Original Article

Prevalence of Gestational Trophoblastic Disease: An Institution Experience

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Abstract

Background: A group of diseases related to normal or abnormal gestation that have a common denominator, the abnormal proliferation of trophoblast tissue, are generically designated gestational trophoblastic diseases (GTDs). Individual disorders differ remarkably in their appearance (morphology) and clinical significance. This study was aimed at characterizing all cases of histologically diagnosed GTDs, seen at the Histopathology Department of the Jos University Teaching Hospital (JUTH). **Materials and Methods:** This study was a 10-year hospital-based retrospective study employing slides and tissue blocks of specimens from uterine evacuation products of gestations of all females diagnosed with GTDs in the Histopathology Department of JUTH from January 2004 to December 2013. The materials used in the study included records from the departmental registry and archival slides and tissue blocks from the archives of the histopathology department of the hospital. **Results:** A total of 151 cases were diagnosed histologically as GTDs, during the period under review. These accounted for 0.8% of all the surgical pathology specimens received. A total of 151 cases of GTD histologically diagnosed met the inclusion criteria and translated to 5.7 cases/ 1000 pregnancies. The following histological subtypes were seen: 63 cases (41.7%) were diagnosed as partial hydatidiform mole (PHM), 42 cases (27.8%) were choriocarcinoma, and 35 cases (25.8%) were diagnosed as complete hydatidiform mole. Four cases diagnosed as invasive mole accounted for 2.7%, which is closely followed by 3 cases of placental site trophoblastic tumor, accounting for approximately 2% of GTDs. However, no case of epithelioid trophoblastic tumor was seen. **Conclusion:** GTD was found to be common in Jos and had a frequency of 5.7 cases/1000 pregnancies in our series. The most common histological subtype was PHM, closely followed by choriocarcinoma. The molar lesions peaked in the second and third decades, while choriocarcinoma peaked in the second decade of life.

Keywords: Gestational trophoblastic diseases, histology, Jos, Jos University Teaching Hospital

Introduction

A group of diseases related to normal or abnormal gestation that have a common denominator, the abnormal proliferation of trophoblast tissue, are generically designated gestational trophoblastic diseases (GTDs). Individual disorders differ remarkably in their appearance (morphology) and clinical significance.[1,2]

This presents the importance of undertaking a study to characterize and essentially, contribute to the data on morphological patterns of GTDs in our center, as similar studies have been done in other places, with assessments of the clinical characteristics and management outcomes.

The spectrum includes interrelated tumors, namely complete hydatidiform mole (CHM), partial hydatidiform mole (PHM), invasive mole, choriocarcinoma, and placental site trophoblastic tumor (PSTT). Variation in the frequency of complete mole for instance is said to be striking. In a study carried out by Hertig, the average incidence for young women in the United States of America (USA) was 1 in 2000 deliveries,[3] whereas the reported incidence in Southeast Asia was four to five times greater than the USA average. Higher incidences have also been reported from Mexico, the Philippines, India, Taiwan, and Indonesia.[4,5]

Although on a global scale, particularly in the developed nations, GTDs are not very common, four separate studies have demonstrated that they are relatively common among women of African descent, especially during their reproductive age bracket.[6-10] Importantly too, they present a unique opportunity

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for early detection and cure, hence, the importance is emphasized here, of increased patronage of histopathological diagnosis, and ancillary investigations to enhance patient follow up, treatment monitoring, as well as improved prognosis. Complete mole is the most common form of GTD, and presenting in the second trimester, it is said to be more common in Asia, Africa, and Latin America.[11] Patients with complete mole, usually tend to be above thirty years of age, and more likely have diets deficient in vitamin A precursors (this may explain some of the geographical differences already mentioned). The risk is, however, reduced by increased carotene consumption, as well as a history of previous term delivery which also confers less risk. On the other hand, for an unexplained reason history of a previous mole greatly increases the probability of developing another molar pregnancy. An increased incidence of choriocarcinoma reportedly follows a history of complete mole, as well as older age (>40 years) which is also a risk factor for choriocarcinoma.[11] Choriocarcinoma is a curable disease and early diagnosis becomes imperative.

Globally, the highest reports of GTDs are from Asian countries, and a relatively higher risk is also documented for women of African descent.[12] Being at extremes of the reproductive age group is an important risk factor associated with molar pregnancy.[12] Low literacy levels, poor socioeconomic status, and lack of antenatal care have been documented as major contributory factors to late presentation, as well as the inability to understand the importance of follow-up in the Asian region of Pakistan.[12] This may not be far from the situation in our own environment, which would have informed the need for the index study to a large extent.

GTDs have been found to be quite common in our environment and owing to the unique challenges of our health-care system, they mostly present late.[13] However, they are quite potentially curable.

The importance of early diagnosis, prompt institution of treatment, and monitoring the effects of therapy, using serial determination of serum beta subunit of human chorionic gonadotropin (β-hCG) are advocated as GTDs are curable. However, β-hCG secretion is by no means restricted to gestational choriocarcinoma or other forms of trophoblastic diseases. It can occur also in nontrophoblastic disorders such as nongestational choriocarcinoma, other ovarian and testicular germ cell tumors, melanoma, lymphoma; carcinomas of the esophagus, stomach, pancreas, kidney, liver, lung, urinary bladder, uterus, adrenal glands, the breast, and other sites.

GTDs are a common health problem among Black and Asian women.[1,14] They present late due to the unique challenges of our health-care delivery system, although they are potentially curable. It is therefore important to undertake this study as it can also form the basis for clinicopathological studies as a collaboration between the clinicians and pathologists.

It is expected to supply an important addition to the already existing body of data on gestational trophoblastic disorders.

This study, therefore, is aimed at reviewing and characterizing all cases of histologically diagnosed GTDs, seen at the Histopathology Department of the Jos University Teaching Hospital (JUTH), between the years 2004 and 2013, all inclusive.

Materials and Methods

This study was a 10-year hospital-based retrospective study employing slides and tissue blocks of specimens from the uterine evacuation products of gestations of all females diagnosed with GTDs in the Histopathology Department of JUTH from January 2004 to December 2013. JUTH is a referral tertiary health centre in North Central Nigeria. The materials used in the study included records from the departmental registry and archival slides and tissue blocks from the archives of the histopathology department of the hospital. The specimens studied included those obtained through uterine evacuation and hysterectomy specimens diagnosed as GTDs, and received in the department. Records of previous diagnosis, specimen number, and ages, were retrieved from the departmental registry of the hospital. Tissue blocks were traced and fresh sections 5-μm thick were cut from paraffin-embedded formalin-fixed blocks and stained with H and E for cases of missing slides. The slides were reviewed by the authors and the modified WHO classification of GTD was used to classify the diseases as presented below:

Modified World Health Organization (WHO) Classification of GTDs (2012)

- Molar lesions
  - Hydatidiform mole
    - CHM
    - PHM
  - Invasive mole
- Nonmolar lesions
  - Choriocarcinoma
  - PSTT
  - Epithelioid trophoblastic tumor (ETT)

All GTD histologically diagnosed between January 2004 and December 2013 in the Histopathology Department of JUTH with traceable archival slides or tissue blocks and clinical data including ages, were included in the study while clinically diagnosed GTDs using imaging and not subjected to histological diagnosis were excluded from the study.

The data were analyzed using the EPI info statistical software version 7. The data were presented in histogram, pie chart, and tables.

Ethical consideration

Ethical clearance was obtained from the Ethical Committee of JUTH and its terms were strictly adhered to in the conduct of this research.

Results

A total of 155 cases were diagnosed histologically as GTD, during the study period. These accounted for 0.8% of all the

surgical pathology specimens received, which were a total of 20,131 specimens within the study period.

The total number of pregnancies and deliveries registered at the Obstetrics and Gynecology Department was 26,319 and 25,395, respectively.

One hundred and fifty-one (97.4%) of the histologically diagnosed cases of GTD were included in the study. Four cases, however, were excluded from the study for not meeting the inclusion criterion, of having complete biodata.

The 151 cases of GTD translate to a frequency of 5.7/per 1000 pregnancies. Alternatively expressed against the total deliveries, the frequency of GTD was 5.9 cases in 1000 deliveries.

Of the 151 histologically diagnosed cases, the following histological subtypes were seen: 63 cases (41.7%) were diagnosed as PHM, 42 cases (27.8%) were choriocarcinoma, and 35 cases (25.8%) were diagnosed as CHM [Table 1]. Furthermore, four cases diagnosed as invasive mole accounted for 2.7%, which is closely followed by 3 cases of PSTT, accounting for approximately 2% of GTDs. However, no case of ETT was seen. Partial and complete mole photomicrographs are depicted in Figures 1 and 2 respectively

The ages of the patients ranged from 17 to 65 years, with a mean age of 30.7 years. The peak age for all GTD was in the second decade.

The most common histologic subtype seen, was PHM (41.7%), with a mean age at 31 years and peak age within the age range 30–39 years. This is followed by choriocarcinoma (27.8%) with a mean age at 30 years and peak age within the age range 20–29 years.

CHM represented 25.8% of cases with a mean age at 30.4 years and peak age within the age range of 20–29 years.

The four cases of invasive mole had a mean age at diagnosis of 40.5 years and a median age of 39.0 years [Table 2].

The cases diagnosed as PSTT had a mean age of 24 years and a median age of 23 years. The peak age was within the age range of 20–29 years [Table 3].

Table 1: The distribution of gestational trophoblastic diseases into specific morphologic/histologic subtypes in Jos University Teaching Hospital, Jos

Histologic type	Frequency (%)
Molar lesions	
PHM	63 (41.7)
CHM	39 (25.8)
Invasive mole	4 (2.7)
Nonmolar lesions	
Choriocarcinoma	42 (27.8)
PSTT	3 (2.0)
ETT	0
Total	151 (100)

PHM: Partial hydatidiform mole, CHM: Complete hydatidiform mole, PSTT: Placental site trophoblastic tumor, ETT: Epithelioid trophoblastic tumor

Table 2: Age distribution of gestational trophoblastic diseases and the histologic subtypes in Jos University Teaching Hospital, Jos

Age range (years)	CHM	PHM	Invasive mole	Choriocarcinoma	PSTT	Frequency (%)
10-19	1	3	0	3	0	7 (4.6)
20-29	21	21	1	18	3	64 (42.4)
30-39	13	30	1	16	0	60 (39.7)
40-49	3	8	1	4	0	16 (10.6)
50-59	1	1	1	0	0	3 (1.9)
60-69	0	0	0	1	0	1 (0.7)
Total	39	63	4	42	3	151 (100)

The overall peak age for all GTDs, in JUTH falls within the age bracket (20-29) mean age (all GTD) = 30.7 + 8.1 yrs: median age = 30.0+ 8.1yrs. Age range (all GTD) = 17-65 years in JUTH. PHM: Partial hydatidiform mole, CHM: Complete hydatidiform mole, PSTT: Placental site trophoblastic tumor, GTD: Gestational trophoblastic diseases, JUTH: Jos University Teaching Hospital

Table 3: Frequencies of histologic types of gestational trophoblastic diseases expressed in relation to total pregnancies and deliveries in Jos University Teaching Hospital

Histologic type	Frequency (%)	Frequency/1000 pregnancies	Frequency/1000 deliveries (births)
CHM	39 (25.83)	1.48	1.54
PHM	63 (41.72)	2.39	2.48
Choriocarcinoma	42 (27.81)	1.60	1.65
Invasive mole	4 (2.65)	0.15	0.16
PSTT	3 (1.99)	0.11	0.12
ETT	0	0	0
Total	151 (100)	5.73	5.95

CHM: Complete hydatidiform mole, PHM: Partial hydatidiform mole, PSTT: Placental site trophoblastic tumor, ETT: Epithelioid trophoblastic tumor

Discussion

The total burden of GTD observed in our study (151 cases) translates to a frequency of 5.7 cases in 1000 pregnancies. Alternatively, the GTD burden in relation to the total deliveries recorded in the Obstetrics and Gynecology Department of JUTH translates to a frequency of 5.9 cases in 1000 deliveries. A study carried out by Mayun[15] in Gombe, Northeastern Nigeria reported a frequency of 6 in 1000 deliveries, which is almost similar to the frequency found in our study. The age range of the Gombe study population was between 15 and 44 years with a mean age of 26.5 years which are quite lower than the same data measured in our study, although the peak age recorded there within the age range, 20–30 years corresponds well with that observed in Jos to be in the second decade. This concurs with the reproductive ages of women. The GTD frequency observed in Jos is much higher than the 3.58/1000

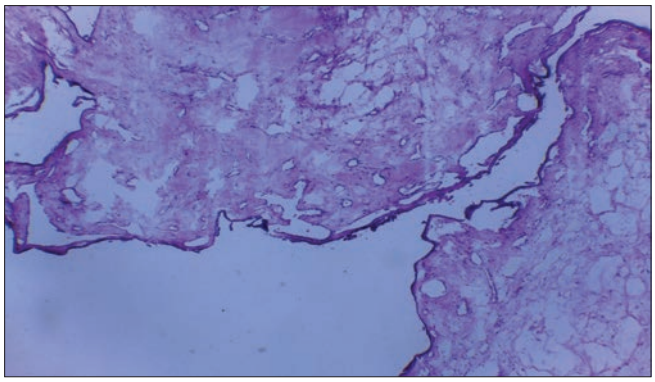

Figure 1: Photomicrograph depicting partial hydatidiform mole with edematous, vascular villous core (H and E ×40)

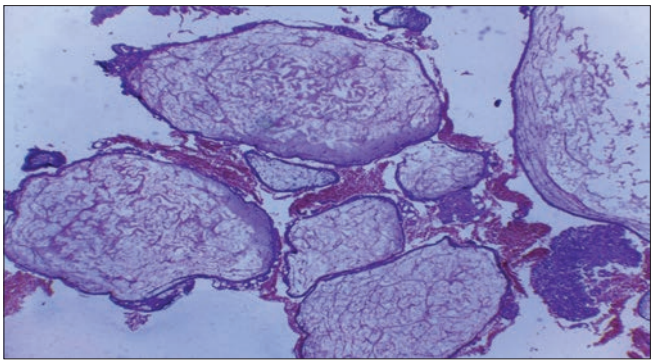

Figure 2: Histological photomicrograph of complete hydatidiform mole showing stromal edema imparted by cisternae, and a rim of roughly uniform basophilic trophoblast (H and E ×20)

deliveries reported in Ebonyi by Anuma *et al.*,[13] who also reported an age range of 19–55 years and a mean age of 33.4 ± 7.4 years. The Jos frequency was, however, much lower than 46 cases/1000 deliveries reported in Nnewi (Southeast Nigeria).[6]

The age range in our study was 17–65 years which is approximately comparable to the age range of 19–55 years in the study done by Anuma *et al*. in Ebonyi.[13] The mean age of patients reviewed in the index study was 30.7 ± 8.1 years and slightly lower than 33.4 years in the Ebonyi series but is comparable or corresponding to a mean of 31.0 ± 8.6 years reported in the Nnewi study.

The age range of our study population is comparably higher than that of the Nnewi series for instance, put at 15–46 years.[6] The higher age range observed in our study may be explained by the fact that choriocarcinoma is the second highest in frequency to PHM as the two most prevalent patterns seen in our series. These two patterns of GTD are generally observed in advanced maternal age and several studies have reliably shown that a risk factor for choriocarcinoma is advanced maternal age.[8,16] Previous hydatidiform mole, particularly CHM as an antecedent risk factor can lead to choriocarcinoma.[1]

The frequency of GTD reported in Benin City (4 in 1000 deliveries) by Aligbe *et al*.[17] was comparatively lower than the observation in our study. The frequency of GTD in Ile-ife put at 1.7 in 1000 deliveries[18] is below the frequency observed in Jos. However, the frequency from Ibadan of 5.8 cases in 1000 deliveries and that from Lagos of 5.4 in 1000 deliveries[19] are seen to correspond comparatively well to the observation in our own study.

A prevalence study in Nigeria reported a frequency ranging from 0.99 to 3.35 cases of molar gestation per 1000 pregnancy[20] which is higher than was reported from Ethiopia as 2.8/1000 deliveries by Negussie *et al*.[21] In the Ethiopian series, the mean age was 30.9 ± 6.5 years, and the median age was 34.5 years while the ages of the patients were in the range 14–53 years. These are approximately corresponding to the observations made in the Jos study.

Compared to the incidences in the United Kingdom and Japan which, respectively, had frequencies of 1.5 and 2.0 in 1000 pregnancies;[22] the frequency of GTD in Jos of 5.7 in 1000 pregnancies is considerably higher.

Several studies appear to show variations in incidence of GTD worldwide.[1,14,23,24] This could be associated with some peculiar geographical factors, pregnancy risks, unknown environmental agents, and genetic factors. The peak age in the present study of 30 years is higher than the observations made in the Benin series by Aligbe *et al*.[17] and the multicenter study by Nggada *et al*.[24] (in Maiduguri, Ilorin, and Nnewi) which were, respectively, in the third, and second and third decades of life. The mean age of the patients reviewed in our study, 30 years is comparatively higher than that observed by Nggada *et al*., which was 27.7 years, as well as that observed by Ocheke *et al*.[25] in a previous gynecological review also in Jos, over a 5-year period (2001-2005), which was 28 ± 3 years.

The mean age of patients in Jos is also slightly higher than that recorded from a South African review of 112 patients which was 28.5 ± 8.1 years.[26] The mean age of a study population reviewed in America, over a 10-year period by Robert *et al*.[7] was 25.2 years, the median age was 25 years while the age range was 14–45 years which are all comparably lower than the corresponding data assessed in our study.

PHM turned out to be the most common histologic type of all GTDs characterized in this study. With a frequency of 63 out of 151 cases, it accounted for 41.7% of the total study population of women diagnosed with one pattern or the other of GTD, which is quite a deviation from what is known and published in standard texts of histopathology and gynecologic pathology from the Western world.[11] The converse, which however is obtained in published literature, is that CHM constitutes the most frequent pattern of GTD seen globally.[11]

Nevertheless, the outcome of PHM seen in Jos does not stand alone as a few other studies previously conducted and indigenous to Nigeria have shown a similar pattern or outcome.[17,24] For instance, the pattern or outcomes observed in the multicenter study by Nggada *et al*.[24] makes it appear

to be an almost similar or reproducible pattern in comparison with our index study. PHM was the most common histological type of GTD seen by Nggada *et al*.,[24] accounting for 64.5%, followed by choriocarcinoma which accounted for 21.5% of cases and then CHM made 12.9% of cases, while invasive mole accounted for 1.1% of all GTDs reviewed, but there was no case of PSTT seen in their series.

Correspondingly, in our study, choriocarcinoma was the second most frequent pattern of GTD at 27.8%, followed by CHM accounting for 25.8%, while the invasive mole and PSTT accounted for 2.65% and 1.99%, respectively. This pattern almost or approximately shows a similarity that mirrors the outcome of the Nggada *et al*.[24] series, except that they had no case of PSTT just as no case of epithelioid trophoblastic tumor was seen in the Jos study.

In Benin city, PHM was the most frequent histologic type encountered accounting for 47.9% of the GTD cases found, followed by choriocarcinoma at 12.5%, and then invasive mole accounting for 2.1%. No CHM or PSTT cases were recorded.[17]

The pattern of GTD observed in our study exhibited a contrast to that reported by Mayun[15] at the Federal Medical Centre, Gombe, in which series CHM constituted 52.9% of the total cases studied, PHM was reported in 47.15% of cases, and no case of invasive mole was seen.[15] However, the pattern of GTDs in Jos, contrast favorably with that reported by Mayun *et al*.[27] in a separate study in Zaria, were choriocarcinoma represented 37% of GTDs and the entire molar pregnancies constituted 63%. Among the molar gestations CHM was the most common type representing 60.7%, while PHM and invasive mole, each accounted for 35.7% and 3.6%, respectively. Moreover, the mean age reported by Mayun *et al*.[27] was 25.7 years which is below the mean age in Jos, but vaginal bleeding appears to be the most common clinical presentation, across board in almost all the studies. In addition, honeycomb uterine appearance on pelvic ultrasound and passage of vesicles per vagina were reported as other modes of clinical presentation by Ocheke *et al*.[25] It is instructive to observe that, in an earlier study in Jos, only 28% of the cases reviewed were actually confirmed by the histopathological examination according to Ocheke *et al*.[25] Thus, this emphasizes a real need for more clinicians to engage and patronize the services of pathologists to procure accurate histologic diagnoses for their clients, especially as it concerns GTDs.

The frequency of GTD reported from Tunisia by Chechia *et al*.[28] which was 1.3 in 1000 pregnancies is considerably lower than our frequency in the present study. However, the mean age of the Tunisian study population of 31.7 years is slightly higher than the mean age of our patients (i.e. 30.7 years). Expectedly, the pattern of the histologic types seen in Tunisia is consistent with that reported in published western literature with CHM accounting for 55% and PHM 45% of the cases of GTD analyzed.

The frequency reported in Uganda (East Africa) was 3.42 cases in 1000 deliveries (particular reference to CHM) by Kaye[29] which again is quite on the lower side compared to the local frequency in Jos. However, the mean age of 29.6 ± 8.5 years in the Ugandan study population corresponds relatively well to the mean age of patients in Jos Nigeria.

The frequency of GTD observed in Morocco by Boufettal *et al*.[30] was 0.4/1000 pregnancies (reference to PHM) which is way below the local frequency in Jos. The mean age of patients in this series was 26 years, while the age range was 16–55 years. A similar study also by same authors in Morocco (reference to CHM), showed a frequency of 4.3 per 1000 pregnancies (or 0.43%) and a mean age of 25 years,[31] which are again lower than the frequency and mean age in our study. However, all the cases analyzed in the Moroccan series were subjected to confirmation by the histopathological examination.[31] CHM was more common at a proportion of 0.43%, than PHM at a proportion of 0.04% reflecting a reversal to the pattern seen in the Jos GTD series.

In addition, the profile of GTD studied in South Africa revealed that choriocarcinoma accounted for 30% in a particular series,[20] which is almost comparable to the 27.8% observed in JUTH, Jos.

In Ethiopia, choriocarcinoma was reported to have accounted for 15.1% of the cases analyzed, invasive mole accounted for 13.9% and CHM was diagnosed in 72% of cases, making it the most common histologic subtype reported by Negussie *et al*.[21] However, no cases were recorded of PHM or placental site trophoblastic tumor.

It is curious that PHM turned out to be the most common histopathologic subtype of GTD seen in this study. In a case–control study by Berkowitz *et al*.,[32] the observation made was that there is a difference in the epidemiologic patterns of complete and PHMs. The risk for PHM is associated with reproductive history, but not with dietary history as observed for CHM, which might serve to explain the pattern observed of the GTD cases reviewed in Jos. Risk factors according to these authors that may predict the development of PHM include:

i. Irregular menstrual cycles
ii. Oral contraceptive use for more than 4 years
iii. Previous pregnancy history including only male infants among prior live births.

Albeit, dietary factors previously postulated for CHM such as low protein, fat, and Vitamin-A or carotene were found not to be related to the risk for PHM. It is, therefore, probable that some of the above given risk factors could have been present in the majority of the population studied, to have made PHM the most prevalent or most common histological pattern of GTD observed in this study. Nevertheless, this observation can provide an area of interest for further collaborative clinicopathological studies on this subject matter, between gynecologists and pathologists, both in our center and elsewhere.

Choriocarcinoma turned out to be the second most common pattern seen, of the GTD series analyzed here, with peak incidence reported in the second decade of life. Some risk

factors that have been established to predict its development include the following:

i. History of spontaneous miscarriages or ectopic pregnancies[28,33]
ii. Advanced/advancing maternal age[16]
iii. Prior CHM; an observation made was that, choriocarcinoma was a thousand times more likely after a CHM, than it was following another normal pregnancy event[16]
iv. Ethnicity; the risk for choriocarcinoma is also increased in Asian women, those of American-Indian descent, and African Americans (Black women)[16]
v. There seems to be increased risk in women on long-term oral contraceptive pills, as well as those of blood Type A.[16]

Our study population was primarily of Black women, although we could not define other risk factors for choriocarcinoma. Hence, another basis for the future collaborative studies is suggested between pathologists and clinicians in this area of interest, more so that a high cure rate is associated with this lesion in particular.

Conclusion

In conclusion, our study has found GTD to be a common condition in Jos in general, and PHM in particular was found to be the most common histologic subtype, closely followed by choriocarcinoma. While the molar lesions peaked in the second and third decades, choriocarcinoma peaked in the second decade of life.

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Conflicts of interest

There are no conflicts of interest.

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