Archives of Gynecology and Obstetrics (2019) 299:801–808
https://doi.org/10.1007/s00404-019-05059-2

GENERAL GYNECOLOGY

Effectiveness of progestin-based therapy for morbidly obese women with complex atypical hyperplasia

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Received: 19 November 2018 / Accepted: 18 January 2019 / Published online: 31 January 2019

Abstract

Objective While progestins can effectively treat women with complex atypical hyperplasia (CAH), the impact of body habitus on treatment outcome is not well studied. We examine the association between body mass index (BMI) and progestin treatment outcomes.

Methods We conducted a retrospective cohort study of patients diagnosed with hyperplasia between 2003 and 2011. Demographics, past medical history, BMI, hormonal therapy, and histologic treatment response were abstracted. Patients with CAH who received progestin therapy were examined, and rates of regression were assessed.

Results Of 623 patients identified, 117 had CAH and satisfied the inclusion criteria. Median age was 34, and nearly, two-thirds (64%) were nulliparous. Mean BMI was 40.2, and 81% were obese (BMI 30–39.9: 36%, BMI ≥ 40: 45%). 103 patients (88%) received systemic progestin therapy and 14 patients (12%) received levonorgestrel-releasing intrauterine devices (LNG-IUS). 47 patients (40%) had a complete response to progestin-based therapy. BMI had no effect on the rate of complete response. The proportions of CAH patients with complete regression after hormonal therapy were BMI < 30: 39%, 30–39.9: 40%, and ≥ 40: 36% ($P = 0.73$). Women treated with LNG-IUS displayed higher rates of complete regression than those receiving systemic therapy (62% versus 38%, $P = 0.096$), and those with class III obesity were more likely than non-obese patients to receive LNG-IUS although neither reached statistical significance (< 40: 6.7% versus ≥ 40: 17%, $P = 0.09$).

Conclusion In this morbidly obese population, response to progestin therapy was generally low; body habitus did not impact treatment outcome for CAH, but local therapy may be more effective than systemic therapy.

Keywords Endometrial hyperplasia · Progestins · Obesity · Intrauterine device

Introduction

Endometrial cancer is the most frequently diagnosed gynecologic malignancy in the developed world with an estimated 63,230 new diagnoses in the U.S. in 2018 [1]. Likely due to rising rates of obesity and related comorbidities, the incidence of endometrial cancer has also been slowly increasing [1]. As a known precursor to endometrial cancer, complex atypical hyperplasia (CAH) is estimated to progress to endometrial cancer in 29% of cases, and at the time of biopsy diagnosis, 43% will already have co-existing endometrial cancer [2, 3]. Risk factors include increasing age and body habitus, as well as hypertension and diabetes mellitus, the presence of which can further increase rates of concurrent endometrial cancer [4].

Though hysterectomy remains the standard treatment for CAH and endometrial cancer, younger women who

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desire future fertility or those who are not surgical candidates may be effectively treated with progesterone therapies, which induce secretory endometrial differentiation and oppose estrogen-stimulated endometrial proliferation [5]. For women desiring future fertility, the goal of treatment is attaining benign endometrial pathology, which in prior literature has been achieved in 70–90% of patients with CAH [6, 7]. However, no established treatment or route of administration exists [6, 7]. Progesterone may be provided in systemic formulations including oral medroxyprogesterone acetate and megesterol acetate, injectable depo medroxyprogesterone (DMPA), and micronized vaginal progesterone, but may also be supplied locally via the levonorgestrel-releasing Intrauterine system (LNG-IUS) [6].

The prevalence of obesity, frequently associated with anovulation, infertility, and unopposed estrogen, and a known risk factor for endometrial hyperplasia and cancer, has been increasing, recently estimated at 36% [8, 9]. Furthermore, obesity is known to play a role in the pharmacokinetics of many drugs and has long been suspected to decrease efficacy of systemic steroid contraception due to altered binding, absorption, metabolism, and distribution in obese compared to normal weight women [10, 11]. Indeed, multiple studies have confirmed lower serum levels of injectable, implantable, and oral contraceptives in obese women [12–14].

Since the same or similar progestins as those found in hormonal contraception serve as uterine preserving therapy for CAH and endometrial cancer, and because obesity itself contributes to extra-ovarian estrogen production, it is reasonable to hypothesize that progestin therapy may not be as efficacious in this population as in women of normal weight. Weight gain associated with systemic progestin administration may compound this problem [15]. One recent study noted that body mass index (BMI) over 35 kg/m^2 was associated with both recurrence and failed regression of endometrial hyperplasia [16]. However, this study included patients with both atypical and non-atypical hyperplasia, and a difference in regression rates was seen in LNG-IUS but not oral progestin users. Furthermore, it did not distinguish between obese and morbidly obese patients; therefore, additional data are needed on the impact of body habitus on treatment response for endometrial hyperplasia.

The objective of our study was to determine if body habitus, as determined by BMI, affects rates of response of CAH to various progestin therapies.

Patients and methods

We conducted a retrospective observational cohort study after obtaining Institutional Review Board approval from the University of Southern California (USC); subjects with any histologic diagnosis of endometrial hyperplasia between 2003 and 2011 at Los Angeles County USC Medical Center were identified through the pathology department's database. Archived charts were subsequently reviewed and the following parameters were abstracted: age, race/ethnicity, gravidity, parity, BMI at diagnosis (grouped as: normal weight BMI < 30 kg/m^2, class I and II obesity BMI 30–39.9 kg/m^2, and class III obesity BMI ≥ 40 kg/m^2 per the World Health Organization (WHO) criteria), medical comorbidities (diabetes mellitus, hypertension, hyperlipidemia, infertility, and polycystic ovarian syndrome), medications at diagnosis and initiated during the course of therapy, initial endometrial histologic categorization, and all subsequent endometrial histology.

The chronologic sequence and types of endometrial sampling performed were recorded with the corresponding histologic diagnosis. Acceptable forms of endometrial sampling included pipelle endometrial biopsy (EMB), VABRA aspiration biopsy (Berkley Medevices, Berkley, CA [17]), uterine curettage, and hysterectomy. The histologic diagnoses were categorized into: simple hyperplasia, complex hyperplasia, simple atypical hyperplasia, and CAH per the World Health Organization (WHO) criteria [18]. Treatment regimens along with follow-up of each regimen were recorded and then categorized into systemic versus localized (LNG-IUS). Though the LNG-IUS is commonly used to treat both CAH and endometrial cancer, it is not FDA approved for this indication.

Subject records were then screened for inclusion and exclusion criteria. Included patients had a confirmed pathological diagnosis of CAH, had been prescribed either an oral or local progestin as treatment, and had at least one documented and interpretable follow-up endometrial assessment performed after 4 or more weeks of therapy. The same forms of sampling previously mentioned were deemed reliable for assessing treatment response in addition to histology on hysterectomy, if performed after hormonal therapy.

Patients with a prior or concurrent diagnosis of endometrial adenocarcinoma and/or patients with known reversible sources of unopposed estrogen, such as granulosa cell tumors of the ovary or exogenous hormone therapy, were excluded, as were those who received progestin therapy in the month preceding the initial CAH diagnosis. We also excluded patients treated with non-progestin therapies such as aromatase inhibitors or GnRH agonists or if they underwent hysterectomy without intervening hormonal therapy. Subjects with inadequate or missing follow-up endometrial sampling were excluded as were those, whose only follow-up endometrial sampling occurred less than 4 weeks after beginning medical treatment. To assess treatment response, only treatments given between the first diagnosis of CAH and the subsequent biopsy were included.

Response to treatment was categorized as: complete regression, partial regression, or persistent/progressive

disease. A complete regression was defined as resolution from CAH to benign endometrium (no residual typical or atypical hyperplasia and no progression to endometrial cancer). A partial regression occurred if the follow-up biopsy revealed non-atypical hyperplasia. Persistent/progressive disease signified either ongoing CAH or progression to cancer. We conducted two separate analyses to examine rates of complete regression and rates of overall regression (partial responders and complete responders). Rates were examined across collected variables. Logistic regression and Fisher's exact test (two-tailed hypothesis) were used for statistical comparison. The magnitude of statistical significance was expressed with odds ratio (OR) and 95% confidence interval (CI).

Results

Study selection schema is shown in Fig. 1. Of the 623 patients with endometrial hyperplasia identified in the database, we identified 253 patients with a histologic diagnosis of CAH. Sixteen of these patients were excluded due to a previous diagnosis of endometrial cancer, and 100 had been treated with either a non-progestin regimen (including hysterectomy and no treatment), mixed, or unavailable regimen. Follow-up biopsies were not available for 11 patients. Nine received a progestin-containing hormonal therapy in the month prior to diagnosis, leaving a total of 117 eligible CAH patients. Of note, 4 (0.6%) of the original 623 patients were diagnosed with granulosa cell tumors.

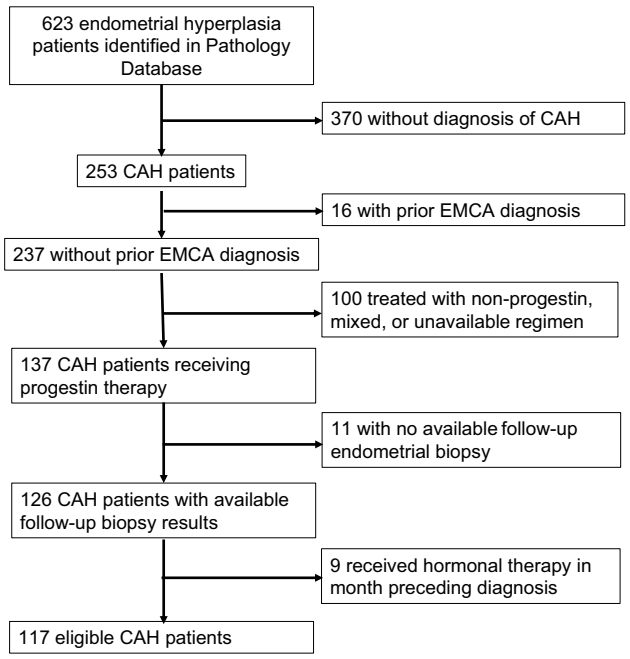

Fig. 1 Selection criteria. *CAH* complex atypical hyperplasia, *EMCA* endometrial cancer. Four cases of endometrial hyperplasia had concurrent granulosa cell tumors and were excluded

Table 1 displays study demographics. The median age of the study population was 34 years, and the mean BMI was 40.2 kg/m^2. Most patients were obese (81%), and nearly half of the study population was morbidly obese (BMI ≥ 40 kg/m^2, 45%). The majority of patients self-identified as Hispanic ethnicity (56%). The majority were nulligravid (55%) and nulliparous (64%). Accordingly, a large number of patients had comorbid infertility (35%) and polycystic ovarian syndrome (17%). Other prevalent comorbidities included diabetes mellitus (26%), hypertension (23%), and hyperlipidemia (12%). The median follow-up time was 17 months (interquartile range, 6–46).

Forty-seven (40%, 95% CI 31–49) of the 117 study participants experienced complete regression of CAH. There were no differences between complete regression rates when stratified by BMI (Table 2); complete regression was seen in 39% of normal and overweight patients, 40% of patients with class I–II obesity, and 36% of patients with class III obesity ($P = 0.73$). Similarly, we detected no significant differences in rates of complete regression between different age groups (age ≤ 30: 45% versus age > 30: 38%) or between patients with and without diabetes mellitus, hypertension, and hyperlipidemia (both, $P > 0.05$). Gravidity and parity did not significantly affect rates of complete regression. Although complete regression rate with LNG-IUS was higher than systemic progestin therapy, this difference did not reach statistical significance (62% with LNG-IUS versus 38% with systemic progestins, OR 2.64, 95% CI 0.70–11.4, $P = 0.096$).

The same comparisons were made for rates of overall regression (to either non-atypical hyperplasia or benign endometrium), as shown in Table 3. Overall, 54 patients (46%) experienced this pattern of regression. Similarly, no significant differences were seen in rates of this pattern of regression in the different BMI or age categories, nor were they seen among patients who had diabetes, hypertension, and hyperlipidemia compared with those who did not. Gravidity and parity did not impact rates of this pattern of regression, nor did the administration of systemic versus local progestin therapy. Similar to what was seen among complete responders, a trend toward higher response in patients treated with the LNG-IUS in comparison with those receiving systemic therapy was noted, though the difference was not statistically significant (OR 2.01, CI 0.54–8.34, $P = 0.24$).

Class III obese patients were more likely than non-obese to receive the LNG-IUS, though this difference did not reach statistical significance (BMI < 40: 6.7% versus BMI ≥ 40: 17%, $P = 0.09$; Table 4). Finally, treatment with other medications (aspirin, metformin, statins, and beta-blockers) was not associated with treatment response (data not shown).

Table 1 Participant demographics

Characteristic	*N* (%)
Number	117
Hispanic ethnicity	
Hispanic or latino	65 (56%)
Not hispanic or latino	7 (6%)
Unknown/not reported	45 (38%)
Race	
White	9 (8%)
Black or African American	2 (2%)
Asian	3 (3%)
Other	36 (31%)
Unknown/not reported	67 (57%)
Gravidity	
Nulligravid	64 (55%)
Gravid	53 (45%)
Parity	
Nulliparous	75 (64%)
Parous	42 (36%)
BMI (kg/m^2)	
Underweight, normal, overweight (< 30)	18 (15%)
Class I and class II obesity (30–39.99)	42 (36%)
Class III obesity (40 +)	53 (45%)
Unknown/not reported	4 (3%)
Comorbidities	
Diabetes	30 (26%)
Hyperlipidemia	14 (12%)
Hypertension	27 (23%)
Infertility	41 (35%)
Polycystic ovarian syndrome	20 (17%)
Other	50 (43%)
None	23 (20%)
	Mean (± SD) / Median (IQR)
BMI (kg/m^2)	40.2 (± 10.5) / 39.7 (13.5)
Age (years)	35 (± 9) / 34 (10)

BMI body mass index, *SD* standard deviation, *IQR* interquartile range

Discussion

In this cohort, comprised mostly of morbidly obese women, overall rates of regression were lower than what has been published previously in the literature with at least partial regression noted in only 46% of patients and complete regression in 40% of patients [6, 7]. Furthermore, BMI did not significantly impact progestin treatment outcomes among obese patients. These data prove similar to findings by Gonthier et al. [19], who found no statistically significant difference when comparing response rates between obese and non-obese women rates with CAH and grade 1 endometrial cancer. Though response rates in their study were higher than seen in our study (76% for non-obese and 67% for obese women, $P = 0.72$), it included 40 women total (only 23 of whom had atypical hyperplasia) and featured a majority of non-obese patients [19]. Thus, our study is more specific to women with CAH.

Several theories explain the low response rates and lack of statistically significant findings noted in this study. The study population was predominantly composed of morbidly obese patients (45%). Though the sample size in this study was considerably larger than others in the literature, only 15% of were of normal weight, resulting in lack of a statistical power. If a true difference in the rate of complete regression exists between obese and non-obese patients, we

Table 2 Rates of complete regression to progestin therapy

	Complete regression *N* (%)			95% CI[b]	*P*
	No (*N* = 70)	Yes (*N* = 47)	OR[b]		
BMI (kg/m^2)[a]					
Underweight, normal, overweight (< 30)	11 (61%)	7 (39%)	(Ref)		
Class I and class II obesity (30–39.99)	25 (60%)	17 (40%)	1.07	[0.35, 3.31]	
Class III obesity (40 +)	34 (64%)	19 (36%)	0.88	[0.29, 2.64]	0.73
Age (years)					
18–30	21 (55%)	17 (45%)	(Ref)		
31–64	49 (62%)	30 (38%)	0.76	[0.35, 1.66]	0.48
Diabetes					
No diabetes	53 (61%)	34 (39%)	(Ref)		
Diabetes	17 (57%)	13 (43%)	1.19	[0.51, 2.76]	0.68
Hyperlipidemia					
No hyperlipidemia	62 (60%)	41 (40%)	(Ref)		
Hyperlipidemia	8 (57%)	6 (43%)	1.13	[0.37, 3.51]	0.83
Hypertension					
No hypertension	51 (57%)	39 (43%)	(Ref)		
Hypertension	19 (70%)	8 (30%)	0.55	[0.22, 1.39]	0.20
Parity					
Nulliparous	45 (60%)	30 (40%)	0.00		
Parous	25 (60%)	17 (40%)	1.02	[0.47, 2.20]	0.96
Gravidity					
Nulligravid	39 (61%)	25 (39%)	(Ref)		
Gravid	31 (58%)	22 (42%)	1.11	[0.53, 2.33]	0.79
CAH treatment type[c]					
Systemic	65 (63%)	39 (38%)	(Ref)		
IUD	5 (38%)	8 (62%)	2.64	[0.70, 11.04]	0.096

BMI body mass index, *OR* odds ratio, *CI* confidence interval, *CAH* complex atypical hyperplasia, *IUD* intrauterine device

[a]BMI missing for 4 participants

[b]OR and 95% CI calculated using logistic regression unless otherwise indicated

[c]OR and 95% CI calculated using exact logistic regression

would need to enroll 473 obese and 473 non-obese patients to achieve 80% power to detect a difference at a significance level of 0.05. Similarly, to detect a significant difference in the rates of at least partial regression, 271 obese and 271 non-obese subjects would be needed. From this aspect, our study may be underpowered, resulting in a type II error.

We noted that providers tended to use localized progestin therapy more often in patients with class III obesity than in those with lower BMIs. This preference likely stems from the same perception that provoked our interest in this study, evidence of altered pharmacokinetics of progestins in obese patients [12–14, 20]. Relatively short follow-up time in our study may result in lead-time bias, as the progestin therapy is a slow process that may take a certain time to demonstrate a treatment response. Another postulation is that physicians may perceive obese patients as less compliant with medical treatment than their lower BMI counterparts [21]. In turn, they may recommend the LNG-IUS, which provides continuous progestin therapy for 5 years in patients who are not able or willing to refill medications or return to clinic visits, as a means of promoting compliance.

Systemic progestins such as megesterol acetate and depo medroxyprogesterone stimulate appetite and can result in weight gain [15, 22], which would be detrimental to several goals of care in this already obese population. Increasing obesity may contribute to endogenous production of unopposed estrogen and associated disease such as polycystic ovarian syndrome, infertility, diabetes mellitus, and hypertension. These comorbidities may further decrease the likelihood of conception and increase the risk of pregnancy complications. Since the main goal of fertility-sparing treatment is obtaining viable offspring, it is easy to see why providers might encourage LNG-IUS placement in this population.

Our results suggest that the LNG-IUS may be more effective than systemic therapy in obese women with CAH. A recent retrospective study reported on the effectiveness of

Table 3 Rates of overall response to progestin therapy

	Overall response[d], *N* (%)			95% CI[b]	*P*
	No (*N* = 63)	Yes (*N* = 54)	OR[b]		
BMI (kg/m^2)[a]					
Underweight, normal, overweight (< 30)	10 (56%)	8 (44%)	(Ref)		
Class I and class II obesity (30–39.99)	22 (52%)	20 (48%)	1.14	[0.37, 3.45]	
Class III obesity (40 +)	31 (58%)	22 (42%)	0.89	[0.30, 2.61]	0.70
Age (years)					
18–30	20 (53%)	18 (47%)	(Ref)		
31–64	43 (54%)	36 (46%)	0.93	[0.43, 2.02]	0.85
Diabetes					
No diabetes	48 (55%)	39 (45%)	(Ref)		
Diabetes	15 (50%)	15 (50%)	1.23	[0.54, 2.83]	0.62
Hyperlipidemia					
No hyperlipidemia	56 (54%)	47 (46%)	(Ref)		
Hyperlipidemia	7 (50%)	7 (50%)	1.19	[0.39, 3.64]	0.76
Hypertension					
No hypertension	46 (51%)	44 (49%)	(Ref)		
Hypertension	17 (63%)	10 (37%)	0.61	[0.25, 1.49]	0.28
Parity					
Nulliparous	41 (55%)	34 (45%)	0.00		
Parous	22 (52%)	20 (48%)	1.10	[0.51, 2.34]	0.81
Gravidity					
Nulligravid	35 (55%)	29 (45%)	(Ref)		
Gravid	28 (53%)	25 (47%)	1.08	[0.52, 2.24]	0.84
CAH treatment type[c]					
Systemic	58 (56%)	46 (44%)	(Ref)		
IUD	5 (38%)	8 (62%)	2.01	[0.54, 8.34]	0.24

BMI body mass index, *OR* odds ratio, *CI* confidence interval, *CAH* complex atypical hyperplasia, *IUD* intrauterine device

[a]BMI missing for four participants

[b]OR and 95% CI calculated using logistic regression unless otherwise indicated

[c]OR and 95% CI calculated using exact logistic regression

[d]Both complete and partial regressions

Table 4 Association of BMI and CAH treatment type

	N (%)		*P*
	Systemic	IUD	
BMI[a] (kg/m^2)			
Underweight, normal, overweight (< 30)	17 (94%)	1 (6%)	
Class I and class II obesity (30–39.99)	39 (93%)	3 (7%)	
Class III obesity (40 +)	44 (83%)	9 (17%)	0.09[b]

Percent per row

BMI body mass index, *IUD* intrauterine device, *CAH* complex atypical hyperplasia

[a]BMI missing for four participants

[b]Class III versus others

LNG-IUS in women with CAH ($n = 15$). The 6-month overall response rate was markedly high at 80% (95% CI 52–96), including a 73% complete regression rate [23]. Their study population was similar to ours in that the majority were obese. Both their study and ours note a benefit of LNG-IUS in obese women with CAH. However, given the limited sample sizes in both ($n = 15$, and $n = 9$, respectively), a larger sample size is required prior to drawing more definitive conclusions.

Future studies should also examine the impact of other medications shown to prevent cancer and/or augment treatment response, such as metformin, aspirin, statins, and beta-blockers [24–27]. Currently, there is an ongoing phase II clinical trial examining the effectiveness of adding metformin to the LNG-IUS for treatment of CAH (NCT02035787). We hope that this will elucidate the value of metformin in the management of CAH.

Finally, our institution is a tertiary care facility caring for an indigent population with a high percentage of under-educated patients, many of whom speak only some or no English. Compliance not only with medication regimens but with clinic visits can be problematic in this population, which may be due to lifestyle and an incomplete understanding of the significance of a diagnosis of CAH or what the medications are for. For the purposes of this study, we were unable to assess compliance with medication regimens, forcing an assumption that medication regimens were taken as prescribed, which may not have been the case.

Strengths of the study include that it is likely the largest single study to date examining treatment outcomes of CAH, particularly obese population. Though meta-analyses have compiled regression data on up to 189 patients with atypical hyperplasia [28, 29], previous individual studies have included a maximum of around 70 subjects. Our study included 117 patients. Furthermore, we studied a large proportion of obese patients (> 80%).

Weaknesses include that many patients were excluded due to lack of treatment data or follow-up biopsy. The population was predominantly hispanic and generalizability to other races/ethnicities is unknown. Furthermore, with no standardized protocol in place for treatment and follow-up of these patients, the study was complicated by a high degree of treatment variability, and we were unable to conduct an agent-specific analysis. Finally, patients frequently underwent variable durations of therapy prior to follow-up biopsy. We required at least 1 month of therapy, but some had more than 6 months of therapy prior to follow-up biopsy, while others may have stopped therapy for several months prior to endometrial sampling.

In conclusion, our study suggests that local progestin therapy with LNG-IUS may be an attractive approach, particularly in morbidly obese patients. Given the current pandemic expansion of obesity worldwide, the incidence of CAH is anticipated to be increasing in the future. Thus, addressing utility of LNG-IUS may be most valuable in obese women with CAH [30]. Further prospective studies are warranted.

Author contributions MAC: conceptualization, data curation, funding acquisition, investigation, methodology, project administration, visualization, and writing (original draft). CLC: data curation and writing (review/edits). SAW: data curation and writing (review/edits). NB: formal analysis, software, visualization, and writing (review/edits). CED: conceptualization, supervision, and writing (review/edits). BO: conceptualization, supervision, and writing (review/edits). KM: funding acquisition, investigation, methodology, project administration, supervision, validation, and writing (review/edits).

Funding Ensign Endowment for Gynecologic Cancer Research (K.M.). ARCS Foundation, Inc., Los Angeles founder chapter-Margaret Kersten Ponty Postdoctoral Fellowship (M.A.C.).

Compliance with ethical standards

Conflict of interest Honorarium, Chugai (K.M.) not related to this study; none for others.

Ethical approval The study involving human participants performed by authors is approved by Institutional Review Board, University of Southern California. This retrospective study of archived medical records waived to obtain informed consents from study participants.

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