Pachyonychia congenita type 1 (Jadassohn-Lewandowsky syndrome) – case report and literature review

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Abstract

Pachyonychia congenita (PC) is a rare genodermatosis of autosomal dominant pattern of inheritance, affecting nails, skin, oral mucosa, larynx, hair and teeth. The clinical phenotype is a result of a pathogenic mutation in one of the genes encoding keratins. Owing to recent clinical and molecular analyses of patients from the International Pachyonychia Congenita Research Registry it was possible to start clinical trial on gene therapy using small interfering RNA molecules to knock out the mutant keratin. This novel approach is opening up a new avenue for the treatment of genetic skin diseases. We report a case of a 9-year-old girl with pachyonychia congenita type 1 (PC-1), previously termed Jadassohn-Lewandowsky syndrome, suffering from the most frequent of the known mutations – KRT6aN172del.

Key words: nails, pachyonychia congenita, Jadassohn-Lewandowsky syndrome, siRNA.

Introduction

Pachyonychia congenita (PC) is an ultra-rare genodermatosis, of mainly autosomal pattern of inheritance, that typically begins in infancy [1, 2]. It is estimated that a few thousand individuals may be affected with PC worldwide [3].

The most striking clinical feature of PC is symmetrical thickening of all nails – hypertrophic nail dystrophy or pachyonychia – which is observed in over 90% of cases. Characteristic changes in the nails include hyperkeratosis of the nail bed, thickening of the nail plate and distortion or curvature of the nail plate, which usually has a yellowish-grey colour. In 91-96% of cases of PC, variable degrees of a focal palmoplantar keratoderma are observed [4]. In the most severe clinical phenotypes deep plantar blisters may even be complicated by acro-osteolysis of bones [5, 6]. Therefore the disease is often debilitating, causing the patient to adopt a compulsory position while walking or to move with crutches, wheelchairs and other walking aids [4, 7]. The other characteristic features of PC include steatocystoma and pilosebaceous cyst formation, keratosis pilaris and leukokeratosis (leukoplakia) of the oral mucosa and larynx that do not lead to a neoplastic process. In infants laryngeal leukokeratosis may present as stridor and even lead to acute respiratory insufficiency [8]. In adults glottal leukoplakia may result in chronic or recurrent hoarseness [4, 8]. In some patients hair abnormalities and natal teeth (teeth erupted at birth or shortly after birth) are also found [4].

The first description of the disease comes from Ireland from 1685. It was included in a letter from Mr St. George Ash to one of the Secretaries of the Royal Society, concerning an Irish girl who had "several horns growing on her body" [9]. In 1716 "monstrous nails" were a subject of a doctoral dissertation by Carl Musaeus [10]. The term "pachyonychia congenita" meaning "thick nails since birth" was introduced in 1906 by Jadassohn and Lewandowsky [11].

The disorder results from mutations in genes encoding keratins K6a, K6b, K16 or K17 – proteins that form the

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cytoskeleton of epithelial cells [12-14]. In most cases the mutations are caused by small deletions and single nucleotide changes of an autosomal dominant pattern of inheritance. However, a few reports on recessive inheritance have also been published, mainly in offspring of consanguineous parents [15]. Spontaneous mutations appear to be relatively common (29%), according to literature reporting a negative family history [16].

The current classification distinguishes two types of the disease. The PC-1 clinical phenotype, or Jadassohn-Lewandowsky syndrome, is associated with mutation in K6a and K16 which is expressed in palmoplantar epidermis, mucosal epithelia and follicular keratinocytes. Therefore PC-1 is characterized by pachyonychia with focal palmoplantar keratoderma, follicular hyperkeratosis and oral and laryngeal leukokeratosis, more pronounced than in pachyonychia congenita type 2 (PC-2). In PC-2, also known as Murray-Jackson-Lawler syndrome, there are widespread pilosebaceous cysts, bushy eyebrows and hair abnormalities such as *pili torti* (twisted hair) or alopecia and additional features such as natal teeth. They are caused by mutations in K6b and K17 expressed in the pilosebaceous unit and basal appendageal keratinocytes [17, 18].

Case report

A 9-year-old girl with suspected Jadassohn-Lewandowsky syndrome was referred to the Department of Pediatrics and Clinical Immunology, Medical University of Lodz, for evaluation of a variant of precocious puberty (isolated breast enlargement or *thelarche praecox*).

All 20 of her fingernails and toenails were thickened, dystrophic, of yellowish-grey colour, with massive subungual hyperkeratosis. The patient could barely walk because of painful callosities and blistering present on her soles. They were hard, non-erythematous and accentuated in weight-bearing points. Severe keratosis pilaris was present especially on the arms, hips and back. These lesions were also widespread across the trunk and the face (mainly on the forehead). Keratotic spikes on the elbows and knees were also observed. Her palms and soles were sweaty. The examination of the mouth revealed angular cheilitis and slight leukokeratosis of the edges of the tongue.

Signs of puberty were also present – thelarche (T) III, pubarche (P) II/III on Tunner's scale. Ultrasound examination of female internal reproductive organs showed evidence of estrogenic stimulation and no masses. The serum concentration of follicle-stimulating hormone (FSH) and oestradiol was above the normal level for the age. Bone age according to the method of Greulich and Pyle was estimated to be for 12 years. She had no neurological symptoms.

The most severe and annoying symptoms of all she complained of was a sharp pain on walking, associated with breaking of blisters under calluses, which sometimes made normal functioning impossible. There were times when she was forced to adopt a compulsory position – even to move on her knees. It occurred usually after extended periods of standing or walking, especially on an uneven surface or during warm weather. Frequent adoption of an unnatural position led to the development of faulty posture.

Thick nail plates created an obvious aesthetic problem, but due to frequent injuries and recurrent bacterial and fungal infections, they were also a cause of physical suffering. After application of regular professional debridgement in a specialized medical cosmetic studio, fingernails and toenails were well maintained, shortly cut and covered with nail enamel, but even then they still looked "monstrous". There were other complaints such as excessive ear wax production and sweating, persistent dandruff and recurrent hoarseness of voice.

The history revealed that thickened, discoloured nails were first noticed on the 3rd day of her life. A few days later, small ulceration and a circumscribed thick white patch on the tongue was spotted (leukoplakia?) and treat-

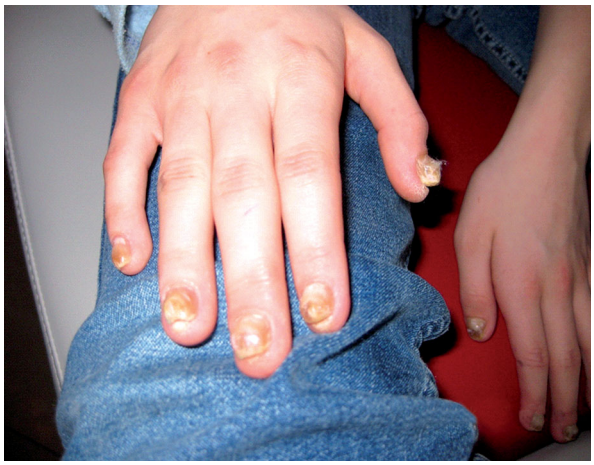

Fig. 1. Hypertrophic nail dystrophy

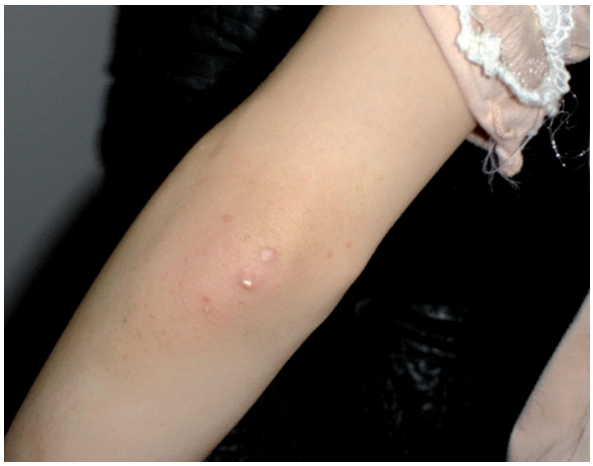

Fig. 2. Follicular hyperkeratosis and keratotic spikes

ed as thrush. She was breastfed one month only due to feeding difficulties (painful suckling?). During the first years of life the first episodes of recurrent painful erythematous swelling, bleeding of the nail folds and pyogenic infections were reported. Painful callosities and blistering on the soles were first noticed when she started to walk. At that time, thickened white patches in her mouth were noticed on the tongue and inside the lips and were treated by the family doctor as a yeast infection. Breast development was first observed when the girl was 1 year and 3 months.

Finally, when she was 9, on the basis of physical examination, radiograph of the carpal bones, and hormonal studies the girl was diagnosed as having a variant of early puberty (thelarche praecox) with no indication for hormonal inhibition of puberty. The girl was born to non-consanguineous parents. None of her family members had similar abnormalities.

Searching the literature in order to find data regarding pachyonychia congenita led us to The Pachyonychia Congenita Project (PC Project) website and the International Pachyonychia Congenita Research Registry (IPCRR) www.pachyonychia.org, from where we learned about the possibility of free genetic testing.

"PC Project", which is a non-profit USA public charity, was founded in November 2003 and supports clinical and research activities related to the treatment of pachyonychia congenita. The recruitment of participating patients is primarily self-referral to the web-based registry (http://www.pachyonychia.org/Registry.html) or a direct referral by a physician. Medical history questionnaires and a series of standard photographs should also be provided. The next step is to consult the patient by telephone with one of the top dermatologists specializing in PC, in order to establish the diagnosis and determine the appropriateness of free-of-charge genetic testing.

The mutation status of our patient was determined after sending a mouth swab by sequence analysis in a research laboratory of the Epithelial Genetic Group, Human Genetics Unit, Dundee University, Scotland and was verified in the clinical laboratory of GeneDx (Gaithersburg, Maryland, USA). The molecular analysis revealed that the mutation found in our patient was KRT6aN172del – a heterozygous deletion of 3 nucleotides (CAA) in exon 1 of the KRT6a gene located on 12q13 chromosome and situated in a highly conserved helix boundary motif of the K6a protein essential for end-to-end overlapping during keratin filament assembly [19]. Almost all of the already identified mutations occur at this site [20].

Discussion

We describe an exceptional case of pachyonychia congenita and a variant of precocious puberty. Such coexistence has not been described in the literature previously. However, on the basis of current knowledge it should be clearly stated that premature breast development or *premature thelarche* is not a phenotypic feature of PC. Among other symptoms previously incorrectly ascribed to PC were deafness, mental disability, cataract formation, corneal dyskeratosis, skeletal abnormalities, patent ductus arteriosus, supernumerary digits and delayed development of genitalia. They are extremely rare and, as in this case, rather not related to PC [20].

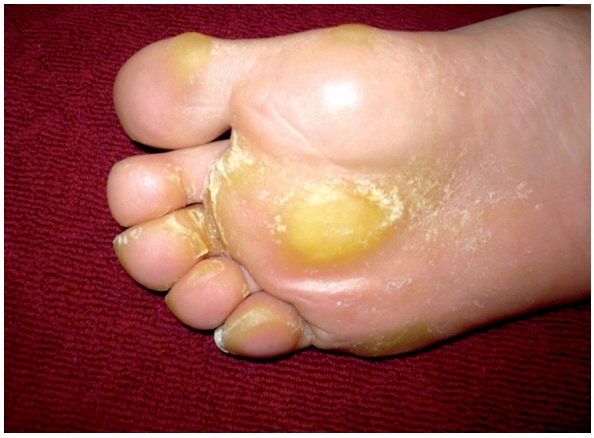

Fig. 3. Plantar keratoderma

The premature thelarche observed in our patient is a benign, usually transient condition of isolated breast development, with no other signs of sexual maturation in girls under 7 or 8 years of age. Growth and osseous maturation are normal or slightly advanced. Menarche occurs at the expected age. Plasma basal levels of FSH and their responses to gonadotropin-releasing hormone stimulation are greater than those seen in normal controls. In contrast, children with true precocious puberty secrete predominantly luteinizing hormone [21].

Owing to PC Project the International Pachyonychia Congenita Consortium, a collaborative team of scientists and clinicians, was established in 2004. Since then, enormous progress in the research on PC has been made. The project includes more than 928 patients from around the world and 66 mutations and clinical phenotypes of 445 people from 200 families have already been studied. Pachyonychia congenita has become exceptional among thousands of other genetically defined disorders because the afflicted patients have a chance of undergoing a disease-targeted therapy.

In 2008, the first clinical trial on humans involving the use of siRNA (small interfering RNA) was started. siRNA are a new class of RNA inhibitors that post-transcriptionally inhibit gene expression of a mutant gene responsible for PC-1 symptoms.

These 20-25 nucleotide-long double-stranded RNAs are homological to a sequence of targeted mutant mRNA. They bind to a protein of ribonuclease activity and cut

mutated RNA into pieces, causing knock out of the mutated protein – in this case keratin K6a. The siRNA called TD101 specifically and potently target mutated allele KRT6aN171K without affecting wild type K6a mRNA [22-24]. As shown in knockout mouse studies, the two major genes K6a and K6b express functional redundancy. This means that knocking out one of these keratins has little or no phenotypic consequences. The complete knock-out of K6a leads to compensative K6b or other keratin expression without development of symptoms of the disease [25-27]. Such a situation occurs in 1 of 4000 healthy people [28].

Starting in 2008, the first-in-human mutation-targeted phase Ib clinical trial for the treatment of PC investigated the safety and tolerability of increasing the volume and concentration of intra-lesional siRNA injections. It was a split-body, double-blind trial. The subject was an adult PC-1 patient. The drug was injected into the plantar keratoderma of one foot and the vehicle into keratoderma of the other foot. No adverse events occurred during the trial or in the three-month washout period. The patient's subjective assessment and the physician's clinical efficacy measures showed regression in the siRNA-treated callus only. It began to fall away and healthy pink skin was revealed underneath. The skin was remarkably non-tender to palpation, which had never been observed by the patient previously. If siRNA proves to be effective in the treatment of PC, there will be a chance of developing effective treatment of dominant genetic skin diseases and many other disorders [26].

Until the siRNA gene therapy is available, the current treatment options may only relieve symptoms. They can be divided into mechanical, surgical, chemical and pharmacological. In general, the therapy should be individualized because the symptoms and pain levels vary in PC patients, even among members of the same family and identical mutations. Although the exquisitely sensitive calluses cannot be removed effectively and completely, patients usually use razor blades or pumice stones to groom them. The pain experienced during grooming can be reduced by the application of oral non-steroidal anti-inflammatory drugs. Emollients are also reported to be somewhat effective for pain and appearance. Ointments and creams containing a high percentage of humectants and keratolytics, such as urea and Lac-hydrin, are also recommended. Mechanical removal of the excessive keratin in thick nails can be done using hand tools such as clippers, curettes, rasps, files, paring knives, pumice stones, electrical hand-held grinders, polishers, and sanders. It should be done routinely, after bathing, to help alleviate the pain and facilitate removal of the outer keratin layers. In order to soften the nails, pastes of 20-40% urea or 15-20% salicylic acid content should be used, especially if applied overnight [27]. It has also been reported by Swartling *et al*. that botulinum toxin injections reduce hyperkeratosis and hyperhidrosis of palms and soles [28]. Oral antihistamines, topical steroids and anaesthetics are effective to some extent in itching relief. Cysts are managed by excision, incision, drainage or hyfrecation and diathermy. The use of oral and/or topical retinoids is somewhat effective for appearance but not in all patients. However, this treatment should be recommended individually with regard to benefits and side effects incommensurable with expectations [27].

Nail infections should be treated with topical and systemic antibiotics [29]. The culture of the mucous membrane leukokeratotic lesions frequently shows the presence of *Candida albicans* strain of fungi. Unfortunately, long-term anti-fungal treatment fails to give desirable results and does not improve the mucous membrane appearance in the majority of cases.

Conclusions

The presented girl is the first Polish PC patient referred to IPCRR and whose disease was confirmed by genetic testing. The mutation turned out to be the most common in the IPCRR patients, which gives a chance of genetic therapy. Owing to PC Project the patient and her family were invited to the Pachyonychia Congenita Patient Support Meeting in Pitlochry, Scotland and had an opportunity to meet other children with PC as well as scientists and clinicians who work on finding a cure for this rare, debilitating disease.

We suggest that physicians treating patients with PC refer them to the PC Project website, www.pachyonychia.org, for up-to-date suggestions regarding management of PC and support.

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