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CASE BASED REVIEW

Infliximab-associated focal segmental glomerulosclerosis in a patient with ankylosing spondylitis

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Abstract

The introduction of tumor necrosis factor-alpha (TNF-α)-targeting drugs has given new opportunities in the treatment of various inflammatory rheumatic diseases and has been the most important development in the treatment of spondyloarthritis (SpA). However, the increasing use and longer follow-up periods of treatment also pose risks of developing various adverse effects ranging from common ones including infections to uncommon renal complications. This report describes a case of infliximab-induced focal segmental glomerulosclerosis (FSGS) in a 40-year-old female patient with ankylosing spondylitis (AS) who presented with asymptomatic proteinuria and microscopic hematuria. To the best of our knowledge, this is the second reported case of FSGS attributed to infliximab (IFX). A review of the English literature was conducted for cases of possible IFX-associated renal disorders in patients with SpA and SpA spectrum diseases. In this respect, the reported renal pathologies were IgA nephropathy, crescentic glomerulonephritis, acute renal artery occlusion, acute tubulointerstitial nephritis (ATIN), FSGS, and membranous glomerulopathy. Furthermore, partial or complete resolution was reported after cessation of therapy. In conclusion, although renal complications of TNF inhibitors (TNFi) are uncommon, spot urine evaluation may be recommended in the follow-up of patients treated with TNFi.

Keywords Infliximab · Focal segmental glomerulosclerosis · Ankylosing spondylitis

Introduction

Infliximab (IFX) is a monoclonal antibody to human tumor necrosis factor (TNF)-α that has potent anti-inflammatory activity and is approved in the therapy of rheumatoid arthritis (RA), spondyloarthritis (SpA), psoriasis, and inflammatory bowel disease (IBD). IFX also has off-label use in Takayasu arteritis [1], Behcet's disease, sarcoidosis, adult-onset Still disease, polychondritis, and inflammatory myopathies [2].

Although there are known common TNF inhibitor (TNFi)-associated complications including infection and increased risk of lymphoma, very rare complications attributed to these drugs have begun to be recognized with their increased use, including lupus-like autoimmune processes, vasculitis, interstitial lung diseases, sarcoidosis, psoriasis, uveitis, demyelinating neurological diseases, and autoimmune hepatitis [3]. Renal complications are also very rarely associated with TNFi drugs. We aimed to describe a case of IFX-induced focal segmental glomerulosclerosis (FSGS)

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that clinically presented with asymptomatic proteinuria and microscopic hematuria after 5 months of therapy.

Case report

A 40-year-old female patient presented with symptoms of groin and back pain. The patient had right groin pain most often at night for 2 months, accompanied by morning stiffness, which was alleviated after activity. The groin pain was partially responsive to nonsteroidal anti-inflammatory drugs (NSAIDs) and spread to the hip and the knee after activity. She had lower back pain and morning stiffness for 22 years that were responsive to NSAIDs. She reported no need for aggressive NSAID or opioid use because of improvement of the pain after activity. At presentation, she had no systemic symptoms such as fever, weakness, weight loss, night sweating, or any other SpA features such as psoriasis, dactylitis, uveitis, and inflammatory bowel disease, or a family history of these features.

On physical examination, sacroiliac compression tests were positive for both sacroiliac joints (SIJ); right hip movements were painful and restricted in all directions. She was thin and weighed only 45 kg. Her systemic examination was normal. On pelvis X-ray, her SIJs were scored as 2–2 according to modified New York criteria and ankylosing spondylitis (AS) was diagnosed (Fig. 1a). Magnetic resonance imaging (MRI) of the hip revealed that the right femoroacetabular joint surface had subcortical bone marrow signal intensity changes consistent with edema, joint effusion, and narrowing of the joint space (Fig. 1b). Based on the MRI findings, hip involvement in AS was concluded.

The patient's laboratory tests showed an erythrocyte sedimentation rate (ESR) of 29 mm/h; the C-reactive protein (CRP) level was 16.4 mg/L (normal, 0.2–5 mg/L). Complete biochemical, hematologic, and urinary analyses were normal and human leukocyte antigen (HLA) B27 was negative. The Baseline Bath AS Disease Activity Index (BASDAI) of the patient was 4.6. Diclofenac (2 × 75 mg/day) and sulphasalazine (SLZ) (2 g/day) were administered. She did not benefit from this treatment; therefore, we switched from diclofenac to indomethacin (150 mg/day) 6 weeks later, and added methotrexate (MTX) (10 mg/week), and methylprednisolone (8 mg/day). Two months later, she presented with the same symptoms and we learned that she did not use MTX because of vomiting. The BASDAI of the patient was 8.7; therefore, pulse steroid (40 mg for 3 days) and etanercept (50 mg/week) were introduced to treat the severe AS flare-up. But the patient reported only 20% improvement at the end of 3 months of treatment. IFX was administered (200 mg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks) because of the ineffectiveness of etanercept with SLZ 2 g/day and indomethacin 150 mg/day (Table 1). After 3 months of IFX treatment, the BASDAI reduced from 6.8 to 2.6 and the need for NSAIDs was reduced. We learned that the patient stopped SLZ because of gastrointestinal symptoms. At the sixth month of IFX treatment, asymptomatic proteinuria and microscopic hematuria were recognized in spot urine. A 24-h urine examination revealed protein excretion of 3.7 g. She was normotensive and her systemic examination was normal. Laboratory results revealed mild normocytic anemia (hemoglobin 11.7 g/dL) with normal ferritin but decreased transferrin saturation. The albumin and globulin were 4 and 2.1 g/dL, respectively. The serum creatinine was 0.5 mg/dL (estimated glomerular filtration rate: 145 mL/min/1.73 m^2) ESR, CRP, immunoglobulin (Ig) G, A, and M were within the normal range, and hepatitis B, C/HIV serology were all negative. The immunologic tests were all negative including anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, C3–C4, rheumatoid

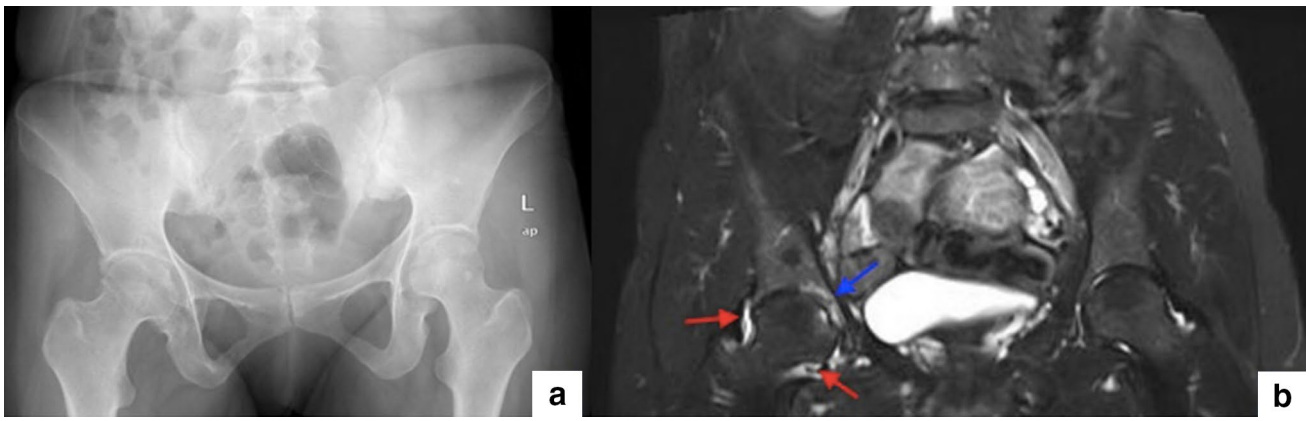

Fig. 1 Radiographic findings of the patient. **a** Pelvis X-ray showed grade 2 sacroiliitis in bilateral sacroiliac joints. **b** Magnetic resonance images (T2-weighted scans) of right femoro-acetabular joint shows effusion (red arrows), subcortical bone marrow edema (blue arrow) and narrowing joint space

Table 1 Drugs used for the treatment of the patient before diagnosing FSGS

Drugs	Duration of the treatment	Latency periods[a]
Diclofenac 2 × 75 mg/day	1.5 months	11 months
Indomethacin – 150 mg/day	12.5 months	0–3 months[b]
Methotrexate 10 mg/week	1 week	10.75 months
Methylprednisolone (8 mg/day)	2 months	9 months
Sulphasalazine (2 g/day)	9.5 months	3 months
Etanercept (50 mg/week)	3 months	6 months
Infliximab (200 mg at 0–2–6. week—every 8 weeks)	6 months	0 month

[a] Latency periods: from cessation of the drug to the occurrence of renal abnormalities

[b] The need for indomethacin reduced 1–2 times a week 25–50 mg last 3 months

factor, anti-citrullinated protein antibody, and anti-ds DNA. Sonography and Doppler sonography of the kidney were both normal.

When asymptomatic proteinuria and microscopic hematuria were diagnosed, IFX, NSAID, and SLZ were stopped and the patient subsequently underwent a percutaneous renal biopsy. The renal biopsy revealed periglomerular fibrosis, mesangial hypercellularity and segmental glomerulosclerosis (Fig. 2a). Advanced hyaline thickening and luminal narrowing were seen in the afferent arteriole (Fig. 2b). Tubular atrophy and interstitial fibrosis were moderate (Fig. 2c, d) and Congo red staining was negative. Focal segmental glomerulosclerosis was diagnosed. At follow-up, we tried to control her inflammatory back and hip pain using pulse steroid injections and started methylprednisolone 8 mg and leflunomide 20 mg for hip arthritis. For the renal pathology, irbesartan was prescribed and NSAIDs were stopped. After 6 months, the right hip was replaced by prosthesis. At the first year of FSGS diagnosis, her proteinuria reduced from 3.7 g/day to 0.8 g/day gradually and the last BASDAI of the patient was 2.

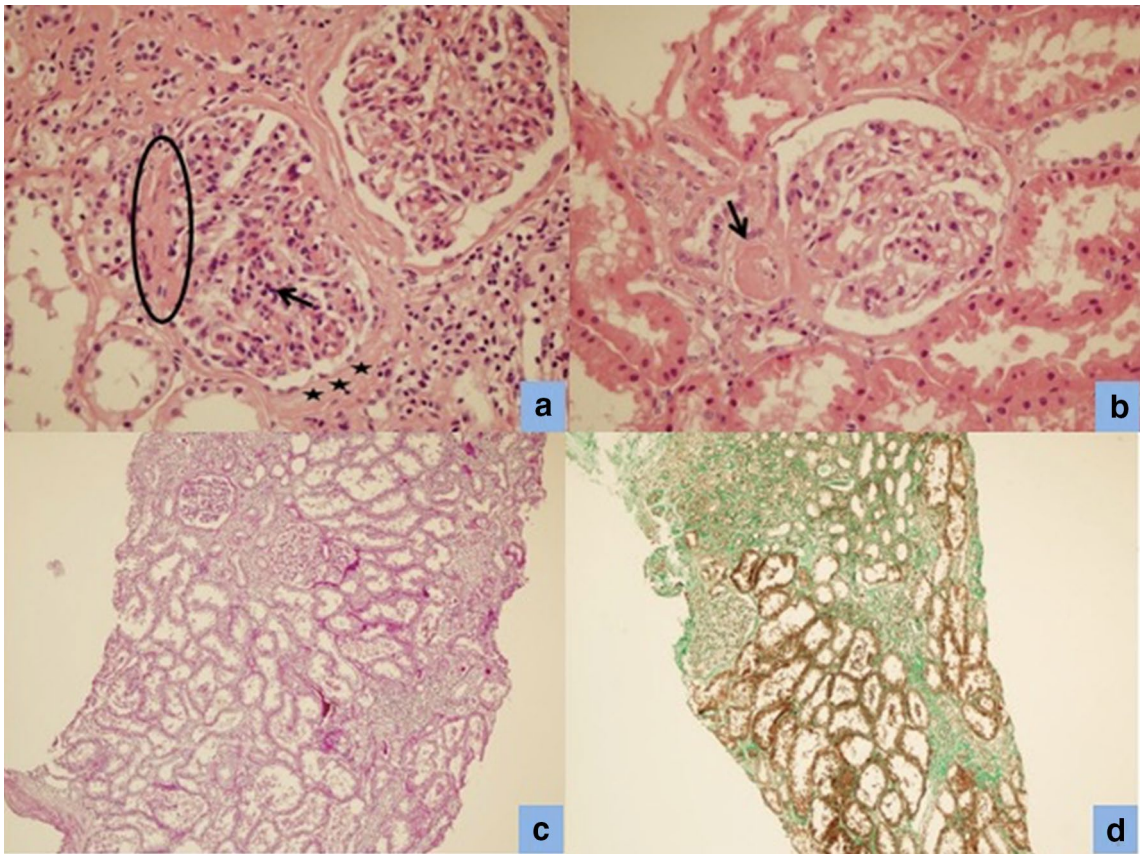

Fig. 2 Glomerular, vascular, tubular and interstitial changes in the needle biopsy of the kidney. **a** Periglomerular fibrosis (asterisks), mesangial hypercellularity (arrow) and segmental glomerulosclerosis (ellipse border) (hematoxylin and eosin × 200). **b** Advanced hyaline thickening and luminal narrowing in the afferent arteriol (arrow) (hematoxylin and eosin × 400). **c** Moderate tubular atrophy (PAS x10). **d** İnterstitial fibrosis (Masson's Trichrome × 10)

Search strategy

We searched PubMed and Scopus databases for articles published between 1990 and 2018 using the keywords renal, kidney, glomerulonephritis, hematuria, proteinuria, focal segmental glomerulosclerosis (FSGS), and IFX. The authors had carefully reviewed 1560 articles and relevant references. Papers written in languages other than English, irrelevant articles, duplicates, and those reporting renal pathologies possibly associated with IFX in diseases other than SpA spectrum disorders (AS, psoriasis, IBD) were excluded. Only eight case reports were related to our current report.

Discussion

In this report, we described a case of AS with FSGS that developed under IFX treatment. The patient was recognized with the findings of asymptomatic proteinuria and microscopic hematuria. As first approach, we investigated renal amyloidosis and IgA nephropathy based on their relatively high prevalence in AS, and interstitial nephritis based on the long-term therapy with NSAIDs. However, the renal biopsy, which was negative for IgA and amyloid deposits and not compatible with interstitial nephritis, excluded our pre-diagnoses. FSGS was defined in the renal pathology of the case, suggesting a rare finding in AS or drug toxicity.

FSGS is a histologic lesion, rather than a specific disease entity, which can be classified into primary and secondary based upon the known and/or hypothesized causes. Although the primary form most often presents with the nephrotic syndrome, the secondary form usually represents with non-nephrotic proteinuria and some degree of renal insufficiency. Causes of secondary FSGS include an adaptive response to glomerular hypertrophy or hyperfiltration (such as unilateral renal agenesis), scarring produced by a previous injury (e.g. active IgA nephropathy, vasculitis), drugs and toxins (heroin, interferon, pamidronate) and viral infections (particularly HIV). The clinical findings of our patient were compatible with secondary FSGS.

The prevalence of renal involvement requiring biopsy was reported as 8% among 681 patients with AS [4]. However, in another study, after secondary renal amyloidosis (62%), IgA nephropathy (30%), mesangioproliferative glomerulonephritis (5%), and membranous nephropathy (1%), FSGS constituted 1% of patients with AS with renal involvement [5]. There was only one case of FSGS associated with AS in our PubMed and Scopus literature search [6]. In our case, the causal relationship between these two diseases appeared highly impossible because the baseline and follow-up urine samples were absolutely normal before infliximab therapy, and proteinuria regressed after the IFX therapy was stopped. Before diagnosing IFX-associated FSGS, several drugs suspected of linking to FSGS should be excluded. Although there are no reported relationships between sulphasalazine, NSAIDs or etanercept and FSGS, the patient had reduced her NSAID intake, and stopped sulphasalazine and etanercept before proteinuria was detected. Furthermore, a patient with Behcet's syndrome and FSGS with nephrotic syndrome was successfully treated with etanercept [7]. Therefore, we concluded that FSGS was associated with IFX and this is the second case reported in the literature.

The first case was a 61-year-old man with ulcerative colitis in whom nephrotic syndrome was revealed after 5 months of IFX treatment [8]. The age, sex, and the indication of IFX were different between the two cases, but both patients were diagnosed in the 5th month of treatment. Our patient was asymptomatic but the previous case presented with aggressive nephrotic syndrome within the 24 h of IFX infusion. After IFX treatment was stopped in our patient, her proteinuria and microscopic hematuria regressed gradually, but the nephrotic syndrome of the previously reported case persisted for a while and a new relapse was experienced.

The presentation of IFX-associated FSGS can be related with age, sex, and comorbidities. If new cases are reported, comments can be made on this issue. All reported IFX-associated renal pathologies in SpA spectrum diseases are summarized in Table 2. Although the age/sex of the patients, duration of disease, and the time period from the initiation of IFX to the onset of renal disease (ranging 2 weeks–9 years) were all different, the renal pathologies and response to TNFi withdrawal were similar.

As a result of increasing use and longer follow-up periods of TNFi treatment, there are a growing number of reports about uncommon adverse events including paradoxical development of systemic and organ-specific autoimmune processes. TNFi-induced autoimmune renal disorders (AIRD) can be grouped as glomerulonephritis associated with systemic vasculitis, glomerulonephritis in lupus-like syndrome, and isolated autoimmune renal disorders. In terms of our patient, there were not any clues of systemic involvement and autoimmune markers were all negative.

A review about biologics-induced AIRD in chronic inflammatory rheumatic diseases reported that more than half of all cases were RA and only 17% were AS. Furthermore, the biologic drug most frequently associated with development of AIRD was etanercept (51.7%), followed by adalimumab (31.0%), and infliximab (10.3%) [16]. In terms of SpA spectrum diseases, IFX was found to be possibly associated with IgA nephropathy, crescentic glomerulonephritis, acute renal artery occlusion, acute tubulointerstitial nephritis (ATIN), FSGS, and membranous glomerulopathy (Table 2). This study shows that the paradoxical development of IFX-induced renal disorders in patients with SpA spectrum diseases is rare, but not exceptional, and apparently unpredictable.

Table 2 Clinical characteristics of patients with renal impairment possibly associated with infliximab in spondyloarthritis spectrum diseases

Ref	Age/sex	IRD (duration)	Latency[a]	Renal pathology	Treatment	Outcomes
[9]	37/M	AS (16 years)	36 months	IgA nephropathy	IFX withdrawal	Partial resolution
[10]	70/F	IBD(11 years)	3 months	Crescentic glomerulonephritis, renal amyloidosis, ATIN	IFX withdrawal Steroid	Partial resolution
[11]	44/M	UC (11 years)	2 weeks	Acute renal artery occlusion	IFX withdrawal Anti-coagulation	Complete resolution
[12]	46/M	Crohn (23 years)	9 years (6 mg/kg) 5 months (10 mg/kg)	ATIN	IFX withdrawal	Complete resolution
[8]	61/M	UC (25 years)	5 months	FSGS	IFX withdrawal Ultrafiltration Steroid MMF ACEİ Relapse: RTX	Transient complete remission Relapse
[13]	25/F	Crohn (5.6 years)	The 19th infusion	ATIN	IFX withdrawal, switched to adalimumab Steroid	Partial resolution
[14]	29/F	Psoriasis	1 month	Membranous glomerulopathy	IFX withdrawal Steroid ACEI Statin Diuretics	Complete resolution
[15]	28/M	Crohn	4.5 years	ATIN	IFX withdrawal	Complete resolution

ACEI angiotensin-converting enzyme inhibitor, *AS* ankylosing spondylitis, *ATIN* acute tubulointerstitial nephritis, *F* female, *IBD* inflammatory bowel disease, *IFX* infliximab, *IRD* inflammatory rheumatic disease, *M* male, *Ref* References, *RTX* rituximab, *UC* ulcerative colitis

[a] Latency: the time period from the initiation of infliximab to the onset of renal disease

IFX has been demonstrated to improve the renal symptoms associated with chronic inflammatory rheumatologic diseases, such as amyloid A amyloidosis. However, there are contrary results about the effect of IFX on IgA nephropathy in patients with rheumatologic diseases. Although there are IgA nephropathy cases that responded well to IFX therapy, new-onset IgA nephropathy and unresponsive cases efficiently controlled for the rheumatologic disease under IFX therapy have also been reported [9, 17, 18].

In reported TNFi-associated renal disorders, partial or complete remission frequently occurs; however, relapse may occur during TNFi withdrawal. Among the biologics, 96% of the AIRDs were induced by TNFi drugs and similar renal pathologies were reported associated with different TNFi drugs [16]. This suggests a class effect of TNFi drugs and the pathogenetic mechanism is still unknown. The variety of renal disorders, different times of induction, response to treatment, and outcomes observed between the various renal pathologies complicate the understanding of the different underlying mechanisms. The pathogenetic mechanisms of TNFi in the kidney are thought to include a self-limited reaction against the drug resulting in an immune complex deposition, direct effect of biologic agents on cytokine production and lymphocyte functions, and autoimmune reactions such as molecular mimicry, bystander activation or epitope spreading due to infections under TNFi treatment [16, 19]. In our case, because of the lack of evidence about immune complex deposition or previous infection, the direct effect of IFX on cytokine production and lymphocyte function may have been the underlying pathogenic mechanism.

Reduction of proteinuria is an important target for FSGS treatment. Before the introduction of renin–angiotensin–aldosterone system (RAAS) inhibitors, NSAIDs were the only choice for reducing proteinuria. Besides the well-known NSAID-induced renal abnormalities, a beneficial effect of NSAIDs in reducing proteinuria in patients with FSGS and other glomerular diseases has been documented [20, 21]. The anti-proteinuric effect of NSAIDs has largely been attributed to the reduction of intraglomerular pressure by predominantly afferent vasoconstriction [22]. On the other hand, the blocking effect of RAAS inhibitors on angiotensin II leads to reduction of glomerular pressure by efferent vasodilation. RAAS inhibitors increase effective renal plasma flow (ERPF) and decrease glomerular filtration rate (GFR) by efferent vasodilation but the prostaglandin inhibition by NSAIDs both decrease ERPF and GFR. McCarthy et al. showed that the presence of a substance in the sera (FSGS factor) of some patients with FSGS increase glomerular albumin permeability in an in vitro assay. This group also demonstrated that indomethacin protects permeability

barrier from FSGS serum in animal models [20]. Borst et al. have proposed that the anti-proteinuric effect of indomethacin is associated with reduced urinary excretion of glomerular and tubular damage markers. But the urinary excretion of inflammation markers was not effected by NSAID treatment and they suggested that the anti-proteinuric effect of NSAIDs is limited to diseases with less renal inflammation [23]. NSAIDs have some unwanted effects on kidneys including water and sodium retention, blood pressure elevation, oedema, papillary necrosis, and acute interstitial nephritis. On the other hand, RAAS inhibitors have renal and cardiovascular protective properties by reducing both blood pressure and proteinuria. Therefore, RAAS inhibitors replaced NSAIDs for the treatment of proteinuria.

In conclusion, TNFi-induced adverse events should consider when physicians come across unexpected conditions in patients taking TNFi therapy. Although renal complications of TNFi are uncommon, besides serum creatinine, spot urine evaluation may be recommended in the follow-up of patients treated with TNFi. If impaired renal function or urinary sediment abnormalities are detected, the possible occurrence of TNFi-associated renal disorders should be investigated. Kidney biopsy should not be delayed if necessary. When renal pathology is diagnosed, or even suspected, the TNFi should be stopped and the patient should be treated according to the clinical manifestations and biopsy findings.

Author contributions All the authorship contributions were declared in line with the ICMJE 4 criteria: Dr. Yarkan Tuğsal and Dr. Birlik wrote the paper. Dr. Zengin and Dr. Kenar searched the databases for review of the literature. Dr. Can and Dr. Önen read the selected articles and evaluated for eligibility. Dr. Ünlü evaluated pathology of the kidney. Dr. Yarkan Tuğsal, Dr. Kenar and Dr. Birlik revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflicts of interest.

Informed consent The patient gave a written informed consent before written.

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