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Clinicopathological importance of colorectal medullary carcinoma

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Summary

Purpose Medullary carcinoma (MC) is a rare tumor with a solid growth pattern without glandular differentiation and constitutes less than 1% of colorectal cancers. Lymph node positivity and distant organ metastasis were reported to be lower than in other poorly differentiated adenocarcinomas. Therefore, the diagnosis of MC is pathologically important in terms of follow-up and treatment. We aimed to investigate the characteristics of medullary cancer in our case series.
Methods 427 patients with colorectal cancer (CRC) who underwent surgery between January 2011 and December 2017 were evaluated retrospectively in 2 groups as MC ($n = 13$) and non-MC ($n = 414$) in terms of demographic characteristics, pathological data, and oncological outcomes.

Results 76.9% ($n = 10$) of the MC group were female while 36% ($n = 149$) of the non-MC group were female ($p = 0.003$). The tumors were located in the right colon in 84.6% ($n = 11$) of the MC patients and in 26.6% ($n = 110$) of the non-MC patients ($p < 0.001$). The rate of laparoscopy was 83.8% for all CRC patients, and 53.8% for the MC group ($p = 0.01$). T4 cases (69.2%) and tumor volume ($131 \pm 87\,cm^3$) in the MC group were significantly higher than in the non-MC group ($p < 0.05$). The rate of high microsatellite instability (MSI) was 85%. 5-year overall survival was 75% for the patients with MC and 82% for non-MC ($p = 0.13$).
Conclusion MC is commonly localized in the right colon, has a large tumor size, and is mostly diagnosed in the T4 stage. As MC most likely have defects in DNA MMR, correct pathological diagnosis is impor-

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tant for postoperative treatment and the prognosis of the patients.

Introduction

Colorectal cancers (CRC) are the second most common type of cancer among females and the third most common among males [1–3]. The World Health Organization (WHO) classification of colorectal cancers indicates that there are various subtypes of colorectal carcinomas; including cribriform comedo type adenocarcinoma, medullary carcinoma (MC), micropapillary carcinoma, mucinous adenocarcinoma, serrated adenocarcinoma, and signet ring cell carcinoma [4].

MC is characterized by tumor-infiltrating lymphocytes and large cells that proliferate in large trabeculae or layers and that have definite nucleoli, eosinophilic cytoplasm, and vesicular nuclei ([4]; Figs. 1, 2 and 3). Even though MC has morphological similarity to
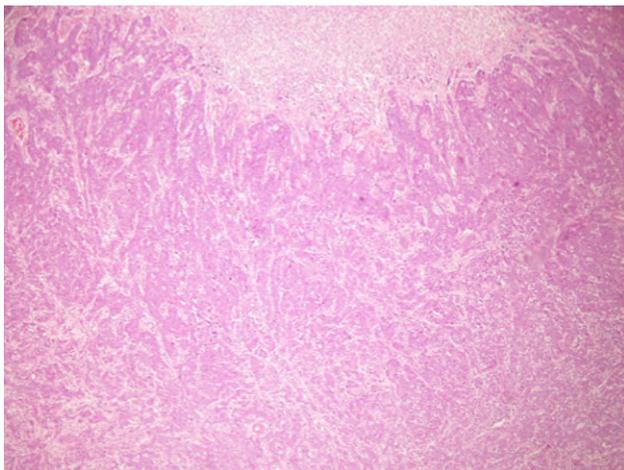

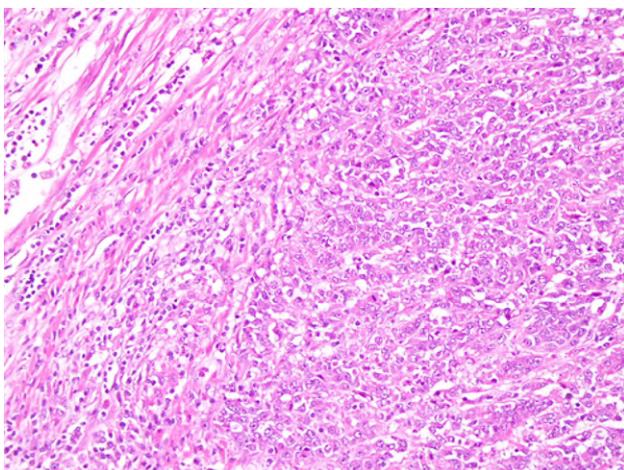**Fig. 1** Medullary carcinoma, hematoxylin and eosin staining (×40)

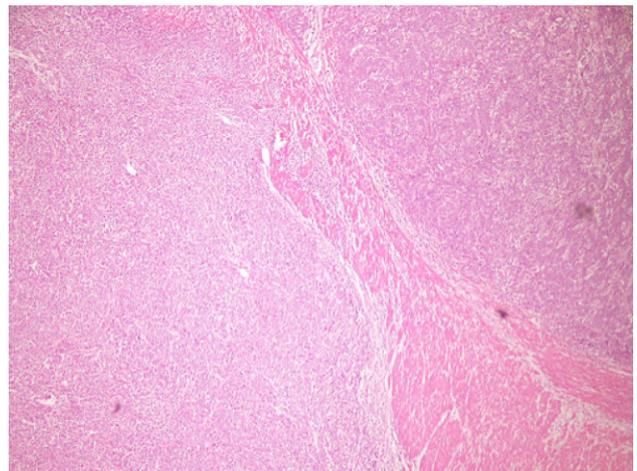**Fig. 2** Intratumoral lymphocytic infiltration (×200)

Fig. 3 Pushing border of the carcinoma within and around tumor (×40)

poorly differentiated adenocarcinomas, it has a relatively better prognosis [5, 6]. The prevalence of MC varies; however, the literature indicates the rate to be between 0.08 and 3% [5, 7].

Another important feature of MC is a high level of microsatellite instability (MSI-H), which can affect the treatment modality [5, 8]. This feature, defined as a mutation in the DNA mismatch repair genes (MMR), is clinicopathologically associated with the hereditary nonpolyposis colon cancer (HNPCC, Lynch syndrome). It is indicated that the prognosis of MSI-H cancers is better compared to the poorly differentiated colon cancers [9, 10].

Materials and methods

The current study includes the retrospective evaluation of 427 colorectal cancer patients who were operated on by the same surgical team at the General Surgery Department of the American Hospital (Istanbul, Turkey) between January 2011 and December 2017. The data of the patients were prospectively recorded during the treatment process. According to the WHO CRC classification of 2010, 13 patients were classified as MC and the remaining 414 patients were non-MC. From each patient, 5 to 12 slides from the primary tumor stained with hematoxylin and eosin (H&E) were available.

All cases were evaluated in terms of demographic characteristics (age, body mass index [BMI], gender), tumor location, type of operation, length of hospital stay, pathological data (tumor volume, tumor deposit, tumor microperforation; lymphatic, venous, and perineural invasion), TNM classification, and survival. Informed consent was obtained from all individual participants included in the study. The mean follow-up time was 37 ± 21 months.

Clinical and pathologic variables were analyzed using IBM SPSS Statistics v. 24.0 (IBM Co., Armonk, NY, USA). The two groups of patients (MC and non-MC)

were compared using the chi-square or Fisher's exact test, as appropriate. Overall survival was calculated from the date of surgery for the primary lesion until death from any cause, or was censored at the last follow-up visit. Survival curves were created using the Kaplan–Meier method and were compared using the log-rank test. *P*-values <0.05 were considered statistically significant, and all *p*-values correspond to two-sided significance tests.

Results

Ten of the 13 MC patients (76.9%) and 149 of the 414 non-MC patients (36%) were females ($p = 0.003$). The two groups were not found to be significantly different in terms of mean age, BMI, and length of hospital stay. The tumors were located in the right colon in 84.6% ($n = 11$) of the MC group and 26.6% ($n = 110$) of the non-MC group ($p < 0.001$). There was no rectal location in the MC group.

The mean operative time was 117 ± 37 min in the MC group and 169 ± 69 min in the non-MC group ($p = 0.02$). In the MC group, 7 patients (53.8%) were operated on with laparoscopy and 5 patients (38.5%) underwent open surgery. In 1 case (7.7%), we started with laparoscopy but due to the size of the tumor and the additional morbidities, we converted to open surgery. The mean tumor size was 224.5 cm³ for the open group and 73.6 cm³ for the laparoscopic group. Four of the MC patients (30.7%) underwent open surgery due to obstruction symptoms. In our series of all CRC surgeries, the laparoscopy rate was 83.8%, whereas in the MC cases, this rate was 53.8% ($p = 0.01$; Table 1).

In the MC group, the mean tumor size was 6.6 ± 3 cm and tumor volume was 131 ± 87 cm³, whereas in the non-MC group, these values were 3.9 ± 2.1 cm and 38 ± 88 cm³, respectively ($p < 0.001$). When the T stages of the tumors according to the TNM classification were evaluated, it was seen that the number of T4 cases was significantly higher in the MC group (MC 69.2%, non-MC 23.2%; $p < 0.001$). R0 resection was performed in all patients in the MC group. There was no statistically significant difference between groups in terms of N and M positivity. There was no peritoneal metastasis in the MC group. Tumor microperforation was significantly higher in the MC group (MC 30.8%; non-MC 9.4%; $p = 0.012$), but there was no statistically significant difference between the groups in terms of other prognostic factors (Table 2).

The microsatellite instability evaluation revealed the presence of MSI-H in 11 MC patients (85%). In our series, there was no mortality during the first 30 postoperative days. In the MC group, local recurrence was detected in two patients 3 months later, and both these patients died at the fifth and sixth months after surgery. There was no distant organ metastasis in the MC group at follow-up. In the stage 3 MC group, four of five patients were in remission

Table 1 Comparison of the demographic features and clinical characteristics

	MC ($n = 13$)	Non-MC ($n = 414$)	*p*-value
Gender	–	–	*0.003*
Female	10 (76.9%)	149 (36%)	–
Male	3 (23.1%)	265 (64%)	–
Age (mean ± SD; years)	59 ± 18	62 ± 13	0.54
BMI (mean ± SD; kg/m²)	27.6 ± 7.2	26.8 ± 5.9	0.49
Length of hospital stay (mean ± SD; days)	7.8 ± 3.2	7.6 ± 4.1	0.48
Operative time (mean ± SD; min)	117 ± 37	169 ± 69	*0.02*
Surgical procedure	–	–	*0.01*
Laparoscopic	7 (53.8%)	347 (83.8%)	–
Open	5 (38.5%)	56 (13.5%)	–
Conversion	1 (7.7%)	11 (2.7%)	–
Tumor location	–	–	*<0.001*
Right colon	11 (84.6%)	110 (26.6%)	–
Left colon	2 (15.4%)	158 (38.2%)	–
Rectum	0	146 (35.3%)	–

MC medullary carcinoma, *non-MC* non-medullary carcinoma, *BMI* body mass index, *SD* standard deviation

Table 2 Comparison of MC and non-MC patients in terms of the pathological outcomes

	MC ($n = 13$)	Non-MC ($n = 414$)	*p*-value
T stage	–	–	*0.002*
T1	1 (7.7%)	52 (12.6%)	0.60
T2	0	61 (14.7%)	0.14
T3	3 (23.1%)	205 (49.5%)	0.06
T4	9 (69.2%)	96 (23.2%)	*<0.001*
Lymph node metastasis (N +)	6 (46.2%)	199 (47.1%)	0.66
Distant metastasis (M+)	2 (15.4%)	63 (15.4%)	0.99
TNM stage	–	–	0.79
Stage I	1 (7.7%)	71 (17.1%)	–
Stage II	5 (38.5%)	121 (29.2%)	–
Stage III	5 (38.5%)	162 (39.1%)	–
Stage IV	2 (15.4%)	60 (14.5%)	–
Tumor size (mean ± SD; mm)	66 ± 28	39 ± 21	*<0.001*
Tumor volume (mean ± SD; cm³)	131 ± 87	38 ± 88	*<0.001*
Tumor microperforation	4 (30.8%)	37 (9.4%)	*0.01*
Tumor deposit	2 (15.4%)	93 (23.5%)	0.49
Harvested lymph nodes (mean ± SD)	35 ± 19	28 ± 11	0.12
Perinodal invasion	3 (23.1%)	86 (22.6%)	0.96
Lymphatic invasion	8 (61.5%)	219 (55.3%)	0.65
Venous invasion	2 (15.4%)	130 (32.9%)	0.18
Perineural invasion	5 (38.5%)	117 (29.6%)	0.49

MC medullary carcinoma, *non-MC* non-medullary carcinoma, *SD* standard deviation

Fig. 4 Kaplan–Meier curves by overall survival for medullary carcinoma (MC) and non-medullary carcinoma (non-MC) (*p* = 0.13)
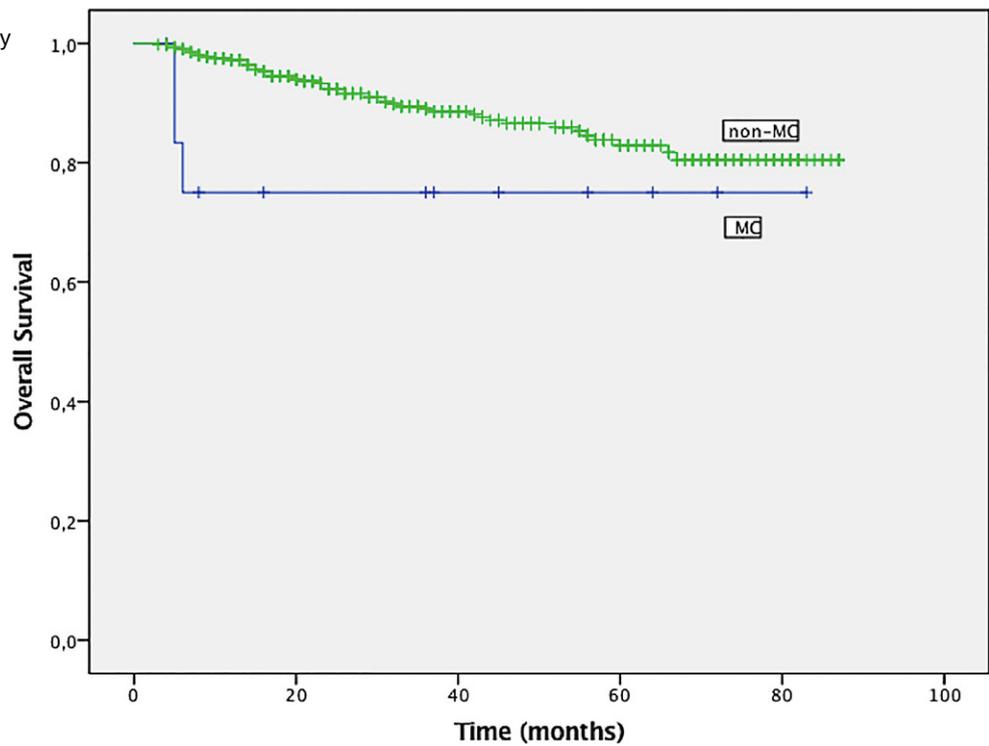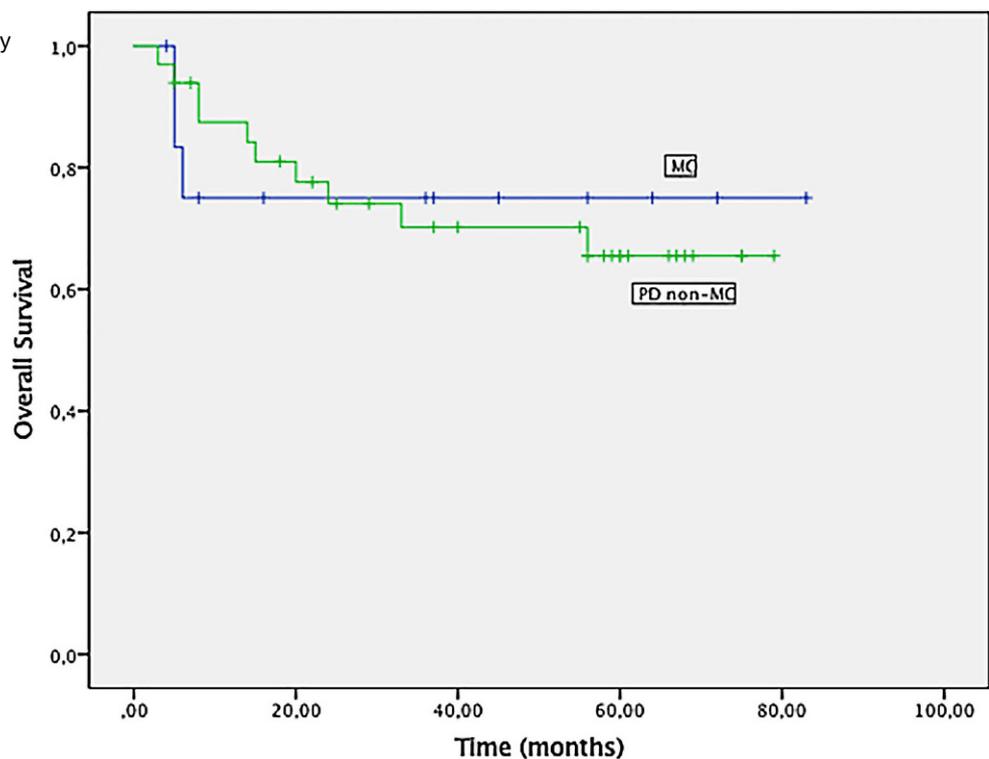

Fig. 5 Kaplan–Meier curves by overall survival for medullary carcinoma (MC) and poorly differentiated non-medullary carcinoma (PD non-MC) (*p* = 0.38)

with chemotherapy, but one patient did not respond to this treatment. The Kaplan–Meier survival analysis revealed a 5-year overall survival rate of 75% for the MC group and 82% for the non-MC group (*p* = 0.13, Fig. 4). However, when the 33 patients with poor differentiation in the non-MC group and the patients in the MC group were compared, it was observed that the 5-year overall survival rate was higher in the MC group, albeit not statistically significantly (MC 75%; poorly differentiated non-MC 65%, *p* = 0.38; Fig. 5).

Discussion

CRC is the third most common cancer in men and the second most common cancer in women, with 1.65 million new cases and approximately 835,000 deaths in 2015 [2]. The prevalence is higher among males than females [11]. Approximately 140,250 new cases of CRC are diagnosed in the United States every year; 97,220 of these are colon cancers, whereas the rest are rectal cancers [3].

In 1977, Gibbs defined a subgroup of colon cancers with a solid growth pattern that reached large sizes and which had a relatively good prognosis [12]. Jessurun [13] and Ruschoff [14] further clarified the presence of these cases in their series published at the end of the 90s, and suggested that the term "medullary carcinoma" be used to distinguish them from other solid CRC.

The WHO classification of colorectal cancers indicates that there are various subtypes of colorectal carcinomas, including cribriform comedo type adenocarcinoma, medullary carcinoma, micropapillary carcinoma, mucinous adenocarcinoma, serrated adenocarcinoma, and signet ring cell carcinoma [4]. According to this classification, MC is characterized by large cells that proliferate in large trabeculae or layers and that have definite nucleoli, eosinophilic cytoplasm, and vesicular nuclei, and by tumor-infiltrating lymphocytes [4]. MC often shows reduced expression of CDX2 [6, 15–18]. A study that compared colorectal MC cases with other microsatellite stable (MSS) and microsatellite instable (MSI) CRCs [19] found that the expression of IDO-1, tRNA (Trp), and the amount of tumor-infiltrated CD8+ and PD-L1+ lymphocytes were significantly higher in the MC group. These parameters were suggested to influence treatment and prognosis [20, 21].

MSI is defined as the result of mutations in the genome and insufficient DNA repair, it is associated with a high mutation rate [22, 23]. MSI is found in approximately 15% of sporadic colorectal carcinomas [24–27]; 3% of these cases are associated with Lynch syndrome [9, 10, 28, 29]. Several studies concerning MC have found high MSI rates [5, 8]. In this study, 11 of the 13 MC patients (84.6%) had MSI-H. Studies investigating the effect of microsatellite instability on treatment indicate that MSI is an important factor for the choice of adjuvant therapy [30–33].

The incidence of MC is generally less than 1% among all CRCs, but the ratios within the series are variable. A study that scanned the Surveillance Epidemiology and End Results (SEER) database found the incidence to be 5–8/10,000 between 1973 and 2006 [5]. Another study found the incidence to be 0.6% between 2002 and 2011 [34]. Knox et al. [7] have studied 102 MC patients and found this rate to be 2.8%. In this study, 13 of the 427 CRC cases were diagnosed with MC (3.04%); thus, the incidence is higher than in the literature. There wasn't a common

consensus regarding the diagnosis of MC before the 2000s thus, the studies may have categorized MC patients as poorly differentiated cancers. The subtypes of CRC (and, thus, MC) were better understood after the year 2000. Also, our center deals especially with the investigation of these subtypes, which we think may have led to the high incidence rate.

MC is a CRC subtype that is most commonly seen in older females and is mostly localized in the right colon. However, there are rare cases in which it is localized in the left colon or the rectum [5, 7, 35–38]. Thirunavukarasu et al. [5] indicated that the mean age of MC patients 69.3 ± 12.5 and the female-to-male ratio is 2.12:1. Knox et al. [7] found the mean age to be 76.8, and the female-to-male ratio to be 3.33:1. Both studies indicated that 86% of the tumors were localized in the right colon [5, 7]. In our study, the female-to-male ratio was 3.33:1 and 84.5% of the tumors were localized in the right colon. However, the mean age is 59 ± 18, which is comparatively young.

Studies have shown that most MC cases are in T3 or T4 stages. Thirunavukarasu et al. [5] found these rates to be 48% for T3 and 32% for T4, whereas Knox et al. [7] reported 43.6% for T3 and 4% for T4. The meta-analysis by Pyo et al. [36] indicates that the lymph node metastasis rates are lower for MC compared to the other poorly differentiated carcinomas. In our study, 10 cases were T4 (76.9%) and 2 cases were T3. Also, the mean tumor size was 7.1 cm and the mean tumor volume was 181 cm^3. 5 patients (38.5%) had lymph node metastasis.

Among all CRC patients, laparoscopic surgery was performed in 83% of the patients, whereas this rate dropped to 53.8% for the MC patients. There was a difference in the tumor volumes of the MC patients who underwent open or laparoscopic surgeries (open 224.5 cm^3; laparoscopy 73.6 cm^3). An advanced T-stage and tumor-related obstruction caused open surgery to be planned from the beginning. There are no clear data in the literature regarding the use of surgical methods for the MC cases.

MSI has a positive effect on the prognosis of CRC; however, the prognosis can vary for different tumor types [39–41]. Some studies investigating the effect of MSI on poorly differentiated CRCs found that MSI-H CRCs had better survival rates, but this finding was not statistically significant [42, 43]. Some new studies have also been carried out, indicating that microsatellite instability does not have a positive effect on survival in metastatic CRC [44, 45].

It is indicated that MC has a better prognosis compared to the other poorly differentiated cancers [5, 35, 36]. Knox et al. performed a large-scale survival analysis and indicated that the 5-year survival rate was 64.6% in the MC group. The same study suggests that the MC survival rate was better than that of the poorly differentiated MSS non-MCs; however, it was similar to the survival rate in poorly differentiated MSI non-MCs. The multivariant analysis indicated that when

the older age group, the high grade, and the tumor stage were taken into consideration, the overall survival rate of MC patients was better than the survival rate of MSI non-MC patients [7]. Pyo et al. also suggested that the survival rate in the MC group was significantly better than for poorly differentiated CRCs, but there is no statistically significant difference compared to the CRCs in general [36]. In our study, the 5-year overall survival rate was 75% for the MC group and 82% for the non-MC group. However, when the MC patients were compared to the 33 poorly differentiated non-MC patients, it was found that the survival rate was higher for the MC patients (MC 75%; poorly differentiated non-MC 65%), but not statistically significantly.

The data from a single institution and the retrospective design of the study are the main limitations, because of possible biases. Although our patient numbers are relatively small, it is difficult to collect large numbers at a single institution because of the low overall incidence of MC. Furthermore, this study does not include information regarding specific genetic mutations and molecular profiling that may influence outcomes.

Conclusion

MC is a rare subtype of colorectal cancer. It is commonly localized in the right colon, has a large tumor size, and is mostly diagnosed in the T4 stage. Minimally invasive procedures can be difficult because of locally aggressive tumor. In general, MC includes an MSI-H pattern; for this reason, the correct pathological diagnosis is important for postoperative treatment and the prognosis of the patients.

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