Case Report

Anti-Tumor Necrosis Factor-α Therapy-Induced Vasculitis: Case Series

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ABSTRACT. As experience with anti-tumor necrosis factor (TNF-α) therapy increases, there has been the expected emergence of reports on uncommon side effects. Large clinical trials identified the development of autoantibodies and postmarketing surveillance has identified problems including tuberculosis. There have been several case reports of drug-induced systemic lupus erythematosus. We describe 8 patients with rheumatoid arthritis treated with anti-TNF therapies who developed presumed vasculitis, with different pathophysiologic causes. We discuss the literature and potential causal mechanisms, including disease activity, the role of autoantibodies, and shifts in T cell responses. (J Rheumatol 2003;30:2287–91)

Key Indexing Terms:
ETANERCEPT INFLIXIMAB VASCULITIS
RHEUMATOID ARTHRITIS

Tumor necrosis factor (TNF-α) blockade is the treatment of choice in patients with moderate to severe rheumatoid arthritis (RA) with poor responses to conventional disease modifying drugs (DMARD). The literature on the side effects of etanercept and infliximab has focused on infective complications and the development of autoantibodies. More recent reports have included cases of drug-induced systemic lupus erythematosus (SLE)[1,2] and episodes of demyelination[3]. Reports concerning vasculitis have been contradictory, with TNF blockade being implicated in both the development[4] and treatment[5] of rheumatoid arthritis (RA)-associated vasculitis. We describe a series of patients developing vasculitis and vasculitic rashes during treatment with TNF blocking agents and speculate on the pathogenic mechanisms involved.

CASE REPORTS

Patient 1. Patient 1 was a 67-year-old man with seropositive, nodular, erosive RA of 5 years' duration (a summary of cases is presented in Table 1). He had failed to respond to combination methotrexate (MTX), sulfasalazine (SSZ), and hydroxychloroquine (HCQ) plus oral prednisolone. Leflunomide 20 mg daily was commenced in combination with weekly oral MTX, 10 mg. However, following 12 weeks of therapy he still had marked inflammatory activity with a C-reactive protein (CRP) of 55 mg/l (normal < 8 mg/l), and an erythrocyte sedimentation rate (ESR) of 84 mm/h. He was rheumatoid factor (RF) positive with a titer of 498 IU/ml (< 20 IU/ml) and antinuclear antibody (ANA) negative. He was entered into an investigational protocol and infliximab was given at 3 mg/kg in combination with leflunomide. After induction he was maintained on 8 weekly infusions. Clinical response was limited, as evidenced by persistent synovitis and unchanged inflammatory markers. He subsequently developed ulceration on his fingers, hands, and forearm. Antinuclear antibodies (ANA) remained negative and antineutrophil cytoplasmic antibodies (ANCA) were also negative. A diagnosis of infliximab-associated vasculitis was made. The infliximab was stopped and he was treated with pulsed cyclophosphamide 15 mg/kg and methylprednisolone (MEP) 10 mg/kg, with subsequent resolution of the lesions.

Patient 2. Patient 2 was a 63-year-old woman with new onset seropositive erosive RA. RF was raised at 63 IU/ml with an ANA of 1:640 IU/ml and raised double-stranded DNA (ds-DNA) 385 IU/ml (< 100 IU/ml). She was commenced on a protocol of weekly oral MTX 7.5 mg and received infusions of infliximab 3 mg/kg at 0 and 2 weeks. Just prior to her third infusion at week 6 she felt increasingly unwell and developed a painful red eye (Figure 1a) and painful ulceration on her right foot (Figure 1b). Examination revealed minimal synovitis, but she had scleritis affecting her right eye, nailfold infarcts on 3 fingers, and ulceration of her right foot. Investigations revealed elevated inflammatory markers, the ANA titer was unchanged, but the ds-DNA had risen to 1200 IU/ml; additionally p-ANCA titer was 1:640 IU/ml, with low complement levels: C3 0.77 g/l, C4 0.09 g/l (normal range C3 0.75–1.2, C4 0.2–0.5 g/l). A diagnosis of acute vasculitis with scleritis was made and infliximab therapy was withdrawn. She was treated with pulsed intravenous MEP and cyclophosphamide in addition to specific eye care. She subsequently had good resolution of the vasculitic lesions.

Patient 3. Patient 3 was a 52-year-old man with new onset RA. His RF was raised at 1520 IU/ml, ANA was 1:160 IU/ml, and ds-DNA was normal. He was commenced on weekly oral MTX 7.5 mg and infusions of infliximab 10 mg/kg at 0, 2, 6, 10, 18, 26, and 34 weeks. The MTX was discontinued after 3 months due to liver function test abnormalities. After 10 months he was in clinical remission and receiving no therapy. Twelve weeks later he presented with acute onset of weakness of left knee extension. He reported that some 3 weeks previously he had noticed numbness in the right ulnar

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Table 1. Summary of case histories.

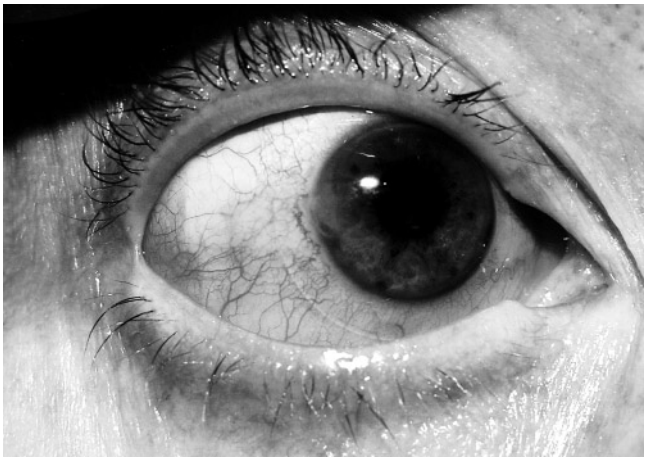
Patient	Age (yr) Sex	Diagnosis	Serology	Previous DMARD	Anti-TNF Therapy	Combination Therapy	Infusions Before Complication, n	Complication	Serology	Management
1	67 M	Seropositive erosive nodular RA	RF 498 IU/ml ANA negative	Gold, SSZ, MTX, HCQ, leflunomide	Infliximab 3 mg/kg	Leflunomide	10	Vasculitic rash	ANA negative	Infliximab withdrawn; treated with 6 pulses of cyclophosphamide 15 mg/kg and MEP 10 mg/kg
2	63 F	Seropositive RA	RF 63l/IU/ml ANA 1:640 IU/ml dsDNA 365 IU/ml	MTX	Infliximab 3 mg/kg	MTX	2	Scleritis, severe cutaneous vasculitis	RF 139 IU/ml ANA homogenous 1:640 IU/ml dsDNA 1200 IU/ml (100) pANCA 1:640 IU/ml	Infliximab withdrawn; treated with 6 pulses cyclophosphamide 15 mg/kg and MEP 10 mg/kg
3	52 M	Seropositive RA	RF 1520 IU/ml ANA 1:160 IU/ml	MTX	Infliximab 10 mg/kg	MTX	8	Mononeuritis multiplex (femoral nerve)	RF 220 IU/ml ANA homogenous 1:160 IU/ml Complement low C4 ANCA negative	Treated with 6 pulses cyclophosphamide 15 mg/kg and MEP 10 mg/kg
4	55 M	Seropositive erosive RA	RF 248 IU/ml ANA negative	SSZ, MTX, leflunomide	Infliximab 3 mg/kg	Leflunomide	2	Biopsy-proven leukocytoclastic vasculitis	RF 746 IU/ml ANA negative ANCA negative	Oral prednisolone; switched to etanercept, reoccurrence of rash
5	61 M	Seropositive erosive RA	RF 71 IU/ml ANA negative	Gold, SSZ, MTX	Etanercept 25 mg twice weekly	Nil	10 mo	Biopsy-proven leukocytoclastic vasculitis	RF 27 IU/ml ANA 1:320 IU/ml pANCA 1:160 IU/ml PR3 negative	Intravenous prostacyclin, oral steroids
6	60 F	Seronegative erosive RA	RF negative ANA negative	SSZ, MTX, gold, leflunomide	Infliximab 3 mg/kg	Leflunomide	3	Pustular rash hands and feet	RF negative ANA negative	Infliximab withdrawn; commenced on oral prednisolone
7	57 M	Seropositive RA	RF 173 IU/ml ANA negative	SSZ, gold (rash), penicillamine, MTX, leflunomide	Infliximab 3 mg/kg	Leflunomide	4	Urticarial rash; rechallenged urticarial rash and vasculitis	RF 189 IU/ml ANA 1:40 IU/ml	Infliximab withdrawn; etanercept substituted with recrudescence of rash
8	45 M	Seropositive erosive RA	RF 777 IU/ml ANA negative	SSZ, gold, MTX, HCQ	Infliximab 3 mg/kg	Leflunomide	1	Central nervous system vasculitis	RF 89 IU/ml ANA negative ANCA negative	Infliximab withdrawn; continued on leflunomide

DMARD: disease modifying antirheumatic drug; RF: rheumatoid factor; ANA: antinuclear antibody; dsDNA: double stranded DNA; SSZ: sulfasalazine; MTX: methotrexate; HCQ: hydroxychloroquine; MEP: methylprednisolone.

nerve distribution that had resolved spontaneously. Examination revealed weakness of left knee extension and diminished knee jerk. He had no synovitis. Investigations found normal inflammatory markers. Serology remained unchanged with an ANA titer 1:160 IU/ml, ds-DNA normal, ANCA was negative, but complement levels were low (C3 0.78 g/l and C4 0.18 g/l). Magnetic resonance imaging (MRI) of the spine was normal, but nerve conduction studies showed an acute femoral nerve lesion. Mononeuritis (? multiplex) was diagnosed and he was treated with 6 cycles of intravenous MEP and cyclophosphamide, resulting in complete recovery of limb function.

Patient 4. Patient 4 was a 55-year-old man with seropositive, erosive RA of 13 years' duration. He was taking 10–15 mg/day of oral prednisolone. RF was 402 IU/ml, ANA was negative, and complement was not measured. He was started on leflunomide 20 mg daily to which infliximab 3 mg/kg was added. He received 2 infusions before developing lesions on his hands (Figure 2a) and legs (Figure 2b). The infliximab was stopped and the lesions were biopsied, with histology revealing a leukocytoclastic vasculitis. Repeat investigations found the ANA negative, ds-DNA 100 IU/ml (0–100), low C4, ANCA negative, cryoglobulins negative, hepatitis serology (A, B, and C) negative, no growth on multiple peripheral blood cultures, and transthoracic echo was normal. The vasculitis was treated with oral prednisolone and settled. Following resolution of the rash he was commenced on etanercept with recurrence of the vasculitis at the same site.

Patient 5. Patient 5 was a 61-year-old man with seropositive erosive RA of 7 years' duration. He had failed to respond to MTX and SSZ and was taking oral prednisolone 20 mg daily. He was RF positive with titer of 71 IU/ml and ANA positive titer 1:320 IU/ml. He was commenced on etanercept 25 mg twice weekly with significant reduction in disease activity. After 10 months of therapy he developed a rash on his legs, ankles, and feet. Biopsy confirmed leukocytoclastic vasculitis, serology showed ANA 1:640 IU/ml, ds-DNA normal, histone antibodies positive, and pANCA 1:160 IU/ml; myeloperoxidase and PR3, however, were negative. He was treated with



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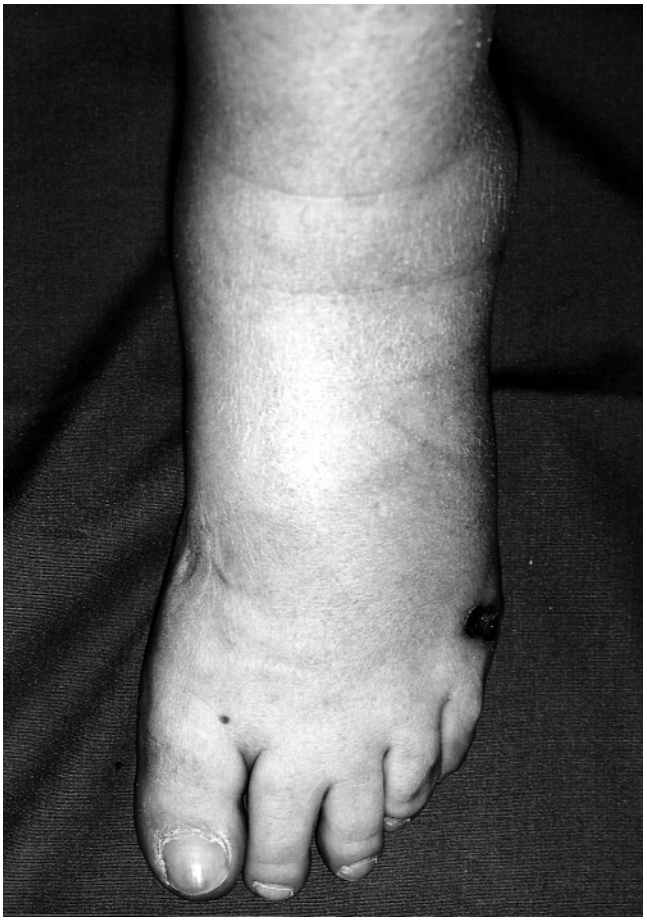

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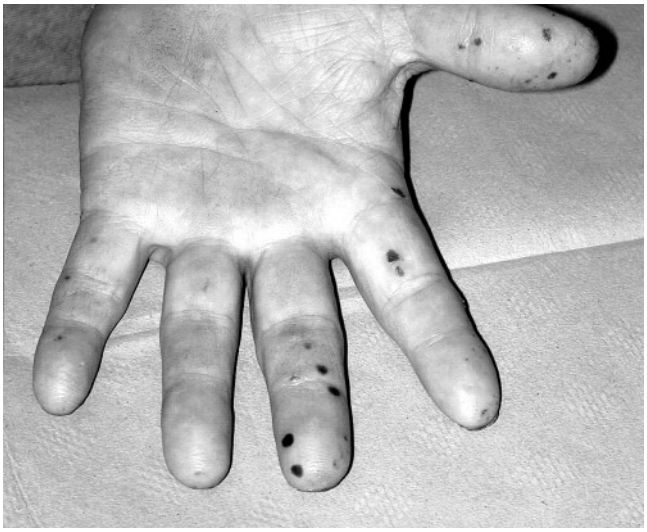
Figure 1. Patient 2. Slit-lamp examination of right eye showing scleritis (A) and vasculitic ulceration of the left foot (B).



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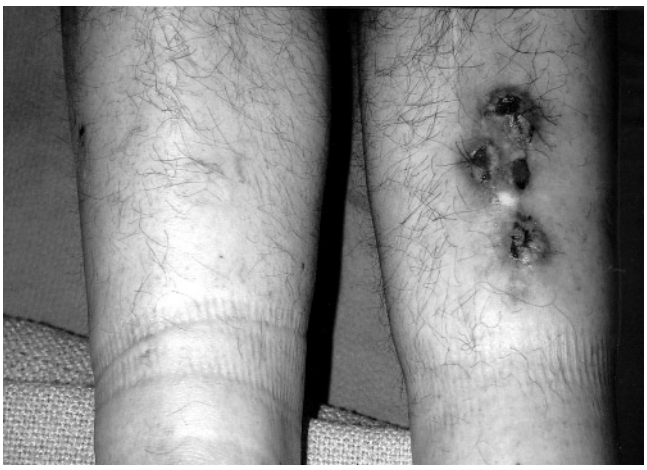

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Figure 2. Patient 4. Biopsy proven vasculitic rash (A) on hands and (B) on legs.

intravenous prostacyclin and oral steroids, with resolution of the vasculitic rash.

Patient 6. Patient 6 was a 60-year-old woman with seronegative erosive RA of 2 years' duration. She had failed to improve taking standard DMARD therapy. At presentation she was negative for RF and ANA. She was commenced on infliximab 3 mg/kg in combination with leflunomide and tolerated 3 infusions before developing a pustular rash on her feet and hands. Serology remained negative. On withdrawal of infliximab and institution of prednisolone 10 mg daily the rash settled.

Patient 7. Patient 7 was a 57-year-old man with a 10 year history of RA. He failed to respond to multiple DMARD; CRP was 54 mg/l, RF 173 IU/ml, and he was ANA negative. He was commenced on leflunomide 20 mg once daily. At 3 months he still had significant disease activity and infliximab 3 mg/kg was added as part of an investigational protocol. He received 4 infusions, with dramatic improvement in synovitis and a marked fall in CRP. During the fifth infusion he developed a severe urticarial rash, which initially responded to antihistamines and parenteral hydrocortisone. On rechallenge with infliximab he tolerated 2 further doses without worsening of the rash; however, synovitis persisted as reflected in his CRP of 138 mg/l; he remained ANA negative. The infliximab was switched to etanercept 25 mg twice weekly. The rash reoccurred and the etanercept was withdrawn.

Patient 8. Patient 8 was a 45-year-old man with seropositive, erosive RA of 14 years' duration. He had multiple DMARD failures including SSZ, intramuscular gold, MTX (oral and intramuscular) and HCQ. He was commenced on leflunomide at a dose of 20 mg daily. In spite of therapy he continued to show marked synovitis and high inflammatory markers. He was commenced on infliximab 3 mg/kg. Four days after the first infusion he noticed his speech becoming clumsy and slurred. Over the next 24 hours, this progressed and assessment revealed marked staccato speech but no other focal neurology. Investigations showed normal glucose and lipids, and normal resting and 24 h electrocardiogram. Echocardiogram was normal, as were carotid Doppler studies. MRI of the brain revealed focal areas of ischemia in the region of the posterior putamen; there were older areas of infarction in the left putamen. Lumbar puncture was normal with no oligoclonal bands seen. Visual evoked response showed no abnormality. A diagnosis of cerebral ischemia, possibly of vasculitic origin, was considered. He made a spontaneous recovery and continued taking leflunomide, but he has not received further infliximab.

DISCUSSION

We report a series of 8 patients who developed vasculitis and/or vasculitic rash on anti-TNF therapy. Seven patients were initially treated with infliximab and one with etanercept; 2 of the infliximab patients were switched to etanercept, with recrudescence of vasculitis or rash suggesting a class effect of TNF blockade. In 2 cases we had histological evidence of vasculitis; in the remaining 6 the diagnosis was clinical. In 2 cases there was an increase in autoantibodies, including one of the biopsy-proven patients.

It has long been accepted that RA is associated with or may evolve into other autoimmune diseases such as SLE and vasculitis. Similarly, the treatment of RA may in itself promote the development of other autoimmune diseases. Drug induced lupus erythematosus has been described following treatment with D-penicillamine, SSZ, and minocycline. Hypersensitive vasculitis has been described with nonsteroidal antiinflammatory drugs. Consequently, the development of complications may be attributable to ongoing disease activity evolution into other disease states, drug induced autoimmunity, or drug reaction.

In our series, Patient 1 with severe nodular disease developed a small vessel vasculitis with nailfold infarcts. Rheumatoid vasculitis is clinically manifest in 2–5% of patients with long-standing RA. The significant risk factors are male sex, duration of disease, nodularity, high titers of RF, erosive changes, and multiple DMARD failures. This patient had all these risk factors and also had a poor response to infliximab in terms of improvement in clinical or biochemical indices. Additionally there was no significant ANA production. These factors would tend to suggest ongoing disease activity as the major trigger. The manufacturer has reported the incidence of vasculitis with infliximab at 0.02%, commenting that most cases resembled rheumatoid vasculitis. A number of these patients were rechallenged without further incident. Consequently, there may be a group of patients in whom vasculitis is a reflection of underlying persistent disease activity. This would explain the improvement in cutaneous vasculitis reported by Broeder, *et al*[5]. They report digital vasculitis occurring in an RA patient treated with lenercept (a soluble p55 TNF-α fusion protein) improving post-infusion in tandem with improved joint scores and inflammatory markers. This group may benefit from ongoing treatment with anti-TNF therapy or change to an alternative form of anti-TNF therapy.

For those patients in our series who had a more significant vasculitis there are a number of possible drug-related mechanisms that may be involved. The development of autoantibodies is well described. Initial studies with infliximab used in combination with MTX found the development of IgM anti-ds-DNA antibodies in 5–8% of patients undergoing active therapy[6]. In the ATTRACT infliximab study, one patient developed pleuropericarditis, fever, and IgG anti-ds-DNA antibodies. A subsequent analysis of 880 RA and Crohn's disease patients treated with infliximab[7] identified a further 2 patients who developed facial rash, polyarthritis, and positive autoantibodies. There was no instance of major organ involvement or vasculitis. With etanercept, 5% developed positivity for anti-ds-DNA antibodies, although two-thirds of these patients were ANA negative[8]. One case series of 4 patients developing clinical SLE while taking etanercept[1] reported positive ANA and ds-DNA in 3 patients and positive anti-histone antibodies in the fourth. There is one case report of a leukocytoclastic vasculitis with etanercept[4]; however, in this case no rise in autoantibodies was detected. Our cases are contradictory, with 2 cases experiencing a rise in autoantibodies, while the other cases did not, including one case of biopsy-proven leukocytoclastic vasculitis. Autoantibody production may therefore not be the whole story.

It has been suggested that anti-TNF/TNF immune complexes may deposit in small capillaries, activating complement, and thereby triggering a type III hypersensitivity reac-

tion. This mechanism, however, would not in itself explain the development of ANA or antibodies to ds-DNA.

One further possible mechanism is the switch from the predominant Th1 profile of T lymphocyte response in RA to a Th2 response. RA is characterized as a Th1 lymphocyte-driven disease, the major T cell cytokines involved being TNF-α, interleukin (IL) 2, interferon-γ, and IL-12. Th2 responses are associated with enhanced activity of IL-4, IL-5, IL-6, IL-10, and IL-13, increased levels of which lead to upregulation of antibody production. Recent evidence suggests that SLE may itself be predominantly a Th2-driven disease, with elevated levels of IL-4, IL-6, and IL-10. TNF-α levels have been shown to be low in SLE, and the presence of TNF-α has been suggested to provide a protective function. In the New Zealand black × New Zealand white F1 mouse model of SLE, blockade of IL-10 by anti-IL-10 antibody delayed the onset of clinical SLE[9]. This protective effect was thought to be due to upregulation of TNF-α as the effect was blocked by the use of anti-TNF-α. While this switch may explain the development of autoantibodies, which is a common phenomenon, the presence of clinical SLE is not, and there may be an additional, presumably genetic, factor. One prototype of this would be the development of a lupus-like syndrome with penicillamine, which appears to be most frequent in individuals who are HLA-DR3 positive[10].

Evidence is also mounting that vasculitis is a Th2 lymphocyte-mediated disease. One study in Wegener's granulomatosis[11] found increased expression of IL-4 and down-regulation of IL-2 in the nasal mucosa of newly diagnosed patients. In the Brown Norway rat, mercuric chloride induces a necrotizing leukocytoclastic vasculitis in the gut with milder manifestations in the lung, liver, skin, and kidney[12]. There is evidence that this is a Th2 response in that there is a T cell-dependent polyclonal rise in immunoglobulin. This rise can be blocked by the use of anti-IL-4 antibody[13]. Support for this assertion comes from the observation that there is upregulation of IL-4 mRNA[14]. When D-penicillamine and gold salts are administered to these rats, a similar leukocytoclastic vasculitis develops in association with the upregulation of IL-4 mRNA[15].

Patients with preexisting autoantibodies may be reflecting the predominance of a Th2 response; the addition of anti-TNF therapy may promote increased expression of this phenotype with consequent vasculitis.

These mechanisms are at present speculative, and further investigation is required to define actual causality.

Worldwide experience with anti-TNF therapy is now extensive; most reactions are minor and related to injection or infusion. In our experience of over 700 infusions of infliximab involving 78 patients with RA there have only been 7 other adverse events necessitating dose modification. Five of these reactions were rashes, one patient developed significant mouth ulceration, and the final patient had a flare of joint disease. All of these reactions occurred early, typically by the fourth infusion. Subsequent infusions have been uneventful. We would suggest that while infliximab and etanercept therapy is generally safe, the occurrence of rare but serious events shows the need for watchfulness and the involvement of physicians experienced in the use of such agents, especially if being considered for the treatment of vasculitis.

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