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LYELL'S SYNDROME: CLINICAL CASE

Abstract

In the article, the interdisciplinary problem of drug allergy is being analyzed, namely its systemic symptoms. The variants of systemic allergic reactions and the characteristics of the toxic epidermal necrolysis or Lyell's syndrome as one of the most serious and rare form of illness have been shown. The analysis of the clinical case of the Lyell's syndrome has been carried out with diagnostic difficulties in the initial phase of the disease and favorable outcome. The dynamics of clinical signs and their reversed development has been proved.

Key words: *drug allergy, Lyell's syndrome, toxic epidermal necrolysis*

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BP — blood pressure, ALT — alanine aminotransferase, AST — aspartate aminotransferase, GGT — gamma-glutamyltransferase, IgG — immunoglobulin G, IgM — immunoglobulin M, DA — drug allergy, ESR — erythrocyte sedimentation rate, TEN — toxic epidermal necrolysis, T° — body temperature, RR — respiratory rate

Introduction

The incidence of drug allergies has become more frequent at the present time. This is believed to be related to the increase in the number of allergic and autoimmune diseases, the use of a large number of medicines for a single patient, the presence of concomitant diseases involving various organs, and the development and use of new medicines [1, 2]. A drug allergy (DA) is an immunologically mediated hypersensitivity to medications that develops with repeated exposure to them. It is one of the most severe allergic reactions with a variety of clinical symptoms that are difficult to treat [1–6]. A physician in any field of specialization can face this pathology. In Russia, adverse drug complications affect 2–3% of outpatients and 10–15% of in-patients [2, 6].

Background

There is DA with systemic clinical manifestations and DA that predominantly results in injury of certain organs [3].

Systemic clinical manifestations of DA are diverse. Anaphylaxis and the following acute severe generalized dermatoses may develop: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome); serum sickness, systemic drug-induced vasculitis, drug-induced lupus erythematosus, drug fever, and drug-induced hypersensitivity syndrome (which is not fully understood) [3].

Clinical manifestations of DA that predominantly affect particular organs include lesions of the skin,

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respiratory system, hematopoietic system, cardiovascular system, gastrointestinal tract, hepatobiliary system, urinary system, and nervous system. Skin lesions are characterized by the following events: maculopapular exanthems, urticaria and angioedema, hypersensitivity vasculitis, allergic contact dermatitis, fixed drug eruption and other toxicodermias, erythema multiforme, photodermatitis, Arthus reaction, exfoliative erythroderma, erythema nodosum, and acute generalized exanthematous pustulosis [3].

Lyell's syndrome, one of the rare life-threatening conditions, is a systemic manifestation of DA. In particular, it is one of the acute severe generalized dermatoses (epidermolytic drug reactions). These conditions are characterized by extensive lesions of the skin and mucosa [1–3, 5–7]. Drugs that can cause these syndromes include sulfonamides, penicillins, and more rarely cephalosporins, fluoroquinolones, vancomycin, rifampicin, nonsteroidal anti-inflammatory drugs, and anticonvulsants [1–4]. According to different authors, morbidity ranges between 0.4 to 6 cases per million [1, 3, 4] and up to 0.3% of all drug allergy cases [2, 7]. It can occur at any age. Drug allergy risk is higher in HIV-positive persons (by a factor of 1,000 times) [4] as well as in patients with systemic lupus erythematosus and cancer [1, 4]. The period between administration and first clinical manifestation can be 2 to 8 weeks. It can take this amount of time to produce an immune response. The pathogenesis is associated with massive death of basal skin keratinocytes and mucosal epithelium caused by Fas-induced and perforin/granzyme-mediated cell apoptosis. Programed cell death results from immune-mediated inflammation, in which cytotoxic T-cells play an important role [2–4]. Stevens-Johnson syndrome with a lesion area of less than 10%, Lyell's syndrome with a lesion area of more than 30%, and an intermediate form with a lesion area of 10–30% have all been identified [4]. In fact, these are just the stages of a single process [1, 3, 4]. The disease prognosis depends on the patient's age, concomitant diseases, and the extent of the skin lesion. Mortality due to epidermolytic drug reactions is 5–12% [4], and it is 30–70%–100% due to Lyell's syndrome [2, 6].

Steven–Johnson syndrome is a severe form of exudative erythema multiforme, in which visceral lesions are observed along with skin and mucosal lesions. Extensive polymorphic rashes as well as the formation of bullae and ulcers of the mucous membranes (two or more) and skin are characteristic. Epidermal necrolysis covers less than 10% of the total skin surface. Severe fever and fatigue are observed [3, 6].

Lyell's syndrome (*toxic epidermal necrolysis, TEN)* is an acute and severe life-threatening disease that is characterized by extended bullous lesions of the skin and mucosa. Appearance of epidermal necrolysis (positive Nikolsky's sign) and skin exfoliation associated with severe intoxication and multiple organ dysfunction are typical [3, 6].

Usually, pathological processes in the skin and mucosa undergo stages from erythema multiforme to Stevens–Johnson syndrome and result in extensive toxic epidermal necrolysis of the skin with 30 to 100% coverage by lesions. The time interval that is needed for TEN to develop may vary from several hours to several days [1, 3, 4].

The disease may start as common urticaria that is resistant to therapy with histamine antagonists and calcium agents [4, 6]. This is succeeded by the following symptoms: nausea, vomiting, joint pain, and fever. Alternatively, fever, chills, weakness, headache, muscle and joint pain, sore throat, rhinitis and pharyngitis may develop initially, often leading to an initial diagnosis of ARVI [1, 2]. Soon, an erythematous edematous rash of various sizes, which is often confluent, develops on the face, torso and mucosae along with tenderness and burning of the skin. After a short time, multiple flabby bubbles are formed, which are confluent, and they form extensive erosions and massive exudation, which results in dehydration and deterioration in the patient's condition. Headache and lesions of the internal organs progress, and loss of consciousness is observed. TEN may take one of several possible courses: a hyperacute disease with fatal outcome, an acute disease with a toxic infectious syndrome with a potentially fatal outcome, and a benign disease with resolution by the 10th–15th day [2].

Fleck's leukocytes agglomeration test, specific immunoglobulin E serum testing, lymphocyte blastogenic response, Shelley's basophil degranulation test, etc., and challenge tests performed by an allergist-immunologist are recommended to perform a laboratory diagnosis of TEN at the present time [2, 3]. It is also necessary to perform a frozen section biopsy of skin lesions where perivascular lymphocytic and eosinophilic infiltrations are discovered [4].

Differential diagnosis of skin lesions is performed during the early stages with severe infectious diseases (chicken pox, measles, scarlet fever, meningococcemia, etc.), and it is performed at the late stages with generalized herpetic skin and mucosa lesions, systemic diseases, bullous pemphigoid, paraneoplastic pemphigus, pustular form of psoriasis, generalized staphylodermia and streptodermia, Duhring's herpetiformis dermatitis, etc. [1–3].

When an epidermolytic drug reaction is identified, the physician, regardless of his/her specialization, must provide emergency medical care to the patient and ensure his/her transportation to the burn center (department) or to the intensive care unit. Treatment of patients with TEN is similar to that of those with burn conditions.

Clinical Case

A 22-year-old female patient S. was admitted to the Infectious Disease Hospital on November 19, 2017, at 12:15 a.m., by ambulance with a diagnosis of "rash of unknown origin". Complaints: body rash, sore throat, eye redness, body temperature (T°) elevation to 38.2 °C.

Medical history: the patient fell ill on November 15, 2017, when she experienced weakness, neck pain, and enlargement of the left neck lymph nodes. Next day T° was 37.3–37.5 °C, and she experienced a burning sensation in the eyes. The patient took one Aspirin pill and one Ciprolet pill (the patient cannot remember the dosage). On November 17, body temperature was normal in the morning but elevated to 37.5–37.7 °C by the afternoon, and a burning sensation in the eyes persisted. The patient applied an ointment with cobra venom to reduce neck pain on the advice of her mother living in another city. The patient took Flemoxin (cannot remember the dosage) and Decaris pills (the patient had been scratched by a cat the day before and assumed that she could get infected with toxocariasis). On November 18, the 4th day of the disease, she experienced a minor cough and a sore throat, and small vesicles appeared in the mouth. A rash appeared on the chest in the evening, and T° was 37.7 °C. The patient called an ambulance and was admitted to an infectious diseases hospital.

It is known from the patient's medical history that she experienced rubella, chicken pox, parotitis in childhood. The patient experienced exacerbation of tonsillitis in mid-October 2017, was treated with amoxicillin 500 mg as an outpatient, and was discharged and allowed to return to work on October 26, 2017. The patient denies having an allergy. Epidemiological history: the patient lives alone in a comfortable apartment, and has had no contacts with infectious patients.

On admission, the patient's condition was assessed as of medium severity. T° was 37.7. Mental status was normal. The patient was active. A few elements of small-spotted skin rash localized on the chest and isolated elements on the back were discovered. The patient had pronounced conjunctival hyperemia and scleral congestion. Diffuse hyperemia was discovered at the oropharyngeal mucosa. The tonsils were not enlarged, mucosal granularity was advanced, and an enanthema was discovered on the hard palate. The anterior neck lymph nodes were enlarged to grade II, and they were not painful. Nasal breathing was not obstructed. Dyspnea was absent. Mild cough was observed. Breath sounds were vesicular. The heart sounds were clear. Pulse volume was normal, and the heart rate was 106 per minute. BP was 136/95 mmHg. The abdomen was soft and not painful. Bladder and bowel function was normal.

Taking into account that the disease began with enlargement of the lymph nodes followed by low-grade fever, sore throat, hyperemia of the oropharyngeal mucosa with pronounced granularity, as well as the absence of leukocytosis and tendency to leukopenia observed in the complete blood count (white blood cells $4.3*10^9$), a viral infection was suspected. Herpetic infections, ARVI, and

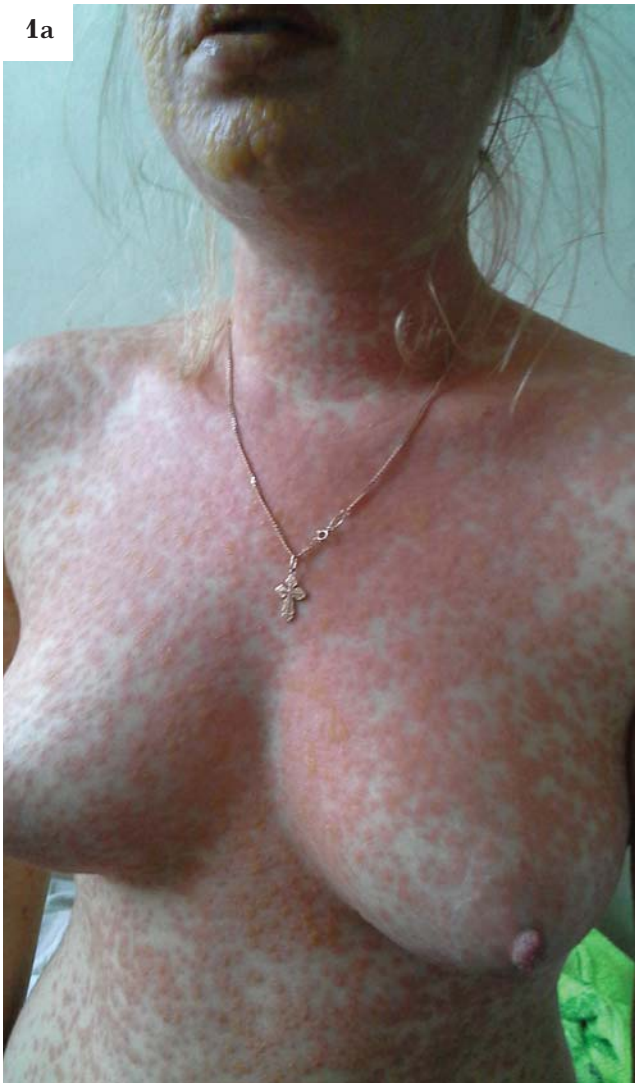
enteroviral infection were the choices that needed to be narrowed down using differential diagnosis. Antiviral treatment (Viferon, aciclovir) and topical antiseptics were prescribed.

In the morning of November 19, the patient presented the same complaints as on admission, but itchy eyes were reported in addition to burning. Her general condition had deteriorated. T° was 37.5. Heart rate was 74 per minute, and respiration rate (RR) was 18 per minute. The pattern of exanthema and its localization were changed. The rash started to resemble small- and medium-sized papules, and it extended to the face, torso, arms and hips; it was profuse, bright pink, and it did not itch. An enanthema on the soft palate, a buccal enanthema, conjunctival hyperemia, injection of scleral vessels, eyelid puffiness were also observed. Antiviral treatment was continued, and detoxication therapy and systematic desensitization were initiated.

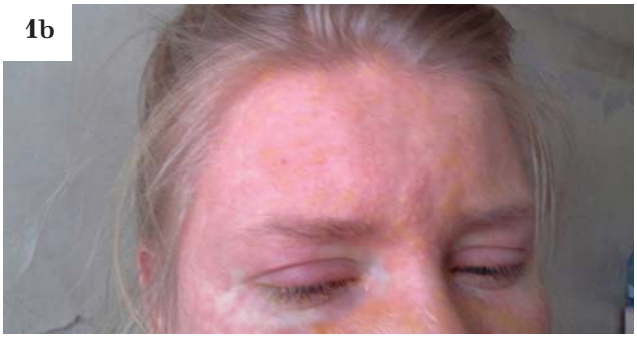
November 20: T° was 37.3. Heart rate was 94 per minute, and RR was 20 per minute. BP was 110/70 mmHg. The patient's condition had worsened considerably. Sore throat and eye redness persisted. A bright, profuse rash in the form of medium-sized papules extended across the entire torso, and they became confluent with purulent content in some places, including the face and limbs (Fig. 1, a, b, c).

Swelling of the face, lips, eyelids, as well as pus discharge from the eyes (Fig. 2), and purulent plaques appeared at the mucous membrane of the hard palate and at the tongue. ENT specialist diagnosed necrotic stomatitis. Purulent discharge

1a



1b



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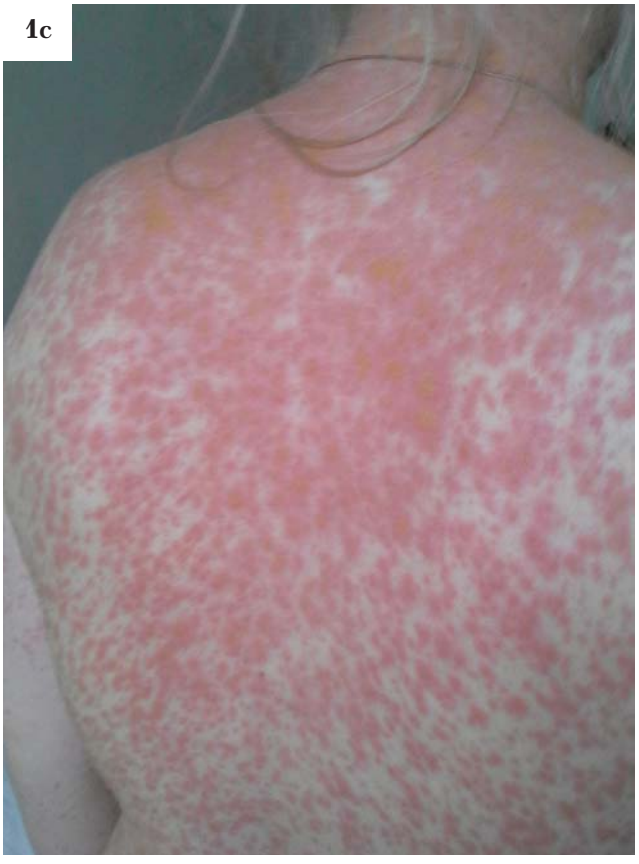

Figure 1 (a, b, c). *Skin and mucous membranes rashes, November 20, 2017*

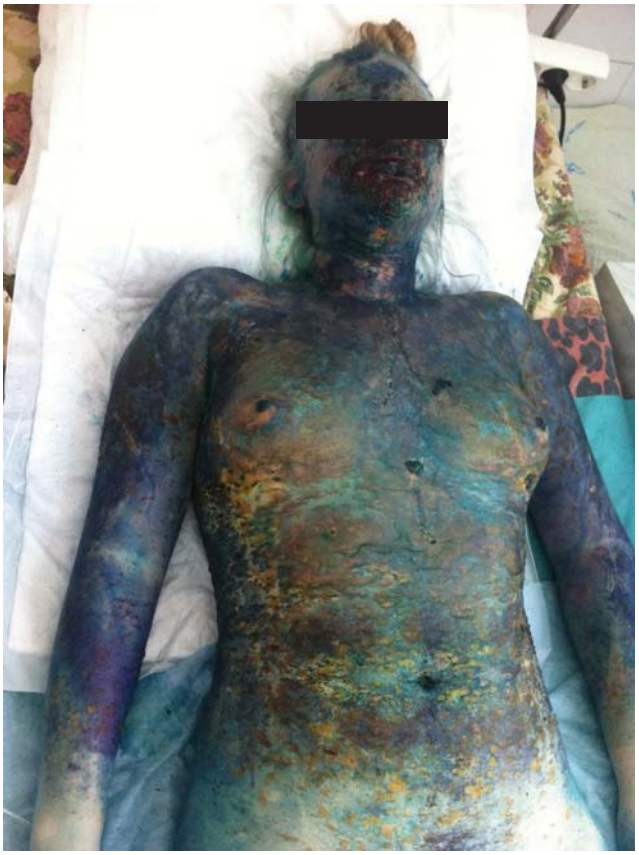

Figure 2. *December 3, 2017*

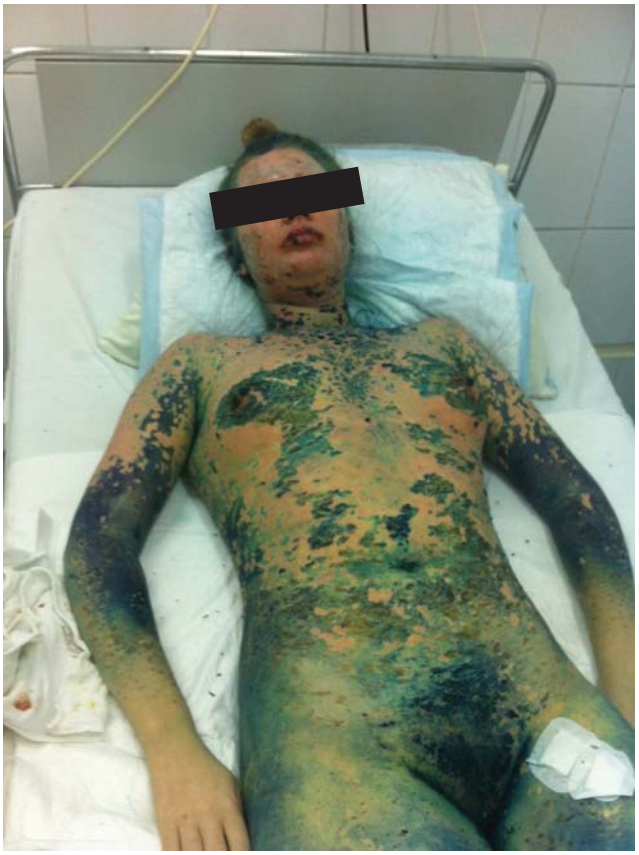

Figure 3. *December 13, 2017*

from the genitals was also observed. Signs of liver injury were discovered while taking into account blood chemistry parameters.

The nature of skin abnormalities in combination with the lesions of the oral and genital mucosa and development of reactive hepatitis syndrome were indicative of an allergic reaction that is probably associated with the use of medicines before the patient was hospitalized, and they provided evidence for diagnosing Lyell's syndrome.

The results of a laboratory examination were obtained.

A complete blood count was performed:

November 19, 2017: Hemoglobin: 144 g/l, ESR: 25 mm/h, WBC: $8.6*10^9$, RBC: $4.27*10^{12}$, PLT: 148, Eos. (eosinophils): 12, bands (banded neutrophils): 14, segs (segmented neutrophils): 53, lymph (lymphocytes): 8, mon (monocytes): 13.

November 20, 2017: Hemoglobin: 129 g/l, ESR: 17 mm/h, WBC: $4.3*10^9$, RBC: $4.74*10^{12}$, PLT: 154, Eos.: 0, bands: 34, segs: 53, lymph.: 11, mon.: 2.

Biochemical blood test, November 20, 2017: Total bilirubin 79.6 μmol/L, direct bilirubin 73.1 μmol/L, indirect bilirubin 6.5 μmol/L, AST 195 U/L, ALT 179 U/L, thymol test 4 U.

Urinalysis: unremarkable.

Serum procalcitonin concentration, November 20, 2017: 0.46 ng/ml (reference values – less than 0.5 ng/ml).

IgG antibodies against the capsid protein with an avidity index of 100% were discovered in a blood test for EBV infection.

A test for parasitic invasions was performed in accordance with the algorithm for examining patients with exanthema syndrome. IgM antibodies against Trichinella were discovered with titer of 1:100, and the degree of positiveness was discovered to be 1.6 (where the parameters do not match the diagnostic value). Total antibodies to lamblia antigen were discovered with a titer of 1:200; and total antibodies to Toxocara and Opisthorchis were not discovered.

The indirect hemagglutination test for pseudotuberculosis turned out negative.

A bacteriological examination of the oropharyngeal mucosa dated November 20, 2017, revealed a culture of pigmented Neisseria and Staphylococcus haemolyticus with heavy growth.

A bacteriological examination of the bullae content dated November 20, 2017, revealed a culture of Staphylococcus aureus.

On November 20, 2017, the patient was diagnosed with Lyell's syndrome and was transferred to the ICU at a multidisciplinary hospital due to the severity of the condition caused by the systemic disease, including extensive lesions of skin (Fig. 3), mucous membranes of the oral cavity and genitals. In addition, involvement of the liver (reactive hepatitis), bone marrow (decrease in RBC count to $3.21*10^{12}$, neutrophil left shift and WBC count to $3.6*10^{9}$, PLT count to $105*10^{9}$), and pancreas (reactive pancreatitis: amylase 1,269 U/L). No abnormalities of other organs and systems were discovered by comprehensive examination. At the same time, the patient had staphylococcal bacteremia (a culture of Staphylococcus aureus was isolated in the blood sterility tests dated November 30 and December 5; no growth was discovered in the test dated December 15), which indicated the need for the administration of an antibacterial treatment. Detoxication, desensitization (Medopred, prednisolone, Suprastin), hepatoprotective therapy, as well as topical treatment of the skin, mucous membranes, eyes (antiseptics, desensitization and wound healing agents), and specialized nutrition supplements were provided. The patient was kept at the ICU for treatment until December 19, 2017. Manifestations on the skin and mucous membranes have epithelized gradually (Fig. 2, 3), whereafter the patient was transferred to the gastroenterological department due to the development of cholestatic drug-induced hepatitis that was difficult to be resolved. (The viral etiology of hepatitis was excluded.) Gradual increases of the total bilirubin values (with maximum of 339.5 μmol/L), mainly due to the conjugated bilirubin fraction (with maximum of 287.1 μmol/L), of GGT (with maximum of 2,484 μkat/L), cholesterol (to 27.4 mmol/L), and alkaline phosphatase (to 28.7 μkat/L) were observed over time. An increase in hepatic transaminases values was less pronounced (maximum of ALT/AST: 25.55/12.57 μkat/L), followed by normalization in 1 month. Glucose and salt solutions for parenteral administration, liver protectors, gastrointestinal adsorbents, and glucocorticosteroids were used as part of a comprehensive treatment.

The patient was discharged from the hospital on January 11, 2018, in satisfactory condition, with persisting clinical and laboratory signs of a cholestatic syndrome. The patient was assigned to the follow-up care of a general practitioner, gastroenterologist, and dermatologist.

Conclusion

The case that we reviewed demonstrates the difficulties of diagnosing and performing a differential diagnosis of Lyell's syndrome at an early stage, when multiple organs are affected by the peak manifestation of the disease. The case history confirms that successful treatment is possible when the lesion area is large. In addition, this case demonstrates the severity and protracted course of reactive cholestatic hepatitis requiring long-term treatment and follow-up. Different types of specialists are required for the correct management of a patient with Lyell's syndrome.

Conflict of Interests

The authors declare no conflict of interests.

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