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Original Article

Duodenal gangliocytic paraganglioma: report of two cases and review of literature

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Abstract: We report two cases of Gangliocytic paraganglioma (GP), one of which was accompanied by lymph node metastasis. Histologically, the tumor was composed of three morphologically distinct cell populations: spindle cells, ganglion-like cells and epithelioid cells. The epithelioid cells were positive for cytokeratin (AE1/AE3), synaptophysin (Syn), chromogranin A (CgA), CD56 and progesterone receptor (PR). Ganglion-like cell types showed positive reactivity for Syn and CD56. In contrast, the spindle-shaped cells showed positive reactivity for S-100. The patient with lymph node metastasis has a good prognosis. Nonetheless, close surveillance is still necessary for patients with GP because a few cases of GP with regional lymph node metastasis and even distant metastasis have been published, including a malignant case of GP showing a lethal course.

Keywords: Gangliocytic paraganglioma, synaptophysin, chromogranin A, CD117

Introduction

Gangliocytic paraganglioma (GP) is a rare tumor that is mainly located in the second portion of the duodenum [1, 2]. It accounts for 6% to 9% of duodenal gastrointestinal neuroendocrine tumors (NETs), ranking the third most frequent histopathologic type after gastrinomas and somatostatinomas [3]. It is featured by its triphasic cellular differentiation, composed of eptihelioid neuroendocrine cells, spindle-shaped cells with Schwannian cell differentiation and ganglion-like cells [1]. According to the World Health Organization (WHO) classification, this tumor has generally been regarded as benign, but a few cases with regional lymph node metastasis and even distant metastasis have been reported. To date, 23 cases of GP with lymph node metastasis and 3 cases with distant metastasis have been published (**Table 1**). Herein we presented two cases of GP, one of which was accompanied by lymph node metastasis (case 1).

Case report

Case 1

A 42-year-old man presented with melana and dizziness for 3 weeks. He was admitted to a local hospital. He denied abdominal pain, nausea, vomiting and fever. His laboratory data revealed anemia (blood hemoglobin value 56 g/L). Computed tomographic (CT) scans showed a mass in the third portion of the duodenum. It was suspected as a leiomyoma. For further examination and treatment he was then transferred to our hospital. CT scans also revealed a mass with 31 mm×24 mm in the third portion of the duodenum. Endoscopic ultrasonography showed a polypoid tumor in duodenum and ulceration on the surface of the lesion. The patient underwent local surgical excision on 7/22/2010. Unfortunately, the follow-up of the patient is not established.

Case 2

A 49-year-old man was admitted to our institute with upper abdominal pain for nine days. He denied nausea, vomiting and changes in bowel habits. Laboratory results were within normal range. CT scans revealed a mass with 38 mm×25 mm near the head of pancreas (**Figure 1**), involving the second portion of the duodenum. Enlarged peripancreatic lymph nodes were observed. Endoscopic ultrasonography detected a lesion with 33 mm×18 mm near the head of pancreas, involving the second portion of the duodenum. The surface of the tumor was

Table 1. Clinicalpathological findings of gangliocytic paraganglioma with lymph node or distant metastasis

No.	Reference	Age (yr)/gender	Tumor site	Tumor size (mm)	Lymph node metastasis	Distant metastasis	Treatment	Follow up (months)
1	Buchler et al [4]	50/male	Ampulla of Vater	30	Yes	No	LR	NED 20 mo
2	Korbi et al [5]	73/female	Duodenum	NA	Yes	No	WP	NA
3	Inai et al [6]	17/male	Duodenum	20	Yes	No	WP	NED 32 mo
4	Hashimoto et al [7]	47/male	Second portion of the duodenum	65	Yes	No	WP	NED 14 mo
5	Dookhan et al [8]	41/male	Duodenum	25	Yes	No	LR+WP	Recurrence 11 years after first LR
6	Takabayashi et al [9]	63/female	Papilla of Vater	32	Yes	No	WP	NED 24 mo
7	Tomic et al [10]	74/female	Pancreas	40	Yes	No	WP	NED 19 mo
8	Henry et al [11]	50/male	Pancreas	25	Yes	Bone	WP	NA
9	Sundararajan et al [12]	67/female	Second portion of the duodenum	50	Yes	No	WP	NED 9 mo
10	Bucher et al [13]	31/female	Papilla of Vater	30	Yes	No	WP	NED 44 mo
11	Wong et al [14]	49/female	Duodenum	14	Yes	No	WP+RT	NED 12 mo
12	Witkiewicz et al [15]	38/female	Papilla of Vater	15	Yes	No	LR+WP	NA
13	Mann et al [16]	17/female	Duodenum	NA	Yes	No	WP	NED 12 mo
14	Okubo et al [1]	61/male	Papilla of Vater	30	Yes	No	WP	NED 6 mo
15	Saito et al [17]	28/male	Papilla of Vater	NA	Yes	No	WP	NA
16	Sandmann et al [18]	62/female	Ampulla of Vater	50	Yes	No	LR	NA
17	Uchida et al [19]	67/female	Second portion of the duodenum	NA	Yes	No	WP	NA
18	Rowsell et al [20]	52/female	Duodenum	10	Yes	Liver	LR	NED 27 mo
19	Ogata et al [21]	16/male	Ampulla of Vater	25	Yes	No	WP	NED 36 mo
20	Barret et al [22]	51/female	Duodenal papilla	35	Yes	No	WP	NED 8 yr
21	Bin Li et al [23]	47/male	Duodenal papilla	30	Yes	Liver and pelvic cavity	WP+RT+CT+pelvic mass resection	Die 13 mo after initial surgery
22	Huijuan Shi et al [24]	47/male	Ampulla of Vater	40	Yes	No	WP	NED 24 mo
23	Okubo et al [25]	74/female	Second portion of the duodenum	23	Yes	No	WP	NED 6 mo

LR: Local resection; WP: Whipple procedure; CT: chemotherapy; RT: Radiotherapy; NA: Not available; NED: No evidence of disease.

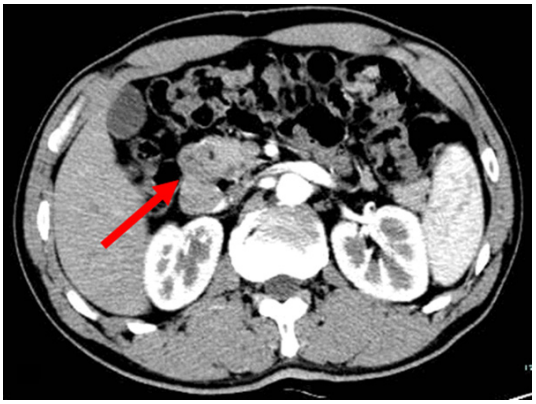

Figure 1. The image of CT in case 2. CT scans revealed a mass between the head of pancreas and the duodenum papilla (red arrow).

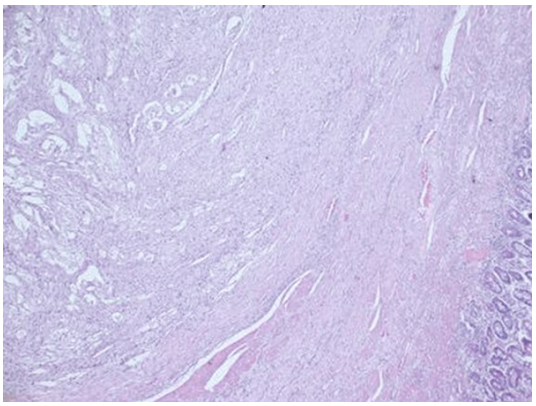

Figure 2. The tumor in case 1. The tumor showed an expansive growth pattern (HE staining with original magnification ×50).

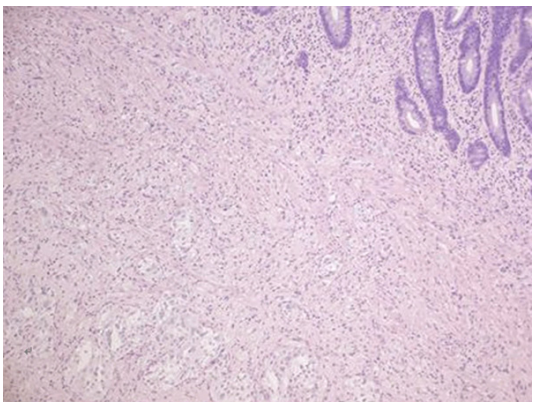

Figure 3. The tumor in case 2. The tumor involved the whole wall of the duodenum (HE staining with original magnification ×100).

smooth without bleeding or ulceration. The patient underwent pancreaticoduodenectomy and lymph node dissection on 2/13/2012.

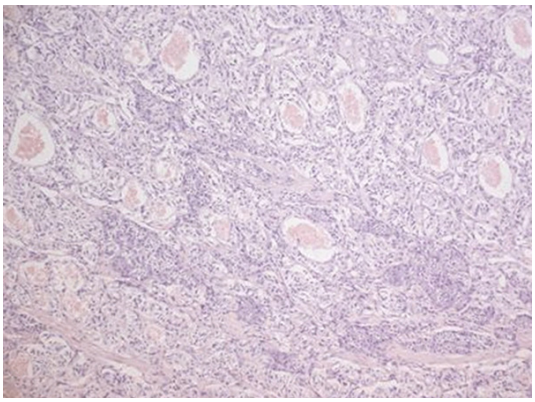

Figure 4. The tumor encroached the nearby pancreas (HE staining with original magnifcation ×100).

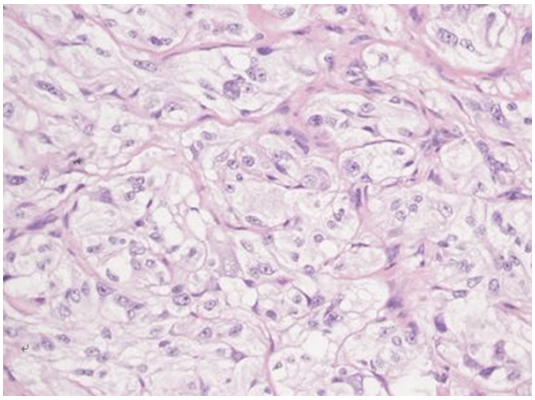

Figure 5. HE staining of the tumor. The tumor was composed of three morphologically distinct cell populations: spindle cells, ganglion-like cells and epithelioid cells (HE staining with original magnifcation ×400).

Subsequently, the patient received chemotherapy for 5 cycles.

To date, the patient remains well and no recurrence has been recognized in a three-year follow-up period.

Pathological findings

Grossly, a mass measuring 30mm in the largest dimension was found in the resected specimen of case 1. It was covered by the mucosa. Ulceration was found on the surface. The surgical specimen of case 2 consisted of the duodenum, bile duct, gallbladder and head of the pancreas. A solid tumor 40×30×30 mm in size was located between the head of pancreas and the duodenum papilla. The mucosa was smooth without bleeding or ulceration. A total of nine lymph nodes were also removed.

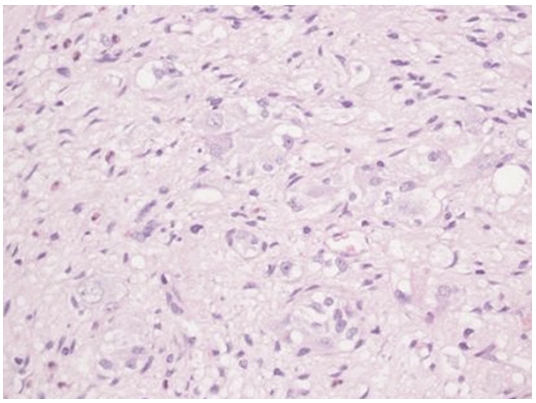

Figure 6. HE staining of Ganglion-like cells. These cells were rarely seen and had a round nucleus with conspicuous nucleolus (HE staining with original magnifcation ×400).

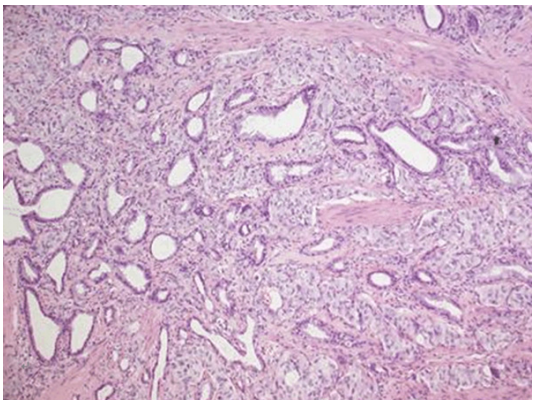

Figure 7. HE staining of case 2. The tumor cells in case 2 focally mixed with the proliferative bile ducts (HE staining with original magnification ×100).

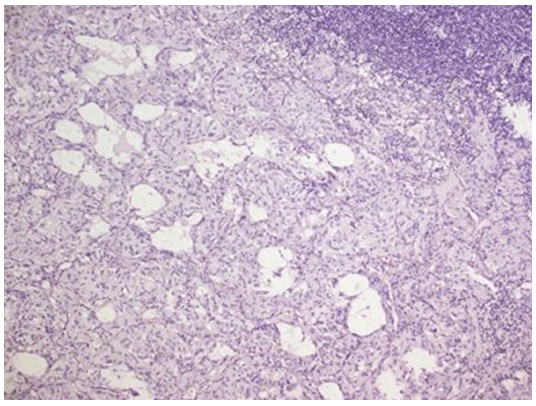

Figure 8. HE staining of the lymph node. The metastatic tumor was found in the lymph node (HE staining with original magnifcation ×100).

Microscopically, the tumor in case 1 was localized in submucosal layer, showing an expansive growth pattern (**Figure 2**). The lesion focally invaded the peri-tissue. Ulceration was observed on the surface of the mucosa. The tumor in case 2 involved the whole wall of the duodenum (**Figure 3**), encroaching on the pancreas (**Figure 4**). The microscopical characteristics of the two cases were similar. The tumor was composed of three morphologically distinct cell populations: spindle cells, ganglion-like cells and epithelioid cells. The epithelial cells arranged in the nests and trabeculae, with round to oval-shaped nucleus and pale eosinophilic cytoplasm. The spindle cells, with an elongated nucleus and attenuated eosinophilic cytoplasm, formed slender fascicles encompassing the nests of epithelioid cells (**Figure 5**). Ganglion-like cells were rarely seen and had a round nucleus with conspicuous nucleolus (**Figure 6**). There was no mitotic figure or necrosis in the foci. Moreover, in case 2, the tumor cells focally mixed with the proliferative bile ducts (**Figure 7**).

The metastatic tumor was found in three of nine lymph nodes in case 2. The histological features in the metastases were identical with the primary lesion (**Figure 8**).

Immunohistochemical findings

Immunohistochemically, the epithelioid cells were positive for cytokeratin (AE1/AE3), synaptophysin (Syn), chromogranin A (CgA), CD56 and progesterone receptor (PR). Ganglion-like cell types showed positive reactivity for Syn and CD56. In contrast, the spindle-shaped cells showed positive reactivity for S-100. The expression of Ki-67 was extremely low (**Figure 9**). Bcl-2 and P53 showed negative reactivity. In addition, in case 2, numerous cells positive for CD117 scattered in the stroma (**Figure 10**), which indicated they were mast cells. Inversely, these cells were relatively scarce in case 1 (**Figure 11**). The expression pattern of these biomarkers in the metastatic tumor in lymph nodes was similar with that in the primary lesion.

Discussion

GP consists of three types of cells: spindle cells, ganglion-like cells and epithelioid cells [1]. Identification of the three components is essential for the diagnosis of GP. The tumor cells always arrange in solid and trabecular pattern, mainly comprising spindle cells, mixed

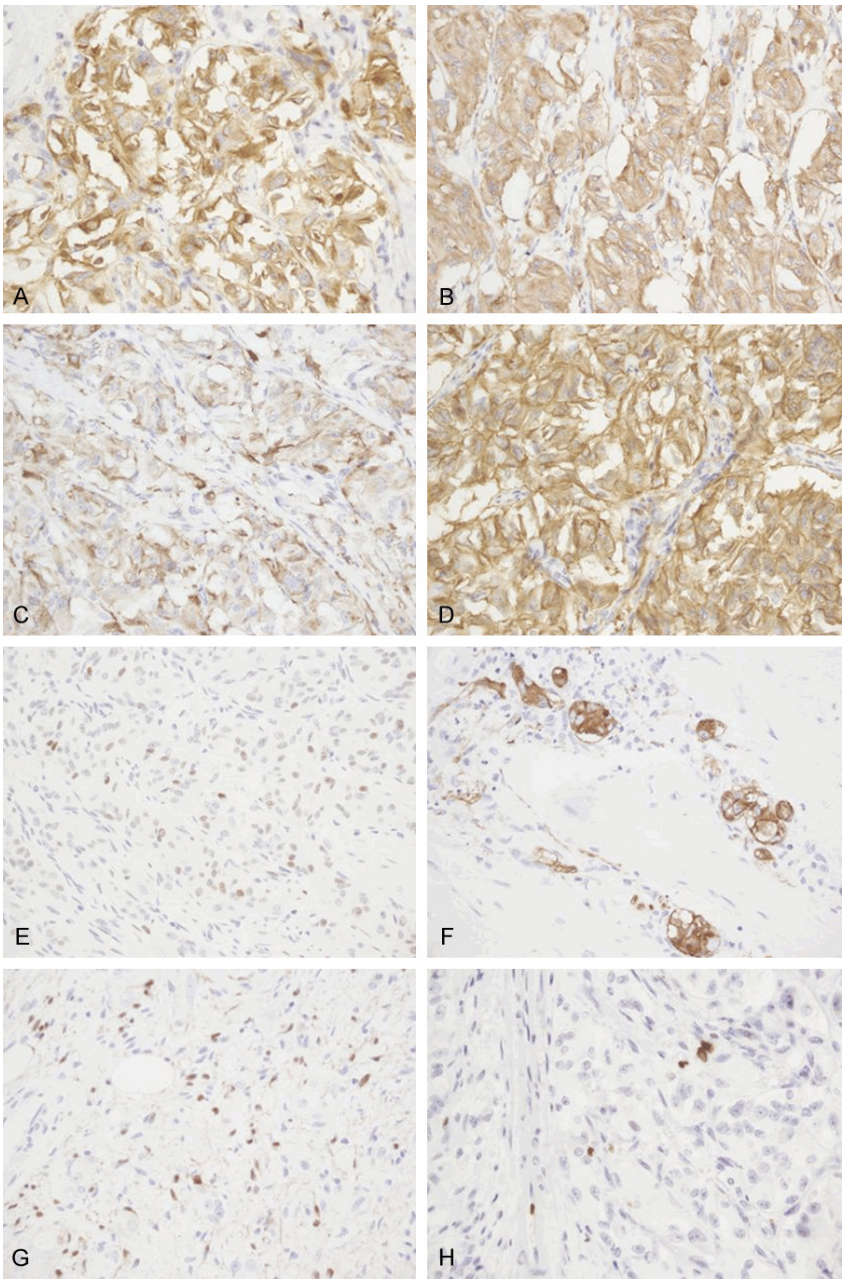

Figure 9. Immunohistochemical analysis of the tumors in the duodenum. The epithelioid cells were positive for CK (A), Syn (B), CgA (C), CD56 (D) and PR (E). Ganglion-like cells showed positive reactivity for Syn (F). The spindle-shaped cells showed positive reactivity for S-100 (G). The expression of Ki-67 was extremely low (H). (A-H: Immunohistochemical staining with original magnification ×400).

with nests of epithelioid cells and large cells with gangliocytic differentiation [24]. Besides, other unusual structures have been reported. Huijun et al reported a case of GP with distinct glandular component embedded in the spindle tumor cells in the primary tumor and the metastatic lymph nodes [24]. Moreover, Ogata et al also found a small glandular component with mucus was present in the primary tumor and more prevalent in the lymph node metastasis [21].

GP should be distinguished from carcinoid tumor, ganglioneuroma, pigmented paraganglioma and spindle cell tumors as gastrointestinal stromal tumor (GIST) [26-28]. Immunohistochemical examination has been regarded as an important diagnostic clue for GP. In epithelial cells and ganglion-like cells, CD56 and Syn showed the highest positive rates. For the identification of the spindle-shaped cells, S-100 protein would be the candidate with no doubt [25]. Moreover, Yoichiro et al demonstrated that the epithelial cells showed significantly higher positive reactivity for PR and pancreatic polypeptide (PP) than duodenal carcinoid tumor [25]. Naturally, PR and PP were also employed to make differential diagnoses of GP from carcinoid tumor. In the present two cases, the epithelial cells showed positive reactivity for PR, which was consistent with the published data.

GP was firstly described by Dahl et al in 1957 [29]. Since then about 200 cases of GP have been reported. Generally, it is regarded as a benign lesion. With the more cases of GP with regional lymph node metastasis and even distant metastasis published, the biological behavior of GP should be redefined, especially after a malignant GP of the duodenum showing a lethal course was reported by Bin et al [23]. Researchers have tried to find out some biomarkers served as prognostic indica-

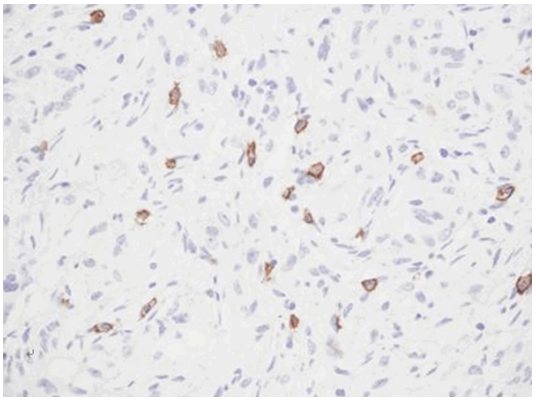

Figure 10. Immunohistochemical staining of CD117 in case 2. Numerous cells positive for CD117 scattered in the stroma (Immunohistochemical staining with original magnification ×400).

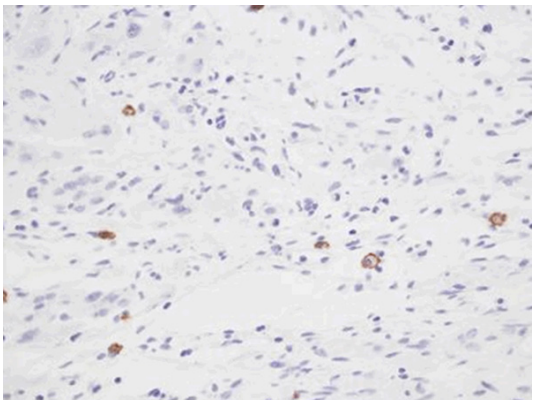

Figure 11. Immunohistochemical staining of CD117 in case 1. The cells positive for CD117 were scarce. (Immunohistochemical staining with original magnification ×400).

tors but failed. Bcl-2, P53 and Ki-67 were acceptable prognostic factors in several kinds of neuroendocrine tumors. However, bcl-2 and P53 showed negative reactivity in all cases of GP [1, 30]. Moreover, no matter whether lymph nodes metastases were present, Ki-67 labeling index was extremely low, even in the lethal case (less than 1% in both primary and metastatic foci) [23, 25, 30]. Similarly, we also demonstrated that the tumor cells showed negative reactivity for bcl-2 and P53 not only in the primary lesion, but also in the metastatic foci. Ki-67 positive staining was rarely present. Therefore, these biomarkers may have limited value in predicting the outcome of GP. In addition, histological features, such as necrosis or mitoses, were hardly seen in the lesion. Some authors suggested other important factors involved in the malignant process of GP and molecular techniques needed to interpret the underlying mechanisms.

Mast cells are immune cells that accumulate in the tumors and their microenviroment during disease progression. They express high levels of the tyrosine kinase receptor Kit (CD117) [31]. In vitro studies have shown that mast cells have the potential to influence many aspects of tumor biology, including tumor development, tumor-induced angiogenesis, and tissue remodeling, and the shaping of adaptive immune responses to tumors [32]. However, the contribution of mast cells to the tumor biology in vivo is still under investigation. In our two cases, we found that the presence of mast cells was more frequently in case 2 than that in case 1. We have no idea whether this is occasional owing to the limited number of cases. More cases should be recruited to elucidate the intrinsic association.

In this article, we report two cases of GP, one of which was accompanied by lymph node metastasis. The patient with lymph node metastasis has a good prognosis. Because of the metastases, close surveillance is still necessary. A long time follow-up is needed to know exactly the prognosis.

Acknowledgements

This study was conducted with the approval of the Ethics Committee of The First Affiliated Hospital, College of Medicine, Zhejiang University.

Disclosure of conflict of interest

None.

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