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Case Report

The First Patient with Poikiloderma and Neutropenia from the Central Balkans and Rare Findings

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Abstract

Introduction: Poikiloderma with neutropenia is a rare autosomal recessive genodermatosis whose main characteristics are early onset poikiloderma and chronic neutropenia. Until now there are around 80 patients described from around the world, with just a few patients from Europe. Patients are prone to recurrent sinopulmonary, middle ear, and skin infections. Also, poikiloderma with neutropenia is regarded as a pre-cancerous state with a predisposition to acute myeloid leukemia, and squamous cell carcinoma.

Case Outline: A thirteen-year-old boy from Serbia was diagnosed with poikiloderma with neutropenia in early childhood. The diagnosis was based on the clinical picture (generalized poikiloderma, pachyonychia, palmoplantar hyperkeratosis, calcinosis cutis) and chronic neutropenia in the blood count, and later confirmed by whole-exome sequencing. This is the first reported patient with this condition from Serbia. Since it is regarded as a precancerous condition, the boy has regular haemato-oncological and dermatological checkups. For prophylaxis of severe bacterial infections that are common in patients with this condition, he is successfully regularly given granulocyte colony-stimulating factor. Although our patient had no severe bacterial infections, he had at the age of ten a complicated form of measles with bilateral interstitial pneumonia (previously, despite the advice, he had not received the MMR vaccine).

Conclusion: We propose the regular use of granulocyte colony-stimulating factor in patients with poikiloderma and neutropenia, but with caution due to potential side effects. Additionally, we advise regular immunization of these patients.

Keywords: *Poikiloderma; Neutropenia; Granulocyte Colony-Stimulating Factor; Precancerous Conditions*

Introduction

Poikiloderma with neutropenia (PN) is a rare autosomal recessive genodermatosis caused by biallelic mutations in the USB1 gene. The main characteristics are early-onset poikiloderma and non-cyclic, chronic neutropenia. The disease was first described by Clericuzio, in Navajo Native Americans [1]. Until now there are around 80 described patients from around the world, with just a few patients from Europe, and none of them from the region of continental Balkans (Serbia).

Skin changes in PN start in the first year of life, from acute rash to chronic poikiloderma with the initial acral distribution and later centrifugal spreading. Severe, non-cyclic neutropenia usually appears between the first months and 20 months of age [2]. Patients are

prone to recurrent, usually respiratory infections. Other major clinical findings include palmoplantar hyperkeratosis, pachyonychia, and facial dysmorphism. Patients with PN have a predisposition to cancer since there are reports about myelodysplasia, acute myeloid leukemia, and squamous cell carcinoma [3].

Case Report

The patient is a 12-year-old Serbian boy. He was born in the 41st gestational week with 3,2 kg and Apgar score 5 in the first minute and 7 in the fifth minute. He had an atrial septal defect (ASD secundum) with no hemodynamic impact. In the first three months of his life, he suffered from gastrointestinal infections and ear infections. He did not gain weight properly. Neutropenia was first seen at the age of three months. The cutaneous manifestations began at one month of age as a rash involving primarily the extensor surface of lower extremities and arms, slowly spreading over his trunk and face during the first 6 months of life.

He was first admitted to the Clinical Immunology department at the age of eight months for the treatment of bilateral pneumonia and urinary infection. At the admission, it was noted that the boy had dry skin with areas of atrophy, telangiectasias, hypopigmented, and hyperpigmented spots on his extremities. Initial differential diagnoses included Rothmund-Thomson syndrome (RTS), dyskeratosis congenita and ichthyosiform erythroderma. Initial laboratory findings showed moderate neutropenia (600 - 970 cells/mm^3) and elevated lactate dehydrogenase levels (1837 IJ/L). He was treated with cephalosporins for 10 days. Abdominal ultrasound showed moderate hepatosplenomegaly, after micturating cystourethrogram was performed, the patient was diagnosed with left vesicoureteral reflux (grade III). He was given antibiotic prophylaxis. Immunophenotyping of peripheral blood lymphocytes showed normal numbers of B lymphocytes and a slightly lower number of CD4+ T lymphocytes with polyclonal hypergammaglobulinemia (IgA 1,23 g/L, IgM 1,4 g/L, IgG 14,4 g/L).

The further analysis excluded viral hepatitis, HIV, intrauterine infections (Toxoplasma gondii, Rubella virus, cytomegalovirus, herpes simplex viruses), and cystic fibrosis.

During the psychological assessment, he has been found to have moderate developmental delay and sensorineural deafness. Both of his parents are deaf but otherwise healthy.

The following hospitalization was at the age of ten months when the patient had another urinary tract infection and bacterial gastroenteritis. After treating acute disease, a bone marrow biopsy was performed and the pathohistological findings were normal at that time (granulocyte lineage was present in all development phases, with a discrete shift to the left). In an attempt to prevent recurrent infections, the patient has been regularly given recombinant human granulocyte colony-stimulating factor (G-CSF) since then. During the second year of life, the boy developed generalized poikiloderma, pachyonychia, palmoplantar hyperkeratosis, and areas of calcinosis cutis (pathophysiologically confirmed diagnosis after skin biopsy). During the next years of his life, he did not have recurrent bacterial infections. At the age of ten, he was hospitalized because of measles complicated by severe bilateral interstitial pneumonia and nearly fatal respiratory failure. Even dough it was advised, he did not receive the MMR vaccine on time. He was successfully treated with broad-spectrum antibiotics and corticosteroids.

At the age of twelve, the boy has evident dysmorphic signs (frontal bossing, prominent ear lobes), poikiloderma and calcinosis cutis (Figure 1), palmar and plantar hyperkeratosis (Figure 2), and dystrophy of fingernails but mostly toenails (Figure 3). His hair and eyelashes have normal quality. Ultrasound examination shows hepatosplenomegaly. He has short stature (z score between -2 and -1 SD) and testicular hypoplasia with non-descendent testicles. Plain radiography of the left hand showed growth arrest lines at the distal part of the radius. Skeletal maturity was estimated at the age of 10 (at the time patient was 12 years old). The clonidine stimulation test is normal. The bone density test is normal.

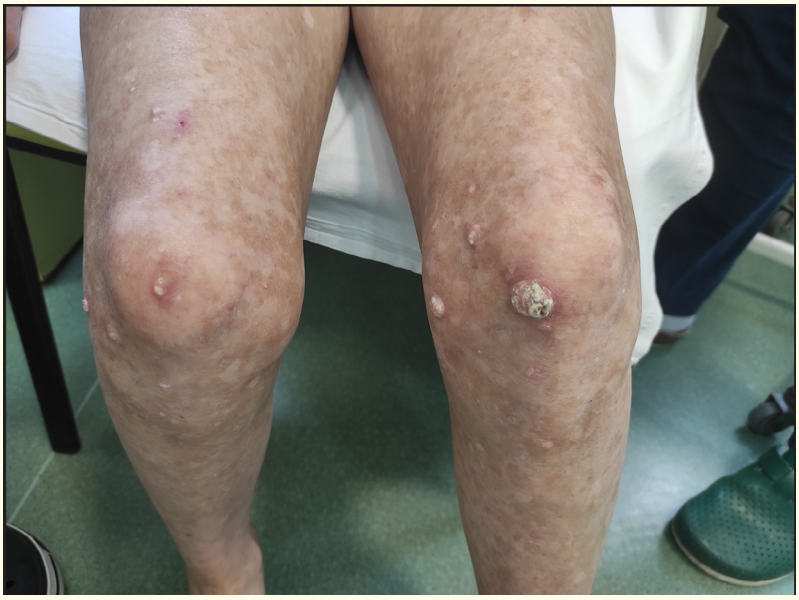

Figure 1

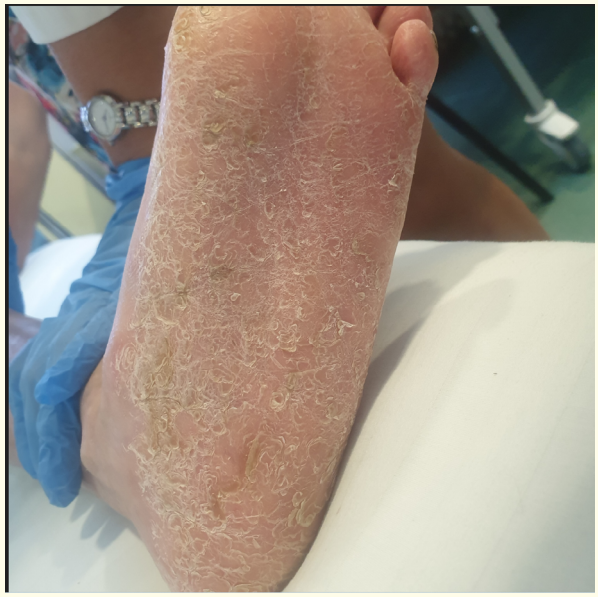

Figure 2

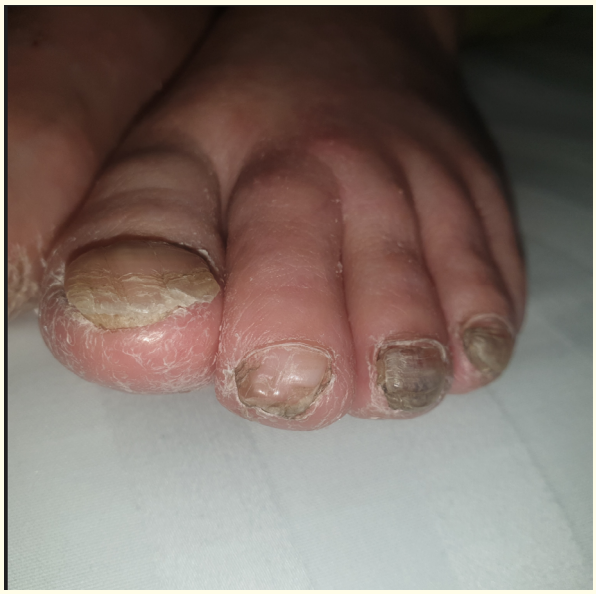

Figure 3

Laboratory findings during the follow-up have shown persistent leukopenia, neutropenia, with an average absolute neutrophil count around 1220/mm^3 (he is still given G-CSF), elevated lactate dehydrogenase levels, and ferritin levels. All the rest of the biochemical analyses and hormone status have been in the reference ranges.

We noticed that our patient has a higher average absolute neutrophil count, which is around 1220/mm^3 (with a range from 86 to 6470 neutrophils/mm^3), since starting the administration of G-CSF compared to an average count of 965/mm^3 (with a range from 45 to 2448 neutrophils/mm^3) before G-CSF therapy.

In order to determine the potential presence of a genetic cause of the condition, whole-exome sequencing was performed when he was eleven years old. The analysis detected the homozygous pathogenic variant c.243G>A in the USB1 gene, which was previously described in patients with poikiloderma and congenital neutropenia.

Since the diagnosis is associated with myelodysplasia and acute myeloid leukemia, a bone marrow examination is done regularly, every six months. Myelogram has shown hypocellular bone marrow, without any pathological cells. The last performed biopsy of bone marrow showed unspecific, moderate hypoplasia of granulocyte lineage and no elements of lymphoproliferative or myeloproliferative disorders. As part of the evaluation, high-resolution computer tomography of the chest was done. There were no reliable signs of bronchiectasis. He is been given regularly antibiotic prophylaxis with cotrimoxazole and fluconazole and his skin is regularly checked for malignancies.

Discussion

Poikiloderma with neutropenia (PN) is a rare, recently described genodermatosis. The diagnosis of PN was suspected according to clinical and laboratory findings and later confirmed with whole-exome sequencing. Arnold., *et al*. proposed clinical and laboratory diagnostic criteria [4]. Our patient meets at least five out of six major criteria (poikiloderma, persistent neutropenia, recurrent infections,

palmoplantar keratoderma, pachyonychia of the great toenail) and at least seven out of thirteen minor criteria (hepatosplenomegaly, non-descendent testicles, verrucous lesions, atrophic scars, dental carries, growth retardation, elevated lactate dehydrogenase levels). Rarely reported findings present in our patient include pathophysiologically diagnosed areas of the calcinosis cutis, heart anomaly, and vesicourethral reflux. To our knowledge, this is the first patient with PN to have sensorineural hearing loss, but we suppose that it is not a part of PN clinical findings since both of his parents are deaf but otherwise healthy. Differential diagnosis includes Rothmund-Thomson syndrome (RTS), ichthyosiform erythroderma and dyskeratosis congenita (DS). The group of hereditary poikilodermas includes also other rare syndromes: Bloom syndrome, xeroderma pigmentosum, and Kindler syndrome. Besides the genetic distinction, there is a clear-cut clinical differentiation between these syndromes.

DS differs from PN because of oral leukoplakia and normal neutrophil count. In RTS initial skin changes start in the face spreading towards the extremities, while PN has an acral presentation [5]. The second main distinctive feature is the permanent neutropenia characteristic of PN. Little is known about the use of granulocyte colony-stimulating factor (G-CSF) in PN. We decided to start using it because of the severe bacterial infections present in the first years of the boy's life and continue to use it because he has been without severe bacterial infections since then. The use of G-CSF is not without hematological risks, so we performed regular hematological investigations even before the molecular diagnosis was made. Some authors also purpose the use of G-CSF only in severe infections in which the neutrophil count does not rise appropriately [6]. Our patient had life-threatening measles-associated interstitial pneumonia with nearly fatal respiratory failure since he was not regularly vaccinated even dough it was advised. To our knowledge, this is the first report of this kind of severe measles complications in a patient with PN. We strongly recommend that these children should be vaccinated regularly, without any delays.

Although the clinical diagnosis of PN was suspected, the definitive diagnosis was made after the molecular genetic testing was done. We purpose that in the absence of a molecular diagnosis, patient treatment should still be the same: poikiloderma managed by an experienced dermatologist and prevention and treatment of infections.

The next-generation sequencing revealed a pathogenic homozygous variant with a premature stop codon in the USB1 gene (previously known as C16orf57). The detected homozygous variant, c.243G>A causes the insertion of a stop codon at position 81 in the amino acid sequence coded by USB1. This gene is highly expressed in the myeloid lineage. USB-1 protein is a specific exoribonuclease, important in the stability of U6 snRNA and therefore in RNA splicing [9]. Mutations in USB-1 impair cell growth leading to arrest in bone marrow maturation and persistent neutropenia.

Three European families with the c243G>A transition have been described in either homozygous or heterozygous states [4,7]. Some of the USB1 mutations have the tendency to reoccur in the same geographic areas. The described families are from the European Mediterranean region, making our patient the first one from the continental part of the Balkan peninsula. Most of the reported patients come from other continents or northwest parts of Europe.

The importance of the genetically confirmed diagnosis lies in regular haemato-oncological checks and skin examinations since PN is regarded as a pre-cancerous state. One family with the same mutation in two affected sisters had the younger one develop skin cancer [8] and the elder sister died from AML [9].

Conclusion

Although molecular diagnosis may not always be immediately available, the diagnosis of this disease can be made according to characteristic clinical findings, poikiloderma and neutropenia. Even though it was first described in Navajo Indians, since then there are reports about these patients from around the world, with just a few patients from Europe. We describe the first one from the central Balkan region with distinctive clinical findings.

Since PN is regarded as a premalignant disease, the importance of the genetically confirmed diagnosis lies in regular haemato-oncological checks and skin examinations.

We also purpose the use of G-CSF for infection prevention but with precaution because of its hematological side effects. With regular administration of G-SCF our patient has no bacterial sinopulmonary, middle ear, or skin infections, and has a higher average neutrophile count compared to the neutrophile count before G-SCF therapy. Patients with PN should be regularly vaccinated to avoid vaccine-preventable diseases.

Conflict of Interest Statement for All Authors

All authors declare that they have no conflicts of interest.

Statement on Consent for Publication

All the authors give their consent for the publication of photographs, case history, and/or details within the text to be published in the above Journal and Article.

Statement on Ethical Approval and Informed Consent

Parents gave full permission to publish photographs and textual material (case history).

Bibliography

1. Clericuzio CL., *et al*. "Immune deficient poikiloderma: a new genodermatosis". *American Journal of Human Genetics* 49 (1991): A661.
2. Concolino D., *et al*. "Clericuzio-type poikiloderma with neutropenia syndrome in three sibs with mutations in the C16orf57 gene: delineation of the phenotype". *American Journal of Medical Genetics Part A* 152A.10 (2010): 2588-2594.
3. Rodgers W., *et al*. "Squamous cell carcinoma in a child with Clericuzio-type poikiloderma with neutropenia". *British Journal of Dermatology* 168.3 (2013): 665-667.
4. Arnold AW., *et al*. "Poikiloderma with neutropenia: a novel C16orf57 mutation and clinical diagnostic criteria". *British Journal of Dermatology* 163.4 (2010): 866-869.
5. Larizza L., *et al*. "Rothmund-Thomson syndrome". *Orphanet Journal of Rare Diseases* 5 (2010): 2.
6. Farrugia P., *et al*. "Poikiloderma with neutropenia: a case report and review of the literature". *Journal of Pediatric Hematology/Oncology* 36.4 (2014): 297-300.
7. Hilcenko C., *et al*. "Aberrant 3' oligoadenylation of spliceosomal U6 small nuclear RNA in poikiloderma with neutropenia". *Blood* 121.6 (2013): 1028-1038.
8. Walne AJ., *et al*. "Mutations in C16orf57 and normal-length telomeres unify a subset of patients with dyskeratosis congenita, poikiloderma with neutropenia and Rothmund-Thomson syndrome". *Human Molecular Genetics* 19.22 (2010): 4453-4461.
9. Porter WM., *et al*. "Hematological disease in siblings with Rothmund-Thomson syndrome". *Clinical and Experimental Dermatology* 24 (1999): 452-454.

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