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Case report

LONGSTANDING, REPETITIVELY MISDIAGNOSED KYRLE'S DISEASE IN A PATIENT WITH END-STAGE RENAL DISEASE: A CASE REPORT

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Abstract

Kyrle's disease (KD) is a rare variant of acquired perforating dermatosis (APD), associated with systemic diseases in adults, particularly chronic kidney disease (CKD) and diabetes mellitus (DM). Hyperkeratotic papules of KD are clinically important as a sign of a systemic disorder that are often misdiagnosed, so clinicopathological correlation is needed to establish the diagnosis. We report a rare case with longstanding KD, associated with end-stage renal disease (ESRD) on hemodialysis for 25 years that was repetitively misdiagnosed as folliculitis, excoriations and prurigo nodularis. The KD skin changes started to develop during earlier stages of CKD, before the kidney disease was suspected, and continued to appear in flares with extensive lesions when the systemic disease in the background was not under control. Dermoscopy revealed a 3-zonal concentric pattern, characterized by bright whitish scales in the centre, a structureless whitish-grey area surrounding the central crusts, and a peripheral, rose/brown pigmentation. Histopathological examination revealed moderately acantathotic epidermal invagination filled with a keratotic plug admixed with cellular debris and neutrophils, and a modest parakeratosis. Our goal is to emphasize that the accurate and timely diagnosis is vital to be able to monitor patients for a life threating, systemic disease such as kidney failure, and attaining better management of the dermatological status which can become longstanding and hindering, as well as to outline the importance of the multidisciplinary approach to improve outcomes in patients affected by KD.

Keywords: Kyrle's disease, acquired perforating dermatosis, chronic kidney disease, end-stage renal disease, hemodialysis

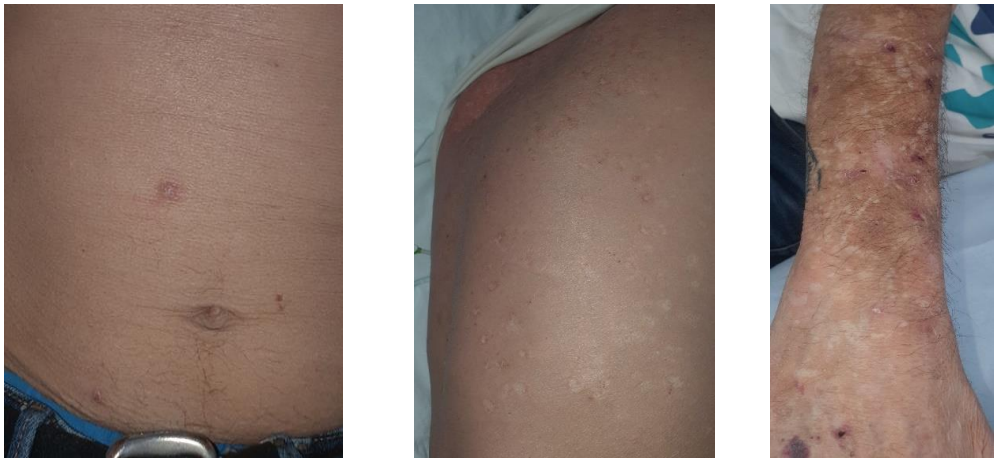
Introduction

In 1916, an Austrian dermatologist named Josef Kyrle first diagnosed *hyperkeratosis follicularis et parafollicularis* in *cutem penetrans*, now known as Kyrle's disease (KD), in a 22-year-old female with diabetes mellitus (DM)[1]. KD is a rare variant of acquired perforating dermatosis (APD), associated with various systemic diseases in adults, particularly chronic kidney disease (CKD) and DM[2,3]. On average, 2-11% of patients with APD are on dialysis[4,5]. It is estimated that 10% of haemodialysis patients will eventually develop KD[6]. The increasing prevalence of renal disease, DM and other chronic diseases will inevitably lead to rising rates of KD in the upcoming years[7]. The clinical features and histological

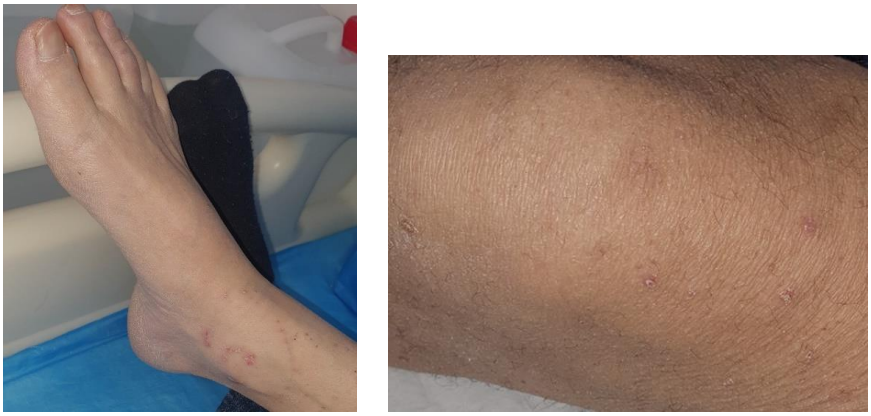
findings of APD may resemble any of the four classic perforating skin diseases; namely, elastosis perforans serpiginosa (EPS), reactive perforating collagenosis (RPC), perforating folliculitis (PF) or KD[8]. Clinically, KD is characterized by hyperkeratotic papules and/or nodules, and histopathologically by transepithelial elimination (TEE) of keratotic material with no collagen or elastic fibers, which differentiates KD from other APD[14]. KD is clinically important as a sign of a systemic disorder and is often underdiagnosed or misdiagnosed[9,10]. A clinicopathological correlation is important to establish the diagnosis[7]. We report a rare case with longstanding KD for near 30 years, associated with end-stage renal disease (ESRD) on chronic haemodialysis program for 25 years that was repetitively misdiagnosed as folliculitis, excoriations and prurigo nodularis. The KD skin changes started to develop during earlier stages of CKD, before the kidney disease was suspected, and continued to appear in flares with extensive lesions when the systemic disease in the background was not under control. Our goal is to emphasize that the accurate and timely diagnosis is vital to be able to monitor the patient for a systemic disease which can prove to be life threating, such as kidney failure, and attaining better management of the dermatological status which can become longstanding and hindering, as well as to outline the importance of the multidisciplinary approach to improve the outcomes in patients affected by KD.

Case report

A 58-year-old male patient with ESRD undergoing haemodialysis for 25 years presented with a multiple, keratotic papules accompanied by intense pruritus. Dermatological examination revealed erythematous papules exhibiting a central depression with keratotic plugging localized on the trunk, upper and lower extremities, and many hypopigmented atrophic scars on the trunk secondary to flares of multiple, more extensive, identical skin changes in the past 30 years (Figure 1 A, B, C). A number of papules on the lower limbs were distributed in a linear arrangement, which was identified as the Koebner phenomenon (Figure 1 D, E). He complained of very severe, generalized pruritus with scoring points of 9 on VAS (visual analogue scale), which is the most commonly used tool for self-report of pruritus intensity[11,12]. He had very severe, generalized xerosis of the skin with scoring points of 4 on Xerosimeter (physician's assessment for objective signs for xerosis cutis)[13]. Hyperkeratotic lesions first appeared a couple of years before kidney disease was diagnosed when the patient was around 30 years old. It is important to note a medical history detail that the dermatological status was dramatically more extensive, especially on the trunk, before we examined the patient. Those flares of extensive hyperkeratotic papules were due to noncompliance of the patient in the past, who was fully aware of it and provided us with this information. He stated that those extensive lesions on the trunk got into remission when he achieved and maintained good compliance. The patient was treated as folliculitis, excoriations, and as prurigo nodularis for near 30 years with topical corticosteroids, antibiotics, and antihistamines, which were temporary, partially effective to suppress pruritus and inflammation, but new lesions appeared all the time.



(A) **(B)** **(C)**



(D) **(E)**

Fig. 1. (A) Erythematous papules exhibiting a central depression with keratotic plugging localized on the trunk and **(B)** many hypopigmented, atrophic scars secondary to previous flares of KD skin changes. **(C)** Hyperkeratotic papules on upper extremity. **(D)** Number of papules on the lower limbs distributed in a linear arrangement - Koebner phenomenon. **(E)** Hyperkeratotic papules on lower limbs

The patient had a history of CKD of unknown etiology (CKDu), hypertension, hyperlipidemia, hyperparathyroidism, rheumatoid arthritis, and dilated cardiomyopathy. He was not a diabetic patient. He underwent total parathyroidectomy, percutaneous coronary intervention (PCI), cardiac resynchronization therapy (CRT) with implantation of a biventricular pacemaker. Abnormal laboratory findings showed the following: 868 μmol/l serum creatinine, 24.1 mmol/l blood urea nitrogen, 6.1 mmol/l blood potassium, 2.8 mmol/l blood calcium, 1.6 mmol/l blood phosphorus, 320.8 pg/mL parathyroid hormone, and anti-HCV positive. Pharmacological history data consisted of anticoagulants, beta-blocker, recombinant erythropoietin (EPO), calcium carbonate, cholecalciferol (Vitamin D3), statin (HMG-CoA reductase inhibitors), sulfasalazine, and prednisone.

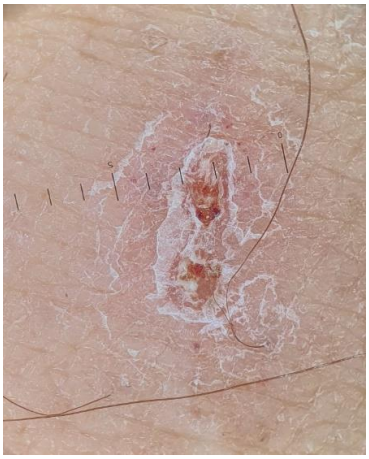


Fig. 2. Dermoscopy of hyperkeratotic papule. A 3-zonal concentric pattern including a crust in the center of the lesion, surrounded with a keratotic scale; a structureless whitish-grey area; a structureless pink/brown area including dotted vessels.

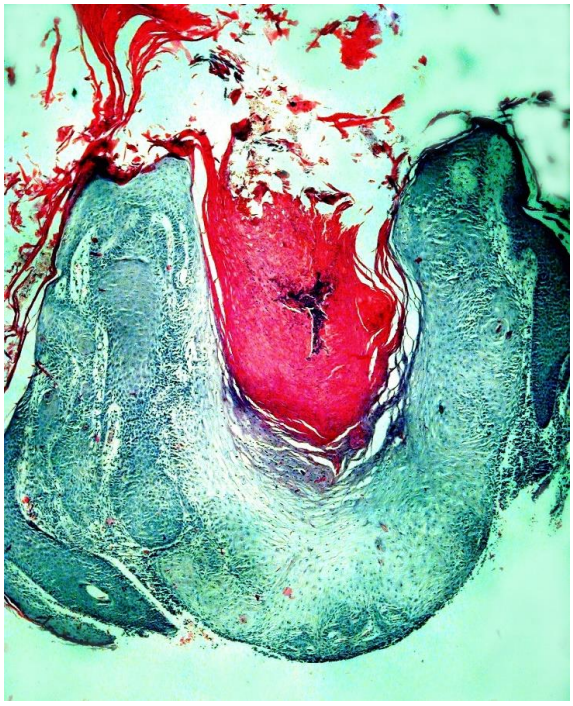


Fig. 3. Histopathological findings. Epidermal invagination with keratotic plug.

Dermoscopy of hyperkeratotic papule revealed a 3-zonal concentric pattern, characterized by bright whitish-brownish scales in the centre, a structureless whitish-grey area surrounding the central crusts, and a peripheral, rose/brown pigmentation including dotted vessels (Figure 2). Biopsy from the hyperkeratotic papule was performed. Histopathological examination revealed moderately acanthotic epidermal invagination filled with a keratotic plug admixed with cellular debris and neutrophils, and a modest parakeratosis. A sparse lymphocytic infiltrate was present in the upper dermis (Figure 3). Masson's trichrome and orcein stains were negative for elimination of elastic and collagen structures. The patient was diagnosed with KD based on the history data, the clinical picture, and the histopathological examination.

Discussion

KD is a rare skin condition classified as a subtype of APD[14]. Perforating dermatoses is a heterogeneous group of disorders characterized by TEE in which material from the

dermis is extruded through the epidermis with little or no disruption of the surrounding structures. The extruded material may include inflammatory cells, red cells, microorganisms and extracellular substances, such as mucin or altered connective tissue components[15]. APD is a term proposed by Rapini in 1989 to designate the four classic perforating dermatosis affecting adult patients with CKD and/or DM, regardless of the eliminated dermal material[16]. It is widely recognized that APD occurs most commonly among those with systemic disorders, especially renal failure and diabetes mellitus[17,18]. Our patient had ESRD treated with maintenance haemodialysis, but was not a diabetic. KD typically occurs during adulthood between the age of 30 and 50 years[15]. Our patient was around 30 years old when KD skin changes appeared for the first time, not yet diagnosed, but with present symptoms and findings in the direction of the diagnosis for CKD in earlier stages.

The lesions of KD are isolated, multiple, discrete, eruptive papules with keratotic plugs, measuring 0.5-2.0 cm in diameter, which can occur on any part of the body but primarily occur on the lower extremities and trunk[6]. Our patient on examination had discrete KD lesions localized on the trunk, upper and lower extremities, and impressive hypopigmented atrophic scars on the trunk and bilateral upper arm, because of similar lesions in the past. Koebnerization, in which skin lesions form at sites of injury, has also been reported[7]. Koebner phenomenon was also noted in our patient localized on lower extremity.

On histopathology, there is a characteristic TEE of keratotic material with no collagen or elastic fibers[14]. This differentiates KD from other APD that exhibit TEE of collagen and elastic fibers, as the histopathological findings in our patient were as well. The histopathological findings in our patient corresponded to the biopsy findings from sixteen KD patients (KD made up for 54% of cases in 30 patients with APD) in a study by Kandasamy *et al*. in 2019[15]. A foreign body granulomatous reaction composed of dermal histiocytic and lymphocytic infiltrates may be present. Orthokeratosis, parakeratosis, and abnormal keratinization may also be observed[19].

The exact etiology of KD has not been elucidated. It is postulated that various metabolic derangements underlie the pathophysiology of this disease. The fact that KD also occurs in non-diabetic renal diseases, as in our patient, suggests uremia rather than hyperglycemia as the causative factor in diabetic and renal failure patients[19]. In patients with diabetic nephropathy, Joseph *et al.* found that the only consistent abnormality was hyperphosphatemia[6]. It is theorized that excess urea and/or phosphate is deposited in the dermis with subsequent extrusion of the material through epidermal follicular openings and the formation of perforating canals[6]. Elevated urea and phosphate levels in our patient support this theory. The serum and immunohistochemical studies have shown an increase in fibronectin levels and deposition, which may play a role in inciting epithelial migration and proliferation, leading to perforation[14]. Others have suggested that advanced glycosylation end-products and oxidized low-density lipoproteins lead to abnormal keratinization, defective differentiation of the epidermis and dermo-epidermal junction, and vasculopathy. This causes a cutaneous response in the form of TEE[20]. It has also been proposed that immune dysregulation in CKD, in addition to other chronic systemic diseases, may contribute to the development of KD through increased expression of interleukin (IL)-31, a predominately T-cell-derived cytokine strongly correlated with pruritus provocation[7]. Our patient had generalized, severe pruritus and history of CKD for 30 years, supporting the theory of immune dysregulation.

KD must be differentiated from prurigo nodularis (some authors argue KD is a variant of prurigo nodularis)[7], multiple keratoacanthomas (can also mimic KD histologically)[19], excoriated lesions (prurigo simplex), folliculitis, arthropod hypersensitivity reaction, perforation of exogenous or endogenous foreign material, dermatofibromas, and of course, from other APD. Patients with APD often have co-existing folliculitis and prurigo nodularis,

and histology may represent various lesions at different stages, which makes diagnosis difficult[19]. Our patient was misdiagnosed for years due to the clinical similarity between KD and its differential diagnoses. Patients who have a history of DM with concomitant renal disease or those on hemodialysis are more likely to have KD as it was the case with our patient. Blood glucose level should be checked to evaluate underlying DM, as well as liver and renal function tests are done for underlying liver and kidney disease in suspected KD[19]. KD is diagnosed based on characteristic clinical and histopathologic findings. Dermoscopy has been shown to facilitate the clinical recognition and can be a helpful tool in making a conclusion in the direction of KD diagnosis[22]. It did help in our case.

Morbidity and mortality are directly associated with the underlying systemic diseases because KD is limited to the skin and it is a sign of a systemic disorder. To date, there have been no controlled studies or guidelines put into place regarding the treatment and can be very difficult to cure KD. Keratolytics such as salicylic acid or urea are considered first-line topical therapy. Topical corticosteroids, emollients and oral antihistamines have been used to relieve pruritus. Cryotherapy, electrocautery, CO_2 laser, topical retinoids, acitretin, isotretinoin, NB-UVB (narrow-band UVB) and PUVA (psoralen plus ultraviolet A radiation) are all alternative treatments. Oral clindamycin 300 mg t.i.d. for one month has also shown beneficial results [7,14]. Discontinuation of these treatment modalities often results in recurrence, as it was the case with our patient. There have been reports of complete regression after renal transplantation in dialysis patients[21]. A novel antipruritic immunomodulatory drugs targeting specific interleukin receptors (IL-4/13/31) and intracellular signalling (e.g. Janus kinase) pathways may have a potential role in the treatment of this disease[7]. In this case, we used only topical keratolytic - urea and emollients, because at the moment when the diagnosis of KD was made, the patient had mild clinical presentation of the disease. These topical treatments helped to alleviate the xerosis and the pruritus.

To the best of our knowledge, this is the first case with longstanding KD reported. From our experience in this case, KD skin changes may appear in flares with extensive lesions when the systemic disease in the background is not under appropriate control, whether it is due to noncompliance of the patient or unrecognized systemic disorder. The clinicopathological correlation is important in establishing the diagnosis of KD because it can be misdiagnosed easily. When operating with a doubtful clinical presentation, dermoscopy is a very helpful instrument in initial differentiation, although biopsy is the gold standard for definitive diagnosis. It is imperative that dermatologists have a high index of suspicion for renal failure and/or DM or potential worsening of these disorders in patients presenting with KD skin changes. In patients with CKD or ESRD on haemodialysis, nephrologists are advised to consult a dermatologist to evaluate the patient for KD when it is suspected because of the disabling symptoms that go together with this entity.

Consent to participate: Written informed consent was obtained from the patient to have the case details and the accompanying images published.

Conflict of interest statement. None declared.

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