysmorphisms, skeletal defects such as widening of femoral metaphysic and osteopenia, and failure to thrive.[7] The presented patient A was the most affected sibling with failure to thrive and severe recurrent pulmonary infections (Table 1).

Table 1. Suggested major and minor criteria for the diagnosis of PN and our patients (ref 6)

Criteria	***Patients***			
	PN	***Patient A***	***Patient B***	***Patient C***
Major criteria				
Poikiloderma	+	+	+	+
Persistent neutropenia	+	+	+	+
Recurrent infections	+	+	+	+
Palmo-plantar keratoderma	+	+	-	-
Pachyonychia	+	+	+	+
Photosensitivity	+/-	+	-	-
Minor criteria				
Hepatosplenomegaly	+/-	+	-	-
Nondescended or retractile testes	+/-	F	-	F
Milia	+/-	-	-	-
Verrucous lesions	+/-	-	-	-
Atrophic scars	+/-	+	+	+
Dental caries	+/-	+	-	-
Lacrimal duct obstruction	+/-	-	-	-
Growth retardation (<10p)	+/-	+	-	-
Elevated lactate dehydrogenase (>1000u/L)	+/-	-	-	-
Transient thrombocytopenia (during infection)	+/-	-	-	-
Transient leucopenia (during infection)	+/-	-	-	-
Elevated ferritin (>1000 g/L)	+/-	ND	ND	ND
Interface dermatitis	+/-	-	-	-
Hand malformation	+/-	+	-	-
Hand hyperflexibility	+/-	-	-	+

(+), generally accepted finding of PN; (+ ⁄-), described occasionally in case reports; (-), absent; (ND), not described; F, Female. To fulfill the diagnosis would require the presence of at least four major and two minor criteria or three major and four minor criteria.

Pachyonychia is defined as thickened and excessive curving nails which affects predominantly toenails, and have been observed commonly in the PN patients. Another cutaneous change, palmo-plantar hyperkeratosis frequently develops later in life.[1] In the presented siblings, pachyonychia was observed all of them in the toenails, however just patient A had hyperkeratotic skin changes in the soles. Lacrimal duct obstruction, ear abnormalities, congenital heart disease, dry and thin hair, hypogonadism, hepatosplenomegaly, dysgammaglobulinemia, intrauterine growth retardation, calcinosis cutis, hyperflexibility and

malformation of hands/feet, and leukoplakia have been reported as rare clinical manifestations of PN patients.[1,7-8] Among these manifestations of PN, hepatosplenomegaly and failure to thrive, and hand malformation were observed in patient A (Figure 2a). Hyperflexibility of hands was observed only in patient C (Figure 4b) (Table 1). In differential diagnosis of poikilodrema, as mentioned in introduction, some genetic syndromes such as RTS, BS, XP, DC, and KS (please see introduction, they were written as full term in introduction) are thought. Also, these syndromes are thought in the differential diagnosis of PN. RTS are the best known syndrome in these syndromes. Patients with RTS have cataracts, alopecia, dysplastic hair, small stature, bone abnormality, and predisposition to malignancies such as osteosarcoma, as well as poikiloderma. Poikiloderma tends to start from the extremities and spread to the trunk and face in the PN patients, whereas poikilodermatous skin changes typically start on the face and spread to the extremities in the RTS. None of these clinical manifestations belongs to RTS (alopecia, sparse hair, leukoplakia, and bony involvement) were observed in the presented siblings. Also, in contrast to the RTS, neutropenia has been reported in all PN patients. All presented siblings had neutropenia which was consistent with literature. In addition to clinical manifestations, patients with RTS usually have mutations in the RECQL4 gene, whereas PN has mutations in the *C16orf57* gene.[1,9] The presented siblings had a homozygous mutation in the *C16orf57* gene. Thus, we excluded RTS in the presented siblings. Other immunologic abnormalities and other disorders causing recurrent respiratory infections such as cystic fibrosis were excluded in the presented siblings. In the medical literature, four malignancies (two AML, two squamous cell carcinoma) and about 10 myelodysplasia have been reported in the PN patients.[4,6,8-13] In the presented siblings, the presented patient A had severe non-cyclic neutropenia (between 130-600/mm^3) and myelodisplastic changes in the bone marrow. In the medical literature, there is little information on the use of granulocyte colony-stimulating factors (GCSF) in the PN patients for neutropania. In only two patients, it has been reported using GCSF with good response.[6,9] In the presented siblings, patient A responded to GCSF. Neutrophil function defects such as defective oxidative burst also have been reported in some PN patients.[4,9] But, neutrophil function test with dihydrorhodamine (phagotest) was normal in the all presented siblings. Recurrent infections in the presented siblings became less frequent over disease course, as previously described in the medical literature.[14]

In summary, herein, we reported three PN siblings. In the presented siblings, the classic erythematous rash evolved into poikloderma in follow-up without eye and bone involvement. Pachonychia was noticed in the toenails and neutropenia caused recurrent infections in all siblings. Mild hepatosplenomegaly was observed just in patient A. Patient A also had severe neutropenia which needed GCSF.

With this study, we would like to draw attention again to PN which is a rarely observed genodermatosis in children.

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