GRANULOMA MULTIFORME

A NEW SKIN DISEASE RESEMBLING LEPROSY[1]

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The first case of this hitherto undescribed disease was seen in a leprosy settlement in West Nigeria. The case was presented as atypical tuberculoid leprosy, not responding to three years of sulfone treatment. Although leprosy was excluded because of lack of hypesthesia, normal perspiration in lesions, and absence of enlarged nerves, a diagnosis could not be made. The following year large numbers of similar cases were seen in leprosy clinics in Southern Benue Province, Northern Nigeria. The local medical superintendent already doubted the diagnosis of leprosy because of the atypical aspect and the lack of response to several years of sulfone treatment. However, two pathologists diagnosed leprosy in 15 out of 16 biopsy specimens. In one case the possibility of granuloma annulare was considered.

It is evident that clinically and histologically this skin condition may resemble some forms of leprosy. The clinical aspect of the disease has been studied in many hundreds of patients in Benue Province. Information about the epidemiology of the disease was derived from an intensive population survey in a part of Benue Province in which the disease was highly endemic. The histopathologic description, which will follow, is based on the study of 140 biopsy specimens.

Clinical aspects.—The first symptom of the disease is a localized itch, soon followed by skin lesions at the same site. The early lesions usually are papulo-nodular. These increase gradually in size, at the rate of about 2 cm. in diameter per month, and develop into plaques or circinate lesions. Often the lesions are slightly to moderately hypopigmented. They are always very well defined. The diameter varies between 1 and 15 cm. Many patients show only one or a few lesions; others show many lesions, and in a few patients the disease becomes nearly generalized.

After some time, usually more than a year, the lesions subside spontaneously. In some patients, however, new lesions appear while older ones subside. Often the whole course of the disease covers more than 10 years.

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The following clinical varieties have been recognized:

1. Papulo-nodular (N).
2. Plaque: (a) with smooth surface (P); (b) consisting of closely set, evenly distributed nodules (NP).
3. Circinate: (a) with coarse nodular edge (CC); (b) with fine papulo-nodular edge (CF); (c) with intermediate edge (C).
4. Atypical: (a) circinate with broad, solid smooth edge; (b) circinate, with scaly edge; (c) with marked atrophy.
5. Residual hypopigmentation.

The papulo-nodular variety (Fig. 1) shows smooth lesions, 1-5 mm. in diameter, elevated 1-3 mm. above the surface of the skin, occurring singly or in groups or scattered. The lesions usually develop into plaques or circinate forms.

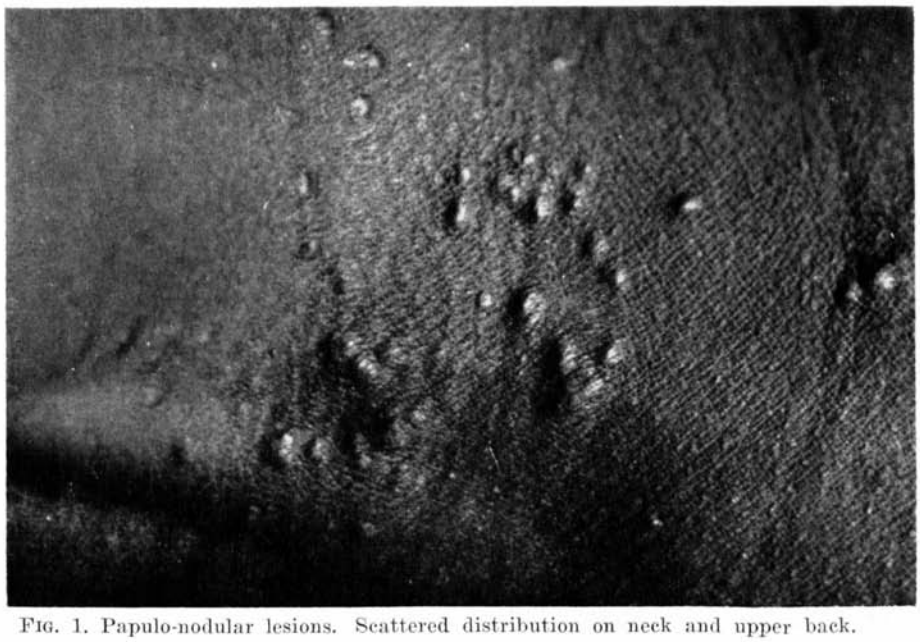

FIG. 1. Papulo-nodular lesions. Scattered distribution on neck and upper back.

The plaques are well defined, elevated 1-4 mm. above the surface of the skin, and are single or multiple. In most cases the surface is smooth, with a "peau d'orange" aspect in the more elevated lesions (Fig. 2), but in other cases the plaque consists of evenly distributed, rather closely set, sometimes coalescing nodules 2-5 mm. in diameter (Fig. 3). The plaques often subside first in the center, thus becoming circinate.

The circinate lesions present an edge of papulo-nodules, smooth and closely arranged around a center, which is often slightly hypopigmented and may show slight atrophy. In many cases the appearance of the skin in the center is nearly normal. The size of the papules varies considerably. In many cases the diameter of the papules is only 1-2 mm. (Fig. 4). The coarse circinate variety shows nodules averaging about 4-5 mm. in diameter (Fig. 5). The papules are usually more or less round but sometimes elliptical or irregularly shaped. Atypical lesions with residual atrophy may be seen (Fig. 6).

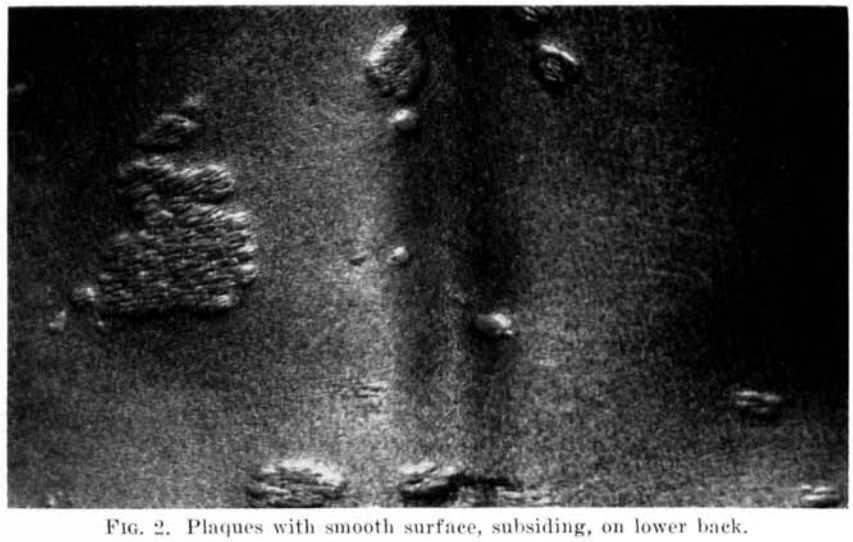

FIG. 2. Plaques with smooth surface, subsiding, on lower back.

Site of lesions.—The majority of the lesions are found on the upper parts of the body (Fig. 1). The upper arms and shoulders, the upper back and the upper chest are sites of predilection.

TABLE 1. *Distribution of first lesions in 278 patients.*

	Number of patients	Percentage
Arms and shoulders	135	49.0
Upper back and chest	87	31.0
Lower back and abdomen	25	9.0
Head and neck	17	6.0
Legs	14	5.0
TOTAL	278	100.0

Lesions are more common on the upper arms than the forearms. Lesions are seldom found on the hands. The legs present a similar distribution. The distribution of initial lesions in the patients seen is presented in Table 1.

Age distribution.—The highest incidence (9.7%) was found in old people. The prevalence is high in the 40-49 year age grouup (6.5%), much lower in the 30-39 year age group (1.6%), and low in people between the ages of 15 and 30 years (0.015%). Not a single case was found in more than 3,000 children examined. Age frequency is tabulated in Table 2.

Sex distribution.—The disease is more common in females than in males. The difference is much more marked in the younger age groups. The male-female sex ratio in the 30-39 year age group is 1:2, but in persons above the age of 50 the sex ratio is 1:1.2 only. In very old people the sex difference is negligible. On the average the disease starts

at an earlier age in females. Table 3 tabulates the sex distribution as observed in our cases.

TABLE 2. *Age frequency distribution in 148 patients.*

Age group in years	Number examined	Number of cases	Prevalence × per cent
10—19	1,262	1	0.01
20—29	1,603	3	0.02
30—39	1,627	26	1.6
40—49	814	53	6.5
50 & over	667	65	9.7

TABLE 3. *Sex distribution and age of patients.*

Age group in years	Males			Females		
	Number examined	Number of cases	Prevalence per cent	Number examined	Number of cases	Prevalence per cent
10—19	625	1	0.02	637	0	0.0
20—29	541	1	0.02	1,062	2	0.02
30—39	610	6	1.0	1,117	20	2.0
40-49	405	17	4.2	409	36	8.8
50 & over	384	34	8.9	283	31	10.5
TOTAL	2,565	59	2.3	3,508	89	2.5

Clinical variety and age.—Although a particular variety is not restricted to a particular age group, the circinate form, with fine edges, is much more common in old people. Younger age groups more often show one of the other varieties (see Table 4).

TABLE 4. *Frequency distribution of varieties according to age of patients.*

Age group in years	Variety			
	CF	C	CC	P
10—19	–		1	–
20—29	–	1	1	2
30—39	10	6	10	4
40—49	29	16	6	2
50 & over	42	15	8	1
TOTAL	81	38	26	9

Histopathology.—The epidermis is normal or slightly atrophic. Usually there is slight to moderate loss of pigment in the basal layer. Clumps of pigment are found frequently in the upper parts of the dermis.

The dermis shows a tuberculoid infiltrate, more intensive in the upper third, but extending not rarely throughout the dermis. The papillary spaces are relatively free from infiltrate, and often a free subepidermal zone is seen. The center of infiltrates shows various degrees of collagen degeneration.

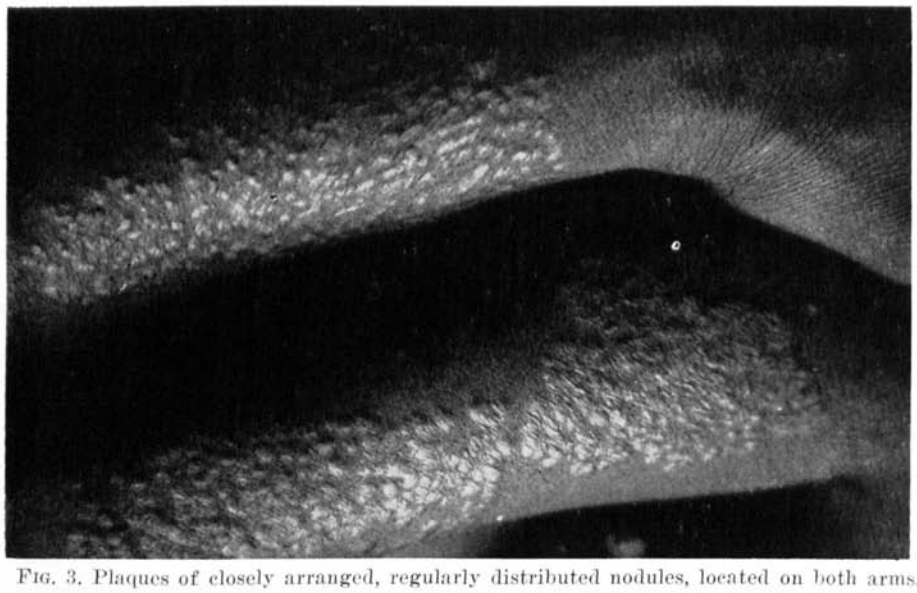

FIG. 3. Plaques of closely arranged, regularly distributed nodules, located on both arms.

The infiltrate consists of histiocytes, lymphocytes, epithelioid cells and many foreign body giant cells. Small numbers of Langhans' giant cells may be present in some cases. In some of the cases an increase of eosinophilic leucocytes was seen. In a few cases the number of plasma cells was increased. The increase of cells of the latter two types is not a constant phenomenon and may be unrelated to the disease. The infiltrate is not connected with appendages of the skin, nor with nerves or sweat glands. Normal nerve branches were often found within an extensive infiltrate. The blood vessels appear to be normal.

Designation.—The condition was first called "Mkar disease" after the town where it was first studied. Because of the granulomatous condition and the variations in clinical aspect "granuloma multiforme" would be a more appropriate name.

Differential diagnosis.—Clinically and histologically there are differences between granuloma multiforme and other granulomatous conditions resembling it. A close resemblance is seen with granuloma annulare. The latter, however, is common in children, frequently on the hands. Histologically a radial arrangement of fibroblasts is seen around centers of necrosis, at least in some of the cases.

In this article special attention is paid to the differential diagnosis between granuloma multiforme and leprosy.

Itching, a typical symptom of granuloma multiforme, is absent in leprosy. Paresthesia in leprosy may be described by some patients as itching; it is present in only a minority of the cases, intermittent, and usually of short duration.

Of very great importance is the absence of any sensory impairment in granuloma multiforme. There is no loss of perspiration. Hairs may be short, as a result of scratching, but they are not completely

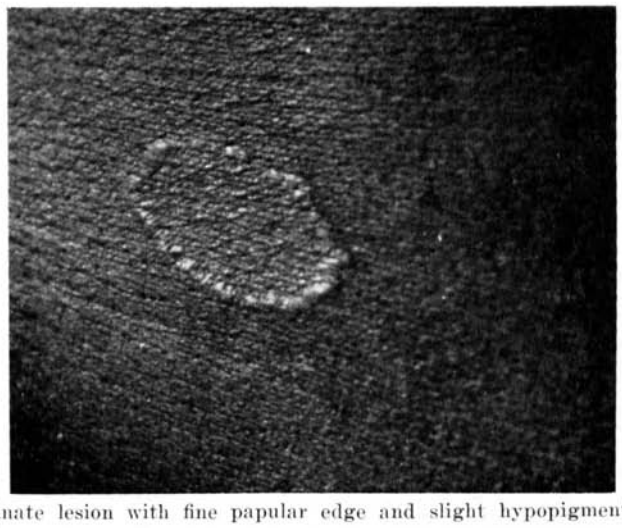

FIG. 4. Circinate lesion with fine papular edge and slight hypopigmentation. Left subclavicular region.

lost. Hypopigmentation may be present in both conditions, particularly in circinate varieties resembling minor tuberculoid leprosy. On the average the degree of hypopigmentation is less than in comparable leprosy lesions. Atrophy may be present, but is usually less marked in granuloma multiforme.

In cases of granuloma multiforme with one or a few lesions the distribution may be similar to that of leprosy. In cases with multiple lesions the distribution usually differs from that in leprosy. The predilection sites, i.e., upper arms, upper back, and upper chest, are not typical for leprosy. Granuloma multiforme patients with many lesions seldom present lesions on the hands, lower legs, and feet. In leprosy cases with many lesions usually a few are seen on these parts of the extremities. Large nerves are never affected.

Histologically some cases of granuloma multiforme may resemble tuberculoid or "dimorphous" (borderline) leprosy. As a rule the differences are sufficiently marked to enable differential diagnosis on a single section of an active lesion.

Nerve branches are not affected. They are usually found without difficulty, even within the infiltrates ([6]). Nerves and sweat glands are not predilection sites of infiltration. In cases with an extensive tuberculoid infiltrate the papillary spaces are almost uninvolved. Often a free subepidermal zone is seen, and atrophy of the epidermis is comparatively slight. Some central collagenous necrosis is usually present. The number of foreign body giant cells is usually large, and far exceeds the number of Langhans' giant cells.

Etiology.—The cause of the disease is as yet unknown. A bacterial origin is not probable. Bacilli have not been found after Gram and Fite-Wade staining. Antibiotics have not produced any effect on the course of the disease. The distribution of the cases in the community

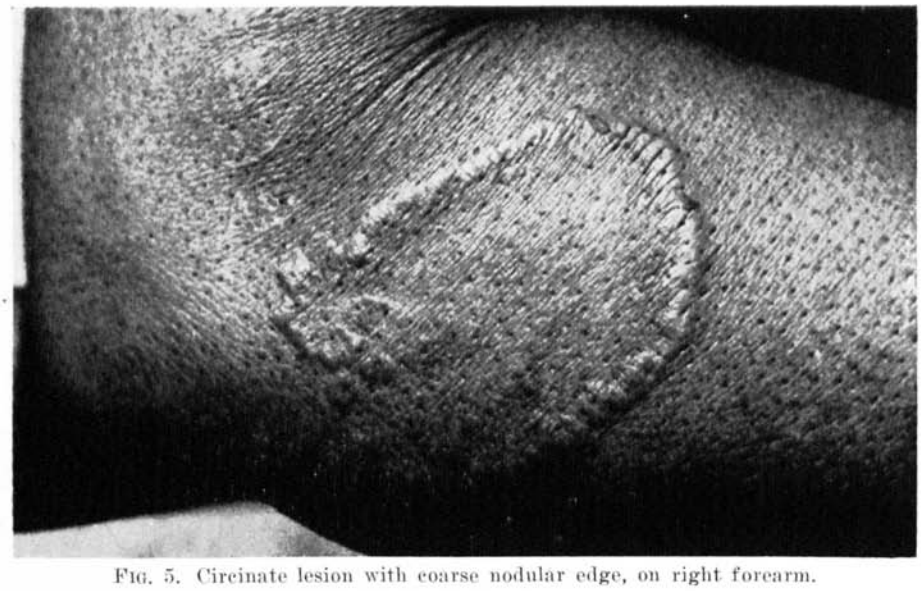

FIG. 5. Circinate lesion with coarse nodular edge, on right forearm.

is not in favor of an infectious agent. PAS staining does not reveal the presence of fungi.

A parasitic origin has been seriously considered. In a number of sections microfilaria and an increased number of eosinophils were found. No tissue reaction, however, was noted around microfilaria, nor have degenerating microfilaria been detected in early infiltrations. This does not entirely exclude the possibility of a late tissue response to completely degenerated parasites that are beyond recognition. However, granuloma multiforme is uncommon in an adjacent area with a very high incidence of microfilariasis. Also the distribution of the lesions is not typical for filariasis. The possibility of another parasite or a biting or stinging insect cannot be entirely excluded.

Another possibility deserving consideration is an agent dropped from loads carried on the heads of patients or from the roof above the fire in huts. This would explain not only the distribution of the lesions on the upper parts of the body, but also the sex differences. Adult females spend more time near the fire than adult males, but in old age the men appreciate the warmth of the fire as much as old females. The causative agent may have an effect similar to that of silica, beryllium, and zirconium. Doubly refractile material, however, was not present in the sections. Microchemical analysis has not yet been made.

Prevalence.—The prevalence of leprosy in the survey area was 1.5 per cent. That for granuloma multiforme was 1.7 per cent. Two cases of granuloma multiforme and tuberculoid leprosy in the same patient were seen, and two cases of granuloma multiforme and lepromatous leprosy. The latter cases are of particular interest in relation to the conception of Sagher and his colleagues[2-6] that lepromatous patients respond to various agents with a lepromatous type of reac-

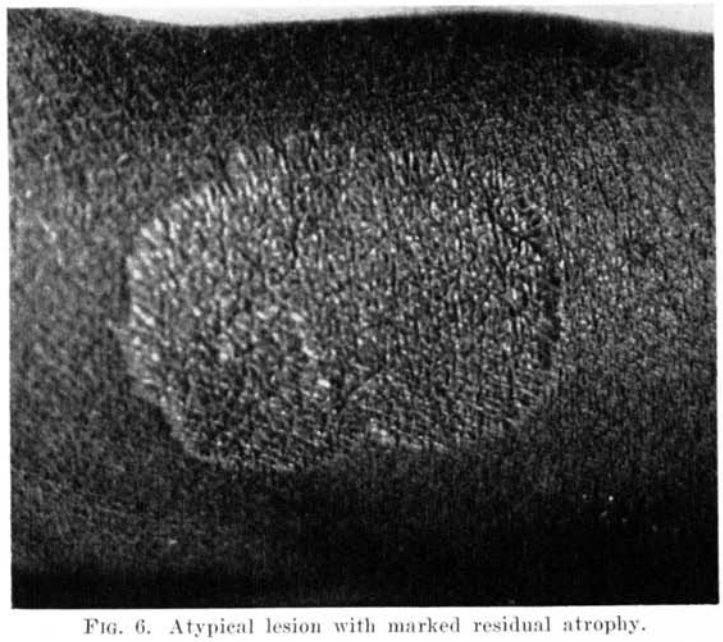

FIG. 6. Atypical lesion with marked residual atrophy.

tion. This is doubted by Kooij. [1] The finding of a tuberculoid type of reaction in the two lepromatous patients points against the opinion of Sagher and is in favor of the hypothesis that lepromatous patients are merely unable to react with a tuberculoid type of response to certain components of acid-fast bacilli.

SUMMARY

Clinical, histologic, and epidemiologic descriptions are presented of a new skin disease resembling tuberculoid leprosy. It is common in old people in Benue Province, Northern Nigeria. Hundreds of cases have been treated with dapsone in leprosy clinics, without effect. Pathologists have diagnosed leprosy on a number of biopsy specimens.

The disease can be differentiated from leprosy by the presence of itching, the atypical distribution of its lesions, which occur mainly on the upper parts of the body, and the absence of certain characteristics of leprosy, including anesthesia, thickened nerves, and loss of perspiration. Histologically the tuberculoid infiltrate characteristic of the disease has no connection with nerves and sweat glands; normal nerve twigs are seen within infiltrates. Central collagenous degeneration is common. Foreign body giant cells are usually present in large number.

The most common clinical varieties are papulo-nodular, circinate, with a fine or coarse papular margin, and plaques with a smooth surface or in groups consisting of closely and evenly distributed nodules.

The cause of the disease is unknown. It is designated "granuloma multiforme" because of the granulomatous structure and the variation in clinical aspect.

RESUMEN

Se presentan descripciones clínicas, histológicas y epidemiológicas de una nueva enfermedad que se asemeja a la lepra tuberculoide. Es común en gente de edad en la Provincia de Benue, Norte de Nigeria. Cientos de casos han sido tratados sin efecto con dapsona en las clínicas de lepra. Los patólogos han diagnosticado lepra en un número de biopsias.

Esta enfermedad puede ser diferenciada de la lepra por la presencia de picazón, la atípica distribución de sus lesiones, las cuales ocurren principalmente en la porción superior del cuerpo, y en la ausencia de ciertas características de la lepra, incluyendo la anestesia, engrosamiento de nervios y pérdida de la perspiración. Histológicamente el infiltrado tuberculoide característico de la enfermedad no tiene conexión con las glándulas sudoríparas ni con los nervios; ramitos nerviosos normales se ven dentro de los infiltrados. Es común la degeneración colágena central. Usualmente están presentes en gran número las células gigantes de tipo cuerpo extraño.

Las variedades clínicas mas comunes son la pápulo-nodular, circinada, con un margen fino o papular grueso, y placas con una superficie lisa o en grupos consistentes de nodulos de distribución cercanos y iguales.

La causa de la enfermedad es desconocida. Se la ha designado como "granuloma multiforme" por la estructura granulomatosa y variación en sus aspectos clinicos.

RÉSUMÉ

Les caractéristiques cliniques, histologiques et épidémiologiques d'une nouvelle maladie cutanée qui ressemble à la lèpre tuberculoïde sont décrites. Cette maladie est courante parmi les gens âgés dans la province de Benue, dans le Nigéria du Nord. Des centaines de cas ont été traités par la dapsone dans les cliniques de lèpre, sans résultat. Les pathologistes ont diagnostiqué la lèpre sur biopsie dans nombre de cas.

La maladie peut être différenciée de la lèpre par la présence de démangeaisons, par la distribution atypique des lésions, qui surviennent principalement sur les parties supérieures du corps, et par l'absence de certaines caractéristiques de la lèpre telles qu'anesthésie, nerfs épaissis et anhydrose. Histologiquement l'infiltrat tuberculoïde caracterisique de la maladie n'est pas en connection avec les nerfs et les glandes sudoripares; des filets nerveux normaux peuvent être vus dans l'infiltrat. Une dégénérescence collagène au centre est courante. Des cellules géantes à corps étrangers sont généralement présentes en grand nombre.

Les variétés cliniques les plus courantes sont les variétés papulo-nodulaire, circinée, avec bords papulaires fins ou rugueux, et la variété à plaques avec surface lisse ou en groupes consistant en nodules rapprochés et distribués de manière uniforme.

La cause de la maladie n'est pas connue. Sur la base de la structure granulomateuse et de la variété dans l'apparence clinique, cette maladie est désigné sous le nom de "granulome multiforme."

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