Sweet's syndrome (acute febrile neutrophilic dermatosis): Report of two cases

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Sweet's syndrome is a self-limiting clinical entity of obscure etiology, with characteristic cutaneous manifestations and a very consistent histologic presentation. Two cases, characteristic of Sweet's syndrome, which occurred in a community hospital during a 12-month-period, are reported. Treatment with prednisone was curative. This entity is undoubtedly more common than currently recognized. The importance of its recognition is emphasized by its association with acute myelogenous leukemia in several reported cases.

In 1964, Robert Sweet[1] described what he believed to be a new, clinically distinct dermatologic entity involving the skin and having associated systemic manifestations, which he termed "acute febrile neutrophilic dermatosis." The chief features were polymorphonuclear leukocytosis, fever, painful raised plaques on the face, neck, and limbs, and histologic evidence of a dense infiltration of the dermis with mature neutrophils. He also described the absence of infection, and a rapid, complete response to corticosteroids.

Both Robinson[2] and Fuld[3] reported cases with similar cutaneous lesions. Fuld[3] suggested that this disorder merely represented a somewhat variable manifestation of hypersensitivity to allergens, and that it did not deserve recognition as a separate entity.

Since that initial report, acute febrile neutrophilic dermatosis has been recognized as a distinct and independent dermatologic entity[4] characterized by various combinations of cutaneous and systemic manifestations.[5] Because the dermatosis is not always acute or febrile, but always presents with characteristic skin lesions, the eponym of Sweet's syndrome is preferred.[5-7]

Sweet updated his observations in 1968[8] and again in 1979.[6] As of the 1979 update, only about one hundred cases had been reported in the world literature. The first reported case in the United States was presented by Shapiro and coauthors[9] in 1971. With Schiff's[10] report of two cases in 1982, there only have been 22 total cases reported in the American literature over an 11-year-period.

This article reports two further cases observed in a community hospital during a 12-month-period. This experience suggests that this entity is probably much more common than is currently noted in the literature.

Report of cases

Case 1

A 67-year-old, Caucasian woman was hospitalized in August 1980 with a rash of 2 days' duration and fever. The patient had first noted a few scattered lesions on her arms. These rapidly spread to encompass the entire body. Two days after the onset of the rash, a temperature of 103 F. developed, at which time her family doctor recommended admission to the hospital.

Examination at admission revealed multiple, discrete, elevated papules, some with associated pustules (Fig. 1). The lesions were noted on the trunk, arms, legs, and abdomen. No lesions were noted on the face at that time. The rash was described by the patient as being "painful," but not pruritic or tender to palpation. The patient was initially maintained on bed rest and given analgesics and anxiolytics.

On the second hospital day, dermatologic consultation was obtained. The lesions were red to reddish-purple papules and nodules, with pustule and vesicle formation on the surface of some of the lesions. The lesions were generalized in distribution, involving the face at that time.

There was much confusion concerning the diagnosis, and the initial differential diagnosis included: Weber-Christian disease, leukemia cutis, cutaneous lymphoma, Pseudomonas sepsis, dermatitis medicamentosa, leukocytoclastic vasculitis, or a manifestation of internal malignancy. Skin biopsy was obtained.

Laboratory data at the time of admission included a complete blood count, which indicated 13,300 leukocytes with a differential count of 14 stab cells, 71 segmented neutrophils, 11 lymphocytes, and 4 monocytes. The

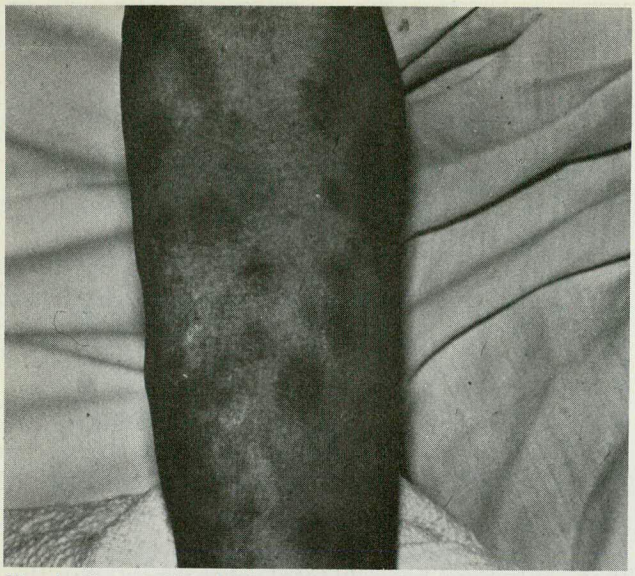


Fig. 1. *Case 1. Skin lesions, consisting of dull, red, elevated, erythematous nodules and plaques.*

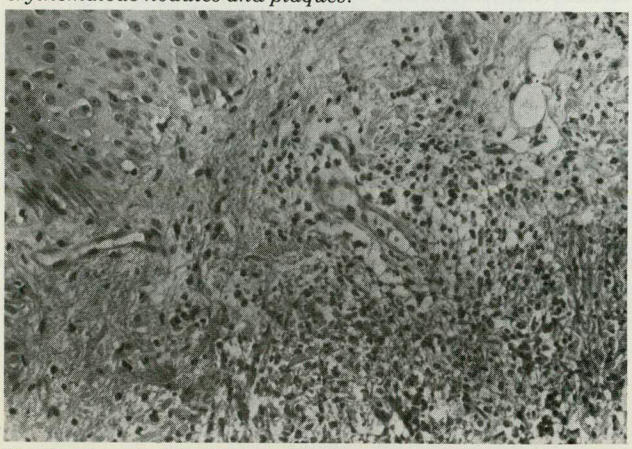


Fig. 2. *Case 1. Skin biopsy specimen shows heavy infiltrate of neutrophils in dermis with "nuclear dust," pronounced around blood vessels. Note subepidermal edema. Hematoxylin and eosin (H and E) stain. Original magnification, × 200.*

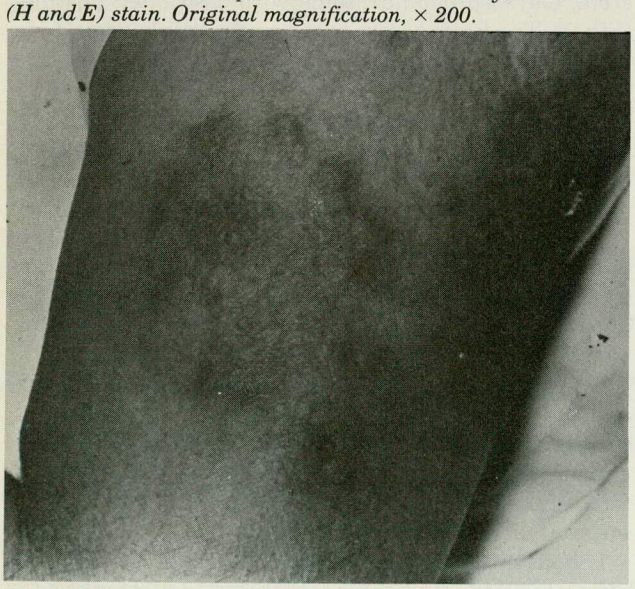


Fig. 3. *Case 2. View of lateral aspect of upper arm shows coalescent, erythematous plaques. (Eschar in lower portion of picture represents biopsy site.)*

platelet count was 379,000. Coagulation studies all yielded results within normal limits. The serum electrolyte studies indicated an abnormal sodium value of 131 mEq./liter and an abnormal potassium of 3.0 mEq./liter. Urinalysis indicated the following: 400 mg./dl. protein; a small amount of occult blood; 1-3 erythrocytes, 10-15 leukocytes, and 2-5 epithelial cells, and 3-5 hyaline casts per high-power field; and 2+ mucus. Gram's staining of the sputum and blood gave negative results. The admission chest x-ray film indicated pleural calcification with multiple pleural scars bilaterally and bilateral apical fibrosis consistent with a history of acid-fast mycobacterial disease. The electrocardiogram indicated a very old inferior wall myocardial infarction.

Further evaluation included throat, blood, urine, and sputum cultures, all of which yielded negative results. The antinuclear antibody titer was 1:20, and agglutination test for antibodies to DNA and a rheumatoid arthritis latex-fixation test were both negative. The sedimentation rate was 36 mm., corrected. Repeat platelet count indicated an increase to 441,000.

The skin biopsy indicated a multifocal acute dermal infiltration, predominantly neutrophilic, consistent with acute febrile neutrophilic dermatosis (Sweet's syndrome) (Fig. 2). The slides were sent to the Armed Forces Institute of Pathology, where a diagnosis of leukocytoclastic vasculitis, consistent with Sweet's syndrome, was determined.

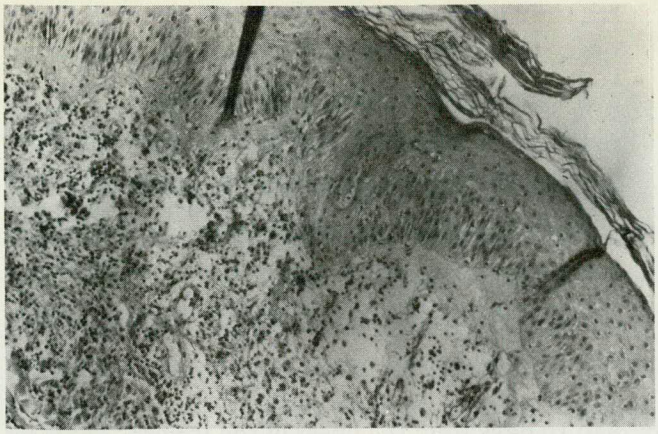
On the fifth hospital day, a course of oral prednisone 60 mg. per day in divided doses was begun. Both the skin lesions and the fever resolved rapidly. Repeat complete blood count indicated a decrease in the leukocyte count to 10,000 with a differential count of 4 stab cells, 75 segmented neutrophils, 12 lymphocytes, 7 monocytes, and 2 eosinophils. Followup showed that the electrolyte and urinary abnormalities evident at admission had resolved. The patient remained afebrile, and was discharged on a tapering dose schedule of oral prednisone.

No recurrence of lesions has been noted during a 12-month followup period, and subsequent complete blood counts and platelet evaluations have indicated no abnormalities.

Case 2

A 49-year-old, Caucasian woman was admitted through the emergency room in August 1981, with a burning kind of skin rash of 7 days' duration. The patient's temperature at the time of presentation was 103 F. The patient had seen her family doctor 10 days and again 2 days prior to admission, with a chief complaint of a severe burning sensation over her arms and legs. Small, erythematous lesions developed, which progressed to large, erythematous plaques with tiny vesicles on the surface (Fig. 3). She had had an upper respiratory tract infection 3 weeks previously. Most of those symptoms had resolved 1 week prior to the development of the burning sensation, but she still complained of the symptoms of conjunctivitis.

Examination at the time of admission revealed erythematous, vesicular, raised lesions on the upper arms, the hands, and the legs. No lesions were noted on



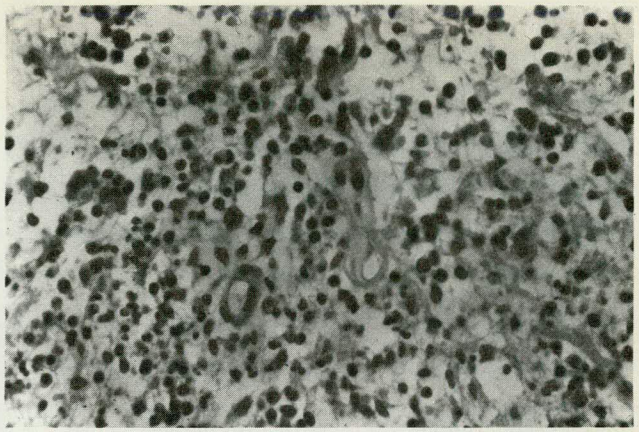


Fig. 4. *Case 2. Skin specimen shows spongiosis, subepidermal edema, and leukocytoclastic neutrophilic infiltration of dermis. H and E stain. Original magnification × 100.* Fig. 5. *Skin specimen demonstrating leukocytoclastic perivasculitis. H and E stain. Original magnification × 400.*

the trunk. A bilateral conjunctivitis was also observed.

Laboratory data at admission indicated a leukocyte count of 14,300 with a differential count of 7 stab cells, 73 segmented neutrophils, 13 lymphocytes, 5 monocytes, and 2 eosinophils. There were 560,000 platelets. The serum electrolyte studies indicated an abnormal sodium value of 132 mEq./liter and an abnormal potassium value of 3.4 mEq./liter. Coagulation values were all within normal limits. Urinalysis indicated occult blood by dipstick evaluation, 10-15 erythrocytes and 10-15 leukocytes per high-power field, occasional epithelial cells, 1+ bacteria, 3+ mucus and 3-5 glitter cells. Gram's staining of a lesion indicated numerous leukocytes but no bacteria were seen. A chest x-ray film indicated a postinflammatory calcification in the right lower lung and hyperinflation of the lung fields bilaterally. The electrocardiogram was reported as normal.

The patient was initially placed on a regimen of broad-spectrum antibiotics, antihistamines, and analgesics. Dermatology consultation was obtained on the second hospital day. The lesions at that time were described as multiple, raised, red plaques with vesicles and tense blisters with surrounding erythema. The lesions had the same distribution as previously described and were reported by the patient to be tender and to have a burning quality.

Differential diagnosis at this time included the following: drug eruption, bullous pemphigoid, bullous erythema multiforme, and acute febrile neutrophilic dermatosis (Sweet's syndrome). A biopsy of a lesion was performed at that time and the patient was continued on symptomatic treatment. The skin lesions remained essentially unchanged and the patient remained febrile.

Further evaluation during the course of the hospitalization included the following: negative results for febrile agglutinin and antinuclear antibody tests, a streptozyme reagent test with a positive agglutination reaction (>166) and a follow-up antistreptolysin O titer with a value of 625 T.U. (range, 12-2,500 T.U.). Culture and sensitivity testing of a skin lesion indicated coagulase-negative Staphylococcus. A repeat complete blood count indicated 11,700 leukocytes with a differential count of 83 segmented neutrophils, 16 lymphocytes, and 1 monocyte. The repeat platelet count indicated an increase of 678,000 platelets. The skin biopsy report indicated a diagnosis of small vessel leukocytoclastic vasculitis consistent with Sweet's syndrome (acute febrile neutrophilic dermatosis) (Figs. 4 and 5). A course of oral prednisone 60 mg./day in divided doses was begun on the fourth hospital day. The patient showed immediate improvement with resolution of the skin lesions and a decrease in temperature. The patient was discharged on the eighth hospital day on a tapering dose of oral prednisone.

The skin lesions resolved over a period of time and there has been no recurrence of the lesions at the time of this writing. Repeat laboratory evaluations, which have included complete blood and platelet counts, have revealed no abnormalities to date. In light of the marked thrombocytosis during the course of the hospitalization, this patient is to be observed closely for subsequent development of a leukemic state. At 16 months following discharge, there has been no recurrence.

Review of the literature

Etiology

The etiology of Sweet's syndrome remains obscure. There has been no consistently present antecedent event. However, the majority of patients have had some preceding disturbance, usually infective in nature, occurring approximately 1 to 4 weeks prior to the onset of symptoms.[5,9,12] The most commonly associated infection has been a respiratory tract infection, not attributable to any specific organism. In view of this association, many authors[13] believe that Sweet's syndrome is perhaps best considered a hypersensitivity reaction to an as yet undetermined antigenic stimulus.

Sweet's syndrome has been associated with acute myelogenous leukemia in several recently

TABLE 1. LABORATORY INVESTIGATIONS ROUTINELY NEGATIVE.

Serum electrolytes	Blood glucose
Blood urea nitrogen	Creatinine
Calcium	Uric acid
Phosphorus	Total bilirubin
Alkaline phosphatase	Lactic dehydrogenase, serum glutamic-oxalocetic and glutamic-pyruvic transaminases
Rheumatoid factor	Cold agglutinins
Venereal Disease Research Laboratory	LE preparations
Antinuclear antibody	Serum protein electrophoresis
Febrile agglutinins	
Blood, urine, throat, skin cultures	

TABLE 2. CONSIDERATIONS IN THE DIFFERENTIAL DIAGNOSIS OF SWEET'S SYNDROME.

Erythema multiforme (atypical)	Dermatitis medicamentosa
Erythema elevatum diutinum	Cutaneous lymphoma
Pyoderma gangrenosum (early)	Erythema nodosum
Bromide or iodide eruption	Lymphangitis
Allergic vasculitis	Cellulitis
Allergic reaction	Erysipelas
Systemic lupus	Leprosy
Panniculitis	Septicemia
Leukocytoclastic angiitis	Dermatomyositis
	Granuloma faciale
	Leukemia cutis
	Viral exanthem

reported cases.[10,14,16] According to Soderstrom,[11] the association has been evident in nearly 10 percent of cases reported. This suggests that the syndrome may be part of a complex of skin lesions associated with leukemias.[14]

Age and sex

This illness predominates in middle-aged women (the mean age being 49 years), who constitute approximately 80-90 percent of patients previously reported in the world literature.[5] Of the 22 cases reported in the United States, 10 have been male and 12 female. The two additional case reports in this article both involved a female. The significance of this propensity for females is not known.[17]

Extracutaneous features

The clinical presentation of Sweet's syndrome shows considerable variability in duration and severity; however, the pattern apparent in most cases is that of a febrile patient who appears acutely ill, with unusual, painful skin eruptions, neutrophilia, an elevated erythrocyte sedimentation rate and thus, a concern for a potentially septic state. Characteristically, viral and bacteriologic investigations, including bacterial cultures and Gram's staining, are unsuccessful in documenting infection, and a trial of antibiotics produces no effects.[18,19]

Although not all cases presenting with typical skin lesions are febrile,[6,15] fever at some time during the course of the disease is highly characteristic.[5,6] The fever most often precedes the skin eruption by several days,[9] tends to be persistent, ranges between 100-102 F., and is usually higher in the evening.[5]

Gunawardena and coworkers[5] have drawn attention to the frequent involvement of the eyes and the musculoskeletal system. The eye signs of conjunctivitis and episcleritis appeared within the first 10 days of the illness and usually followed the skin lesions by 1 to 6 days.[5] Migratory polyarthralgia, with a tendency toward asymmetry, involving all major joints and generalized myalgia developed 2 to 10 days from the onset of the illness.[5]

Cutaneous lesions

The cutaneous lesions are characteristic.[13,20] They are well defined, dull red, elevated, painful, edematous, and erythematous nodules and plaques, which tend to coalesce (Figs. 1 and 3). Considerable variation in size, ranging from 0.5 to 4.0 cm. in greatest diameter, has been reported.[1,21]

The eruption occurs acutely or episodically[14] and the lesions usually appear between 2 and 7 days from the onset of the illness. Fresh lesions continue to appear, and older lesions enlarge slowly and irregularly, becoming confluent. Partial central clearing may occur, resulting in target-like lesions. Vesicles or small sterile pustules may appear on the surface of the lesions.[12,21] The end result of the presentation of the lesions has been likened to the appearance of a relief map of a mountain range.[20]

The lesions, though usually bilateral, appear asymmetrically and centrifugally. They can involve any part of the body, but most commonly occur on the extensor aspects of the upper extremities, the face, the neck, and the lower extremities. Lesions seldom involve the trunk from the lower chest to the thighs.[5,12]

An essential aspect of the manifestations of the cutaneous lesions is the absence of subsequent scarring. There are no cases reported in the literature in which residual scarring occurred after resolution of the lesions. Occasionally, a reddish-brown discoloration, attributable to hemosiderin deposition, remains after resolution.[13]

Laboratory features

The charactertistic laboratory findings in Sweet's syndrome are an elevated leukocyte count with a neutrophil polymorphonuclear leukocytosis (80-86 percent), [11,12,22] which usually follows the skin lesions by several days,[8] and a moderately elevated erythrocyte sedimentation rate.[1] Other frequent observations include proteinuria with or without

microscopic hematuria,[16] transient albuminuria[1,5], and anemia.[16] Table 1 lists those additional laboratory evaluations that have been repeatedly performed and have been routinely negative.

Histologic appearance

The characteristic cutaneous lesion in Sweet's syndrome, histologically, is the presence of a massive dermal infiltrate composed of mature neutrophils. This neutrophilic infiltration is most pronounced perivascularly, and blood vessels in the dermis exhibit endothelial swelling.[20] The entire thickness of the dermis may be involved, as well as subcutaneous structures. Subepidermal edema may be prominent and may progress to the formation of subepidermal vesicles.

Another characteristic feature is the presence of "nuclear dust,"[20] or leukocytoclasis. Sweet's syndrome is, therefore, classified as one of the small-vessel leukocytoclastic vasculitides.[23]

The concentration of neutrophils in a particular site may mimic the appearance of a microabscess. Although fibrin microthrombi may be present in small vessels, the fibrinoid necrosis of collagen, characteristic of collagen vascular disease, is not present.

The epidermis is relatively well preserved. There may be parakeratosis or crusting. There also may be spongiosis and the presence of a few infiltrating neutrophils. In many areas of a biopsy specimen, however, the epidermis may be normal.[5,20]

Differential diagnosis

On histologic grounds, the differential diagnoses include granuloma faciale and erythema elevatum diutinum, both of which are characterized by small-vessel leukocytoclastic vasculitis.[13] These two conditions, however, differ from Sweet's syndrome on clinical grounds.

The clinical spectrum of Sweet's syndrome is varied, and it may cause considerable diagnostic problems. This condition may be easily confused with a large number of other disease states, as listed in Table 2. In general, Sweet's syndrome may be considered part of those disease entities with a vascular reaction pattern.[7]

Four criteria were suggested by Gunawardena and coworkers[5] to be used to differentiate Sweet's syndrome: (1) The cutaneous lesions have the characteristic morphologic features noted by Crow and associates;[20] (2) the disease fails to respond to antibiotics, but improves rapidly with systemic corticosteroids; (3) the lesions resolve completely without subsequent scarring; and (4) histologic study shows dermal edema and a perivascular inflammatory infiltrate especially in the upper and mid dermis, the cell type varying among mature polymorphonuclear leukocytes, lymphocytes, and other inflammatory cells. No changes in vessel walls or connective tissue are demonstrable.

Course of disease

The duration of the illness varies with the severity. In Sweet's[1] original description, the duration of the lesions ranged from 6 weeks to 6 months, and subsequent studies[12] have confirmed this range. Untreated, most cases undergo spontaneous resolution within 6 to 8 weeks.[12] In approximately one third of all reported cases, a tendency for recurrence has been described.[12,13]

Therapy

A remarkable diagnostic feature of the syndrome is the response to systemic steroids, with an abrupt termination of symptoms. Prednisone, 30-60 mg. per day in divided doses, is recommended for initial treatment.[5,13,22] Administration of the steroid may have to continue for weeks to months, and the dose should be tapered very gradually since numerous reports indicate that a rapid reduction is associated with exacerbations and recurrence of lesions.[9,18,20,22] Treatment with steroids is curative.[1,22]

Although corticosteroids have been the mainstay of therapy, other treatment modalities have been reported to achieve success apparently comparable to that with steroids. Hoffman[24] reported dramatic improvement using indomethacin, 50 mg. initially, followed by 25 mg. four times a day and then gradually tapering the dose over a 3-month-period. Jacyk[25] reported resolution of symptoms over a 3-week-period utilizing only aspirin (500 mg.), six tablets daily for a 5-day-period. Most recently, Horio and coworkers[4] achieved excellent results with potassium iodide, 900 mg. per day, administered systemically. The potassium iodide regimen was begun shortly after the initial onset of symptoms, and was continued for approximately 2 weeks.

Comment

The diagnosis of Sweet's syndrome can be made easily from the distinctive clinical appearance of the lesions, coupled with the characteristic histologic features. It is recommended that a skin biopsy be considered routine in the evaluation of any patient with clinical findings suggestive of Sweet's syndrome.

There has been a significant association of Sweet's syndrome with acute myelogenous leukemia. The diagnosis of Sweet's syndrome should

prompt the clinician to proceed with a complete hematologic evaluation.

The two patients in the cases reported here had the well defined, typical clinical and histologic features of Sweet's syndrome. The cases throw no additional light on the etiology of this syndrome. Treatment was accomplished with systemic corticosteroids, and excellent results were obtained. Subsequent evaluation of the two patients has indicated no recurrence of the skin lesions and no hematologic abnormalities associated with a leukemic process.

Many questions remain unanswered concerning Sweet's syndrome. Is it a hypersensitivity reaction or a preleukemic state? What is the significance of the predominance of the disease in women? What is the most appropriate treatment modality?

It is the contention of this article that this syndrome is more common than is apparent from the number of reported cases. The scarcity of reports is most likely due to misdiagnosis.

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