A Case of Noonan Syndrome and Kyrle Disease: Casualty or Causality?

Dear Editor,

A 39-year-old Caucasian woman affected by Noonan Syndrome (NS) mutated in RAF1 was referred to us with itchy lesions on her limbs that had appeared two months earlier. Clinically, there were multiple umbilicated papules with a hyperkeratotic central plug, localized on the upper and lower limbs (Figure 1, a-b). The patient had no personal history of diabetes mellitus or chronic renal failure, but suffered from hypertrophic cardiomyopathy. Blood tests showed no abnormalities. On histological examination of a skin lesion, an ectatic hair follicle with a hyperkeratotic ostium was observed with fragments of hair, inflammatory cells, and epidermal perforation. A final diagnosis of Kyrle disease (KD) was established. The patient underwent narrowband UVB (NB-UVB) phototherapy with residual atrophic scars (Figure 1, c-d), but with a complete and long-lasting resolution of symptoms.

KD belongs to perforating dermatoses (PD), a heterogeneous group of skin diseases characterized by the transepidermal elimination of dermal components. Despite the classification of PD still being under debate, four primary forms are traditionally recognized: reactive perforating collagenosis, elastosis perforans serpiginosum, perforating folliculitis, and KD (1).

The typical skin manifestation of KD is an eruption of dome-shaped papules and nodules, with a whitish central keratotic plug, mainly localized on the extremities and the buttocks. Described by Kyrle in 1916, KD is frequently associated with systemic dis-

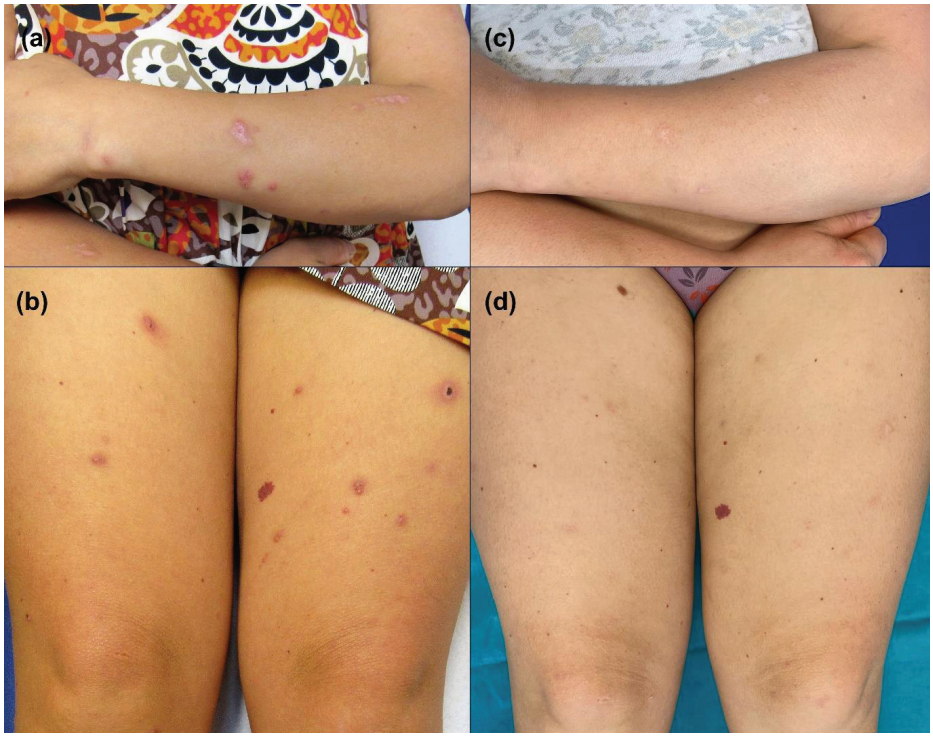

Figure 1. (a, b) Multiple umbilicated papules with a hyperkeratotic central plug, localized on the upper and lower limbs. (c, d) Residual atrophic scars after narrowband UVB phototherapy.

eases, especially chronic renal failure and diabetes mellitus. Other associated conditions include chronic hepatic disease, internal malignancies, and congestive heart disease (1).

Despite the absence of a consensus, the control of the underlying disease remains the first therapeutic target. Both topical (keratolytics, retinoids, and corticosteroids) and systemic treatments (corticosteroids, retinoids, antibiotics, and phototherapy) have been reported to control skin manifestations (2). In our experience, NB-UVB is an effective option as first-line therapy in case of diffuse lesions, both in KD and in other PD (3).

NS is a relatively common RASopathy, a heterogenous group of genetic diseases characterized by a defect of the Ras-mitogen-activated protein kinase (Ras-MAPK) pathway, with an estimated prevalence of 1/1000-2500. PTPN11 is the most frequent mutated gene, accounting for 50% of cases, but more than ten genes have been identified as causing NS (4). Classical features include a distinctive facial dysmorphism, short stature, pulmonic stenosis, and other anomalies of different organs. The skin is commonly involved. Keratinization disorders and hair abnormalities such as keratosis pilaris, ulerythema ophryogenes, wavy or curly hair, and scarce scalp hair, are often described. Other cutaneous signs include easy bruising, skin hyperlaxity, multiple lentigines, and café-au-lait spots (5).

To the best of our knowledge, no cases of KD in patients with NS have been previously reported to date. The exact etiopathogenesis of KD is not clear, but it has been hypothesized that systemic diseases, such as diabetes and chronic renal failure, can cause a deposit of substances or dermis alterations, which triggers the inflammatory process with subsequent transepidermal extrusion (1). In our patient, we ruled out all the causes commonly associated with KD.

It is however possible that this manifestation could be a direct result of the patient's illness. Our patient suffered from diffuse keratosis pilaris, and an abnormal epidermal keratinization with a secondary inflammatory dermic response is among the suggested possible pathogenetic mechanisms of KD (1). On the other hand, the hyperlaxity and fragility of the skin typical of NS suggest the presence of altered connective tissue, which could trigger an abnormal keratinization and, subsequently, the transepidermal extrusion, as well as perforating elastosis, which is associated with genetic connective tissue diseases (1). Moreover, our patient suffered from a cardiac disease, another condition associated with KD (5).

Although these explanations have their appeal, there is currently insufficient evidence of a link between KD and NS, and it will be necessary to collect additional data to confirm this hypothesis.

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