

Renal dysfunction in psoriatic patients

Nefrologo in corsia

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ABSTRACT

Psoriasis is a common chronic inflammatory disease of the skin that is increasingly being considered as a systemic inflammatory disorder due to its association with cardiovascular, metabolic, pulmonary, renal, liver, and neurologic diseases. Renal involvement is rare but well documented and psoriasis is recognized as an independent factor for CKD and ESKD. A careful monitoring of the urinalysis and of renal function is recommended in psoriatic patients, especially those with moderate-to-severe disease. In case of pathologic findings, the execution of a renal biopsy appears necessary to make an accurate diagnosis and to establish the most appropriate therapeutic strategies to prevent the progression of kidney damage. The mechanisms of kidney involvement are different and not yet fully clarified. We present here two case reports of renal dysfunction during psoriasis. In one case, we diagnosed IgA nephropathy with particularly severe clinical presentation; in the other, an advanced kidney injury due to nephrotoxicity after prolonged CNI treatment.

KEYWORDS: psoriasis, chronic inflammation, renal involvement, IgA nephropathy, drug nephrotoxicity

Introduction

Psoriasis affects approximately 1.4–2% of the world's population, with wide variability among countries and ethnic groups [1]. It shows a lower prevalence in Asian and some African populations, while in Caucasian and Scandinavian populations it is estimated that psoriasis can affect up to 11% [2-5].

The dermatologic manifestations are varied: *psoriasis vulgaris*, also called plaque-type psoriasis, is the most prevalent type (almost 90% of cases) and is characterized by sharply demarcated, erythematous, pruritic plaques covered in silvery scales, typically localized on the extensor surfaces of the limbs, the trunk and the scalp. However, there are different clinical subtypes:

- *inverse psoriasis*, so called because it affects flexor surfaces),
- *guttate psoriasis*, a variant with an acute onset of small erythematous plaques that usually affects children or adolescents (often triggered by group-A streptococcal infections of tonsils), although about one-third of patients will develop plaque psoriasis in adulthood,
- *pustular psoriasis*, characterized by multiple, coalescing sterile pustules that can be localized or generalized (in the latter case it is often associated with systemic symptoms),
- *erythrodermic psoriasis*, an acute condition in which over 90% of the total body surface is erythematous and inflamed. Erythroderma can develop on any kind of psoriasis type and requires emergency treatment [6-10].

Psoriatic inflammation of the joints, called *psoriatic arthritis*, develops in up to 40% of psoriasis patients and is usually preceded by skin manifestations. The polyarticular variant is frequently associated with nail involvement [11].

The fact that psoriasis has a genetic component is supported by patterns of familial aggregation. First and second-degree relatives of psoriasis patients have an increased incidence of developing psoriasis [12], while monozygotic twins have a 2 to 3-fold increased risk compared to dizygotic twins [13]. Genome-wide linkage studies allowed to identify at least 60 chromosomal loci linked to psoriatic susceptibility; the most prominent locus is PSORS1, located on chromosome 6p21 within the major histocompatibility complex, to which up to 50% of the heritability of the disease has been attributed [14]. Despite the central role of PSORS1, these studies have highlighted the presence of at least 50 single-nucleotide polymorphisms (SNPs) associated to psoriasis [15-17].

The pathogenesis of psoriasis is not yet fully clarified. In the past, it was attributed to the hyperproliferation of keratinocytes, but the good therapeutic responses to drugs targeting the immune system suggest the existence of a dysfunction in immuno-regulation. Currently, different stimuli such as trauma, infections, psychophysical stress, drugs, and endocrine–metabolic factors are considered as triggers for the activation of the immune system, in particular plasmacytoid dendritic cells, T cells and other innate immune cells in the skin. These immune cells synthesize and release various cytokines and chemokines, such as TNF- α and interleukin. TNF- α activates the dendritic cells in the skin, while interleukin promotes attraction, activation, and differentiation of T cells. This process leads to uncontrolled keratinocyte proliferation and dysfunctional differentiation. The histology of the psoriatic plaque shows acanthosis (epidermal hyperplasia), which overlies inflammatory infiltrates composed of dermal dendritic cells, macrophages, T cells, and neutrophils. Neovascularization is another prominent feature [18-19].

Psoriasis is a chronic relapsing disease that often necessitates of a long-term therapy. The choice of therapy is essentially linked to the severity of the disease. Psoriatic patients are generally categorized into two groups: mild-to-moderate or moderate-to-severe, depending on the clinical

severity of the lesions, the percentage of affected body surface area (usually measured by PASI score: Psoriasis Area Severity Index) and patient quality of life. Mild-to-moderate psoriasis can be treated topically with a combination of glucocorticoids, vitamin D analogues, and phototherapy. Moderate-to-severe psoriasis often requires systemic treatment. In the '80s Methotrexate and Cyclosporin were commonly used; in the last two decades the therapeutic options have significantly expanded thanks to the advent of biological drugs, in particular anti-TNF α (etanercept, infliximab, adalimumab certolizumab), anti-IL-12/IL-23 (ustekimumab), anti-IL-17 (secukinumab, ixekizumab, brodalumab), anti-IL-23 (guselkumab, rizankizumab and tildrakizumab) and, more recently, inhibitor of signaling pathways such as JAK/STAT [20]. Nowadays psoriasis is in fact considered a systemic inflammatory disorder. Alterations of the innate and adaptive cutaneous immune responses are responsible for the development and sustainment of an inflammatory status which is not limited to the skin. In these patients we often also find an increase in oxidative stress with endothelial dysfunction, impaired glucose metabolism, high levels of uric acid.

Several studies have shown that patients affected by psoriasis have a higher risk of developing comorbidities such as cardiovascular, pulmonary, hepatological, gastrointestinal, and neurologic diseases, arterial hypertension, diabetes mellitus, metabolic syndrome. As for kidney involvement, recent large population studies have demonstrated that moderate-to-severe psoriasis is an independent risk factor for CKD and for ESKD, beyond traditional risk factors [21, 22-24]. The exact mechanisms underlying the link between psoriasis and renal dysfunction remain not completely understood. Different damage mechanisms, direct or indirect, seems to be involved. They can be summarized in 3 categories: immune-mediate kidney damage, chronic kidney damage without immunological mechanism, drug-induced damage (Tab. 1).

We present below two case reports regarding patients affected by moderate-to-severe psoriasis with renal impairment.

| Type of kidney damage | Pathogenetic factors |
|---|--|
| Immuno-mediated damage | <ul style="list-style-type: none"> - T-cell dysfunction - systemic inflammatory status - increased levels of immune complexes |
| Chronic kidney damage without immunological mechanism | <ul style="list-style-type: none"> - high uric acid levels - high serum amyloid A levels - atherosclerosis, arterial hypertension, and diabetes |
| Drug-induced damage | <ul style="list-style-type: none"> - CNI nephrotoxicity - autoimmune renal disorders or granulomatous interstitial nephritis induced by biologics agent |

Tab. 1: Mechanism of renal involvement in psoriatic patients

Case report 1

A 48-year-old Italian man suffering from psoriasis entered the emergency room for high blood pressure levels and pitting edema on his legs, hands and face. He had been diagnosed with psoriasis with joints involvement 20 years before and his twin brother was affected by psoriasis too. He had initially been treated with methotrexate (the patient was unable to report how much and for how long) but given the unsatisfactory results in 2011 he had started therapy with adalimumab, up to November 2019, when he shifted to generic anti-TNF α . Six years ago, during a hospitalization in another Center, urinalysis had documented proteinuria and hemoglobinuria,

but there had been no nephrological follow up, nor any further exams. He reported having an addiction to smoking tobacco, with an average of 10-20 cigarettes per day, and that he had stopped 2 months before.

At admission to our Center, in December 2019, blood pressure was 130/70 mmHg, heart rate 74 bpm and weight 107 Kg. Physical examination showed pitting edema on his legs, hands and face. Blood tests revealed high serum creatinine level (3.56 mg/dl) with nephrotic proteinuria; all autoantibodies and immunologic tests were negative, except for a decrease in IgG (due to severe proteinuria) and a slight increase in SAA (Tab. 2). Thus, we performed a kidney biopsy and administered a high dose of diuretics without any prompt clinical benefit; on the contrary, we noticed a further worsening of kidney function, with serum creatinine up to 6 mg/dl: urgent hemodialytic treatment was needed.

| Biochemical Test | | Immunological test | |
|---------------------|-----------------|--------------------------|------------------|
| Hemoglobin | 13,3 g/dl | Rheumatoid factor | <10 U/ml |
| Creatinine | 3,56 mg/dl | IgG/IgA/IgM | 378/270/53 mg/dl |
| Urea | 102 mg/dl | C3/C4 | 112/26 mg/dl |
| Cystatin C | 3,4 mg/dl | Serum amiloid A | 5.25 mg/dl |
| eGFR | 19 ml/min | ANCA | NEG |
| Beta2 microglobulin | 7,3 mg/L | ANA | NEG |
| Albuminuria | 400 mg/dl | AntiPLA2R | NEG |
| Proteinuria | 18 g/24h | Antibodies Trombospondin | NEG |
| Haematuria | 261 blood cells | Antibodies citrulline | NEG |

Tab. 2: Case report 1: lab test at admission

After 3 hemodialytic treatments and corticosteroids in endovenous bolus (500 mg for 3 days), and despite the clinical course being complicated by blood MSSA infection treated with oxacillina and daptomicina, the patient gradually recovered a good renal function (serum creatinine at discharge 1.06 mg/dl), with a significative reduction of edema (weight loss of 15.5 Kg) but persistent nephrotic proteinuria (17 g/24h, down from a maximum reached of 30 g/24 h) (Fig. 1).

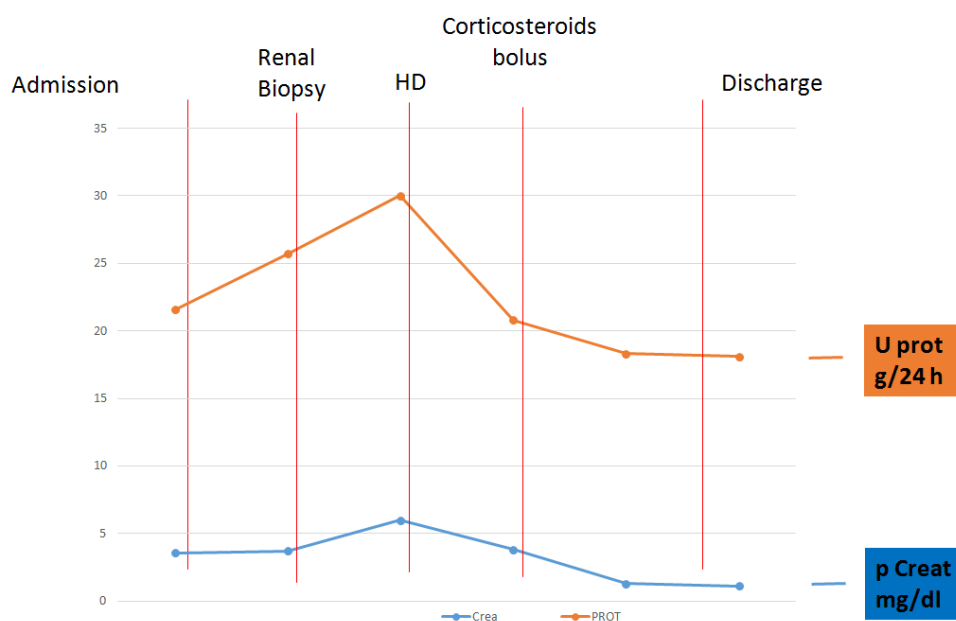


Fig. 1: Case report 1: clinical course

At the histological examination, the sample for light microscopy contained 9 glomeruli (1 in global sclerosis and 2 in segmental sclerosis), mild increase of mesangial matrix and endocapillary hypercellularity, arteriolar ialinosis and mild acute tubular necrosis with 10% of tubular atrophy and interstitial fibrosis. Congo red was negative. Immunofluorescence microscopy performed on the renal tissue with 4 glomeruli using standard staining techniques showed IgA 3+, C3 1+, kappa light chains 1+, lambda light chains 3+. We then diagnosed glomerulonephritis with IgA mesangial deposits with MEST score according to the Oxford classification: M0, E1, S1, T0, C1. Interestingly, at electron microscopy, besides electrodense mesangial deposit, there was an extended effacement of the foot processes (Figs. 2, 3, 4, 5).

The patient is still on follow-up at our Center and he is continuing a steroid pulse regimen ("Pozzi's cycle"), while adalimumab is temporarily suspended.

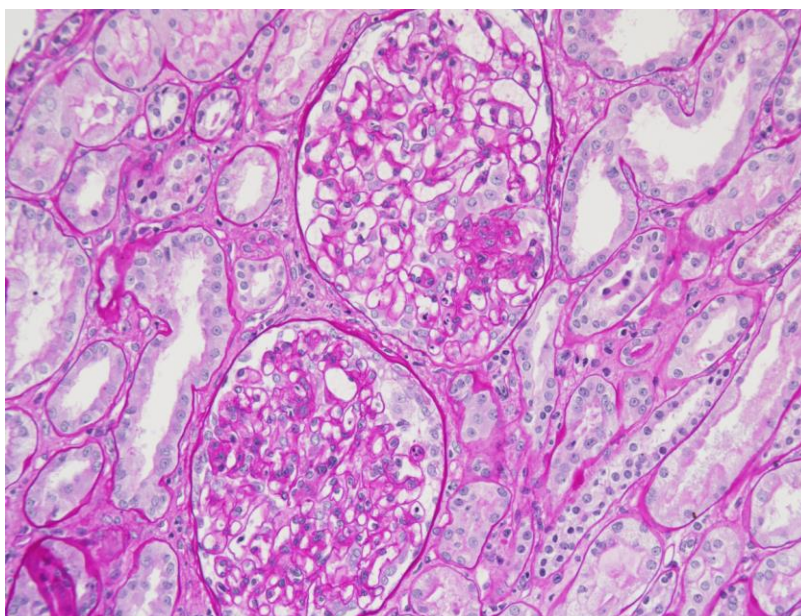


Fig. 2: Mesangial expansion and segmental sclerosis

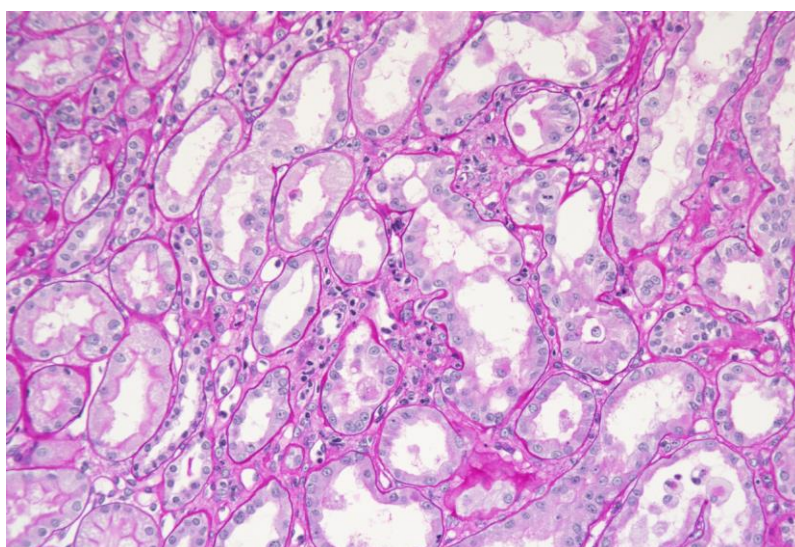


Fig 3: Acute tubular necrosis

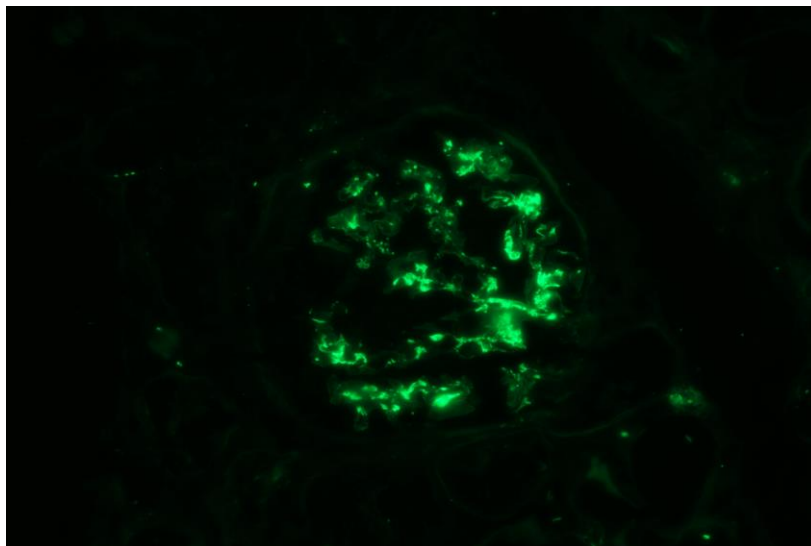


Fig 4: Immunofluorescence staining IgA 3+

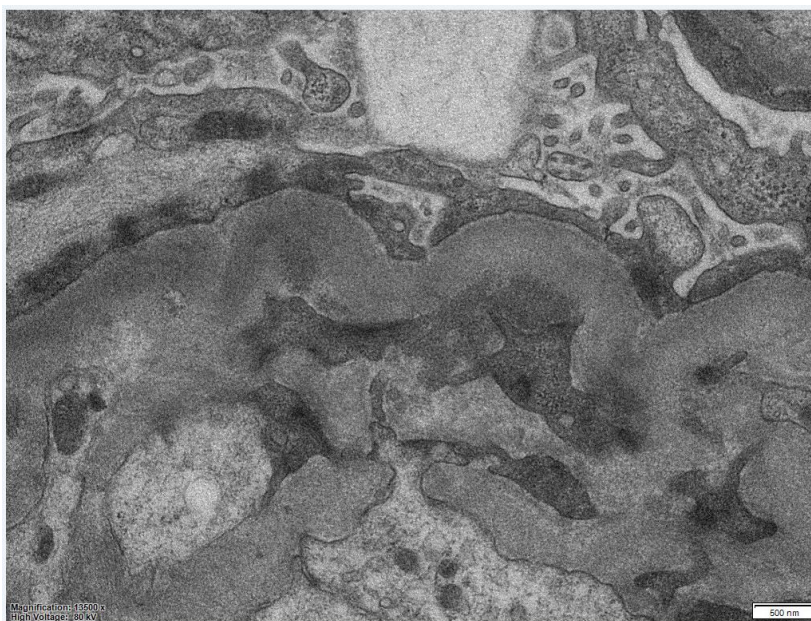


Fig 5: Electron microscopy: electron-dense mesangial deposit, pedicellar fusion

Case report 2

A 35-year-old Italian man, with both parents affected by psoriasis, had started presenting typical plaque-lesion at the age of 23. He had been treated with Cyclosporin at the dosage of 200 mg/die (2.5 mg/kg) for more than 10 years, with satisfactory symptoms control. In 2015 a routine laboratory check had revealed a creatinine value of 1.5 mg/dl. Urinalysis was not available at the time, and the patient did not perform any further investigations.

On December 2017, asthenia, dyspnea and fever appeared. A pulmonary HRTC raised a suspicion of atypical sarcoidosis. On February 2018 the patient was hospitalized in our Centre for the first time with acute respiratory failure, severe hypertension, anemia and acute kidney failure

(creatinine 12 mg/dl) requiring urgent hemodialytic treatment. Cyclosporine was discontinued and steroid therapy was started. Blood tests showed negative autoantibodies, C3/C4 in the norm, proteinuria 500 mg/die. Abdominal ultrasound showed small kidneys with signs of medical nephropathy. TC/PET for sarcoidosis resulted negative. A kidney biopsy was performed and the sample for light microscopy contained 12 sub-capsular glomeruli in global sclerosis. plus 14 more glomeruli, 10 of which were in global sclerosis; there was severe arteriolar ialinosis, fibrosis, extensive tubular atrophy and interstitial fibrosis. Immunofluorescence microscopy performed on the renal tissue with 2 glomeruli using standard staining techniques with antibodies to IgA, IgG, and IgM, complements C3c, C4c, and C1q, fibrinogen, and kappa and lambda light chains was negative. Therefore, in light of the history of long-standing therapy with Cyclosporin, a nephropathy from chronic toxicity by calcineurin inhibitors was diagnosed. Kidney function was not recovered, and the patient continued RRT with peritoneal dialysis (Fig. 6).

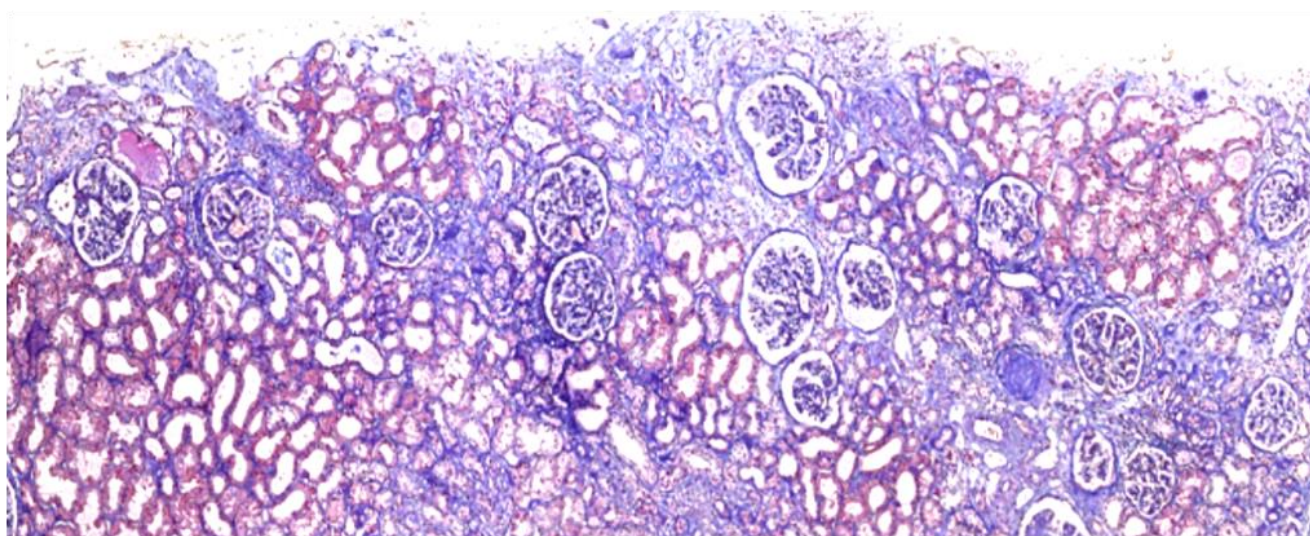


Fig. 6: Severe interstitial fibrosis, tubular atrophy and glomerular sclerosis

A month later, the patient was hospitalized again for severe exacerbation of the psoriasis, in the erythrodermic form, associated with mucositis and diarrhea. High dose steroid therapy was administered, with initial benefit. Due to alterations of liver function (AST 97 U/L, ALT 266U/L, GGt 325 U/L), a biopsy was performed; the histological examination showed autoimmune hepatitis overlapping with primitive biliary cirrhosis (autoantibodies were negative). Based on the hepatological evaluation, a therapy with Azathioprine was started. A colonoscopy was also performed, due to the worsening of the diarrhea, showing endoscopic features of Crohn disease (the subsequent histological examination was compatible with acute CMV colitis).

After a multi-specialistic evaluation and due to severity of skin lesion and systemic symptoms, a therapy with monoclonal antibody (anti-IL17, ixekizumab) and budesonide was started, obtaining a complete and stable remission of symptoms.

A year later the patient underwent kidney transplant from a living donor (his father). The induction therapy was based on ATG and steroids, the maintenance therapy on steroids, tacrolimus and mycophenolic acid. The patient achieved a good recovery of kidney function (creatinine at discharge 1.1 mg/dl) and is now continuing therapy with ixekizumab and budesonide, with good control of psoriasis and without side effects.

Discussion

The patient described in the first case report had a history of psoriasis over twenty year long and presented a particularly severe IgAN with nephrotic presentation (rare but possible clinical onset, estimated in about 10% of cases) and contextual acute renal failure requiring dialysis, with initial clinical benefit from intravenous steroid therapy according to the Pozzi scheme.

The term *psoriatic nephropathy* was first introduced by Singh in 2005, based on case reports of glomerulonephritis in patients with psoriasis, in particular 1 case of IgA nephropathy, 1 case of membranous nephropathy and 1 case of focal proliferative glomerulonephritis with focal deposit of C3 at immunofluorescence. The Author concluded:

"It is premature for us to push forward the existence of "psoriatic nephropathy" or "psoriatic kidney disease" solely on the basis of this article and the review there in, but we are more than justified in nurturing the thought that this entity is in conception, nearing the horizon, and the sunrise may not be far away. This paper would certainly prompt a more diligent screening and investigation of kidney disease in psoriasis by not only dermatologists and general practitioners but also nephrologists" [25].

Indeed, this paper has laid the foundation for subsequent several studies, carried out with the aim of clarifying and better defining the link between psoriasis and kidney damage. In 2017 Ren et al, comparing 97 patients affected by uncomplicated psoriasis and 96 healthy control subjects, demonstrated that prevalence of abnormal urinalysis was significantly increased in psoriatic patients, with a significant correlation between pathologic albuminuria (more than 0.4 g/24 h) and PASI score, as also reported in other previous studies [26].

Several glomerular diseases have been histologically documented in psoriatic patients and IgA nephropathy has been recognized as the most common glomerulonephritis among them [27-28]. An immune mechanism was proposed to explain the close association between psoriasis and IgA nephropathy, due to the fact that both diseases have been mediated by various immunologic mechanisms [29-30]. High serum IgA levels were reported in up to 50% of psoriatic patients and this could reflect a general hyperfunction of the immune response, as in other autoimmune diseases, or may reflect an antibody response to a hypothetical infectious agent. Abnormalities of the gastrointestinal mucosa have also been described in some patients with psoriasis and, recently, a genome-wide association study showed that most loci associated with IgAN also are associated with immune-mediated inflammatory bowel diseases, maintenance of the intestinal barrier, and response to gut pathogens. The importance of the kidney-gut axis in IgAN pathogenesis has been well documented in the literature of the last decade and the association between IgAN and celiac disease, a condition often present in psoriatic patients, is well known, as recently demonstrated by Acharya [31].

Besides, a genetic predisposition to the development of IgA nephropathy may also exist: HLA B-27, present in 25% of psoriatic patients, may predispose to a structural defect in IgA, leading to its deposition in the mesangium. However, no pathological evidences supporting any immunologic mechanisms common for these two entities have yet been found.

In 2017 Grewal et al. published a population-based cohort study investigating incident IgAN and other glomerular diseases (GD) in psoriasis patients, using data from The Health Improvement Network (THIN) of the United Kingdom from 1994 to 2014. Subjects with IgAN or GD prior to the start of the follow-up were excluded. They identified 205.815 psoriasis patients (mild: 193.013; moderate-to-severe: 12.806) and 1.019.140 patients without psoriasis. Patients in both mild and

moderate-to-severe psoriasis groups were more likely to develop IgAN; however, this risk was statistically significant only for moderate-to-severe psoriasis (HR 4.75, 95% CI 1.92–11.76). The excess risk of IgAN and GD attributable to moderate-to-severe psoriasis was 1 in 8.888 and 1 in 10.562 patients, respectively [32].

In the literature regarding psoriatic patients are reported, among other glomerular diseases, rare associations with membranous glomerulonephritis, amyloidosis AA, and sporadic case reports of membranoproliferative glomerulonephritis, FSGS and C3 nephropathy [33-40].

Another recognized cause of kidney damage in psoriatic patients is the nephrotoxicity of the drugs employed for the treatment of skin and joint symptoms. Nonsteroidal anti-inflammatory drugs (NSAIDs) have the strongest association with CKD in patients with psoriasis, as demonstrated by Chiu et al. (adjusted odds ratio 169, 95% CI 114–249) [23]. In the '80s, when the pathogenic mechanism of psoriasis began to be clarified and the active selective recruitment of T-helper cells into psoriasis plaques was demonstrated [41-42], cyclosporine started to be routinely and effectively used for the treatment of psoriasis. Today, there is substantial evidence for the efficacy of ciclosporin in psoriasis vulgaris, but its use is limited by the relatively narrow therapeutic index [43]. Nephrotoxicity and hypertension are the most significant common risks of ciclosporin. Since nephrotoxicity is directly related to the dose and duration of ciclosporin treatment, single or intermittent short courses of up to 16 weeks are recommended [43-44]. Ciclosporin is thus particularly effective for patients who need rapid or short-term disease control (such as psoriasis flare-up).

In the second case we reported, the duration of cyclosporin therapy was very long (almost 10 years) and surely the cumulative dose played an important role in the onset of kidney damage, considering also that renal function was already impaired since in 2015 (serum creatinine 1.5 mg/dl). In both cases above signs of renal impairment were already present years before the patients came to our attention, but they were underestimated. Thus, in psoriatic patients, careful screening of the urine test and of the renal function is required and, in case of pathological findings, renal biopsy should be performed in order to make an accurate diagnosis as early as possible and implement the most appropriate therapeutic strategies to prevent the progression of kidney damage. In particular, Takeshita et al. suggest that patients with psoriasis affecting >3% of their body surface area (BSA) (level of evidence III) are submitted to a closer monitoring of renal function with serum creatinine, blood urea nitrogen, and urinalysis to screen for microalbuminuria [45]. Regardless of the cause of kidney damage, recent extensive population studies have in fact shown that the presence of psoriasis is in itself an independent risk factor for CKD and ESKD.

In a UK cohort study of cause-specific mortality among patients with psoriasis, severe psoriasis was associated with a four-fold increase in the risk of death from nephritic or non-hypertensive kidney disease [46]. A Swedish cohort study also found mild psoriasis to be associated with more than a two-fold increase in the risk of death from kidney disease [47]. In 2013, another UK cohort study found that severe psoriasis may, in fact, be a risk factor for CKD and ESRD, independent of traditional risk factors such as age, sex, BMI, CVD, diabetes, hypertension, hyperlipidemia, and nephrotoxic medications (HR for CKD 1.93, 95% CI 1.79–2.08, and HR for ESRD 4.15, 95% CI 1.70–10.11) [48]. In 2019 Lee et al. [24] published a nationwide population-based cohort study. A total of 2.121.228 adults (1.590.921 in the control group and 530.307 in the psoriasis group) were enrolled from January 2010 to December 2013. During the follow-up period (up to 2015), 1.434 of the subjects in the psoriasis group developed ESRD. After adjusting for confounding factors, psoriasis was associated with the risk of ESRD (HR 1.58, 95% confidence interval [95% CI] 1.47–1.68). The psoriatic arthritis group (HR 7.60, 95% CI 1.90–30.41) had a higher risk of ESRD than the control group. Interestingly, no such association was detected in the systemically treated group. Among

the various proinflammatory factors associated with both ESRD and psoriasis, the authors stressed the importance of interleukin-17 because its levels are high in psoriasis skin lesions and in the serum of psoriatic patients and are positively correlated with the PASI score severity; but, also, IL-17 plays a role in the development of kidney diseases, including glomerulonephritis, nephrotic syndrome, diabetic nephropathy, and acute renal allograft rejection, as well as in atherosclerosis and hypertension. Therefore, the sustained high serum levels of IL-17 in psoriatic patients may induce renal inflammation and ultimately ESRD. The levels of proinflammatory cytokines may have been lower in the subjects in the systemically treated group than those in the non-systemically treated group. Cyclosporin, whose nephrotoxic effect is well documented, did not seem to impact the risk of ESRD in this study. This may be due to the small number of patients treated with cyclosporine and/or to the low doses administered, or to the alert regarding the danger of administering cyclosporin to patients with reduced renal function or hypertension.

In literature there are some case reports of autoimmune renal disorders (AIRD) induced by biologics agent. Biologics-induced AIRD are mostly, but not exclusively, associated with anti-TNF α treatment; this is particularly true for systemic vasculitis, glomerulonephritis in lupus-like syndrome and, rarely, IgA nephropathy, granulomatous interstitial nephritis and nephritic syndrome due to minimal change disease or membranous nephropathy [49-55]. Although rare, AIRD may be life-threatening and may lead to renal failure and death, which is why the treatment with biologic drugs must be stopped as soon as the disorder appears. Treatment of AIRD should be tailored to clinical manifestations and kidney biopsy findings.

Although in the first case we reported is not possible to exclude with absolute certainty a causative role of adalimumab on the onset of renal damage, we think it is most likely a form of IgAN associated with psoriasis, especially considering the amount of time between the start of therapy and the onset of kidney damage.

Conclusions

Psoriasis is a common chronic inflammatory disease of the skin that is increasingly being considered as a systemic inflammatory disorder. A rapidly expanding body of literature in various populations and settings supports additional associations between psoriasis and multisystemic disorders, among which kidney disease is not frequent but well documented. We think these two cases are representative of the different modalities and complexities through which psoriasis can cause kidney damage, which can be summarized in 3 categories: immune-mediate kidney damage, chronic kidney damage without immunological mechanism and drug-induced damage. Certainly, the association with glomerular nephropathies, and IgAN in particular, must be considered, as well as the possibility of tubular damage or vascular damage, secondary to atherosclerosis, arterial hypertension, and diabetes, comorbidities often found in psoriatic patients and that may contribute to renal dysfunction. In addition, the balance between risks and benefits of potentially nephrotoxic drugs should be carefully considered in patients with moderate-to-severe psoriasis.

Periodical routine exams are necessary to monitor renal function in these patients: urinalysis to assess the presence of urinary abnormalities (hematuria and proteinuria) and blood tests, such as blood urea nitrogen and serum creatinine, to estimate GFR. These tests are essential and, when pathological elements are detected, a renal biopsy is then necessary in order to make an early diagnosis of renal involvement and promptly start the most effective therapies to slow the progression of kidney damage and related complications.

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