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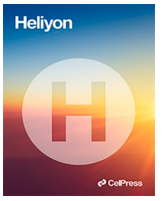

Case report

Primary hepatic neuroendocrine tumor with repeated diarrhea and flushing face: A case report and literature review

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ABSTRACT

Introduction and importance: Primary hepatic neuroendocrine tumors (PHNET) are neuroendocrine tumors (NETs) originate from liver, they are rare kind of NETs, and only account for about 0.3 % of all NETs. The main symptom of PHNET is abdominal pain, diarrhea and flushing only account for about 7.2 % and 4.3 %, respectively. We report a PHNET patient with diarrhea and flushing face and review cases in the literature.

Case presentation: A 50-year-old male patient came to our hospital for repeated diarrhea and flushing face for more than 2 years. The patient was hepatitis B virus carrier. Contrast-enhanced computed tomographic scan of the abdomen showed multiple tumors in both right and left hepatic lobes. An ultrasound-guided percutaneous needle biopsy was performed. Pathological examination of the biopsy showed the neoplasm were consisted of cells having an eosinophilic cytoplasm and round to oval hyperchromatic nuclei, indicating adenocarcinoma. To further identify the nature of the masses, immunohistochemical examination was performed, the result was positive for β-catenin, Ber-EP4, CgA, CK19, Syn, Ki-67 (3 %). Finally, the patient accepted transcatheter arterial chemoembolization treatment, and his symptoms did not occur ever after.

Clinical discussion: PHNET is neuroendocrine tumor which originates from liver, it is a rare disease. The main clinical manifestation of PHNET is abdominal pain, in comparison, abdominal mass, weight loss, nausea, vomiting, diarrhea and flushing are relatively rare,In our case, the patient had repeated diarrhea, and his face turned blushing each time when diarrhea occurred. Fine needle aspiration biopsy guided by ultrasound was made, after immunohistochemical examinations, the patient was diagnosed PHNET. Treatments of PHNET include surgical resection, chemotherapy, TACE, percutaneous ethanol injection treatment (PEIT) and transplantation. The patient accepted TACE treatment, his diarrhea and blushing face were controlled.

Conclusion: We reported a PHNET patient who had symptoms of repeated diarrhea and flushing face, and accepted transcatheter arterial chemoembolization treatment. Transcatheter arterial chemoembolization is an effective treatment for PHNET patient with diarrhea.

Abbreviations: PHNET, Primary hepatic neuroendocrine tumors; NETs, neuroendocrine tumors; TACE, transcatheter arterial chemoembolization; PEIT, percutaneous ethanol injection treatment; CT, computed tomographic; HCC, hepatocellular carcinoma.

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Table 1
Laboratory data before treatment.

Laboratory test	Result	Normal range
White blood cell count	13.51 × 10^9/L	3.5–9.5 × 10^9/L
Red blood cell	5.97 × 10^{12}/L	4.3–5.8 × 10^{12}/L
Hemoglobin	156 g/L	130–175 g/L
Platelet	386 × 10^9/L	125–350 × 10^9/L
Urea nitrogen	6.86 mmol/L	3.1–8 mmol/L
Creatinine	212 μmol/L	55–95 μmol/L
Glomerular filtration rate	24.1 ml/min × 1.73m^2	≥90 ml/min × 1.73m^2
Alpha fetoprotein (AFP)	1.24 ng/ml	≤7 ng/ml

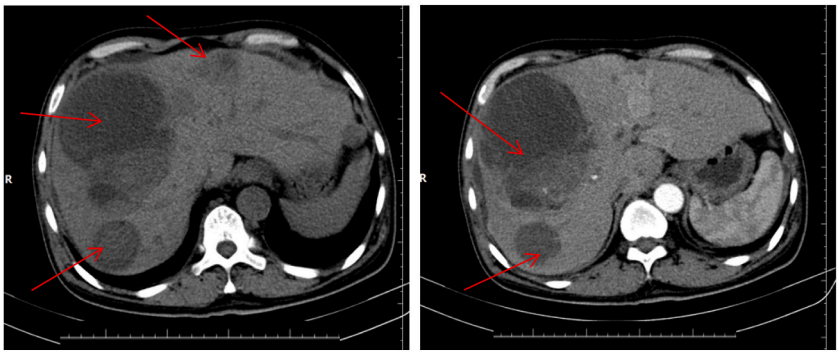

Fig. 1. CT scan of the abdomen. Multiple soft tissue shadows (red arrows) in both the right and left lobes. The largest (13 0.4 × 11.3 × 11.6 cm) in the right lobe. The masses showed heterogeneous enhancement in the arterial phase.

1. Background

Neuroendocrine tumors (NETs) are tumors that derive from the neuroendocrine system. NETs mainly occur in the gastrointestinal system, with small intestines and rectum accounting for more than 50 % of all origins [1]. Primary hepatic neuroendocrine tumors (PHNET) are NETs originate from liver, they are rare kind of NETs, and only account for about 0.3 % of all NETs [2]. It was first reported by Edmonson in 1958 [3]. Due to its rarity, less than 150 cases were reported until 2017 [4]. Most PHNET patients are asymptomatic, but some may present with the carcinoid syndrome [5]. The main symptom of PHNET is abdominal pain, diarrhea and flushing only account for about 7.2 % and 4.3 %, respectively [5]. Herein, we report a case of PHNET in a patient with repeated diarrhea and flushing face.

2. Case presentation

2.1. Case history

A 50-year-old male patient was admitted to our hospital because of repeated diarrhea for more than 2 years. 2 years ago, the patient presented diarrhea, yellow watery stool, with a maximum of more than 10 times per day, accompanied by nausea and vomiting of stomach contents, fatigue, thirst, oliguria, palpitation, flushing face, without chills, fever, no chest tightness or pain. The patient was hepatitis B virus carrier. The patient reported smoking 2 packs a day for more than 30 years. The patient's diarrhea was controlled after receiving octreotide subcutaneous injection treatment. Ever after, the patient had repeated diarrhea, and he had to receive large amount of octreotide micro pumping to control diarrhea.

Two months ago, the patient readmitted to our hospital. Admission examination: body temperature: 36.3 °C, pulse: 119 beats/min, respiration: 20 beats/min, blood pressure: 119/91 mmHg. Clear consciousness, flushed face, heart rate of 119 beats/min, no obvious murmurs in the heart and lungs, flat abdomen, the liver was palpable with slightly hard texture, spanning 6 cm below the right costal margin, negative shifting dullness, no percussion pain in the liver and kidneys, active bowel sounds, 7 beats per minute. Urine routine, stool routine, liver function, and coagulation function were normal. Other laboratory data was shown in Table 1.

Plain computed tomographic (CT) scan of the abdomen showed multiple low density masses in both right and left lobes, the largest mass measured 13 0.4 × 11.3 × 11.6 cm. Enhanced CT scan of the abdomen showed heterogeneous enhancement of masses in the arterial phase (Fig. 1).

Plain CT scan of the chest was performed to rule out the possibility of metastasis from lungs, the result showed no malignancy. Gastroduodenoscopy and colonoscopy were performed to rule out the possibility of metastasis from gastrointestine, the results also

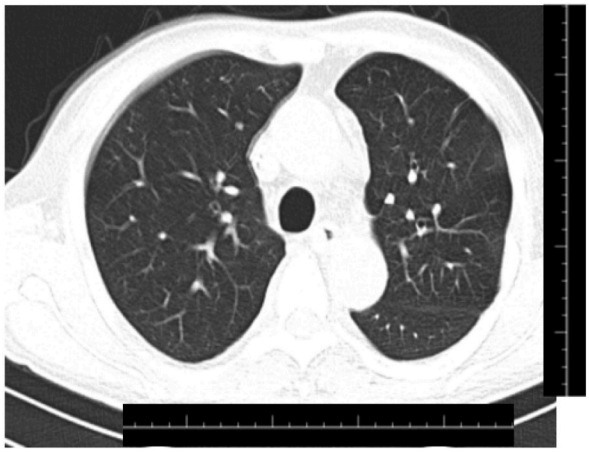

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Fig. 2. CT scan of the lungs. No malignancy was found in both left and right lungs.

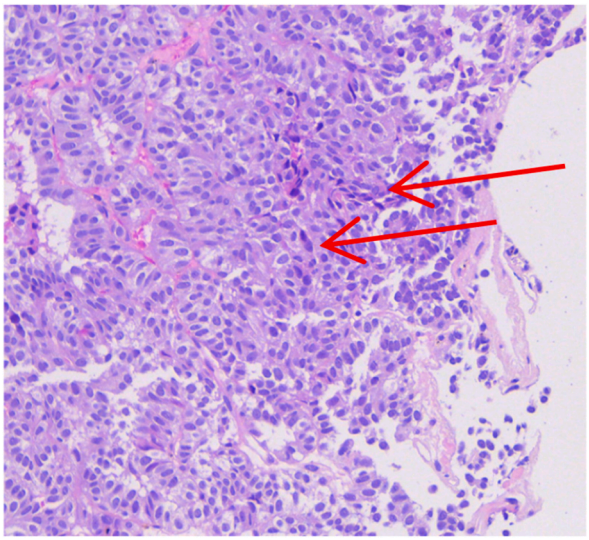

Fig. 3. HE stain of the biopsy (magnification × 100). The neoplasm are consisted of cells having an eosinophilic cytoplasm and round to oval hyperchromatic nuclei.

showed no malignancy (Fig. 2).

2.2. Pathology and immunohistochemistry

An ultrasound-guided percutaneous needle biopsy was performed. Pathological examination of the biopsy showed the neoplasm were consisted of cells having an eosinophilic cytoplasm and round to oval hyperchromatic nuclei, indicating adenocarcinoma (Fig. 3). To further identify the nature of the masses, immunohistochemical examination was performed, the result was positive for β-catenin, Ber-EP4, CgA, CK19, Ki-67 (3 %), Syn (Fig. 4). According to the 2013 North American Neuroendocrine Tumor Society (NANETS) Consensus Guidelines for the Diagnosis of Neuroendocrine Tumor, the tumor should be classified as G2 PHNET [6].

2.3. Treatment

Soon after the onset of severe diarrhea, the patient's white blood cell count, hemoglobin, platelet, creatinine were increased signigicantly, the glomerular filtration rate was decreased significantly, which indicated the patient had severe dehydration. After fluid replacement therapy and control of diarrhea using octreotide (25 μg/h) micro pumping, blood tests were taken and showed in Table 2. White blood cell count, hemoglobin, platelet, creatinine were decreased, and the glomerular filtration recovered partially.

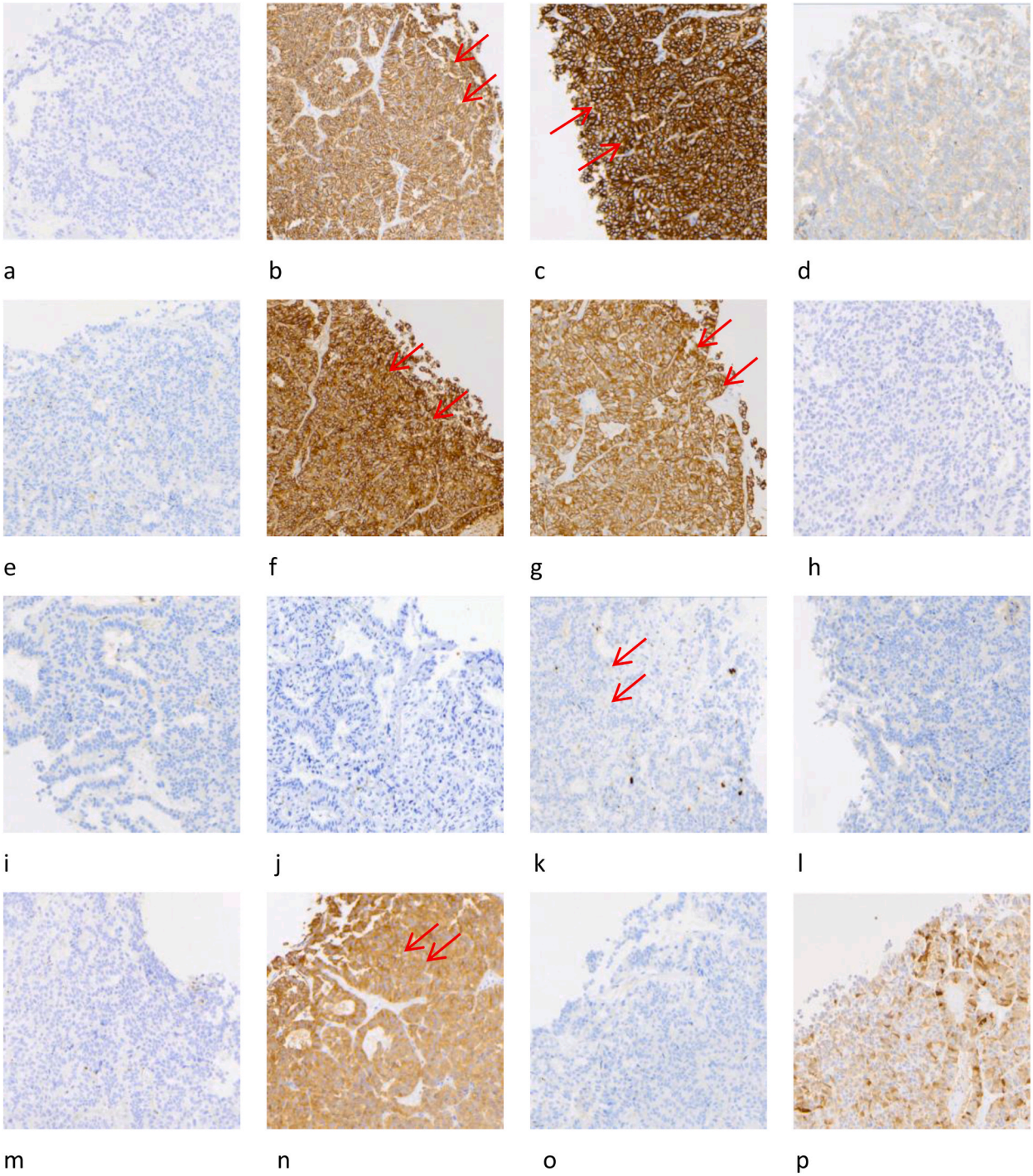

Fig. 4. Immunohistochemical stain of the biopies (magnification × 100). a ARG1 (negative); b β-catenin (positive); c Ber-EP4 (positive); d CD56 (negative); e CDX-2 (negative); f CgA (positive); g CK19 (positive); h CK20 (negative); i CK7 (negative); j GPC-3 (negative); k Ki-67 (positive 3 %); l PAX-8 (negative); m SATB2 (negative); n Syn (positive); o TTF-1 (negative); p Villin (negative).

After detailed discussion and preparation, transcatheter arterial chemoembolization (TACE) was performed. During the operation, hepatic artery angiography showed large masses staining, his branches of right hepatic artery supplying tumor blood were embolized using iodine oil and gelatin sponge (Fig. 5). Days after the operation, the patient was discharged from the hospital without diarrhea and blushing face. Five months later, the patient readmitted to the hospital for check without any symptoms, a plain CT scan of the abdomen showed multiple high density masses mixed with low density masses in the liver (Fig. 6).

Table 2
Laboratory data after treatment.

Laboratory test	Result	Normal range
White blood cell count	5.53×10^9/L	$3.5–9.5 \times 10^9$/L
Red blood cell	3.95×10^{12}/L	$4.3–5.8 \times 10^{12}$/L
Hemoglobin	106 g/L	130–175 g/L
Platelet	223×10^9/L	$125–350 \times 10^9$/L
Urea nitrogen	2.4 mmol/L	3.1–8 mmol/L
Creatinine	94 μmol/L	55–95 μmol/L
Glomerular filtration rate	70.7 ml/min × 1.73m^2	≥90 ml/min × 1.73m^2
Human growth hormone	2.56 mmol/L	0.126–9.88 mmol/L
Insulin	2.13 uIU/ml	2.6–24.9 uIU/ml
Parathyroid hormone	34.88 pg/ml	15–65 pg/ml
Cortisol 8:00 a.m.	482.1 nom/L	171-536 nom/L
Insulin like growth factor	31.77 ng/ml	76.44–244.1 ng/ml
Gastrin	17.4 ng/L	13–115 ng/L
Corticotropin	17.07 ng/L	7–65 ng/L
Aldosterone	42.18 pg/ml	28–239 pg/ml
Angiotensin II	39.76 pg/ml	25.1–110.9 pg/ml
Renin activity	0.48 ng/ml/h	0.15–2.33 ng/ml/h
Serotonin	481 ng/ml	40–400 ng/ml

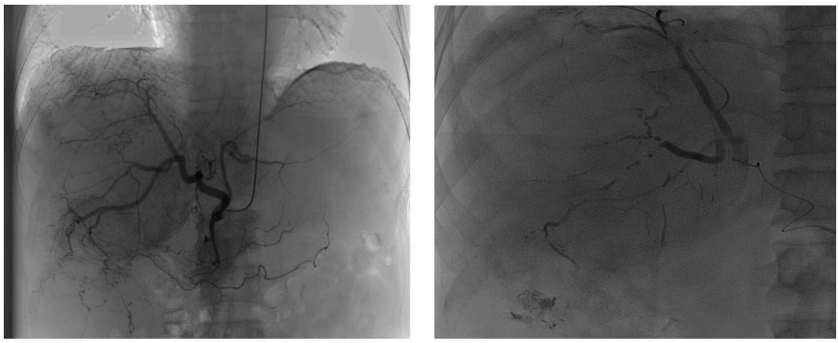

Fig. 5. Angiography with the iodine contrast agent. A hepatic artery angiography showed large masses staining (before treatment). B embolization of arteries supplying tumor blood using iodine oil and gelatin sponge (after treatment).

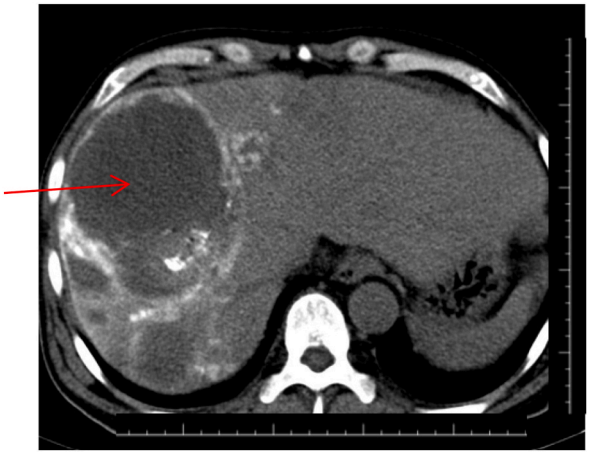

Fig. 6. Plain CT scan of the abdomen 1 month after TACE showed multiple high density masses mixed with low density masses in the liver.

2.4. Patient consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

3. Discussion

PHNET is neuroendocrine tumor which originates from liver, it is a rare disease. it affects more women than men [7], the median age of diagnosis was 63 years, and more than 40 % patients were older than 65 years [8].

The main clinical manifestation of PHNET is abdominal pain, in comparison, abdominal mass, weight loss, nausea, vomiting, diarrhea and flushing are relatively rare [9], it was reported that diarrhea and flushing only accounted for about 7.2 % and 4.3 %, respectively [5]. In our case, the patient had repeated diarrhea, and his face turned blushing each time when diarrhea occurred.

The tumor size was reported to range from 0.4 cm to 19 cm [10]. Many patients had very large tumors when they were discovered [11–15]. Our patient also had very large tumors when he was diagnosed, the largest mass measured 13 0.4 × 11.3 × 11.6 cm.

PHENT is often misdiagonased as hepatocellular carcinoma (HCC). A few reports have indicated that fine needle aspiration biopsy and histopathological as well as immunohistochemical examinations [16,17] are useful diagnostic tools. In our case, the patient was misdiagnosed as hepatocellular carcinoma 5 years ago. When the patient admitted to our deparment, as the patient was a hepatitis B virus carrier, and his liver was touchable, spanning 6 cm below the right costal margin, he was preliminally diagnosed as HCC. After the patient finished the abdominal CT check, the director of the imaging department carefully reviewed the patient's films, and considered the masses as HCC most likely. Patients with HCC (especially those patients with late-stage HCC) ofter had abnormal liver function and elevated AFP level, however, the patient's liver function was almost normal, and AFP was normal. After the patient finished fine needle aspiration biopsy guided by ultrasound, histopathological diagnosis of adenocarcinoma was made by the director of pathology department. Only after immunohistochemical examinations were done, was the diagnosis of PHNET finally made.

Our patient had repeated diarrhea and flushing face, we tested the patient's serotonin level in the blood and found serotonin level was elevated even after octreotide treatment. It is well known that serotonin is one of the key mediators of the carcinoid syndrome, and is especially involved in the development of diarrhea [18].

Treatments of PHNET include surgical resection, chemotherapy [19], TACE [20], percutaneous ethanol injection treatment (PEIT) [21] and transplantation [22]. Surgical resetion remains the main treatment modality for PHNET [2,8]. TACE is used in downstaging unresectable lesion and recurrent tumor post resection [23,24]. In this case, the patient had tumors in both his right and left lobes, he was not suitable for surgical resection, and he received TACE treatment. After TACE treatment, his diarrhea and blushing face were controlled, and in a month's follow-up, his symptoms did not recover. It seemed TACE was effective in control his symptoms. However, he was only followed-up for about 1 month, the long term effect of TACE on PHNET was not clear, we would continue to follow the patient's situation.

4. Conclusion

We reported a PHNET patient who had symptoms of repeated diarrhea and flushing face, and accepted transcatheter arterial chemoembolization treatment. Transcatheter arterial chemoembolization is an effective treatment for PHNET patient with diarrhea.

Data availability statement

The datasets generated and/or analyzed during the current study are available in the Jiaming Huang repository.

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CRediT authorship contribution statement

Xingyan Liu: Writing – original draft, Data curation. **Jiaming Huang:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] A. Frilling, G. Åkerström, M. Falconi, et al., Neuroendocrine tumor disease: an evolving landscape, Endocr. Relat. Cancer 19 (2012) R163–R185.
[2] Quartey, Primary hepatic neuroendocrine tumor: what do we know now? World J. Oncol. 2 (2011) 209–216.
[3] H.A. Edmonson, Tumors of the liver and intrahepatic bile ducts, Atlas Tumor Pathol 7 (1958) 129–131.

[4] P.C. Wong, W.H. She, U.S. Khoo, T.T. Cheung, A case of primary hepatic neuroendocrine tumor and literature review, Case Rep. Oncol. 14 (1) (2021 Feb 25) 90–97.
[5] G. Gravante, N. De Liguori Carino, J. Overton, T.M. Manzia, G. Orlando, Primary carcinoids of the liver: a review of symptoms, diagnosis and treatments, Dig. Surg. 25 (5) (2008) 364–368.
[6] P.L. Kunz, D. Reidy-Lagunes, L.B. Anthony, et al., Consensus Guidelines for the management and treatment of neuroendocrine tumors, North American neuroendocrine tumor society, Pancreas 42 (4) (2013) 557–577.
[7] Pak Chiu Wong, Hoi She Wong, Ui Soon Khoo, et al., A case of primary hepatic neuroendocrine tumor and literature review, Case Rep. Oncol. 14 (1) (2021) 90–97.
[8] Y.F. Li, Q.Q. Zhang, W.L. Wang, Clinicopathological characteristics and survival outcomes of primary hepatic neuroendocrine tumor: a surveillance, epidemiology, and end results (SEER) population-based study, Med Sci Monit 26 (2020 Jul 11) e923375.
[9] C.W. Lin, C.H. Lai, C.C. Hsu, et al., Primary hepatic carcinoid tumor: a case report and review of the literature, Cases J 2 (2009) 90.
[10] Y. Lv, C. Huang, H. Xu, et al., Clinicopathological characteristics of the primary and metastatic hepatic neuroendocrine tumors and the relevant prognosis-related factors: a retrospective study of 81 cases in a single Chinese center, J. Cancer 9 (2018) 479–487.
[11] Z.M. Zhao, J. Wang, U.C. Ugwuowo, et al., Primary hepatic neuroendocrine carcinoma: report of two cases and literature review, BMC Clin. Pathol. 18 (2018) 3.
[12] C. Qu, L.L. Qu, C.Z. Zhu, et al., Treatment of primary hepatic neuroendocrine tumors with associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): a case report and literature review, Medicine (Baltim.) 97 (2018) e12408.
[13] D.I. Cha, T.W. Kang, K.M. Jang, et al., Hepatic neuroendocrine tumors: gadoxetic acid-enhanced magnetic resonance imaging findings with an emphasis on differentiation between primary and secondary tumors, Abdom Radiol (NY) 43 (2018) 3331–3339.
[14] W. Li, B.W. Zhuang, Z. Wang, et al., Case report of contrast-enhanced ultrasound features of primary hepatic neuroendocrine tumor: a care-compliant article, Medicine (Baltim.) 95 (2016) e3450.
[15] H.X. Hu, T. Yu, Primary hepatic neuroendocrine tumors: a case report, Medicine (Baltim.) 98 (50) (2019 Dec) e18278.
[16] L. Skagias, O. Vasou, A. Ntinis, et al., Primary hepatic neuroendocrine tumor with exophytic growth report of a case with diagnosis by fine needle aspiration biopsy, Acta Cytol. 54 (2010) 202–204.
[17] A.K. Gorla, R.K. Basher, L. Kaman, et al., 68Ga-DOTATATE PET/CT in primary hepatic neuroendocrine tumor, Clin. Nucl. Med. 42 (2017) 118–120.
[18] T. Ito, L. Lee, R.T. Jensen, Treatment of symptomatic neuroendocrine tumor syndromes: recent advances and controversies, Expert Opin Pharmacother 17 (16) (2016 Nov) 2191–2205.
[19] S. Andreola, L. Lombardi, R.A. Audisio, V. Mazzaferro, D. Koukouras, R. Doci, L. Gennari, et al., A clinicopathologic study of primary hepatic carcinoid tumors, Cancer 65 (5) (1990) 1211–1218.
[20] Z. Touloumis, S.G. Delis, C. Triantopoulou, N. Giannakou, C. Avgerinos, C. Dervenis, Primary hepatic carcinoid; a diagnostic dilemma: a case report, Cases J 1 (1) (2008) 314.
[21] Y.Q. Huang, F. Xu, J.M. Yang, B. Huang, Primary hepatic neuroendocrine carcinoma: clinical analysis of 11 cases, Hepatobiliary Pancreat. Dis. Int. 9 (1) (2010) 44–48.
[22] N. de Liguori Carino, T.M. Manzia, L. Tariciotti, M. Berlanda, G. Orlando, G. Tisone, Liver transplantation in primary hepatic carcinoid tumor: case report and literature review, Transplant. Proc. 41 (4) (2009) 1386–1389.
[23] S.C. Krishnamurthy, V. Dutta, S.A. Pai, et al., Primary carcinoid tumor of the liver: report of four resected cases including one with gastrin production, J. Surg. Oncol. 62 (3) (1996) 218–221.
[24] Y. Iimuro, Y. Deguchi, Y. Ueda, A. Tanaka, Y. Iwasa, M. Ishihara, K. Mizuta, et al., Primary hepatic carcinoid tumor with metachronous lymph node metastasis after long-term follow up, J. Gastroenterol. Hepatol. 17 (10) (2002) 1119–1124.