RESEARCH

Changes in clinical patterns of Chinese patients with primary hyperparathyroidism in the past 12 years: a single-center experience

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Abstract

The clinical presentation of primary hyperparathyroidism (PHPT) differs between patients from developed and developing countries. In China, the clinical pattern has changed over the past few decades. Our aim was to elucidate general changes in the clinical characteristics of PHPT from 2010 to 2021. We enrolled 343 patients with PHPT at the Qilu Hospital of Shandong University, Jinan, China, from January 2010 to May 2021, including both surgical and non-surgical patients. Patients were divided into two subgroups, 2010–2016 (group A, $n = 152$) and 2017–2021 (group B, $n = 191$), based on the time span. We compared clinical manifestations and laboratory result data between these two groups. The mean patient age was 52.59 ± 13.55 years, and the male-to-female ratio was 1:2.54. Of the 343 patients, 183 (53.35%) had symptomatic PHPT; bone pain, urolithiasis, and fatigue were the most common symptoms. Post-operative pathology showed that 96.20% of the patients had parathyroid adenoma, whereas 2.41% had parathyroid carcinoma. Great changes occurred between 2010 and 2021; the percentage of patients with asymptomatic PHPT (aPHPT) increased from 36.18% in group A to 54.97% in group B. Moreover, patients in group B showed significantly lower serum calcium, alkaline phosphatase, parathyroid hormone, and urinary phosphate levels but higher serum 25-hydroxyvitamin D levels than those in group A. Clinical presentations in group B were also milder. In conclusion, the clinical characteristics of Chinese PHPT patients changed dramatically from 2010 to 2021, with asymptomatic PHPT (aPHPT becoming the predominant type over the last 3 years.

Key Words

- primary hyperparathyroidism
- asymptomatic primary hyperparathyroidism
- China
- clinical features

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Introduction

In the 1970s, due to the popularization of serum calcium (Ca) examination, a novel type of primary hyperparathyroidism (PHPT) called asymptomatic PHPT (aPHPT) emerged. It lacks the typical clinical symptoms caused by excessive secretion of parathyroid hormone (PTH). Epidemiological studies have shown that aPHPT has replaced classic symptomatic PHPT as the primary clinical type, comprising 80–95% of PHPT cases in most Western countries (1, 2, 3). However, in developing countries such as China, India, and South Africa, symptomatic PHPT remains the primary type (4, 5, 6).

An investigation conducted in 455 PHPT patients in Beijing from 1974 to 2009 showed that aPHPT represented only 4.6% of all cases (7). However, a trend of aPHPT

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tending to predominate over symptomatic PHPT has been reported in several single-center studies in China (4, 8). A study conducted in Shanghai showed that the percentage of aPHPT increased from 15 to 21% during the period 2000–2006 to 42.4–52.5% during the period 2007–2010 (9). However, more recent changes in the clinical profile of PHPT in China remain unclear.

Therefore, we performed a retrospective single-institution study in a tertiary hospital to analyze data on sporadic PHPT and to elucidate the clinical pattern of PHPT at our hospital between 2010 and 2021.

Patients and methods

We retrospectively reviewed the medical records of PHPT patients who had been admitted to our hospital between January 2010 and May 2021. The diagnosis of PHPT was established by the presence of hypercalcemia and concomitant aberrantly elevated or inappropriately normal serum PTH level – specifically, PTH >20 pg/mL when serum Ca was >2.6 mmol/L (10). The diagnosis of aPHPT was based on the absence of typical symptoms or signs related to hypercalcemia; diagnoses were made incidentally during serum Ca examination or neck ultrasound (US). According to Silverberg & Bilezikian (42), PHPT symptoms were defined as symptoms caused by hypercalcemia. Typical symptoms are mainly musculoskeletal (bone pain, fracture), urological (urolithiasis, polyuria, and hematuria), gastrointestinal (nausea, vomiting, and loss of appetite), and neuropsychiatric (fatigue, dizziness, and depression). Hypercalcemic crisis is defined as a serum Ca level >3.75 mmol/L. Secondary or tertiary hyperparathyroidism and multiple endocrine neoplasia were excluded. The study protocol was approved by the Clinical Research Ethics Committee of Qilu Hospital, Shandong University, Jinan, China. We waived informed consent due to the retrospective design of the study.

Laboratory assays included serum Ca (reference range, 2.00–2.60 mmol/L), serum phosphate (0.60–1.60 mmol/L), fasting blood glucose (FBS; 3.7–6.0 mmol/L), alkaline phosphatase (AKP; 50–135 U/L), serum creatinine (sCr; 58–133 umol/L), PTH (15–65 pg/mL; Roche Diagnostics GmbH), and 25-hydroxyvitamin D (25(OH)D; ≥30 ng/mL; Roche Diagnostics GmbH). We calculated albumin (ALB)-corrected serum Ca levels (mmol/L) using the following formula:

$$\text{Serum Ca concentration} = \text{measured serum Ca}\left(\text{mmol/L}\right) + \left(40 - \text{serum albumin}\left[\text{g/L}\right]\right) \times 0.02$$

US was used to detect parathyroid nodules and kidney stones. Diagnoses of parathyroid carcinoma (PC), adenoma, cysts, and hyperplasia were confirmed by pathological examination after surgery.

We performed all statistical analyses using SPSS software version 24.0 (IBM Corp.). Normally distributed continuous data (assessed using the Kolmogorov–Smirnov test) were presented as mean ± s.d. and analyzed using an independent sample *t*-test. Non-normally distributed data were presented as median (percentage) and analyzed using the Mann–Whitney *U* test. We presented categorical variables as numbers (*n*) with percentages (%) and analyzed them using the chi-square test. Results were considered significant at $P < 0.05$.

Results

Demographics and general characteristics of patients with PHPT

Between January 2010 and May 2021, 343 patients were diagnosed with PHPT at our hospital, including 97 men and 246 women, for a male-to-female ratio of 1:2.54 in the present study. Mean age was 52.59 ± 13.55 years; the age group of 50–59 years was the largest (Fig. 1).

Of the 343 patients, 183 (53.35%) had symptomatic PHPT. The clinical manifestations of these patients are presented in Table 1. Bone pain, urolithiasis, and fatigue were the most common symptoms. Of the remaining 160 aPHPT cases, 98 were diagnosed by neck US and 62 by serum Ca examination.

In total, 290 patients with PHPT met the criteria for surgery and underwent parathyroidectomy (PTX). Post-operative pathology showed that 279 of these patients had parathyroid adenoma (96.20%), two had hyperplasia (0.69%), two had parathyroid cysts (0.69%), and seven had PC (2.41%).

Changes in PHPT profiles during the period 2010–2021

In recent years, the number of PHPT patients in our hospital has gradually increased (Fig. 2). In particular, the number of those with aPHPT has increased greatly, from 1 in 2010 to 32 in 2020. Moreover, the proportion of aPHPT cases exceeded 50% for the first time in 2019 and rose to 58.18% in 2020 and to 82.32% within the first 5 months of 2021.

Of the total 343 patients, 55.69% were identified in the last 5 years. We divided these 12 years into two periods,

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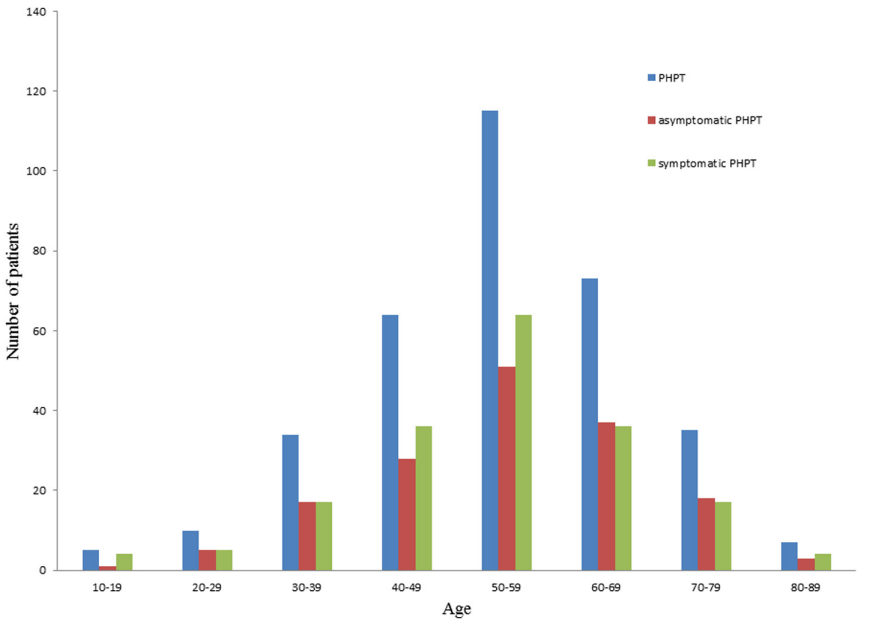

Figure 1
Age distribution of the primary hyperparathyroidism (PHPT) patients.

2010–2016 (group A) and 2017–2021 (group B), to investigate the patterns of change in PHPT patients over the past 12 years. A total of 152 and 191 patients were diagnosed with PHPT during these two time periods, respectively. No significant differences in gender were found between the two groups; however, patients in group B were older than those in group A. Compared with group A, a higher percentage of patients in group B had aPHPT (54.97 vs 36.18%; $P < 0.01$), but the incidence of hypercalcemic crisis was lower (7.33 vs 14.47%; $P < 0.05$; Table 2). Moreover, 62 patients in group A complained of bone pain, a much higher percentage than in group B (40.79 vs 20.94%; $P < 0.01$), and urolithiasis was also more common in group A than in group B (26.97 vs 15.71%; $P < 0.05$).

Laboratory values changed greatly as well. Patients in group B had significantly lower serum Ca, AKP, PTH, and urinary phosphate levels but higher serum 25(OH)D levels than those in group A. Urinary Ca was also lower in group B, but this difference was not statistically significant (Table 2).

A total of 37 patients had histories of cancer when they were diagnosed with PHPT, and another five were newly diagnosed with papillary thyroid carcinoma (PTC) during pre-PTX examinations. Of these 42 patients, 27 had PTC, and diagnoses for the remainder included breast cancer ($n = 4$), lymphoma ($n = 3$), endometrial carcinoma ($n = 2$), pharyngeal cancer ($n = 2$), leukemia ($n = 1$), prostate cancer ($n = 1$), colon cancer ($n = 1$), and gastric cancer ($n = 1$). No difference in the incidence of cancer was found between groups A and B (10.53 vs 13.61%; $P = 0.41$).

Table 1 Clinical manifestations of the symptomatic PHPT patients (n = 183).

Manifestations	**Number** (%)
Bone pain	102 (55.74)
Urolithiasis	71 (38.80)
Fatigue	55 (30.05)
Nausea and vomiting	48 (26.23)
Polydipsia and polyuria	11 (6.01)
Fracture history	12 (6.56)
Palpitation and chest distress	8 (4.37)
Constipation	2 (1.09)
Gastric ulcer	4 (2.19)
Psychiatric symptoms	4 (2.19)

Discussion

In this retrospective single-institution study, we analyzed the data of 343 patients with PHPT to investigate changes in clinical patterns of the disease in China between 2010 and 2021. We observed a remarkable increase in the number of patients with PHPT at our center, from 7 in 2010 to 55 in 2020. Women aged 50–60 years represented the subpopulation with the highest risk, in agreement with previous studies (3, 11, 12). The clinical spectrum of PHPT also changed greatly. Patients in group B were much older than those in group A, but group B had a higher incidence of aPHPT.

Previous studies have shown that clinical PHPT presentation differs between patients from developed countries and developing countries like China and India; patients in developing countries are younger than those in

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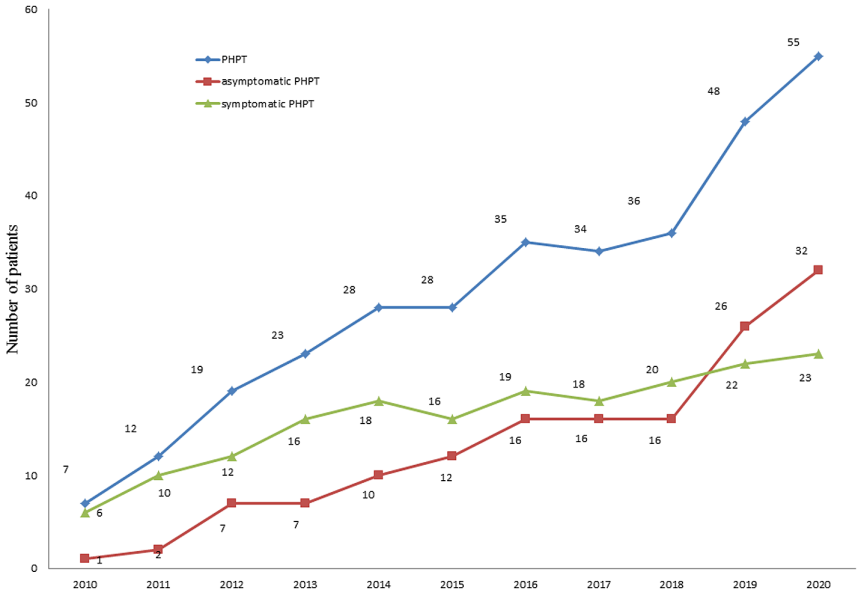

Figure 2
Number of patients with primary hyperparathyroidism (PHPT), asymptomatic PHPT (aPHPT), and symptomatic PHPT from 2010 to 2020. The number of patients with PHPT increased greatly from 2010 to 2020.

developed countries (4, 13, 14). According to the literature, 80–95% of the PHPT patients in Western countries are aPHPT (1, 2, 3, 6), and the percentage of aPHPT has not changed substantially over the past four decades (2, 4). However, symptomatic PHPT is more prevalent in developing countries such as China and India (9, 15, 16). In a review published in 2020, 17 literatures about the presentation of PHPT in developing countries were analyzed, including India, Brazil, Turkey, and Pakistan. Results showed that the symptomatic PHPT was still the predominant type in these countries (17). Moreover, of the symptomatic PHPT patients, those in developing countries have more severe symptoms (14, 18). On one hand, the popularization of Ca and US examinations in Western countries has greatly facilitated the diagnosis of PHPT in its early stage; on the other hand, lower dietary Ca intake and vitamin D deficiency in patients from developing countries promote the secretion of PTH, leading to early onset and more severe clinical presentations (13, 19).

However, in recent years, there has been an increasing proportion of aPHPT patients in mainland China (9, 20). We summarize the literature in Table 3. Our findings revealed that the proportion of aPHPT patients increased from 3% in the 20th century to 26.90–54.82% in the 2010s (13, 21, 22, 23). Two studies reported on the predominance of aPHPT. Zhao *et al.* found that the proportion of aPHPT patients reached 52.53% at their center during the 2009–2010 period (9). However, this result was an anomaly;

Table 2 Comparison of clinical and biochemical characteristics between group A and group B.

	Total PHPT (*n* = 343)	**Group A** (2010–2016, *n* = 152)	**Group B** (2017–2021, *n* = 191)	***P* value**
Age	52.59 ± 13.55	51.18 ± 13.31	55.50 ± 13.48	<0.01
Female/male ratio	2.54:1	1.98:1	3.15:1	0.055
aPHPT	160	55	105	<0.01
Hypercalcemic crisis	36	22	14	<0.05
Ca, mmol/L	2.92 (2.74, 3.24)	2.98 (2.77, 3.34)	2.89 (2.71, 3.14)	<0.05
Albumin-corrected Ca, mmol/L	2.92 (2.75, 3.25)	2.99 (2.77, 3.34)	2.89 (2.72, 3.15)	<0.05
Phosphate, mmol/L	0.75 ± 0.21	0.74 ± 0.22	0.75 ± 0.21	0.499
AKP, U/L	122.00 (89.00, 190.00)	135.00 (94.25, 220.50)	115.00 (87.00, 172.00)	<0.05
PTH, pg/mL	288.00 (144.98, 737.20)	395.55 (198.40, 1050.25)	208.75 (121.23, 564.25)	<0.01
25(OH)D, ng/mL	11.63 (6.87, 17.52)	4.32 (3.00, 8.16)	12.74 (8.52, 18.28)	<0.01
Urinary Ca, mmol/24 h	10.70 ± 5.80	12.42 ± 7.04	9.89 ± 4.98	0.061
Urinary phosphate, mmol/24 h	17.32 (11.36, 24.53)	23.40 ± 12.92	16.90 (10.38, 23.15)	<0.05
FBS, mmol/L	5.02 (4.63, 5.56)	5.02 (4.62, 5.45)	5.03 (4.65, 5.59)	0.451
Creatinine, umol/L	62.33 ± 20.98	61.72 ± 21.08	63.72 ± 20.86	0.517
Tumor size, cm	2.00 (1.50, 2.58)	2.00 (1.50, 2.50)	2.00 (1.50, 3.00)	0.274

AKP, alkaline phosphatase; aPHPT, asymptomatic primary hyperparathyroidism; FBS, fast blood glucose; PTH, parathyroid hormone; PHPT, primary hyperparathyroidism; 25(OH)D, 25-hydroxyvitamin D.

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Table 3 Increasing trend of aPHPT in published literature.

	Case number	City	Research period	aPHPT (%)	Serum Ca (mmol/L)	Serum PTH (pg/mL)	Reference
1	134	Beijing	1958–1993	3	3.09 ± 0.27	21.4-fold of upper limit	14
2	455	Beijing	1974–2009	4.60	not mentioned	not mentioned	7
3	59 (pediatric)	Beijing	1975–2015	1.70	3.01 ± 0.30	7.69-fold of upper limit (3.13, 28.29)	22
4	115	Beijing	1975–2015	10.20	3.00 ± 0.37	7.62-fold of upper limit (3.64, 13.32)	22
5	31	Hong Kong	1983–1992	39.00	3.02 ± 0.06	342 ± 64	8
	190		1993–2002	59	2.93 ± 0.02	155 ± 11	
6	84	Shanghai	2000–2006	19.05	2.93 ± 0.35	402.10 (103.22, 2700.62)	9
	165		2017–2010	48.48			
7	457	Shanghai	2005–2019	31.30	2.83 (2.70, 3.10)	168.35 (115.30, 370.98)	21
8	260	Shanghai	2005–2016	26.90	2.93 ± 0.41	539.79 (128.40, 533.10)	25
9	44	Harbin	2008–2012	15.91	3.01 ± 0.40	1025.54 ± 887.69	26
	153		2013–2017	66.01	2.03 ± 0.48	657.10 ± 806.75	
10[a]	32	Beijing	1/2010–3/2013	19.29	3.96 ± 0.54	290 (94.5, 2603)	23
	108		4/2013–6/2016		2.82 ± 0.34	193 (40.6, 2269)	
11	232	Beijing	2016–2019	46.10	2.72 (2.59, 2.87)	146.3 (109.6, 245.2)	24
12	152	Jinan	1/2010–12/2016	36.18	2.98 (2.77, 3.34)	395.55 (198.40, 1050.25)	The present study
	191		1/2017–5/2021	54.97	2.89 (2.71, 3.14)	208.75 (121.23, 564.25)	

[a]The definition of aPHPT was different in this study. aPHPT, asymptomatic primary hyperparathyroidism; PTH, parathyroid hormone.

more recent studies conducted in the same city showed that symptomatic PHPT continued to predominate from 2010 to 2019 (20, 24). Another study conducted in Harbin, a northern city of China, showed that the percentage of aPHPT patients was 54.82% at the research team's center during the period 2008–2017 (25). However, selection bias might have occurred, as the cohort was surgically treated, and 11.17% of the patients had concomitant PTC, which greatly increases the hospitalization rate in aPHPT. In the present study, we found that aPHPT predominated at our center from 2017 to 2021, especially since 2018; the proportion of aPHPT patients increased to 54.16% in 2019 and continued to increase to 58.18% in 2020 and to 82.35% in the first 5 months of 2021. Our study is the first to confirm aPHPT predominance in an unselected Chinese inpatient cohort.

The fast-increasing number of PHPT patients, especially aPHPT patients, mainly stems from the popularization of neck US and serum Ca screenings (9, 26). Our study included 160 patients with aPHPT, which was the largest cohort of aPHPT patients in China. Blood Ca screening and US examination are not only the leading reasons for the rapid increase in aPHPT patients but have also greatly affected the clinical manifestation profile of symptomatic PHPT cases. According to studies conducted before 2016, the classic symptoms of PHPT patients in China included bone pain, polyuria, fracture, and urolithiasis (9, 24). However, in our study and another one published in 2021 (20), bone pain, nephrolithiasis, and fatigue were the three most common symptoms, with the fracture rate declining remarkably in symptomatic PHPT patients. Previous studies have suggested that disease duration was an important factor mediating PHPT symptoms. Many symptoms such as bone pain and nephrolithiasis could be complications of longstanding mild hypercalcemia that had previously gone undetected (27). At our center, hospitalized patients were conventionally screened for serum Ca, while US was broadly performed during annual physical examinations; both tests greatly facilitated the diagnosis of PHPT at an early stage. Meanwhile, socioeconomic status (SES) is another factor that greatly influences the detection of PHPT. According to a study from India, SES critically affects clinical presentation: among higher-SES patients, the proportion of aPHPT is higher, and those with symptomatic PHPT show milder symptoms (18, 28). Also, as the economy of the whole society improves, the popularization of US examination greatly increases. In the present study, 30.05% of PHPT patients at our hospital complained of fatigue, which points out the need to measure serum Ca in patients with this complaint in order to rule out the possibility of PHPT.

PHPT is also associated with various cancers. In studies conducted in 9782 PHPT patients in Sweden, hematopoietic malignancies and breast cancer were the two most common cancers (29, 30, 31). The high levels of PTH and 1,25-hydroxyvitamin D in PHPT patients might exert an inhibitory effect on various parameters of the immune system and favor carcinogenesis (32, 33, 34). However,

increased mitotic activity induced by hypercalcemia and elevated concentrations of angiogenic growth factors and fibroblast growth factor induced by PTH could stimulate tumor growth (35, 36, 37). In our study, PTC was the most common cancer, and the aforementioned study conducted in Harbin also found a high incidence of PTC, 11.17% (25). One possible explanation for this phenomenon is that the popularization of neck US has increased the detection of PTC in recent years (38). Some researchers believe that PTC in PHPT cases is overdiagnosed because in PHPT patients with concomitant PTC, the tumor diameter is significantly smaller than in patients with PTC alone (39, 40). However, in our previous study, we found that PTC in aPHPT patients showed a higher rate of microscopic extrathyroidal invasion than PTC in the general population (41). Therefore, the relationship between these two diseases needs further investigation.

Our research had certain limitations. We performed a retrospective single-institution study, and all patients in the cohort were hospitalized. Although we included both surgical and non-surgical patients, we might have still underestimated the number of aPHPT patients. Therefore, multi-center studies with larger populations are needed to create a more comprehensive profile of PHPT in China. Also, the lack of dual-energy X-ray data for all patients before and after surgery impeded us in fully estimating the effect of PHPT on bone mineral density.

In conclusion, in this retrospective single-center study, we demonstrated the significant changes in the clinical characteristics of PHPT patients in China during the period 2010–2021. The number of patients increased greatly, while the prevalence of hypercalcemic crisis decreased. In addition, this study is the first to confirm the predominance of aPHPT in Chinese PHPT patients. Moreover, serum Ca examination and neck US were the leading reasons for these changes.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

Study design: Xiaoli Zhang and Ling Jiang. Study performance: Yuan Liu. Data collection: Siyi Guo, Nan Liu, and Yan Liu. Data analysis: Siyi Guo, Jinsong Wu, and Rongai Wang. Data interpretation: Xiaoli Zhang, Bin Lv, and Jinbo Liu. Manuscript drafting: Yuan Liu and Siyi Guo. Revision of manuscript content: Xiaoli Zhang and Ling Jiang. Approval of final version of manuscript: Xiaoli Zhang, Yuan Liu, and Ling Jiang. Siyi Guo and Xiaoli Zhang were responsible for the integrity of the data analysis.

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