Finger-nail onycholysis, leukonychia and acrocyanosis in a patient treated with valproic acid – case report

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Abstract

We present a case of a 30-year old female patient presenting with acrocyanosis and nail changes (leukonychia, onycholysis), who has been treated with valproic acid for 3 years. Acrocyanosis, listed in the group of acrosyndromes, is a painless condition, characterized by symmetrical discoloration of various shades of blue colour, localized within the hands, feet and face, often associated with hyperhidrosis of hands and feet and exacerbated by cold. Due to possible multifactorial aetiology of symptoms, this case may be considered as a diagnostic challenge. Valproic acid has been described as a causative factor of various skin and nail conditions, including onycholysis. On the other hand, nail abnormalities have been observed in patients with acrosyndromes (for example erythromelalgia). Capillaroscopy and photoplethysmography revealed numerous abnormalities. The patient needs further observation and monitoring of any possible signs and symptoms of connective tissue diseases.

Key words: leukonychia, onycholysis, acrocyanosis.

Introduction

Leukonychia is defined as white discoloration of the nails and onycholysis is defined as separation of the nails from the nail beds. Both of these abnormalities may be associated with various medications (bleomycin, vincristine, retinoids), but may also be due to zinc deficiency. Acrocyanosis is defined as symmetric and painless discoloration of different shades of blue colour within distal parts of the body [1-3].

We report on a patient with acrocyanosis who developed onycholysis and leukonychia of the finger-nails after three years of treatment with valproic acid (VPA).

Case report

The 30-year-old female patient has been treated for 3 years with VPA (dose of 300 mg twice daily), due to recurrent convulsions. A few months prior to hospitalization she developed finger-nail onycholysis and leukonychia. She also suffered from recurrent hand and feet viral warts and complained of poor tolerance of cold manifesting with hand and feet cyanosis and burning sensation, but without fully expressed Raynaud's phenomenon. The patient admitted smoking 10 cigarettes a day.

At admission we could observe violaceous slightly mottled, dusky erythema localized within the distal part of the dorsal hand surface (Figure 1). Distal onycholysis most prominently involved finger-nails II-IV (Figure 2), and also crescent-shaped leukonychia could be observed within nails IV and V of the right hand (Figure 3). Both hands were cold and sweaty.

Full blood count, erythrocyte sedimentation rate, electrolytes, creatinine, liver function tests and urine examination were normal. Antinuclear antibody titre was 1/80. Serum cryoglobulins and antiphospholipid antibodies were negative. Capillaroscopy and photoplethysmography revealed numerous abnormalities. In capillaroscopy almost exclusively tortuous, meandering and arborised capillary loops were revealed. Some of them were enlarged. Several megacapillaries and 1 avascular area were also observed. The subpapillary plexus was invisible, while the background was pink. Photoplethysmography revealed microangiopathic changes within fingers II, III and V of the right hand as well as I, II and III of the left hand.

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We also performed patch testing with the European standard set of contact allergens and a patch test with sodium valproate 12.5% in white petrolatum. Patch testing revealed contact hypersensitivity to sodium dichromate 0.5% in white petrolatum and no hypersensitivity to the drug.

Cryotherapy was used for the treatment of viral warts with no significant complications.

Discussion

The patient we hereby describe, due to possible multifactorial and complex pathogenesis of dermatological symptoms, presented a true diagnostic challenge. She was particularly concerned about cosmetic aspects of onycholysis and leukonychia and regarded the drug she was taking as a potential cause of her problems. Indeed, valproic acid is an effective, frequently used anticonvulsant drug, but it is known to have various cutaneous side effects, such as transient alopecia [4], exanthems (reversible pellagra-like syndrome in a child due to sodium valproate induced nicotinic acid deficiency) [5] and vasculitis [6]. Grech and Vella [1] described generalized onycholysis in a 2-year-old, previously healthy male associated with sodium valproate therapy. Diffuse onycholysis of toe- and fingernails developed after 13 weeks of treatment. Poretti *et al*. [2] reported on a case of onychomadesis as a possible rare side-effect of valproic acid medication. Complete separation and subsequent shedding of the left toe nail appeared after 4 years of therapy. Treatment discontinuation resulted in proper nail regrowth, and as the treatment stopped, the nails regrew normally. The authors speculate that nail and cutaneous abnormalities may be associated with zinc deficiency caused by VPA therapy, due to the combination of malabsorption and systemic chelation of zinc by sodium valproate. However, zinc deficiency has not been observed in children suffering from epilepsy being treated with VPA and there are no indications for supplementation of this microelement.

Apart from nail changes, in both of the described cases no additional skin manifestations have been observed. Therefore our patient seems to be different because of acrocyanotic symptoms of hands and feet. According to the original definition by Croq [7] established in 1896, acrocyanosis is a painless condition, characterized by discoloration of various shades of blue, most commonly appearing in the hands, feet and face, marked by symmetry and persistence of colour changes, aggravated by cold exposure and frequently associated with hyperhidrosis of hands and feet. Due to similarity of clinical picture, acrocyanosis is listed in the group of conditions known as *acrosyndromes* [3].

What is worth emphasizing, these acrosyndromes may overlap, making the diagnosis truly challenging. Acrocyanosis should be distinguished from Raynaud's phenomenon, pernio, acrorygosis and erythromelalgia. Acrocyanosis is differentiated from Raynaud's phenomenon by relative persistence of skin colour changes, symmetry, and absence of paroxysmal pallor. However, in some patients Raynaud's may be superimposed on acrocyanosis, complicating the diagnosis. What is more,

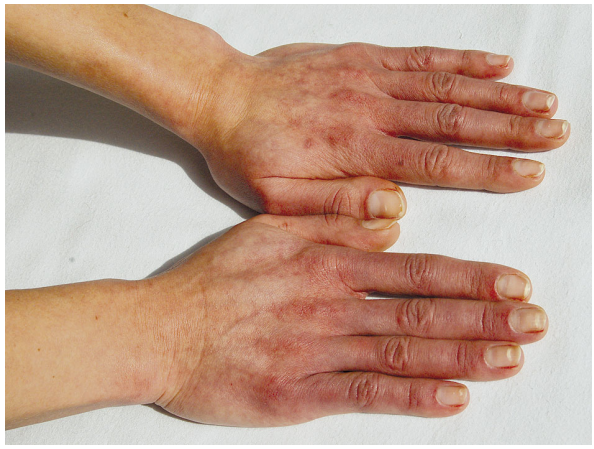

Fig. 1. Violaceous, slightly mottled, dusky erythema localized within dorsum of both hands

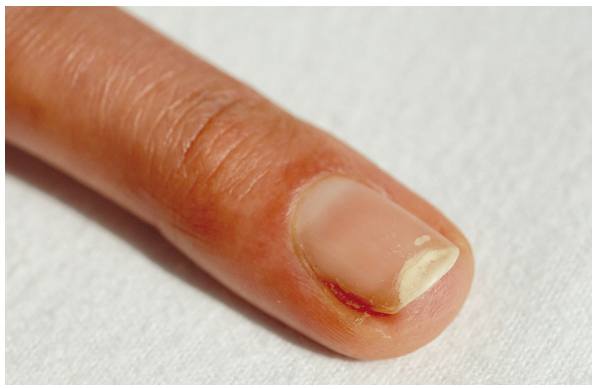

Fig. 2. Distal onycholysis within left finger-nail IV

Fig. 3. Crescent-shaped leukonychia observed on right nails IV and V

according to some authors, acrocyanosis should be included as a Raynaud's phenomenon variant [8].

Acrocyanosis is considered primary if no apparent cause can be determined. It is believed to be a benign condition that typically requires no specific treatment, does not evolve into connective tissue disease or other serious diseases, and may spontaneously resolve. Secondary acrocyanosis may be associated with numerous conditions: lung disease, connective tissue diseases (overlap syndrome, rheumatoid arthritis, lupus erythematosus), haematological disorders, toxicities and psychiatric disorders (e.g. bipolar disorder). Drugs may also be associated with acrocyanosis and among them tricyclic antidepressants, interferons, amphotericin B, benzocaine, bleomycin and butyl nitrite are mentioned. There are however no reports on sodium valproate. On the other hand, there are rare reports on the combination of erythromelalgia with leukonychia and distal onycholysis with Raynaud's phenomenon (although observed in a patient with Candida onychomycosis) [3, 9, 10].

Nailfold capillary microscopy or capillaroscopy provides useful information on capillary morphology *in vivo* and has been widely used as a tool to investigate the microcirculation in various connective tissue diseases and in acrosyndromes. It may be helpful in distinguishing between primary acrocyanosis and connective tissue diseases in their early stages when other clinical symptoms are not yet present [3]. Indeed, capillaroscopy performed in our patient within the nail folds revealed various abnormalities. There is lack of agreement on capillaroscopic criteria of acrocyanosis and connective tissue diseases. According to the quantitative capillaroscopy by Monticone *et al.* [11], slightly reduced capillary density, regular distribution of capillary bed, the absence of avascular zones, the different widened capillary diameters, and the presence of less than 2 megacapillaries per finger allow the diagnosis of acrocyanosis. Tortuous capillaries are non-specific and may be seen in individuals without acrocyanosis. Detection of megacapillaries may be helpful as they are not normally present in systemic lupus erythematosus or rheumatoid arthritis. They are also uncommon in polymyositis, but are common in scleroderma and mixed connective tissue disease [11, 12]. Therefore, the patient will remain under supervision of our outpatient clinic and will be monitored in terms of any other symptoms or laboratory abnormalities typical for connective tissue diseases. The patient was in addition advised to quit smoking and protect acral regions from the cold. We are also planning to introduce a course of low-molecular weight dextran in hospital conditions for the treatment in the upcoming future.

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