Scleromyxedema associated with IgG lambda multiple myeloma[1]

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Scleromyxedema (papular mucinosis) is a rare disorder characterized by proliferation of fibroblasts and cutaneous deposition of acid mucopolysaccharides, usually without disturbances of thyroid function. Associated abnormal proteins in the serum, identified as paraproteins, are a main feature of this disease. The association of scleromyxedema with classicial plasmacytoma or multiple myeloma is extremely rare. We report a case of scleromyxedema associated with multiple myeloma of the IgG lambda type.

Index terms: Myeloma • Scleromyxedema • Skin, diseases
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Scleromyxedema[1] (generalized lichen myxedematosus) is a rare variant of papular mucinosis characterized clinically by generalized waxy papules and marked cutaneous induration of the skin involving the arms, chest, and face. Histologically, there is cutaneous deposition of mucin, specifically hyaluronic acid, in the superficial dermis. In the diffusely thickened skin, one finds extensive proliferation of large, stellate, elongated fibroblasts in the dermis associated with irregularly arranged bundles of collagen. Most patients with this disorder have a monoclonal serum protein that is extremely cationic and of the IgG lambda type.[2–4] Immunochemical studies have shown that this paraprotein is an incomplete IgG molecule that is missing a significant antigenic portion of the Fd fragment.[5,6] Many patients with scleromyxedema have been followed for years without evidence of developing multiple myeloma.

We present the first case of scleromyxedema associated with classic multiple myeloma in the English literature.

Case report

An 83-year-old black woman, referred to the Cleveland Clinic in June 1981, gave a history of pruritus and swelling of the skin on her forearms, which had extended cephalad to her arms, shoulders, and face since April 1980. She complained of "hardness and bumps" in all affected areas and gradual diffuse loss of scalp hair. There was no associated pain. Laboratory examination during a hospitalization in January 1981 had revealed a monoclonal spike on serum protein electrophoresis and a marked plasmacytosis of the bone marrow, which had persisted unchanged from 1976, at which time a diagnosis of benign monoclonal gammopathy had been made. A skin biopsy in January 1981 revealed nonspecific changes with evidence of dermal fibrosis.

Other medical problems included hypothyroidism, diagnosed in 1978, treated with levothyroxine (Synthroid), 0.1 mg daily; bilateral cataracts; arthritis limited to the hands; hypertension; and cardiac arrthythmias. An ovarian tumor had been removed in 1941.

On physical examination, she had erythematous induration, hyperpigmentation, and densely grouped papules, giving a pebbly appearance and cobblestonelike texture to the face, arms, and chest. Patchy nonscarring alopecia of the scalp and eyebrows was present. Pupils were anisocoric and the right lens was opaque. Examination of the chest revealed grade II/VI systolic murmur at the left sternal border. The remainder of the physical examination was unremarkable.

The laboratory and diagnostic studies were performed in June 1981. The electrocardiogram (ECG) demonstrated a left anterior hemiblock and a first degree atrioventricular block. The chest roentgenogram showed moderate cardiomegaly, with a left ventricular prominence. The skull roentgenogram demonstrated mild hyperostosis frontalis interna without fractures or bone destruction; however, the sella

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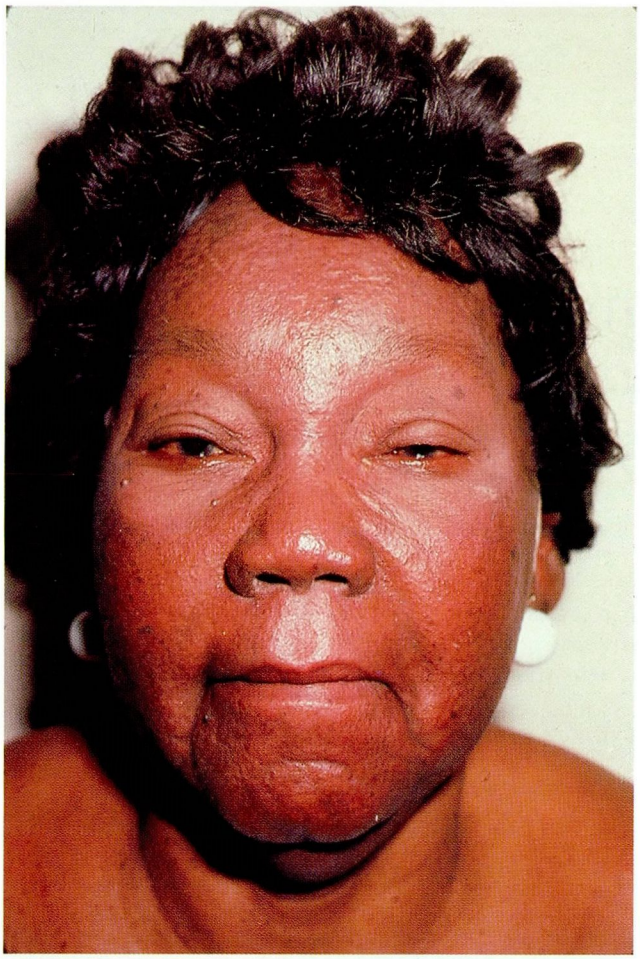

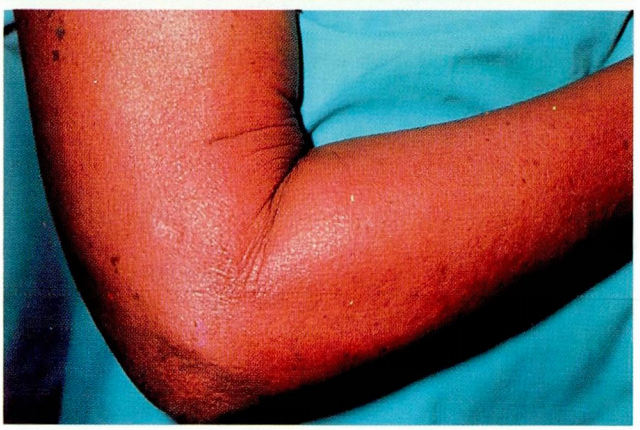

Figure 1. Erythematous induration, hyperpigmentation, densely grouped papules with furrowing of the glabella, producing a saddened appearance.

Figure 2. Erythematous induration, hyperpigmentation, and densely grouped papules give the skin a cobblestonelike texture.

turcica and acoustic meati were normal. The skeletal survey demonstrated scattered hypertrophic changes. A computed tomography (CT) scan of the orbits was normal. The SMA-18 biochemical profile demonstrated a decreased albumin of 3.0 mg/dl (normal, 3.5 to 5.0 mg/dl), decreased calcium of 8.2 mEq (normal, 9.0 to 10.5 mEq), and an increased

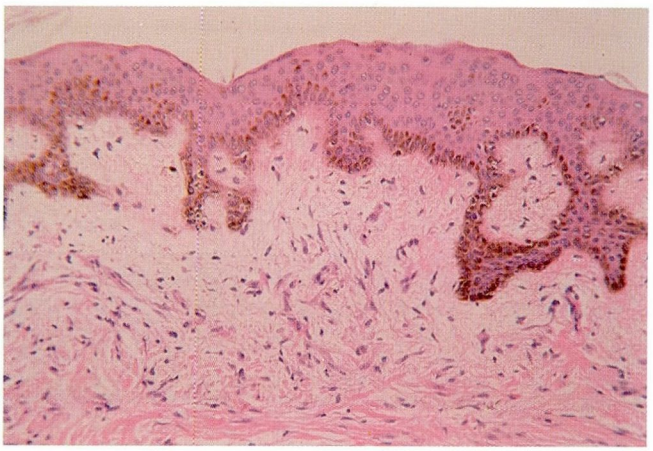

Figure 3. Skin biopsy from the arm. The epidermis is normal; note increased fibroplasia and vacuolization between collagen bundles in the upper dermis.

cholesterol of 267 mg/dl (normal, 150 to 240 mg/dl). The hemoglobin was 11.9 g/dl, hematocrit 36.2%, white blood cell count 7,200, with 63 polymorphonuclear leukocytes, 6 bands, 24 lymphocytes, 5 monocytes, 1 eosinophil, and 1 basophil. The platelet count was 197,000/mm^3. The urinalysis demonstrated 3–5 white blood cells per high power field with no red cells, glucose, or protein. RPR serology was negative.

The following studies were normal or negative: prothrombin time, partial thromboplastin time, thyroxine (T4) and thyroid stimulating hormone (TSH), rheumatoid factor, C1q binding, 24-hour urine for protein and creatinine, and stool for occult blood on two occasions. The antinuclear antibody titre was 1:180, C-reactive protein was 4.0 mg/dl (normal, less than 2.88 g/dl). The Westergren sedimentation rate was elevated at 100 mm/hr. The serum protein electrophoresis demonstrated a spike in the gamma region, and quantitative immunoglobulins demonstrated elevated IgG of 3036 mg/dl (normal, 604 to 1572 mg/dl $\bar{X}$ = 1033 mg/dl). IgA was 92 mg/dl (normal, 50–491 $\bar{X}$ = 214 mg/dl). IgM was 103 mg/dl (normal, 38–380 mg/dl $\bar{X}$ = 179 mg/dl). Myeloma typing was consistent with monoclonal gammopathy of the IgG type. The urine Bence Jones protein showed a small amount of urinary protein migrating over the whole electrophoretic spectrum. Bone marrow aspiration and biopsy showed 33% plasma cells and 6% immature plasma cells consistent with plasmacytosis. Atypical trinucleate forms were observed (*Fig. 5*). The interpretation of the bone marrow biopsy was consistent with plasma cell myeloma. Staining with crystal violet and Congo red demonstrated amyloid in the small vessels of the bone marrow.

Skin biopsies from the left arm demonstrated normal epithelium. Within the superficial and mid-reticular dermis were prominent increased fibroplasia and vacuolization between the collagen bundles. Colloidal iron and digested colloidal iron stains demonstrated increased hyaluronic acid within the dermal connective tissue. There was no evidence of amyloid by crystal violet or Congo red stains.

A diagnosis of scleromyxedema associated with multiple myeloma was made. The patient was treated with Hytone cream (hydrocortisone), 2.5% to her face, axilla, and groin. She was instructed to apply Topicort cream (desoximetasone), 0.25% to the involved areas of her trunk and extrem-

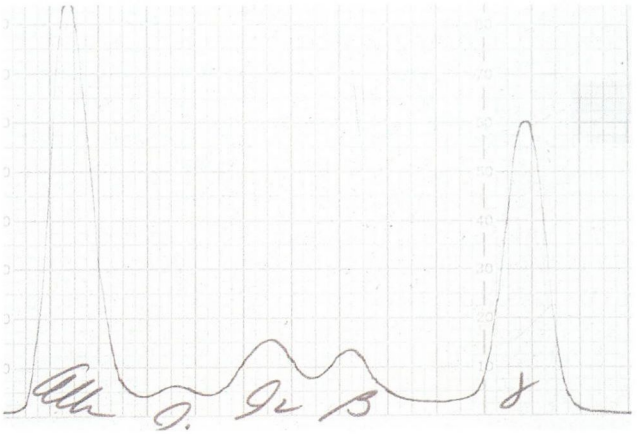

Figure 4. Serum protein electrophoresis demonstrates a spike or peak in the gamma region.

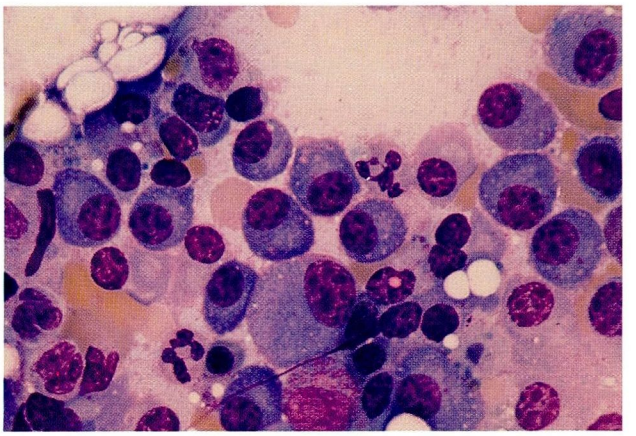

Figure 5. Bone marrow smear demonstrates plasmacytosis and immature and atypical trinucleate forms.

ities twice daily. Atarax (hydroxyzine) was given to control pruritus. No treatment was instituted for multiple myeloma since the patient was asymptomatic, clinically stable with normal calcium, and had no evidence of abnormal renal function. This indicated a low tumor burden.

In October 1981, several months after hospital discharge, her skin had become asymptomatic; however, she experienced excruciating low back pain, prostration, and a weight loss of 30–40 pounds. Examination at another hospital at this time demonstrated increased plasmacytosis of the bone marrow and areas of increased uptake in the T4 and T10 costochondral junctions bilaterally on bone scan. Roentgenograms of the thoracic spine demonstrated several compression fractures. No metastatic or osteolytic lesions were seen.

A diagnosis of progression of multiple myeloma was made, and combination chemotherapy with melphalan, cyclophosphamide, prednisone, fluoxymesterone, and vincristine sulfate was instituted. Clinical improvement was significant, with decreased musculoskeletal pain and near complete resolution of the skin changes and hyperpigmentation.

Discussion

Scleromyxedema (synonyms: papular mucinosis, generalized lichen myxedematosus, lichen fibromucinidosus, nodular diffuse scleroderma, myxodermis, and mucinothesaurosis) is a rare disease usually characterized by (1) infiltrated skin lesions formed by the deposition of mucinous material in the dermis, (2) demonstration of a monoclonal serum protein of cathodal mobility, and (3) the absence of thyroid dysfunction. One case of lichen myxedematosus was reported in a patient whose thyroid function showed myxedema[8] and in one patient who underwent thyroidectomy for treatment of thyrotoxicosis.[9] Nagy et al[10] described Hashimoto's thyroiditis in a patient with scleromyxedema.

The clinical manifestations are variable, and several types have been described by Perry et al[11]: (1) generalized lichenoid eruption with discrete papules over the entire body, especially the hands, forearm, upper part of the trunk, face, and neck; (2) a discrete papular eruption on the trunk and extremities; (3) localized or generalized lichenoid papules over the body; and (4) urticarial plaques and nodular eruptions.[11] The confluent papular and sclerotic form was described by Gottron[1] as scleromyxedema.

The histologic examination of the skin shows accumulation of acid mucopolysaccharides in the upper third of the dermis in association with large, stellate, elongated fibroblasts. The increased mucopolysaccharide content is primarily hyaluronic acid. Reliable techniques to determine this mucopolysaccharide deposition are the Alcian blue stain, either alone or in combination with PAS, and the colloidal iron method.[7] Electron microscopic examination confirms the impression of increased ground substance and fibroblasts given by light microscopic examination.[12] Immunofluorescent studies of the skin demonstrate IgG in some instances,[3,8,13,14] but not in others.[8,15–17] In one patient, IgG was synthesized in the tissue cultures of the skin fibroblasts despite negative immunofluorescence.[8,17] The majority of patients have the M component of the IgG class.[8,18] The light chain of the lambda type is far more common than the kappa type.[8] Other M components reported have been of the IgA[8,19] and IgM classes.[8,18] The usual electrophoretic mobility is a slow gamma with rare mid-gamma and beta patterns of migration.[8] Total serum protein values are usually normal. Results of urinalysis, values for hemoglobin level, leukocytes, platelet count, and sedimentation rate are usually normal.[8] Bone marrow studies may show a mild plasmacytic infiltration.[8] In two patients

Table 1. Clinical manifestations of multiple myeloma

Bone involvement-osteolysis due to OAF: * pain; pathologic fractures, hypercalcemia
Anemia-decreased RBC production plus mild hemolysis
Renal failure due to calcium nephropathy, L chains, uric acid amyloid, infection, proteinuria (hypertension is rare), uremia; occasionally acute, oliguric renal failure
Recurrent infections-especially respiratory
Amyloidosis (develops in about 15% of cases)
Plasmacytomas
Rare paraprotein-associated syndromes-hyperviscosity syndrome, cryoglobulinemia, hyperlipoproteinemia
Hemorrhagic diatheses
Very high erythrocyte sedimentation rate and rouleaux formation on blood smear (with serum M-component)

Table 1 is reproduced with permission from Cecil.[26]
* *Osteolysis activating factor.*

with normal bone marrows, the bone marrows synthesized the M component in vitro.[8,15,17] Radiologic surveys of the skeleton yield normal findings. Associated diseases have included dermatomyositis,[8,10,20] amyloidosis,[8,21] pachydermoperiostosis,[3,8] coronary artery disease[2,7,8] and cerebrovascular accident,[2,7,8] herpetic encephalitis,[22] and meningioma.[22] Four cases of lichen myxedematosus or scleromyxedema associated with multiple myeloma have appeared in the literature to date.[20,23–25] An additional case has been reviewed, and in retrospect, the bone marrow of the patient at the time failed to provide sufficient changes to substantiate the diagnosis of multiple myeloma based on present day criteria.[8,1]

Multiple myeloma (plasma cell myeloma) is a disseminated malignant disease in which a clone of transformed plasma cells proliferates in the bone marrow, disrupting its normal function as well as invading the adjacent bone. The disease is frequently associated with extensive skeletal destruction, hypercalcemia, anemia, impaired renal function, immunodeficiency, and increased susceptibility to infection; and occasionally associated with amyloidosis, clotting disorders, and other plasma abnormalities. The neoplastic plasma cells usually produce or secrete M component immunoglobulins, the amount of which in any given case varies proportionally with the total body tumor burden.[26] The clinical manifestations of multiple myeloma are summarized in *Table 1*. Clinical staging is useful in projecting the prognosis for individual patients and for deciding on the approach and intensity of therapy (*Table 2*).

Table 2. Myeloma staging system

Stage	Criteria	Measured myeloma cell mass (cells, $10^{12}/m^2$)
I.	All of the following:	<0.6 (low)
	1. Hemoglobin value >10 g/dl	
	2. Serum calcium value (≤12 mg/dl)	
	3. On x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only	
	4. Low M-component production rates	
	a. IgG value <5 g/dl	
	b. IgA value <3 g/dl	
	c. Urine L chain M-component on electrophoresis <4g/24 hours	
II.	Fitting neither Stage I nor Stage III	0.06–1.20 (intermediate)
III.	One or more of the following:	>1.20 (high)
	1. Hemoglobin value <8.5 g/dl	
	2. Serum calcium value >12 mg/dl	
	3. Advanced lytic bone lesions (scale 3)	
	4. High M-component production rates	
	a. IgG value >7 g/dl	
	b. IgA value >5 g/dl	
	c. Urine L chain M-component on electrophoresis >12 g/24 hours	
Subclassification:		
A = Relatively normal renal function (serum creatinine value <2.0 mg/dl)		
B = Abnormal renal function (serum creatinine value ≤2.0 mg/dl)		
Examples:		
Stage IA = Low cell mass with normal renal function		
Stage IIIB = High cell mass with abnormal renal function		

Reprinted with permission from Durie and Salmon.[28]

Table 3. Scleromyxedema with documented multiple myeloma

	Sex/age at time of diagnosis	Date of diagnosis	Paraprotein	Associated clinical or autopsy findings	Clinical stage of MM	Treatment
Proppe et al[21] 1969 (German)	M/49	1969	Not performed	Cardiovascular disease	?	Not recorded
Bataille et al[23] 1978 (French)	F/64	1974	IgG/lambda	Ichthyosis, amyloid (skin) cerebral vascular bulbar accident	IIA-IIIA	Melphalan
Schnyder and Kaufmann[24] 1979 (German)	F/68	1976	IgG/kappa	Osteolytic lesions on skull	?	Melphalan Prednisone
Krebs and Müller[25] 1980 (Swiss)	M/64	1977	IgG/kappa	...	...	Melphalan Prednisone Cyclophosphamide Vincristine
Muldrow and Bailin (1983) (American)	F/83	1980	IgG/lambda	Hypothyroidism amyloid (in bone marrow blood vessels)	IA	Melphalan Prednisone Cyclophosphamide Vincristine Fluoxymesterone
Perry* et al[11] 1960	M/53	1957	Not performed	...	?	Mechlorethalamine Hydrochloride Urethane

* Case initially reported as scleromyxedema associated with multiple myeloma not substantiated by later review of case and histology of bone marrow.
MM = multiple myeloma.

In a study of 241 cases of monoclonal gammopathy without evidence of multiple myeloma, macroglobulinemia, amyloidosis, or lymphoma followed for five years, 27 patients (11%) developed multiple myeloma, macroglobulinemia, or amyloidosis.[27] Six cases (including ours) of lichen myxedematosus or scleromyxedema with multiple myeloma have been reported in the literature (*Table 3*).

The patient observed by Proppe et al[21] died after three years with a suspected diagnosis of plasmacytoma associated with scleromyxedema. The autopsy showed a diffuse plasmacytoma with amorphous and crystalline protein deposits between the spongiosa of the thoracic vertebra and in the compact bone of the periosteum. Diffuse congophilic deposits in almost all organs; especially the arterial walls of the lung, spleen, small intestine, kidney, adrenal, and skin; were noted. Diffuse plasma infiltrates were present in the bone marrow and spleen; however, the percentage of plasma cell infiltration in the bone marrow was not mentioned.

Bataille et al[23] described a 64-year-old woman with papular mucinosis associated with ichthyosis and multiple myeloma. The paraprotein was of the IgG lambda type. The patient died after an illness of 33 months of pancytopenia induced by melphalan therapy.

Schnyder and Kaufmann[24] described a 72-year-old woman who developed scleromyxedema at age 68. Examination by an internist showed a plasmacytoma of the IgG kappa type paraproteinemia, atypical plasma cells in the bone marrow, and numerous "cherry"-sized osteolytic defects in the skull. Therapy with melphalan (Alkeran) and prednisone did not improve the condition.

Krebs and Müller[25] described lichen myxedematosus and multiple myeloma of the IgG kappa type in a 60-year-old man. Specifically, they identified characteristics that indicated a true myeloma (myeloma with high tumor mass), which include anemia, plasmacytosis of the bone marrow, and Bence Jones kappa and IgG kappa paraproteins in the urine.

Our patient, an 83-year-old black woman, presented with a history of long-standing benign monoclonal gammopathy and cutaneous involvement, originally diagnosed as nonspecific dermatitis and, subsequently, scleromyxedema. She had a history of hypothyroidism and was receiv-

ing thyroid supplementation. Consultation with the Department of Hematology and Medical Oncology supported the diagnosis of multiple myeloma of the low tumor burden variety in our patient. According to the myeloma staging system of Durie and Salmon,[28] our patient had stage IA disease and, therefore, a favorable prognosis. This also corresponds to the "indolent form"[29,30] of multiple myeloma, which can exist relatively asymptomatically for several years. Treatment is indicated only if the patient experiences major morbidity, changes in the level of myeloma protein and hemoglobin, and bone lesions develop, specifically, compression fractures of the vertebra or recurrent infections. Our patient became increasingly symptomatic from the multiple myeloma with roentgenographic evidence of osteoporosis with compression fractures and bone scan evidence of increased activity in the thoracic vertebral spine. Our patient's response to combined chemotherapy is similar to that seen in the case of Krebs and Müller.[25]

The initial patient described in 1960 by Perry et al,[11] a 53-year-old man, demonstrated lichen myxedematosus, bone marrow plasmacytosis of atypical trinucleate plasmacytoid cells, and a narrow beta M gradient on serum protein electrophoresis. In 1979 this patient was described as having a "coincidental" lichen myxedematosus treated with mechlorethamine hydrochloride (administered in three injections for two weeks) and urethane (administered for six months) in an attempt to treat a plasma cell dyscrasia, but no response to the skin lesions occurred. In retrospect, review of the bone marrow of the patient at this time failed to provide significant changes in the marrow to substantiate the diagnosis of multiple myeloma.[8] This patient eventually experienced skin pain and deep pain (of the bone) and died in 1961. The cause of death is unknown, and no autopsy was performed (personal communication with Dr. Perry). It is possible that this patient had multiple myeloma with a low tumor burden as described by Durie and Salmon.[28]

One may speculate that the association of scleromyxedema or lichen myxedematosus in multiple myeloma is "coincidental," with the incidence of multiple myeloma being approximately the same as that of Hodgkin's disease or 3 per 100,000 and that of scleromyxedema, significantly less. The reports of several cases of lichen myxedematosus and paraproteinemia that do not demonstrate findings diagnostic of multiple myeloma may represent a prolonged preclinical asymptomatic phase of that disease in patients with lichen myxedematosus as well as in "normal" patients.

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