ANTISYNTHETASE SYNDROME: A RARE AND CHALLENGING DIAGNOSIS – CASE REPORT AND LITERATURE REVIEW

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Abstract. Antisynthetase syndrome (ASS) is rare idiopathic inflammatory myopathy (IIM) characterized principally by myositis, generally symmetrical arthritis and interstitial lung disease (ILD) in association with serum autoantibodies to aminoacyl-transfer RNA synthetases. More variable features include arthralgia, Raynaud phenomenon, heliotrophic rash, distal esophageal dysmotility and mechanic’s hands. In this case report we describe a 46-years old woman who initially presented with arthritis and subtle myositis which delayed the recognition of ASS and contributed for considering the condition as seronegative rheumatoid arthritis for several years. During the next few years, the patient was progressively worsening, with a disability to stand up from a sitting position, gradual onset of exertional dyspnea, difficult-to-control dry cough and thick, hyperkeratotic skin of both hands (mechanic’s hands). This constellation of symptoms was highly suspicious for ASS and additional serological and radiological examinations were done which confirmed the diagnosis. The need for further detailed investigation when an interstitial lung disease overlaps with a known rheumatoid condition is obligatory, as shown in this case. A multidisciplinary evaluation is highly recommended to evaluate the clinical, serological and radiological findings in each patient suspected for ASS in order to establish early diagnosis and timely management.

Key words: Antisynthetase syndrome (ASS), interstitial lung disease (ILD), mechanic hands, autoantibody

Introduction

Antisynthetase syndrome (ASS) is a rare multisystemic autoimmune disease with variable manifestations ranging from myositis, interstitial lung disease (ILD) and non-erosive arthritis, to less common features such as fever, Raynaud’s phenomenon and skin changes [1, 2]. Laboratory hallmark of ASS is presence of one (or more) antibodies directed against aminoacyl-tRNA synthetases [1, 3]. The synthetases are enzymes located in cytoplasm of the cells and facilitate attachment of particular amino acid to transfer RNA. The most prevalent in ASS is anti-Jo-1 antibody (against histidyl-tRNA synthetase), encountered in 80% of cases, followed by PL-7 (threonyl-tRNA), PL-12 (alanyl-tRNA), OJ (isoleucyl-tRNA) and EJ (glycyl-tRNA) antibodies [2, 4]. The syndrome is considered as a subgroup of idiopathic inflammatory myopathies, occurring in 20% to 40% of patients with dermatomyositis (DM) or polymyositis (PM) [3]. The disease is extremely rare with prevalence of 1.5 per 100,000 population, usually affecting females in fourth or fifth decade of life [1].

The gold standard for the ASS diagnosis are Solomon’s criteria [5]. According to this criteria, the diagnosis of ASS requires the presence of autoantibodies along with two major criteria (ILD and fulfillment of Bohan and Peter’s criteria for DM/PM) or one major and two minor criteria (arthritis, Raynaud’s phenomenon and mechanic’s hands). Affection of the lungs is the major prognostic factor and pulmonary fibrosis with pulmonary hypertension is the most common cause of death in patients with ASS [6]. The course of the disease is non-specific, often requiring many years until the initiation of therapy.

We report a patient with ASS, initially diagnosed and treated as seronegative rheumatoid arthritis. After occurrence of myopathy and pulmonary symptoms, additional serological and radiological examination were done, confirming the diagnosis of ASS.

Case report

A 46-year old Caucasian female, an ex-smoker with no alcohol abuse and no confirmed atopy/allergies, without significant past medical history, was treated since 2005 as seronegative rheumatoid arthritis, with conventional DMARDS, available in North Macedonia. After showing no substantial improvement, she appeared in 2016 on one of her control appointments with a decreased ability to...
stand up from a sitting position, requiring help from another person. She also complained of slowly progressing dyspnea and tachypnea that begun eight years ago, and weren’t evaluated by a pulmonologist. She described occasional left side chest pain that worsened during inspiration. Her everyday functioning was disturbed, she couldn’t comb her hair as usual, or brush her teeth.

Physical examination revealed bilateral fine basal crepitation on auscultation, with oxygen saturation of 96% on room air, tachycardia and blood pressure of 120/85 mmHg. Cardiovascular, abdominal and neurological examinations were unremarkable. She had symmetrical polyarthritis and livid distal parts of her fingers (Raynaud phenomena), with extreme proximal phalangeal hyperkeratosis of the hands that felt tender to touch, with thickened and cracked skin so called “mechanic hands”. Routine blood test results (including liver and renal function analyses) were in normal range, except the platelet count – 568 x 10^9/l (normal 150-450 x10^9/l) and white blood cells – 11.7 x 10^9/l (normal 4-9x10^9/l) which were slightly elevated. The rheumatology workup showed elevated C-reactive protein (CRP) level of 10μg/l (normal < 6 μg/l) accompanied by positive titer for Anti-double stranded DNA (anti-dsDNA): 60 UI/ml (positive > 55 UI/ml) and Anti Jo1 antibodies: 114 UI/ml (positive > 12.5 UI/ml). Test results for antinuclear antibody (ANA), anti-U1-ribonucleoprotein (anti-U1RNP), antineutrophil cytoplasmic antibodies (ANCA), anti-topoisomerase I (anti Scl-70) were negative.

The initial pulmonary function tests (PFTs) revealed moderate restrictive deficit of ventilation with FVC=51% predicted (normal 80-120% predicted), blood gas values in reference range, and plain chest X-ray with fine interstitial reticulation consistent with pulmonary fibrosis. The pulmonary work-up was completed with 6-Minute Walking Test (6MWT) (Table 1) and contrast-enhanced chest CT (Figure 1A). Echocardiography assessment showed no signs for pulmonary hypertension, with right hearth calibers and blood flow in reference range, accompanied with mild tricuspid regurgitation.

The subsequent musculoskeletal ultrasound of hands and feet detected synovial effusions of the metatarsophalangeal and proximal interphalangeal joints bilaterally, as well as changes in metatarsophalangeal joints on left foot. The electromyography (EMG) showed abnormally small amplitude and short duration of the motor unit potentials (MUP) in the deltoid and biceps muscles bilaterally, consistent with active myopathy. Similar but less prominent MUP pattern was found in proximal muscles of lower extremities. Muscle biopsy was not done, even though it was recommended. Nevertheless, our patient fulfilled 2 major and 3 minor criteria for ASS, as a prerequisite for modifying the original diagnosis of rheumatoid arthritis into ASS.

Between October 2016 and March 2019 the patient was treated with azathioprine (150 mg/daily) and moderate doses of oral prednisolone combined with bone protective and gastro protective therapy. Due to the stable course of the disease including significant improvement in pulmonary function tests, in the year 2019 oral azathioprine was discontinued and the patient was treated only with prednisone, chloroquine (250 mg/daily) and sildenafil (25 mg/ every second day). In October 2020 the patient had COVID-19 pneumonia, treated in local center and after that she experienced a new deterioration of ASS.

### Table 1. 6-Minute Walk Test Results

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>6MWT distance (m)</td>
<td>350</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>At-rest heart rate (beats/min)</td>
<td>86</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td>Post-test heart rate (beats/min)</td>
<td>102</td>
<td>133</td>
<td></td>
</tr>
<tr>
<td>At-rest SpO2_2</td>
<td>97</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Post-test SpO2_2</td>
<td>92</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Oxygen desaturation (%)</td>
<td>5.15</td>
<td>9.09</td>
<td></td>
</tr>
<tr>
<td>Pre-test Dyspnea severity MBG (0-10)</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Post-test Dyspnea severity MBG (0-10)</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Pre-test Fatigue severity MBG (0-10)</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Post-test Fatigue severity MBG (0-10)</td>
<td>7</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Distance reduction (%)</td>
<td></td>
<td>51.43</td>
<td></td>
</tr>
<tr>
<td>Oxygen desaturation declining (%)</td>
<td>56.65</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6-MWT, Six Minute Walk Test; MBG, Modified Borg Scale; SpO2_2, oxygen saturation measured by pulse oximetry
with dyspnea and fatigue. In November 2021 we started therapy with mycophenolate mofetil (2000 mg/daily) combined with prednisone (5 mg/daily) and chloroquine. On the first control after initiating the new immunosuppressive therapy the patient showed initial reversal of the symptoms. The patient continued to take the prescribed therapy with regular monthly control appointments. Her 6 minute walking test results are described in Table 1 and the CT scans are shown in Figure 1.

**DISCUSSION**

ASS is a rare autoimmune syndrome of unknown etiology, with several clinical features, in particular inflammatory myopathy, ILD and presence of antisynthetase antibodies needed for establishing diagnosis. To reach the final diagnosis, a multidisciplinary evaluation is highly recommended to evaluate the clinical, serological and radiological findings in each patient [3, 7]. Clinical features, rather than laboratory investigations, are of greater value for the further diagnostic work-up of ASS. Patients with ASS have a characteristic clinical picture consisting of myositis, ILD and chronic polyarthritis [1-6]. ASS is one subtype of inflammatory myopathies and myositis is found in more than 90% of the patients [2].

Muscle inflammation usually involves proximal skeletal muscles and patients find it difficult to stand up or climb the stairs. Levels of serum creatinine kinase (CK), aldolase, alanine aminotransferase
(ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) are elevated [1-4]. Electromyography findings are nonspecific and may include small amplitude, spontaneous fibrillations, positive spikes at rest, irritability and repetitive discharges [2]. Histopathological evaluation of muscle’s biopsy specimens reveals perimysial inflammation rich in macrophages and lymphocytes with necrosis and regeneration of muscle fibers at the same time [1].

Joint symptoms affect 60% of individuals with ASS and are more common in anti-Jo-1 positive patients [4]. Typically the arthritis is mild and non-deforming, without erosions and/or subluxations of affected joints [28]. Subluxation is unusual manifestation described in only 19% of anti-Jo-1 ASS patients and typically involve IP joints of both hands [29]. Meyer et al. noticed that all anti-citrullinated peptide/protein antibodies (ACPA) positive ASS patients suffered from arthritis versus 41% in the control group (P < 0.0001). The number of affected joints was significantly higher (7.0 ± 5.0 vs 2.9 ± 3.9, P < 0.005), and has distribution similar to that of rheumatoid arthritis. Radiographic damages with erosion were also more frequent in ACPA-positive ASS patients (87% vs 11%, P < 0.0001) [29]. This suggest that this subgroup of patients with ASS is closely connect to RA, probably sharing some pathophysiological mechanisms and patterns of disease activity.

Raynaud’s phenomenon is probably the earliest sign of ASS, which precede the occurrence of other symptoms in years. Skin affection form of vasculitic or hyperkeratotic, non-pruritic erythema on radial and palmar aspects of fingers in both hands.

Interstitial lung disease (ILD) is one of the most prevalent feature of ASS affecting 71-100% of patients [8], being in correlation with the severity of the disease and emerging as a major determinant of its morbidity and mortality. ILD may precede myopathy in more than one third of cases, in up to 55% of the cases [8, 9, 10, 11]. The severity and type of lung involvement correlates with the prognosis of the disease. The clinical presentation of ILD consists of sudden or gradual onset of exertional dyspnea and difficult-to-control dry cough. In the later course, ILD can be complicated with pulmonary hypertension (PAH) [9-11]. Fortunately, control echocardiogram in our patient did not show evolution into PAH. The clinical sequence in our case was in reverse order, with musculoskeletal manifestations presenting as initial clinical manifestation, which delayed the recognition of ASS and contributed for considering the condition as rheumatoid arthritis for several years [12]. It also might contribute for the decision not to order anti-Jo1 antibodies at the beginning, and thus seize the opportunity for earlier recognition of lung involvement. Namely, the presence of anti-Jo-1 antibodies is the strongest predictor of ILD in patients with ASS and nearly 70% of patients with ILD as a part of ASS have detectable anti-Jo-1 antibodies. Furthermore, in patients with ASS-associated ILD, disease activity is strongly related to the titer of anti-Jo-1 antibodies [1]. Concomitant occurrence of ILD and myositis increases the likelihood of positive anti-Jo-1 antibodies, and if anti-Jo-1 antibodies are not present, a search for non-Jo-1 antibodies should be made in patients with clinical suspicion of ASS [1, 2, 5].

The prevailing hypothesis states that Anti-SS ILD begins as a cellular inflammatory process that fails to terminate appropriately and progresses to a fibroproliferative condition [13]. This emphasizes the importance of high-resolution computed tomography (HRCT) of the chest for adequate assessment of these patients, playing a key role in the diagnosis and monitoring of treatment responses [3]. The radiological characteristics of ASS are often nonspecific, with broad differential diagnosis comprising of idiopathic and secondary ILD [14]. Current evidence on HRCT patterns in ASS-associated ILD is based predominantly on retrospective case series and case reports [8]. The three common HRCT patterns seen in ASS, sorted by frequency, are as follows: nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP) and mixed NSIP/OP pattern [8, 15, 16, 17]. Less common is the occurrence of usual interstitial pneumonia (UIP) [18]. In previous reports, the UIP pattern has been reported to be associated with a worse prognosis [19].

Given the scarce radiologist’s description (no suggestion for particular CT-pattern), we found out that the first chest CT in 2016 as most consistent with NSIP pattern (ground-glass attenuation with reticulation and bibasilar sub-pleural predominance). The gradual progression of pulmonary fibrotic changes was evident through annual CT controls, the ultimate chest CT in 2021 revealing honeycombing with bibasilar and sub-pleural predominance. Although honeycombing is the defining characteristic of UIP CT-pattern [20], fibrosing NSIP may be also associated with CT evidence of honeycombing, but in such cases only the pathologist can make the distinction with the UIP pattern [21]. Bearing in mind the current clinical practice
and available treatment for ASS [22], it can be concluded that the course of therapy (i.e. corticosteroid and steroid-sparing azathioprine) has in some extent slowed down the progression of lung disease. Nevertheless, the several reports from recent years raise the question of potential role of monoclonal antibodies and anti-fibrotic therapy as better solution for treatment of ILD in ASS [10, 17, 23, 24, 25].

The typical pulmonary function tests (PFTs) finding in ASS-associated ILD are: restrictive pattern of ventilatory defect (vital capacity of less than 80%), diffusing capacity for carbon monoxide of less than 70% predicted [1,3] and impaired gas exchange. In 2016, our patient started the pulmonary function follow-up with reduction of FVC (51% of predicted) and resting blood gases in reference range. During the period 2016-2019, the PFTs follow-up showed no significant changes, despite three intercurrent episodes of lower respiratory tract infections (LRTI) and apparent worsening of chest CT. The restrictive defect stabilized within the range of moderate-to-severe impairment (FVC 51..56..51%), and resting blood gasses showed occasional worsening in terms of mild hypoxemic respiratory failure, while SpO2 on puls-oximetry continuously stayed within reference range (94-99%). Unfortunately, we couldn’t provide diffusing capacity assessment, due to technical issues. We strongly believe that the combined therapy (glucocorticoid plus azathioprine) has accomplished remission of the disease activity and stabilization of pulmonary function and PFTs parameters.

Facing the pandemics of SARS-CoV-2 in 2020 and 2021, we avoided performing of PFTs, and control visits were reduced ad maximum. Nevertheless, at the end of 2021, the 6MWT was repeated in a safe environment, uncovering reduction of functional capacity, with more pronounced declining of O2 saturation and diminishing the distance achieved (table 1). Exercise capacity may decline in DM due to complex factors – including muscle weakness by myositis, lung dysfunction, and medications (especially corticosteroids) [26]. Since the pandemics of Covid 19 in March 2019, this list was expanded with SARS-CoV-2 infection [10]. Considering the prior stability of pulmonary function, constant value of BMI and remission of the disease activity, as well as Borg scale results, the most likely reason for worsening was the SARS-CoV-2 infection in October 2020 – despite being treated ambulatory, and without apparent radiological or functional worsening. It has been noted that the high prevalence of mild COVID-19 in patients with rheumatic disease might be associated with ongoing anti-inflammatory or immunomodulating treatments frequently used in these conditions [27], as well rheumatic diseases flares during COVID-19 and development of new autoimmune features [10].

Affection of kidneys is an exception, usually in form of mesangio-proliferative glomerulonephritis with good prognosis [28, 30].

ASS can be easily misdiagnosed as: interstitial lung disease, myositis, rheumatoid arthritis, Raynaud’s phenomenon, systemic scleroderma, overlap syndromes, idiopathic pulmonary fibrosis, dermatomyositis. Cases with predominantly musculoskeletal symptoms are difficult to distinguish from electrolyte disturbances, inherited muscle enzyme deficiencies, muscular dystrophies, myasthenia gravis, hypothyroidism and abuse of drugs and alcohol [1, 2].

Scientific data about the treatment of ASS are scarce and mostly limited to a case reports/series or small cohorts of patients. There is no standardized regimen for ASS treatment; however, the drug of choice for initial therapy of ASS remains high dose of prednisone (1 mg/kg/day) with achieved remission in 25-68% of treated patients [2, 3]. Witt et al. noticed that patients treated with corticosteroid monotherapy have frequent lung disease recurrence which impose a need of using additional immunosuppressive agents as azathioprine, mycophenolate mofetil, tacrolimus, rituximab, and cyclophosphamide [22]. Some of the treatment options for ASS are presented in Table 2.

Tumor necrosis factor (TNF) inhibitors, such as etanercept (Enbrel) and adalimumab (Humira), are medications typically used for rheumatoid arthritis. If arthritis symptoms are predominant in a patient with antisynthetase syndrome, these medications may be preferred [2]. They should be used with caution, however, as these biologic drugs are sometimes associated with the development of myositis [2, 22].

The emerging new therapeutic options of ASS-associated ILD are being referred in the past decade, mostly as salvage therapy when ILD appears with acute respiratory failure, being refractory to corticosteroids and steroid-sparing medicines, or relapses after a period of remission [10, 17, 23].

According to the previous studies and current guidelines, rituximab (RTX) should be considered for refractory IIM and refractory ILD. Increasing number
of retrospective studies have shown the benefit and safety of RTX in ASS-associated ILD, with reported objective improvement in PFTs, ground-glass opacities or fibrosis on HRCT [10]. In refractory cases of ASS, IL6 inhibitor tocilizumab, may be considered as a second or third option.

Nintedanib, an oral triple kinase inhibitor targeting pro-fibrotic pathways, has also been reported as a salvage agent in ASS-associated ILD [10]. Primarily used as standard antifibrotic drug for IPF, the indication field of nintedanib has recently expanded on patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) [31, 32], and the indication field is further expanding to various forms of ILD with progressive fibrosing phenotype.

Namely, the primary results of the INBUILD Phase III clinical trial showed that nintedanib significantly reduced the annual rate of decline in FVC over 52 weeks compared with placebo in patients with ILD with progressive fibrosing phenotype, including those with ILD associated with CTD (such as rheumatoid arthritis, SSc, dermatomyositis/olyomyositis, mixed connective tissue disease, Sjogren’s syndrome, and even ASS). [33]. Subsequent analysis throughout the study (early view) not only confirmed the previous finding, but also showed an improvement in the prognosis in the nintedanib group (in terms of acute exacerbation and fatal outcome) [33].

Although we have extensive experience with rituximab, it’s application is within the scope of current EMA-approved list of hematological and rheumatological indications, and to our knowledge rituximab has not been used in our country to treat ASS so far [34]. The use of nintedanib is even more strictly limited, and in our country it is reserved to patients with IPF only [36].

Regarding the prognosis of ASS, the presence of anti-PL7/PL12 autoantibodies is associated with a more aggressive form of ILD as crucial predictor of survival in patients with ASS [6]. There is a decreased rate of survival in affected patients with deteriorated pulmonary status, given the fact that this syndrome is usually later diagnosed which slows the initiation of the right therapy protocol [22]. Contrary, patients with anti-Jo1 positivity, are likely to have milder form of the disease, which will be mainly affect their joints [22]. The 10 year survival rate in a 2015 study was 70% for anti-Jo1 positive patients, and 49% for non-anti-Jo1 patients [18]. According to this study, the most common cause of death was pulmonary fibrosis.

Table 2. Spectrum of demographic, clinical, laboratory, radiological findings and treatment options in patients with ASS reported in the literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Age at diagnosis/ gender</th>
<th>Signs and symptoms</th>
<th>Positive Serology</th>
<th>Initial diagnosis</th>
<th>Pattern of pulmonary involvement on CT</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quershi M et al. [4]</td>
<td>48, male</td>
<td>Breathlessness, fever, swollen MCP and PIP on both hands</td>
<td>Anti-Ro Anti-Jo1</td>
<td>No data</td>
<td>NSIP with lower lobes predomination</td>
<td>Corticosteroids Cyclophosphamide Oxygen support</td>
</tr>
<tr>
<td>Kumar N et al. [3]</td>
<td>63, female</td>
<td>Breathlessness, fever spikes, Raynaud’s phenomenon Mechanic’s hands Pitting pedal edema Bilateral swelling of both wrists and MCP</td>
<td>ANA</td>
<td>Community-acquired pneumonia</td>
<td>Bilateral diffuse NSIP with organizing pneumonia in both upper lobes</td>
<td>Pulsed doses of corticosteroids (1mg/kg/day) cyclophosphamide (1500mg, 7 cycles every 3-4 weeks)</td>
</tr>
<tr>
<td>Theilacker L. et al. [28]</td>
<td>61, female</td>
<td>Raynaud’s phenomenon Followed by: Dyspnea Fever Swollen first PIP right</td>
<td>Anti Jo1</td>
<td>Myositis</td>
<td>Diffuse ground glass image with residual fibrous in the right lower lobe</td>
<td>No data</td>
</tr>
<tr>
<td>Theilacker L. et al. [28]</td>
<td>78, female</td>
<td>DM symptoms: Proximal muscle weakness, heliotrope rash, joint pain, Raynaud’s phenomenon Present time: Deformity of first DIP joints and dyspnea</td>
<td>Anti Jo1</td>
<td>DM for 11 years</td>
<td>Slight reticular pattern, subpleural lines and ground glass opacities in the lung periphery</td>
<td>DM treated with corticosteroids for 11 years with symptoms of remission No data after setting the diagnosis for ASS</td>
</tr>
</tbody>
</table>
Continuation of table 2

<table>
<thead>
<tr>
<th>Badshah A et al. [1]</th>
<th>27, male</th>
<th>Dyspnea</th>
<th>Arthralgia</th>
<th>Weight loss</th>
<th>Low to high-grade fever</th>
<th>Anti Jo1</th>
<th>Pneumonia</th>
<th>Treated with antibiotics with temporary improvement</th>
<th>i.v. prednisone 1g for 3 days followed by oral corticosteroids</th>
<th>azathioprine</th>
</tr>
</thead>
</table>

PIP – proximal interphalangeal joints; DIP – distal interphalangeal joints; MCP – metacarpal joints; UIP – usual interstitial pneumonia; NSIP – nonspecific interstitial pneumonia

with pulmonary hypertension, both requiring lung transplantation, which leads us to the first conclusion that physicians should consider early admission to centers capable of this kind of transplantation when disease fails to respond to the given treatment or progresses rapidly.

In conclusion, antisynthetase syndrome is a rare, autoimmune-mediated, often misdiagnosed disease due to the variable clinical presentation which are not specific, with milder forms of the disease not being recognized at all. ASS should be considered in the differential diagnosis of many rheumatologic, pulmonary and neurological diseases, because it often takes years for full disease expression that lead to delay diagnosis and late initiation of therapy. In patients clinically suspected for ASS, a multidisciplinary approach and combination of serological and radiological test are essential in order to establish early diagnosis and provide early and aggressive treatment.

References

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