Case Report

Obstructive Jaundice Caused by Metastatic Neuroendocrine Tumor of the Ampulla of Vater in a Young Adult: A Case Report

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Abstract

Introduction: Ampullary neuroendocrine tumors (NETs) are usually diagnosed in the 5th–6th decades of life, and no cases were reported in <20 years of age. We report a rare case, presenting at a very young age, of well-differentiated NET involving the ampulla of Vater with lymph node metastasis. ***Case Presentation:*** An 18-year-old man presented with a 3-month history of upper abdominal pain and jaundice. Abdominal ultrasound showed a dilated common bile duct, and endoscopic retrograde cholangiopancreatography revealed two duodenal polypoid lesions, one of them overlying the ampulla of Vater, with an erythematous and ulcerated surface. Histopathological examination confirmed the diagnosis of NET grade 1. Octreotide scan revealed 2 para-aortic lymph nodes with intense radiotracer uptake. The patient had undergone Whipple surgery with para-aortic lymph node dissection. Histopathological examination of the surgical specimens was confirmatory of NET grade 2 and paraganglioma in a few of the dissected lymph nodes. Postoperatively, the patient was kept on monthly intramuscular octreotide. Follow-up gallium-68 DOTATATE is unremarkable apart from an avid left para-aortic lymph node which is showing stability over 12 months of follow-up. ***Conclusion:***

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This case demonstrates that NETs of the ampulla of Vater can present at a very young age. Radical surgical excision with extended lymph node dissection and postoperative octreotide is associated with better patient outcomes and survival.

Introduction

Neuroendocrine tumors (NETs) are heterogeneous group of malignancies that arise from diffuse neuroendocrine cells throughout the body. Most frequently, NETs originate from the digestive system, followed by the lungs. The incidence rate of small intestinal NETs has risen over the last decades. Registry-based studies have reported an incidence rate of 0.6–1.2 per 100,000 [1]. A recent report from the Taiwan Cancer Registry showed an increased incidence rate of 3.162 per 100,000 in 2015 compared to 0.244 per 100,000 in 1996 [2]. Studies from the USA, Europe, and Canada showed a similar increase in the incidence of small intestinal NETs [3]. An autopsy registry analysis from Sweden reported a mean annual incidence of 5.33 per 100,000 individuals [1]. Ampullary NETs are extremely rare and represent less than 0.3% of all gastroenteropancreatic neuroendocrine neoplasms [4].

In small intestinal NETs, the diversity in tumor morphology, prognostic factors, biological behavior, pseudo-glandular patterns, and clinical presentations are depended on the tumor site of origin [5]. Ampullary NETs show both gastrointestinal and pancreato-biliary features and similarities with adenocarcinoma. Thus, the lack of unique characteristics, nonspecific clinical manifestations, and divergent prognoses make the preoperative diagnosis challenging. Abdominal pain and jaundice due to bile duct obstruction are the most common symptoms. The highly vascularized nature of the ampulla of Vater enhances its metastatic potential. Half of the reported cases showed metastasis and it is regardless of the tumor size [6, 7].

The diagnosis of NETs requires a combination of laboratory, radiologic, and histo-pathological investigations. Upper gastrointestinal endoscopy with biopsies is considered the most sensitive diagnostic test. Precise localization and staging involve a combination of multiple imaging modalities. Endoscopic ultrasound-assisted procedures help stage the disease and identify local lymph node metastases. Although the standard of care is surgical resection, a multimodal treatment including systemic and liver-directed therapies is required in the management of small intestinal NETs [8].

Here, we present a case of small intestinal NET occurring at a very young age. To the best of the authors' knowledge, this is the first case of NET of the ampulla of Vater with lymph node metastases reported in a patient <20 years of age [4, 9]. This case highlights the importance of a multidisciplinary approach in the diagnosis and management of NETs and demonstrates the efficacy of radical surgical treatment on these tumors. The CARE Checklist has been completed by the authors for this case report and is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538260).

Case Presentation

An 18-year-old Saudi male was referred to our hospital with a 3-month history of upper abdominal pain and yellowish discoloration of the sclera. The pain was colicky and non-radiating, with a severity of 3/10, and was not related to food intake or position. Six months prior to the presentation, the patient was diagnosed with diabetes mellitus type 1 and started

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on insulin aspart 14/16/8 units and glargine 38 units HS. There was no family history of hepatobiliary, hemoglobinopathy, or gastrointestinal malignancy. Two weeks prior to the presentation, the patient was admitted to another hospital during which magnetic resonance cholangiopancreatography (MRCP) was performed and showed a filling defect in the distal common bile duct (CBD). Endoscopic retrograde cholangiopancreatography (ERCP) could not be done there due to unavailability.

His physical examination was unremarkable, apart from scleral jaundice. Liver function test revealed a total bilirubin of 6 mg/dL, alanine aminotransferase 70 U/L, alkaline phosphatase 258 U/L, and gamma-glutamyl transferase 474 U/L. Complete blood count, renal function test, calcium level, amylase, and lipase levels were normal. The parathyroid hormone was elevated (171 pg/mL); however, TSH, free T4, LH, FSH, prolactin, ACTH, cortisol, and testosterone levels were normal.

Abdominal ultrasound revealed a dilated CBD of 8 mm and a single gallbladder stone (Fig. 1). During the ERCP, two duodenal polypoid lesions were noted, one of them overlying the ampulla of Vater, with erythematous and ulcerated surface (Fig. 2). The common bile duct was cannulated, and the cholangiogram revealed dilated extra and intrahepatic bile ducts and a lower CBD filling defect (Fig. 3). Multiple biopsies were obtained from both the duodenal lesions, and a plastic stent was inserted in the CBD. CT scan of the abdomen with IV contrast showed multiple enhanced well-defined lesions in the peri-ampullary area as well as the pancreaticoduodenal groove. No distant metastasis was detected (Fig. 4).

The histopathological evaluation revealed infiltration of the intestinal mucosa by a few small solid nodules. These nodules were composed of cells with round uniform nuclei and stippled chromatin. Immunohistochemical studies of the nodules showed positive reactivity for CK7, CDX2, CD56, chromogranin A, and synaptophysin and stained negative for CD20 (Fig. 5). Less than 2% of the cells were labeled with the proliferation marker Ki-67, and the mitotic rate was $1/2 \text{ mm}^2$. Accordingly, a histopathological diagnosis of NET grade 1 was made.

Tc-Octreotide scan showed multiple large intraluminal and extraluminal duodenal masses with no radiotracer uptake due to necrotic component. Two left para-aortic lymph nodes, the larger one measuring 2.6 cm × 2.8 cm, showed intense radiotracer uptake (Fig. 6). There was no abnormal focus of activity in the liver, bones, and rest of the body.

Further workup showed an elevated 24-h urinary normetanephrine of 4,394 μg/24 h; however, the 24-h urinary metanephrine was normal as was the chromogranin (52 ng/mL; reference value <93), urine 5-hydroxyindoleacetic acid, gastrin, somatomedin, and glucagon. Tumor markers including carcinoembryonic antigen, alpha-feto protein, and CA19-9 were normal. Colonoscopy, MRI pituitary, and parathyroid ultrasound were unremarkable. Sequence analysis of MEN1 gene was negative for any pathogenic variants.

After a multidisciplinary team discussion, the patient underwent a conventional Whipple procedure followed by para-aortic lymph node dissection. Lymph nodes draining the head of the pancreas and duodenum were dissected, and the surgeon was keen on removing as many lymph nodes as possible. Gastrointestinal reconstruction was done as follows: pancreaticojejunostomy was performed as a two-layer end-to-side full-thickness pancreatic neck inside the jejunum; hepaticojejunostomy was done with end-to-side common hepatic duct to antimesenteric border of the jejunum 15 cm distal to pancreaticojejunostomy, and gastro-jejunostomy was done using handsewn anastomosis. Jejunojejunostomy was created around 60 cm from the biliary-enteric anastomosis. All the surgical margins were negative for tumor, and among the 39 lymph nodes excised, 12 lymph nodes showed metastatic NET. The tumor was confirmed to be NET grade 2. Two presumed para-aortic lymph nodes turned out to be paragangliomas.
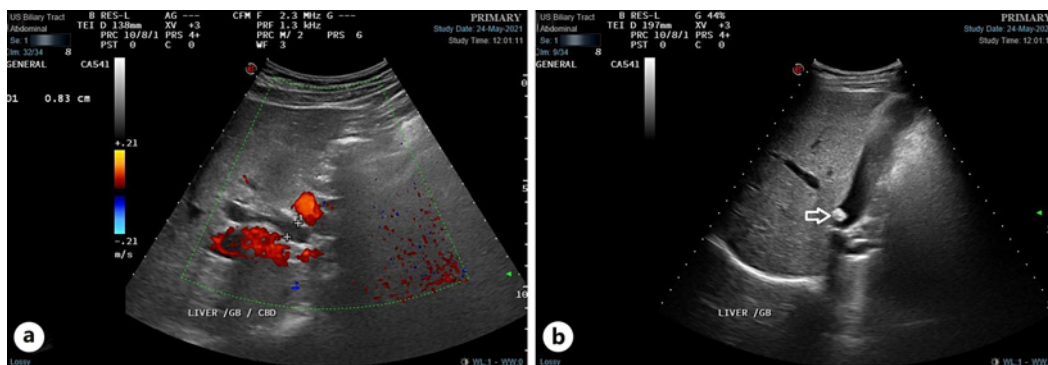
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Fig. 1. Selected ultrasound images at the porta hepatis (**a**) and at the gallbladder (**b**), showing ductal dilatation (cursor in **a**) and gallstone at the gallbladder neck (arrow in **b**).
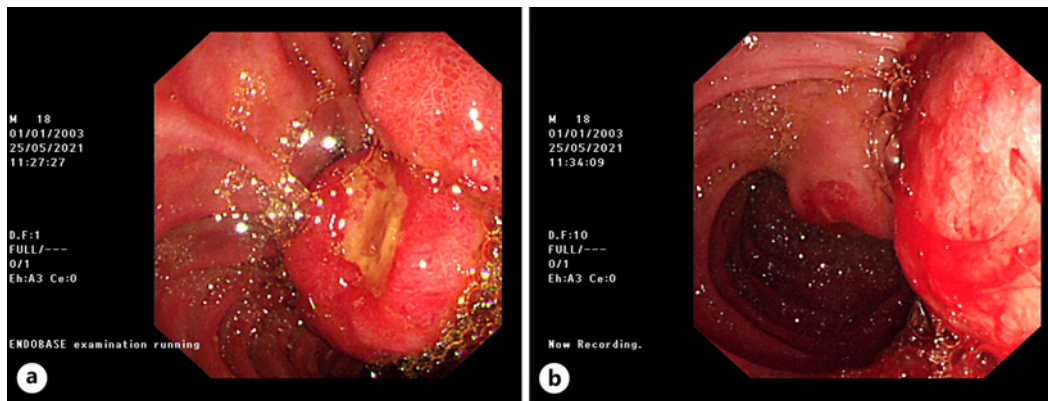

Fig. 2. Selected endoscopic images of the duodenum showing 2 polypoid lesions (**a**), one of them overlying the ampulla with ulcerated surface (**b**).
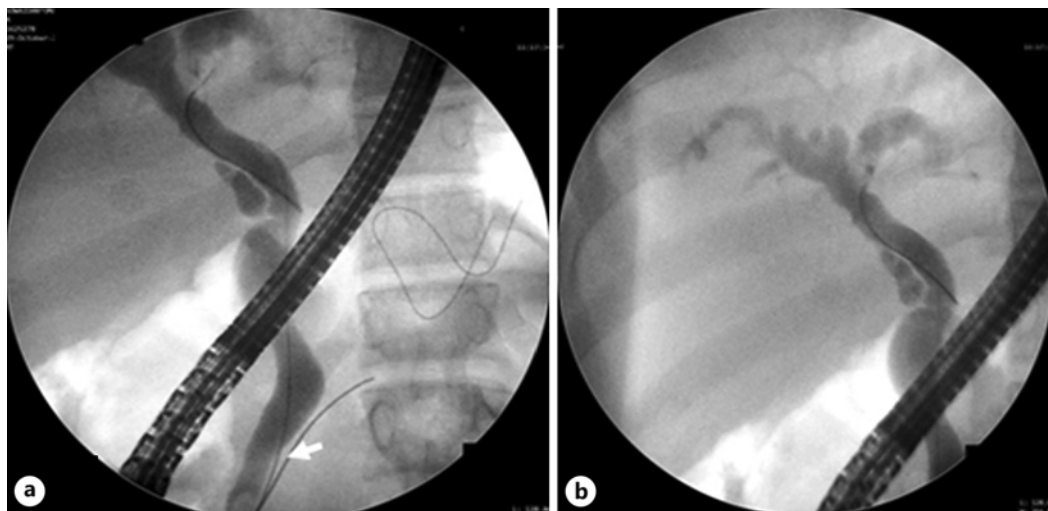

Fig. 3. Selected images from ERCP. Demonstrates distal CBD filling defect denoting stone arrow in (**a**) and intra-and extrahepatic ductal dilatation (**b**).

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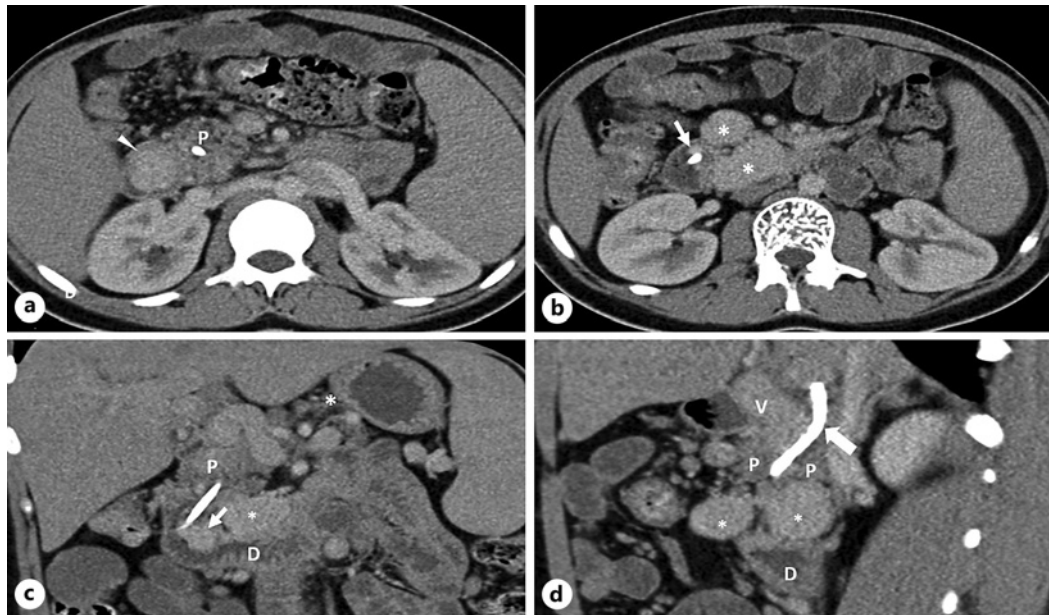Alsalman et al.: Ampullary Neuroendocrine Tumor in a Young Adult

Fig. 4. Enhanced CT scan images of the abdomen: axial (**a**, **b**); coronal (**c**); and sagittal (**d**). Shows multiple enhancing well-defined lesions. There are at least 2 duodenal lesions: one peri-ampullary (white arrow, in **b**, **c**) and one endo-luminal (arrow head in **a**). Also, it shows multiple pancreaticoduodenal groove lesions (* in **b**, **c**, **d**). Biliary stent in place (thick white arrow in **d**). D: duodenum, P: pancreatic head, V: portal vein.

After the surgery, the patient had improved apart from diarrhea responding to pancreatic enzymes. The patient was started on intramuscular octreotide 30 mg monthly based on the oncology recommendation and considering the presence of lymph node metastasis. Gallium-68 DOTATATE showed no residual uptake in the postoperative bed, and apart from an avid left para-aortic lymph node, no other DOTATATE-avid lymph node was noted. Over the 18-month follow-up, gallium-68 DOTATAE and CT scan have been showing the stability of the avid left para-aortic lymph node with no local recurrence.

Discussion

Studies have shown a steadily rising age-adjusted incidence rate in small intestinal NETs. The highest incidence was in the population between 70 and 79 years, and the lowest was between 20 and 29 years; however, no cases were reported <20 years of age [4, 9, 10]. The patient in this case presented at the age of 18 years with symptoms of abdominal pain and jaundice suggestive of biliary obstruction. Early detection of small intestinal NETs remains challenging due to their delay in the presentation of symptoms and non-specificity. In the majority of cases, symptoms like obstruction are present only after the tumors have metastasized. In addition, the likelihood of lymph node metastases being present at the time of diagnosis is about 60% [11]. However, recent advancements in diagnostic techniques have improved the detection of gastroenteropancreatic NETs at an early stage [12].

In the current case, besides the elevated bilirubin, the ultrasound showed dilatation of the common bile duct which necessitated an ERCP, considering the high probability of CBD stone. The ERCP revealed duodenal and ampullary lesions. The differential diagnosis of these lesions
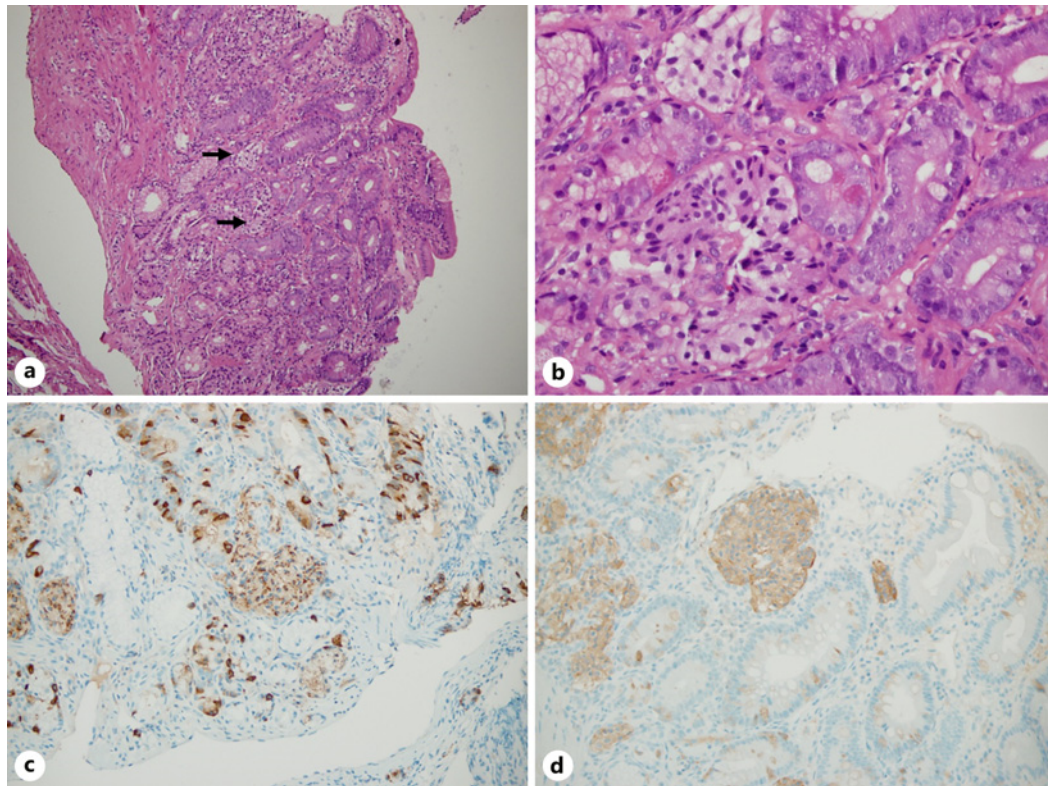
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Fig. 5. a Small intestinal mucosa depicting nodules in between the crypts (arrows) (hematoxylin and eosin, original magnification ×100). **b** Higher magnification revealing the nodules composed of round cells with amphophilic cytoplasm (hematoxylin and eosin, original magnification ×400). **c, d** Chromogranin A and synaptophysin, respectively, highlighting the neoplastic cells as well as non-neoplastic neuroendocrine cells within the glands (original magnification ×200).
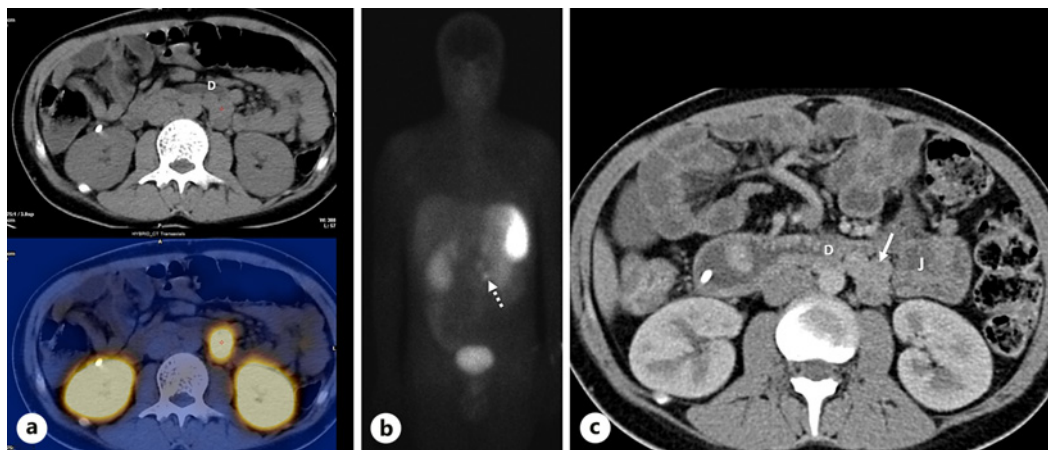

Fig. 6. Octreoscan: axial SPECT-CT (**a**) and frontal planar (**b**) images show an abnormal focal area of avid octreotide uptake (dotted arrow in **b** and red cursor on **a**). This is seen posterior and inferior to the fourth part of the duodenum. No other abnormal activity seen. On axial enhanced CT done earlier (**c**), the uptake corresponds to well-defined heterogeneous soft tissue (arrow in **c**). D, duodenum; J, jejunal loop.

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includes adenoma, gastrointestinal stromal tumor, carcinoid, lymphoma, and adenocarcinoma. This diverse differential diagnosis leads to difficulty in reaching a definitive preoperative diagnosis. Thus, histopathological characterization of the lesions is crucial to reach a definitive diagnosis. A key feature of NET is that they stain positive for synaptophysin and chromogranin A immunostaining. Assessing the level of differentiation, mitotic count, and Ki-67 index help to further classify the tumor into NET grades 1–3, neuroendocrine carcinoma, and mixed neuroendocrine-non-neuroendocrine neoplasm [8, 13].

To stage the tumor, a CT scan and PET scan were performed, and distant metastases were excluded in our patient. It is important to choose the right type of PET scan as the gallium-68 DOTATATE PET is better suited for the detection of well-differentiated tumors as these tumors have an abundance of somatostatin receptors. However, FDG PET is more suited for the detection of poorly differentiated tumors that show high glucose consumption [8, 14].

The optimal management of NETs requires a multidisciplinary approach. The selection of treatment modality should be based on the symptoms, tumor burden, the extent of infiltration, and tumor growth. Observation can be an option in asymptomatic patients with low-burden slow-growing tumors. Surgery is recommended for most localized NETs. Localized liver disease can be managed with debulking surgery, ablation, or chemoembolization. Elective Whipple procedure with extended para-aortic lymph node excision followed by octreotide injection was the treatment modality adopted in the present case. In the absence of liver metastases, primary tumor resection with extensive resection of associated mesenteric lymph nodes is recommended. In addition, metastatic mesenteric lymph node resection is associated with prolonged survival [11].

Systemic therapies include somatostatin analogs, like octreotide or lanreotide which are used in metastatic disease and proven to improve the time to progression or tumor-related death [8, 15]. Molecularly targeted biologic approaches using everolimus have reported effective anti-tumor activity and significant improvement in progression-free survival [16]. Peptide receptor radionuclide therapy using 177Lu-Dotatate also showed longer progression-free survival and was approved for the treatment of gastroenteropancreatic NETs [8, 17]. However, the reports of the ongoing clinical trials are important to ensure the clinical benefits and tolerability of targeted drugs like sunitinib [18]. Tumor site, functionality of the tumor, disease stage, and metastatic status are important when choosing the appropriate systemic therapy for the management of gastroenteropancreatic NETs.

Several factors correlate with metastatic risk in NET including size larger than 2 cm, high mitotic index, and involvement of the muscularis propria. However, when it comes to duodenal NETs, the size of the tumor does not correlate with its metastatic potential as even tumors <1 cm can metastasize. This metastatic potential is even higher with NET of the ampulla of Vater [6, 7, 19]. The long-term survival of patients with small intestinal NETs can be influenced by several factors. Younger age was identified to be associated with a better prognosis [10, 20]. The type of surgery has a significant prognostic implication. Elective surgery carries a better outcome compared with acute surgery [9]. Open surgery is recommended as laparoscopic procedures are challenged by the presence of small and multifocal lesions [20]. In those with nodal metastasis, primary tumor resection along with an extended regional mesenteric lymphadenectomy is associated with improved survival. Further, mesenteric tumor deposits found in the mesenteric perivisceral adipose tissue are associated with an increased risk of disease-specific death [21]. The use of high-dose somatostatin analog (octreotide long-acting release ≥30 mg) was reported to be associated with survival benefits [22]. However, further studies are required to determine the patient selection, optimal dose, and dose-response relationships of these agents in managing NETs of the digestive system.

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Our patient was successfully managed with an elective Whipple procedure with extended para-aortic lymph node excision followed by octreotide injection. The patient had steatorrhea after the procedure which was adequately managed with pancreatic enzymes. No recurrence was noted during the 18-month follow-up.

Conclusion

NET of the ampulla of Vater could present at a very young age with obstructive jaundice and have a high metastatic potential. For patients with lymph node metastasis, radical surgical excision with extended lymph node dissection and postoperative octreotide is associated with better patient outcomes and survival.

Acknowledgments

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose in association with this case report.

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Author Contributions

Literature review was done by J.S. and A.Q. Patient's data and follow-up were collected by J.S. Initial and final drafts of the article were written by J.S. and A.Q. M.Y. reviewed the article and contributed in writing histopathology part of the case presentation and discussion. O.D. reviewed the article and contributed in writing radiology part of the case presentation and

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discussion. I.Z. reviewed and approved the manuscript. J.S. submitted the article for publication and followed the co-authors in all steps. All authors have critically reviewed and approved the final draft.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Eriksson J, Norlén O, Ögren M, Garmo H, Ihre-Lundgren C, Hellman P. Primary small intestinal neuroendocrine tumors are highly prevalent and often multiple before metastatic disease develops. Scand J Surg. 2021;110(1): 44–50. doi: 10.1177/1457496919874484.

2 Chang JS, Chen LT, Shan YS, Chu PY, Tsai CR, Tsai HJ. An updated analysis of the epidemiologic trends of neuroendocrine tumors in Taiwan. Sci Rep. 2021;11(1):7881. doi: 10.1038/s41598-021-86839-2.

3 Fraenkel M, Kim M, Faggiano A, De Herder WW, Valk GD; Knowledge NETwork. Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. Endocr Relat Cancer. 2014; 21(3):R153–63. doi: 10.1530/ERC-13-0125.

4 Karlafti E, Charalampidou M, Fotiadou G, Abba Deka I, Raptou G, Kyriakidis F, et al. Ampullary large-cell neuroendocrine carcinoma, a diagnostic challenge of a rare aggressive neoplasm: a case report and literature review. Diagnostics. 2022;12(8):1797. doi: 10.3390/diagnostics12081797.

5 Han SL, Cheng J, Zhou HZ, Guo SC, Jia ZR, Wang PF. Surgically treated primary malignant tumor of small bowel: a clinical analysis. World J Gastroenterol. 2010;16(12):1527–32. doi: 10.3748/wjg.v16.i12.1527.

6 Tsukagoshi M, Hosouchi Y, Araki K, Mochida Y, Aihara R, Shirabe K, et al. Neuroendocrine tumor of the ampulla of Vater with distant cystic lymph node metastasis: a case report. Surg Case Rep. 2016;2(1):173–5. doi: 10.1186/s40792-016-0202-1.

7 Kleinschmidt TK, Christein J. Neuroendocrine carcinoma of the ampulla of Vater: a case report, review and recommendations. J Surg Case Rep. 2020;2020(6):rjaa119. doi: 10.1093/jscr/rjaa119.

8 Scott AT, Howe JR. Management of small bowel neuroendocrine tumors. J Oncol Pract. 2018;14(8):471–82. doi: 10.1200/JOP.18.00135.

9 Snorradottir S, Asgeirsdottir A, Rögnvaldsson S, Jonasson JG, Björnsson ES. Incidence and prognosis of patients with small intestinal neuroendocrine tumors in a population based nationwide study. Cancer Epidemiol. 2022; 79:102197. doi: 10.1016/j.canep.2022.102197.

10 Van Den Heede K, Chidambaram S, Van Slycke S, Brusselaers N, Warfvinge CF, Ohlsson H, et al. Long-term survival of metastatic small intestine neuroendocrine tumors: a meta-analysis. Endocr Relat Cancer. 2022; 29(3):163–73. doi: 10.1530/ERC-21-0354.

11 Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut. 2012;61(1):6–32. doi: 10.1136/gutjnl-2011-300831.

12 Dai M, Mullins CS, Lu L, Alsfasser G, Linnebacher M. Recent advances in diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms. World J Gastrointest Surg. 2022;14(5):383–96. doi: 10.4240/wjgs.v14.i5.383.

13 Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76(2):182–8. doi: 10.1111/his.13975.

14 Raphael MJ, Chan DL, Law C, Singh S. Principles of diagnosis and management of neuroendocrine tumours. CMAJ. 2017;189(10):E398–404. doi: 10.1503/cmaj.160771.

15 Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009;27(28): 4656–63. doi: 10.1200/JCO.2009.22.8510.

16 Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, nonfunctional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387(10022):968–77. doi: 10.1016/S0140-6736(15)00817-X.

17 Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumors. NEJM. 2017;376(2):125–35. doi: 10.1056/NEJMoa1607427.

18 Tsoli M, Chatzellis E, Koumarianou A, Kolomodi D, Kaltsas G. Current best practice in the management of neuroendocrine tumors. Adv Endocrinol Metab. 2019;10:2042018818804698. doi: 10.1177/2042018818804698.

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Case Rep Gastroenterol 2024;18:204–213

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Alsalman et al.: Ampullary Neuroendocrine Tumor in a Young Adult

19   Clements WM, Martin SP, Stemmerman G, Lowy AM. Ampullary carcinoid tumors: rationale for an aggressive surgical approach. J Gastrointest Surg. 2003;7:773–6. doi: 10.1016/s1091-255x(03)00114-8.

20   Howe JR, Cardona K, Fraker DL, Kebebew E, Untch BR, Wang YZ, et al. The surgical management of small bowel neuroendocrine tumors: consensus guidelines of the north American neuroendocrine tumor society. Pancreas. 2017;46(6):715–31. doi: 10.1097/MPA.0000000000000846.

21   Grillo F, Albertelli M, Malandrino P, Dotto A, Pizza G, Cittadini G, et al. Prognostic effect of lymph node metastases and mesenteric deposits in neuroendocrine tumors of the small bowel. J Clin Endocrinol Metab. 2022;107(12):3209–21. doi: 10.1210/clinem/dgac326.

22   Lau SC, Abdel-Rahman O, Cheung WY. Improved survival with higher doses of octreotide long-acting release in gastroenteropancreatic neuroendocrine tumors. Med Oncol. 2018;35(9):123. doi: 10.1007/s12032-018-1189-1.