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CASE REPORT

Two cases of atypical hemolytic uremic syndrome (aHUS) and eosinophilic granulomatosis with polyangiitis (EGPA): a possible relationship

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Abstract Atypical hemolytic uremic syndrome (aHUS) is a rare disease characterized by hemolysis, thrombocytopenia, and renal failure. It is related to genetic mutations of the alternative complement pathway and is difficult to differentiate from other prothrombotic microangiopathies. Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss syndrome, CSS) is a systemic ANCA-associated vasculitis and a hypereosinophilic disorder where eosinophils seem to induce cell apoptosis and necrosis and therefore, vasculitis. Here, we report the case of two CSS patients with a genetic complement disorder consistent with aHUS diagnosis. Both patients showed histologic features that supported the diagnosis of CSS, and a genetic complement study confirmed the suspected aHUS diagnosis. In the case where eculizumab was administered, the global response was excellent. There is very limited understanding of the genetics and epidemiology of both, atypical HUS and EGPA, but considering our two patients we suggest that an etiopathogenic link exists among patients diagnosed with both entities.

Keywords aHUS · EGPA · Churg–Strauss syndrome · ANCA · Vasculitis · Eosinophilia · Eculizumab · TMA · Complement

Introduction

Hemolytic uremic syndrome (HUS) is a rare disease characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury. Typical HUS accounts for over 90% of cases and atypical HUS (aHUS) or non-Shiga-toxin-HUS accounts for 5–10% of cases. aHUS prognosis is poor and the disease is characterized by overactivation of the alternative complement pathway. aHUS causes inflammation, platelet activation and thrombotic microangiopathy (TMA), which induce multisystem failure or even death [1, 2]. Genetic alteration could be the basis of complement dysregulation but environmental contributions are also essential to trigger the disease. Traditionally, aHUS treatment included plasma infusion (PI) and plasma exchange (PEX); however, the underlying complement dysregulation and thrombotic microangiopathic processes are likely to persist with these therapies. Relapses are frequent and 65% of patients die, require dialysis, or develop permanent renal damage within the first year of diagnosis despite treatment with PI or PEX [3]. A deeper understanding of the pathogenesis of the disease has led to the successful introduction of eculizumab. Eculizumab is a complement inhibitor and it has demonstrated to be effective in over 80% of patients in controlling hemolysis and improving renal function [4].

Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss syndrome, CSS) is a systemic ANCA-associated vasculitis and a hypereosinophilic disorder [5]. Lung involvement typically occurs in people with asthma

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but clinical presentations are heterogeneous. Pathogenesis remains unclear but apparently T and B cells are involved. Eosinophils might induce cell apoptosis and necrosis and, therefore, vasculitis. Pathological triad includes necrotizing vasculitis, eosinophilic infiltration and extravascular granuloma formation [6]. Clinical renal involvement is uncommon. As regards to the therapy, glucocorticoids and cyclophosphamide may be helpful. Azathioprine or methotrexate is also used. Biologic therapies are currently under investigation [7–10].

In CSS, the most commonly involved organ is the lung, followed by the skin. However, CSS can affect any organ system, including the cardiovascular, gastrointestinal, renal and central nervous systems. Vasculitis of extrapulmonary organs is largely responsible for the morbidity and mortality associated.

The association of eosinophilia with TMA is unusual. Some authors describe that eosinophil degranulation may produce endothelial injury in the renal microvasculature to trigger TMA [11–14]. We report what we believe are the first two cases of Churg–Strauss syndrome (CSS) associated with aHUS.

Case report 1

A 50-year-old man was admitted to our institution because of dyspnea, weakness and malaise lasting 4 weeks. He had high blood pressure, eosinophilia and an acute renal failure. The patient's history demonstrated hypertension under two control drugs, recurrent nasal polyposis, chronic sinusitis and mild asthma ongoing for 3 years. He had never smoked. He had been under a renal evaluation for the previous 2 years due to a progressive increase in creatinine levels up to 1.5 mg/dL, associated with mild proteinuria (0.5 g/24 h), hematuria and a slight decrease in C3 levels. Otherwise, the complete blood count was normal. A renal biopsy was performed. Histological features were suggestive of TMA (Figs. 1, 2, 3). Retinal hemorrhage was found on fundoscopic exam. Based on the results, renal failure was attributed to malignant hypertension and antihypertensive therapy was increased.

However, 1 month later, the patient was admitted at the hospital and his creatinine level had increased to 6.49 mg/dL. He also developed acute hypoxic respiratory failure, likely due to flash pulmonary edema. At that moment, blood pressure was high (160/100 mmHg) but there was no clinical or laboratory evidence of hemolysis (Fig. 4). Further investigations showed proteinuria of 1.68 g/24 h, hypereosinophilia associated with high Ig E and tryptase levels (Table 1).

Immunology, coagulation and microbiological studies were normal or negative (ANA, pANCA, cANCA, anti-GBM, cryoglobulinemia, immunoglobulins A, G, M and complement levels included. Coombs, ADAMTS 13). 6 days after admission, renal dysfunction persisted despite adequate blood pressure control. Therefore, a new renal biopsy was performed revealing diffuse interstitial eosinophilic infiltration that was not present in the previous biopsy (Fig. 5, Supplementary Figures). IFI technique showed mesangial and capillary walls diffuse and widespread IgM deposits of granular type. C3 deposits were less intense. Deposits of C4 were present in arterial segments of focal and segmental type. C1Q deposits were similar to C3 and followed the same distribution.

Chronic TMA changes were also observed. Considering the previous history of asthma, eosinophilia >10%,

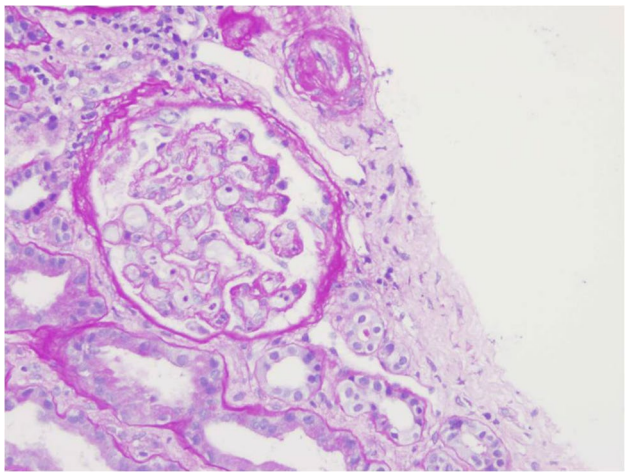

Fig. 1 Glomerular ischemic changes; glomerular lumen reduction, basement membrane double contours and aneurysmatic dilatation of some capillary loops

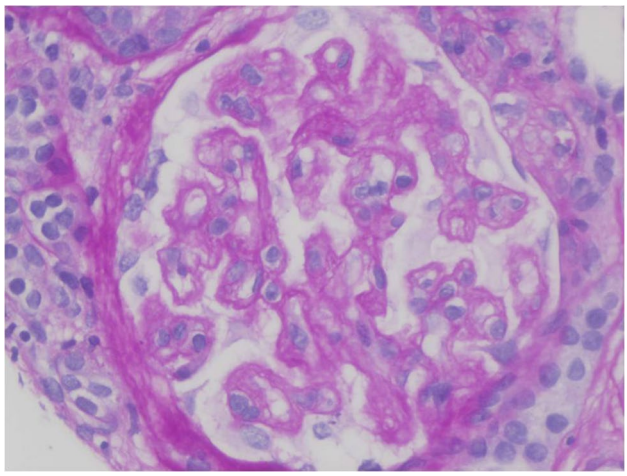

Fig. 2 At higher magnification, wrinkling and duplication of the glomerular basement membrane is more evident

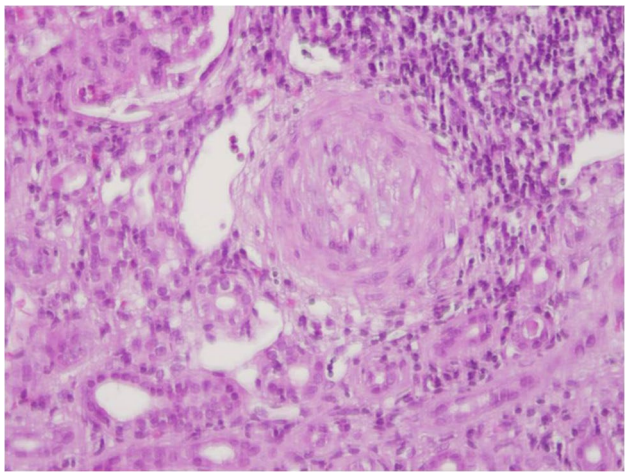

Fig. 3 Vascular lesion, concentric thickening of the intima, with concentric reduction of the luminal area

paranasal sinus abnormality and extravascular eosinophils, diagnosis of Churg–Strauss syndrome was established. Treatment with high-dose intravenous steroids (500 mg for 3 days) and cyclophosphamide (0.5 g/m^2) was initiated, which yielded a decrease in eosinophil count and clinical improvement. Yet, renal function did not recover; hence, permanent hemodialysis was initiated, creating an upper-arm native arteriovenous fistula. Unexpectedly, within few hours after the procedure, a hematoma expanded around the fistula. Laboratory results at that moment were suggestive of TMA (Fig. 4). Consequently, the patient was diagnosed with hemolytic-uremic syndrome (HUS). Following several daily PEX procedures, the patient suffered from aphasia, vision loss, somnolence and stupor; therefore, ICU admission was required. Brain CT scan showed a right parietal lobar hematoma with ipsilateral ventricle collapse and a minor left temporal.

Due to the high risk of cerebral hemorrhage while under PEX treatment, eculizumab was initiated (900 mg every week). Previous to treatment initiation, a single dose of meningococcal vaccine and prophylactic antibiotic were administered to prevent meningococcal infection. 48 h after the first dose of eculizumab, neurological symptoms dramatically improved. After the second dose renal function began to improve. Hemodialysis was discontinued after the third dose and hemolysis parameters had normalized at the fourth dose. Maintenance therapy of 1200 mg every 2 weeks was prescribed. After administration of only one bolus of cyclophosphamide (0.5 g/m^2) and low doses of steroids (10 mg/day) the patient did not present eosinophilia nor respiratory tract manifestations. Complete neurological recovery was achieved after 6 months and only residual abnormalities were detected on the CT scan. After 18 months of follow-up, hematological parameters were normal and the patient remained hemodialysis-free. (CCR of 25–30 mL/min).

Several months later, genetic analysis revealed a mutation in the complement factor H (CFH) gene. A risk polymorphism in CFH in heterozygosis: (c. 1231T > To; p. Ser411Thr) in exon 9, was detected. This mutation is not defined in the Exome Sequencing Project (ESP). This mutation implies the lost of signal in the exon 6 of CFHR1, and gain of signal in the exon 23 of CFH. This mutation confers a poor prognosis, since CFHR1 acts as a competitive antagonist of Factor H, and amplifies the degree of CFH's dysregulation.

Case report 2

A 52-year-old woman presented to the emergency of our hospital with complaint of cutaneous lesions in the feet and weakness in the arms and legs. Medical history was unknown. She had never smoked, and no

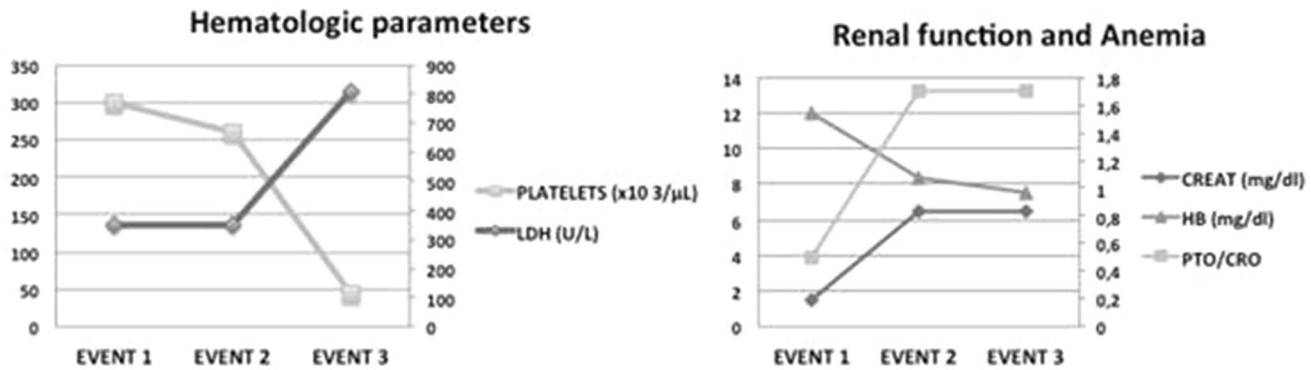

Fig. 4 Evolution of renal and hematologic parameters throughout the three episodes described. *Event 1*: No severe hemolytic and renal alterarations. *Event 2*: AKI + minor proteinuria. No hemolytic parameters. *Event 3*: Severe alteration of renal function (hemodialysis) and hemolysis

Table 1 Laboratory, image, microbiology, immunology and genetic results of both cases with diagnosis of vasculitis ANCA + (Churg–Strauss syndrome)

Vasculitis (CSS)	Case 1 (aHUS)	Case 2 (EGPA)
Main symptoms	Dyspnea + HTA + AKI + central neurological deficits	Cutaneous lesion + peripheral neurological deficits
Backgrounds	HTA + nasal polyposis + chronic sinusitis + asthma	Asthma
Hemoglobin (mg/dL)	7,5	12
Platelets (10^9 /L)	44	548
Eosinophils (10^8 /L)	3.79 (29%)	16.491 (69%)
LDH (U/L)	808	802
Schistocytosis	Positive	Negative
Tripthasa	–	19.8 (0–11)
Ig E (ku/L)	284	814
Coagulation	Normal	Normal
Immunology	Negative	PR3-, MPO +(1:98), ANA +(1:80)
Serology	Negative	Epstein Barr +
Stool culture	Negative	Negative
Chest X-ray	Pulmonary edema	Normal
Brain CT/EMG	Parietal and temporal lobar hematoma	Peripheral polyneuropathy
Biopsy	Kidney: diffuse interstitial eosinophilic infiltration + TMA features	Skin: dermatitis with abundant eosinophilic infiltration
Genetic study	CFH risk polymorphism (c. 1231T > To; p. Ser411Thr) (heterozygosis)	Mother: MCP (c.286 + 2T > G), CFI (c.1534 + 5G > T), CFH risk haplotype (homozygous) Daughter: MCP (c.286 + 2T), CFI CFH risk haplotype (homozygous)

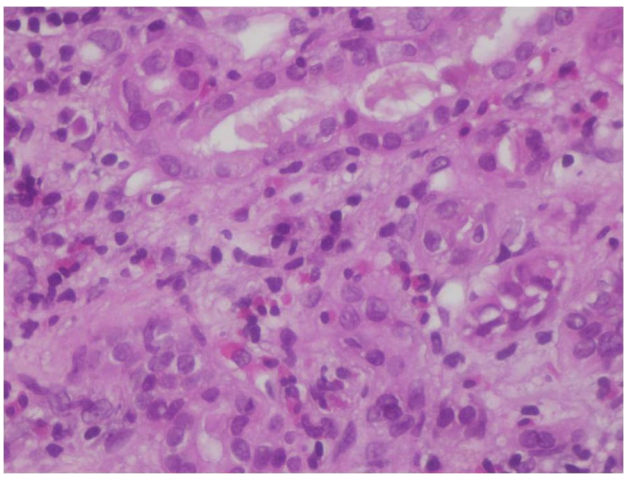

Fig. 5 Eosinophilic infiltration

arterial hypertension, dyslipidemia or diabetes mellitus was reported. She had chronic bronchial asthma, which was treated with bronchodilators and inhalatory steroids. A month after completion of steroid treatment for an asthma outbreak, the patient presented with blistering skin lesions in the sacral region that were considered and treated as Herpes zoster, resolving in around 1 week. Subsequently, she presented with symptoms of progressive weakness of the lower extremities, with paresthesia, dysesthesia and hypoesthesia. She was evaluated by a neurologist, who diagnosed sacral polyradiculoneuritis at L5–S1, of probable herpetic etiology. Because of this, treatment with oxcarbazepine was initiated, leading to progressive remission of the paresthesia and dysesthesia, but with persistence and progression of lower limbs' weakness. This created difficulties in ambulation and was also associated with asymmetrical distal upper limb weakness (predominantly in the left upper limb). The previous week, she noticed the appearance of new bullous of different size, tense and confluent or broken lesions in the dorsum of both feet and in the soles, which resembled those in the sacral region. During this period, she experience a weight lost of 10 kg. No other infectious processes, diarrhea or digestive or urinary alterations were reported.

At physical examination, the patient was in a good general state, although with a slight cutaneous-mucous paleness. She was normotensive, normohydrated, not dypsneic, with temperature of 37.2 °C. Neurological examination confirmed the symptoms reported by the patient. Laboratory analysis revealed hypereosinophilia, high levels of IgE, ANA and MPO antibiodies (PR3 negative). Also, IgG and IgM for EBV was positive. The rest of the analysis was otherwise normal (Table 1). Neuromuscular function was assessed by electromyography (EMG) and

electroneurography. Severe decreases in the motor and sensory amplitudes of the median, cubital and radial nerves in the right and left upper limb were detected. These were suggestive of diffuse, asymmetrical peripheral sensorimotor axonal neuropathy, corresponding to a polyneuropathic pattern.

Skin biopsy confirmed blistering dermatitis with abundant eosinophilic infiltration, compatible with Wells syndrome. IF was negative. Given the previous history and the presence of p-ANCA, while supportive but not necessary, a diagnosis of EGPA was established. Treatment with glucocorticoids and cyclophosphamide was started. In parallel, rehabilitation treatment was initiated, which led to a relative improvement and the patient could walk some steps with support. She was then discharged from the hospital.

There was a progressive improvement, with a maintenance treatment of cyclophosphamide and steroids, although difficulty in ambulation persisted, and the patient walked with a step-page gait and had symptoms of peripheral paresthesia and dysesthesia, mainly in feet.

1 year later, her daughter was diagnosed with aHUS. A genetic study showed that she carried a mutation in MCP (c.286 + 2T) and complement factor I genes. Besides, she was homozygous for the risk CFH haplotype. A genetic analysis of the mother (our patient in this case) revealed mutations in those same genes (Table 1) although she has never shown any symptoms suggestive of aHUS.

Discussion

Hemolytic uremic syndrome (HUS) is part of a spectrum of thrombotic microangiopathies [1]. The most common etiologies of HUS are the ones seen in childhood caused by an infection of Shiga toxin-producing *Escherichia coli*, those caused by an infection with *Streptococcus pneumoniae* and HUS due to abnormalities in the alternative pathway of the complement system [2]. The analysis of genes encoding for complement regulatory proteins is a valuable diagnostic tools in patients with HUS [15].

Regulators of the alternative complement pathway, such as CFH, CFI and MCP, play an important role in the pathogenesis of aHUS [15, 16]. Abnormalities in genes encoding these complement regulatory proteins have been reported. Based on these data, it has recently been suggested that aHUS patients probably have a specific genetic complement profile, which makes them vulnerable to develop aHUS, especially in the presence of certain triggers [17]. Examples of environmental triggers are infections, pregnancy, drugs, surgery or hematopoietic stem cell transplantation. The role of these environmental triggers deserves special attention. In an individual patient, it is impossible to discern if the underlying condition is the sole cause of aHUS. Thus, an evaluation of the complement system must always be considered in patients with otherwise 'explained' HUS [18].

We report two cases of EGPA. In the first case, the patient developed hemolytic anemia secondary to aHUS and a life-threatening hemorrhagic stroke. In this patient, it was difficult to assess the primary cause of renal failure. This could be either explained because of (a) TMA secondary to malignant hypertension or (b) aHUS, but with normal LDH levels and lack of schistocytes on the initial analysis. Malignant hypertension was the first contemplated diagnosis, considering that hemolysis intensity is higher in aHUS than in malignant hypertension. However, the presence of TMA features in renal biopsy led us to consider the diagnosis of aHUS. More so as up to 20% of cases could be subclinic (without hemolysis and thrombocytopenia), with a poorer prognosis. In this uncommon scenario, patients develop a silent chronic renal failure with progressively increasing proteinuria [1–4]. In this case, it is noteworthy that a second renal biopsy was suggestive of EGPA as a cause of renal failure. The absence of ANCA or fibrinoid necrosis of the artery does not exclude the diagnosis. In addition, only 10 days later, a dramatic aHUS flare occurred 48 h after vascular surgery. In our opinion, the patient had a progressive subclinical renal failure secondary to aHUS. Over this condition, an unknown environment factor triggered EGPA onset and probably the mean AKI cause in this case. Then, vascular surgery set off a near-fatal aHUS flare.

In the second case, a patient with a history of bronchial asthma, eosinophilia and peripheral neuropathy was admitted to the hospital due to skin lesions and loss of strength, predominantly distal, which impeded ambulation and standing. Her daughter was diagnosed with aHUS and genetic analysis revealed a pathogenic mutation in MCP in both mother and daughter.

Although several cases of hypereosinophilia and TMA have been reported [11–14], to date, very little evidence supports this association. However, a recent case published by Fukui et al. [19] describes a case with TMA and EGPA and TMA history has been reported in pediatric patients with aHUS [20]. Therefore, considering all the facts, it might be possible that a relationship between EGPA and aHUS exists. It may be that both entities share a genetic base and both diseases are manifested only when patients are exposed to certain environmental factors. Nevertheless, it is well described that a silent genetic alteration in the complement system may be manifested in the context of endothelial cell damage [17]. Both conditions could induce endothelial cell injury and the manifestation of aHUS: in the case of CSS, the discharge of eosinophil granule proteins may induce cell apoptosis and necrosis, producing vasculitis. However, we could miss other factors since, as

observed in clinical case 2, even in the presence of severe eosinophilia (1.6×10^8 /L) and genetic background that confers susceptibility, there is neither hemolysis nor kidney failure. In the case of vascular surgery, the damage would be direct.

Eculizumab is a monoclonal antibody that binds specifically to the complement protein C5, blocking the complement cascade and inhibiting the production of cell-killing protein complexes, which may modify the disease progression [17, 18]. Furthermore, in contrast to PEX, eculizumab treatment seems to be effective in aHUS regardless of the underlying complement mutation [17]. Despite plasma therapy is considered the standard treatment for aHUS, many do not respond [21]. No effect is expected in patients with a mutation in MCP [22, 23]. Based on the results of two recently published prospective open label phase 2 trials and a retrospective analysis of a cohort of treated children, eculizumab was approved for treatment of aHUS [24, 25]. The data suggest that the more rapid the initiation of therapy with eculizumab is, the greater the improvements in renal function; preferably within 1 week after disease onset [25]. Consequently, in a patient responding poorly to PEX therapy, eculizumab might be initiated [26–32]. In cases where diagnosis of aHUS is known at the time of acute presentation (previous mutation studies), first-line therapy with eculizumab should be considered in place of PEX [19, 21]. In our patient, eculizumab led to hemodialysis cessation even in the presence of severe and chronic lesions. Indeed, the patient remained with glomerular filtration above 20 mL/min after 18 months. Nevertheless, renal function recovery was not complete, probably due to delayed eculizumab introduction and presence of a mutation that confers a poor prognosis.

New drugs are under investigation in phase I and phase II trials. Some of them include anti-C5 antibodies (which are more purified, less immunogenic and absorbed orally) [33], and anti-C3 antibodies (which are more powerful, but potentially less safe). Additionally, infusions of recombinant complement-regulatory proteins are a potential future therapy [34].

In conclusion, aHUS and CSS are two rare diseases whose etiopathogeneses are thought to be different. Therefore, their co-existence should be exceptional. However, a genetic link might be plausible among patients suffering from both. Although very little evidence supports this association so far, our two cases are quite suggestive of this connection. It would be of great interest to report some similar cases in order to confirm or dismiss this possible relationship.

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Compliance with ethical standards

Availability of data and materials Not applicable.

Conflict of interest The authors declare not to have conflict of interest.

Ethics and consent to participate Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the editor.

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