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Kyrle disease: a case report and literature review

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Abstract. – BACKGROUND: Perforating dermatoses are heterogeneous skin disorders characterized by transepidermal elimination of dermal tissue components. Acquired perforating dermatoses can be divided into four types, according to the eliminated dermal materials: Kyrle disease, perforating reactive collagenosis, elastosis perforans serpiginosa, and perforating folliculitis. They characterize adult patients with coexisting systemic diseases, regardless of the dermal materials eliminated. The association between Kyrle disease and renal failure or diabetes mellitus is common.

CASE REPORT: We reported the case of Kyrle disease in a patient with chronic kidney disease. A literature review was performed with the aim to highlight the associated comorbidities and point out the role of early and specific treatment of the cutaneous symptoms and manifestations.

CONCLUSIONS: Being Kyrle disease a pruritic condition which adversely affects the patient's quality of life, it would be desirable to place greater therapeutic attention on the alleviation of itching and on the correct management of the underlying comorbidity.

Key Words:
Kyrle disease, Perforating dermatosis, Acquired perforating dermatosis, Comorbidity, Treatment.

Background

Perforating dermatoses are a group of papulonodular skin diseases characterized by the transepidermal elimination of connective tissue elements or ejection through the dermis[1]. These findings may be the primary manifestation of familial or acquired systemic conditions. Rare familial primary perforating disorders typically present in childhood and are histopathologically-characterized by the transepidermal elimination of collagen (reactive perforating collagenosis) or elastic fibers (elastosis perforans serpiginosa). Perforating dermatoses that appear in adult patients suffering from systemic diseases have also been recognized[2], therefore the "acquired perforating dermatosis" (APD) has been proposed. APD include four separate clinicopathologic entities: elastosis perforans serpiginosa (EPS), reactive perforating collagenosis (RPC), perforating folliculitis (PF) and Kyrle's disease (KD), being characterized by elastin, collagen and keratotic material removal, respectively[3]. In particular, KD is a dermatosis which was firstly described by Kyrle in a woman affected by diabetes under the name of "hyperkeratosis follicularis et parafollicularis in cutem penetrans" in 1916[1]. KD mainly affects women between the third and fifth decades, and is also associated with certain systemic conditions, especially renal failure, diabetes mellitus, hemodialysis, and hepatic failure[4]. Moreover, it may be associated with liver failure, congestive heart failure, hyperlipidemia, infectious diseases, and endocrinological disorders[1].

Although the etiology of KD is still unknown, a complex interaction between epithelium, connective tissue, and inflammatory mediators is most likely involved. Regardless, KD is strongly associated with pruritic conditions, while superficial trauma to the epidermis is probably the major trigger in predisposed patients. This is supported by the evidence that many patients present with prurigo nodules in addition to the classic perforating lesions typical of the disease. These data are further supported by the fact that the interruption of the manipulation or trauma leads to the resolution of the lesions. Predisposing conditions include diabetes mellitus-related vascular disease or angiopathy, and micro-deposition of exogenous materials within the dermis, including calcium and silicon salts. This evidence is supported by the increased frequency of per-

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forating dermatoses in dialysis patients. Finally, epidermal or dermal changes related to metabolic disorders, including vitamin A deficiency, are consideredamong the predisposing conditions[5,6]. Moreover, the role of advanced glycation end product (AGE)-modified collagens I and III has been evaluated. Traumatized keratinocytes bind to these extracellular matrix proteins *via* AGEs receptor cluster of differentiation (CD) 36, inducing keratinocyte terminal differentiation and upward movement of keratinocytes along with glycated collagen[7].The role of fibronectin was also evaluated as it connects keratinocytes with type IV collagen within the basement membrane, thus playing a vital role in signaling, migration, and differentiation of epithelial cells. In support of this, increased levels of fibronectin have been found in the serum of patients with diabetes and uremia, as well as within the skin at transepidermal elimination sites[8]. Finally, imbalances in transforming growth factor-β3 (TGF-β3), matrix metalloproteinase- (MMP)- 1, and tissue inhibitor of metalloproteinase-1 were also detected in the lesions[9].As already said, KD is characterized by transepidermal extrusion of abnormal keratin and hyperkeratotic papules/nodules with epidermal invaginations in the skin, usually involving the extensor surface of upper and lower limbs, as well as the trunk[1]. The lesions may affect the follicle or be extrafollicular, and the linear disposition is ordinary[10]. Patients usually complain of severe pruritus[1]. In fact, prurigo nodularis represents the most relevant differential diagnosis of KD, since they both share the same conditions[1]. With the increasing use of dermoscopy in daily practice, various dermoscopic patterns have proved useful in recognizing this spectrum of cutaneous conditions. Recently, a 3-zone-concentric pattern has been described[11,12], characterized by bright whitish-brownish scales in the center (due to dilated infundibulum filled with keratin and extruded cell debris), a destructured whitish-gray area surrounding the central crust (which is probably a consequence of the combination of epidermal and dermal changes), and a peripheral brown pigmentation (related to post-inflammatory epidermal pigment). A fourth structure has also been described[13]as a structureless pink area characterized by dotted vessels (caused by dermal inflammation and increased vascularization following the inflammatory process). Dermoscopic features are closely linked to the histological changes[14]. Histologic examination is usually characterized by orthokeratotic and parakeratotic plugs that invaginate in the epidermis at the follicular level as well as in the parafollicular position. Under the pressure of the plug, the prickle and basal layers become thinner and disappear. It follows that the horny mass penetrates the epidermis until contact with the dermis[15]. Multiple skin biopsies are usually recommended to evaluate the possible invagination in the epidermis, filled with degenerated basophilic material[12]. Clinical-pathological correlation supports its differential diagnosis with other keratinization disorders, such as hypertrophic and verrucous lichen planus, pityriasis rubra pilaris type I, Darier's disease, disseminated superficial actinic porokeratosis, hyperkeratosis lenticularis perstans, Flegel disease, and other classic perforating dermatoses[1,16-18]. Laboratory evaluation for comorbidities should include fasting glucose, glucose tolerance test, serum creatinine, glomerular filtration rate or creatinine clearance, serum uric acid, liver function tests, and thyroid function tests[1].

Lastly, the treatment of KD is frequently unsatisfactory. Therapeutic options include topical corticosteroids and retinoids, keratolytic agents, narrowband ultraviolet B (nb-UVB), and Psoralen Ultra-Violet A (PUVA) phototherapy; antibiotics and local and systemic treatment with Vitamin A acid may also be used. Moreover, removal of single lesions with carbon dioxide (CO_2) laser, surgery, and cryotherapy may also represent a therapeutic option[19]. However, treatment discontinuation usually results in lesions' recurrence[4]. The purpose of this manuscript is to investigate the therapies available so far for the treatment of this perforating disease. Furthermore, being associated with systemic conditions, the association with the latter was investigated, with the aim of proposing diagnostic tests to identify them early, as well as specific therapies for the treatment of the systemic conditions and, consequently, for the resolution of the skin manifestation.

Case Report

The case of a 55-year-old male patient, who complained of generalized pruritus and skin lesions on the upper limbs and trunk for about six months,was reported. Pathological history revealed both systemic arterial hypertension (HT) and chronic kidney disease (CKD), for which the patient had been on hemodialysis for more than three years. Laboratory tests highlighted the sharp rise in urea and serum creatinine. The patient de-

nied any family history of similar dermatologic conditions. Dermatological examination revealed brownish papules and nodules with central keratotic plugs on the upper limbs and trunk (Figure 1a-b), some in linear arrangement, suggesting the Koebner phenomenon. Histopathological examination highlighted a large invagination in the epidermis filled with degenerated basophilic material mixed with inflammatory cells and keratin. On dermoscopy evaluation, a concentric pattern was observed, characterized by a crust in the center of the lesion, crowned by a keratotic scale, a destructured whitish-gray area,and a peripheral brown pigmentation (Figure 1c). Based on the clinical, dermoscopic, and histologic features, the diagnosis of KD was established. The patient was submitted to outpatient treatment with antihistamines and oral antibiotics (doxycycline), achieving partial improvement.

Literature Review

A bibliographic search was conducted on PubMed using the following keywords: "Kyrle's disease", "Kyrle's disease" AND "Treatment". We included only papers, out of 82 studies, that met the following criteria: case report or case series, complete clinical presentation of the case by photos or text. Studies that did not fit into the above categories, together with reviews, clinical trials, or meta-analyses, were excluded. Only papers written in the English language and concerning humans were examined. No restrictions on the year of publication were applied. According to these criteria, we selected28 case reports and 5 case series[11-13,15,20-48]. For each publication included, we recorded the author(s), study year, demographic and clinical features, associated disease, treatments, and outcomes (Table I).

Results

We found 40 cases of KD that included patients with a mean age of 48.7 ± 16.4 (ranged from 11 to 82 years). The mean age at the onset of the disease was 43.8 ± 18.5 years. No relevant gender differences for the risk of KD (M:F=1.2:1) were observed. Diabetes was the most common comorbidity associated with KD (8 cases)[12,22,25,36,38,39,41,46]. Chronic renal failure was the second most frequent association (4 cases[29,30,39,42]). In 5 cases[13,32,33,43,47], these comorbidities were simultaneously described. In 18 cases (21 patients, 52.5%), pruritus was the main symptom whereas pain was the second most common symptom, reported in 3 cases[21,31,41] (7.5%), followed by a sensation of pricking in one case (2.5%) and oral and ocular discomfort in another case (2.5%). In the remaining 11 cases[11,12,15,22-26,28,37,41] (14 patients, 35%), patients were asymptomatic. Upper and lower limbs were simultaneously involved in 29 patien ts[11,13,15,20,22,23,25-30,32-34,36-38,40-45,48] (72.5%): 4 without any other site involved[11,36,41,48], 16 with the concurrent involvement of the trunk[13,15,23,25,26,29,30,32-34,38,42-45], 3 with the simultaneous involvement of the trunk and other less common sites[23,34,38], 6 with the simultaneous involvement of other less common sites (dorsa of the hands and/or feet, palms and soles, face, ocular and oral mucosa).

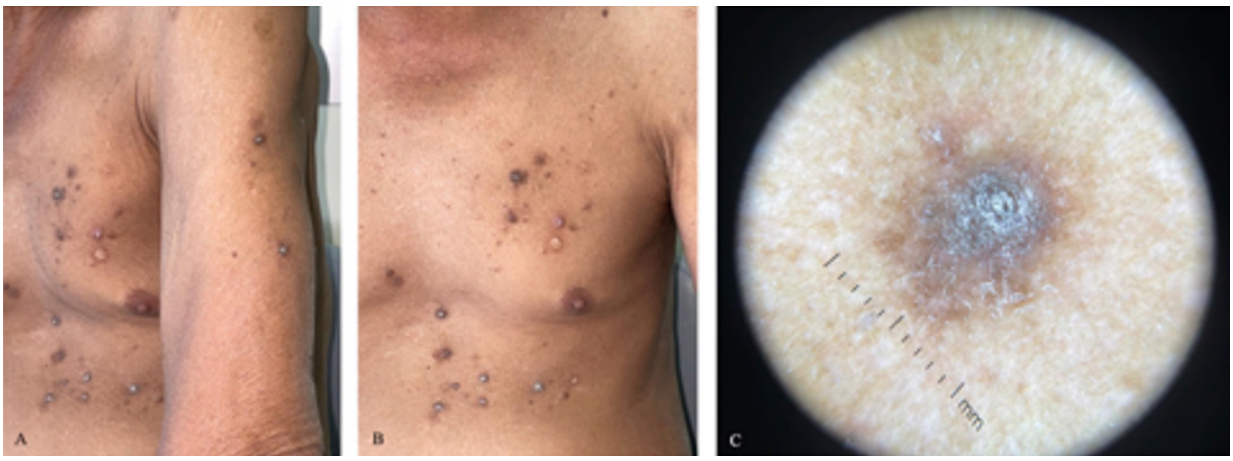

Figure 1. Clinical image: brownish papules and nodules with central keratotic plugs on the upper limbs (**A**) and trunk (**B**). Dermoscopic image: concentric pattern with a crust in the center of the lesion, crowned by a keratotic scale, a structureless whitish-gray area, and peripheral brown pigmentation (**C**).

Table I. Study characteristics.

Authors, reference number and year	Type of study	Sex/age (year)	Duration	Distribution	Clinical features/ Symptoms	Associate disease	Treatments/ Outcomes
Simpson[20], 1943	Case report	F/63	7 years	Upper + lower limbs, dorsa of the hands and feet	Keratotic plugged papules/ Sensation of pricking	Mild otitis externa, bronchitis, brachial neuritis	Vitamin A, 100.000 i.u./ Marked regression
Arnold et al[21], 1947	Case report	M/32	3 years	Palms	Papules with crater-like depressions/Pain	None reported	Not reported
Abele et al[22], 1961	Case report	M/58	8 months	Upper + lower limbs, face	Hyperpigmented, hyperkeratotic papulonodules and plaques/No symptoms	DM, FP, HT, TBC	Not reported
Peterson et al[23], 1963	Case report	F/77	43 years	Upper + lower limbs, trunk, dorsa of feet	Scaling papules/ No symptoms	Obesity	Topical keratolytic/No response
Bernstein et al[24], 1968	Case report	F/64	4 years	Face	Hyperkeratotic papules/ No symptoms	Asthma, obesity	300 r of grenz (H.V.L. of 20 u of Aluminum), salicylic acid cream 3%, topical flurandrenolone/ Marked regression
Tessler et al[25], 1973	Case series	Family members - F/33 - F/37 - M/19 - M/58	 - 3 yerars - 10 years - / - /	Upper + lower limbs, trunk	Keratotic plugged papules/ No symptoms	- Corneal opacities, cataract - Corneal opacities, cataract - Cataract - DM	Not reported
Elmofty et al[26], 1974	Case report	F/38	8 months	Upper + lower limbs, trunk	Hyperpigmented keratotic papules/No symptoms	Pseudoxanthoma elasticum	Not reported
Ruiz-Maldonado and Tamayo[15], 1977	Case report	M/11	7 years	Upper + lower limbs, trunk	Hyperkeratotic patches with horny plugs in the center/No symptoms	Pachyonychia congenita (Jadassohn-Lewandowsky) type II	Not reported
Schamroth et al[28], 1986	Case report	M/23	2 years	Upper + lower limbs, dorsa of hands and feet, palm and soles	Hyperkeratotic papules with central keratotic plugs/No symptoms	Esophagitis, gastritis, arthritic lesions in the ankles	Not reported
Kuokkanen et al[27], 1987	Case report	M/54	3 years	Upper + lower limbs, face, palms, soles	Hyperkeratotic plugs and scales/Pruritus	Myeloma	Melphalan, vincristine, cyclophosphamide, lomustine/ Complete remission
Igarashi et al[29], 1991	Case report	F/64	2 months	Upper + lower limbs, trunk	Keratotic, brownish, plugged papules/Pruritus	Sarcoidosis, CKD	Escalating doses of oral prednisolone/Complete remission

Continued

Table I *(continued)*. Study characteristics.

Authors, reference number and year	Type of study	Sex/age (year)	Duration	Distribution	Clinical features/ Symptoms	Associate disease	Treatments/ Outcomes
Chang et al[30], 1992	Case report	M/48	4 months	Upper + lower limbs, trunk	Hyperkeratotic papulonodules/Pruritus	CKD	Not reported
Dyall-Smith et al[31], 1994	Case report	M/48	15 years	Dorsa of both feet	Keratotic plugged papules/ Pain	Ulcerative colitis	Not reported
Habte-Gabr et al[32], 1996	Case report	M/28	4 months	Upper + lower limbs, trunk	Hyperkeratotic papules / Pruritus	CKD, DM, pyomyositis	Surgery, nafcillin 2 g/Complete remission
Harman et al[33], 1998	Case series	- M/54 - M/14	- 2 years - 1 year	- Upper + lower limbs, trunk	Keratotic plugged papules and nodules/Pruritus	DM, CKD	Acitretin 20 mg/Partial response
Alyahya et al[34], 2000	Case report	M/52	47 years	Upper + lower limbs, trunk, oral + ocular mucosa, dorsa of hands and feet	Hyperkeratotic plugged papules/Oral and ocular discomfort	None reported	Not reported
Lee et al[35], 2005	Case series	- F/61 - F/82	- 4 months - 3 months	- Neck - Left upper limb	- Crateriform papules / Pruritus - Umbilicated papules / Pruritus	Chronic dermatitis treated with saltwater emulsion	None/Self-resolution
Khalifa et al[36], 2007	Case report	M/41	1 year	Upper + lower limbs	Hyperkeratotic papules / Pruritus	DM	Metronidazole 500 mg/ Complete remission
Shivakumar et al[37], 2007	Case report	M/30	25 years	Upper + lower limbs, oral + ocular mucosa, palms, soles	Hyperkeratotic papules and nodules/No symptoms	None reported	Not reported
Shih et al[38], 2011	Case report	F/66	3 years	Upper + lower limbs, trunk, face	Excoriated and crusted papulonodules, hyper-pigmented macules / Pruritus	DM	Allopurinol 100 mg/Marked regression
Ataseven et al[39], 2014	Case series	- F/38 - F/62	- 4 months - 3 months	Lower limbs	Erythematous, keratotic plugged papules/Pruritus	- CKD, total blindness of the left eye; - DM, HT, asthma, HL	Topical retinoic acid (0.1%)/ Not reported
Kasiakou et al[40], 2015	Case report	M/44	1 year	Upper + lower limbs, face	Hyperkeratotic papules, plaques, and burrows/ Pruritus	None reported	Surgery and clindamycin 300 mg/Partial response
Bodman et al[41], 2015	Case series	- M/57 - F/44	- 6 months - 1 year	- Upper + lower limbs - Lower limbs	- Hyperpigmented, hyper-keratotic nodules/ No symptoms - Hyperpigmented, hyper-keratotic papules and plaques / Pain	- DM, BPH, PAD, gout, obesity, bilateral nephrectomies for RC - DM, MS, HT, asthma, depression	Topical triamcinolone 0.5%/Marked regression

Continued

Table I *(continued)*. Study characteristics.

Authors, reference number and year	Type of study	Sex/age (year)	Duration	Distribution	Clinical features/ Symptoms	Associate disease	Treatments/ Outcomes
Fernandes et al[42], 2016	Case report	M/57	6 months	Upper + lower limbs, trunk	Keratotic plugged papules / Pruritus	HT, CKD	Antihistamines, oral/intravenous antibiotics, allopurinol 100 mg/Partial response
Kinoshita et al[43], 2016	Case report	M/49	3 ears	Upper + lower limbs, trunk	Erythematous papules with keratotic plugs/Pruritus	DM, CKD	Topical 0.1% tacrolimus/ Partial response
Russo et al[11], 2016	Case report	F/38	2 years	Upper + lower limbs	Hyperpigmented, keratotic papulonodules/ No symptoms	None reported	Not reported
Tampa et al[44], 2016	Case report	M/69	3 years	Upper + lower limbs, trunk	Umbilicated keratotic papules with central keratotic plugs/Pruritus	Delusions of parasitosis	Clindamycin, antihistamines, isotretinoin/Partial response
Maurelli et al[45], 2017	Case report	F/63	3 years	Upper + lower limbs, trunk	Hyperkeratotic, erythematous- brown nodules and plaques / Pruritus	None reported	Isotretinoin 20 mg/day/ Complete remission after 4 months
Lokesh et al[46], 2017	Case report	F/52	3 months	Lower limbs, trunk	Hyperkeratotic papules with central keratotic plugs/Pruritus	DM	Oral vitamin A 25 000 IU, hydroxyzine 10 mg, topical urea, propylene glycole and tretinoin 0.1% gel/Marked regression
Nogueira Farias et al[47], 2018	Case report	M/51	1 month	Upper limbs, trunk, face	Hyperchromic macules and papules / Pruritus	DM, CKD, HT, HIV	Keratolytic soap (Actine)/ Marked regression
Idoudi et al[12], 2020	Case report	M/65	2 months	Lateral edge of the small toe of the left foot	Hyperpigmented, hyperkeratotic plugged papules/ No symptom	DM	Not reported
Ozbagcivan et al[13], 2020	Case report	F/61	1 month	Upper + lower limbs, trunk	Erythematous, excoriated, umbilicated papules with central keratotic plugs/ Pruritus	DM, CKD	Not reported
Babino et al[48], 2020	Case report	F/42	3 years	Upper + lower limbs	Hyperpigmented, keratotic papulonodules/ Pruritus	HS, RA	Adalimumab/ Marked regression

BPH=benign prostatic hyperplasia, CKD=chronic kidney disease, DM=diabetes mellitus, FP=fibrinous pericarditis, HS=hidradenitis suppurativa, HT=hypertension, MS=multiple sclerosis, PAD=peripheral arterial disease, RA=rheumatoid arthritis, RC=renal carcinoma, TBC=tubercolosis.

The involvement of one or both lower or upper limbs with or without the other sites was observed in the remaining 6 cases[12,21,31,35,39,41]. Limbs were not involved in 5 cases[12,21,24,31,35]. The most common clinical feature was the presence of multiple keratotic papules/nodules. Both treatment and outcome were described in most cases (55%), although the medium- and long-term duration were not always specified. Therefore, the therapeutic effectiveness was not exactly estimated.

Discussion

KD is a chronic keratinization disorder characterized by hyperkeratotic parafollicular or follicular papules and nodules with a centrally localized cone-shaped plug[49]. From the literature summarized in Table I, it emerges that papules are typically non-confluent, but they may sometimes merge to form circinate plaques and may usually appear in the extensor surface of upper and lower limbs and the trunk[33]; however, also head, neck, and face may be affected[22,24,27,35,38,40,47]. Although KD generally does not involve mucous membranes, plantar or palmar surfaces, some studies[21,27,28,34,37] reported the presence of lesions in these localizations; however, it is often difficult to understand whether mucosal involvement is a comorbidity or a spectrum of the disease[25]. Patients often experience pruritus and Koebner's phenomenon[39,42,46], but the clinical similarity of KD lesions with other pruritic dermatoses makes differential diagnosis difficult. As mentioned, the exact pathogenesis of KD remains unknown, despite the disease having been described almost a century ago[49]. Several hypotheses have been proposed[35,36,38,40,42], including a genetic or acquired connective tissue abnormality, diabetic vasculopathy, disposition of substances such as uric acid or hydroxyapatite, mechanical injury, enzyme release from neutrophils (metalloproteinase), TGF-β3 over-expression and abnormal vitamin A or D metabolism. The contribution of infectious agents in the pathogenesis of KD has also been proposed[49], since the association with some infectious diseases, including viral hepatitis, tuberculosis, pulmonary aspergillosis, and scabies, has been described[1]. The regression of the lesions of KD with antibiotic treatment such as metronidazole[36] or clindamycin[40] suggests that infectious agents (probably anaerobic bacteria) may play a role in the pathogenesis of the disease. A single case report[47] described the occurrence of perforating dermatosis in association with HIV infection. In HIV-positive immunocompromised patients, there is a decrease in the number and function of antigen-presenting cells and CD_4^+ T lymphocytes, making the skin more vulnerable to opportunistic and neoplastic infectious agents[5,50]. This may be one of the explanations for KD manifesting in immunocompromised patients. The association with multiple disorders represents a peculiar characteristic of KD, including diabetes mellitus, renal and liver diseases, congestive heart failure, hyperlipidemia, paraneoplastic disease, and abnormal metabolism of vitamin A[27,33,39,41]. The link between KD and CKD is more common in hemodialysis patients[30], as also observed in our case. Other rarer associations reported in the literature include pseudoxanthoma elasticum[26], pachyonychia congenita[15], sarcoidosis[29], hidradenitis suppurativa[48] and ulcerative colitis[31]. In addition, mechanical trauma, photodamage and exogenous agents (as the accidental exposure of calcium salts) could induce the onset of perforating disorder[35]. An interesting predisposing factor might be delusions of parasitosis, which would act as a trigger due to the presence of pruritus[44]. The combination of KD with other disorders like pyomyositis remains unexplained[32]. Nevertheless, KD may also affect healthy persons. KD treatment is challenging, often requiring treatment of the associated disease. A wide variety of treatment regimens for KD has been reported in the literature, including topical/systemic retinoids[33,39,44-46], topical keratolytics[23,24,46,47], oral/systemic/injectable steroids[24,29,41], vitamin A[20,46], antihistamines[42,44], allopurinol[38,42], metronidazole[36], clindamycin[40,44] and surgery for severe, refractory cases[32,40]. Although not always effective, phototherapy has been suggested as an appropriate treatment choice[45]. However, combination regimens are the most performed therapeutic approach to KD[49]. Discontinuation of these therapies often results in the recurrence of skin lesions[49]; hence, treatment of KD is frequently unsatisfactory[49]. Systemic retinoids are vitamin A derivatives that reduce inflammation and hyperkeratinization, a particular hallmark of KD and other perforating disorders[49]. Maurelli et al[45] described a rapid regression of the papulonodular rash after the use of oral isotretinoin. Acitretin, an alternative oral retinoid, has also been used in KD[33]. However, in the case series conducted by Harman et al[33], treatment with acitretin resulted in partial regression of the rash. The same result was shown in a study carried out by Simpson[20] on

the use of vitamin A. Treatment with topical retinoic acid (0.1%) was also reported[39], but the outcome was not clarified. Keratolytic agents, for the treatment of KD, are most used concurrently with other agents. Nogueira Farias et al[47] noted the complete rash regression of the skin lesion after the use of keratolytic soap (Actine) as a monotherapy. However, in another study conducted by Peterson et al[23], this improvement was not highlighted. Topical steroids, used in monotherapy or in combination with other agents, alleviate itch by tempering the immune system response. Bodman et al[41] noted a marked regression of KD after the use of topical triamcinolone 0.5%. In a single case report conducted by Igarashi et al[29], escalating doses of oral prednisolone in a patient with sarcoidosis led to the resolution of KD eruption through the improvement of sarcoidosis-related renal failure. Allopurinol has also proven good therapeutic results, through the inhibition of the enzyme xanthine oxidase, thus reducing the synthesis of free radicals, which in turn damage collagen[49]. However, its exact antipruritic mechanism is still speculative. This agent was successfully used in the report of Shih et al[38], in which there was the recurrence of KD 6 months following allopurinol discontinuation, but complete regression was achieved after the reintroduction of the drug. Interleukin-2 has a well-documented[49] role in the induction of pruritus. The inhibition of calcineurin phosphatase and subsequent reduction in IL-2 production, attributed to tacrolimus, may provide value for the treatment of KD[49]. Moreover, topical 0.1% tacrolimus has a direct effect on the suppression of CD36 and MMP-9 expressions, which are deeply associated with the development of skin lesions of KD[43]. In fact, the report of Kinoshita et al[43] described the complete clearance of KD using topical tacrolimus 0.1%; the timeline of rash regression was not clarified. Phototherapeutic modalities have also been considered[49] for the treatment of KD, likely due to their antipruritic effects. The success of UVB phototherapy for the treatment of pruritus has been attributed to its provocation of dermal mast cell apoptosis and regulatory T-cell induction[49]. Furthermore, it has been suggested that protease-activated receptor 2 (PAR2) on itch-mediating nerve fibers represents a therapeutic target for the treatment of cutaneous neurogenic inflammation and pruritus[49]. Tetracycline antibiotics, particularly doxycycline and minocycline, have been proposed to attenuate pruritus through their inhibition of PAR2, which is widely expressed in human epidermal keratinocytes and sensory nerves[49]. Clindamycin and metronidazole have both been investigated in KD as monotherapies, according to a few isolated reports[36,40]. Monotherapy with clindamycin reportedly achieved complete clearance after 8 months in one case[40]. Similarly, metronidazole use demonstrated complete rash regression after 1 year[36]. These reports also suggest the possible involvement of anaerobic bacteria in the pathogenesis of KD[36,40]. The use of combination therapy is perhaps the most widely used treatment approach seen in KD[49]. Bernstein[24] noted a marked regression of the skin lesions after the use of topical keratolytic associated with topical steroids. Some reports feature the addition of oral antihistamines, antibiotics, and allopurinol[42] or isotretinoin[44] with partial response. In a single case report conducted by Lokesh et al[46], urea cream was used alongside a topical retinoid and oral antihistamine, thus achieving complete rash clearance after 2 months of treatment. It is worth noting that antihistamines ordinarily help with the modulation of pruritic symptoms in histaminergic itch; since the chronic pruritus found in KD most likely originates from a predominately non-histaminergic pathway, the utility of this agent is questionable and its function in KD may be simply that of a sleep aid, limiting the night-time scratching that can exacerbate KD lesions[49]. Babino et al[48] reported an interesting case of KD associated with HS successfully treated with adalimumab therapy. Adalimumab is a highly specific tumor necrosis factor (TNF)-alpha inhibitor, binding to both soluble and membrane-bound TNF-alpha[51,52]. TNF-alpha is a proinflammatory cytokine with a pathogenetic role in several immune-mediated diseases such as HS and psoriasis[51-54] and may represent a promising therapeutic strategy for treating multiple concomitant skin disorders, even if the eventual common pathogenic mechanisms between KD and HS are still unknown. The response to adalimumab in KD lesions could be explained by the inhibition of the inflammatory response caused by the characteristic large keratotic and parakeratotic plugs penetrating from the epidermis through the dermis[48]. However, further clinical observations will be helpful to establish the efficacy and safety of adalimumab in treating KD. To date, there are no randomized trials regarding the treatment of KD. Treatments reported in the literature include several approaches. However, no truly effective treatment has been proven to date. Increasing evidence[55] suggests that cytokines and chemokines

play crucial roles in acute and chronic itch. Being tumor necrosis factor-alpha (TNF-α)/TNF receptor subtype-1 (TNFR1) signaling required for the full expression of acute and chronic itch *via* peripheral and central mechanisms[55], anti-TNF-α monoclonal antibodies such as Adalimumab could potentially provide relief in KD. In the same way, a growing body of evidence from recent clinical trials[49,56]supports other antipruritic immunomodulatory drugs targeting specific interleukin receptors (IL-4/13/31) and intracellular signaling, e.g., Janus kinase (JAK), pathways as promising emerging therapies for a variety of pruritic disorders. A major driver of pruritic responses and a probable pathogenic agent in KD, namely IL-31, govern a wide range of immunomodulatory effects, including proinflammatory cytokines and chemokine release, cell proliferation regulation, and the stimulation of dorsal root ganglia sensory neurons responsible for itch sensation[49]. Thus, IL-31 receptor monoclonal antibodies may potentially provide relief in KD[49]. Furthermore, sensory neuron-specific deletions of IL-4 receptor subunit a (IL-4Ra) or JAK1 have been shown to significantly reduce chronic itch[49]. Accordingly, tofacitinib, a JAK inhibitor, and dupilumab, a human monoclonal antibody directed against IL-4Ra of IL-4 and IL-13 receptors, demonstrate broad antipruritic properties and may prove valuable for the treatment of KD[49]. Since itching can become incredibly painful for patients, causing a negative impact on quality of life (QoL), much of the therapeutic focus in KD should be based on itch mitigation, sometimes achievable with proper management of the underlying systemic disease.

Conclusions

We reviewed the literature, reporting a rare case of KD in a patient with chronic renal failure on hemodialysis. KD is an acquired dermatologic condition that lacks a standardized treatment approach and can be notoriously difficult to cure. This article provides an overview of the most frequent comorbidities and treatment methodologies previously reported in the literature. If KD is suspected, underlying systemic disorders need to be investigated. Among these, the most frequent are kidney failure and diabetes mellitus. KD remains stationary for years, with possible clearing of lesions when the associated illness is under control. The increasing prevalence of renal disease, DM and other chronic diseases will inevitably lead to rising rates of KD in the upcoming years. Being a pruritic disease, which adversely affects the patient's QoL, it would be desirable to place greater therapeutic attention on the alleviation of itching and on the correct management of the underlying comorbidity.

Conflict of Interest
The authors declare no conflict of interest.

Ethics Approval
Not applicable.

Informed Consent
Written informed consent to image recording for academic purposes was obtained.

Authors' Contribution
Conceptualization, L.M. and M.V.; methodology, L.M. and F.V.; software, F.V.; validation, L.M., M.V.; formal analysis, L.M., F.L.P, F.B. and M.V.; investigation, L.M., F.L.P, F.B. and M.V.; resources, L.M. and M.V.; data curation, M.V.; writing—original draft preparation, L.M., F.L.P. and F.V.; writing—review and editing, L.M., N.I. and M.V.; visualization, N.I.; supervision, M.V. and N.I.; All authors have read and agreed to the published version of the manuscript.

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